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Energetics of guest binding to calix[4]arene molecular containers

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Dedicated to the memory of Dmitry M. Rudkevich

ABSTRACT

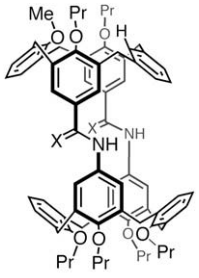
The synthesis of calix[4]arene-based molecular containers **1** and **2** along with the thermodynamic behaviors of cation binding are reported. The containers encapsulated *N*-methylpicolinium salts to form 1:1 host–guest complexes in chloroform. The thermodynamic investigations of the containers provide contrastive pictures for the process of their guest encapsulations. The encapsulation of **1** with the *N*-methylpicolinium cations, bearing a series of counter anions, was primarily enthalpy-driven. The enthalpic difference among the host–guest complexes of the salts was directly related to the total electrostatic stability of the ion-pairs. When **2** encapsulated a series of the *N*-methylpicolinium cations within its cavity, negative heat capacity changes were observed. This suggests that the changes in the solvation spheres of the container and its guest before and after the formation of the host–guest complex depend on temperature.

1. Introduction

Molecular containers,[1] rigid hollow organic host compounds, are of great interest in the field of supramolecular chemistry because of their unique guest encapsulation properties. Most containers have confined inner cavities and are based on macrocyclic compounds. These include calixarenes, cavitands, cyclodextrins, cyclotriveratrylenes, and cucurbiturils.[2] These containers can accommodate a suitable organic molecule, or even more than one guest molecule within their cavities.

Previously, Cram and co-workers synthesized molecular containers composed of two cavitands linked by covalent bonds, termed carcerands and hemicarcerands.[3] These containers demonstrated the ability to encapsulate reactive intermediates as well as organic molecules within the confined inner cavities. Rebek and co-workers synthesized cavitand-based cylindrical dimers and resorcinarene-based hexameric assemblies via hydrogen bonding.[4] Noncovalent interactions, including π–π, CH–π, van der Waals, and hydrogen bonding interactions are responsible for their guest encapsulations. It is particularly striking that reactive intermediates and unusual molecular species were stabilized within the cavity.

Molecular containers based on calixarenes have been extensively investigated as well.[5] Shinkai[6] and Reinhoudt[7] reported pioneering work in this field. Calix[4]arene-based molecular containers were developed by linking the upper rims through covalent bonds; some of these containers took up guest molecules into the confined cavity. Our group has been developing calixarene-based containers that show unique guest-binding properties.[8] In this paper, we report the synthesis of a new class of double-calix[4]arene containers, **1** and **2**,[9] composed of calix[4]arene and monodeoxycalix[4]arene, and the detailed discussion of the thermodynamic behavior of guest complexation by hosts **1** and **2**.



1: X = H_2
2: X = O

2. Results

2.1. Synthesis of container molecules

The synthesis of double-bridged container **1** is shown in Scheme 1. Propylation of the phenolic hydroxy groups of monodeoxycalix[4]arene **3**[10] with NaH and propyl iodide in DMF yielded **4**. Lithiation of the two iodine groups of **4** with *n*-butyl lithium in THF, followed by the addition of dimethylformamide, afforded dialdehyde **5**. A selective coupling reaction of dialdehyde **5** and diaminocalix[4]arene **6**[11] in CH_2Cl_2 afforded diimine **7**, which was

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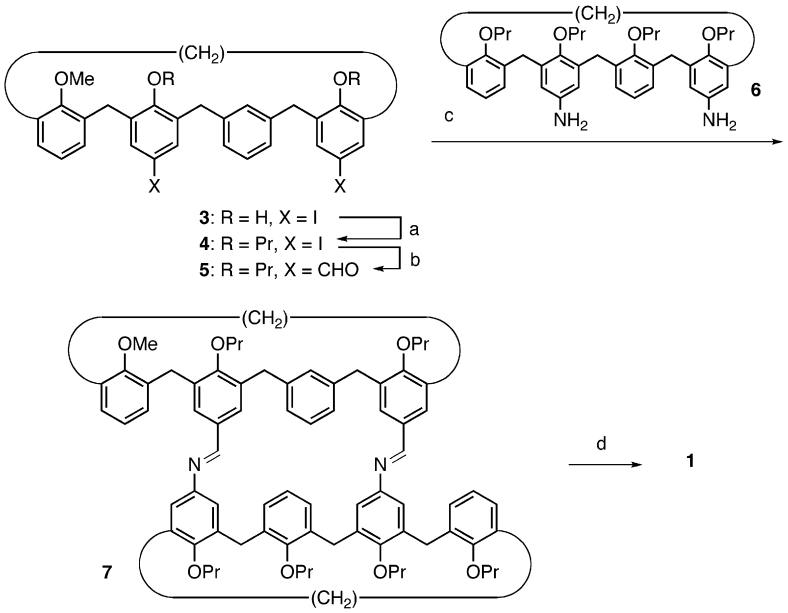
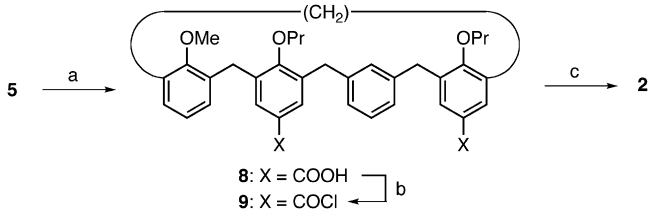


Scheme 1. Reagents and conditions: (a) *n*-PrI, NaH, DMF, 40%; (b) *n*-BuLi, THF then DMF, 69%; (c) **6**, CH_2Cl_2, 70%; (d) $NaBH_3CN$, MeOH, THF, 89%.

reduced with $NaBH_3CN$ in MeOH and THF to yield the desired container molecule **1**.

The synthesis of the double-bridged container **2** is shown in Scheme 2. Oxidation of **5** with $KMnO_4$ in aqueous acetone produced diacid **8**, which was converted to acid chloride **9**. Coupling of **9** and diaminocalix[4]arene **6** in THF furnished the desired container molecule **2**.



Scheme 2. Reagents and conditions: (a) $KMnO_4$, acetone, H_2O, 98%; (b) $(COCl)_2$, THF, 97%; (c) **6**, THF, 25%.

2.2. Encapsulation of π-planar *N*-methylpicolinium salts within molecular containers

The binding behavior of molecular containers **1** and **2** with π-planar *N*-methylpicolinium salts was examined by ^{1}H NMR titration. The ^{1}H NMR spectrum of *N*-methylpicolinium trifluoroacetate in the presence of **1** showed two sets of peaks, assigned to the protons of the complexed and free guests. This indicated that a significant kinetic barrier exists in the exchange of the guest into and out of the container at room temperature. When the host–guest complex formed, a large up-field shift of the guest protons was observed, with $\Delta\delta$=−5.24, −4.44, −2.17, and −2.29 ppm for α-C*H*, β-C*H*, γ-CH_3, and *N*-CH_3, respectively. These significant up-field shifts indicate that the guest was in a highly shielded cavity surrounded by the eight aromatic rings. The substantial up-field shifts of the aromatic protons suggested that the confined space permits the guest to adopt lateral orientations inside the cavity (Fig. 1).

When **2** encapsulated its guest, α-C*H*, β-C*H*, γ-CH_3, and *N*-CH_3 of the *N*-methylpicolinium cation showed complexation-induced shifts of $\Delta\delta$=−5.17, −4.46, −2.20, and −2.24 ppm. These values supported the lateral orientation of the guest inside the confined cavity of **2**.

2.3. Determination of association constants for host–guest complexation

To investigate the binding ability of the molecular containers **1** and **2**, titration experiments with the *N*-methylpicolinium salts bearing a series of the counter anions in chloroform were carried out using absorption spectroscopy. Figure 2 shows the UV–vis absorption spectra of **1** at 293 K in the presence of various concentrations of *N*-methylpicolinium trifluoroacetate. Plotting the changes of the absorption at 350 nm versus the concentration of the salt produced a hyperbolic curve, which fit well to a 1:1 host–guest model with an association constant (K_a) of 7600±200 L mol^{-1}.[12] Titration experiments with the *N*-methylpicolinium salts with trifluoromethanesulfonate, tetrafluoroborate, iodide, tosylate, benzenesulfonate, nitrate, picrate, and mesylate as counterions were examined in an analogous manner. UV–vis absorption spectra of *N*-methylpicolinium iodide at 293 K in the presence of various concentrations of **2** in chloroform are shown in Figure 3. An isosbestic point was observed at 370 nm, and Job's plots confirmed the 1:1 stoichiometry of the host–guest complex. Curve-fitting analysis of the absorption at 340 nm yielded a K_a of 9400±300 L mol^{-1}.

Association constants are summarized in Table 1. Container **2** showed stronger guest-binding affinities than **1**, while both container molecules **1** and **2** displayed the largest association constant

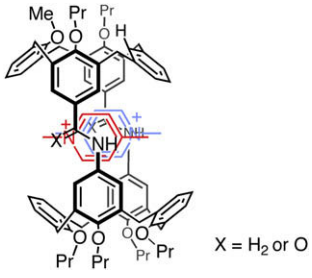


Figure 1. The lateral orientations of the *N*-methylpicolinium cation in the confined cavity. The orientation in red is a conformational isomer of the orientation in blue.

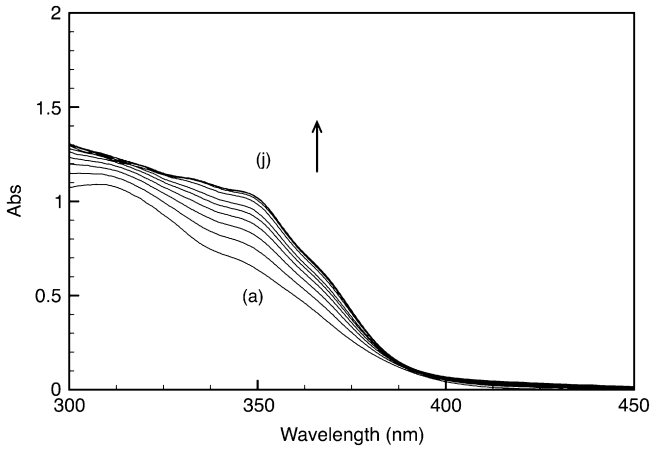


Figure 2. UV–vis absorption spectra of **1** (2.4×10^{-4} mol L^{-1}) in the presence of *N*-methylpicolinium trifluoroacetate at 293 K in chloroform. The concentrations of the picolinium salt are, from the bottom, (a) 0.0, (b) 0.96×10^{-4}, (c) 1.92×10^{-4}, (d) 2.88×10^{-4}, (e) 3.84×10^{-4}, (f) 4.8×10^{-4}, (g) 7.2×10^{-4}, (h) 9.6×10^{-4}, (i) 12×10^{-4}, and (j) 14.4×10^{-4} mol L^{-1}.

for *N*-methylpicolinium trifluoromethanesulfonate. Mesylate and iodide anions produced the lowest guest affinities of the cation for the containers. Clearly, the counter anions influence the stability of the host–guest complex; however, the reason for this effect remains unclear.

2.4. Determination of thermodynamic parameters for host–guest assemblies

To gain further insight into the guest encapsulation by the container molecules, van't Hoff analyses were performed to characterize the thermodynamics of this process. The association constants of *N*-methylpicolinium trifluoromethanesulfonate to container **1** were determined by UV–vis titration experiments in a temperature range from 273 to 298 K. The van't Hoff plots gave good linear correlations (Fig. 4) and provided the following thermodynamic parameters: $\Delta H^\circ=-12.7\pm0.85$ kcal mol^{-1} and $\Delta S^\circ=-23.6\pm2.9$ cal mol^{-1} K^{-1}. Binding studies of the *N*-methylpicolinium salts with other counter anions produced linear van't Hoff plots, allowing estimation of their thermodynamic parameters (Table 2).

Plotting the values of ΔH° against ΔS° from Table 2 gave a good linear correlation, which is commonly seen in host–guest complexation (Fig. 5). This compensation relationship between the enthalpic and entropic changes reflects the entropic cost of strong binding: the stronger the attractive interaction between the host and guest, the more reduced the freedom of the guest movement in the supramolecular complex.[13]

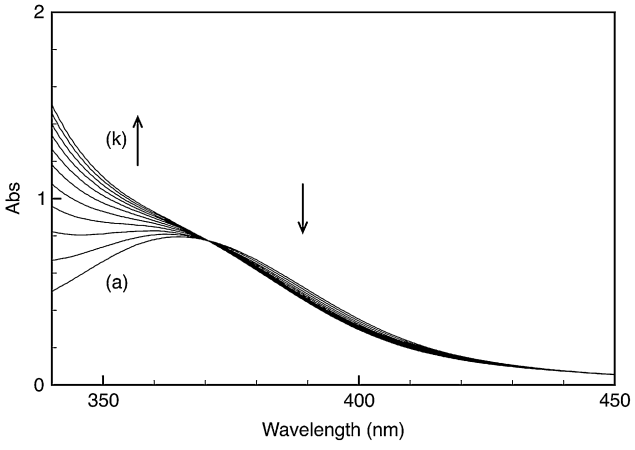


Figure 3. UV–vis absorption spectra of *N*-methylpicolinium iodide (2.0×10^{-4} mol L^{-1}) in the presence of **2** at 293 K in chloroform. The concentrations of **2** are, from the bottom, (a) 0.0, (b) 0.4×10^{-4}, (c) 0.8×10^{-4}, (d) 1.2×10^{-4}, (e) 1.6×10^{-4}, (f) 2.0×10^{-4}, (g) 2.4×10^{-4}, (h) 2.8×10^{-4}, (i) 3.2×10^{-4}, (j) 3.6×10^{-4}, and (k) 4.0×10^{-4} mol L^{-1}.

Table 1
Association constants (K_a/L mol^{-1}) for the host–guest complexation of **1** and **2** with various *N*-methylpicolinium salts in chloroform at 293 K

Counter anion	1	2
TfO^-	18,000±1000	200,000±10,000
BF_4^-	5800±500	13,000±500
$CF_3CO_2^-$	7600±200	97,000±5000
TsO^-	6400±300	50,000±2000
I^-	—[b]	9400±300
$PhSO_3^-$	6100±300	52,000±2000
NO_3^-	5600±100[a]	130,000±5000
Br^-	6100±90	—[b]
Pic^-	—[b]	33,000±1000
MsO^-	3200±100	45,000±1000

[a] Measured at 298 K.
[b] Not examined.

UV–vis titration experiments of **2** with *N*-methylpicolinium iodide were carried out to determine the association constants across a variety of temperatures. A van't Hoff analysis gave non-linear plots, suggesting that this host–guest complexation involves a heat capacity change (Fig. 6).

$$R\ln K = \left(\Delta H_0 + T\Delta C_p^\circ\right)(1/T) + \left(\Delta S_0 + \Delta C_p^\circ \ln T\right) \quad (1)$$

$$\Delta H^\circ = \Delta H_0 + T\Delta C_p^\circ \quad (2)$$

$$\Delta S^\circ = \Delta S_0 + \Delta C_p^\circ \ln T \quad (3)$$

Curve-fitting analysis with a non-linear van't Hoff equation (Eq. 1) provided values for enthalpy change ($\Delta H^\circ_{298}=-4.6\pm0.47$ kcal mol^{-1}), entropy change ($\Delta S^\circ_{298}=2.7\pm1.6$ cal mol^{-1} K^{-1}), and heat capacity change ($\Delta C_p^\circ=-300\pm63$ cal mol^{-1} K^{-1}). Table 3 shows the thermodynamic parameters in the complexation of

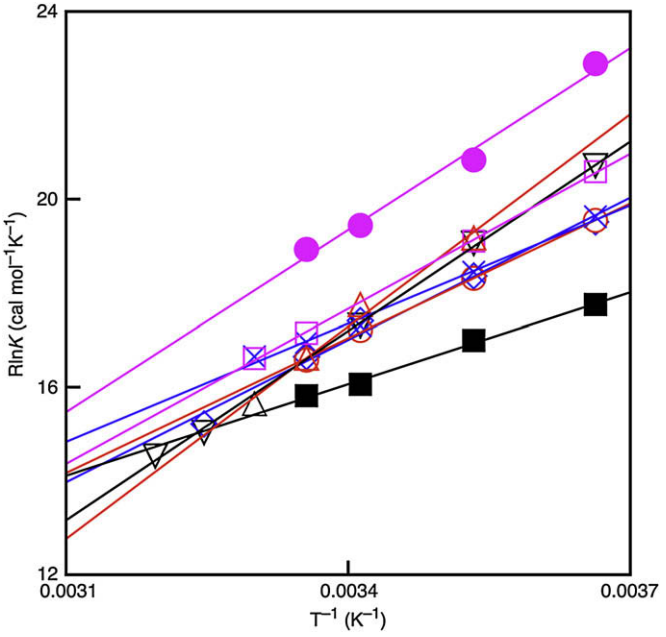


Figure 4. van't Hoff plots for the host–guest complexation of **1** with *N*-methylpicolinium salts. TfO^- (●); BF_4^- (○); $CF_3CO_2^-$ (△); TsO^- (◇); $PhSO_3^-$ (×); NO_3^- (□); MsO^- (■); Br^- (▽).

Table 2
Thermodynamic parameters for the host–guest complexation of **1** with *N*-methylpicolinium salts in chloroform

Counter anion	ΔG°_{298} (kcal mol^{-1})	ΔH° (kcal mol^{-1})	ΔS° (cal mol^{-1} K^{-1})
TfO^-	−5.64	−12.7±0.85	−23.6±2.9
$CF_3CO_2^-$	−4.95	−15.1±1.30	−34.0±4.6
Br^-	−4.50	−13.6±0.34	−20.2±1.2
$PhSO_3^-$	−5.05	−8.42±0.49	−11.3±1.7
TsO^-	−4.96	−8.95±0.65	−13.2±2.3
NO_3^-	−5.11	−10.8±0.31	−19.1±1.0
BF_4^-	−4.93	−9.63±0.20	−15.7±0.70
MsO^-	−4.71	−6.43±0.27	−5.80±0.97

the *N*-methylpicolinium salts with the other entries of the counter anions.

3. Discussion

3.1. Effect of counter anion in guest encapsulation by container molecule 1

The large effect of the counter anion was observed in the host–guest complexation of **1** and the *N*-methylpicolinium salts.[14] This dependence reflects the electrostatic properties of the ion-pairs of the salts formed in chloroform. To investigate the effect of the counter anions on the encapsulation of the *N*-methylpicolinium salts by **1**, the stabilization energies[15] (ΔEs) of ion-pairs and the electrostatic potentials (EPs) on their van der Waals surfaces were calculated. ΔEs and EPs are useful indicators for understanding the contributions of a counter ion toward the formation of the host–guest complex. The ΔEs and EPs were obtained from HF/6-31G* calculations, and are shown in Table 4 together with their respective enthalpies.[16] Plotting ΔE versus ΔH° values gave an excellent linear correlation with R^2=0.941 (Fig. 7), but the correlation between EP and ΔH° was moderate (R^2=0.548). Roelens and a coworker have previously studied binding of tri- and tetraalkylammonium salts to a cyclophane receptor;[17] the binding energies correlated more with EP than with ΔE. Their flexible cyclophane binds to the cation from one side via a cation–π interaction, while the opposite side is left open, from which the counter anion can access the cation, forming the ion-pair even within the host–guest

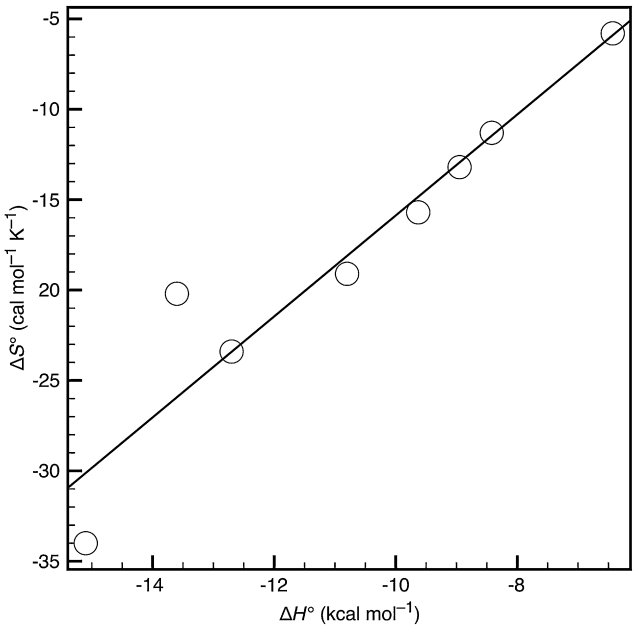


Figure 5. Enthalpy–entropy compensation plot for **1** with a series of *N*-methylpicolinium salts in chloroform. All plots in the graph refer to values from Table 2.

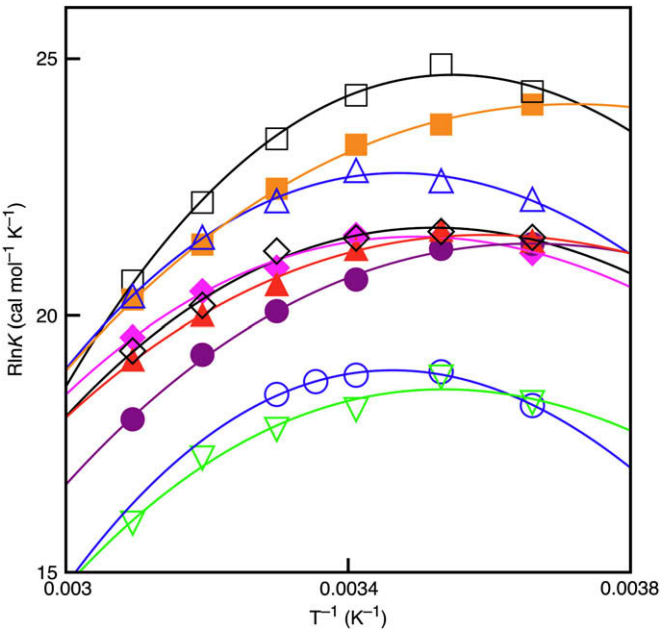


Figure 6. van't Hoff plots for the host–guest complexation of **2** with *N*-methylpicolinium salts and curve-fitting analysis with the non-linear van't Hoff equation. TfO^- (□); BF_4^- (○); $CF_3CO_2^-$ (△); TsO^- (◇); I^- (▽); $PhSO_3^-$ (◆); NO_3^- (■); Pic^- (●); MsO^- (▲).

complex. The formation of the ion-pair reduces the positive charge density of the cationic counterpart. The more dispersed the positive charge of the ion-pair is on the electrostatic surface, the lower is its EP value.[17] Thus, the host–guest complexation of their cyclophane depends on the EP values of the ion-pairs, since EP values reflect the cationic character of the pairs. On the other hand, container **1** wraps the *N*-methylpicolinium cation within a confined cavity; the counter anion is thus forced to remain outside of the container (Fig. 8). This microscopic separation of the ion-pair prevents the cation from interacting electrostatically with its counter anion. Thus, the naked cationic counterpart gives rise to a cation–π interaction to create a large energetic gain when the host–guest complex forms, although the microscopic separation of the ion-pair pays a large energetic cost. ΔE represents the change in the total electronic energy as a result of the microscopic separation of the ion-pair. This rationalizes that ΔH° provided a better correlation with ΔE than with EP in our study.

3.2. Heat capacity change

The previously described van't Hoff analysis yielded negative ΔC_p° values in the host–guest complexation of **2** (Table 3). Numerous studies have measured negative heat capacity changes in host–guest complexation in aqueous media,[18] and some reports

Table 3
Thermodynamic parameters for host–guest complexation of **2** with the *N*-methylpicolinium salts in chloroform

Counter anion	ΔG°_{298} (kcal mol^{-1})	ΔH°_{298} (kcal mol^{-1})	ΔS°_{298} (cal mol^{-1} K^{-1})	ΔC_p° (cal mol^{-1} K^{-1})
TfO^-	−7.74	−7.4±0.32	−0.92±1.1	−460±42
BF_4^-	−4.51	−4.0±0.52	5.3±1.7	−430±45
$CF_3CO_2^-$	−3.98	−3.8±0.20	9.9±0.66	−380±27
TsO^-	−4.56	−4.3±0.29	7.0±0.96	−300±39
I^-	−5.06	−4.6±0.47	2.7±1.6	−300±63
$PhSO_3^-$	−3.58	−3.3±0.24	10.0±0.80	−280±32
NO_3^-	−7.24	−7.1±0.18	−0.81±0.60	−240±24
Pic^-	−6.49	−6.3±0.18	−0.68±0.61	−250±24
MsO^-	−4.86	−4.6±0.26	5.6±0.88	−230±35

Table 4
Calculated stabilization energies (ΔE) and electrostatic potentials (EP) of *N*-methyl picolinium salts, and enthalpy energies of binding (ΔH°) of 1:1 complexes of the corresponding *N*-methylpicolinium salts with **1**

Anion	ΔE (kcal mol^{-1})	EP[a] (kcal mol^{-1})	ΔH° (kcal mol^{-1})
TfO^-	−79.8330	48.4786	−12.7±0.85
$CF_3CO_2^-$	−85.0997	47.3607	−15.1±1.30
Br^-	−77.9053	51.2645	−13.6±0.34
$PhSO_3^-$	−86.0341	43.1445	−8.42±0.49
NO_3^-	−84.6015	47.3186	−10.8±0.31
TsO^-	−86.3924	43.4405	−8.95±0.65
BF_4^-	−83.8711	49.1187	−9.63±0.20
MsO^-	−88.8554	42.9276	−6.43±0.27

[a] Largest positive value of the electrostatic potential on the van der Waals surface of the ion-pair.

have found negative heat capacity changes in organic polar solvents.[19] In contrast, the observation of negative heat capacity changes in non-polar aprotic organic solvent is unusual. Anslyn and co-workers reported that the differences in the solvation of the host and guest versus solvation of the host–guest complex cause heat capacity changes in water.[18d] A negative heat capacity change upon complexation suggests that solvation of individual host and guest molecules is more structured than that of the host–guest complex. Ogoshi and co-workers also reported that negative heat capacity changes result from solvation differences upon complexation in protic organic solvent.[19b]

The solvation of ion-pairs and their separated ions in chloroform likely plays a dominant role in the thermodynamics of complexation involving **2**. Figure 9 displays a schematic representation of the thermodynamic behavior of the host–guest complexation between **2** and the guest ion-pair. Enthalpy is described according to Eq. 4, with a concomitant change in heat capacity.

$$\Delta H^\circ_{T2} = \Delta H^\circ_{T1} + (T2 - T1)\Delta C^\circ_p \quad (4)$$

The negative change in heat capacity results from the increased stability of host–guest complexation at elevated temperatures. Both **2** and the guest ion-pair in the free state are extensively solvated with chloroform. As the temperature increases, the large solvent

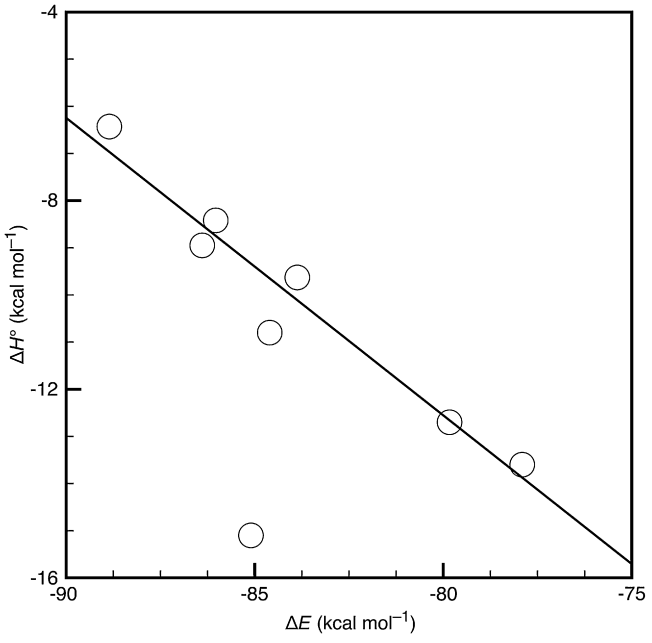


Figure 7. Plot of ion-pair stabilization energy versus enthalpy of binding to **1** for the set of *N*-methylpicolinium salts. Symbols indicate experimental ΔH° and calculated ΔE data points from Table 4; the solid line is the best-fit line calculated by linear regression (slope=−0.6307; intercept=−63.011; coefficient of determination R^2=0.941).

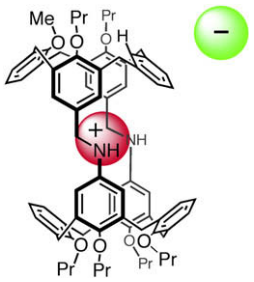


Figure 8. Schematic representation of the separated ion-pair in the host–guest complex of **1**.

sphere around the ion-pairs becomes smaller and numerous solvent molecules are released into the bulk media, leading to a high enthalpy level for the overall system. When the host–guest complex forms, the solvent spheres of both **2** and the ion-pair are disrupted. The hydrogen bonds of the counter anion to the amide N–H constrain the anion to lie close to **2**. The desolvation of the anion as well as of the encapsulated cation occurs due to this steric constraint, which is rationalized by the positive and the slightly negative entropy values associated with the formation of the host–guest complex (Table 3). The changes in the solvation spheres before and after the formation of the host–guest complex depend on temperature. At low temperatures, the ion-pair has a structured solvent shell that must be liberated upon complexation, creating a large enthalpic cost, whereas the structured solvent shell is already reduced at high temperature, providing a large enthalpic gain. Therefore, the negative ΔC_p° values result from the different degrees of desolvation of the structured solvent shells during host–guest complexation.

4. Conclusion

We have synthesized molecular containers **1** and **2**, which can bind the planar cationic molecules. A series of thermodynamic and structural studies on the host–guest complex between molecular container **1** and the *N*-methylpicolinium salts have demonstrated that in these systems, the cation is encapsulated by the molecular containers and is therefore separated from its counter anion. The stability of the host–guest complex correlates directly with the electrostatic energies (ΔE) of the ion-pairs rather than with the electrostatic potential (EP) on the van der Waals surface of the ion-pairs. In contrast, the host–guest complexation of **2** led to negative heat capacity changes (ΔC_p°=−230 to −460 cal mol^{-1} K^{-1}), which are unusually observed in non-polar aprotic media. The difference in the thermodynamic behavior of the two containers can be attributed to desolvation of the counter anion. The counter anion binds more strongly to the two amide linkages of **2** via hydrogen bonding; therefore, the anion is more desolvated after complexation with **2** than with **1**. The extensive desolvation of the counter anion causes the negative heat capacity changes in this encapsulation of the cationic guest in the container molecule. Although containers **1** and **2** have a slight structural difference of their linkages, their thermodynamic behaviors of the guest encapsulations are quite contrastive and provide the detailed picture of the guest-binding process. It is obvious that thermodynamic studies are potential to characterize the formation of host–guest complexes and to provide further understanding of fundamental binding forces.

5. Experimental section

5.1. General methods

The ^{1}H and ^{13}C NMR spectra at high field were recorded with a JEOL-Lambda 500 and Varian-Mercury 300 NMR spectrometer.

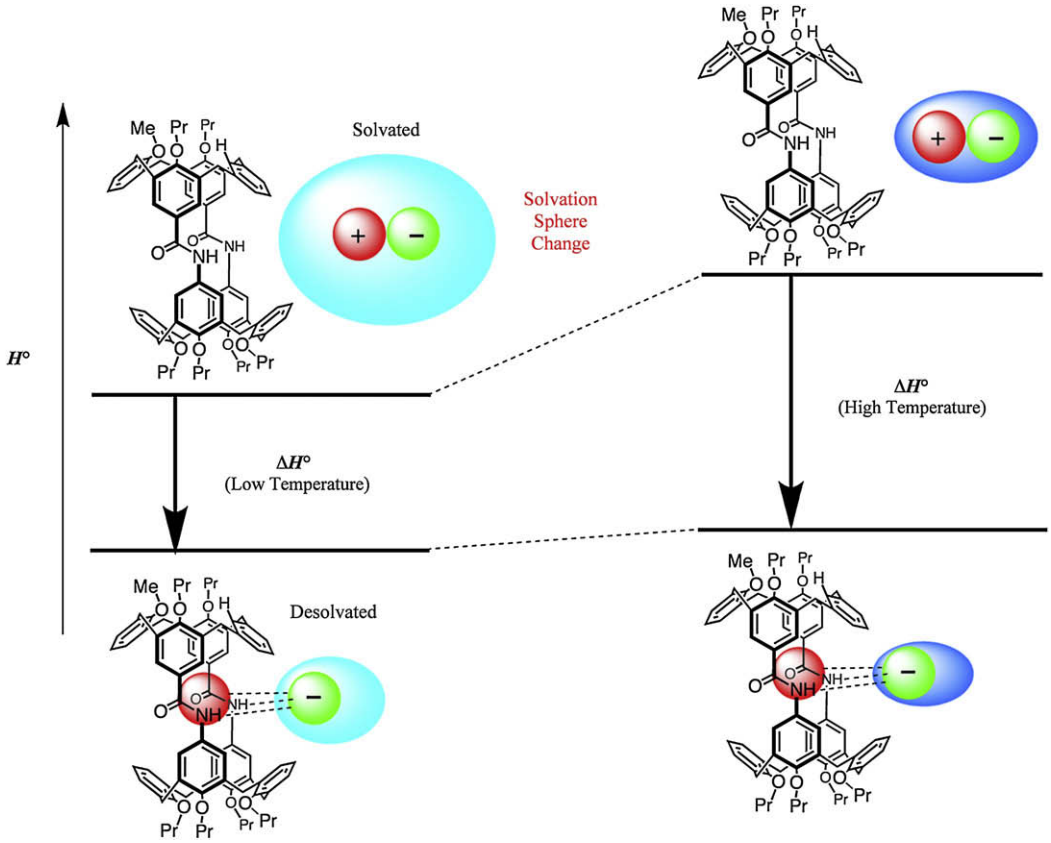


Figure 9. Plausible mechanism to explain the thermodynamic behavior of host–guest complexation.

^{1}H NMR chemical shifts (δ) are given in parts per million using the residual solvent as internal standard. ^{13}C NMR chemical shifts (δ) are given in parts per million from internal chloroform-*d* (δ=77.0). All melting points were determined with a micro melting apparatus (Yanagimoto) and are uncorrected. IR spectra were measured using a JASCO FT/IR-420 infrared spectrophotometer. The mass spectra were taken with a JEOL JMS-SX 102A high-resolution double-focusing mass spectrometer at the Instrument Center for Chemical Analysis, Hiroshima University. Elemental analyses were performed on a Perkin–Elmer 2400CHN elemental analyzer. UV spectra were measured on a JASCO V-560 spectrometer.

All reactions were carried out under an argon atmosphere unless otherwise noted. THF was freshly distilled over sodium benzophenone. Dichloromethane and dimethylformamide were freshly distilled over CaH_2. Column chromatography was performed using Merck silica gel (70–230 mesh). All reagents were of commercial grade and were used without further purification.

Electrostatic potentials and stabilization energies of *N*-methylpicolinium ion-pairs were calculated using the Spartan'06 program package. Initial geometries were determined by molecular mechanics methods, using the MMFF force field of the Macromodel software package. The initial geometries were then subjected to geometry optimization by HF, using the 6-31G* basis set. The stabilization energies were obtained as the difference between the total ion-pairs energy and the energy of the individual ions optimized independently.

5.2. General procedure for UV–vis titration

Stock solutions of hosts and guests were prepared in $CHCl_3$. The host (or guest) solution was added to the guest (or host) solution, and continuous changes of absorbance in UV spectra were recorded each time. Plots of the observed absorbance changes versus the concentration of the added host or guest were performed by non-linear least square regression analysis to determine the binding constants. The binding curves were fitted to the following equation:

$$\Delta A_{obs} = \frac{b\Delta\varepsilon_{11}}{2K_{11}}\left\{1 + K_{11}[H]_0 + K_{11}[G]_0 - \sqrt{(1 + K_{11}[H]_0 + K_{11}[G]_0)^2 - 4K_{11}^2[H]_0[G]_0}\right\}$$

where ΔA_{obs} is the observed absorbance change at the concentration, b is light path length, $\Delta\varepsilon_{11}=\varepsilon_{11}-\varepsilon_H-\varepsilon_G$, ε_{11}, ε_H, and ε_G are molar absorptivities of 1:1 host–guest complex, host, and guest, K_{11} is binding constant (L mol^{-1}), and $[H]_0$ and $[G]_0$ are the total concentrations of host and guest molecules (mol L^{-1}).

5.3. Synthesis

*5.3.1. 26,28-Dipropoxy-25-methoxy-pentacyclo [19.3.1.13,7.19,13.115,19]octacosa-1(25),3,5,7(28), 9,11,13(27),15,17,19(26),21,23-dodecaene-5,17-dial (**4**)*

To a suspension of NaH (385 mg, 9.9 mmol; 60% in mineral oil, washed previously with hexane) in DMF (60 mL), **3** (1.3 g, 1.9 mmol) and *n*-propyl iodide (0.6 ml, 5.8 mmol) were added at −60 °C under Ar. After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated NH_4Cl and extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ and was dried over anhydrous Na_2SO_4. After removing Na_2SO_4 by filtration, the solvent was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (30% benzene in hexane), followed by GPC to give **4** (560 mg, 40%). Mp 177–179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.230–7.029 (m, 6H),

7.005 (d, 2H, J=2.1 Hz), 6.802 (d, 2H, J=1.8 Hz), 4.250 and 3.209 (ABq, 4H, J=13.8 Hz), 4.192 and 3.523 (ABq, 4H, J=15.0 Hz), 3.704–3.632 (m, 4H), 3.594 (s, 3H), 1.836–1.767 (m, 4H), 1.043 (t, 6H, J=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.198, 156.608, 142.244, 137.439, 137.242, 137.192, 136.657, 135.247, 129.437, 128.366, 127.394, 126.570, 123.726, 87.013, 76.984, 60.757, 35.078, 30.916, 23.813, 11.023; IR (KBr) 3020, 2960, 2921, 2872, 1603, 1569 cm^{-1}; HR-FABMS (NBA) m/z calcd for $C_{35}H_{36}I_2O_3$ 758.0754, found 758.0762 $[M]^+$.

5.3.2. 26,28-Dipropoxy-25-methoxy-pentacyclo [19.3.1.13,7.19,13.115,19]octacosa-1(25),3,5,7(28),9,11,13(27), 15,17,19(26),21,23-dodecaene-5,17-dicarboxaldehyde (**5**)

To a solution of **4** (564 mg, 0.74 mmol) in THF (53 mL), n-BuLi (1 ml, 1.6 mmol) and DMF (230 μl, 3 mmol) were added at −78 °C under Ar. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. After removing Na_2SO_4 by filtration, the solvent was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (7% ethyl acetate in hexane) to yield **5** (290 mg, 69%). Mp 132–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.416 (s, 2H), 7.233–7.157 (m, 3H), 7.134 (d, 2H, J=2.1 Hz), 7.061 (t, 1H, J=7.5 Hz), 6.883 (d, 2H, J=1.8 Hz), 5.830 (s, 1H), 4.320 and 3.291 (ABq, 4H, J=14.1 Hz), 4.262 and 3.634 (ABq, 4H, J=15.0 Hz), 3.766–3.708 (m, 4H), 3.502 (s, 3H), 1.863–1.794 (m, 4H), 1.060 (t, 6H, J=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.599, 161.874, 157.885, 141.881, 136.788, 136.302, 133.896, 132.066, 130.492, 129.882, 129.751, 128.506, 127.616, 126.677, 123.900, 77.017, 60.502, 35.194, 31.032, 23.804, 10.957; IR (KBr) 2965, 2925, 2859, 2838, 2801, 2739, 1683, 1602, 1592 cm^{-1}; HR-FABMS (NBA) m/z calcd for $C_{37}H_{39}O_5$ 563.2797, found 563.2790 $[M+H]^+$.

5.3.3. Molecular container **7**

A solution of **6** (187 mg) and **5** (85.4 mg, 0.15 mmol) in CH_2Cl_2 (100 mL) was refluxed for 3 days. Subsequently, the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (7% ethyl acetate in hexane) to give **7** (120 mg, 69%). Mp >250 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.280–6.982 (m, 12H), 7.073 (d, 2H, J=1.5 Hz), 6.692 (d, 2H, J=1.5 Hz), 6.048 (d, 2H, J=2.7 Hz), 6.016 (d, 2H, J=2.7 Hz), 5.838 (s, 1H), 4.445 and 3.145 (ABq, 4H, J=13.1 Hz), 4.435 and 3.145 (ABq, 4H, J=13.1 Hz), 4.289 and 3.241 (ABq, 4H, J=14.0 Hz), 4.206 (ABq, 2H, J=15.3 Hz), 4.100–4.044 (m, 4H), 3.697–3.597 (m, 10H), 3.619 (s, 2H), 3.411 (s, 3H), 2.081–2.001 (m, 4H), 1.935–1.815 (m, 4H), 1.815–1.720 (m, 4H), 1.098 (t, 6H, J=7.5 Hz), 1.034 (t, 6H, J=7.5 Hz), 0.906 (t, 3H, J=6.9 Hz), 0.903 (t, 3H, J=6.9 Hz); ^{13}C NMR (125 MHz, $CD_3CN/CDCl_3$=1:4) δ 158.767, 157.124, 157.736, 157.687, 155.232, 155.1, 141.486, 136.393, 136.286, 136.170, 134.695, 132.676, 132.412, 131.399, 130.739, 129.149, 128.720, 128.572, 128.259, 128.242, 126.808, 126.471, 126.174, 125.704, 123.092, 121.592, 121.023, 120.446, 119.186, 76.514, 76.209, 76.003, 75.904, 60.073, 34.847, 31.007, 30.595, 30.406, 23.071, 22.956, 22.395, 22.321, 22.074, 13.495, 10.264, 10.083, 9.201, 9.152; IR (KBr) 2960, 2933, 2874, 1625, 1580 cm^{-1}; HR-FABMS (NBA) m/z calcd for $C_{77}H_{85}N_2O_7$ 1149.6357, found 1149.6334 $[M+H]^+$.

5.3.4. Molecular container ***1***

A suspension of double-calix[4]arene **7** (50 mg, 0.043 mmol) and $NaBH_3CN$ (40 mg, 0.64 mmol) in a mixture of EtOH (10 mL) and THF (10 mL) was stirred for 3 h at room temperature. Subsequently, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4. After removing Na_2SO_4 by filtration, the solvent was concentrated in vacuo. The residue was purified by column chromatography on silica gel with 10% ethyl acetate in hexane to give **1** (45 mg, 89%). Mp >250 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.217 (d, 2H, J=7.2 Hz) 7.161–7.093 (m, 7H), 7.061 (t, 1H, J=7.2 Hz), 6.993 (t, 1H, J=7.4 Hz), 6.926 (t, 1H, J=7.4 Hz), 6.459 (s, 2H), 6.212 (s, 2H), 5.732 (s, 1H), 5.458 (s, 2H), 5.412 (s, 2H), 4.417 and 3.085 (ABq, 4H, J=13.4 Hz), 4.396 and 3.065 (ABq, 4H, J=12.9 Hz), 4.282 and 3.185 (ABq, 4H, J=13.8 Hz), 4.232 (ABq, 2H, J=16.2 Hz), 4.059–3.988 (m, 4H), 3.659–3.558 (m, 10H), 3.545 (s, 4H), 3.489 (s, 3H), 1.998–1.919 (m, 4H), 1.887–1.722 (m, 8H), 1.077 (t, 6H, J=7.5 Hz), 1.010 (t, 6H, J=7.5 Hz), 0.856 (t, 6H, J=7.4 Hz); ^{13}C NMR (125 MHz, $CD_3CN/CDCl_3$=1:4) δ 163.926, 158.627, 157.523, 157.383, 157.350, 151.441, 141.486, 136.393, 136.286, 136.170, 134.695, 132.676, 132.412, 131.399, 130.739, 129.149, 128.720, 128.572, 128.259, 128.242, 126.808, 126.471, 126.174, 125.704, 123.092, 121.592, 121.023, 120.446, 119.186, 76.514, 76.209, 76.003, 75.904, 60.073, 34.847, 31.007, 30.595, 30.406, 23.071, 22.956, 22.395, 22.321, 22.074, 13.495, 10.264, 10.083, 9.201, 9.152; IR (KBr) 3407, 2960, 2933, 2874, 2349, 1608 cm^{-1}; HR-FABMS (NBA) m/z calcd for $C_{77}H_{88}N_2O_7$ 1152.6592, found 1152.6619 $[M]^+$. Anal. Calcd (%) for $C_{77}H_{88}N_2O_7 \cdot H_2O$: C, 78.94; H, 7.74; N, 2.39. Found: C, 78.87; H, 7.49; N, 2.58.

5.3.5. 26,28-Dipropoxy-25-methoxy-pentacyclo [19.3.1.13,7.19,13.115,19]octacosa-1(25),3,5,7(28),9,11,13(27), 15,17,19(26),21,23-dodecaene-5,17-dicarboxylic acid (***8***)

To a solution of **5** (320 mg, 0.57 mmol) in acetone (40 mL), a solution of $KMnO_4$ (400 mg, 2.5 mmol) in H_2O (20 mL) was added. After being refluxed for 3 h, the reaction mixture was diluted with ethyl acetate, washed with 1 M HCl, and the organic layer was dried over Na_2SO_4. After removing Na_2SO_4 by filtration, **8** (338 mg, 98%) was obtained by concentration in vacuo. Mp >250 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.423 (d, 2H, J=2.4 Hz), 7.238–7.083 (m, 7H), 7.060 (t, 1H, J=8.1 Hz), 5.759 (s, 1H), 4.267 and 3.244 (ABq, 4H, J=14.0 Hz), 4.196 and 3.636 (ABq, 4H, J=15.5 Hz), 3.740–3.679 (m, 4H), 3.386 (s, 3H), 1.831–1.761 (m, 4H), 1.043 (t, 6H, J=7.5 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.895, 161.281, 157.869, 141.824, 137.036, 135.758, 132.684, 130.954, 130.583, 129.668, 128.424, 127.377, 126.413, 124.163, 123.751, 76.761, 60.296, 35.251, 30.941, 23.837, 10.998; IR (KBr) 2964, 2926, 2875, 1693, 1603 cm^{-1}; HR-FABMS (NBA) m/z calcd for $C_{37}H_{38}O_7$ 594.2618, found 594.2614 $[M]^+$.

5.3.6. 26,28-Dipropoxy-25-methoxy-pentacyclo [19.3.1.13,7.19,13.115,19]octacosa-1(25),3,5,7(28),9,11,13(27), 15,17,19(26),21,23-dodecaene-5,17-dicarbonyl dichloride (9)

To a solution of **8** (142 mg, 0.23 mmol) in THF (10 mL), catalytic amounts of DMF and oxalyl dichloride (125 μL, 1.43 mmol) were added under Ar. After the reaction mixture was stirred for 12 h at room temperature, compound **9** (145 mg, 97%) was obtained by concentration in vacuo and used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.449 (d, 2H, J=2.4 Hz), 7.265–7.141 (m, 7H), 7.078 (t, 1H, J=7.5 Hz), 5.798 (s, 1H), 4.289 and 3.2789 (ABq, 4H, J=14.4 Hz), 4.230 and 3.654 (ABq, 4H, J=15.0 Hz), 3.744 (t, 4H, J=6.5 Hz), 3.452 (s, 3H), 1.864–1.773 (m, 4H), 1.059 (t, 6H, J=7.4 Hz); IR (KBr) 2964, 2930, 2875, 1752, 1594 cm^{-1}.

5.3.7. Molecular container ***2***

A solution of **9** (143 mg) in THF (25 mL) and a solution of **6** (145 mg, crude) in THF (25 mL) were mixed dropwise in 40 ml of THF under Ar. After being stirred for 12 h, the reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography on silica gel with 10% ethyl acetate in hexane to yield **2** (70 mg, 25%). Mp >250 °C (dec); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.276–7.087 (m, 5H), 7.320 (d, 2H, J=7.5 Hz), 7.231 (d, 2H, J=7.5 Hz), 7.143 (t, 1H, J=7.5 Hz), 7.101 (s, 2H), 7.062 (t, 1H, J=7.5 Hz), 7.015 (t, 1H, J=6.9 Hz), 6.962 (d, 2H, J=1.8 Hz), 6.828 (d, 2H, J=2.4 Hz), 6.344 (d, 2H, J=2.1 Hz), 6.248 (d, 2H, J=2.4 Hz), 5.938 (s, 1H), 4.440 and 3.165 (ABq, 4H, J=13.4 Hz), 4.423 and 3.135 (ABq, 4H, J=13.4 Hz), 4.322 and 3.275 (ABq, 4H, J=12.2 Hz), 4.274 (ABq, 2H, J=15.3 Hz), 4.089–4.020 (m, 4H), 3.655 (s, 3H), 3.680–3.581 (m, 10H), 2.049–1.920 (m, 4H), 1.886–1.764 (m, 8H), 1.084 (t, 6H, J=7.5 Hz), 1.027 (t, 6H, J=7.5 Hz), 0.876 (t, 3H, J=7.5 Hz), 0.863 (t, 3H, J=7.8 Hz); ^{13}C NMR (500 MHz, $CD_3CN/CDCl_3$=1:4) δ 164.651, 158.759, 158.479, 158.083, 157.729, 151.952, 142.409, 137.250, 137.060, 136.689, 134.069, 133.327, 132.866, 132.717, 131.844, 130.360, 129.355, 129.091, 129.017, 128.226, 127.962, 127.212, 126.874, 126.405, 122.878, 121.441, 121.658, 120.751, 120.273, 77.066, 76.555, 76.407, 60.790, 35.136, 31.081, 30.958, 29.672, 23.590, 23.483, 22.931, 22.824, 10.825, 10.718, 9.787, 9.737; IR (KBr) 3629, 3398, 2961, 2934, 2875, 1655, 1604, 1537 cm^{-1}; HR-FABMS (NBA) m/z calcd for $C_{77}H_{84}KN_2O_9$ 1219.5814, found 1219.5840 $[M+K]^+$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.021.

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