Modulation of a Supramolecular Bowl and Pot by Changing Solvent Systems and/or Metal/Ligand Ratios

Seong Jin Park,[a] Jae Woo Lee,[a] Shigeru Sakamoto,[c] Kentaro Yamaguchi,[c] and Jong-In Hong*[a, b]

Abstract: A resorcin[4]arene-based ligand **2a** with four pyrimidine substituents at the upper rim was synthesized, and the generation of different metal-mediated superstructures from the same ligand and metal ions utilizing the unfavorable incorporation of the third and fourth Pd^{II} ions to ligand **2a** was investigated. The supramolecular bowl **3a**, which comes from a 1:2 combination of ligand **2a** and [Pd(en)(NO$_3$)$_2$], was obtained in water even though excess of Pd^{II} complexes were employed. By adding methanol, the supramolecular pot **4** gradually formed, which was the major product when the ratio of mixed solvent reached methanol/water = 5:1 (v/v). Host–guest complexation phenomena of **3a** toward several aromatic carboxylates were demonstrated by isothermal titration calorimetry (ITC) and by ^{1}H NMR spectroscopy; both the enthalpy gain from electrostatic and hydrophobic interactions, and the entropy gain from desolvation cooperatively contribute to the binding of anionically charged guests. The crystal structure of supramolecular pot **4** shows direct evidence for the hydrogen bonding between water and the aromatic π electrons in the solid state. The modulation between supramolecular bowl **3a** and pot **4** was also made possible by changing the metal/ligand ratios in aqueous methanol solution as well as by varying the water content of the mixed solvent.

Keywords: metal/ligand ratios · pi interactions · self-assembly · solvent effects · supramolecular chemistry

Introduction

Metal-induced self-assembly is a flourishing area of study in the field of host–guest and supramolecular chemistry. There are many examples of metal-mediated self-assembly such as squares,[1] helices,[2] grids,[3] catenanes,[4] cylinders,[5] circular helicates,[6] and cages.[7] In particular, *cis*-protected, square-planar Pd^{II} or Pt^{II} complexes have been widely used to incorporate 90° bond angles and to avoid the formation of any oligomeric products owing to its convergent nature. With the simple combination of *cis*-protected, square-planar metal complexes and pyridine-based ligands, a great number of self-assembled superstructures, for example, molecular triangles, squares, catenanes, cages, tubes, and capsules, have been designed and synthesized.[8] Only a few examples, however, have been reported in which pyrimidine-based ligands were used as building blocks for the construction of supramolecules, because it is unfavorable to coordinate at the 1,3-position of a pyrimidine ring due to the cationic repulsion between two adjacent metal ions and the electron-withdrawing effects of the adjacent metal–pyrimidine bonds.[9, 10]

We recently described that an intramolecularly assembled cavity **3b** was constructed by the addition of two equivalents of [Pd(en)(NO$_3$)$_2$] to a suspension of **2b** in an aqueous solution.[11] From CPK and computer-aided modeling, the formation of a supramolecular pot **4** was expected from the combination of **2a** with pyrimidine (Prm) moieties instead of pyridine moieties as pendent groups and four equivalents of *cis*-protected Pd^{II} ions.[12] Also, the formation of a supramolecular bowl **3a** was expected to arise from the unfavorable coordination at the 1,3-position of a pyrimidine ring.

Herein, we demonstrate how different metal-mediated superstructures are generated from the same ligand and metal ions; supramolecular bowl **3a** is predominantly formed in water, while the construction of pot **4** is accomplished in a water/methanol solvent mixture when ligand **2a** and four equivalents of [Pd(en)(NO$_3$)$_2$] were employed. Also, the formation of bowl **3a** is achieved by changing the metal/ligand ratios in a water/methanol solvent mixture.

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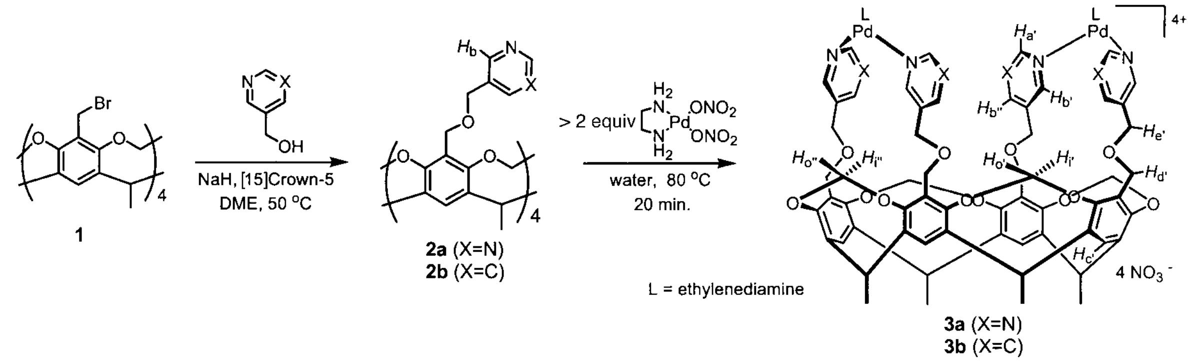


Scheme 1.

Results and Discussion

Synthesis and characterization of a resorcin[4]arene-based pyrimidine ligand 2a and a self-assembled supramolecular bowl 3a: A resorcin[4]arene-based ligand **2a** with four pyrimidine substituents at the upper rim was synthesized from a tetrakis(bromomethyl)cavitand **1** by nucleophilic substitution with 5-hydroxymethylpyrimidine (Scheme 1).[13, 14] When a suspension of ligand **2a** and [Pd(en)(NO_3)$_2$] (4 equiv) in water was heated at 80 °C for 20 min, a clear solution was obtained. ^1H NMR spectroscopic analysis, contrary to our expectations, showed the formation of a C_{2v}-symmetric bowl **3a**, which comes from a 1:2 combination of **2a** and [Pd(en)(NO_3)$_2$]; not only do H_b protons divide into two signals ($H_{b'}$, $H_{b''}$), but also the bridging methylene protons split into two sets of signals ($H_{i''}/H_{o''}$, $H_{i'}/H_{o'}$). Since protons $H_{i''}$ and $H_{o''}$ exist in the shielding region between the two pyrimidine ligands interacting with the Pd^{II} ion, they are expected to move further upfield than $H_{i'}$ and $H_{o'}$.[11] Also the benzylic protons ($H_{d'}$) at the upper rim become desymmetrized by the hindered rotation upon Pd^{II} complexation and appear as a pair of doublets.[15] This also indicates the formation of a rigid C_{2v}-symmetric superstructure.[16] Additional evidence for the formation of supramolecular bowl **3a** was obtained by a coldspray ionization mass spectrometric (CSI-MS) spectrum (Figure 1): [**3a** − 2 NO_3^-]$^{2+}$ (769.0).

Abstract in Korean:

위쪽 네 가장자리에 피리미딘 치환체가 도입된 레속신[4]아렌 리간드 **2a**를 합성하였고, 세 번째와 네 번째의 팔라듐(II) 이온의 쉽지않은 배위를 이용하여 리간드 **2a**와 금속이온으로부터 유도되는 서로 다른 초분자의 형성을 연구하였다. 물에서는 비록 과량의 팔라듐(II) 이온이 존재하더라도 리간드 **2a**와 (en)Pd(NO_3)$_2$의 1:2 조합으로 형성된 초분자 사발 **3a**가 얻어졌다. 여기에 메탄올을 첨가해보니 초분자 항아리 **4**가 점차적으로 형성되었으며, 메탄올과 물의 부피비가 5:1에 도달하자 **4**가 산물의 대부분이 되었다. 몇 가지 방향족 카르복시산의 나트륨염에 대한 **3a**의 호스트-게스트 결합현상을 핵자기공명(NMR) 뿐만 아니라 등온열량 측정기(ITC) 실험에 의해 조사하였다: 정전기적 인력과 협수성 상호 작용에서 기인한 엔탈피의 이득 뿐만 아니라 탈용매화 작용에 의한 엔트로피의 증가가 음이온의 포획에 상호적으로 작용하고 있다. 초분자 항아리 **4**의 결정구조는 고체상에서 물과 방향족성 고리의 파이(π) 전자 사이의 수소결합에 대한 직접적인 증거를 제시하고 있다. 초분자 사발 **3a**와 초분자 항아리 **4** 사이의 조절은 혼합용매의 물 함량의 변화 뿐만 아니라, 물을 함유한 메탄올 용액에서 금속과 리간드 비율의 변화로도 가능하다.

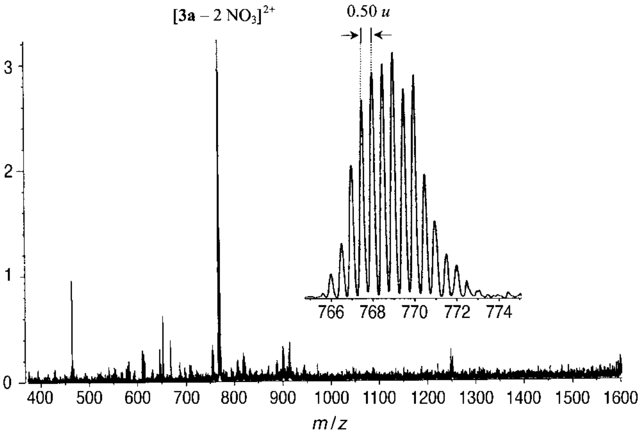


Figure 1. CSI-MS spectrum of **3a** (needle voltage: 2.3 kV, orifice voltage: 21 V, ringlens voltage: 78 V, ion source temperature: 293 K).

Binding phenomena of supramolecular bowl 3a: The host–guest complexation with supramolecular bowl **3a** was demonstrated by the complexation-induced changes in the chemical shift observed in the ^1H NMR binding titrations in [D_2]water (Table 1). Analysis of the titration data of **3a** with several aromatic guests showed that the binding isotherms are well fitted by a 1:1 binding model. The 1:1 stoichiometry of the complex formed between **3a** and the sodium salt of *p*-anisic acid was further confirmed by a Job plot (Figure 2).

The binding constants of **3a** for anionic guests showed the same trend, but were smaller that those for **3b** (Table 1). Presumably, the repulsive interaction between the carboxylate group of the guests and the directional dipole of

Table 1. Binding constants of the 1:1 host–guest complexes in [D_2]water.[a]

	K_{bind} [M^{-1}] of **3a**	K_{bind} [M^{-1}] of **3b**
1,4-dimethoxybenzene	4200	4500
benzoic acid (sodium salt)	250	1040
p-toluic acid (sodium salt)	9700	70000
p-anisic acid (sodium salt)	38000	> 100000

[a] Binding constants were obtained by ^1H NMR titrations on the basis of the 1:1 binding model at 300 K.

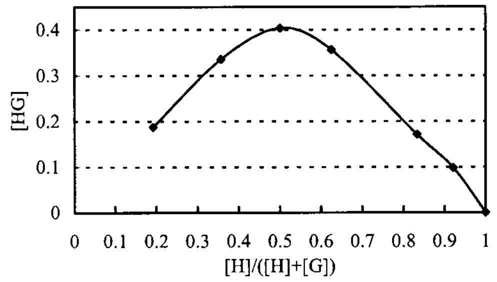


Figure 2. Job plot for **3a** with the sodium salt of *p*-anisic acid.

pyrimidine's non-coordinated nitrogen atoms of **3a** contributes to the lowering of the binding constants.[17, 18]

To elucidate the thermodynamic parameters controlling the complexation process, isothermal titration calorimetry was carried out for the complex formation between **3a** and the sodium salt of *p*-toluic acid at 30 °C in water (Figure 3).

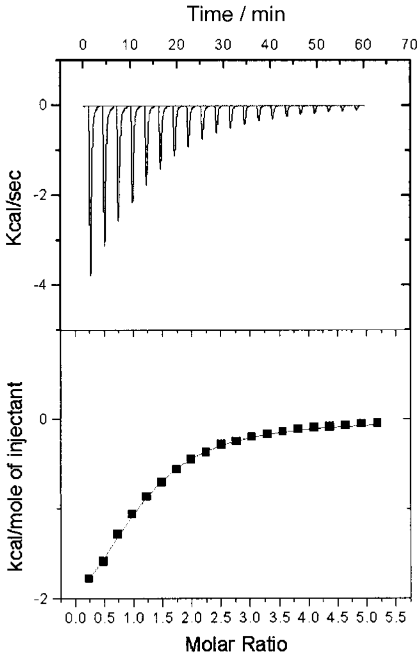


Figure 3. ITC titration data for **3a** with the sodium salt of *p*-toluic acid at 30 °C in water.

It was shown that the complexation process is both enthalpically ($\Delta H^\circ = -2.80 \pm 0.09$ kcal mol^{-1}) and entropically favored ($\Delta S^\circ = 9.07$ cal K^{-1} mol^{-1}), which indicates that both the enthalpy gain from electrostatic and hydrophobic interactions, and the entropy gain from desolvation cooperatively contribute to the binding. The complexation process of **3b** toward the sodium salt of *m*-toluic acid has been proven to be enthalpically favored, but entropically disfavored.[11] It is presumed that the difference in entropy originates from the binding site of **3a** being more solvated than **3b** owing to the pyrimidine's non-coordinated nitrogens.

The energy-minimized structure of the self-assembled supramolecular bowl **3a** shows the generation of a hydrophobic binding site by the Pd^{II}-induced self-assembly (Figure 4a).[12] Moreover, inspection of the computer-generated structure of the complex between **3a** and the sodium salt of *p*-anisic acid indicates that the guest molecule induces a conformational change of **3a** to maximize the resulting hydrophobic and electrostatic interactions (Figure 4b). The guest molecule is oriented in a manner whereby its methyl group is embedded within the resorcin[4]arene-backbone and its carboxylate group is located near the clipping Pd^{II} ions.[12] This indicates that an appropriate length of the alkyl chain of the aromatic carboxylate guest is required for the most effective hydrophobic and electrostatic interactions.

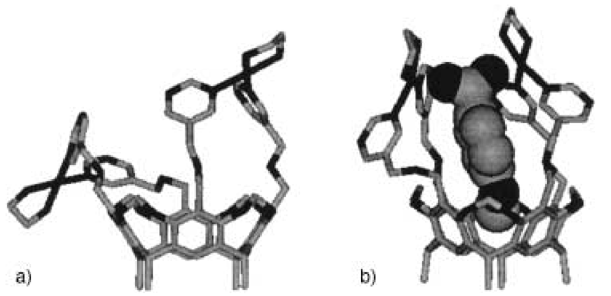


Figure 4. Energy-minimized structures: a) the self-assembled supramolecular bowl **3a**; b) the complex between supramolecular bowl **3a** and sodium salt of *p*-anisic acid.

Synthesis and characterization of a self-assembled supramolecular pot 4: To construct the supramolecular pot **4** by the incorporation of the third and fourth Pd^{II} ions, we attempted to change the solvent system by adding methanol.[19] Gentle heating with gradual addition of methanol to an aqueous solution of **3a** and two equivalents of [Pd(en)(NO$_3$)$_2$] resulted in a slow increase in intensity of a new set of ^{1}H NMR peaks (Figure 5). Moreover, these new peaks are the only ones observed when the mixed solvent system reached a ratio of [D$_4$]methanol/[D$_2$]water = 5:1 (v/v).[20, 21]

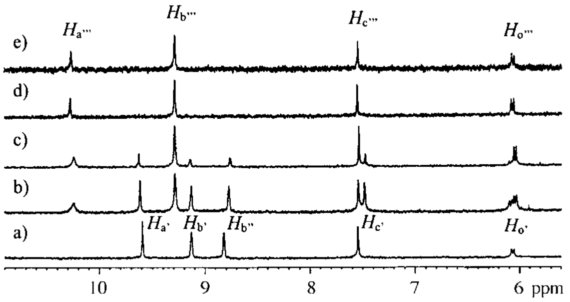
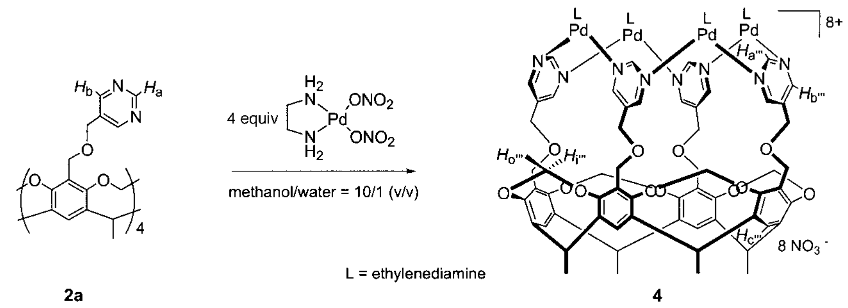


Figure 5. Portion of the ^{1}H NMR spectra with gradual addition of methanol to an aqueous solution of **3a** and two equivalents of [Pd(en)(NO$_3$)$_2$] (300 MHz, 300 K): a) in [D$_2$]water; b) in [D$_4$]methanol/[D$_2$]water = 1:1 (v/v); c) in [D$_4$]methanol/[D$_2$]water = 3:1 (v/v); d) in [D$_4$]methanol/[D$_2$]water = 5:1 (v/v); e) in [D$_4$]methanol/[D$_2$]water = 10:1 (v/v).

One- and two-dimensional NMR measurements allowed us to deduce that the new sets of ^{1}H NMR signals correspond to a C_{4v}-symmetric structure. The new structure was assigned as the supramolecular pot **4**, in which four Pd^{II} ions were incorporated into the ligand **2a** (Scheme 2). This was confirmed by a CSI-MS spectrum (Figure 6):



Scheme 2.

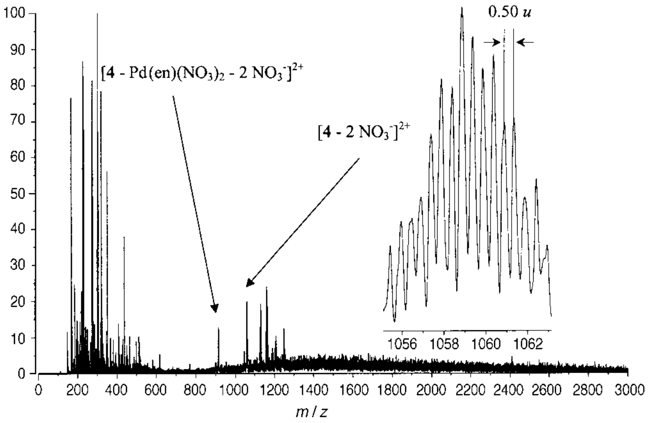


Figure 6. CSI-MS spectrum of **4** (needle voltage: 2.2 kV, orifice voltage: 56 V, ringlens voltage: 175 V, ion source temperature: 288 K).

[**4** – Pd(en)$(NO_3)_2$ – $2NO_3^-$]$^{2+}$ (914.0) and [**4** – $2NO_3^-$]$^{2+}$ (1058.9).[22]

The structure of the supramolecular pot **4** was determined by an X-ray crystallographic analysis (Figure 7).[23] A single crystal suitable for an X-ray structure analysis was obtained by standing a solution of **4** in a water/methanol mixture at ambient temperature for two days. The crystal structure of **4** clearly demonstrates that the resorcin[4]arene-based pyrimidine ligands are clipped by four Pd^{II} ions. The N_{Prm}-Pd-N_{Prm} angles range from 91.4–91.7°, which are close to the ideal bond angle of 90°. The adjacent Pd···Pd distances are 5.82 and 5.90 Å, and the distance between the two remote Pd atoms is 8.30 Å. Interestingly, supramolecular pot **4** crystallized with two water molecules entrapped within the cavity in spite of the hydrophobic nature of its interior.[24] The O···O distance of the two entrapped H_2O molecules is 3.89 Å, and the water molecules are over 4.1 Å away from the four inward-pointing ether oxygen atoms of **4**; this indicates that there is very weak or no hydrogen-bonding interaction between them. This water-entrapping phenomenon is elucidated by the fact that the entrapped water molecules are surrounded by four aromatic rings and that the distances of centroid··· O in aromatic rings···H_2O range from 3.5 to 4.1 Å. This clearly shows the existence of an OH–π(aromatic) interaction between entrapped water molecules and the surrounding aromatic rings.[25]

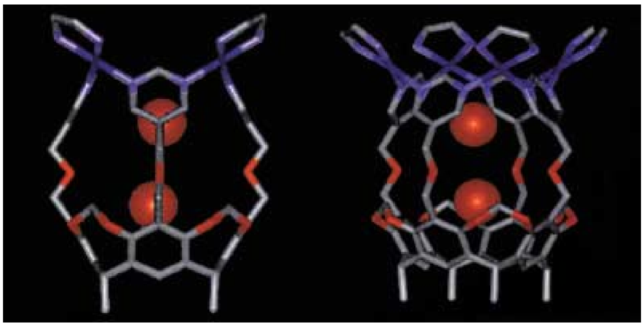
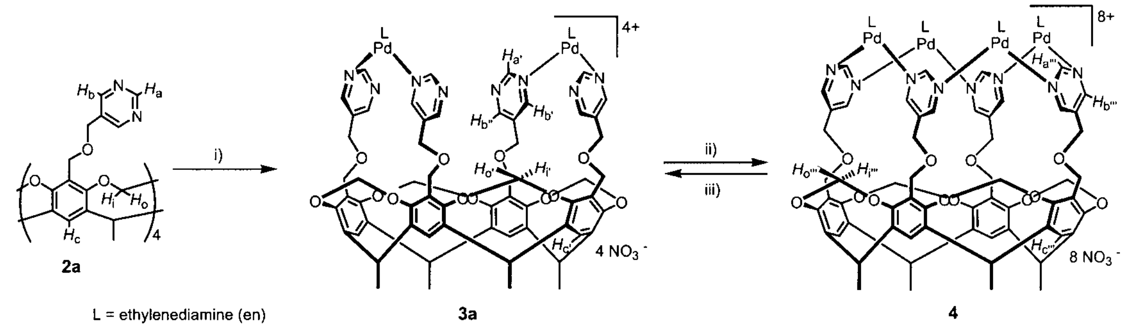


Figure 7. The X-ray crystal structure of **4**: two side views. The nitrate anions and solvent molecules outside cavity are omitted for clarity.

Modulation of supramolecular bowl 3a and pot 4 by changing solvent systems with four equivalents of [Pd(en)$(NO_3)_2$] and by altering metal/ligand ratios in a water/methanol solvent mixture: To investigate the reversible modulation of supramolecular bowl and pot by changing the solvent system (Scheme 3), a ^1H NMR study was performed by varying the water/methanol ratio of solution containing **4** (Figure 8). Gradual addition of [D_2]water to a solution of the C_{4v}-symmetric pot **4** in [D_2]water/[D_4]methanol = 1:5 (v/v) resulted in a slow increase in the intensity of signals for the C_{2v}-symmetric bowl **3a**. When the ratio of mixed solvent reached [D_2]water/[D_4]methanol = 2:1 (v/v), only **3a** remained.

To investigate the tuning of the structure between supramolecular bowl and pot by changing metal/ligand ratios, a



Scheme 3. Changing solvent systems: i) 4 equiv [Pd(en)$(NO_3)_2$], [D_2]water, 80 °C, 20 min; ii) add [D_4]methanol; iii) add [D_2]water. Altering metal/ligand ratios: i) 2 equiv [Pd(en)$(NO_3)_2$], [D4]methanol/[D_2]water = 10:1 (v/v); ii) add 2 equiv [Pd(en)$(NO_3)_2$]; iii) add 2 equiv **2a**.

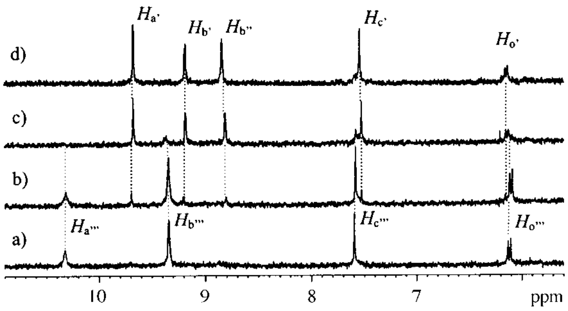


Figure 8. Portion of the ^{1}H NMR spectra with gradual addition of water to a solution of **4** in a water/methanol mixed solvent (300 MHz, 300 K): a) in [D$_2$]water/[D$_4$]methanol = 1:5 (v/v); b) in [D$_2$]water/[D$_4$]methanol = 1:2.5 (v/v); c) in [D$_2$]water/[D$_4$]methanol = 1.5:1 (v/v); d) in [D$_2$]water/[D$_4$]methanol = 2:1 (v/v).

^{1}H NMR study was performed in a water/methanol mixture ([D$_4$]methanol/[D$_2$]water = 10:1 (v/v)) with different metal/ligand ratios (Figure 9). It turned out that the C_{2v}-symmetric bowl **3a** was constructed immediately after mixing of **2a** and two equivalents [Pd(en)(NO$_3$)$_2$]. Also mixing **2a** and four equivalents of the Pd^{II} complex gave rise to a simple ^{1}H NMR spectrum that corresponds to the C_{4v}-symmetric pot **4**.[26] Furthermore, with a 1:3 mixture of **2a** and [Pd(en)(NO$_3$)$_2$], both **3a** and **4** resulted.

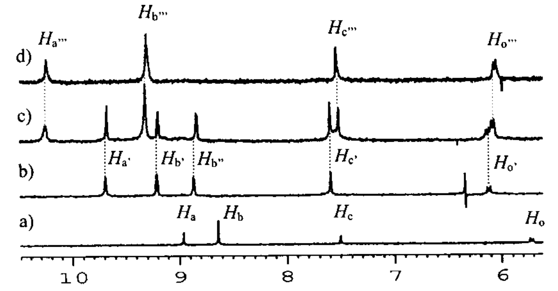


Figure 9. Portion of the ^{1}H NMR spectra with changing metal/ligand ratios in an aqueous methanol solution (300 MHz, [D$_4$]methanol/[D$_2$]water = 10:1 (v/v), 300 K): a) free **2a**; b) **2a**/[Pd(en)(NO$_3$)$_2$] = 1:2; c) **2a**/[Pd(en)(NO$_3$)$_2$] = 1:3; d) **2a**/[Pd(en)(NO$_3$)$_2$] = 1:4.

Conclusion

We could modulate the formation of the supramolecular bowl **3a** and pot **4** by using the unfavorable incorporation of the third and fourth Pd^{II} ions into the resorcin[4]arene-based pyrimidine ligand **2a** by changing the metal/ligand ratios in a water/methanol solvent mixture, as well as by varying the water content of the mixed solvent. When a 1:4 ratio of ligand **2a** and Pd^{II} ions were employed, the supramolecular bowl **3a** was predominantly formed in water, while the formation of the supramolecular pot **4** was accomplished in a water/methanol mixture. Also, the formation of bowl **3a** was achieved when **2a** and two equivalents of Pd^{II} ions were mixed in a water/methanol solvent mixtuer. Host–guest chemistry of **3a** and various aromatic carboxylates in water showed the importance of the desolvation energy as well as the cooperative effect of electrostatic and hydrophobic interactions. The crystal structure of supramolecular pot **4** shows direct evidence for hydrogen bonding between water molecules and the aromatic π electrons in the solid state.

Experimental Section

General: All the chemicals were of reagent grade and used without any further purification. The complex [Pd(en)(NO$_3$)$_2$] was prepared according to a published method.[27] All of the aromatic carboxylate guests were obtained by treating the aqueous solution of the corresponding commercially available acids with an equimolar amount of NaOH. Deuterated solvents were acquired from Cambridge Isotopic Laboratories and used as such for the complexation reactions and NMR measurements. ^{1}H, ^{13}C NMR, and other 2D NMR spectra were recorded either on a Bruker Avance DPX-300 or a Bruker Avance 500 spectrometer. Chemical shifts are given in ppm, with the residual resonances of deuterated solvents as internal references ($\delta = 7.27$ ppm for chloroform; $\delta = 4.80$ ppm for water; $\delta = 4.87$ ppm for methanol). FAB-MS (Fast atom bombardment mass spectroscopy) data were obtained on a JEOL JMS-AX505WA mass spectrometer, with NBA (*m*-nitrobenzyl alcohol) as a matrix. CSI-MS data were measured on a four-sector (BE/BE) tandem mass spectrometer (JEOL JMS-700T) equipped with a CSI source. ITC experiments were performed on an isothermal titration calorimeter purchased from Microcal Inc. Molecular modeling was performed on a Silicon Graphics O2 machine with the modified Amber* force field in the MacroModel 7.0 program. Data for the crystal structure of the supramolecular pot **4** were recorded with an Enraf-Nonius Kappa-CCD diffractometer equipped with a graphite crystal incident-beam monochromator *Lp*.

Preparation of ligand 2a: A mixture of 5-hydoxymethylpyrimidine (332 mg, 3 mmol), NaH (720 mg, 3 mmol), [15]crown-5 (661 mg, 3 mmol), and tetrakis(bromomethyl)cavitand **1** (482 mg, 0.5 mmol) in dry DME (10 mL) was stirred under nitrogen atmosphere at 50 °C for 12 h. The solvent was evaporated and the residue was dissolved in CHCl$_3$ (50 mL). The solution was washed with water and brine, and dried (Na$_2$SO$_4$). The solution was evaporated to dryness under vacuum. The crude solid was purified by chromatography on silica gel with CH$_2$Cl$_2$/MeOH (10:1) to provide **2a** (323 mg, 60% yield). ^{1}H NMR (300 MHz, [D]chloroform, 300 K): $\delta = 9.16$ (s, 4H; PrmH_a), 8.68 (s, 8H; PrmH_b), 7.22 (s, 4H; ArH_c), 5.69 (d, ^3J(H,H) = 6.55 Hz, 4H; ArOCH_oH$_i$OAr), 4.95 (q, ^3J(H,H) = 7.02 Hz, 4H; CHCH$_3$), 4.50 (s, 8H; PrmCH_2O), 4.33 (s, 8H; OCH_2Ar), 4.25 (d, ^3J(H,H) = 6.65 Hz, 4H; ArOCH$_o$$H_i$OAr), 1.72 ppm (d, ^3J(H,H) = 7.78 Hz, 12H; CHCH_3); ^{13}C NMR (75 MHz, [D]chloroform, 300 K): δ = 158.28, 156.63, 153.43, 138.72, 130.98, 12287, 120.23, 99.18, 67.83, 62.48, 30.97, 15.90 ppm; FAB-MS: *m/z* calcd: 1081.4096; found: 1081.4066 [M+H]$^+$; elemental analysis calcd (%) for $C_{60}H_{56}N_8O_{12}$: C 66.66, H 5.22, N 10.36; found: C 66.29, H 5.33, N 10.18.

Preparation, physical, and spectroscopic properties of 3a

Method 1: Ligand **2a** (108 mg, 0.1 mmol) and [Pd(en)(NO$_3$)$_2$] (>2 equiv, >59 mg, >0.2 mmol) were suspended in water (3 mL), and the mixture was heated at 80 °C for 20 min. Ethanol was added to the clearly dissolved reaction solution, and the precipitate was collected. The white precipitate was collected by filtration, washed with aqueous ethanol and dried under vacuum to give **3a** (103 mg, 62% yield).

Method 2: Ligand **2a** (1.1 mg, 10 μmol) and [Pd(en)(NO$_3$)$_2$] (2 equiv, 0.6 mg, 20 μmol) were mixed in [D$_4$]methanol/[D$_2$]water = 10:1 (v/v) (0.5 mL) in an NMR tube. ^{1}H NMR (300 MHz, [D$_2$]water, 300 K): $\delta = 9.62$ (s, 4H; Prm$H_{a'}$), 9.17 (s, 4H; Prm$H_{b'}$), 8.87 (s, 4H; Prm$H_{b''}$), 7.59 (s, 4H; Ar$H_{c'}$), 6.09 (d, ^3J(H,H) = 6.32 Hz, 2H; ArOC$H_{o'}$H$_{i'}$OAr), 4.9 (b, 6H ArOC$H_{o''}$H$_{i''}$OAr + CHCH$_3$), 4.60 (s, 8H; PrmCH_2O), 4.43 (d, ^3J(H,H) = 9.81 Hz, 4H; OCHHAr), 4.11 (m, 6H; OCHHAr + ArOCH$_{o'}$$H_{i'}$OAr), 3.62 (d, ^3J(H,H) = 6.38 Hz, 2H; ArOCH$_{o''}$$H_{i''}$OAr), 2.90 (s, 8H; NC$H_2CH_2$N), 1.79 ppm (d, ^3J(H,H) = 6.40 Hz, 12H; CHCH_3); CSI-MS: *m/z*: 769.0 [**3a** − 2NO$_3^-$]$^{2+}$; elemental analysis calcd (%) for $C_{64}H_{72}N_{16}O_{24}\,Pd_2 \cdot 2H_2O$: C 45.26, H 4.51, N 13.20; found: C 45.02, H 4.46, N 12.82.

Preparation, physical, and spectroscopic properties of 4: Ligand **2a** (108 mg, 0.1 mmol) and [Pd(en)(NO$_3$)$_2$] (4 equiv, 117 mg, 0.4 mmol) were mixed in the mixed solvent MeOH/H$_2$O (10:1 (v/v), 10 mL), and the mixture was gently heated. Ethanol was added to the reaction solution, and then the precipitate was collected. The white precipitate was collected by filtration, washed with aqueous ethanol, and dried under vacuum to give **4** (174 mg, 78 % yield). ^{1}H NMR (300 MHz, [D$_4$]methanol/[D$_2$]water = 10:1 (v/v), 300 K); $\delta = 10.24$ (s, 4H; Prm$H_{a'''}$), 9.28 (s, 8H; Prm$H_{b'''}$), 7.53 (s, 4H; Ar$H_{c'''}$), 6.05 (d, ^3J(H,H) = 7.11 Hz, 4H; ArOC$H_{o'''}$H$_{i'''}$OAr), 4.96 (q, ^3J(H,H) = 7.53 Hz, 4H; CHCH$_3$), 4.57 (s, 8H; PrmCH_2O), 4.39 (s, 8H; OCH_2Ar), 4.26 (d, ^3J(H,H) = 7.24 Hz, 4H; ArOCH$_{o'''}$$H_{i'''}$OAr), 2.9 (m, 16H; NC$H_2CH_2$N), 1.78 ppm (t, ^3J(H,H) = 7.47 Hz, 12H; CHCH_3); CSI-MS: *m/z*: 1058.9 [**4** $-$ 2NO$_3^-$]$^{2+}$, 914.0 [**4** $-$ Pd(en)(NO$_3$)$_2$ $-$ 2NO$_3^-$]$^{2+}$; elemental analysis calcd (%) for $C_{68}H_{88}N_{24}O_{36}$ $Pd_4 \cdot 2H_2O$: C 35.83, H 4.07, N 14.75; found: C 34.32, H 4.48, N 14.83.

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[15] The other type of benzylic protons ($H_{e'}$) does not split upon Pd^{II} complexation, presumably due to the fast N$_{Prm}$–Pd bond cleavage and formation rate on the NMR timescale in water at ambient temperature.

[16] Overheating the aqueous solution containing **2a** and more than two equivalents of [Pd(en)(NO$_3$)$_2$] gave a mixture of **3a** and a small quantity of **4**. However, continuous heating resulted in dark gray precipitates that turned out to be decomposed complexes.

[17] From the analysis of ^{1}H NMR titration data, it also turned out that the cooperative effect of electrostatic and hydrophobic interactions contributes to strong complex formation in aqueous media. Phenylpyruvate, a classical diagnostic factor of phenylketonuria that can lead to severe mental retardation, showed quite a small binding constant ($K_a = 350\,\mathrm{M}^{-1}$), and this accentuates the importance of the terminal methyl group properly residing inside the resorcin[4]arene hydrophobic cavity.

[18] The possibility of an artificial metallo-hydrolase utilizing pyrimidine's non-coordinated nitrogens as a Lewis base is under study.

[19] The change of a solvent system may cause variation in the donor ability of solvent molecules and/or in the solubility of charged molecules. Modulation of coordination structures by using solvent donating abilities was reported: E. C. Constable, J. V. Walker, D. A. Tocher, M. A. M. Daniels, *J. Chem. Soc. Chem. Commun.* **1992**, 768–771.

[20] When the ratio of [D$_4$]methanol/[D$_2$]water reached 20:1, a white precipitate formed.

[21] The encapsulation study with several neutral and cationic guests such as CH_3CN, EtOH, *i*-PrOH, *n*-BuOH, benzene, $N(CH_3)_4NO_3$, $NaNO_3$, KNO_3, and $CsNO_3$ was in vain.

[22] Although CSI-MS spectrum showed the existence of a 1:3 complex in which three Pd^{II} ions were incorporated into **2a**, it was not detected by ^{1}H NMR spectroscopy.

[23] Crystal structure of $C_{34}H_{44}N_{12}O_{22.5}Pd_2$, $M_r = 1193.61$, colorless crystal $0.15 \times 0.50 \times 0.10$ mm^3, monoclinic $P2_1/m$; $a = 17.348(5)$, $b = 14.080(5)$, $c = 24.875(5)$ Å, $\alpha = 90°$, $\beta = 103.616(5)°$, $\gamma = 90°$, $V = 5905.2(30)$ Å^3, $Z = 4$; $T = 100$ K, $\rho_{calcd} = 1.343$ g cm^{-3} (including solvent), μ(Mo$_{K\alpha}$, $\lambda = 0.71073$ Å) = 0.684 mm^{-1}, $2\theta_{max} = 50.70°$; 19417 measured reflections, with 10785 unique reflections of which 3891 were observed with $I > 2\sigma(I)$. The structure was solved by direct methods and refined by full-matrix least-squares calculations with SHELX-93. The final $R_1 = 0.1008$, $wR_2 = 0.3166$ for 3891 reflections of $I > 2\sigma(I)$; $R_1 = 0.2257$, $wR_2 = 0.3804$ for all 10785 reflections; measure-

ments: Enraf-Nonius Kappa-CCD equipped with a graphite crystal incident-beam monochromator *L*p. Owing to the high degree of disorder of the counterions, further refinement was unsuccessful. CCDC-189894 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallogrphic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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