Assembly and Binding Properties of Osmate Ester-Bridged Binuclear Macrocycles

Kyu-Sung Jeong,* Young Lag Cho, Sung-Youn Chang, Tae-Yoon Park, and Jung Uk Song

Department of Chemistry, Yonsei University, Seoul 120-749, Korea

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Osmium (VI)-bridged macrocycles **1a**−**c**, **2**, and **3** assemble spontaneously when osmium tetraoxide, olefins, and L-shaped bispyridyl ligands are mixed in $CHCl_3$. The macrocycles possess well-defined square or rectangular cavities enclosed by aryl walls and act as host molecules. Hydrogen-bond donors on the inner surface of the hosts offer binding sites to acceptors of guests with complementary dimensions. The host **1a** binds adipamide **G2** ($K_a = 3.6 \times 10^4$ M^{-1}) and terephthalamide **G6** ($K_a = 2.0 \times 10^4$ M^{-1}), while it binds negligibly ($K_a < 10$ M^{-1}) benzamide **G5**, isophthalamide **G9**, or 1,4-naphthalenedicarboxamide **G10**. The larger hosts **2** and **3** bind the longer guests biphenyldicarboxamide **G12** and terphenyldicarboxamide **G17**, respectively, but shorter guests such as adipamide **G2** and terephthalamide **G6** are not well-bound ($K_a < 10$ M^{-1}). Hosts **1a**−**c** with different remote substituents (H, OMe, NO_2) but identical cavity size were prepared and their binding affinities were measured. The relative binding affinities of the hosts **1a**−**c** to the keto amide **G19**, ester amide **G20**, and diester **G21** are in the order of **1c** (NO_2) ≫ **1a** (H) > **1b** (OCH_3). The substituent effects on the binding strength are interpreted in terms of the electron density at the pyridine nitrogen of the hosts and its effect on bifurcated hydrogen bonding.

Introduction

Macrocycles such as cyclodextrins, crown ethers, calixarenes, carcerands, and other related molecules have been used as a powerful tool for the study and evolution of host−guest or supramolecular chemistry over the last 3 decades.[1] These compounds have advanced the understanding of weak, noncovalent interactions and have provided models for recognition in biological systems. More recently, self-assembled macrocycles have attracted a great deal of attention. In these frameworks some covalent bonds are replaced by relatively weak intermolecular forces including hydrogen bonding[2,3] and metal−ligand interactions.[4−13] These features give the systems the advantages of reversible formation such as error checking and cooperativity during assembly.[5] Maverick reported the first example of a discrete, self-assembled macrocycle, a Cu(II) and β-diketone complex that bound 1,4-diazabicyclo[2.2.2]octane.[6] Subsequently, impressive systems were reported by Fujita, who prepared molecular squares and cages. These featured hydrophobic cavities created by self-assembly of rigid tertiary amine ligands with transition metals that prefer square planar coordination such as Pd(II) and Pt(II).[11] These assemblies encapsulated aromatic and adamantane guests through hydrophobic interactions in aqueous solution. Stang

* To whom correspondence should be addressed. Tel: +82-2-361-2643. Fax: +82-364-7050. E-mail: ksjeong@alchemy.yonsei.ac.kr.

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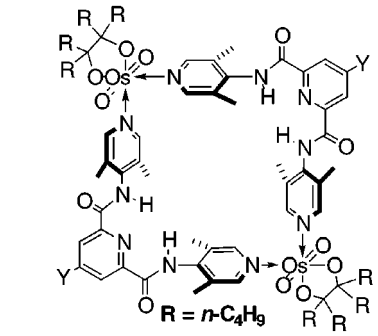
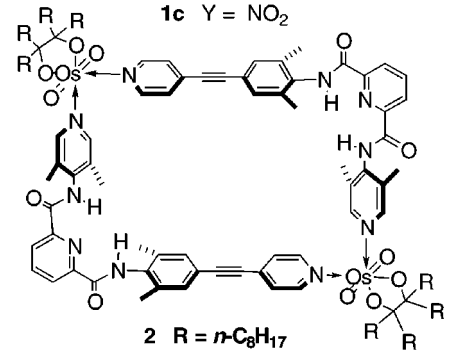
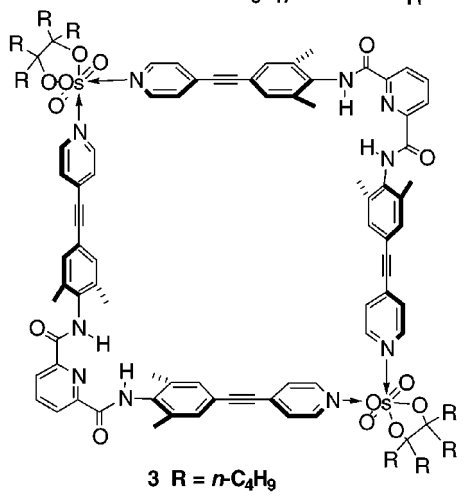
developed a parallel self-assembling motif for the construction of a series of molecular boxes soluble in organic solvents and capable of binding neutral organic guests.[12] Hunter synthesized a self-assembled Zn−porphyrin complex containing hydrogen-bonding sites inside the cavity and reported a strong complexation with terephthalamide through hydrogen-bonding interactions in $CDCl_3$.[13]

Osmium tetraoxide is a reliable oxidant for converting olefins to the corresponding *cis*-1,2-diols. The reaction proceeds efficiently in the presence of tertiary amines such as pyridine via Os(VI)−ester intermediate.[14] The structural features of the octahedral intermediates have been characterized in the solid state and in solution, wherein two pyridines are coordinated in the equatorial position with a cis relationship.[14c,15] On the basis of this feature we were able to assemble octahedral osmium(VI) ester-bridged molecular squares having well-defined cavities.[16] The macrocycles were spontaneously assembled from osmium tetroxide, olefins, and bispyridyl ligands. This self-assembling motif was further extended to the macrocyclic host **1a** by introducing two hydrogen-bonding sites at the diagonal corners into the cavity and, in the present work, to four related hosts **1b**, **1c**, **2**, and **3**.



1a Y = H
1b Y = OCH_3
1c Y = NO_2





In the preliminary communication,[16] we reported two X-ray crystal structures of osmate ester-bridged macrocyclic boxes. The Os(VI) ester has a distorted octahedral geometry, where two pyridine ligands are coordinated in the equatorial position with an approximately right N−Os−N angle (89.5°). This geometry is nearly ideal for assembly of molecular squares or rectangles. The ligands **4a**−**c**, **5**, and **6** comprise the 2,6-pyridinedicarboxamide unit in which internal N(pyridyl)···H−N(amide) hydrogen bonds[17] (about which more, later) can accommodate an angle near 90° and provide a bend in the structure to form the macrocycle. The juxtaposition of the osmate esters with the ligands results in the formation of discrete macrocyclic boxes with a square or rectangular geometry. The *o*-methyl substituents on the aromatic ring enforce a boxlike (as opposed to a flattened) shape for the molecule. Moreover, these substituents increase the solubility of the ligands and their derived macrocycles. The incorporation of polar binding sites inside the macrocycle offers an opportunity to bind guests with complementary functions on their outer surfaces.

Results and Discussion

Synthesis. The dichlorides **7b** and **7c**[18] and 4-amino-3,5-lutidine (**8**)[19] were prepared according to literature procedures. The amine **9** was synthesized from 4-bromo-2, 6-dimethylaniline as described in Scheme 1 (35% yield).[20] The coupling reactions of dichlorides **7a**−**c** with 2 equiv of amine **8** or **9** provided the corresponding ligands **4a**−**c** and **6** (52−76% yield). The unsymmetrical ligand **5** was obtained by reaction of the acid chloride **7a** with 1 equiv of each of the amines **8** and **9** in 30% yield. The macrocycles **1a**−**c**, **2**, and **3** were formed in $CHCl_3$ from osmium tetraoxide and a 1:1 mixture of olefin and ligands **4a**−**c**, **5**, and **6**, respectively. More soluble square macrocycles **1a**−**c** and **3** were assembled in the presence of 5,6-dibutyl-5-decene; however, 9,10-dioctyl-9-octadecene[21] was used for the preparation of less soluble rectangular macrocycle **2**. The reactions went to completion usually within a few minutes at room temperature, and the desired macrocycles were obtained in 61−89% yield.

Characterization of Macrocycles. The products **1a**−**c**, **2**, and **3** are soluble in various organic solvents

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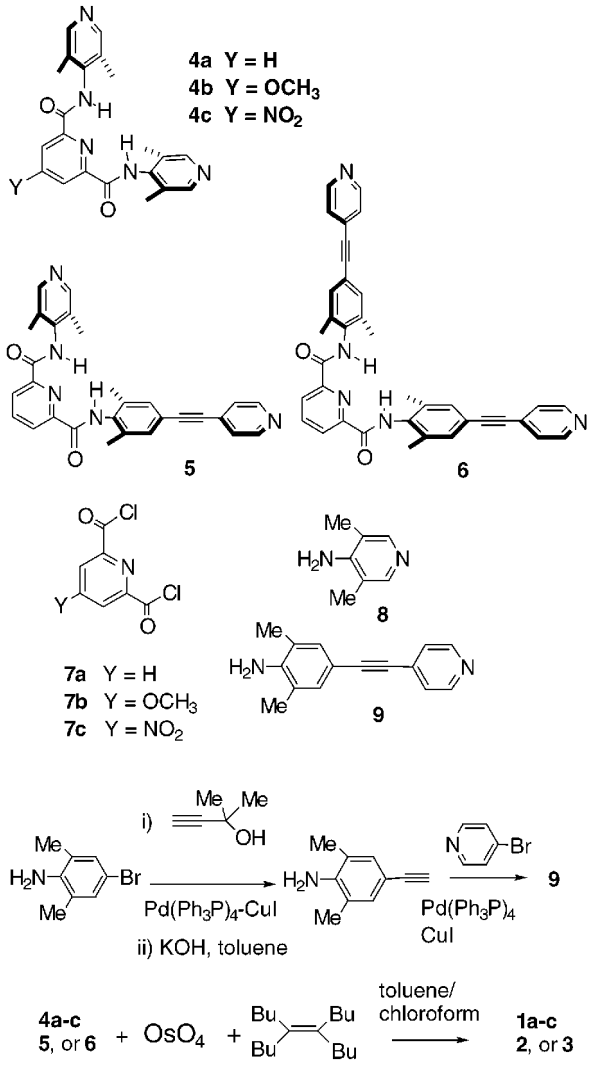
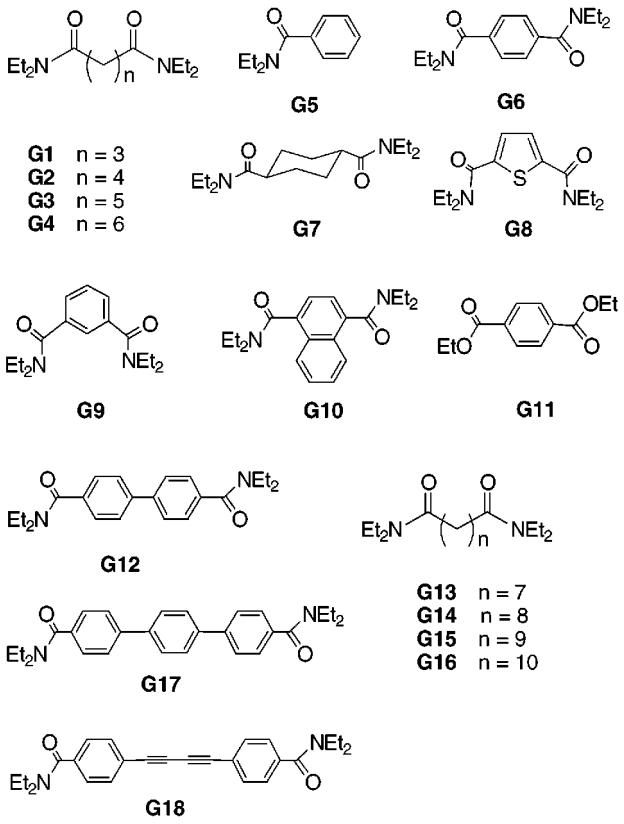
Scheme 1



including dichloromethane, chloroform, tetrahydrofuran, acetone, and dimethyl sulfoxide. The 1:1:1 stoichiometry of the osmium tetroxide, the olefin, and the ligand was confirmed by elemental analysis of the products. The infrared spectra show a strong, characteristic band near 830 cm^{-1}, diagnostic of the trans O═Os═O moiety of the octahedral dioxoosmium(VI) complexes.[14c,15] The ^1H and ^{13}C NMR spectra of **1a**−**c**, **2**, and **3** were well-correlated to the symmetrical structures. The ^1H NMR integrations confirmed a 1:1 molar ratio of olefin and ligand. The coordinating pyridyl C−H (α to the nitrogen) resonances of the macrocycles are shifted downfield from those for free ligands ($\Delta\delta = 0.2-0.3$ ppm). In the FAB-MS analyses, the molecular ion peak $[M]^+$ could not be detected, probably due to the presence of labile Os(VI)−N and Os (VI)-O bonds under ionization conditions. Nevertheless, peaks of a weak intensity (0.1−0.2%) were observed which could be attributed to one and two glycol loss from the binuclear macrocycles, $[M - ((OC(C_4H_9)_2)_2]^+$ and $[M - 2(OC(C_4H_9)_2)_2]^+$, respectively. In addition to these physical and spectroscopic properties, the binding data described below strongly support the formation of discrete binuclear macrocycles in solution.

^1H NMR Titrations. The binding properties were revealed in $CDCl_3$ at 24 ± 1 °C by ^1H NMR titration experiments, and time-averaged resonances for the free and the complexed species were always observed under

Chart 1



the titration conditions. The chemical shifts and splitting patterns in the ^1H NMR spectra of macrocyclic hosts **1a**−**c**, **2**, and **3** remain constant in a wide range of the concentration (0.25−20 mM) in $CDCl_3$. This precludes aggregation or dissociation of **1a**−**c**, **2**, and **3** under titration conditions. Therefore, any changes in ^1H NMR spectra of **1a**−**c**, **2**, and **3** upon guest addition are only due to host−guest complexation. The experiments were performed by adding the guest solution (5−10 mM in $CDCl_3$) to the host stock solution (1−2 mM in $CDCl_3$) in small portions and monitoring the downfield shift of the host NH signal. The association constants (K_as, M^{-1}) were determined by nonlinear least-squares fitting analysis of the titration curves: plots of $\Delta\delta$(N−H) vs equivalents of guest were well-fitted to the expression of a 1:1 binding isotherm (see the Experimental Section).[22] Each titration experiment was duplicated and the association constants (K_a) were reproducible within 20%.

Binding Properties of 1a. Diamide guests evaluated for host **1a** are given in Chart 1. Flexible dicarboxamides **G1**−**G4** with various chain lengths were first examined. The signal for the amide N−H of the host **1a** was gradually downfield shifted on the guest addition (Figure 1a), indicative of intermolecular hydrogen-bond formation. For example, the addition of adipamide **G2** ($n = 4$) caused the N−H signal of **1a** to shift downfield from 9.2 to 10.7 ppm, and the saturation was reached at about 1 equiv of added guest. This suggested a 1:1 stoichiometry with a high association constant ($K_a = 3.6 \times 10^{-4}$ M^{-1}). Any small variation in the chain length of the guests greatly decreases the association constants: $K_a = 1.5 \times 10^3$ for **G1** ($n = 3$), 9.3×10^2 for **G3** ($n = 5$), and $3.3 \times$

(22) For more details, see: Macomber, R. S. *J. Chem. Educ.* **1992**, *69*, 375−378.

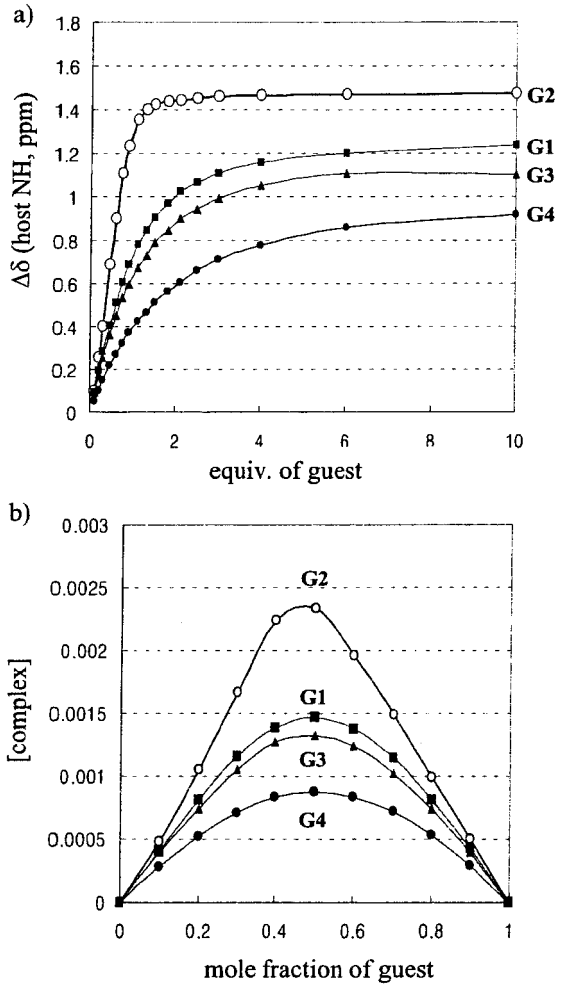


Figure 1. (a) Titration curves between host **1a** and guests **G1**−**G4**, plotting the host NH chemical shift changes (Δδ) vs molar equivalents of the guest and (b) Continuous variation method (Job plots) between **1a** and **G1**−**G4**.

10^2 M^{-1} for **G4** ($n = 6$) (Table 1). All guests in this series showed a 1:1 complexation with **1a**, as confirmed by Job's plots[23] (Figure 1b).

Rigid diamides, terephthalamide **G6**, 1,4-cyclohexanedicarboxamide **G7**, and 2,5-thiophenedicarboxamide **G8**, exhibited high affinities for **1a**, while the monoamide **G5** shows nearly no binding.[24] This suggests that two hydrogen-bonding sites of the host **1a** must be simultaneously involved in the association with diamide guests. Remarkably, 1,4-napnthalenedicarboxamide **G10** bound negligibly, despite its similarity in structure to **G6**.[24] Likewise, **G9**—only slightly larger than **G8**—showed nearly no binding. For the poor guests **G9** and **G10**, the CPK models indicated severe steric repulsion between the host lutidyl surfaces and the guest aryl residues (see, for example Figure 3).

Binding Properties of 2 and 3. The ^{1}H NMR spectrum of the macrocycle **2** with a rectangular shape showed two distinct N−H signals: N−H (lutidyl) δ 8.98 ppm and N−H (pyridylethynylphenyl) δ 9.30 ppm in $CDCl_3$. On complexation of **2** with 4,4′-biphenylcarboxamide **G12**, characteristic downfield shifts of both N−H signals were observed: $\Delta\delta$ 1.25 ppm for the lutidyl N−H and $\Delta\delta$ 1.70 ppm for the pyridylethynylphenyl N−H. The titration curves plotted using either $\Delta\delta$ gave essentially identical association constants within experimental error (<5%), indicating that both NHs are involved in a single binding event. Rigid carboxamide **G12** is nearly a perfect fit for the space inside the rectangular box **2** and binds strongly ($K_a = 4.5 \times 10^4$ M^{-1}). However, smaller guests such as adipamide **G2** and terephthalamide **G6** enjoy the freedom of entering and leaving the host's cavity without sticking ($K_a < 10$ M^{-1}). In a series of experiments with flexible guests **G13**−**G16**, the chain length selectivity of **2** was shown to be less than that of **1a** (Table 1). This is a reasonable consequence of the larger cavity presented by **2**.

Table 1. Association Constants (K_a ± 20%, M^{-1}) at 297 ± 1 K in $CDCl_3$ and the Observed and Calculated Maximum Chemical Shift Changes of the Host NH Signals

entry	guest	$\Delta\delta_{max}$(obsd) (NH, ppm)[a]	$\Delta\delta_{max}$(calcd) (NH, ppm)[a]	K_a (M^{-1})
		Host **1a**		
1	**G1** ($n = 3$)	1.23	1.38	1450
2	**G2** ($n = 4$)	1.47	1.47	35,500
3	**G3** ($n = 5$)	1.16	1.37	930
4	**G4** ($n = 6$)	0.90	1.36	330
5	**G5**	0.12	1.24	6
6	**G6**	1.23	1.23	20,000
7	**G7**	0.95	1.09	910
8	**G8**	0.95	1.18	640
9	**G9**	0.08	1.24	4
10	**G10**	<0.02		nd[b]
11	**G11**	<0.02		nd[b]
		Host **2**		
12	**G6**	0.07, 0.10	0.84, 0.94	8
13	**G12**	1.37, 1.91	1.46, 1.91	45,000
14	**G13** ($n = 7$)	0.69, 0.81	1.26, 1.37	170
15	**G14** ($n = 8$)	1.26, 1.41	1.39, 1.52	2150
16	**G15** ($n = 9$)	1.29, 1.37	1.40, 1.50	1650
17	**G16** ($n = 10$)	1.09, 1.19	1.27, 1.41	1030
		Host **3**		
18	**G17**	1.27	1.58	780
19	**G18**	1.26	1.53	910

[a] The NH chemical shifts of the free hosts are 9.19 ppm for **1a**, 8.98 and 9.30 ppm for **2**, and 9.08 ppm for **3**. [b] Not determined.

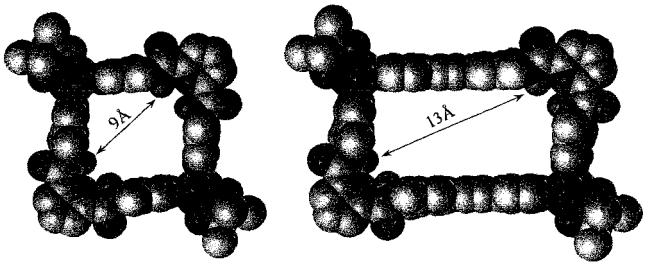


Figure 2. Energy-minimized (Tripos) CPK models of hosts **1a** (left) and **2** (right). The butyl groups in the Os(VI) corners have been replaced by methyl groups and some hydrogens omitted for clarity.

The even larger size of the square macrocycle **3** permitted inclusion of dicarboxamide **G17** (containing a terphenyl spacer) or **G18** (having a diphenylbutadienyl spacer). The association constants, 780 and 910 M^{-1}, respectively, are lower than those expected for an ideal guest as established by **1a** and **2**.

Substituent Effects on the Host−Guest Complex Stability. Three hosts, **1a**, **1b**, and **1c**, contain different

(23) Corners, K. A. *Binding Constants*; John Wiley & Sons: New York, 1984; p 24.

(24) In the cases of the guests **G5**, **G9**, **G10**, and **G11**, the chemical shift changes of the host NH signal were too small ($\Delta\delta_{max} \leq \sim 0.1$ ppm) to determine the association constants accurately under the titration conditions.

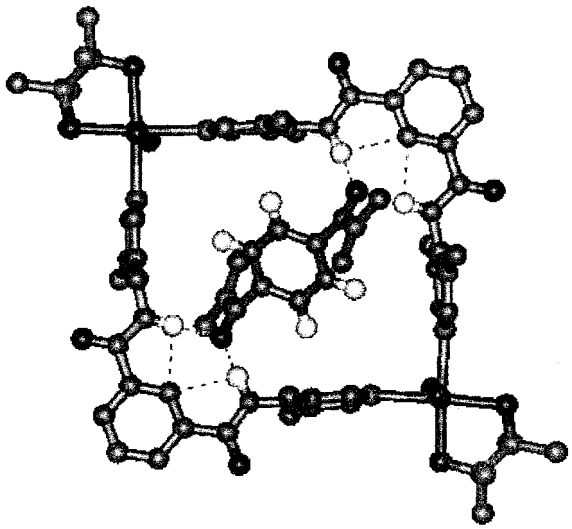
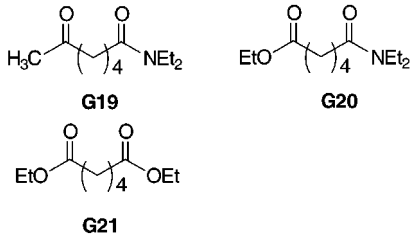


Figure 3. Energy-minimized (Tripos)[26] structure of the complex between hosts **1a** and *N*,*N*,*N*′*N*′-tetramethylterephthalamide. Some hydrogens have been omitted for clarity.

Table 2. Association Constants (K_a ± 20%, M^{-1}) of the Hosts 1a−c with Guests G19−G21 at 297 ± 1 K in $CDCl_3$

	association constants (K_a, M^{-1})		
guest	host **1a** (H)	host **1b** (OCH_3)	host **1c** (NO_2)
G19 (keto-amide)	2230	1170	25000
G20 (ester-amide)	1200	740	17000
G21 (diester)	60	45	350

substituents (H, OMe, and NO_2) at the para position of the corner pyridine ring. Attempts to find differences in binding affinities of **1a**−**c** with adipamide **G2** were unsuccessful, since this guest bound too strongly to all of the hosts ($K_a > 10^4$ M^{-1}). Differences were found in the binding abilities of these hosts to guests **G19**−**G21**, containing a poor hydrogen-bond acceptor. These guests bind more weakly to the host **1b** (OMe) but much more strongly to the host **1c** (NO_2) than to the reference host **1a** (H) (Table 2). These differences were outside the experimental errors of the titration protocols but were not easily explained. The remote substituents should have little effect on the acidity of hydrogen-bond donors of the amides. Indeed, the NH resonance of **1b** appeared at δ 9.24 ppm, **1c** at δ 9.05 ppm, and **1a** at δ 9.19 ppm. This order is inconsistent with direct inductive effects on the N−H because the most electron-withdrawing group has the most shielded proton. The substituent effects, we believe, are due to changes in the electron density at the pyridine nitrogen. As mentioned earlier, the conformations of the amides at the pyridine-2,6-dicarboxamide corners are those that are expected from intramolecular hydrogen bonds between the secondary amides and the pyridyl nitrogen. This is not a good intramolecular hydrogen bond (the N···H−N angle is far from ideal), but the hydrogen and heavy atoms are polarized as expected. On complexation, the hydrogen-bond donors of the host converge on the guest's carbonyl oxygen acceptor. The oxygen will experience the pyridyl nitrogen in a repulsive way. Such repulsion is a universal feature of bifurcated hydrogen bonding, and the substituent can effect the degree of this repulsion. The host **1b** (OMe), with an electron-donating group, is therefore the poorest host, but the host **1c** (NO_2) with a strong electron-withdrawing group is the best host for the guests **G19**, **G20**, and **G21**. This can also be viewed as another case of secondary effects on hydrogen bonding as introduced by Jorgensen.[25]



Complex Geometry. Computer modeling studies[26] were used to characterize the hydrogen-bonding sites of the macrocyclic hosts **1a** and **2** (Figure 2). The diagonal distances between the amide hydrogens of the two binding sites are approximately 9 Å in **1a** and 13 Å in **2**. If good hydrogen bonds are to be formed, the carboxamide O···O distance of the guest should complement the diagonal distance of the host.

Guests **G6** and **G12** were the best fits for **1a** and **2**, respectively. Binding of **G6** to the rectangular host **2** was not favorable because the cavity was too roomy for this small guest. These results clearly indicate that two binding sites are simultaneously involved in the recognition event. The structure proposed for the complex between the host **1a** and terephthalamide derivative is shown in Figure 3. The *N*,*N*-dialkyl groups twist the planes of amide and aromatic of the guest in such a way that additional substituents on the aromatic ring are directed at the walls of the host. The limited space remaining in the cavity explains the difficulty in binding the isophthalamide **G9** and 1,4-naphthalenedicarboxamide **G10**.

Additional evidence for locating the guests inside the cavity was obtained from ^{1}H NMR spectroscopy (Figure 4). As mentioned earlier, time-averaged ^{1}H NMR signals between free and complex species were observed at room temperature (the exchange rate is fast on the NMR time scale). The separated signals could be, however, seen in the cases of $K_a > 10^4$ M^{-1} in $CDCl_3$ by lowering temperature down to −40 °C. Shielding by the anisotropic environment of the aromatic walls of the host **1a** caused characteristic upfield shifts of the aryl C−H signals of the terephthalamide **G6** ($\Delta\delta = 2.0$ ppm). Additionally, in the homonuclear NOE difference experiment using a 1:1 molar mixture of the host **1a** and the guest **G6**, irradiation of the guest aryl resonance yielded the NOE enhancement (~1%) of the host aryl signal. These two observations support the proposed complex structure in Figure 3. Likewise, upon complexation of the guest **G12** with the host **2**, the guest aryl signal for the ortho hydrogens (H_3) to the carboxamide group experiences an upfield shift of $\Delta\delta = 1.3$ ppm, while the meta hydrogen (H_2) signal remains nearly unchanged. The CPK molecular models show that the H_3 hydrogens are directed to

(25) (a) Pranata, J.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 2810−2819. (b) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008−2010. For related experimental studies, see: (a) Gardner, R. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 10411−10412. (b) Murray, T. J.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1992**, *114*, 4010−4011. (c) Jeong, K.-S.; Tjivikua, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 3215−3217.

(26) Molecular modeling was performed on a Silicon Graphics Indigo 2 workstation with Tripos force field in the Sybyl 6.3 program. Clark, M.; Cramer, R. D., III.; Opdenbosch, N. V. *J. Comput. Chem.* **1989**, *10*, 982−1012.

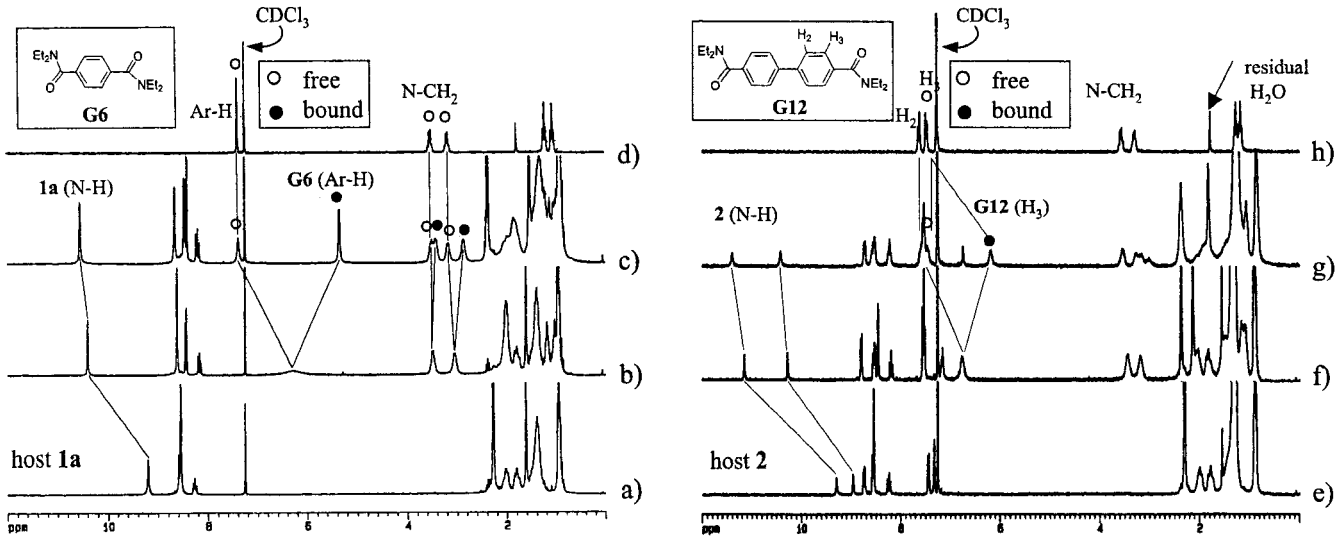


Figure 4. ^{1}H NMR spectra (left) of (a) **1a** (5.0 mM) at 23 °C, (b) **1a** (5.0 mM) + **G6** (7.5 mM) at 23 °C, (c) **1a** (5.0 mM) + **G6** (7.5 mM) at −40 °C, and (d) **G6** (5.0 mM) at −40 °C, and ^{1}H NMR spectra (right) of (e) **2** (2.0 mM) at 23 °C, (f) **2** (2.0 mM) + **G12** (4.0 mM) at 23 °C, (g) **2** (2.0 mM) + **G12** (4.0 mM) at −40 °C, and (h) **G12** (4.0 mM) at −40 °C

the π face of the aryl wall of the host **2**, but the H_2 hydrogens are not.

Conclusions. Five cyclophane-like macrocycles, **1a**−**c**, **2**, and **3**, with square and rectangular cavities were spontaneously assembled in one pot by simply mixing osmium tetraoxide, symmetrical olefins, and L-shaped bispyridyl ligands. The cavity size and shape of the macrocycles were varied by modification of the ligands. Specifically, incorporation of inwardly directed hydrogen-bond donors on the ligands resulted in the macrcocyclic hosts that strongly and selectively bound the diamide guests with complementary dimensions. In addition, the stability of host−guest complexes could be influenced by the subtle effect of the remote substituents with different electronic natures.

Experimental Section

General. All commercial reagents, unless otherwise noted, were ACS reagent grade and used without further purification. Methylene chloride, chloroform, and dimethoxyethane (DME) were distilled from CaH_2 under nitrogen. Toluene and ethyl ether were distilled from Na/benzophenone under nitrogen. Diethylamine was distilled from KOH. All of the amide guests were prepared by coupling reactions of the corresponding commercially available acids or acid chlorides with diethylamine.

Melting points were uncorrected. ^{1}H NMR spectra were recorded at 250 or 500 MHz spectrometer, and ^{13}C NMR spectra were recorded at 62 or 125 MHz spectrometer. Mass spectra were obtained with a JMS−HS 110/110A mass spectrometer (JEOL Inc., Japan) and nitrobenzyl alcohol was used as a matrix in $CHCl_3$ as solvent. Molecular modeling[26] was performed on a Silicon Graphics Indigo 2 workstation with Tripos force field in the Sybyl 6.3 program.

***N,N′*-Bis(3,5-dimethylpyridin-4-yl)-pyridine-2,6-dicarboxamide (4a).** To a CH_2Cl_2 (20 mL) solution of pyridine-2,6-dicarbonyl dichloride (**7a**) (0.61 g, 3.0 mmol) at 0 °C were added 4-amino-3,5-lutidine (0.77 g, 6.3 mmol)[19] and 2.5 equiv of *N,N*-diisopropylethylamine (1.3 mL, 7.5 mmol). The solution was stirred at room temperature for 2 h and subsequently heated at reflux for 2 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated. The solid residue was washed with diethyl ether and recrystallized in CH_2Cl_2/EtOAc solvent to provide **4a** as a white solid (0.59 g, 52%): mp 228−230 °C; IR (KBr) 3308, 3224, 1683, 1659 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.33 (s, NH, 2H), 8.57 (d, J = 7.7 Hz, 2H), 8.36 (s, 4H), 8.21 (t, J = 7.7 Hz, 1H), 2.29 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 162.1, 149.8, 142.8, 140.3, 131.2, 126.8, 16.2. Anal. Calcd for $C_{21}H_{21}N_5O_2$: C, 67.37; H, 5.38; N, 18.70. Found: C, 67.30; H, 5.26; N, 18.79.

Ligand 4b. The preparation of **4b** was performed under the same conditions as those described for **4a**, except that 4-methoxy-2,6-pyridinedicarbonyl dichloride (**7b**)[18] was used instead of 2,6-pyridinedicarbonyl dichloride. **4b** was obtained in 65% yield as a white solid: mp 222−224 °C; IR (KBr) 3321, 3186, 1690, 1665 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.34 (s, NH, 2H), 8.36 (s, 4H), 8.02 (s, 2H), 4.05 (s, 3H), 2.29 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 161.5, 150.5, 149.5, 142.1, 130.4, 112.2, 56.5, 15.7. Anal. Calcd for $C_{22}H_{23}N_5O_3$: C, 65.16; H, 5.72; N, 17.27. Found: C, 65.09; H, 5.90; N, 17.35.

Ligand 4c. The preparation of **4c** was performed under the same conditions as those described for **4a** except that 4-nitro-2,6-pyridinedicarbonyl dichloride (**7c**)[18] was used instead of 2,6-pyridinedicarbonyl dichloride. **4c** was obtained in 76% yield as a pale yellow solid: mp 266−268 °C; IR (KBr) 3278, 3232, 1695 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.44 (s, NH, 2H), 9.21 (s, 2H), 8.36 (s, 4H), 2.28 (s, 12 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 157.2, 152.1, 149.5, 141.9, 130.8, 119.5, 15.7. Anal. Calcd for $C_{21}H_{20}N_6O_4$: C, 59.99; H, 4.79; N, 19.99. Found: C, 59.95; H, 4.98; N, 19.99.

2,6-Dimethyl-4-(pyridin-4-yl-ethynyl)aniline (9). To a degassed solution of 4-bromo-2,6-dimethylaniline (3.0 g, 15 mmol) in Et_2NH (50 mL) under argon were added 2-methyl-3-butyn-2-ol (2.9 mL, 30 mmol), CuI (0.19 g, 1.0 mmol), and $(PPh_3)_4Pd$ (0.32 g, 0.28 mmol). The reaction mixture was heated at reflux for 2 days, cooled to room temperature, and evaporated. The residue was redissolved in EtOAc (50 mL), filtered, and concentrated. Purification by flash column chromatography (EtOAc/hexanes 1:2) to give 4-(3-hydroxy-3-methylbutynyl)-2,6-dimethylaniline as pale yellow solid (2.0 g, 66%): mp 78−79 °C; IR (KBr) 3432, 3353, 2215, 1633 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.03 (s, 2H), 3.69 (br s, NH_2, 2H), 2.13 (s, 6H), 1.97 (s, OH, 1H), 1.59 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 143.2, 131.8, 121.5, 111.5, 91.4, 82.9, 65.7, 31.7, 31.1, 17.4. Anal. Calcd for $C_{13}H_{17}N_1O_1$: C, 76.81; H, 8.43 N, 6.89. Found: C, 76.83; H, 8.40; N, 6.87.

A suspension of 4-(3-hydroxy-3-methylbutynyl)-2,6-dimethylaniline and KOH (1.1 g, 20 mmol) in toluene (30 mL) was heated at reflux for 9 h. The reaction mixture was filtered, concentrated, and purified with flash column chromatography (EtOAc/hexane 1:3) to furnish 4-acetylenyl-2,6-dimethylaniline as pale yellow oil (2.6 g, 91%): IR (KBr) 3397, 3289, 2104, 1625

cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.11(s, 2H), 3.73(br s, NH_2, 2H), 2.92(s, 1H), 2.14 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 143.8, 132.2, 121.3, 110.5, 84.9, 74.6, 17.4. Anal. Calcd for $C_{10}H_{11}N_1$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.70; H, 7.52; N, 9.63.

Finally, 4-bromopyridine hydrochloride (1.88 g, 9.67 mmol), CuI (0.092 g, 0.48 mmol), and $(PPh_3)_4Pd$ (0.17 g, 0.15 mmol) were added to a degassed solution of 4-ethynyl-2,6-dimethylaniline (0.70 g, 4.82 mmol) in Et_2NH (50 mL) under argon. The mixture was heated at reflux for 9 h and Et_2NH was removed in vacuo. The residue was taken up in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The crude product was purified with flash column chromatography (EtOAc/CH_2Cl_2 1:2) to give 2,6-dimethyl-4-(4-pyridylethynyl)aniline (**9**) as pale yellow solid (0.60 g, 56%): mp 121−122 °C; IR (KBr) 3354, 3225, 2202, 1626 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.55 (dd, J_1 = 6.1 Hz, J_1 = 1.5 Hz, 2H), 7.32 (dd, J_1 = 6.1 Hz, J_1 = 1.5 Hz, 2H), 7.17 (s, 2H), 3.83 (br s, NH_2, 2H), 2.18 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 149.9, 144.8, 132.5, 121.8, 110.6, 96.4, 85.2, 17.8. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.09; H, 6.48; N, 12.53.

***N*-(3,5-dimethylpyridin-4-yl)-*N*′-(4-(pyridin-4-yl-ethylnyl)-2,6-dimethylphenyl)pyridine-2,6-dicarboxamide (5).** To a solution of pyridine-2,6-dicarbonyl dichloride (**7a**) (0.33 g, 1.62 mmol) in CH_2Cl_2 (25 mL) at 0 °C were added 4-amino-3,5-lutidine (0.20 g, 1.62 mmol), 2,6-dimethyl-4-(pyridin-4-ylethynyl)aniline (**9**) (0.36 g, 1.62 mmol), DMAP (0.1 g), and *N*,*N*-diisopropylethylamine (1 mL). The reaction mixture was heated at reflux for 2 h, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The crude product was purified by flash column chromatography (EtOAc) to give **5** as a pale yellow solid (0.23 g, 30%) (side products were 0.09 g of **4a** and 0.19 g of **6**): mp 238−239 °C; IR (KBr) 3288, 2214, 1686 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.35 (s, NH, 1H), 9.30 (s, NH, 1H), 8.52−8.58 (m, 4H), 8.34 (s, 2H), 8.20 (t, J = 7.8 Hz, 1H), 7.33−7.35 (m, 4H), 2.31 (s, 6H), 2.28 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 161.4, 149.6, 149.4, 149.1, 148.3, 142.0, 139.8, 136.0, 135.0, 131.9, 131.7, 130.4, 126.4, 126.0, 125.8, 121.3, 94.1, 86.7, 18.6, 15.7. Anal. Calcd for $C_{29}H_{25}N_5O_2$: C, 73.25; H, 5.30; N, 14.73. Found: C, 73.22; H, 5.38; N, 14.67.

***N*,*N*′-Bis(4-(pyridin-4-yl-ethylnyl)-2,6-dimethylphenyl)pyridine-2,6-dicarboxamide (6).** To a solution of pyridine-2,6-dicarbonyl dichloride (**7a**) (0.22 g, 1.08 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added 2,6-dimethyl-4-(pyridin-4-ylethynyl)aniline (**9**) (0.48 g, 2.16 mmol), DMAP (0.1 g), and *N*,*N*-diisopropylethylamine (1 mL). The reaction mixture was refluxed for 2 h and worked up under the same conditions used for **5**. The desired product **6** was obtained as a pale yellow solid (0.38 g, 62%): mp 298−299 °C; IR (KBr) 3297, 2213, 1685 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.36 (s, NH, 2H), 8.53−8.56 (m, 6H), 8.22 (t, J = 8.0 Hz, 1H), 7.29−7.33 (m, 8H), 2.30 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 149.7, 148.9, 139.8, 135.9, 134.8, 131.9, 131.7, 126.1, 125.7, 121.3, 94.0, 86.8, 18.7. Anal. Calcd for $C_{37}H_{29}N_5O_2$: C, 77.20; H, 5.08; N, 12.17. Found: C, 77.28; H, 5.03; N, 12.08.

General Procedure for the Preparation of Hosts 1a−c, 2, and 3. To a solution of ligand (0.5 mmol, **4a**−**c**, **5**, or **6**) and olefin (0.6 mmol, 5,6-dibutyl-5-decene was used for the preparation of hosts **1a**−**c** and **3**, and 9,10-dioctyl-9-octadecene for host **2**) in $CHCl_3$ (10 mL) was added a 0.1 M solution of OsO_4 in toluene (6 mL, 0.6 mmol) at room temperature. After the solution was stirred for 10−30 min, the solvent was removed. The dark-brown residual solid was repeatedly washed with hexane and diethyl ether, and dried under vacuum to give the corresponding host (**1a**−**c**, **2**, or **3**).

1a: 67% yield; mp >200 °C (dec); IR (KBr) 3307, 1691, 829 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.19 (s, NH, 4H), 8.59 (d, J = 7.8 Hz, 4H), 8.55 (s, 8H), 8.28 (t, J = 7.8 Hz, 2H), 2.28 (s, 24H), 2.08−1.98 (m, 8H), 1.87−1.75 (m, 8H), 1.52−1.29 (m, 32H), 0.96 (t, J = 6.6 Hz, 24H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 160.8, 149.5, 148.6, 145.7, 131.5, 127.3, 94.4, 34.7, 27.5, 24.6, 16.9, 15.1; FAB-MS m/z = 1480 [M − $(OC(C_4H_9)_2)_2]^+$, 1194 [M − 2$(OC(C_4H_9)_2)_2]^+$. Anal. Calcd for $C_{78}H_{114}N_{10}O_{12}Os_2$: C, 53.10; H, 6.51 N, 7.94. Found: C, 53.15; H, 6.57; N, 7.98.

1b: 74% yield; mp >200 °C (dec). IR (KBr) 3305, 1695, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, NH, 4H), 8.54 (s, 8H), 8.04 (s, 4H), 4.06 (s, 6H), 2.26 (s, 24H), 2.03−2.01 (m, 8H), 1.83−1.79 (m, 8H), 1.50−1.38 (m, 32H), 0.96 (t, J = 6.6 Hz, 24H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 160.7, 150.1, 149.0, 145.2, 130.9, 112.5, 93.8, 56.7, 34.2, 27.0, 24.1, 16.3, 14.6; FAB-MS m/z = 1540 [M − $(OC(C_4H_9)_2)_2]^+$, 1256 [M − 2$(C_4H_9)_2)_2]^+$. Anal. Calcd for $C_{80}H_{118}N_{10}O_{14}Os_2$: C, 52.67; H, 6.52 N, 7.68. Found: C, 52.73; H, 6.50; N, 7.65.

1c: 61% yield; mp >200 °C (dec). IR (KBr) 3232, 1695, 829 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.25 (s, 4H), 9.05 (s, NH, 4H), 8.57 (s, 8H), 2.28 (s, 24H), 2.03−2.01 (m, 8H), 1.83−1.79 (m, 8H), 1.50−1.38 (m, 32H), 0.96 (t, J = 6.4 Hz, 24H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 157.2, 151.7, 149.1, 144.7, 131.4, 119.7, 93.9, 34.2, 27.0, 24.1, 16.3, 14.6; FAB-MS m/z = 1570 [M − $(OC(C_4H_9)_2)_2]^+$, 1286 [M − 2$(OC(C_4H_9)_2)_2]^+$. Anal. Calcd for $C_{78}H_{112}N_{12}O_{16}Os_2$: C, 50.53; H, 6.09; N, 9.06. Found: C, 50.54; H, 6.05; N, 9.13.

2: 67% yield; mp >200 °C (dec). IR (KBr) 3312, 2212, 1695, 830 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.30 (s, NH, 2H), 8.97 (s, NH, 2H), 8.75 (d, J = 5.3 Hz, 4H), 8.55−8.58 (m, 8H), 8.24 (t, J = 7.7 Hz, 2H), 7.45 (d, J = 6.4 Hz, 4H), 7.32 (s, 8H), 2.30 (s, 24H), 1.96−2.01 (m, 8H), 1.78−1.82 (m, 8H), 1.28−1.42(m, 96H), 0.86−0.95(m, 24H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 160.6, 149.4, 148.8, 148.0, 145.5, 140.3, 140.0, 135.8, 135.0, 132.3, 130.9, 126.7, 126.4, 120.6, 97.0, 93.0, 85.8, 34.4, 32.1, 31.1, 30.0, 29.6, 24.7, 22.9, 18.8, 16.4, 14.3; FAB-MS m/z = 1903 [M − $(OC(C_8H_{17})_2)_2]^+$, 1395 [M − 2$(OC(C_8H_{17})_2)_2]^+$. Anal. Calcd for $C_{126}H_{186}N_{10}O_{12}Os_2$: C, 62.71; H, 7.76; N, 5.80. Found: C, 62.72; H, 7.71; N, 5.86.

3: 89% yield; mp >200 °C (dec). IR (KBr) 3315, 2211, 1689, 834 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.08 (s, NH, 4H), 8.71 (s, 8H), 8.57 (d, J = 7.7 Hz, 4H), 8.22 (t, J = 7.5 Hz, 2H), 7.46 (s, 8H), 7.37 (s, 8H), 2.33 (s, 24H), 2.02−2.20 (m 8H), 1.74−1.82 (m, 8H), 1.38−1.43 (m, 32H), 0.95 (t, J = 7.5 Hz, 24H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 149.3, 148.7, 140.1, 135.9, 135.2, 132.3, 126.9, 126.2, 120.6, 97.2, 93.9, 85.8, 34.2, 27.0, 24.1, 18.8, 14.6; FAB-MS m/z = 1594 [M − 2$(OC(C_4H_9)_2)_2]^+$. Anal. Calcd for $C_{110}H_{130}N_{10}O_{12}Os_2$: C, 61.03; H, 6.05; N, 6.47. Found: C, 61.06; H, 6.01; N, 6.51.

***N*,*N*,*N*′,*N*′-Tetraethyl-*p*-terphenyl-4,4″-dicarboxamide (G17).** A mixture of *N*,*N*-diethyl-4-bromobenzamide (0.37 g, 1.44 mmol) and $(PPh_3)_4Pd$ (0.05 g, 0.04 mmol) in dimethoxyethane (8 mL) was stirred under argon. To this was added a solution of 1,4-benzenediboronic acid[27] (0.12 g, 0.72 mmol) in ethanol (5 mL) and 2 M aqueous Na_2CO_3 (8 mL). The resulting mixture was heated at reflux for 19 h. The reaction mixture was cooled to room temperature, extracted with diethyl ether (20 mL x 2), dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (EtOAc) to give 0.15 g of **G17** as a white solid (48%): mp 201−202 °C; IR (KBr) 2974, 1620, 1289, 1098 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.69 (s, 4H), 7.67 (d, J = 8.5 Hz, 4H), 7.47(d, J = 8.4 Hz, 4H), 3.56 (br s, 4H), 3.35 (br s, 4H), 1.22 (br s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 141.4, 139.7, 136.4, 127.6, 127.0, 43.4, 39.4, 14.4, 13.0. Anal. Calcd for $C_{28}H_{32}N_2O_2$: C, 78.47; H, 7.53; N, 6.54. Found: C, 78.55; H, 7.50; N, 6.47.

***p*-(4-(*p*-Diethylcarbamoylphenyl)-1,3-butadiynyl)-*N*,*N*-diethylbenzamide (G18).**[20] To a degassed solution of *N*,*N*-diethyl-4-bromobenzamide (2.55 g, 9.92 mmol) were added 2-methyl-3-butyn-2-ol (2.9 mL, 30 mmol), CuI (0.19 g, 1.0 mmol), and $(PPh_3)_4Pd$ (0.32 g, 0.28 mmol) in Et_2NH (50 mL) under argon. The solution was heated at reflux for 11 h, cooled to room temperature, and concentrated by rotary evaporation. The residue was dissolved in EtOAc (50 mL), filtered, and purified by flash column chromatography (EtOAc/hexanes 1:1) to give *p*-(3-hydroxy-3-methyl-1-butynyl)-*N*,*N*-diethylbenzamide as a pale yellow oil (1.64 g, 64%) that was slightly contaminated with some impurity.

(27) Nielsen. D. R.; McEwen. W. E. *J. Am. Soc. Chem.* **1957**, *79*, 3081−3084.

Without further purification, a suspension of *p*-(3-hydroxy-3-methyl-1-butynyl)-*N*,*N*-diethylbenzamide and KOH (0.39 g, 7.0 mmol) in toluene (15 mL) was heated at reflux for 1 h. The mixture was filtered and concentrated to afford *p*-acetylenyl-*N*,*N*-diethylbenzamide (0.65 g, 51%) as pale brown oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H) 3.53 (br s, 2H), 3.24 (br s, 2H), 3.13 (s, 1H.), 1.26 (br s, 3H), 1.13 (br s, 3H).

Tetramethylethylenediamine (0.28 mL, 1.9 mmol) was added to a suspension of CuCl (0.056 g, 0.57 mmol) in acetone (10 mL) under argon and stirred for 30 min at room temperature, and then the resulting mixture was slowly added to an acetone (20 mL) solution of *p*-ethynyl-*N*,*N*-benzamide (0.5 g, 2.5 mmol) at 0 °C (ice−water bath). The mixture was stirred for 20 h under oxygen and concentrated. The residue was redissolved in EtOAc (20 mL) and washed sequentially with 1 N HCl (20 mL), water (20 mL × 2), and brine. The crude product was purified by flash column chromatography (EtOAc/hexanes 1:1) to afford the desired product **G18** as a pale yellow solid (0.26 g, 53%): mp 123−124 °C; IR (KBr) 2973, 1623, 1287, 1092 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (d, J = 8.3 Hz, 4H), 7.35 (d, J = 8.3 Hz, 2H) 3.53 (br s, 4H), 3.24 (br s, 4H), 1.25 (br s, 6H), 1.12 (br s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 138.0, 132.7, 126.6, 122.6, 81.4, 74.9, 43.3, 39.4, 14.3, 12.9. Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05; N, 6.99. Found: C, 77.96; H, 7.01; N, 6.95.

^{1}H NMR Titrations. Chloroform was stored over 4 Å molecular sieves, and filtered through basic alumina prior to use. A 1.0−5.0 mM solution of the host and 10−50 mM solution of guest in $CDCl_3$ (1.5−2 mL) were separately prepared where the concentrations were decided on the basis of the magnitude of the association constant approximately estimated by a rough pretitration. A 500 μL portion of the host solution was transferred to a NMR tube, and an initial NMR spectrum was taken to determine the initial chemical shift (δ_{free}) of free host. Aliquots of the guest solution (10 μL initially, then 20−30 μL, and finally 50−100 μL) were added to the host solution. The spectrum was recorded after each addition, and overall 15−20 data points were obtained. The association constants (K_a) were determined by using the nonlinear least-squares fitting of the titration curves plotting $\Delta\delta$ of the host NH signals against the molar equivalent of the guest. All of the titration curves were well fitted to the expression of a 1:1 binding isotherm shown below.

$$H + G \overset{K_a}{\rightleftharpoons} HG$$

$$\Delta\delta = \frac{\Delta\delta_{max}}{2[H]}[K_a^{-1} + [H]_t + [G]_t] - \sqrt{(K_a^{-1} + [H]_t + [G]_t)^2 - 4[H]_t[G]_t}$$

$$\chi^2 = \sum(\Delta\delta_{calcd} - \Delta\delta_{obsd})^2$$

Here, $[H]_t$ and $[G]_t$ are the total concentrations of host and guest, and K_a is the association constant. The $\Delta\delta$ is the chemical shift change at the each titration point, and the $\Delta\delta_{max}$(calcd) and $\Delta\delta_{max}$(obsd) are the calculated and observed maximum chemical shift change when complexation is completed. Minimizing the sum of the squared deviations χ^2 affords the association constant (K_a), along with $\Delta\delta_{max}$(calcd).

Stoichiometry by Job plots. Stock solutions of host (5.0 mM) and guest (5.0 mM) in $CDCl_3$ (4 mL) were prepared in separate volumetric flasks. Ten 5 mm o.d. NMR tubes were separately filled with 500 μL total solution of the host and guest in the following ratios (μL, host/guest): 500:0, 450:50, 400:100, 350:150, 300:200, 250:250, 200:300, 150:350, 100:400, 50:450. The ^{1}H NMR spectra were obtained for each tube and the host NH signal was used to calculate the complex concentration, $[HG] = [H]_t(\delta_{obsd} - \delta_{free})/(\delta_{com} - \delta_{free})$. This value was plotted again the mole fraction of the guest, and the resulting curve always showed a maximum at 0.5 mol fraction, indicative of host/guest 1:1 binding.

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