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Guest recognition of a tetrapyridinohemicarcerand through hydrogen bonding and constrictive binding interactions

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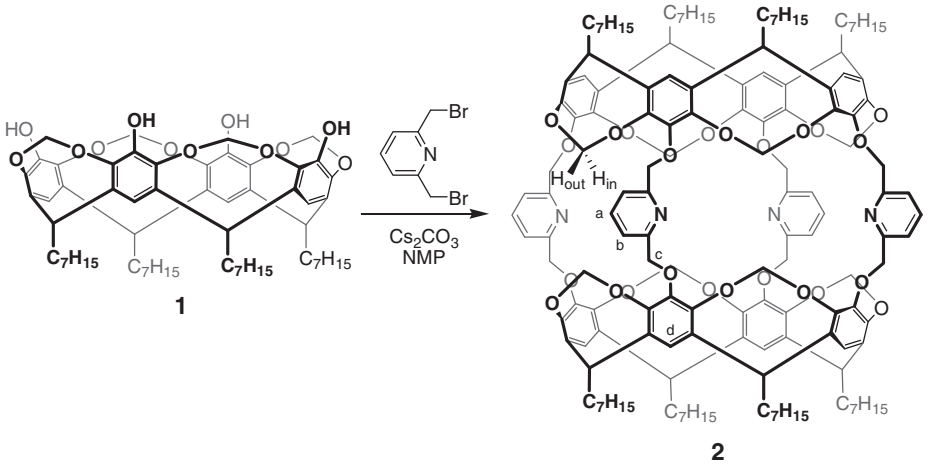
ABSTRACT

Tetrapyridinohemicarcerand **2** having four hydrogen-bonding acceptors of inward-directing pyridyl units was synthesized and their binding properties for a variety of organic guest molecules have been investigated. Tetrapyridinohemicarcerand **2** formed kinetically stable complexes with various sulfonic acids via intermolecular $-SO_3H$–pyridyl hydrogen bonding and constrictive binding interactions in $C_2D_2Cl_4$ at 25 °C. But carboxylic acids or alcohols cannot be a stable guest at the same conditions. Tetrapyridinohemicarcerand **2** also binds various disubstituted benzenes. Especially 1,4-diiodobenzene forms stable hemicarceplex 1,4-diiodobenzene@**2**, which seems to be stabilized by constrictive binding as well as by –C–H···I interactions between dioxymethylene of **2** and iodo group of guest.

Container molecules control the dynamics of guest molecules to enter or leave their inner cavity by the height of their activation energy barriers of complexation and decomplexation which depend on the comparative size of portals and binding interactions between two partners. These characteristic properties have allowed them to function as molecular reactor, selective storage, and delivery or controlled-releasing system in the field of supramolecular chemistry.[1]

Most organic container molecules bind their complementary guests mainly by constrictive binding which gives a maximum van der Waals interaction through maximum close contact.[2,3] The introduction of additional secondary noncovalent interactions such as hydrogen-bonding or charge-dipole interaction could improve the stability and selectivity of container molecules.[4]

Resorcin[4]arene-based C_{4h} hemicarcerand **2**[5] having potential four-way hydrogen-bonding acceptors of four inward-directing



Scheme 1. Synthesis of tetrapyridinocavitand **2**.

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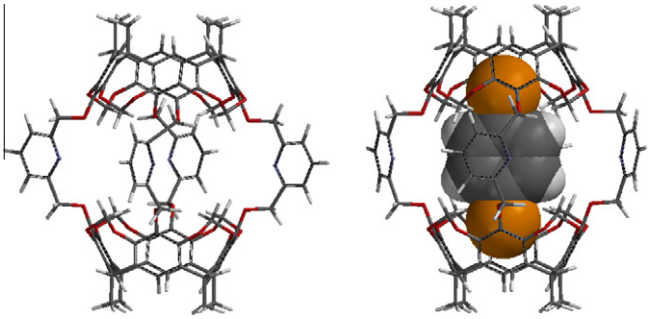


Figure 1. The energy-minimized structures of tetrapyridinohemicarcerand **2** (left) and hemicarceplex 1,4-diiodobenzene@**2** (right) using Spartan'04 V1.03 (Molecular Mechanics MMFF).

pyridyl units on equatorial region was synthesized by the shell-closing reaction between tetrol **1**[6] and 2,6-bis(bromomethyl)pyridine in a mixture of Cs_2CO_3/NMP at 60 °C in 8% yield (Scheme 1).

The energy-minimized structures of tetrapyridinohemicarcerand **2** using Spartan'04 V1.03 (Molecular Mechanics MMFF) showed four pyridyl groups on equatorial region are directing inward and the cavity is large enough for 1,4-diiodobenzene (Fig. 1).

The complexation phenomena of tetrapyridinohemicarcerand **2** were observed by ^{1}H NMR spectroscopy in $C_2D_2Cl_4$ at 25 °C (Fig. 2a–d). The addition of 4 equiv sulfonic acids to tetrapyridinohemicarcerand **2** solution gave new signals corresponding to the protons of the complexed guests. The 2:1 integration ratio of complexed CH_3SO_3H and hemicarcerand **2** and the two singlets of complexed CH_3SO_3H at −1.60 and −1.83 ppm on ^{1}H NMR spectrum support the formation of a 2:1 hemicarceplex (2 CH_3SO_3H@**2**). When hemicarcerand **3**[6] with three butylene and a pyridyl bridging units was employed under the same conditions, only one CH_3SO_3H was complexed (CH_3SO_3H@**3**). For hemicarcerand **4**[5] having *m*-phenyl bridging units and free from hydrogen-bonding acceptor, no complexation with sulfonic acids was observed. These results support the importance of hydrogen bonding for the complexation between hemicarcerands **2** or **3** and sulfonic acids.

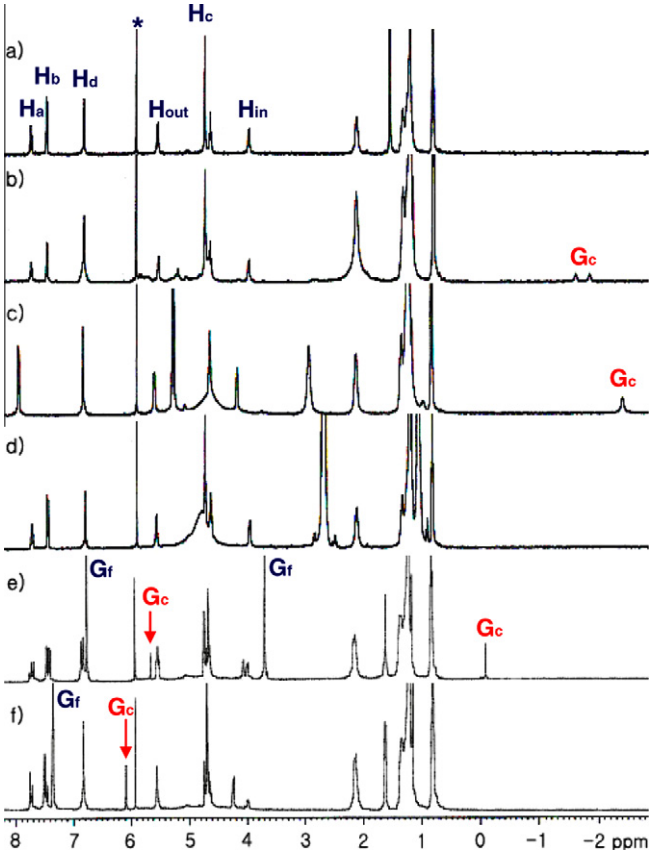
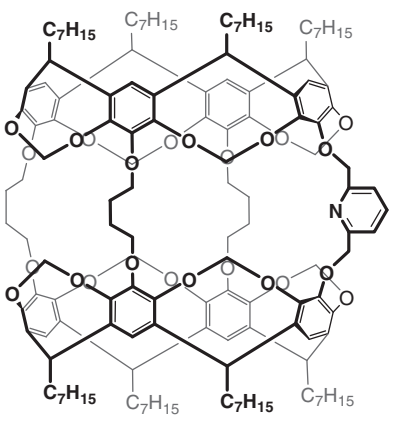


Figure 2. ^{1}H NMR (400 MHz) spectra in $C_2D_2Cl_4$ at 25 °C; (a) $C_2D_2Cl_4$@**2** (2 mM), (b) $C_2D_2Cl_4$@**2** + 4 equiv of CH_3SO_3H, (c) $C_2D_2Cl_4$@**2** + 4 equiv of $CH_3CH_2SO_3H$, (d) ($C_2D_2Cl_4$@**2** + 4 equiv of $CH_3CH_2SO_3H$) + 6 equiv NEt_3, (e) $C_2D_2Cl_4$@**2** + 4 equiv of 1,4-dimethoxybenzene, (f) $C_2D_2Cl_4$@**2** + 4 equiv 1,4-diiodobenzene: (*) solvent peak, G_f = free guest, G_c = complexed guest.



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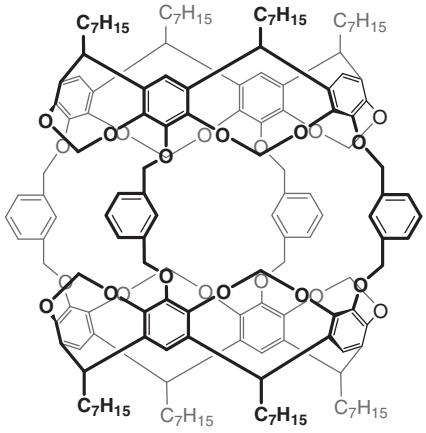

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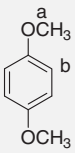
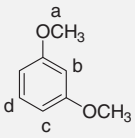
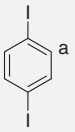
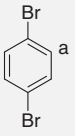
For the larger $CH_3CH_2SO_3H$, a 1:1 hemicarceplex ($CH_3CH_2SO_3H$@**2**) was formed. The complexation and decomplexation of a hemicarceplex stabilized by hydrogen-bonding could be dynamically controlled by the pH switching (Fig. 2c and d). When NEt_3 was added to the $C_2D_2Cl_4$ solution of hemicarceplexes $CH_3CH_2SO_3H$@**2** or 2 CH_3SO_3H@**2**, the proton resonance signals of the complexed sulfonic acids disappeared completely. But when more sulfonic acid was added to the same solution, the signals of complexed sulfonic acid were detected again. These reversible guest exchanges could be observed until the acid-catalyzed

Table 1
^{1}H NMR chemical shift changes (ppm) of free and complexed guests in host **2** and the association constants K_a (M^{-1}) (400 MHz, $C_2D_2Cl_4$, 25 °C)

Guest	H	Free δ	Compl δ	$\Delta\delta$	K_a (M^{-1})
a CH_3SO_3H	a	3.07	−1.60 −1.83	4.67 4.90	—[a]
a b $CH_3CH_2SO_3H$	a b	1.21 2.99	−2.42 0.97	3.63 2.02	—[a]
	a b	3.67 6.76	−0.16 5.64	3.85 1.12	99
	a b c d	3.67 6.37 6.43 7.11	−0.10 5.27 5.52 6.18	3.77 1.10 0.91 0.93	63
	a	7.34	6.06	1.28	323
	a	7.29	6.06	1.23	13

[a] 100% complexation.

decomposition of dioxymethylene bridges (–OCH_2O–) in hemicarcerand **2**. These pH-controlled reversible complexation phenomena were similar to those for hemicarcerand **3**.[6]

Tetrapyridinohemicarcerand **2** did not form kinetically stable complexes via intermolecular –O–H···pyridyl hydrogen-bonding with other hydrogen-bonding donors such as carboxylic acids or alcohols. Even bis- or tris-carboxylic acids cannot be a guest in tetrapyridinohemicarcerand **2**. It seems that for the guests of lower acidity the constrictive binding property of tetrapyridinohemicarcerand **2** is larger than the hydrogen-bonding interaction between tetrapyridinohemicarcerand **2** and guest, which prefers a hemicarceplex with $C_2D_2Cl_2$ which is in large excess and a better complementary than carboxylic acids or alcohols.

Tetrapyridinohemicarcerand **2** also binds various disubstituted benzenes (Figs. 1 and 2e and f). The complexations with these guests were observed in $C_2D_2Cl_4$ at 25 °C. High structural recognition in complexation was observed; tetrapyridinohemicarcerand **2** prefers *p*-disubstituted benzene to *o*- and *m*-disubstituted benzenes as guest. The complexation with *o*-disubstituted benzene was not observed. For 1,4-dimethoxybenzene@**2**, the methyl protons and aryl protons of the guest appeared at −0.16 ppm ($\Delta\delta$ = 3.85 ppm) and 5.64 ppm ($\Delta\delta$ = 1.12 ppm), respectively, which implies that methyl groups are close to the host's aromatic shells and the aryl hydrogens are located near the host's equatorial region.

Table 3
Thermodynamic parameters for complexation of host **2** in $C_2D_2Cl_4$ at 25 °C

	ΔG (kcal mol^{-1})	ΔH (kcal mol^{-1})	ΔS (cal mol^{-1} K^{-1})
1,4-Dimethoxybenzene@**2**	−2.72	−5.25	−7.59
1,3-Dimethoxybenzene@**2**	−2.45	−1.52	2.82
1,4-Diiodobenzene@**2**	−3.42	−9.59	−18.8

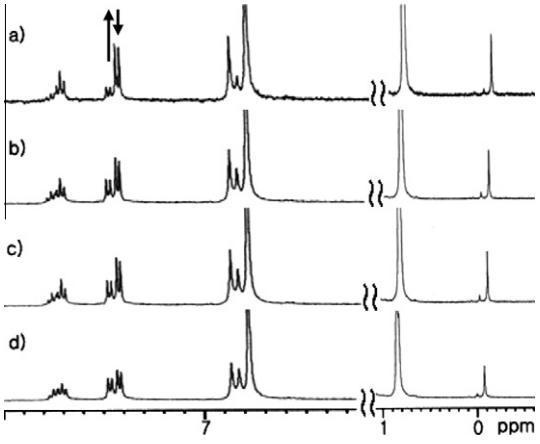


Figure 3. The partial ^{1}H NMR (400 MHz) spectra in $C_2D_2Cl_4$ at 25 °C showing the change of complexation ratio of 1,4-dimethoxybenzene@**2** ([**2**] = 2 mM, [1,4-dimethoxybenzene] = 0.25 mM): (a) 5 min, (b) 30 min, (c) 60 min, (d) 360 min (↑ = $C_2D_2Cl_4$@**2**, ↓ = 1,4-dimethoxybenzene@**2**).

Table 1 shows the chemical shift changes of guests and the association constants K_a (M^{-1}) of hemicarceplexes G@**2** in $C_2D_2Cl_4$ at 25 °C. The $\Delta\delta$ values of methyl protons in guests were observed ranging from $\Delta\delta$ = 3.63 to 4.90 ppm. The largest $\Delta\delta$ = 4.90 ppm for CH_3SO_3H supports the proximity of a methyl to the host's aromatic shell due to the steric repulsion between two CH_3SO_3H. The size (–OCH_3 > –I > –Br > –Cl) and the shape (*para*- > *meta*-, ≫ *ortho*-) of substituents play important roles in the stability of hemicarceplex. The K_a values (M^{-1}) of 1,4-dihalobenzene@**2** are 323, 13, and negligible for iodo-, bromo-, and chloro-, respectively. The most stable hemicarceplex 1,4-diiodobenzene@**2** seems to be stabilized by constrictive binding as well as by –C–H···I– interactions between CH_{in} of dioxymethylene bridges (–$OCH_{in}H_{out}O$–) of host and iodo group of guest.[7]

The chemical shifts of main-body hydrogens (H_{in}, H_{out}, and H_{a-d}) change upon complexation (Table 2). The inner protons of dioxymethylene bridges (–$OCH_{in}H_{out}O$–) in tetrapyridinohemicarcerand **2** showed the downfield shifts ($\Delta\delta$ = −0.04 to −0.25 ppm) upon

Table 2
^{1}H NMR (400 MHz) spectral chemical shift changes (ppm) of hemicarcerand **2**'s guest sensitive protons and the differences between the chemical shifts of free and complexed hosts ($\Delta\delta$)[a] in $C_2D_2Cl_4$ at 25 °C

Guest	Chemical shifts (ppm)					
	H_{in}	H_{out}	H_a	H_b	H_c	H_d
None	3.97	5.52	7.73	7.44	4.72	6.80
1,4-Dimethoxybenzene	4.04 (−0.07)	5.50 (0.02)	7.68 (0.05)	7.40 (0.04)	4.65 (0.07)	6.84 (−0.04)
1,3-Dimethoxybenzene	4.02 (−0.05)	5.57 (−0.05)	7.71 (0.02)	7.46 (−0.02)	4.70 (0.02)	6.83 (−0.03)
1,4-Diiodobenzene	4.22 (−0.25)	5.52 (0.00)	7.73 (0.00)	7.41 (0.03)	4.68 (0.04)	6.80 (0.00)
1,4-Dibromobenzene	4.01 (−0.04)	5.52 (0.00)	7.73 (0.00)	7.44 (0.00)	4.66 (0.06)	6.80 (0.00)

[a] $\Delta\delta = \delta_{free} - \delta_{complexed}$.

complexation. Especially the largest $\Delta\delta = -0.25$ ppm for CH_{in} of hemicarceplex 1,4-diiodobenzene @2 supports that its chemical shift change is due to C–H···I interactions, but not due to heavy atom effect of iodo which usually results up-field shift for near protons. All the H_c protons, which are close to complexed guest, showed the upfield shifts ranging from $\Delta\delta = 0.02$–0.07 ppm due to the ring current effect of aromatic guests.

Table 3 shows thermodynamic parameters for complexation obtained from Van't Hoff equation by variable-temperature ^{1}H NMR experiments. The complexations of 1,4-dimethoxybenzene and 1,4-diiodobenzene are enthalpically favored but entropically disfavored. But the complexations of 1,3-dimethoxybenzene are enthalpically and entropically favored.

When $C_2D_2Cl_4$ NMR solvent was added to the mixture of tetrapyridinohemicarcerand **2** and 4 equiv 1,4-dimethoxybenzene guest at 25 °C, the complexation ratio changes as time goes (Fig. 3). The ratio of two hemicarceplexes ([1,4-dimethoxybenzene@**2**]:[$C_2D_2Cl_4$@**2**]) changes from 96:4 (taken within 5 min) to 52:48 (taken after 6 h), which suggests that hemicarceplex 1,4-dimethoxybenzene@**2** is a kinetic product, but not a thermodynamic product in a large excess of $C_2D_2Cl_4$.

In summary, tetrapyridinohemicarcerand **2** having four inward-directing pyridyl bridging units as potential hydrogen-bonding acceptors was synthesized and their binding properties for various guest molecules were characterized. Tetrapyridinohemicarcerand **2** formed kinetically stable hemicarceplexes with various sulfonic acids through intermolecular –SO_3H···pyridyl hydrogen bonding and constrictive binding interaction and with various disubstituted benzenes through constrictive binding interaction. The stability order of hemicarceplexes G@**2** in $C_2D_2Cl_4$ at 25 °C decreases as follow; sulfonic acids@**2** ≫ 1,4-diiodobenzene@**2** ≫ 1,4-dimethoxybenzene@**2** > 1,3-dimethoxybenzene@**2** > 1,4-dibromobenzene@**2**.

Acknowledgments

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5. *Compound* **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 6.8 Hz, 24H, –CH_3), 1.25–1.43 (m, 80H, –$(CH_2)_5$–), 2.20 (m, 16H, –CH_2–), 4.21 (d, J = 6.8 Hz, 8H, –$OCH_{in}H_{out}O$–), 4.74 (t, J = 8.0 Hz, 8H, –CH–), 4.97 (s, 16H, –OCH_2–Py), 5.61 (d, J = 6.8 Hz, 8H, –$OCH_{in}H_{out}O$–), 6.82 (s, 8H, ArH), 7.50 (d, J = 7.6 Hz, 8H, PyH), 7.79 (t, J = 7.6 Hz, 4H, PyH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.7, 27.9, 29.4, 29.8, 30.0, 31.9, 37.0, 75.9, 100.1, 114.0, 120.9, 137.4, 138.9, 144.5, 147.4, 157.0; Maldi-TOF MS m/z 2398.3 (M+H); Anal. Calcd (%) for $C_{148}H_{180}N_4O_{24}$: C, 74.10; H, 7.56; N, 2.34. Found: C, 74.13; H, 7.49; N, 2.32.
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