Molecular engineering. Part 5.[1] Tuning the constrictive binding of container host by the atomic order of portal pillars

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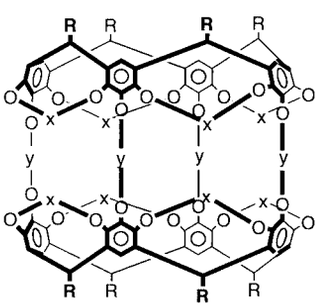
Two D_{4h} container hosts **12** and **13** with 4(CH_2–O–bridge–O–CH_2) portal pillars were obtained in good yields by stepwise synthetic routes and showed complementary complexation behaviors to their analogues with (O–CH_2–bridge-CH_2–O)$_4$ portal pillars. ^{1}H NMR spectral chemical shifts of host's inward-turned OCH_2O protons were sensitive to guest change. The stability orders of hemicarceplexes were **12**–*p*-$(CH_3CH_2)_2C_6H_4$ > **12**–*p*-$(CH_3O)_2C_6H_4$ ≫ **12**–*o*-$(CH_3O)_2C_6H_4$ > **12**–*m*-$(CH_3O)_2C_6H_4$ and **13**–$CH_3COCH_2CH_3$ > **13**–$CH_3COCH_2CH(CH_3)_2$ > **13**–$CH_3CON(CH_3)_2$ > **13**–$CH_3COOCH_2CH_3$ > **13**–$CH_3CH_2CON(CH_3)_2$ in terms of the activation energy barrier for decomplexation. Large solvent effects on the activation energy for decomplexation of hemicarceplexes were observed.

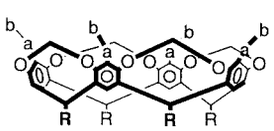
Introduction

Since the pioneering work of Professor Cram on container molecules numerous carceplexes and hemicarceplexes have been studied as a new phase of matter.[2] The mechanisms of the shell closing reaction[3] and the decomplexation process[4] have been extensively studied. Mainly three strategies have been adopted for the dynamic control of complexation–decomplexation processes: the number of portal pillars, the length of the portal pillars, and the dimensions of the hemispheres. Various tuning strategies on complexation–decomplexation dynamics between container hosts and guests, such as redox or photochemical[5] switchable pillars, are necessary for the practical application of these systems as analytical devices, timed release or delivery systems, radiation diagnostics or therapy, or protected molecular reactors.

Most of the resorcin[4]arene-based typical container hosts such as **1**,[6] **2**,[7] **3**,[8,9] and **4**[8,9] are based on tetrol **5** and have (O–CH_2–bridge–CH_2–O)$_n$ (n = 2–4) portal pillars except in four cases.[10,11] To understand and manipulate the nature of the so-called constrictive binding, a mechanical inhibition of hemicarceplex decomplexation,[7,12] various types of pillars should be adopted and studied. The easy access to tetrabromide **7** allowed various new synthetic routes to noble container hosts[11,13] and here a new stepwise route to container hosts with 4(CH_2–O–bridge–O–CH_2) pillars and the kinetic properties of their hemicarceplexes are reported, which demonstrates a tuning of the constrictive binding through the atomic order of portal pillars.



1: x = y = CH_2
2: x = CH_2, y = *o*-$(CH_2)_2C_6H_4$
3: x = CH_2, y = *m*-$(CH_2)_2C_6H_4$
4: x = CH_2CH_2, y = *m*-$(CH_2)_2C_6H_4$



5 : a = O, b = H
6 : a = CH_2, b = H, R = propyl
7 : a = CH_2, b = Br, R = propyl

Results and discussion

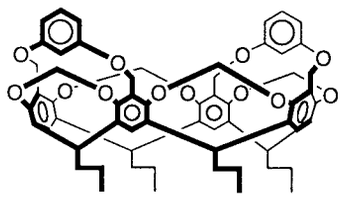
Tetrabromide **7** was efficiently obtained from tetramethylcavitand **6** by NBS bromination in refluxing CCl_4 in 90% yield.[11] When tetrabromide **7** was subjected to a one-pot shell-closing reaction with resorcinol in Cs_2CO_3–DMA or DMF mixture to obtain a hemicarcerand **12**, only intrabridged cavitand **8** was obtained in 27% yield. The same trial with **7** and catechol to get hemicarcerand **13** gave an unidentifiable mixture. Compared to the successful one-pot shell closing under similar conditions between tetrol **5** and α,α′-dibromo-*o*-xylene or α,α′-dibromo-*m*-xylene to give hemicarceplex **2** (~23%)[7] or **3** (~50%),[8] the solvent templation effect seems to be too weak to assemble two tetrabromide **7** molecules due to the large steric repulsions of its bromo groups.

As a step-wise approach tetrabromide **7** was reacted with an excess of resorcinol, catechol, or 2-methylresorcinol in a mixture of DMF–K_2CO_3 at 50 °C or refluxing CH_3CN–K_2CO_3 to give compounds **9**, **10**, and **11** in 50, 52, and 38% yields, respectively. The capping of compound **9** with tetrabromide **7** in a mixture of DMF–K_2CO_3 at room temperature gave free hemicarcerand **12** in 13% yield. The capping of compound **10** with tetrabromide **7** in the same reaction conditions gave no hemicarcerand **13**, but in a refluxing mixture of CH_3CN–K_2CO_3 free hemicarcerand **13** was obtained in 11% yield. The attempted capping of compound **11** with tetrabromide **7** under various conditions to obtain **14** was unsuccessful. The intended self-templating by the inward-turned four methyl groups of **11** or the corresponding reaction intermediates seems unfavorable.

Hemicarcerands **12** and **13** are analogues of hemicarcerands **3** and **2**, respectively. A Corey–Pauling–Koltun (CPK) molecular model suggests that new hosts **12** and **13** could stabilize incarcerated guests such as DMA, *p*-$(CH_3O)_2C_6H_4$ or *p*-xylene through their constrictive binding by twisting the two hemispheres in opposite directions which accordingly minimizes the dipole–dipole repulsion among oxygen atoms and maximizes the van der Waals interactions by close atom-to-atom contacts.

Hemicarceplexes **12**–guest and **13**–guest were obtained using the reported procedure.[7] Hemicarcerands **12** or **13** were dissolved in a guest solvent. The solution was stirred at 120 °C or at boiling temperature for 2 days, cooled, and then MeOH was added to give a precipitate, which was filtered and dried at room temperature. ^{1}H NMR spectra showed that 58–100% of host was complexed.

Table 1 shows the complexation ratios and ^{1}H NMR spectral



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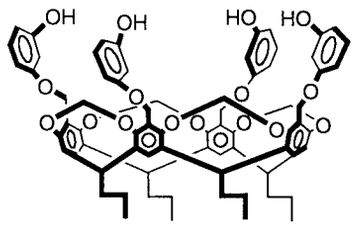

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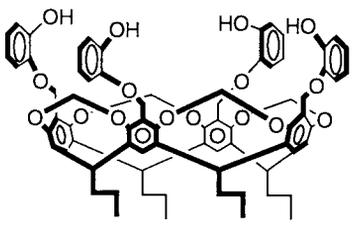

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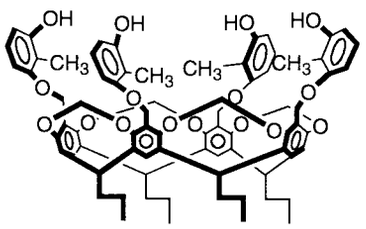

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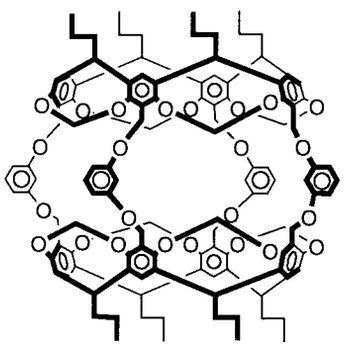

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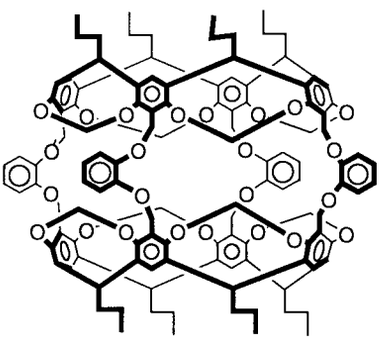

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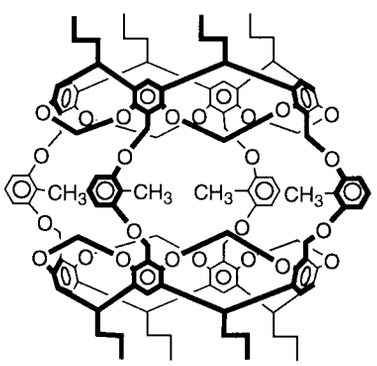

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Table 1 Effect of guest changes on the ^{1}H NMR spectral chemical shifts ($CDCl_3$, 400 MHz, 25 °C) of the inward-turned OCH_2O protons of hosts **12** and **13**

Hemicarceplex **12**			Hemicarceplex **13**		
Guest	obsd δ (%)[a]	$\Delta\delta$[b]	Guest	obsd δ (%)[a]	$\Delta\delta$[b]
None	4.55 (0%)		None	4.30 (0%)	
p-$(CH_3O)_2C_6H_4$	4.35 (100%)	0.20	$CH_3COCH_2CH_3$	4.17 (79%)	0.13
o-$(CH_3O)_2C_6H_4$	4.32 (70%)	0.23	$CH_3COOCH_2CH_3$	4.24 (100%)	0.06
p-$(CH_3CH_2)_2C_6H_4$	4.10 (100%)	0.45	$CH_3CON(CH_3)_2$	4.28 (64%)	0.02
1,2,4,5-$(CH_3)_4C_6H_2$	4.41 (58%)	0.14	$CH_3CH_2CON(CH_3)_2$	4.26 (93%)	0.04
			$CH_3COCH_2CH(CH_3)_2$	4.36 (100%)	−0.06
			Pyrazine	4.24 (84%)	0.06

[a] Complexation ratio from the peak integrations of guest's Me and/or host's inward-turned OCH_2O. [b] $\Delta\delta = \delta_{free} - \delta_{complex}$.

chemical shifts of the inward-turned OCH_2O protons of hemicarceplexes **12** and **13** in $CDCl_3$ at 25 °C. High structural recognition in complexation was observed for hemicarcerand **12** to favor binding *p*-disubstituted as compared to *o*- and *m*-disubstituted benzenes as guests. The formation of hemicarceplexes **3**–G (G = *o*-, *m*-, and *p*-$(MeO)_2C_6H_4$) failed,[9] which implies that hemicarcerands **3** and **12** are complementary in their complexation properties. Hemicarcerand **13** also formed stable hemicarceplexes with linear guests having 6–7 heavy atoms, but was less adaptable in complexation than host **2**. The $\Delta\delta$ values of hemicarceplexes **12** decreased in the order 0.45 for **12**–*p*-$(CH_3CH_2)_2C_6H_4 \gg$ 0.20 for **12**–*p*-$(CH_3O)_2C_6H_4 >$ 0.19 for **12**–*o*-$(CH_3O)_2C_6H_4 >$ 0.14 for **12**–1,2,3,4-$(CH_3)_4C_6H_2$, which is the same as the order of decreasing kinetic stability. The more hemicarceplex **12**–guest is stretched by the guest, the more the inward-turned OCH_2O proton of **12** is upfield-shifted. The $\Delta\delta$ values of hemicarceplexes **13** were not consistent with the size or shape of guest and were generally less significant except that for $CH_3COCH_2CH_3$, which might be due to the smaller conformational change of hemicarcerand **13** compared to hemicarcerand **12** upon complexation.

Table 2 Chemical shift changes of guest in hemicarceplexes **12**–G and **13**–G ($CDCl_3$, 400 MHz, 25 °C)

Guest	H	δ_{free}	δ_{comp}	$\Delta\delta$
Hemicarcerand **12**				
p-$(CH_3O)_2C_6H_4$	a	3.75(s)	0.55(d)	3.20
a b	b	6.82(s)	6.33(s)	0.49
m-$(CH_3O)_2C_6H_4$	a	3.78(s)	0.58(d)	3.20
a b	b	6.50(m)	5.72(m)	0.78
o-$(CH_3O)_2C_6H_4$	a	3.89(s)	2.30	1.59
a b	b	6.92(m)	6.09(b)	0.83
p-$(CH_3CH_2)_2C_6H_4$	a	1.24(t)	−2.53(t)	3.77
a b c	b	2.61(q)	1.64(m)	0.97
	c	7.09(s)	6.78(s)	0.31
1,2,4,5-$(CH_3)_4C_6H_2$	a	2.17(s)	1.05(s)	1.12
a b	b	6.89(s)	6.46(s)	0.43
Hemicarcerand **13**				
$CH_3COCH_2CH_3$	a	2.15(s)	−0.35(s)	2.50
a b c	b	2.45(q)	1.13(s)	1.32
	c	1.05(t)	−2.02(s)	3.07
$CH_3COOCH_2CH_3$	a	2.08(s)	−0.54(q)	2.62
a b c	b	4.10(q)	—	—
	c	1.25(t)	−2.28	3.53
$CH_3CON(CH_3)_2$	a	2.09(s)	−0.60(s)	2.69
a b(*trans*)	b	2.94(s)	—	—
c(*cis*)	c	3.02(s)	0.09(s)	2.93
$CH_3CH_2CON(CH_3)_2$	a	1.14(t)	−2.39(m)	3.53
a b c(*trans*)	b	2.34(q)	0.62	1.72
d(*cis*)	c	2.95(s)	0.24	2.71
	d	3.00(s)	−0.32(two s)	3.32
$CH_3COCH_2CH(CH_3)_2$	a	2.11(s)	−1.45(m)	3.56
a b c d	b	2.30(q)	—	—
	c	0.91(s)	—	—
	d	0.91(s)	−1.65(two s)	2.56
Pyrazine a	a	8.60(s)	5.84(s)	2.76

Table 2 shows the chemical shift changes of the guest in hemicarceplexes **12** and **13** in $CDCl_3$ at 25 °C. The $\Delta\delta$ values of guest illustrate its orientation in the host. The methyl and aryl groups of the guest in **12**–*p*-$(CH_3CH_2)_2C_6H_4$ gave the largest $\Delta\delta$ 3.77 and the smallest $\Delta\delta$ 0.31, which implies that the methyl groups are mostly close to the host's aromatic shell and that the aryl hydrogens are quite strictly staying around the host's tropical region. The straightest orientation of *p*-$(CH_3O)_2C_6H_4$ through the C_4 axis among the three isomers, *p*-$(CH_3O)_2C_6H_4$, *m*-$(CH_3O)_2C_6H_4$, and *o*-$(CH_3O)_2C_6H_4$, can also be seen from its largest $\Delta\delta$ for the methoxy group (3.20) and the smallest $\Delta\delta$ for the aryl hydrogens (0.49). In hemicarcerand **13**, the larger guest showed the larger $\Delta\delta$ in general, $CH_3COCH_2CH(CH_3)_2 > CH_3CH_2CON(CH_3)_2 \geq CH_3COOCH_2CH_3 > CH_3COCH_2CH_3 > CH_3CON(CH_3)_2 >$ pyrazine.

Table 3 shows the half-lives (h) for decomplexation of hemicarceplexes **12**–guest at different solvents and temperatures as well as their activation energies, which were determined from the concentration decrease of the incarcerated guest in ^1H NMR spectra. The order of stability of hemicarceplexes is **12**–*p*-$(CH_3CH_2)_2C_6H_4 >$ **12**–*p*-$(CH_3O)_2C_6H_4 \gg$ **12**–*o*-$(CH_3O)_2C_6H_4 >$ **12**–*m*-$(CH_3O)_2C_6H_4$. Hemicarceplex **12**–*m*-$(CH_3O)_2C_6H_4$ was too labile to determine the pseudo-first order decomplexation rate constant (k) in $CDCl_3$ at room temperature. It seems that *m*-$(CH_3O)_2C_6H_4$ has the optimal geometry for moving through the portal of **12**. The stability of the *p*-isomers may be due to the egg-shaped cavity of **12** which helps to hold a linear guest snugly. It is reported that the attempt to obtain the analogous **4**–$(CH_3O)_2C_6H_4$ was unsuccessful for *m*- and *p*-isomers and **4**–*o*-$(CH_3O)_2C_6H_4$ was indefinitely stable at 25 °C in $CDCl_3$,[9] and the stability order of **4**–xylene was reported to be *m*- < *p*- < *o*-xylene, even though **12**–xylene was not stable enough to be isolated. This is presumably due to the rather flat orientation of the hemispheres and the steric crowding at the portals of host **4** compared to those of host **12**, which also makes hosts **4** and **12** complementary to each other in their complexation abilities.

Notice that the solvent effect on E_a of decomplexation is striking. When G = *p*-$(CH_3O)_2C_6H_4$, E_a (kJ mol^{-1}) in polar solvents (49 in C_5D_5N and 43 in $C_6H_5NO_2$) is substantially lower than in nonpolar solvents (70 in $CDCl_3$ and 63 in $C_2D_2Cl_4$). But when G = *p*-$(CH_3CH_2)_2C_6H_4$, the results were reversed. In particular, E_a values in polar solvents increased more than 34 kJ mol^{-1} (83 in C_5D_5N and 79 in $C_6H_5NO_2$). These results coincide with Cram's conclusion that the transition state of the container host's decomplexation process is product-like, which means that polar solvents favour the decomplexation of polar guest and disfavour that of the nonpolar guest and *vice versa*.

Table 4 shows the half-lives (h) for the decomplexation of

Table 3 Half-lives for decomplexation of **12**–G and its activation energy in various solvents[a]

		$t_{1/2}$/h								
Hemicarceplex	Solvent	25 °C	35 °C	45 °C	55 °C	65 °C	75 °C	85 °C	95 °C	E_a/kJ mol^{-1}[b]
12–*p*-$(CH_3O)_2C_6H_4$	$CDCl_3$	3.85	1.93	0.64						70.9
	$C_2D_2Cl_4$		0.96	0.48	0.21					63.1
	C_6D_5N			0.96	0.64	0.38				49.3
	$C_6D_5NO_2$				0.96	0.64	0.39			43.8
12–*p*-$(CH_3CH_2)_2C_6H_4$	$CDCl_3$		2.75	0.96	0.48					73.3
	$C_2D_2Cl_4$			1.93	0.96	0.48				65.8
	C_6D_5N					0.64	0.39	0.12		83.9
	$C_6D_5NO_2$						2.14	0.96	0.48	79.4
12–*o*-$(CH_3O)_2C_6H_4$	$CDCl_3$	0.48								—

[a] Estimated error <10%. [b] Calculated from least-squares fit to straight line.

Table 4 Half-lives for decomplexation of **13**–G and its activation energy in various solvents[a]

Hemicarceplex	Solvent	$t_{1/2}$/h 50 °C	60 °C	70 °C	80 °C	90 °C	100 °C	E_a/kJ mol^{-1}[b]
13–$CH_3COCH_2CH_3$	$C_2D_2Cl_4$	7.45	2.08	0.93				95.6
	C_6D_5N		1.18					
13–$CH_3COOCH_2CH_3$	$C_2D_2Cl_4$			8.89	6.42	2.82		59.2
	C_6D_5N		3.73					
13–$CH_3CON(CH_3)_2$	$C_2D_2Cl_4$			7.45	5.02		1.15	68.1
	C_6D_5N		2.68					
13–$CH_3COCH_2CH(CH_3)_2$	$C_2D_2Cl_4$	7.22	2.13	1.25				81.3
13–$CH_3CH_2CON(CH_3)_2$				3.39	1.96	1.17		55.1

[a] Estimated error < 10%. [b] Calculated from least-squares fit to straight line.

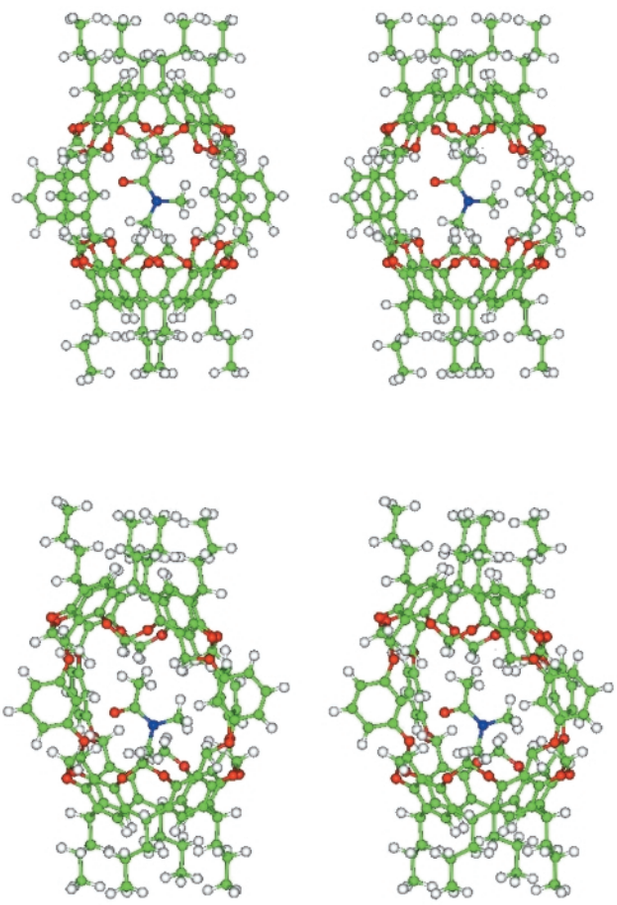

Fig. 1 The stereo-views of the energy-minimized (MM + force-field) structures of **3**–DMA (upper) and **12**–DMA (lower).

hemicarceplexes **13**–guest in different solvents and at different temperatures as well as their activation energies. Host **13** has a smaller sphere and portals than host **12** has and subsequently host **13** included smaller guests but its decomplexation activation energies are overall larger than those of **12**. The smallest, butan-2-one resulted in the largest E_a, 95.6 kJ mol^{-1}, which shows the efficient constrictive binding property of host **13**.

A molecular mechanics study using HyperChem® (MM + force-field) supports the idea that hemicarcerands **12** and **13** would have substantial intrinsic binding properties in the gas phase, $\Delta E = 19$ and 23 kcal mol^{-1} for *N*,*N*-dimethylacetamide, 19 and 16 kcal mol^{-1} for toluene, 24 and 21 kcal mol^{-1} for *p*-xylene, and 23 and 0 kcal mol^{-1} for *p*-dimethoxybenzene, respectively. Fig. 1 shows the stereo-views of the energy-minimized structures of **3**–DMA and **12**–DMA. Hemicarceplex **12**–DMA is more twisted to give better atom-to-atom close contacts between two hemispheres than **3**–DMA.

In conclusion, an efficient stepwise synthetic route for two container hosts with $(CH_2–O–bridge–O–CH_2)_4$ portal pillars and the potential of tuning of their constrictive binding properties through the atomic order of the portal pillars are reported. The host's portal adaptability to the shape of the guest for complexation–decomplexation was partially complementary between two hosts with $(CH_2–O–bridge–O–CH_2)_4$ and $(O–CH_2–bridge–CH_2–O)_4$ portal pillars.

Experimental

General details

All chemicals were reagent grade and used directly unless otherwise specified. All anhydrous reactions were conducted under an argon atmosphere. Melting points were measured on an Electrothermal 9100 apparatus and were uncorrected. IR spectra were taken with a Mattson 3000 FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Bruker Avance DPX300 (300 MHz), JEOL lambda-400 (400 MHz) or Bruker AMX-500 (500 MHz) instrument in $CDCl_3$ unless stated otherwise. Residual solvent protons were used as the internal standard and chemical shifts are given relative to tetramethylsilane (TMS). FAB mass spectra were run on an HR MS (VG70-VSEQ) at the Korea Basic Science Institute using *m*-nitrobenzyl alcohol as a matrix. Gravity column chromatography was performed on silica gel 60 (E. Merck, 70–230 mesh ASTM). Flash chromatography was performed on silica gel 60 (E. Merck, 230–400 mesh ASTM). Thin layer chromatography was done on silica plastic sheets (E. Merck, silica gel 60 F_{254}, 0.2 mm). Elemental analyses were performed by Galbraith Laboratories (Knoxville, Tennessee) and the Center for Biofunctional Molecules (Pohang, Korea).

1,21,23,25-Tetrapropyl-7,11,25,28-tetrakis(bromomethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (7)

Under an argon atmosphere, NBS (11.7 g, 65.5 mmol) and a catalytic amount of benzoyl peroxide were added to a solution of cavitand **6**[11] (10.0 g, 13.1 mmol) in CCl_4 (20 cm^3). The mixture was refluxed for 3–4 h. NBS gradually dissolved to give a light orange solution. The color slowly discharged with the precipitation of succinimide and the product around the flask. TLC conducted during the course of the reaction revealed the presence of the final product as well as two or three other spots presumably corresponding to mono, bis or tris bromocavitands, which disappeared as the reaction progressed. After the mixture was cooled to room temperature, EtOH (100 cm^3) was poured into the mixture and the precipitate was collected by filtration. The filtrate was dissolved in CH_2Cl_2, washed with water and brine, and then dried over $MgSO_4$. The residue was purified by silica gel column chromatography using CH_2Cl_2–hexane (1:2, v/v) to give a white solid product **7** (12.7 g, 90%), mp 228.5 °C (decomp.); δ_H (300 MHz; $CDCl_3$) 1.04 (12 H, t, CH_3), 1.32–1.45

(8 H, m, CH_2CH$_3$), 2.17–2.30 (8 H, m, CH$_2$), 4.42 (8 H, s, ArCH$_2$Br), 4.54 (4 H, d, *J* 6.7, inner OCH$_2$O), 4.81 (4 H, t, ArCH), 6.04 (4 H, d, *J* 6.7, outer OCH$_2$O), 7.16 (4 H, s, ArH).

Resorcinol-intrabridged cavitand (8)

Tetrabromocavitand **7** (100 mg, 0.09 mmol) and resorcinol (20 mg, 0.19 mmol) were dissolved in DMA (30 cm^3). This solution was added dropwise over 12 h to a stirred mixture of DMA (20 cm^3) and Cs_2CO_3 (300 mg, 0.92 mmol) at 60 °C. The mixture was stirred for another 24 h. After cooling to room temperature, 3 M HCl (50 cm^3) was poured into the reaction vessel and the mixture was extracted with CH_2Cl_2. The organic phase was washed with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 10% EtOAc in hexane as eluent to yield the product **8** (24 mg, 27%), mp 226 °C; δ_H (400 MHz; $CDCl_3$) 0.90 (6 H, t, CH$_3$), 1.06 (6 H, t, CH$_3$), 1.21 (4 H, m, CH_2CH$_3$), 1.47 (4 H, m, CH_2CH$_3$), 2.06 (4 H, m, CH$_2$), 2.28 (4 H, m, CH$_2$), 3.23 (2 H, d, *J* 7.1, cyclic inner OCH$_2$O), 4.27 (4 H, d, *J* 12.1, inner ArCH$_2$O), 4.37 (2 H, d, *J* 8.0, noncyclic inner OCH$_2$O), 4.60 (2 H, t, ArCH), 4.84 (2 H, d, *J* 7.1, cyclic outer OCH$_2$O), 5.01 (2 H, t, ArCH), 5.38 (4 H, d, *J* 12.1, outer ArCH$_2$O), 5.91 (2 H, d, *J* 8.0, noncyclic outer OCH$_2$O), 6.78 (4 H, d, ArH), 7.12 (4 H, s, ArH), 7.29 (2 H, t, ArH).

1,21,23,25-Tetrapropyl-7,11,25,28-tetrakis(3-hydroxyphenoxymethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (9)

Tetrabromocavitand **7** (3.0 g, 2.77 mmol), resorcinol (6.13 g, 55.7 mmol) and K_2CO_3 (9.62 g, 69.6 mmol) were dissolved in DMF (50 cm^3) and stirred at 50 °C for 1 d. The temperature was increased to 80 °C and the mixture was stirred for 1 d. After cooling to room temperature, the mixture was filtered through celite. The filtrate was evaporated under reduced pressure. The residue was dissolved in 3 M HCl and CH_2Cl_2. The organic phase was separated, washed with water and brine, and then dried over $MgSO_4$. After the concentration of the solvent, the crude mixture was purified by silica gel column chromatography using EtOAc–hexane (1:1, v/v) as an eluent to give the product **9** (1.67 g, 50%), which was recrystallized from CH_2Cl_2–hexane, mp 192 °C (decomp.) (Found: C, 71.08; H, 6.51. $C_{72}H_{72}O_{16}$·1/2EtOH·H_2O requires C, 71.03; H, 6.29%); ν_{max}/cm^{-1} 3410 (OH); δ_H (500 MHz; DMSO-d$_6$) 1.03 (12 H, t, CH$_3$), 1.34–1.38 (8 H, m, CH_2CH$_3$), 2.42–2.45 (8 H, m, CH$_2$), 4.46 (4 H, d, *J* 7.5, inner OCH$_2$O), 4.68–4.73 (12 H, m, ArCH and ArCH$_2$O), 5.76 (4 H, d, *J* 7.5, outer OCH$_2$O), 6.27–6.34 (12 H, m, resorcinol's ArH), 6.96 (4 H, s, ArH), 7.74 (4 H, s, OH); FAB$^+$ MS, *m*/*z* 1193 (M$^+$, 30%), 974 (M$^+$ − 2OC$_6$H$_4$OH, 60%).

1,21,23,25-Tetrapropyl-7,11,25,28-tetrakis(2-hydroxyphenoxymethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (10)

Tetrabromocavitand **7** (5.0 g, 4.64 mmol), catechol (10.0 g, 90.8 mmol) and K_2CO_3 (12.9 g, 93.3 mmol) were dissolved in DMF (60 cm^3) and stirred at 50 °C for 1 d. The temperature was increased to 80 °C and the mixture was stirred for 1 d. After cooling to room temperature, the mixture was filtered through celite. The filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and 3 M HCl. The organic phase was washed with water and brine and then dried over $MgSO_4$. After the concentration of the solvent, the residue was purified by silica gel column chromatography with EtOAc–hexane (1:5, v/v) as eluent to give the product **10** (2.9 g, 52%), mp 195 °C (decomp.) (Found: C, 71.49; H, 6.41. $C_{72}H_{72}O_{16}$·H_2O requires C, 71.39; H, 6.16%); ν_{max}/cm^{-1} 3430 (OH); δ_H (400 MHz; $CDCl_3$) 0.86 (12 H, t, CH$_3$), 1.22–1.27 (8 H, m, CH_2CH$_3$), 2.06–2.12 (8 H, m, CH$_2$), 4.37 (4 H, d, *J* 7.3, inner OCH$_2$O), 4.67–4.72 (12 H, m, ArCH and ArCH$_2$O), 5.37 (4 H, d, *J* 7.3, outer OCH$_2$O), 6.55–6.75 (16 H, m, catechol's ArH), 7.09 (4 H, s, ArH), 7.20 (4 H, s, OH); FAB$^+$ MS, *m*/*z* 1192 (M$^+$, 2%), 974 (M$^+$ − 2OC$_6$H$_4$OH, 95%).

1,21,23,25-Tetrapropyl-7,11,25,28-tetrakis(3-hydroxy-2-methylphenoxymethyl)-2,20:3,19-dimethano-1*H*,21*H*,23*H*,25*H*-bis[1,3]dioxocino[5,4-*i*:5′,4′-*i*′]benzo[1,2-*d*:5,4-*d*′]bis[1,3]benzodioxocine (11)

A solution of tetrabromocavitand **7** (1.0 g, 0.93 mmol), 2-methylresorcinol (2.3 g, 18.5 mmol) and K_2CO_3 (2.7 g, 19.5 mmol) in acetonitrile (50 cm^3) was refluxed for 3 d. The solvent was evaporated under reduced pressure and partitioned between CH_2Cl_2 and 3 M HCl. The organic phase was washed with water and brine and then dried over $MgSO_4$. After the concentration of the solvent, the residue was purified by silica gel column chromatography using EtOAc–hexane (1:1, v/v) as an eluent to give the product **11** (0.47 g, 38%), mp 165 °C (decomp.); ν_{max}/cm^{-1} 3440 (OH); δ_H (300 MHz; $CDCl_3$) 1.07 (12 H, t, CH$_3$), 1.41 (8 H, m, CH_2CH$_3$), 2.22–2.29 (20 H, m, CH$_2$ and ArCH$_3$), 4.29 (4 H, d, *J* 11.8, inner OCH$_2$O), 4.79–4.94 (12 H, m, ArCH and ArCH$_2$O), 5.47 (4 H, d, *J* 11.8, outer OCH$_2$O), 5.71 (4 H, m, ArH), 6.34 (4 H, d, ArH), 6.55 (4 H, t, ArH), 6.94 (4 H, s, ArH), 7.19 (4 H, s, OH).

Resorcinol D_{4h} hemicarcerand (12)

Tetrakis(resorcinol)cavitand **9** (700 mg, 0.59 mmol), tetrabromocavitand **7** (695 mg, 0.64 mmol) and K_2CO_3 (1.16 g, 8.39 mmol) were dissolved in DMF (300 cm^3). The solution was stirred at room temperature for 1 d. The color of the solution changed from colorless to pink. The temperature of the solvent was increased to 80 °C and the solution was stirred for 6 h. After cooling to room temperature, the mixture was partitioned between CH_2Cl_2 (50 cm^3) and 3 M HCl (80 cm^3). The organic phase was washed with water, brine and dried over $MgSO_4$. After the concentration of solution, the residue was purified by silica gel column chromatography using CH_2Cl_2–hexane (1:1, v/v) to give the product **12** (148 mg, 13%), mp 252 °C (decomp.) (Found: C, 71.74; H, 6.51. $C_{120}H_{120}O_{24}$·7/2H_2O requires C, 71.73; H, 6.37%); δ_H (400 MHz; $CDCl_3$) 1.02 (24 H, t, CH$_3$), 1.35–1.42 (16 H, m, CH_2CH$_3$), 2.20–2.24 (16 H, m, CH$_2$), 4.55 (8 H, d, *J* 7.3, inner OCH$_2$O), 4.76–4.85 (24 H, m, ArCH and ArCH$_2$O), 5.69 (8 H, d, *J* 7.3, outer OCH$_2$O), 6.02 (4 H, s, resorcinol's ArH), 6.61 (8 H, d, resorcinol's ArH), 7.14–7.22 (12 H, m, ArH and resorcinol's ArH); FAB$^+$ MS, *m*/*z* 1947 (M$^+$, 100%).

Catechol D_{4h} hemicarcerand (13)

A solution of tetrakis(catechol)cavitand **10** (500 mg, 0.41 mmol), tetrabromocavitand **7** and K_2CO_3 (1.15 g, 8.32 mmol) in acetonitrile (250 cm^3) was refluxed for 1 d. The mixture was concentrated under reduced pressure and partitioned between 3 M HCl and CH_2Cl_2. The organic phase was washed with water and brine and dried over $MgSO_4$. After the concentration of solution, the residue was purified by silica gel column chromatography using CH_2Cl_2–hexane (2:1, v/v) to give the product **13** (89 mg, 11%), mp 256 °C (decomp.); δ_H (400 MHz; $CDCl_3$) 0.81 (24 H, t, CH$_3$), 1.01–1.24 (16 H, m, CH_2CH$_3$), 2.21 (16 H, m, CH$_2$), 4.25 (8 H, br s, inner OCH$_2$O), 4.79–4.85 (24 H, m, ArCH and ArCH$_2$O), 5.70 (8 H, br s, outer OCH$_2$O), 6.83 (16 H, m, catechol's ArH), 7.16 (4 H, s, ArH).

Formation of hemicarceplex 12–guest

Hemicarcerand **12** (10 mg, 0.005 mmol) and guest (5.1 mmol) as a solvent were stirred at 120 °C for 2 d. The solution

was cooled and methanol was poured into the mixture. The precipitate was filtered and dried to give the hemicarceplex **12**–G.

Hemicarceplex 12–*p*-dimethoxybenzene. (Found: C, 73.03; H, 6.24. $C_{128}H_{130}O_{26}\cdot CH_3OH$ requires C, 73.21; H, 6.38%); δ_H (400 MHz; $CDCl_3$) 0.55 (6 H, d, *J* 14.6, guest OCH_3), 1.02–1.06 (24 H, m, CH_3), 1.40–1.42 (16 H, m, CH_2CH_3), 2.24–2.29 (16 H, m, CH_2), 4.35 (8 H, d, *J* 3.9, inner OCH_2O), 4.65–4.86 (24 H, m, $ArCH_2O$ and ArCH), 5.68 (8 H, d, *J* 3.9, outer OCH_2O), 6.01 (4 H, s, ArH), 6.33 (4 H, s, guest ArH), 6.61 (8 H, d, ArH), 7.19–7.32 (12 H, m, ArH).

Hemicarceplex 12–*p*-diethylbenzene. (Found: C, 75.16; H, 6.56. $C_{130}H_{134}O_{24}$ requires C, 75.05; H, 6.49%); δ_H (400 MHz; $CDCl_3$) −2.53 (6 H, t, guest CH_3), 1.01–1.53 (40 H, m, CH_2CH_3 and CH_2CH_3), 1.64 (4 H, m, guest $ArCH_2$), 2.15–2.24 (16 H, m, CH_2), 4.10 (8 H, d, *J* 3.5, inner OCH_2O), 4.62–4.83 (24 H, m, $ArCH_2O$ and ArCH), 5.67 (8 H, d, *J* 3.5, outer OCH_2O), 6.28 (4 H, s, ArH), 6.57 (8 H, d, *J* 3.9, ArH), 6.78 (4 H, s, guest ArH), 7.16–7.22 (12 H, m, ArH).

Hemicarceplex 12–*o*-dimethoxybenzene. δ_H (400 MHz; $CDCl_3$) 0.96–1.08 (24 H, m, CH_3), 1.41–1.46 (16 H, m, CH_2CH_3), 2.22–2.33 (16 H, m, 70% guest OCH_3 and $CHCH_2$), 4.36 (8 H, d, *J* 3.4, 70% inner OCH_2O), 4.57 (d, *J* 3.4, 30% free inner OCH_2O), 4.74 (16 H, s, $ArCH_2O$), 4.81–4.90 (8 H, m, ArCH), 5.67–5.72 (8 H, m, outer OCH_2O), 5.89 (4 H, s, ArH), 6.04 (4 H, s, ArH), 6.09 (s, 70% guest ArH), 6.65 (8 H, d, ArH), 7.23 (4 H, t, ArH), 7.35 (8 H, s, ArH).

Hemicarceplex 12–*m*-dimethoxylbenzene. δ_H (400 MHz; $CDCl_3$) 0.55 (d, 15% guest OCH_3), 0.94–1.04 (24 H, m, CH_3), 1.37–1.42 (16 H, m, CH_2CH_3), 2.15–2.24 (16 H, m, $CHCH_2$), 4.55 (d, *J* 3.4, inner OCH_2O), 4.79–4.86 (24 H, m, $ArCH_2O$ and ArCH), 5.72 (10 H, m, outer OCH_2O and guest ArH), 6.03 (4 H, s, ArH), 6.61 (8 H, d, *J* 4.3, ArH), 7.20–7.22 (12 H, m, ArH).

Hemicarceplex 12–1,2,4,5-tetramethylbenzene. δ_H (400 MHz; $CDCl_3$) 1.01–1.09 (31 H, m, CH_2CH_3 and 58% guest $ArCH_3$), 1.38–1.42 (16 H, m, CH_2CH_3), 2.23–2.28 (m, 58% guest OCH_3 and $CHCH_2$), 4.41 (d, *J* 3.7, 58% complex inner OCH_2O), 4.55 (d, *J* 3.5, 42% free host inner OCH_2O), 4.64–4.70 (m, 58% ArCH and $ArCH_2O$), 4.79–4.87 (m, 42% free host ArCH and $ArCH_2O$), 5.69 (8 H, d, *J* 3.5, outer OCH_2O), 5.89 (s, 58% ArH), 6.03 (s, 42% free host ArH), 6.46 (s, 58% guest ArH), 6.59 (8 H, d, ArH), 7.14–7.22 (4 H, m, ArH), 7.33 (8 H, s, ArH); FAB(+) MS, *m*/*z* 2080 (M^+, 15%), ($M - C_{10}H_{14}^+$, 50%).

Formation of hemicarceplex 13–guest

A solution of hemicarcerand **13** (50 mg, 0.026 mmol) in guest solvent (0.10 mmol) was heated to reflux or to 120 °C for 2 d, and the solution was cooled to room temperature. Methanol was added to the solution and the precipitate was filtered and dried to give hemicarceplex **13**–G.

Hemicarceplex 13–butan-2-one. (Found: C, 72.74; H, 6.25. $C_{124}H_{128}O_{25}\cdot 2H_2O$ requires C, 72.50; H, 6.48%); δ_H (300 MHz; $CDCl_3$) −2.02 (3 H, s, $COCH_2CH_3$), −0.35 (3 H, s, $COCH_3$), 0.92 (24 H, t, CH_3), 1.13 (2 H, s, $COCH_2$), 1.35 (16 H, m, CH_2), 2.20 (16 H, m, CH_2), 4.17 (8 H, br s, inner OCH_2O), 4.76–4.88 (24 H, m, $ArCH_2O$ and ArCH), 5.74 (8 H, br s, outer OCH_2O), 6.87 (16 H, m, catechol's ArH), 7.18 (8 H, s, ArH); FAB(+) MS, *m*/*z* 2018 (M^+, 5%), 1947 ($M - C_4H_8O^+$, 99%).

Hemicarceplex 13–*N*,*N*-dimethylacetamide. δ_H (300 MHz; $CDCl_3$) −0.60 (3 H, s, $COCH_3$), 0.09 (3 H, s, NCH_3), 0.92 (24 H, t, CH_3), 1.36 (16 H, m, CH_2), 2.14 (16 H, m, CH_2), 4.28 (8 H, br s, inner OCH_2O), 4.75–4.93 (24 H, m, $ArCH_2O$ and ArCH), 5.67 (8 H, br s, outer OCH_2O), 6.89 (16 H, m, catechol's ArH), 7.16 (8 H, s, ArH); FAB(+) MS, *m*/*z* 2034 (M^+, 17%), 1946 ($M - C_4H_9NO^+$, 100%).

Hemicarceplex 13–ethyl acetate. (Found: C, 72.00; H, 6.26. $C_{124}H_{128}O_{26}\cdot 2H_2O$ requires C, 71.94; H, 6.43%); δ_H (400 MHz; $CDCl_3$) −2.28 (3 H, s, OCH_2CH_3), −0.54 (3 H, q, $COCH_3$), 1.02 (24 H, t, CH_3), 1.38 (16 H, m, CH_2), 2.21 (16 H, m, CH_2), 4.24 (8 H, br s, inner OCH_2O), 4.77–4.89 (24 H, m, $ArCH_2O$ and ArCH), 5.67 (8 H, br s, outer OCH_2O), 6.87 (16 H, m, catechol's ArH), 7.19 (8 H, s, ArH); FAB(+) MS, *m*/*z* 2034 (M^+, 29%), 1946 ($M - C_4H_8O_2^+$, 100%).

Hemicarceplex 13–4-methylpentan-2-one. δ_H (300 MHz; $CDCl_3$) −1.65 (6 H, two s, CH_3), −1.45 (3 H, m, $COCH_3$), 0.90 (24 H, t, CH_3), 1.36 (16 H, m, CH_2), 2.20 (16 H, m, CH_2), 4.36 (8 H, br s, inner OCH_2O), 4.75–4.90 (24 H, m, $ArCH_2O$ and ArCH), 5.65 (8 H, br s, outer OCH_2O), 6.84 (16 H, m, catechol's ArH), 7.17 (8 H, s, ArH).

Hemicarceplex 13–pyrazine. δ_H (300 MHz; $CDCl_3$) 1.02 (24 H, t, CH_3), 1.37 (16 H, m, CH_2), 2.22 (16 H, m, CH_2), 4.24 (8 H, br s, inner OCH_2O), 4.66–4.86 (24 H, m, $ArCH_2O$ and ArCH), 5.63 (8 H, br s, outer OCH_2O), 5.84 (4 H, s, pyrazine ArH), 6.83 (16 H, m, catechol's ArH), 7.15 (8 H, s, ArH).

Hemicarceplex 13–*N*,*N*-dimethylpropionamide. δ_H (300 MHz; $CDCl_3$) −2.39 (3 H, m, $COCH_2CH_3$), −0.32 (3 H, two s, NCH_3), 0.24 (3 H, two s, NCH_3), 0.62 (2 H, m, $COCH_2$), 0.91 (24 H, t, CH_3), 1.37 (16 H, m, CH_2), 2.20 (16 H, m, CH_2), 4.26 (8 H, br s, inner OCH_2O), 4.75–4.91 (24 H, m, $ArCH_2O$ and ArCH), 5.61 (8 H, br s, outer OCH_2O), 6.87 (16 H, m, catechol's ArH), 7.18 (8 H, s, ArH).

Determination of half-lives of pseudo 1st-order decomplexation of 12–guest and 13–guest

Hemicarceplexes **12**–G or **13**–G (2–3 mg) were dissolved in deuterated solvent (0.5 cm^3). The probe temperatures were calibrated against $HOCH_2CH_2OH$ as standard. The tubes were placed in the probe of the NMR spectrometer at fixed temperatures (25–100 °C), and 6–10 spectra were recorded at appropriate time intervals. The first-order decomplexation rate constants were calculated on the basis of the spectral changes. Plots of $-\ln(A/A_0)$ *vs.* time gave good straight lines which provided first-order rate constants (k) for decomplexation (eqn. (1)). The activation energies of decomplexation (E_a) were obtained from the slope of the linear plot of $\ln k$ *vs.* $1/T$ (eqn. (2)).

$$\ln(A/A_0) = -kt \quad (1)$$

$$\ln k = \ln A - E_a/RT \quad (2)$$

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