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Tetrahedron Letters 45 (2004) 9119–9122

Tetrahedron Letters

Molecular engineering. Part 9: Enhanced binding ability and selectivity of C_{2v} cavitands

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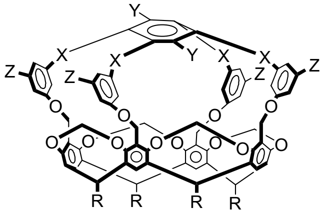
Received 31 August 2004; revised 30 September 2004; accepted 4 October 2004
Available online 22 October 2004

Abstract—Two new C_{2v} cavitands with protective side chains were synthesized and their binding properties for small molecules were studied. Cavitand **7** having benzyl side chains binds ethanol most strongly with $K_a = 1508\,M^{-1}$ at 20 °C in $CDCl_3$, which was driven entropically. Cavitand **8** having coumarinyl side chains showed weaker binding due to its steric hindrance. ^1H NMR spectra show that carceroisomers of ethanol or acetonitrile@cavitand **7** exist in 3:1 ratio at 20 °C. The binding tendencies of the guest molecules were increased in nonpolar solvent media.

Numerous container molecules such as carceplexes, hemicarceplexes, or cavitands have been studied by tuning the number of portal pillars, the length of portal pillars, and the dimension of hemispheres due to their potential applicabilities as molecular reactor, selective storage, delivery, or controlled-releasing systems as well as information storage system.[1] Hemicarcerand has large portals enough to allow guest molecules to enter and exit its inner phase. When guest molecule is included, the portal pillars twist and the inner volume decreases forming many new atom-to-atom close contacts, which is called constrictive binding.[2] Hemicarcerand also releases guest molecules by rotating the portal pillars toward the opposite direction.

The control of complexation stability and selectivity of container molecules by constrictive binding is rather difficult. The secondary interactions such as hydrogen bonding, charge–charge or charge–dipole interactions, or steric protection should be added for the fine tuning. The introduction of additional side chains to the main portals of C_{2v} cavitands was attempted to control the in-and-out dynamic process.[3]

We have reported resorcin[4]arene-based C_{2v} container hosts **1**, **2**, and **3** having a phenyl cap and four $(–CH_2O–m\text{-phenyl-}X)_4$ pillars bind small molecules.[4–6]



1: $R = CH_2CH_2CH_3$, $X = OCH_2$, $Y = H$, $Z = H$
2: $R = CH_2CH_2CH_3$, $X = O$, $Y = CN$, $Z = H$
3: $R = CH_3$, $X = OCH_2$, $Y = H$, $Z = COOH$

Cavitand **1** showed only weak binding ($K_a = \sim 200\,M^{-1}$) for EtOH or MeOH at low temperature (−40 °C) due to its low constrictability.[4] The basic water soluble cavitand **3** showed still weak binding of alcohol at room temperature. Cavitand **2** and **5** which have a smaller cavity than cavitand **1** and **3** complex various small molecules such as ethanol, *n*-propanol, ethylene glycol, acetaldehyde, acetonitrile, and methylene chloride.[6] However, their binding affinities in $CDCl_3$ at room temperature are weak ranging from 5 to $260\,M^{-1}$. In order to increase binding affinities, we designed and characterized cavitands **7** and **8** having additional side functional

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Keywords: Cavitand; Selectivity; Carceroisomerism.

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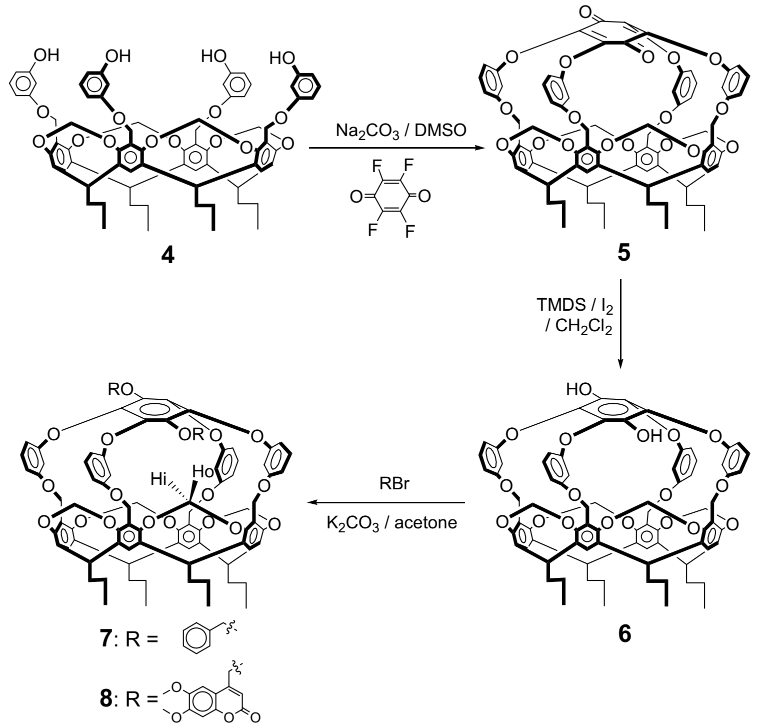
doi:10.1016/j.tetlet.2004.10.005



Scheme 1. Synthesis of C_{2v} cavitands **7** and **8**.

groups on phenyl cap, which are expected to play the role of 'doorman' to protect the portals (Scheme 1).

Cavitand **5** was synthesized from compound **4** using tetrafluoro-1,4-benzoquinone as capping agent.[6] Then, cavitand **5** was reduced with an excess of TMDS and a catalytic amount of iodine in refluxing CH_2Cl_2 to give cavitand **6** in over 90% yield (Scheme 1). Cavitand **6** was further functionalized with benzyl bromide or 4-(bromomethyl)-6,7-dimethoxycoumarin in refluxing acetone to afford cavitand **7** or **8**, respectively. These cavitands were characterized by ^{1}H NMR, FAB(+) MS spectra and elemental analysis.[7] Their ^{1}H NMR spectra showed that cavitands **7** and **8** have a C_{2v} symmetry and hydrophobic cavity, which causes the upfield shift of 2-hydrogens of 1,3-dioxyphenyl unit appearing at 5.85 and 6.03 ppm in $CDCl_3$, respectively.

The CPK molecular model shows that cavitands **7** and **8** can accommodate various small molecules. The complexation of ethanol, acetaldehyde, acetonitrile, nitromethane, ethylene glycol, and methylene chloride was observed by ^{1}H NMR spectra at 20 °C. Figure 1 shows the spectral changes of cavitand **7** upon complexation with ethanol or acetonitrile in $CDCl_3$ at 20 °C. When cavitand **7** binds with ethanol or acetonitrile, the multiplet at 4.12 ppm of inner hydrogen (H_i) of dioxymethylene bridge of free caivitand **7** was sharpened, spilt to doublets and slightly downfield shifted to 4.32 and 4.29 ppm, respectively. The broad singlets at 5.42 and 5.77 ppm of outer hydrogen (H_o) of dioxymethylene bridge's were also sharpened and downfield shifted.

Especially, the peak of 2-H protons (H_a) of 1,3-dioxyphenyl unit were shifted downfield up to 0.90 ppm.

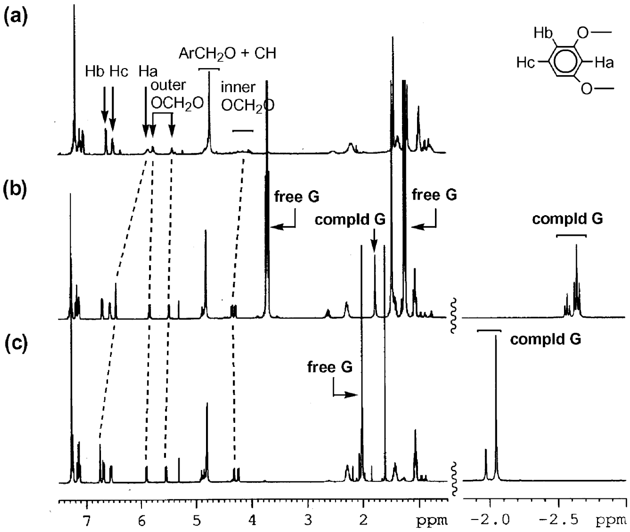


Figure 1. ^{1}H NMR spectra of (a) [cavitand **7**] = 5.0×10^{-3} M; (b) addition of [CH_3CH_2OH] = 2.5×10^{-2} M; (c) addition of [CH_3CN] = 2.5×10^{-2} M in $CDCl_3$ at 20 °C.

The chemical shifts of complexed ethanol and acetonitrile protons were far upfield shifted up to 4.07 ppm because the guest protons are located in the shielding zone of cavitand. Especially, the methyl group of complexed ethanol and acetonitrile appeared as two peaks in the ratio of about 3:1, showing the carceroisomerism[8] by the different orientation of guests through the C_2 axis and their slow inversion at 20 °C.

The distinct peaks of free and complexed guest enable the direct calculation of association constant K_a. Table 1

Table 1. ^{1}H NMR spectral chemical shift changes of guest-hydrogen's (*italic*) chemical shifts and the association constants K_a (M^{-1}) in $CDCl_3$ at 20 °C of free and complexed guests in cavitands **7** and **8**

Cavitand	Guest	Free δ	Compl δ	$\Delta\delta$ (ppm)	K_a (M^{-1})
7	$\mathrm{C}\mathit{H}_3\mathrm{CH_2OH}$	1.25	−2.65	3.90	1508
7	$\mathrm{HOC}\mathit{H}_2\mathrm{CH_2OH}$	3.73	−0.27	4.02	378
7	$\mathrm{C}\mathit{H}_3\mathrm{CHO}$	2.22	−1.34	3.56	698
7	$\mathrm{C}\mathit{H}_3\mathrm{NO_2}$	4.33	0.31	4.02	1176
7	$\mathrm{C}\mathit{H}_3\mathrm{CN}$	2.02	−2.05	4.07	914
7	$\mathrm{C}\mathit{H}_2\mathrm{Cl_2}$	5.30	4.08	1.22	94
8	$\mathrm{C}\mathit{H}_3\mathrm{CH_2OH}$	1.25	−2.59	3.84	543
8	$\mathrm{C}\mathit{H}_3\mathrm{CHO}$	2.22	−1.26	3.48	227
8	$\mathrm{C}\mathit{H}_3\mathrm{NO_2}$	4.33	0.35	3.98	114
8	$\mathrm{C}\mathit{H}_3\mathrm{CN}$	2.02	−1.98	4.00	325

shows the chemical shift differences ($\Delta\delta$ in ppm) of guest's hydrogen in $CDCl_3$ at 20 °C and the association constants K_a (M^{-1}). The typical far upfield shifts of complexed guest's peak by the aromatic shells of cavitands were observed ranging from $\Delta\delta = 1.22$ to 4.07 ppm. The more upfield shifts of protons of alcohols, nitromethane, and acetonitrile compared to that of methylene chloride mean that the methyl groups are far better deeply nested in the cavity of resorcin[4]arene.

Cavitands **7** and **8** show enhanced K_a values than those of cavitands **1**, **2**, **3**, and **5** because they have large functional groups in the portal acting as 'doormans', which impose high-energy barrier for complex and decomplex process and so enable the guest molecules to stay in the cavity more snugly. But unexpectedly the K_a values of cavitand **7** are about three times larger than those of cavitand **8**, which implies that there will be an optimal 'doorman' for the most stable and selective cavitand. Cavitands **7** and **8** are highly selective to ethanol among other alcohols. Especially, the K_a value of ethanol in cavitand **7** is the largest ($K_a = 1508\,M^{-1}$). As far as we know, cavitand **7** is one of the smallest and most stable ethanol container. Although the selective ethanol binding tendency is similar to that of cavitand **2** and **4** as reported before,[6] it seems that the high K_a value in cavitand **7** is caused by the role of 'doorman' unit protecting the guest molecules to exit.

Thermodynamic parameters for complexation obtained by the van't Hoff equation are shown in Table 2. The complexations of acetaldehyde, methylene chloride, and acetonitrile (in cavitand **7**) are enthalpically favored, but entropically disfavored. But the complexations of alcohols in cavitand **7** or **8** are enthalpically and entropically favored.

Table 2. Thermodynamic parameters for complexation at 293 K in $CDCl_3$

Caviplex	ΔG (kcal mol^{-1})	ΔH (kcal mol^{-1})	ΔS (cal mol^{-1})
7@ethanol	−4.3	−1.7	8.9
7@ethylene glycol	−3.4	−1.8	5.5
7@acetaldehyde	−4.4	−7.3	−11.8
7@nitromethane	−4.1	−4.4	−1.0
7@acetonitrile	−4.0	−6.9	−9.9
7@methylene chloride	−2.6	−6.4	−13.0
8@ethanol	−3.7	−2.8	3.1
8@acetaldehyde	−3.2	−5.3	−7.2
8@acetonitrile	−3.4	−2.1	4.4
8@nitromethane	−2.8	−0.5	7.8

Table 3. Association constants K_a (M^{-1}) of complexation of acetonitrile in cavitand **8** in various solvents at 20 °C

Caviplex	Solvent	K_a (M^{-1})
8@acetonitrile	Chloroform-*d*	325
	Pyridine-d_5	250
	DMF-d_7	270
	DMSO-d_6	157

In order to investigate the solvent effect to complexation of the cavitands, the K_a values in various solvents were obtained as shown in Table 3. As the polarity of solvents increased, the K_a values of acetonitrile in cavitand **8** decreased. It means that the polar guest molecule is better bound in the nonpolar cavity due to the relatively increased van der Waals interaction by solvophobic interaction as solvent polarity becomes low.[9]

In conclusion, two new C_{2v} cavitands **7** and **8** functionalized with benzyl or coumarine group as a doorman were synthesized and their binding properties for various guest molecules were characterized. Enhanced binding ability and selectivity for small molecules, especially ethanol, are achieved. Currently isosteric luminescent doormans for these cavitands are being studied.

Acknowledgements

Support of this work by a grant from the Ministry of Science and Technology, Korea (M1-0213-03-0005) is gratefully acknowledged.

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   8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, 12H, CH_3), 1.49 (m, 8H, CH_2), 2.34 (m, 8H, CH_2), 3.72 (t, 6H, OCH_3), 3.98 (s, 6H, OCH_3), 4.27 (m, 4H, inner OCH_2O), 4.90–5.02 (m, 12H, CH and $ArCH_2O$), 5.09 (d, 4H, $ArCH_2O$), 5.52 (d, 2H, outer OCH_2O), 5.74 (d, 2H, ArH), 5.95 (d, 2H, outer OCH_2O), 6.03 (s, 4H, ArH), 6.35 (s, 2H, ArH), 6.55–6.65 (m, 8H, ArH), 6.85 (s, 2H, ArH), 7.11 (m, 4H, ArH), 7.34 (m, 4H, ArH); MS (FAB+) *m/z* 1732.3 (M^+, 100%); Anal. Calcd (%) for $C_{102}H_{90}O_{26} \cdot 5/3CH_2Cl_2$: C, 66.45; H, 5.03. Found: C, 66.42; H, 5.33.
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