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Tetramidocavitand: strong anion receptor by well-organized four $-(C{=}O)N{-}H\cdots X^-$ interactions

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ABSTRACT

Resorcin[4]arene-based tetramidocavitands containing four secondary amide groups on their upper rim showed strong RSO_3^- (R = methyl or ethyl) binding properties. The caviplex formation through hydrogen bonds of $-(C{=}O)N{-}H\cdots X^-$ was supported by ^{1}H NMR and crystal structure analyses. In a mixture of $C_2D_2Cl_4$/DMSO/D_2O = 5:15:2 at 25 °C, the thermodynamic parameters for caviplex $CH_3SO_3^-$@**1**, ΔG (kcal mol^{-1}), ΔH (kcal mol^{-1}), and ΔS (cal K^{-1} mol^{-1}), are −3.7, −8.6, and −16.7, respectively.

The concave organic receptors, cavitands have great potentials as an attractive host due to their versatile hydrophobic cavity as well as a variety of functional groups attachable on their rims.[1] These resorcin[4]arene-based cavitands are capable of functions as neutral molecular receptors[2] or molecular capsules.[3] Even, some of them can recognize and bind anions with limited accomplishments though.[4] Using hydrogen bonding interactions, $Y{-}H\cdots X^-$ (Y = C,[5] O,[6] or N;[7] X^- = anions) is an efficient manner for recognizing anions, which has got a great attention recently. Especially, amide,[8] urea,[9] and pyrrol[10] groups can convey those interactions and work efficiently in many strong and selective anion receptors. Here, we present resorcin[4]arene-based tetramidocavitands that can recognize and capture effectively organic sulfonates by forming multiple hydrogen bonds comprising amido donors and oxygen acceptors.

Resorcin[4]arene-based tetramidocavitands which could form well-organized four $-(C{=}O)N{-}H\cdots X^-$ hydrogen bonds upon the addition of X^- were designed and characterized. Tetramidocavitands **1**–**3** were synthesized from tetrakis(chlorocarbonyl)cavitand **4**[4b] and *t*-butylamine, *p*-nitroaniline, or *N*,*N*-dimethylamine in the presence of triethylamine at room temperature in $CHCl_3$ (Scheme 1). Pure compounds of **1**, **2**, and **3** were obtained by recrystallization from the mixtures of CH_2Cl_2 and MeOH in 40%, 45%, and 50% yields, respectively, and were characterized by ^{1}H NMR, ^{13}C NMR, MALDI-TOF, and elemental analyses.

Figure 1 shows ^{1}H NMR spectral changes of **1** by the addition of tetrabutylammonium methanesulfonate ($TBACH_3SO_3$) in $CDCl_3$ at 25 °C, and the chemical shift changes of the hydrogen atoms near the cavity are summarized in Table 1. When 0.5 equiv $TBACH_3SO_3$ was added to **1**, the peaks of H_b and H_{in} were split into two 1:1 peaks for free and complexed hosts, respectively. In addition, two new peaks for an amido proton H_a of **1** and methyl protons of the methanesulfonate appeared at 7.64 and −1.81 ppm, respectively, which is strongly indicative of the formation of a caviplex, $CH_3SO_3^-$@**1**. It is noticeable that the signal for the inner proton H_{in} of the dioxymethylene bridge ($O{-}CH_{in}H_{out}{-}O$) also moved to downfield slightly ($\Delta\delta$ = 0.25 ppm). This observation suggests that there is a weak interaction between $-H_{in}$ and $^-O_3SCH_3$.[4a] When 1 equiv $TBACH_3SO_3$ was added to **1**, the peaks H_b and H_{in} for the free cavitand **1** disappeared and only the peaks for caviplex $CH_3SO_3^-$@**1** remained. There were no further chemical shift changes for caviplex $CH_3SO_3^-$@**1** by the addition of 2 equiv $TBACH_3SO_3$, which confirms that cavitand **1** and methanesulfonate ion form a 1:1 complex.

For the caviplex $CH_3SO_3^-$@**2** in $CDCl_3$: DMSO-d_6, ^{1}H NMR spectra showed the upfield shift of the $-NH_a$ signal from 10.48 to 9.76 ppm ($\Delta\delta$ = −0.72 ppm) upon complexation. This implies that a hydrogen bonding partner of the amido group was changed from DMSO-d_6 to a methanesulfonate donor. As shown in the case of **1**, the inner proton H_{in} of **2** moved also to downfield from 4.68 to 5.05 ppm ($\Delta\delta$ = 0.37 ppm). The guest peak for caviplex $CH_3SO_3^-$@**2** appeared at −1.40 ppm, which indicates that $CH_3SO_3^-$ in caviplex $CH_3SO_3^-$@**2** nests less snugly than that in caviplex $CH_3SO_3^-$@**1**.

When cavitand **1** or **2** was titrated in $CDCl_3$ at 25 °C with tetrabutylammonium ethanesulfonate, only caviplex $CH_3CH_2SO_3^-$@**2** was formed. It is presumable that the blocking *t*-butyl groups of cavitand **1** limit the size of guest. ^{1}H NMR spectrum of caviplex $CH_3CH_2SO_3^-$@**2** shows that methyl peak of complexed ethanesulfonate appeared at −1.54 ppm. It is upfield shift of 2.70 ppm from that of free ethanesulfonate at 1.16 ppm which is rather small compared to that of methanesulfonate, 4.08 ppm. The negative mode MALDI-TOF Mass spectra of caviplex $CH_3SO_3^-$@**1** and $CH_3SO_3^-$@**2** showed strong peaks at 1,419.9 for [$CH_3SO_3^-$ + **1**] and 1680.8 for [$CH_3SO_3^-$ + **2**], respectively.

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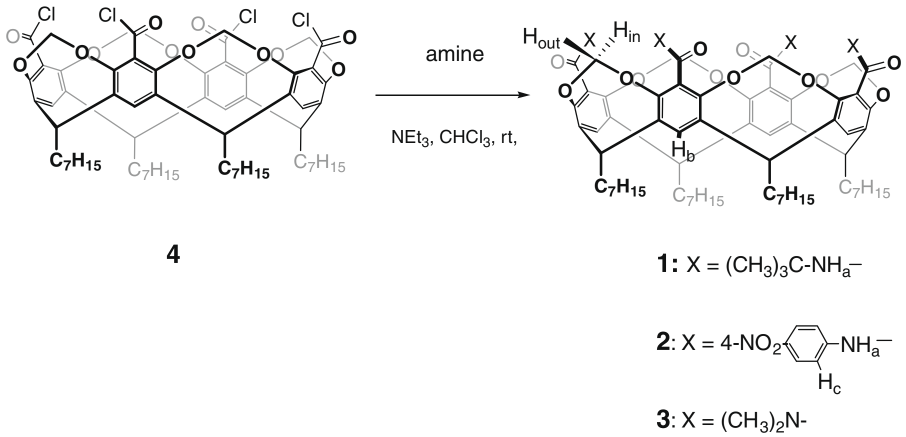

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1: X = $(CH_3)_3C\text{-}NH_a$–

2: X = 4-NO_2-⟨ring⟩-NH_a–

3: X = $(CH_3)_2N$-

Scheme 1. Syntheses of tetramidocavitands **1**, **2**, and **3**.

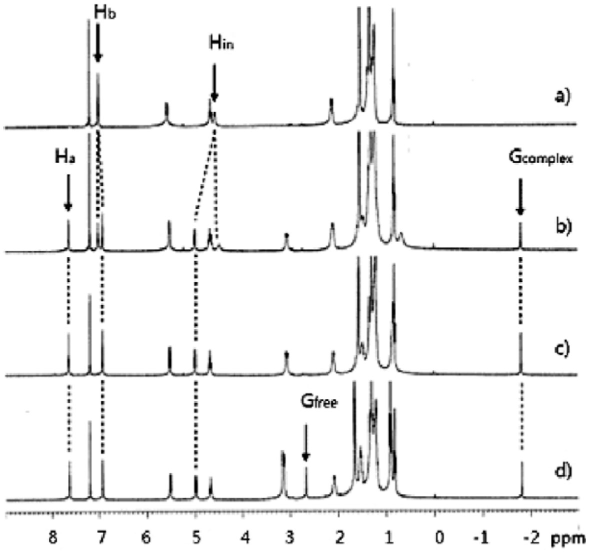

Figure 1. The partial ^{1}H NMR spectra showing the chemical shift changes of cavitand **1** by the addition of tetrabutylammonium methanesulfonate (**G**) in $CDCl_3$ at 25 °C; (a) 0.0 equiv **G**, (b) 0.5 equiv **G**, (c) 1.0 equiv **G**, (d) 2.0 equiv **G**.

Table 1

Chemical shift changes of selected protons of cavitands **1** and **2** in ^{1}H NMR spectra by the addition of $TBACH_3SO_3$ (**G**) in $CDCl_3$ for cavitand **1** and $CDCl_3$/DMSO-d_6 for cavitand **2** at 25 °C

Cavitand		Chemical shift (δ in ppm) of proton					
		H_a	H_b	H_{in}	H_c	$CH_3SO_3^-$	
						Free	Complexed
No **G**	**1**	–	7.00	4.75	–	–	–
	2	10.48	7.50	4.68	7.86	–	–
2 equiv **G**	**1**	7.64	6.93	5.00	–	2.68	−1.81
	2	9.76	7.41	5.05	7.95	2.68	−1.40
$\Delta\delta$	**1**	–	−0.07	+0.25	–	–	−4.49
	2	−0.72	−0.09	+0.37	0.09	–	−4.08

Table 2

Thermodynamic parameters of caviplexes **G@1** and **G@2** at 25 °C

Host	Guest	Solution	K^a	ΔG^b	ΔH^b	ΔS^c
1	$CH_3SO_3^-$	$C_2D_2Cl_4$/DMSO/D_2O = 5:15:2	560	−3.7	−8.6	−16.7
		$C_2D_2Cl_4$/DMSO/D_2O = 5:15:4	14	−1.6	−6.7	−17.1
2	$CH_3SO_3^-$	$C_2D_2Cl_4$/DMSO = 9:1	380	−3.5	−7.1	−12.2
		$C_2D_2Cl_4$/DMSO = 8:2	61	−2.4	−6.6	−14.1
	$CH_3CH_2SO_3^-$	$C_2D_2Cl_4$	36	−2.1	−5.3	−10.9

[a] M^{-1},
[b] kcal mol^{-1}.
[c] cal K^{-1} mol^{-1}.

Table 2 shows thermodynamic parameters of caviplexes **G@1** and **G@2** at 25 °C. Caviplex $CH_3SO_3^-$**@1** is extremely inert in most organic solvents and only showed a slow equilibrium shift in an aqueous solution. In a mixture of $C_2D_2Cl_4$/DMSO/D_2O = 5:15:2 at 25 °C, the thermodynamic parameters, ΔG (kcal mol^{-1}), ΔH (kcal mol^{-1}), and ΔS (cal K^{-1} mol^{-1}), are −3.7, −8.6, and −16.7, respectively. All the binding processes in Table 2 are enthalpy driven. Caviplex **G@1** is much more inert than caviplex **G@2** which dissociates completely in a mixture of $C_2D_2Cl_4$/DMSO/D_2O = 5:15:2 at 25 °C. The corresponding thermodynamic parameters of caviplex $CH_3SO_3^-$**@2** in $C_2D_2Cl_4$: DMSO = 9: 1 are −3.5, −7.1, and −12.2, respectively. Caviplex $CH_3CH_2SO_3^-$**@2** shows an equilibrium shift even in $C_2D_2Cl_4$ and those corresponding thermodynamic parameters are −2.1, −5.3, and −10.9, respectively. Caviplex $CH_3SO_3^-$**@2** is much more stable than caviplex $CH_3CH_2SO_3^-$**@2**.

The crystal structure of caviplex $CH_3SO_3^-$**@1** shown in Figure 2 supported the spectroscopic observation studied in solution.[11] The anion is captured in the host with its methyl group directing to the inner cavity, and the three sulfonate oxygen atoms are lying on the plane defined by four amide N atoms of **1**. The closest distances between amide H atoms and three oxygen atoms in $CH_3SO_3^-$ are in the range of 2.054–2.284 Å (av. 2.140 Å) (Fig. 3). These values are within the range of normal hydrogen bonding distance, 1.2–2.2 Å.[12] In addition, the oxygen atoms (O1G, O2G, and O3G) seem to involve with non-conventional hydrogen bonds with C–H_{in} groups, too; their distances are 2.541, 2.450, and 2.341 Å (av. 2.444 Å), respectively, which are within the range of weak hydrogen bonding distance, 2.2–3.2 Å.[12] All these hydrogen bonds play a cooperative role in holding the guest because O1G and O2G interact, respectively, with a pair of one CH and one NH while O3G does with a pair of one CH and two NH groups as shown in Figure 3. The bulky tetrabutylammonium is apart from the cavity of **1** as expected.

The requirement of the secondary amide groups for anion binding has been assessed again by the experiments with cavitand **3**

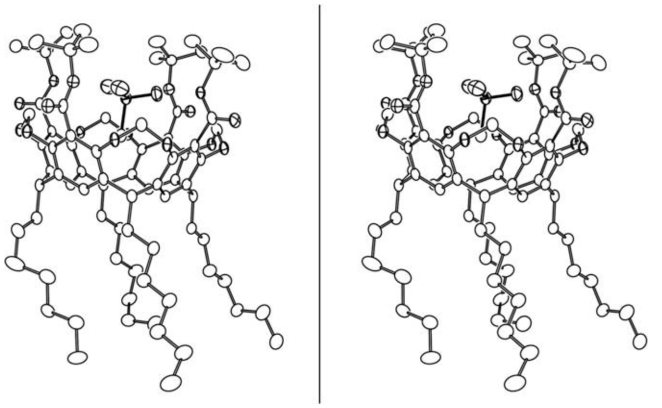

Figure 2. A stereo-view of caviplex $CH_3SO_3^-$@**1** depicted by ORTEP with 50% ellipsoids. Hydrogen atoms are omitted for simplicity.

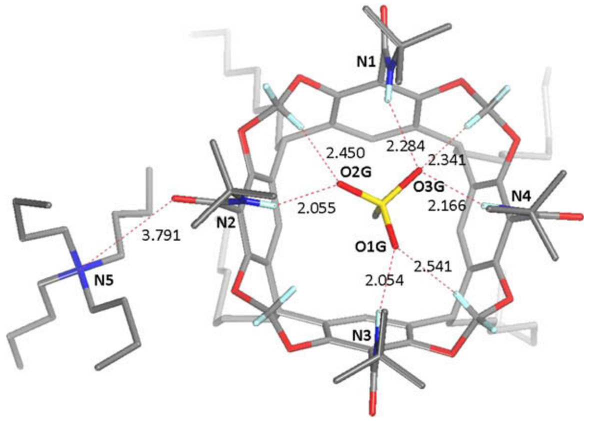

Figure 3. Crystal structure of (TBA)($CH_3SO_3^-$@**1**) with selected inter-atomic distances (Å). The amide and methylene hydrogen atoms (light blue) of **1** are only shown for clarity.

having four tertiary amide groups. The addition of 2 equiv $TBACH_3SO_3$ to cavitand **3** in $CDCl_3$ resulted in no chemical shift changes of cavitand **3** in ^1H NMR spectrum, and no signals for the would-be complexed $CH_3SO_3^-$ in the range of 0 to −4 ppm either. When the energy minimization of a caviplex $CH_3SO_3^-$@**3** model structure was conducted using SPARTAN'04 V1.03 (Molecular Mechanics MMFF), the $CH_3SO_3^-$ ion was ejected from the cavity, indicating that cavitand **3** cannot act as a methanesulfonate receptor. In this aspect, it is certain that tetramidocavitands **1** and **2** bind anions mainly via $(C{=}O)N{-}H\cdots X^-$ interactions. This conclusion can lead to such an interpretation that the combined interaction of the weak $O_2HC{-}H\cdots X^-$ hydrogen bondings and the size complementarity between host and guest cannot be enough for the caviplex formation in the conditions studied here.[4a]

In this work, we have presented that resorcin[4]arene-based tetramidocavitands **1** and **2** containing four secondary amide groups on their upper rim showed strong anion binding properties. These bind strongly $CH_3SO_3^-$ and $CH_3CH_2SO_3^-$ in a 1:1 ratio mainly through hydrogen bonds of $-(C{=}O)N{-}H\cdots X^-$ supported by ^1H NMR and crystal structure analyses. Both caviplexes **G@1** and **G@2** are extremely stable in most organic solvents. Caviplex $CH_3SO_3^-$@**1** only showed slow equilibrium shift in an aqueous solution. In a mixture of $C_2D_2Cl_4/DMSO/D_2O$ = 5:15:2 at 25 °C, the thermodynamic parameters, ΔG (kcal mol^{-1}), ΔH (kcal mol^{-1}), and ΔS (cal K^{-1} mol^{-1}), are −3.7, −8.6, and −16.7, respectively. Caviplex **G@2** is much less inert than caviplexes **G@1**. All the binding processes are enthalpy driven. Various derivatives of tetramidocavitands **1** and **2** and their kinetic and thermodynamic properties for various anions are being studied to tune their binding properties.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.144.

References and notes

1. Cram, D. J.; Cram, J. M.. In Stoddart, J. F., Ed.; Container Molecules and Their Guests, Monographs in Supramolecular Chemistry; Royal Society of Chemistry: Cambridge, England, 1994. Chapter 5.
2. (a) Ihm, C.; In, Y.; Park, Y.; Paek, K. *Org. Lett.* **2004**, *6*, 369–372; (b) Choi, H.-J.; Park, Y.-S.; Song, J.; Youn, S. J.; Kim, H.-S.; Kim, S.-H.; Koh, K.; Paek, K. *J. Org. Chem.* **2005**, *70*, 5974–5981; (c) Choi, H.-J.; Nguyen, Q.-Y.; Park, Y. S.; Choi, C.-H.; Paek, K.; Kim, E.-H. *Chem. Commun.* **2009**, 4971–4973; (d) Biavardi, E.; Favazza, M.; Motta, A.; Fragalà, I. L.; Massera, C.; Prodi, L.; Montalti, M.; Melegari, M.; Condorelli, G. G.; Dalcanale, E. *J. Am. Chem. Soc.* **2009**, *131*, 7447–7455; (e) Nikan, M.; Sherman, J. C. *J. Org. Chem.* **2009**, *74*, 5211–5218.
3. (a) Ajami, D.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2008**, *47*, 6059–6061; (b) Cave, G. W. V.; Antesberger, J.; Barbour, L. J.; McKinlay, R. M.; Atwood, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5263–5266; (c) Gibb, C. L. D.; Sundaresan, A. K.; Ramamurthy, V.; Gibb, B. C. *J. Am. Chem. Soc.* **2008**, *130*, 4069–4080; (d) Fochi, F.; Jacopozzi, P.; Wegelius, E.; Rissanen, K.; Cozzini, P.; Marastoni, E.; Fisicaro, E.; Manini, P.; Fokkens, R.; Dalcanale, E. *J. Am. Chem. Soc.* **2001**, *123*, 7539–7552.
4. (a) Zhu, S. S.; Staats, H.; Brandhorst, K.; Grunenberg, J.; Gruppi, F.; Dalcanale, E.; Lützen, A.; Rissanen, K.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 788–792; (b) Park, Y. S.; Paek, K. *Org. Lett.* **2008**, *10*, 4867–4870; (c) Ihm, C.; Cho, S.; Paek, K. *Bull. Korean Chem. Soc.* **2007**, *28*, 1867–1870; (d) Park, H. S.; Paek, K. *Bull. Korean Chem. Soc.* **2009**, *30*, 505–508.
5. (a) Li, Y.; Flood, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12111–12112; (b) Chellappan, K.; Singh, N. J.; Hwang, I.; Lee, J. W.; Kim, K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2899–2903.
6. (a) Custelcean, R.; Gorbunova, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 16362–16363; (b) Wu, J. S.; Zhou, J. H.; Wang, P. F.; Zhang, X. H.; Wu, S. K. *Org. Lett.* **2005**, *7*, 2133–2136.
7. (a) Amendola, V.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M. *Acc. Chem. Rev.* **2006**, *39*, 343–353; (b) Kang, S. O.; Day, V. W.; Bowman-James, K. *Org. Lett.* **2008**, *10*, 2677–2680.
8. (a) Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7882–7894; (b) Bernier, N.; Carvalho, S.; Li, F.; Delgado, R.; Flix, V. *J. Org. Chem.* **2009**, *74*, 4819–4827.
9. (a) Jeon, N. J.; Ryu, B. J.; Lee, B. H.; Nam, K. C. *Bull. Korean Chem. Soc.* **2009**, *30*, 1675–1677; (b) Amendola, V.; Boiocchi, M.; Colasson, B.; Fabbrizzi, L. *Inorg. Chem.* **2006**, *45*, 6138–6147; (c) Oshovsky, G. V.; Verboom, W.; Fokkens, R. H.; Reinhoudt, D. N. *Chem. Eur. J.* **2004**, *10*, 2739–2748.
10. (a) Sessler, J. L.; Karnas, E.; Kim, S. K.; Ou, Z.; Zhang, M.; Kadish, K. M.; Ohkubo, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2008**, *130*, 15256–15257; (b) Sessler, J. L.; Kim, S. K.; Gross, D. E.; Lee, C. H.; Kim, J. S.; Lynch, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 13162–13166.
11. A suitable crystal for the X-ray crystallography was grown by a slow diffusion of benzene into a mixed solution of CH_2Cl_2 and MeOH containing (TBA)($CH_3SO_3^-$@**1**). Crystal data of (TBA)($CH_3SO_3^-$@**1**)$\cdot(C_6H_6)_{0.5}$: $C_{100}H_{158}N_5O_{15}S$, M_r = 1702.37, triclinic, space group $P(-1)$, a = 17.094(3) Å, b = 17.800(4) Å, c = 19.804(4) Å, α = 116.32(3), β = 105.02(3), γ = 98.39(3), V = 4974.2(17) $Å^3$, Z = 2, d_{calc} = 1.137 g/cm^3, T = 100(2) K, $\lambda(MoK_\alpha)$ = 0.71073 Å, 2θ = 39.56, 8325 independent reflections, GOF = 1.054, R_1 = 0.0557 ($I > 2\sigma(I)$, 7827 reflections), wR_2 = 0.1612 (all data).
12. Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*, 2nd ed.; John Wiley & Sons Ltd: UK, 2009. Chapter 1.