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LETTERS

Selective Chloromethylation of Cavitand at the Upper Rim and Induced Fit Type Complexation with Metal Cations by New Cavitands : Aza-Crown-Modified Cavitands.

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Abstract: Regioselective mono and dis-chloromethylation of cavitands have been prepared as an intermediate of a new cavitand derivative. Mono- and bis-aza-15-crown-5 modified cavitands (**4** and **5**, respectively) have been obtained from mono- and bis-chloromethylated cavitands, respectively. The metal binding properties of native cavitand (**1**), **4** and **5** were studied by ^{1}H-NMR and UV-Vis spectroscopy.

The synthesis of cavitand has been reported by Cram and co-workers[1]. For last two decades, many analogues of cavitand have been prepared to investigate their host-guest complexation properties[2]. Tetra-chloromethylated cavitand, which was reported by Cram et al, was a good intermediate for synthesis of a new derivative of cavitand because it is easy to introduce functional groups on a upper rim of the cavitand[3]. To our best knowledge, selective chloromethylation of cavitand has not been reported yet. In this communication, we report a synthesis of mono and bis-chloromethyl cavitands (**2** and **3**, respectively) and mono- and bis-aza-15-crown-5 modified cavitands (**4** and **5**), which were prepared from **2** and **3**, respectively. Compounds **2** and **3** were synthesized from cavitand using excess amounts of chloromethyl methyl ether in the presence of $ZnCl_2$[4,5]. Compound **2** was converted into **3** with a longer reaction time or with using further addition of $ZnCl_2$. Particularly the regioselectivity observed in the bis-chloromethylation is noteworthy in which 1,3-bis-chloromethylated derivative is the major product, and no 1,2-isomer is detected. The ^{1}H-NMR spectrum of **2** shows signals at 4.48 (d, 2H, J=7.2Hz) and 4.58 ppm (d, 2H, J=7.2Hz) attributed to the inner and 5.74 (d, 2H, J=7.2Hz), 5.87 (d, 2H, J=7.2Hz) ppm attributed to the outer methylene protons, respectively. It suggests that chloromethyl group affects the chemical shift of methylene protons. On the other hand, in the ^{1}H-NMR spectrum of bis-chloromethylated derivative (**3**), a signal attributed to inner and outer methylene protons appear at 4.61 (d, 4H, J=7.4Hz) and 5.87 ppm (d, 4H, J=7.4Hz), respectively. It means that each inner or outer proton is equivalent. It is suggested that the chloromethyl groups were introduced at 1 and 3 position of the cavitand as shown in Figure 1. Mono- and bis-aza-15-crown-5 appended cavitands (**4** and **5**) were prepared from **2** and **3** with aza-15-crown-5[4,5] to investigate their metal binding properties. To clarify the complexation characters of **4** and **5** with metal in aprotic solvent, ^{1}H-NMR and UV-Vis spectroscopy studies have been carried out. Figure 2 show the ^{1}H-NMR spectra of the free ligand and of its sodium thiocyanate complex of **4**. By adding variable amounts of NaSCN in CD_3OD to a $CDCl_3$ solution of the

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ligand the ^{1}H-NMR spectrum of the latter changes. The variation in chemical shift is noted by outer methylene protons appeared at 5.84 ppm which moves 0.12 ppm downfield and of its signal is changed as br. doublet into as a clear doublet.

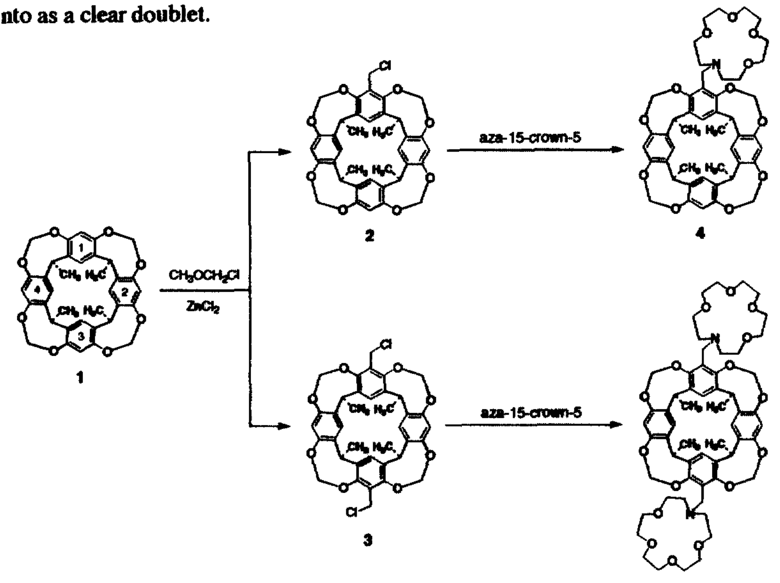


Fig. 1 Preparations of **2**, **3**, **4**, and **5**.

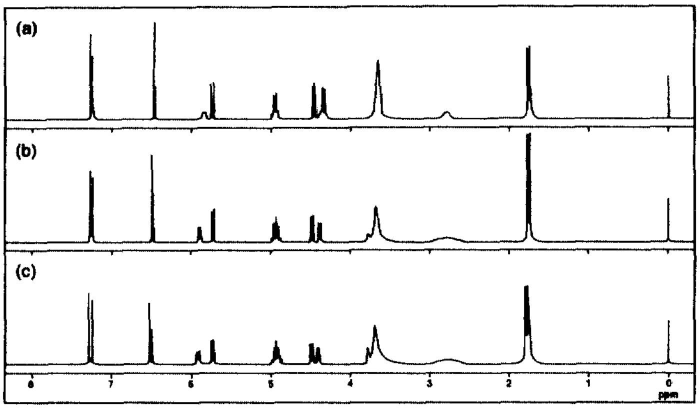


Fig. 2 ^{1}H-NMR spectra of the free and complexed form of ligand **4** in $CDCl_3$ at 25 °C. : (a) R=[NaSCN]/[**4**]=0; (b) R=0.5; (c) R=1; where [**4**]=1.33×10^{-2} M in $CDCl_3$. Aliquots from a 1.0 M solution of NaSCN in CD_3OD were added directly to a $CDCl_3$ solution of **4** in a NMR tube.

The signal attributed to crown ether methylene protons appeared at 3.66 ppm changes splitted two signals at 3.77 and 3.68 ppm. The signals attributed to aromatic-protons at 6.47, 6.48 and 7.26 ppm were small down shifted to 6.49, 6.52 and 7.28 ppm, respectively. These behaviors are due to the contribution of the complexed cation, which induces downfield shifts on protons adjacent to the binding sites, and also to conformation changes. The ^{1}H-NMR titration experiment clearly indicates a 1:1 stoichiometry for the NaSCN complex with ligand (**4**), because all signals remain unchanged after the ratio of the salt/ligand ratio has reached the unity value. The stoichiometry for the NaSCN complex with ligand (**5**) is clarified as a 1:2 host-guest formation by the ^{1}H-NMR titration experiment. On the other hand, the spectrum of native cavitand (**1**) was not absolutely changed by adding of NaSCN.

Figure 3 shows the absorption spectra of **1** and **4**, alone or in the presence of NaSCN.

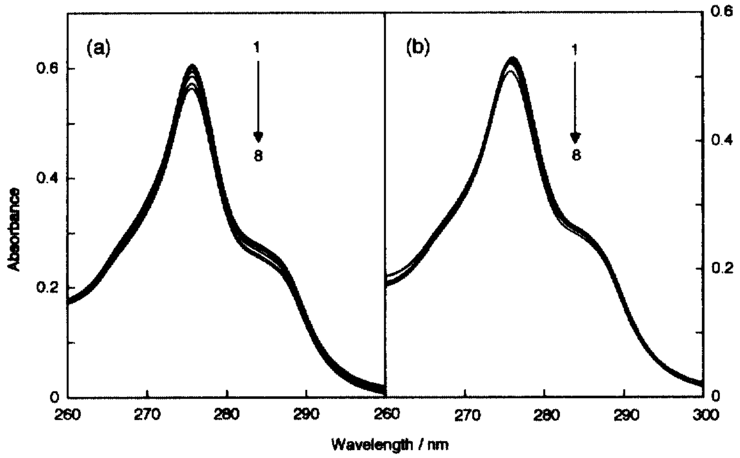


Fig. 3 Absorption spectra of **1** (a) and **4** (b) (1×10^{-4} M) in chloroform at various concentration of NaSCN in MeOH (1:0, 2:2.0×10^{-5}, 3:4.0×10^{-5}, 4:6.0×10^{-5}, 5:1.2×10^{-4}, 6:2.0×10^{-4}, 7:2.9×10^{-4}, 8:4.0×10^{-4} M).

Addition of variable amounts of NaSCN in MeOH to a 10^{-4} M $CHCl_3$ solution causes a bathochromic shift of **1** and **4**. The absorption spectra change of **1** between without or with NaSCN was observed as almost same as for **4**. It means that cavitand (**1**) also can make metal complex in aprotic solvent. It is supposed that metal binding affinity of **1** is weaker than that of **4**, because the ^{1}H-NMR change with sodium cation was not observed in contrast to that of clear changes for **4**. The binding constants (K / mol^{-1} dm^3) of **1** and **4** were obtained by the analysis of the absorbance variations using Eq. 1[6].

$$K = \frac{A_h - A_x}{(A_x - A_c)\left[C_g - C_h\,\dfrac{A_h - A_x}{A_h - A_c}\right]} \qquad \text{Eq. 1}$$

Here, A is absorbance at 276 nm, A_x for sample, A_h for ligand alone, A_c for complex, C_h is total ligand concentration, and C_g is total NaSCN concentration. When metal cation is in large excess, we used Eq. 2 which derives from Eq. 1.

$$\frac{A_h - A_x}{C_g} = KA_x - KA_c \qquad \text{Eq. 2}$$

When metal cation is not in large excess, a curve-fitting method was used as alternative method. Figure 4 shows the curve-fitting data for **1** and **4**. The binding constants obtained are 960 and 3400 for **1** and **4**, respectively. This indicates that **4** can detect Na cation with almost three times than that of **1**. These results suggest that aza-15-crown-5 appended moiety of **4** works as an arm to catch with metal cation and introduce it into the cavity of **4** as depicted in Scheme 1. In conclusion, mono- and bis-aza-15-crown-5

modified cavitands are made to investigate their metal binding properties in $CHCl_3$ solution, in which aza-crown moieties of these compounds work to elevate a metal binding ability.

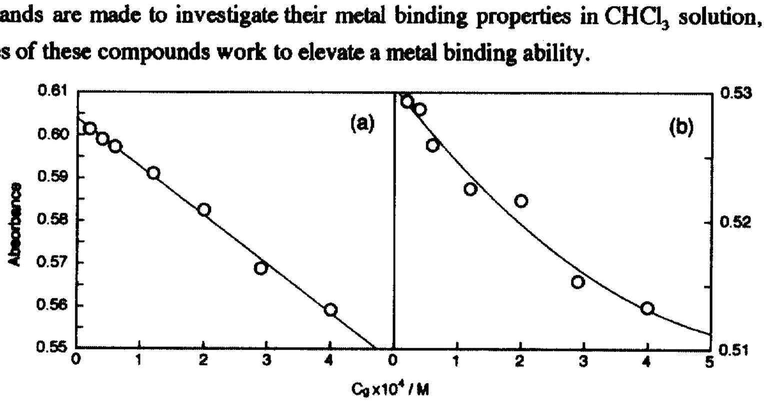
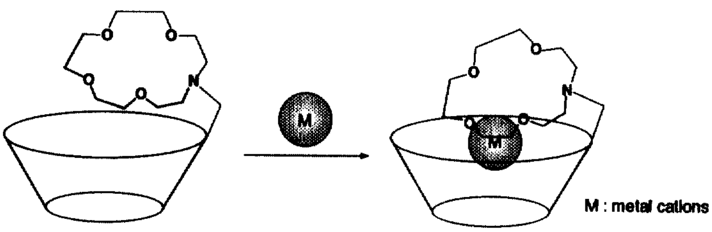


Fig. 4 The plot of absorbance (276 nm) of **1** (a) and **4** (b) as a function of NaSCN concentration.



Scheme 1 Induced-fit type complexation for inclusion of metal cations in the cavity of **4**.

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4) Experimental procedure : a) Preparations of **2** and **3**. A mixture of cavitand (200 mg, 0.34 mmol), $ZnCl_2$ (1.5 mg, 0.01 mmol), and chloromethyl methyl ether (4.3 g, 0.05 mol) was stirred at room temperature for 1 h. The reaction mixture was diluted with chloroform and washed with water, the organic layer was dried and concentrated in vacuo. The crude product was purified by column chromatography using hexane and ethyl acetate as an eluting solvent to give mono-chloromethyl cavitand **2** (yield : 15 %). Compound **3** was prepared by the same procedure of **2** (yield : 35 %) with large amount of $ZnCl_2$. b) Preparations of **4** and **5**. A mixture of mono-chloromethyl cavitand **2** (880 mg, 1.40 mmol), aza-15-crown-5 (330 mg, 1.50 mmol) and potassium carbonate (207 mg, 1.5 mmol) in 85 mL of DMF was stirred at 80 °C for 2 h under a nitrogen atmosphere. The reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography to give mono-chloromethyl cavitand (**4**) (yield : 30 %). Compound **5** was prepared by the same procedure of **4** (yield : 30 %).

5) All compounds synthesized **2** - **5** give satisfactory element analyses and show molecular ion on FAB mass spectra. ^{1}H NMR spectra ($CDCl_3$, 300 MHz) **2**: δ = 1.76 (6H, d, J=7.8Hz, $C\underline{H}_3CH$), 1.77 (6H, d, J=7.2, $C\underline{H}_3CH$), 4.48 (2H, d, J=7.2Hz, inner of CH_2), 4.58 (2H, d, J=7.2Hz, inner of CH_2), 4.66 (2H, s, CH_2Cl), 4.97 (4H, q, J=7.5Hz, $CH_3C\underline{H}$), 5.74 (2H, d, J=7.2Hz, outer of CH_2), 5.87 (2H, d, J=7.2Hz, outer of CH_2), 6.47 (2H, s, Ar-H), 6.54 (1H, s, Ar-H), 7.26 (4H, s, Ar-H). **3**: δ = 1.76 (12H, d, J=7.4Hz, CH_3), 4.61 (4H, d, J=7.4Hz, inner of CH_2), 4.65 (4H, s, CH_2Cl), 4.99 (4H, q, J=7.4Hz, $CH_3\underline{CH}$), 5.87 (4H, d, J=7.4Hz, outer of CH_2), 6.47 (2H, s, Ar-H), 7.26 (4H, s, Ar-H). **4**: δ = 1.76 (12H, d, J=7.5Hz, $C\underline{H}_3CH$), 2.75 (2H, br.s , CH_2N), 3.66 (20H, s, CH_2 of crown ether), 4.34 (2H, d, J=6.9Hz, inner of CH_2), 4.47 (2H, d, J=7.2Hz, inner of CH_2), 4.96 (4H, q, J=7.5Hz, $CH_3C\underline{H}$), 5.74 (2H, d, J=7.2Hz, outer of CH_2), 5.84 (2H, br.s, outer of CH_2), 6.47 (1H, s, Ar-H), 6.48 (2H, s, Ar-H), 7.26 (4H, s, Ar-H). **5**: δ = 1.75 (12H, d, J=7.2Hz, $C\underline{H}_3CH$), 2.74 (4H, br.s, CH_2N), 3.65 (40H, s, CH_2 of crown ether), 4.36 (4H, d, J=7.2Hz, inner of CH_2), 4.96 (4H, q, J=7.2Hz, $CH_3C\underline{H}$), 5.80 (4H, d, J=7.2Hz, outer of CH_2), 6.45 (2H, s, Ar-H), 7.26 (4H, s, Ar-H).

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