



Syntheses and Cation Complexation Studies of New Cavitand Derivatives

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(Received: 5 November 2002; in final form: 12 June 2003)

Key words: alkali cation, cavitand, complexation, ionophore, recognition, resorcinarene

Abstract

A series of new cavitands containing four esters, nitriles, 2-pyridyl, or 3-pyridyl groups were synthesized from tetrahydroxycavitand. Their binding properties towards various metal ions are investigated.

Introduction

Compared to calix[4]arene derivatives [1], it has been only a few years since cavitand derivatives have been used extensively as ionophores. Cavitands are rather rigid and have enforced cavities compared to calix[4]arenes. Recent efforts to improve the yield of tetrabromocavitand [2] or tetrakis(bromomethyl)cavitand [3] initiated the recent reports utilizing these intermediates for the syntheses of various host compounds based on cavitand moiety. Recently, various cavitand derivatives have been synthesized as host compounds for metal ion recognition [4], anion recognition [5], and organic guests [6].

Noteworthy and most related was a paper reported by Paek and his co-worker in which tetrakis(bromomethyl)cavitand was used as a starting material for the syntheses of cavitand derivatives containing four imidazolyl, pyrazolyl, benzimidazolyl, indazolyl or 2-pyridinyl groups [7]. In this report, we report the syntheses of four different cavitand derivatives containing four esters, nitriles, 2-pyridyl, or 3-pyridyl groups utilizing tetrahydroxycavitand as an intermediate for these syntheses. Also, the binding properties of these cavitands towards metal ions are investigated.

Experimental

Instruments and chemicals

NMR spectra were recorded at 200 MHz (for ¹H-NMR) and at 50 MHz (for ¹³C-NMR) using a Varian Gemini200 Spectrometer. Mass spectra and elemental analysis were obtained using the JEOL-JMS-HX 110A/110A High Resolution Tandem Mass Spectrometry and Vario EL of Elemental Analyzer in the Korea Basic Science Institute in

Taejon, Korea. Melting points were determined in open capillaries, and are uncorrected. UV absorption spectra were obtained on UVIKON 933 Double Beam UV/VIS Spectrometer. ICP-IRIS from Thermo Jarrell Ash was used to obtain the concentrations of metal ions. Flash chromatography was carried out using Merck silica gel 60 (230 to 400 mesh). Thin layer chromatography was carried out using Merck 60 F₂₅₄ plates with a 0.25-mm thickness.

Most of the chemicals were obtained from Sigma-Aldrich Chemical Company, Milwaukee, WI. The CHCl₃, CH₂Cl₂, and MeOH were distilled from CaH₂.

Synthesis

Tetrakis[(methoxycarbonyl)methoxy]cavitand (2)

To a stirred solution of tetrahydroxy cavitand **1** (500 mg, 0.492 mmol) and K₂CO₃ (1.40 g, 10.0 mmol) in anhydrous acetone (80 ml) was slowly added methylbromoacetate (0.47 ml, 5.0 mmol). The reaction mixture was stirred at 56 °C for 2 days. After the reaction mixture was filtered through celite, the filtrate was concentrated *in vacuo* to dryness. Recrystallization with dichloromethane-methanol gave tetraester cavitand **2** as a white solid (546 mg, 85%). M.p. 285 °C dec. ¹H NMR (CDCl₃, 200 MHz) δ 2.47–2.67 (m, 16H), 3.78 (s, 12H), 4.44 (d, *J* = 7.0 Hz, 4H), 4.58 (s, 8H), 4.81 (t, *J* = 7.6 Hz, 4H), 5.77 (d, *J* = 7.0 Hz, 4H), 6.85 (s, 4H), 7.20 (m, 20H). ¹³C NMR (CDCl₃, 50 MHz) δ 32.4, 34.5, 37.0, 51.9, 69.9, 114.1, 126.0, 128.3, 138.6, 141.5, 144.0, 147.5, 169.5. MS (FAB, NBA) *m/z* = 1305 (M + H⁺). Anal. Calcd for C₇₆H₇₂O₂₀: C, 69.93; H, 5.56. Found: C, 69.80; H, 5.75.

Tetrakis(cyanomethoxy)cavitand (3)

To a stirred solution of tetrahydroxy cavitand **1** (500 mg, 0.492 mmol), K₂CO₃ (1.40 g, 10.0 mmol) and NaI (600 mg, 4.0 mmol) in anhydrous acetone (15 ml) was slowly added bromoacetonitrile (0.28 ml, 4.0 mmol). The reaction mixture was stirred at 56 °C for 2 days. The reaction mixture

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was then passed through a celite, and further eluted with CH_2Cl_2 (20 ml). The combined filtrate was then concentrated under reduced pressure, and the residue was purified using flash chromatography (CH_2Cl_2 : EtOAc, 20 : 1) to afford **3** (490 mg, 85%) as a white solid. M.p. 310 °C dec. ^1H NMR (CDCl_3 , 200 MHz) δ 2.46–2.68 (m, 16H), 4.41 (d, $J = 7.0$ Hz, 4H), 4.69 (s, 8H), 4.83 (t, $J = 7.6$ Hz, 4H), 5.95 (d, $J = 7.0$ Hz, 4H), 6.93 (s, 4H), 7.20 (m, 20H). ^{13}C NMR (CDCl_3 , 50 MHz) σ 32.4, 34.5, 37.0, 51.9, 69.9, 99.9, 114.1, 126.0, 128.3, 128.5, 138.6, 141.5, 144.1, 147.5, 169.5. MS (FAB, NBA) $m/z = 1117$ ($\text{M} + \text{H}^+$). Anal. Calcd for $\text{C}_{72}\text{H}_{60}\text{O}_{12}\text{N}_4 \cdot \text{H}_2\text{O}$: C, 72.59; H, 5.25; N, 4.70. Found: C, 72.53; H, 5.37; N, 4.55.

Tetrakis(2-pyridinylmethoxy)cavitand (4)

Procedure A. To a solution of tetrahydroxy cavitand **1** (200 mg, 0.197 mmol), K_2CO_3 (1.09 g, 7.88 mmol) in degassed DMF (30 ml) was added 2-(chloromethyl)pyridine (650 mg, 3.9 mmol). The reaction mixture was stirred at 80 °C for 60 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 30 ml of EtOAc and washed several times with distilled water and finally with brine. The organic layer was concentrated under reduced pressure, and the residue was purified using flash chromatography (EtOAc : MeOH, 5 : 1) to afford **4** (200 mg, 75%) as a white solid. M.p. 330 °C dec. ^1H NMR (CDCl_3 , 200 MHz) δ 2.53–2.71 (m, 16H), 4.50 (d, $J = 7.0$ Hz, 4H), 4.87 (t, $J = 7.6$ Hz, 4H), 5.13 (s, 8H), 5.79 (d, $J = 7.0$ Hz, 4H), 6.91 (s, 4H), 7.20 (m, 20H), 7.61 (d, $J = 7.6$ Hz, 4H), 7.73 (m, 4H), 8.55 (d, $J = 4.0$ Hz, 4H). ^{13}C NMR (CDCl_3 , 50 MHz) δ 32.3, 34.4, 37.1, 99.1, 114.3, 121.5, 122.6, 126.0, 128.3, 128.5, 136.4, 139.1, 141.8, 144.2, 148.3, 149.0, 149.2. MS (FAB, NBA) $m/z = 1381$ ($\text{M} + \text{H}^+$). Anal. Calcd for $\text{C}_{88}\text{H}_{76}\text{O}_{12}\text{N}_4 \cdot \text{H}_2\text{O}$: C, 75.52; H, 5.62; N, 4.00. Found: C, 75.60; H, 5.57; N, 4.17.

Tetrakis(3-pyridinylmethoxy)cavitand (5)

Application of procedure A to 200 mg of tetrahydroxy cavitand **1** (0.197 mmol), 1.09 g of K_2CO_3 (7.88 mmol), 30 ml of DMF, and 650 mg of 3-(chloromethyl)pyridine (3.9 mmol) gave 196 mg (72%) of **5** after column chromatography (EtOAc : MeOH, 5 : 1). M.p. 330 °C dec. ^1H NMR (CDCl_3 , 200 MHz) δ 2.48–2.68 (m, 16H), 4.47 (d, $J = 7.0$ Hz, 4H), 4.85 (t, $J = 7.5$ Hz, 4H), 4.99 (s, 8H), 5.84 (d, $J = 7.0$ Hz, 4H), 6.90 (s, 4H), 7.20 (m, 20H), 7.76 (d, $J = 7.6$ Hz, 4H), 8.57 (d, $J = 3.3$ Hz, 4H), 8.64 (s, 4H). ^{13}C NMR (CDCl_3 , 50 MHz) δ 32.3, 34.5, 37.0, 72.8, 99.4, 114.4, 123.2, 126.0, 128.3, 128.5, 133.0, 135.3, 138.8, 141.5, 144.3, 148.4, 149.1, 149.2; MS (FAB, NBA) $m/z = 1381$ ($\text{M} + \text{H}^+$). Anal. Calcd for $\text{C}_{88}\text{H}_{76}\text{O}_{12}\text{N}_4 \cdot \text{H}_2\text{O}$: C, 75.52; H, 5.62; N, 4.00. Found: C, 75.59; H, 5.77; N, 4.22.

Extraction, transport and NMR titration experiments

Competitive extraction experiment

A mixture of the metal nitrate (5 mL, 0.15 mM in water) and the host (5 mL, 0.3 mM in chloroform) in a centrifuge tube

was shaken for 2 hours using Vortex-Genie and then centrifuged at 5000 rpm for 5 min. After being kept for 30 min in a thermostat at 25 °C, the concentration of remaining metal ions in aqueous solution was measured using ICP.

Competitive transport experiments

The host (5 mL, 0.3 mM in chloroform) was added to a U-tube. After adding 15 mL of double distilled water (out), a mixture of the metal nitrate (5 mL, 0.15 mM in water) was added to a U-tube (in). After this chloroform layer was stirred by a magnetic stirrer for 48 hours, the concentration of remaining metal ions in aqueous solution was measured using ICP.

Picrate extraction experiment of silver and zinc picrates

A two-phase liquid-liquid extraction experiment was carried out between an aqueous solution (0.5 mL, [metal picrate] = 0.015M) and a chloroform solution (0.1 mL, [Host] = 0.075M). The two-phase mixture in a tightly-stoppered centrifuge tube was shaken with a Voltex-Genie for 1 min at 25 °C and then centrifuged at 1600 rpm for 1 min. The extractability was determined spectrophotometrically from the decrease of the picrate ion in the aqueous phase.

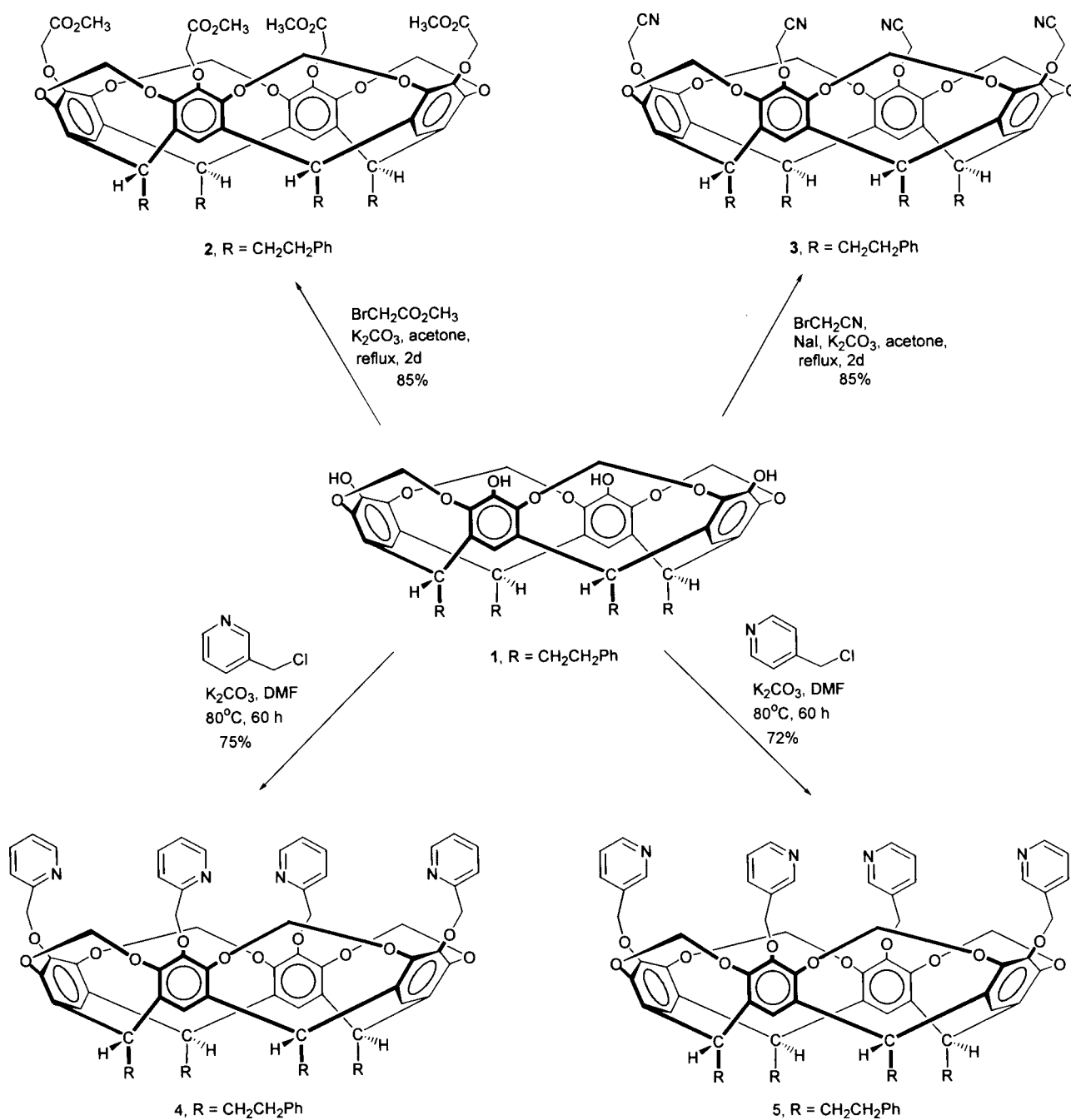
NMR titration method

All NMR experiments were performed on a Bruker 250 (250 MHz) spectrometer at 298 K. A solution (1 mM) of hosts in CDCl_3 was titrated with an aliquot of a stock solution (10 mM) of guests as acetoacetone salts in the same solvent. Data analysis was made using the WinEQNMR computer program. Every titration was repeated at least once till consistent values are obtained.

Results and discussion

Tetrahydroxycavitand **1** is better known as an intermediate for the syntheses of carcerands or hemicarcerands [8]. Our synthesis began with this tetrahydroxycavitand **1**, which was prepared using the published procedure [9, 2]. Kiafer and co-worker recently developed a new method to improve the yield of tetrabromocavitand, a precursor of **1** [2]. Syntheses of cavitands (**2**, **3**, **4** and **5**) were quite straightforward. Treatment of tetrahydroxycavitand **1** with methylbromoacetate and potassium carbonate in acetone afforded cavitand **2** in a yield of 85% after recrystallization from dichloromethane-methanol. In a similar way, treatment of cavitand **1** with bromoacetonitrile and potassium carbonate gave cavitand **3** in 85% yield after column chromatography. Finally, when cavitand **1** was reacted with 2-(chloromethyl)pyridine or 3-(chloromethyl)pyridine in the presence of potassium carbonate in DMF, cavitand **4** or cavitand **5** was obtained in 75% or 72% yield after column chromatography.

These four different compounds contain four carbonyl groups, cyano groups, 2-pyridinyl groups or 3-pyridinyl groups, respectively. Four carbonyl groups can generate a representative hard binding site while nitrogen atoms in cyano groups can make a soft binding site with sp lone pairs.



Scheme 1. Synthesis of four different cavitands 2, 3, 4 and 5.

Finally, sp² hybridised nitrogen atoms in pyridine can also make soft binding sites in 4 and 5. From the CPK model, unlike cavitand 5, host 4 can converge to form a binding site for a spherical cation in an inclusion fashion, which can generate the additional cation- π interactions. Paek and his coworkers recently reported that a cavitand bearing four pyrazole groups showed such a binding mode with silver ion [7b].

Competitive transport of metal ions with hosts 2, 3 and 5 were conducted following the published procedure (Table 1) [9]. The concentrations of metal ions were determined using ICP atomic emission spectrometer. In particular, cavitand 5

Table 1. Competitive transport of metal ions by bulk liquid membrane using cavitands (%)

Host	Na ⁺	K ⁺	Mg ²⁺	Ca ²⁺
2	12.8	1.96	1.52	6.6
3	11.6	2.46	1.94	6.80
5	11.1	0	1.26	14.9

showed a moderate selectivity for Ca²⁺ compared to host 2 and 3.

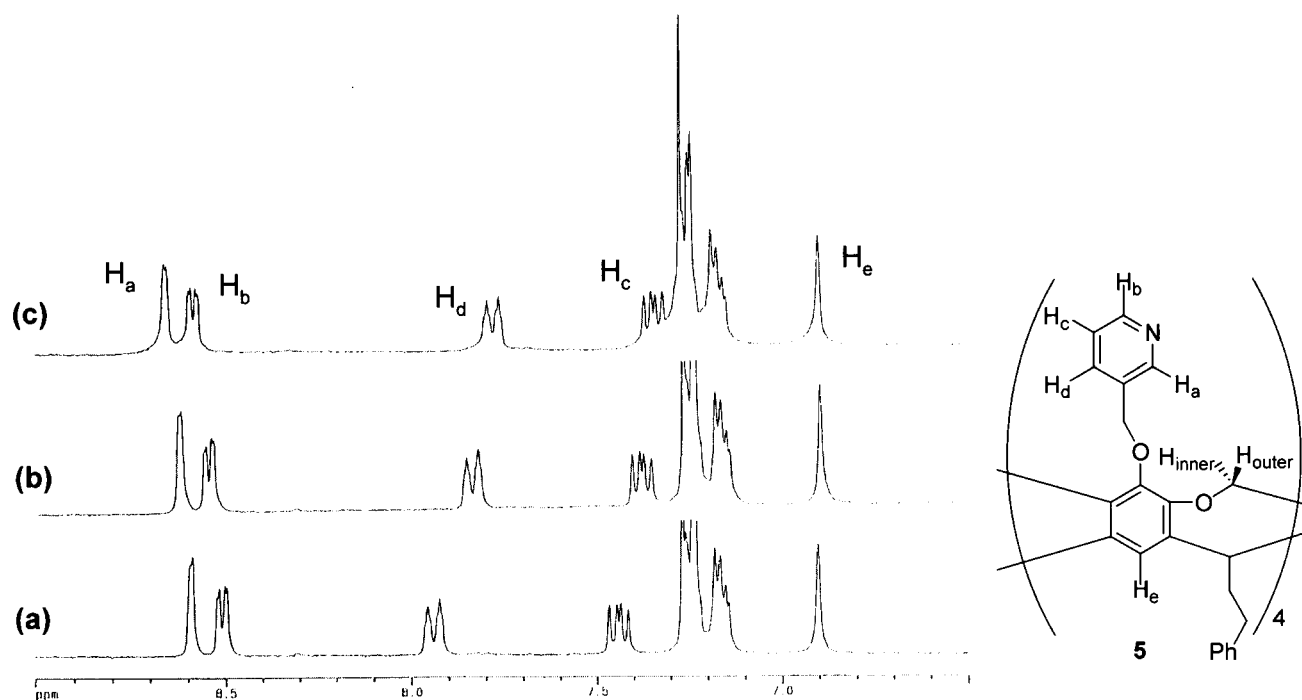


Figure 1. Partial ^1H NMR (250 MHz) of **5** (1 mM) in CDCl_3 . (a) Compound **5** only; (b) **5** + 2 equiv of zinc acetylacetonate; (c) **5** + 5 equiv of zinc acetylacetonate.

Table 2. Competitive extraction of alkali metal ions by cavitands (%)

Host	Na^+	K^+	Rb^+
2	0	0	10.04
3	0	0	11.65
5	0	0	11.88

Table 3. Percentage extraction of metal picrates by cavitands at 298 K (%)

Metal picrates	Host 2	Host 3	Host 4	Host 5
Ag^+	0	9	–	90
Zn^{2+}	0	5	64	65

These cavitands show selective extractabilities for Rb^+ among the alkali metal ions examined (Table 2). The concentrations of metal ions in aqueous phase were also determined using ICP atomic emission spectrometer.

Extraction experiments of silver and zinc picrates by cavitands **2**, **3**, **4** and **5** clearly demonstrate the different binding affinities among these host compounds (Table 3). The percentage extraction (Ex %) was calculated by measuring the picrate concentration in the aqueous phase. Tetrapyrrolyl cavitands **4** and **5** showed high extractabilities for silver and zinc picrates. On the other hand, tetraester cavitands **2** and tetranitrile cavitand **3** did not extract those metal picrates into organic phase. These results suggest that sp^2 hybridised nitrogen atoms of cavitands **4** and **5** make a

good soft binding site for silver or zinc ions. The extraction experiment of silver picrate with cavitand **4** failed because of precipitation problem.

Partial ^1H NMR spectra of **5** upon the addition of Zn^{2+} acetylacetonate in CDCl_3 are shown in Figure 1. For example, the deshielding effects (as large as 0.25 ppm) were observed for H_d of cavitand **5**. For cavitand **5**, deshielding effects as large as 0.1 ppm were also observed for H_{inner} and H_{outer} (Figure 1). On the other hand, small shielding effects were observed in the case of cavitand **4**, which can lead to the conclusion that the acetylacetonate ions are located close to the cavitand pocket. From the ^1H NMR titrations in CDCl_3 , the association constants for Zn^{2+} acetylacetonate with cavitand **4** and **5** are calculated as 220 and 610 M^{-1} (errors < 10%), respectively. The methylene peaks (OCH_2CN) in cavitand **3** also shifted to downfield, however, the values are too small to obtain the association constant. On the other hand, cavitand **2** did not display any change in its chemical shifts upon the addition of Zn^{2+} acetylacetonate (up to 20 equiv). The ^1H NMR titrations with acetylacetonate salts of Al^{3+} , Co^{2+} and Ni^{2+} caused precipitation problems in CDCl_3 . The stoichiometry of the complex (1 : 1) was confirmed by a Job plot utilizing the NMR titrations of **5** with Zn^{2+} acetylacetonate in CDCl_3 (Figure 2).

Conclusions

Cavitands are rather rigid and have enforced cavities compared to calix[4]arenes. Therefore, cavitands may provide rather rigid and preorganized binding sites for metal ions. Four different cavitands bearing four esters, nitriles, 2-pyridyl or 3-pyridyl groups have been synthesized from

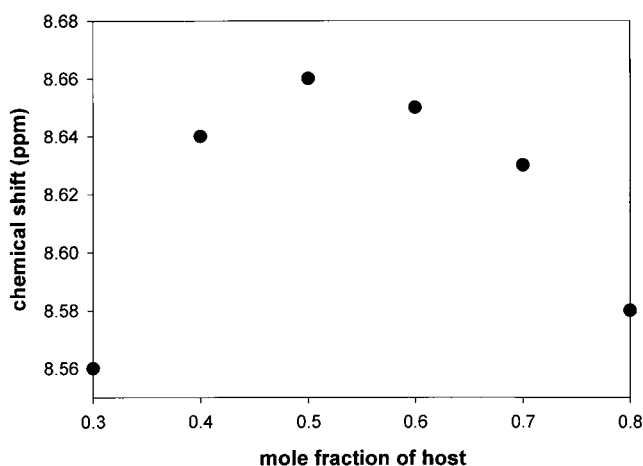


Figure 2. Job plot between host **5** and zinc acetylacetonate using ^1H NMR changes.

tetrahydroxycavitand. These compounds represent four different kinds of binding sites such as a relatively hard binding site from four carbonyl oxygens, sp lone pairs of nitrile, sp^2 hybridized nitrogen atoms and cation- π interaction in 2-pyridyl groups and finally just sp^2 hybridized nitrogen atoms in 3-pyridyl groups. Cavitands **4** and **5** bearing sp^2 hybridized nitrogen atoms showed high extractabilities for silver and zinc ions, on the other hand, cavitands **2** and **3** did not extract silver and zinc ions. The association constants of cavitands **4** and **5** with Zn^{2+} were calculated as 220 and 610 M^{-1} , respectively.

Acknowledgment

This work was supported by the Dongguk University Fund.

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