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Cation Recognition by Picolyl-Armed Calix[4]crown-5-azacrown-5s

JONG SEUNG KIM[1,*], JEONG AH RIM[1], OK JAE SHON[1], KWAN HO NOH[1], EUN-HEE KIM[2], CHAEJOON CHEONG[2] and JACQUES VICENS[3,*]

[1]*Department of Chemistry, Konyang University, Nonsan 320-711, Korea;* [2]*Magnetic Resonance Team, Korea Basic Science Institute, Daejon 305-333, Korea;* [3]*ECPM, Laboratoire de Chimie des Interactions Moléculaires Spécifiques, associé au CNRS, 25 rue Becquerel, F-67087 Strasbourg, Cédex 2, France*

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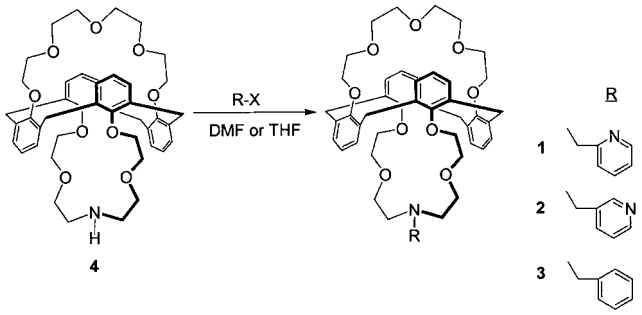
Abstract

A series of *N*-pivot calix[4]crown-5-azacrown-5 ethers substituted by 2-picolyl, 3-picolyl and benzyl groups respectively were synthesized. The nitrogen atom of the 2-picolyl group is found to participate in the silver ion complexation through three dimensional encapsulation.

Introduction

The 1,3-alternate conformation of calix[4]arenes has been useful to construct 1,3-calix[4]-*bis*-crowns type receptors presenting structural peculiarities [1]. They present two binding sites situated on both sides of the calixarene and linked to each other by a π-basic benzene tunnel [2]. This symmetrical arrangement is well adapted for the formation of 1:1 and 1:2 metal complexes. For example in the 1:1 complexes with 1,3-calix[4]-*bis*-crown-5, the cation switches from one binding site to the other through the π-basic benzene tunnel [3]. The replacement of the central O donor atom by one or two N*H* groups in the crown loops lead to 1,3-calix[4]azacrowns in which the switching of the cation (in the case of ammonium) is stopped probably due to a better binding of the ammonium by the N*H* function [4].

We previously reported the synthesis and metal ion complexation studies of 1,3-calix[4]-*mono*-azacrowns in which the central N*H* group is substituted by a 2-hydroxy-5-nitro benzyl and 2-picolyl, 3-picolyl and benzyl groups [5, 6]. In both cases the presence of a chelating function at the 2-position of the benzyl group was assumed to favor the complexation in the crown loop by encapsulation of the metal cation. This led us to prepare 1,3-calix[4]crown-azacrowns **1-3** composed of a calix[4]arene unit in the 1,3-alternate conformation and bearing on one side one crown ether and on the other side a *N*-pivot azacrown ether substituted by 2-pycolyl, 3-picolyl and benzyl groups, respectively. By this means we anticipated to differentiate one cavity from the other.



Scheme 1. Reaction pathway to prepare compounds **1–3**.

Results and discussion

The introduction of a pyridine moiety to the azacrown framework has been reported to produce a powerful binding site for metal cations [6–11]. This stimulated us to design a picolyl-armed calix[4]azacrown ether in which a picolyl-armed azacrown loop links to the 1,3-alternate calix[4]arene framework. The synthetic schemes for preparing the picolyl- and benzyl-armed calixazacrown ethers are shown in Scheme 1. Starting material **4** having 1,3-alternate conformation could be prepared from calix[4]arene [5]. The coupling reaction with 2-picolyl or with 3-picolyl chloride in the presence of triethylamine in DMF gave the desired products **1** and **2** in moderate yields. In the case of the reaction with benzyl bromide, the reaction solvent should be changed to THF. All of the products were confirmed to be in the fixed 1,3-alternate conformation based on ^{1}H and ^{13}C NMR spectral assignments.

A preliminary evaluation of the binding efficiencies of **1-3** was carried out by solvent extraction of cation picrates into chloroform at 25 °C under neutral conditions. The results are given in Table 1. The largest % extraction values were observed for ligand **1** for hard and soft metal cations. This

* Corresponding authors: E-mail : jongskim@konyang.ac.kr. Fax: +82-41-733-5240 (J. S. Kim) E-mail : vicens@chimie.u-strasbg.fr. Fax: +33-(0)-388136932 (J. Vicens)

Table 1. Extraction of metal picrate by calixazacrown ethers **1–3**.[a]

Ligand	Extraction (%)						
	Na^+	K^+	Rb^+	Cs^+	NH_4^+	Ag^+	Pb^{2+}
1	37.3	62.7	43.0	43.6	52.3	78.9	41.4
2	36.3	22.7	19.8	12.1	16.1	24.2	9.30
3	4.30	25.8	23.5	16.1	15.0	21.2	15.9

[a] Average extraction determined by three independent experiments at 25 °C.

behavior was attributed to the presence of the nitrogen atom at the 2-position of the aromatic ring assisting the chelation of the cation. To better understand cation complexation, we performed ^{1}H NMR spectroscopy in CD_3CN solution for the complexes. These ^{1}H NMR studies based on the chemical shifts of selected proton signals of the calixazacrown **1** can provide cation selectivity, the extent of pyridyl unit participation, and the possibility of cation-π interaction in cation complexation. The shifted values for the induced proton signal that we have obtained were highly dependent upon the nature of the guest ion. Silver ion showed the greatest changes in chemical shift (ppm) reflecting silver ion selectivity, which is consistent with the results from the two-phase extraction experiments. Compound **3** which has a benzyl group, showed no chemical shift changes for the aromatic hydrogen atoms, providing an important clue for the three-dimensional participation of the pyridyl group (in the case of **1**) in metal ion complexation [6].

In order to obtain more information on the chelation process, we further focused on the complexation of the two most extracted cations: K^+ (as representative of a hard cation) and Ag^+ (as representative of a soft one). Thus, ^{1}H-NMR studies were aimed at locating these cations in the receptor presenting two discrete binding sites. Ligand **1** (∼20 mg) was mixed with an excess of $KClO_4$ or $AgClO_4$ for 5 h in CD_3CN. The unreacted solid was filtered off before recording ^{1}H-NMR spectra. Table 2 gives the cation-induced changes in the ^{1}H-NMR chemical shifts of selected signals of ligand **1**. Both spectra show free ligand leading us to conclude that the complexes are probably 1:1. For the **1**·Ag^+ complex, we observed a remarkable chemical shift for $H_a - H_d$ of the pyridine unit as well as for H_g (+0.19) and H_h (+0.12). This ^{1}H NMR investigation clearly demonstrates that the silver ion can be encapsulated by the cavity distally located azacrown ring of the calix[4]arene, by the cation-π interaction, and by the nitrogen atom of the 2-picolyl unit as indicated in Figure 1. On the other hand, for the **1**·K^+ complex, only small changes for $H_a - H_d$ were observed, implying that the K^+ ion was not likely to take part in the azacrown. Instead, H_j and H_k show chemical shift changes of +0.19 ppm and +0.08 ppm, respectively. H_l and H_m of the ethylene glycol unit of the crown also show large chemical shifts of +0.47 ppm and +0.63 ppm, respectively, which were not observed in the case of the **1**·Ag^+ complex, indicating that the K^+ ion is surrounded by the crown-5 part in preference to the azacrown part (see Figure 1).

Future work will be devoted to temperature dependent NMR spectroscopy to show evidence of possible inter- and intramolecular metal-ligand exchanges as observed in 1,3-calix[4]-*bis*-crown-5 [3]. Also, the determination of thermodynamical parameters of complexation are in current development.

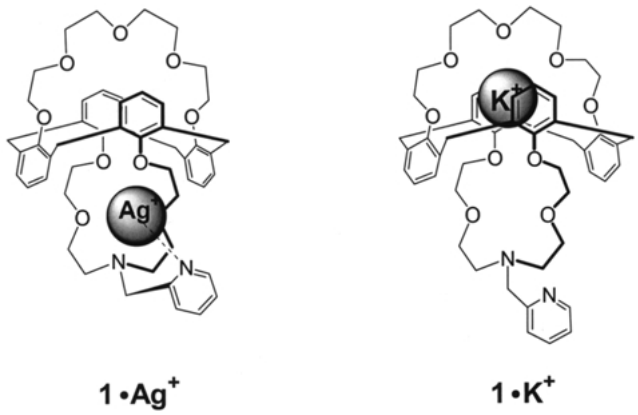


Figure 1. Metal ion complexation behavior.

Experimental

Instruments and chemicals

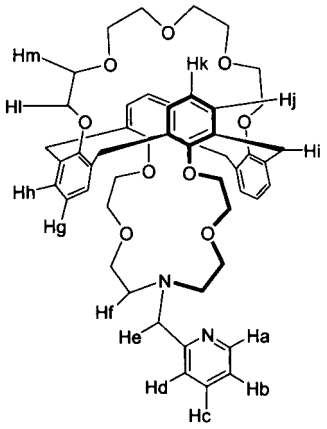
Analytical procedures: Mps, capillaries under nitrogen, Büchi 500, Al_2O_3 (507C, neutral, 100–250 mesh), SiO_2 (Art. 11567). ^{1}H NMR (δ in ppm from TMS, J in Hz) in $CDCl_3$, Bruker ARX-600 at Taejon (KBSI). Elemental analysis, Vario EL Elemental Analyzer. Commercial grade reagents were used without further purification. THF was freshly distilled from sodium, DMF was dried over 4 Å molecular sieves. Compound **4** was prepared as described in the literature [5].

Synthesis

*N-(2-Picolyl) calix[4]crown-5-azacrown-5 (**1**)*

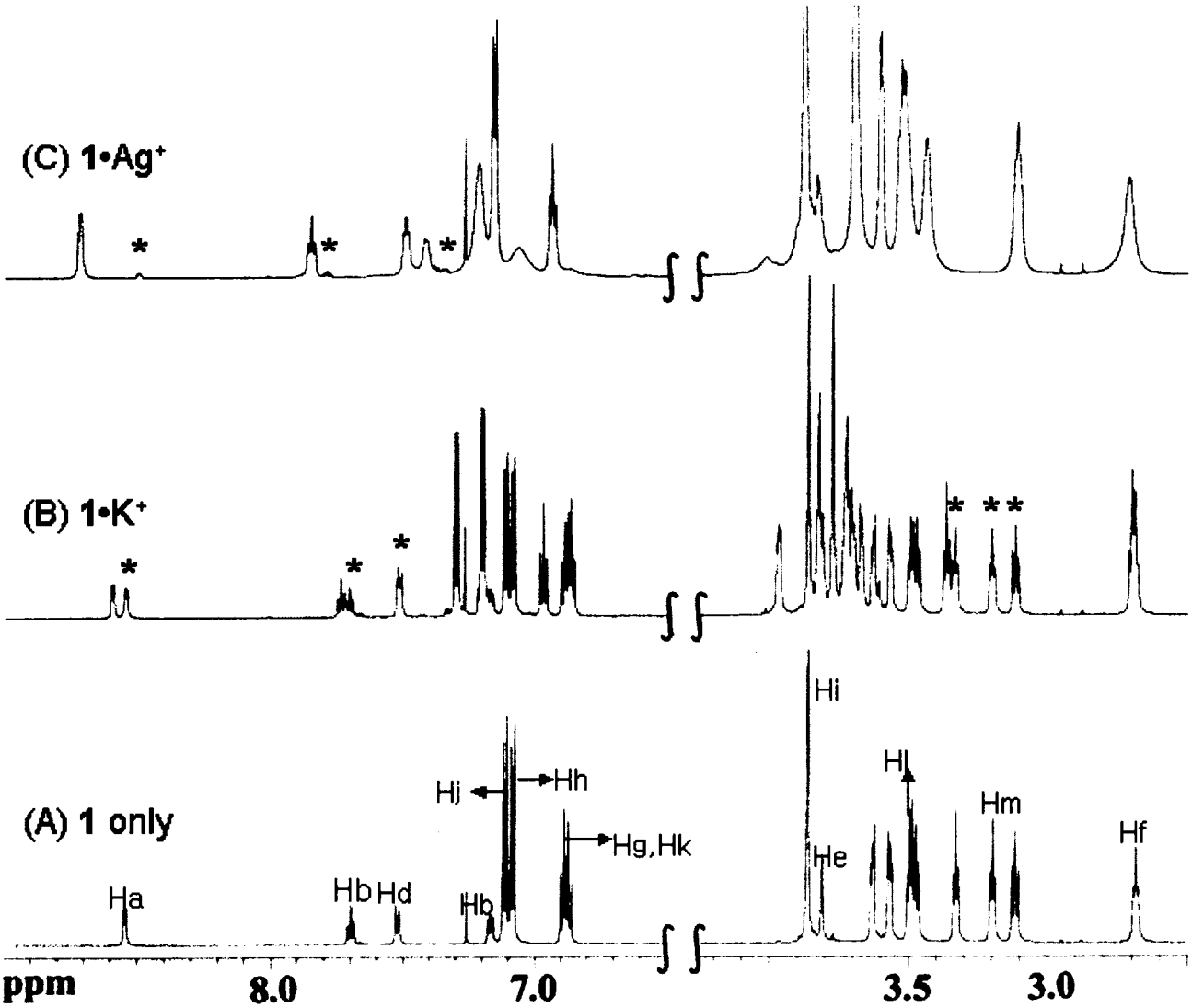
Calix[4]azacrown (**4**) (1.016 g, 1.5 mmol) was reacted with triethylamine (0.62 mL, 4.7 mmol) in DMF (70 mL) by heating at 150 °C for 30 min. 2-Picolyl chloride (0.270 g, 1.6 mmol) dissolved in DMF (50 mL) was added dropwise during 1 h and the mixture was stirred for an additional 24 h. After evaporation of the solvents *in vacuo*, the residue was chromatographed on an Al_2O_3 column with a 1:2 ethylacetate:hexane mixture as eluent. Recrystallization from *n*-hexane gave **1** as white solid. Yield 35%. Mp 105-107 °C. IR (KBr pellet, cm^{-1}): 2911, 1451, 1359, 1243, 1127, 756, 633. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.55–7.16 (m, 4 H, pyridyl unit), 7.12 (d, J = 7.5 Hz, 4 H, ArH_m-calix), 7.09 (d, J = 7.5 Hz, 4 H, ArH_m-calix), 6.90–6.86 (m, 4 H, ArH_p-calix), 3.86 (s, 8 H, Ar-CH_2-Ar), 3.81 (s, 2 H, pyridyl-CH_2-N), δ 3.64–3.11 (m, 28 H, OCH_2CH$_2$N, OCH_2CH_2O), 2.69 (t, J = 5.2, 4 H, OCH$_2$CH_2NCH_2CH$_2$). ^{13}C NMR (125 MHz, $CDCl_3$): ppm 157.6, 157.0, 134.8, 134.6, 130.2, 123.5, 123.4, 73.7, 71.5, 71.3, 70.3, 70.1, 68.7, 54.1, 38.8, 30.4. Anal. Calcd for $C_{50}H_{58}N_2O_9$: C, 72.28; H, 6.98. Found C, 72.31; H: 6.97.

Table 2. Cation-induced changes in ^{1}H NMR chemical shifts of lariat calixazacrown ether **1**.



Metal	Induced chemical shift (ppm)[a]												
	a	b	c	d	e	f	g	h	i	j	k	l	m
K^+	+0.05	+0.03	+0.04	+0.00	+0.00	+0.02	−0.01	+0.12	−0.09	+0.19	+0.08	+0.47	+0.63
Ag^+	+0.17	+0.32	+0.15	−0.11	+0.02	+0.03	+0.19	+0.12	+0.01	+0.04	+0.05	+0.03	+0.08

[a] Induced chemical shift (ppm) = (chemical shift of the complex) – (chemical shift of the parent ligand); (+) and (−) refer to down-field and up-field shifts.



*N-(3-Picolyl) calix[4]crown-5-azacrown-5 (**2**)*

The preparation method is same with that of **1**. Oil. Yield 34%. IR (neat, cm^{-1}): 2911, 1453, 1359, 1200, 1096, 1039, 949, 841, 780, 633. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.56–7.26 (m, 4 H, pyridyl unit), 7.12 (d, J = 7.5 Hz, 4 H, ArH_m-calix), 7.09 (d, J = 7.56 Hz, 4 H, ArH_m-calix), 6.89–6.83 (m, 4 H, ArH_p-calix), 3.84 (s, 8 H, Ar-CH_2-Ar), 3.62–3.08 (m, 30 H, pyridyl-CH_2-N, OCH_2CH$_2$N, OCH_2CH_2O), 2.59 (broad s, 4 H, OCH$_2$CH_2NCH_2CH$_2$O). ^{13}C NMR (125 MHz, $CDCl_3$): ppm 156.9, 156.3, 150.2, 148.3, 136.6, 135.2, 134.1, 133.9, 133.6, 129.7, 129.6, 129.5, 129.4, 129.0, 128.2, 123.3, 123.2, 122.7, 118.9, 73.0, 70.8, 69.7, 69.6, 67.9, 67.1, 59.0, 57.6, 53.2, 38.12, 30.0. Anal. Calcd for $C_{50}H_{58}N_2O_9$: C, 72.28; H, 6.98. Found C, 72.30; H: 7.10.

*N-(Benzyl) calix[4]crown-5-azacrown-5 (**3**)*

Compound (**4**) (1.023 g, 1.5 mmol) and triethylamine (0.46 mL, 3.18 mmol) were refluxed in THF (70 mL) for 30 min. Benzylbromide (0.19 mL, 1.6 mmol) dissolved in THF (50 mL) was added dropwise for 1 h. Refluxed for an additional 24 h. Column chromatography on SiO_2 with a 1:2 ethylacetate:hexane mixture as eluent. Oil. Yield 36%. IR (neat, cm^{-1}): 2919, 1451, 1359, 1197, 1088, 1042, 949, 772, 633. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5 H, NCH$_2$Ar-H), 7.12 (d, J = 7.5 Hz, 4 H, ArH_m-calix), 7.10 (d, J = 7.5 Hz, 4 H, ArH_m-calix), 6.91–6.85 (m, 4 H, ArH_p-calix), 3.86 (s, 8 H, Ar-CH_2-Ar), 3.64–3.12 (m, 30 H, Ar-CH_2-N, OCH_2CH$_2$N, OCH_2CH_2O), 2.62 (broad s, 4 H, OCH$_2$CH_2NCH_2CH$_2$). ^{13}C NMR (125 MHz, $CDCl_3$): ppm 156.8, 156.3, 134.1, 133.9, 129.5, 129.4, 128.9, 128.16, 122.8, 122.6, 72.9, 70.8, 70.5, 69.9, 69.7, 68.0, 60.4, 53.4, 38.1, 31.0. Anal. Calcd for $C_{51}H_{59}NO_9$: C, 73.82; H, 7.12. Found C, 73.81; H: 7.18.

^{1}H NMR of Complexes

Samples of metal picrate complexes were prepared for ^{1}H NMR as follows. A mixture of **1** (20 mg) and excess metal perchlorate (at least 5 equivalents) in CD_3CN (3 mL) was stirred for 5 hr. After filtration of the precipitated metal picrate, the proton-NMR (600 MHz) spectra of the filtrate was obtained (see Table 2).

Two-phase extraction

The picrate concentration in the organic layer was analyzed with a UV-vis spectrometer. Metal picrate was prepared by reacting picric acid and metal carbonate [12]. To obtain the extractability (%), an aqueous solution (2.0 mL) containing 0.20 mM metal picrate and chloroform solutions of the same volume according to the extractant concentration (0.1 mM) were mixed and equilibrated by shaking for 30 min at 25 °C. Concentrations of picrate anion extracted from the aqueous phase into the organic layer were determined by UV spectrophotometry (λ_{max} = 373 nm).

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