Journal of Inclusion Phenomena and Macrocyclic Chemistry **47:** 167–171, 2003.

Picolyl Armed C-1,2 Alternate Tetrahomodioxacalix[4]arene Tetraamides

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(Received: 14 April 2003; in final form: 4 September 2003)

Key words: calixarene, homooxacalixarene, complexation, X-ray crystal structure

Abstract

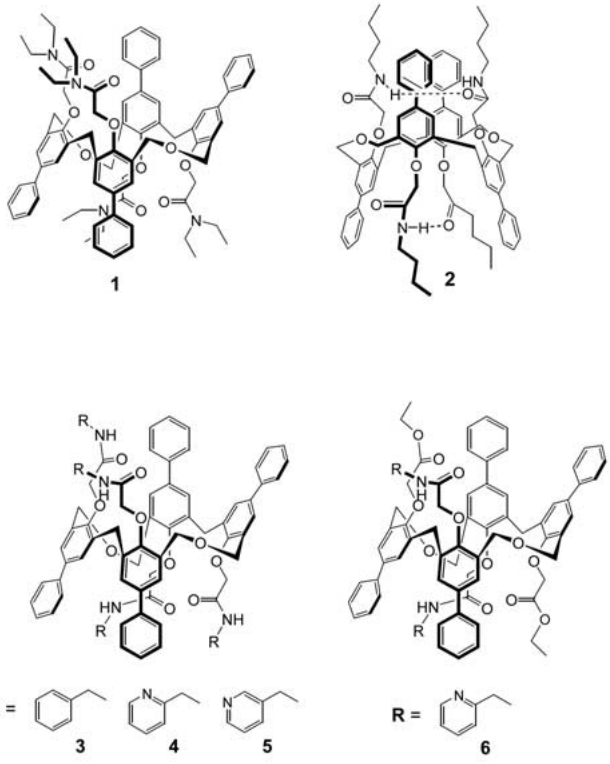
A series of benzyl, 2-picolyl, 3-picolyl armed tetrahomodioxacalix[4]arene tetraamides with four *p*-phenyl groups on the upper rim were synthesized. They were found to be in the C-1,2-alternate conformation by ^{1}H, ^{13}C NMR, and X-ray crystal structure. The nitrogen atom of the 2-picolyl group played an important role in the metal ion complexation.

Introduction

Calixarenes have been of interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures [1–3]. However, homooxacalix[4]arenes have rarely been studied not only because of synthetic difficulties but also because of the low complexability toward metal cations compared to conventional calix[4]arene derivatives [4–7].

Recently, we reported that C-1,2-alternate tetrahomodioxacalix[4]arene tetraamide (**1**) selectively encapsulates Pb^{2+} over other metal ions in such a manner that the lead ion is bound to the carbonyl oxygen atoms of two adjacent amide substituents and an aryl-alkyl ether oxygen of one of them [8]. We also reported that N-butylamido tetrahomodioxacalix[4]arene (**2**) is always in the 1,3-alternate conformation due to its stable intramolecular hydrogen bonding between N–H and the facing oxygen atoms of the carbonyl O=C group [9]. This hydrogen bonding decreases the metal ion complex ability [9].

In a continuation of constructing homooxacalix[4]arene amide-based receptor containing nitrogen atom which is sensitive to silver ion due to their biological, environmental and industrial significance, we have synthesized a series of homooxacalix[4]arene amides (**3–6**) bearing NH-picolyl arms.



Experimental

Synthesis

*7,13,21,27-tetra-phenyl-29,30,31,32-tetrakis(benzylcarbamoyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (**3**)*

To a solution of tetraester **8** (1.21 g, 1.07 mmol) in absolute ethanol (100 mL) and toluene (50 mL) was added (7.0 mL, 67.18 mmol) of benzylamine under an Ar atmosphere.

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The mixture was refluxed for 7 days. Solvent was evaporated to dryness and the residue was triturated with MeOH. The precipitated solid was purified by the recrystallization from chloroform and methanol to afford the desired product (956 mg, 64.9%) as colorless crystalline solid. Mp 254 °C. IR (KBr) 1664 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.48–7.25 (m, 32, ArH & NH), 6.99 − 6.96 (m, 12, ArH), 6.86 − 6.82 (m, 8, ArH), 4.89 (d, 2, $ArCH_2Ar$, J = 14.4 Hz), 4.48 (d, 4, OCH_2CO, J = 14.4 Hz), 4.45 (d, 4, OCH_2CO, J = 14.4 Hz), 4.01 (d, $ArCH_2OCH_2Ar$, J = 13.8 Hz), 3.93 (d, $ArCH_2OCH_2Ar$, J = 13.8 Hz), 3.87 (d, 4, NCH_2Ar, J = 5.9 Hz), 3.86 (d, 4, NCH_2Ar, J = 5.9 Hz), 3.44 (d, 2, $ArCH_2Ar$, J = 14.4 Hz). ^{13}C NMR ($CDCl_3$): 168.06 (C=O), 154.79, 139.71, 138.36, 137.77, 135.21, 130.18, 130.13, 129.79, 129.07, 128.40, 127.69, 127.63, 127.11, 127.06 (Ar), 73.77 ($ArCH_2O$), 68.15 (OCH_2CO), 42.83 ($ArCH_2N$), 31.23 ($ArCH_2Ar$) ppm. Anal. Calcd. for $C_{90}H_{80}O_{10}N_4$: C, 78.47; H, 5.85. Found: C, 78.52; H, 5.76.

*7,13,21,27-tetra-phenyl-29,30,31,32-tetrakis(2-methylpyridyl-carbamoyl)-methoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (**4**)*

To a solution of tetraester **8** (1.21 g, 1.07 mmol) in absolute ethanol (100 mL) and toluene (50 mL) was added (9.0 mL, 79.34 mmol) of 2-aminomethylpyridine under an Ar atmosphere. The mixture was refluxed for 7 days. Solvent was evaporated to dryness and the residue was triturated with MeOH. The precipitated solid was purified by the flash chromatography (eluent was 24 : 1 mixture of methylene chloride and methanol) to afford the desired product (1.12 g, 75.9%) as colorless crystalline solid. Mp 295 °C; IR (KBr) 1662 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.21 − 6.85 (m, 44, ArH & PyH), 7.22 (t, 4, NH, J = 5.8 Hz), 4.73 (d, 2, $ArCH_2Ar$, J = 13.7 Hz), 4.64 (d, 4, OCH_2CO, J = 11.2 Hz), 4.42 (d, 4, OCH_2CO, J = 11.2 Hz), 4.19 (d, $ArCH_2OCH_2Ar$, J = 13.7 Hz), 4.00 (d, $ArCH_2OCH_2Ar$, J = 14.0 Hz), 4.02 (d, 2, NCH_2Py, J = 5.8 Hz), 3.99 (d, 2, NCH_2Py, J = 5.8 Hz), 3.87 (d, 2, NCH_2Py, J = 5.8 Hz), 3.83 (d, 2, NCH_2Py, J = 5.8 Hz), 3.62 (d, 2, $ArCH_2Ar$, J = 13.7 Hz). ^{13}C NMR (DMSO-d_6): 168.30 (C=O), 158.21, 155.41, 149.08, 140.23, 136.91, 136.71, 135.56, 130.94, 129.99, 129.37, 129.25, 127.65, 127.24, 122.21, 121.15 (Ar), 73.95 ($ArCH_2O$), 67.72 (OCH_2CO), 44.42 ($PyCH_2N$), 30.90 ($ArCH_2Ar$) ppm. Anal. Calcd. for $C_{86}H_{76}O_{10}N_8$: C, 74.76; H, 5.54. Found: C, 74.82; H, 5.44.

*7,13,21,27-tetra-phenyl-29,30,31,32-tetrakis(3-methylpyridylcarbamoyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (**5**)*

Same as for **3**. Yield: 57.9%. Colorless crystalline solid. Mp 263 °C; IR (KBr): 1662 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.25 (br. d, 4, ArH & PyH, J = 2.9 Hz), 8.16 (br. s, 4, ArH & PyH), 7.64 (d, 4, ArH & PyH, J = 2.2 Hz), 7.56 (d, 8, ArH & PyH, J = 7.2 Hz), 7.50 (t, 4, NH, J = 6.1 Hz), 7.46 (d, 4, ArH & PyH, J = 2.2 Hz), 7.38 (t, 8, ArH, J = 7.7 Hz), 7.30 (d, 4, ArH, J = 7.7 Hz), 7.27 (d, 4, ArH, J = 7.7 Hz), 7.02 (d, 2, ArH, J = 7.7 Hz), 7.01 (d, 2, ArH, J = 7.7 Hz), 4.77 (d, 4, OCH_2CO, J = 11.0 Hz), 4.49 (d, 2, $ArCH_2Ar$, J = 13.6 Hz), 4.34 (d, 4, OCH_2CO, J = 11.0 Hz), 4.17 (d, $ArCH_2OCH_2Ar$, J = 13.5 Hz), 3.99 (d, $ArCH_2OCH_2Ar$, J = 13.5 Hz), 3.86 (d, 2, NCH_2Py, J = 6.2 Hz), 3.83 (d, 2, NCH_2Py, J = 6.2 Hz), 3.58 (d, 2, $ArCH_2Ar$, J = 13.6 Hz), 3.48 (d, 2, NCH_2Py, J = 6.2 Hz), 3.45 (d, 2, NCH_2Py, J = 6.2 Hz). ^{13}C NMR (DMSO-d_6): 168.01 (C=O), 155.06, 149.03, 148.40, 140.17, 137.08, 135.30, 135.20, 134.74, 131.19, 130.24, 129.47, 129.29, 127.78, 127.34, 123.54 (Ar), 73.62 ($ArCH_2O$), 67.87 (OCH_2CO), 39.94 ($PyCH_2N$), 30.48 ($ArCH_2Ar$) ppm. Anal. Calcd. for $C_{86}H_{76}O_{10}N_8$: C, 74.76; H, 5.54. Found: C, 74.80; H, 5.47.

*7,13,21,27-tetra-phenyl-29,31-bis(ethoxycarbonyl)-methoxy-30,32-bis(2-methylpyridylcarbamoyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (**6**)*

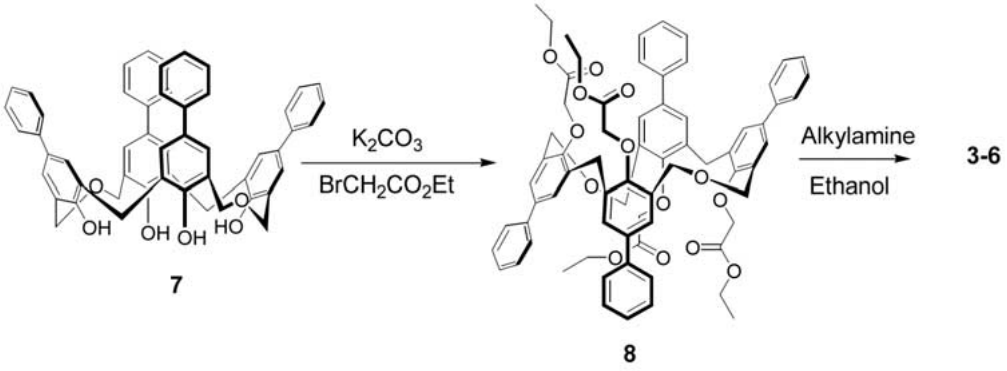
Same as for **3** except the 2 equivalents of 2-aminomethylpyridine used. Yield: 38.0%. Colorless crystalline solid. Mp 271 °C; IR (KBr, cm^{-1}): 3384, 1756, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.66 (t, 2, NH, J = 3.2 Hz), 7.59 − 6.16 (m, 36, ArH & PyH), 5.50 (d, 2, $ArCH_2Ar$, J = 13.6 Hz), 4.72 (d, 1, $NHCH_2Py$, J = 16.8 Hz), 4.71 (d, 1, $NHCH_2Py$, J = 16.8 Hz), 4.68 (d, $ArCH_2OCH_2Ar$, J = 11.6 Hz), 4.60 (d, $ArCH_2OCH_2Ar$, J = 11.6 Hz), 4.58 (d, 2, OCH_2Ar, J = 9.6 Hz), 4.55 (d, 2, OCH_2CO, J = 14.4 Hz), 4.38 (d, 1, $NHCH_2Py$, J = 16.8 Hz), 4.37 (d, 1, $NHCH_2Py$, J = 16.8 Hz), 4.24 (d, 2, OCH_2CO, J = 14.4 Hz), 4.12 (d, 2, OCH_2Ar, J = 9.6 Hz), 4.08 (d, 2, OCH_2CON, J = 17.4 Hz), 3.60 (d, 2, OCH_2CON, J = 17.4 Hz), 3.54 (d, 2, $ArCH_2Ar$, J = 13.6 Hz), 3.46 (q, 1, OCH_2, J = 7.2 Hz), 3.43 (q, 1, OCH_2, J = 7.2 Hz), 3.09 (q, 1, OCH_2, J = 7.2 Hz), 3.06 (q, 1, OCH_2, J = 7.2 Hz), 0.40 (t, 6, CH_3, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 170.15, 168.37 (C=O), 156.66, 155.36, 154.20, 148.58, 140.51, 140.39, 138.43, 136.65, 136.29, 136.26, 135.80, 131.30, 130.11, 129.94, 129.25, 129.13, 128.91, 128.66, 127.27, 127.23, 127.06, 127.03, 121.83, 121.10 (Ar), 74.05 (OCH_2CO), 71.18 (OCH_2CON), 68.19, 66.72 ($ArCH_2O$), 60.31 (OCH_2), 43.83 ($PyCH_2N$), 31.48 ($ArCH_2Ar$), 13.72 (CH_3) ppm. Anal. Calcd. for $C_{76}H_{72}O_{12}N_4$: C, 74.01; H, 5.88. Found: C, 74.12; H, 5.77.

Metal picrate extraction

Metal picrates were prepared by reaction of picric acid with the appropriate metal carbonate [10]. To determine the extractability of the ligand for a metal picrate, an aqueous solution (2.0 mL) containing 0.05 mM metal picrate and a 1,2-dichloroethane solution (2.0 mL) of the extractant (0.025 mM) were shaken for 30 min at 25 °C. The concentration of picrate anion extracted from the aqueous phase into the organic layer was determined by UV spectrophotometry (λ_{max} = 373 nm). Three independent experiments were carried out for each combination of ligand and metal picrate. The extractability values listed in Table 1 are averages.

Crystal structures

Crystal data for **6**: $C_{78}H_{72}N_4O_{12}\cdot CH_3OH$, M = 1289.44, monoclinic, space group P21/c, a = 23.3344(17), b = 18.0917(14), c = 16.1554(11) Å, β = 97.563(2)°, V =



Scheme 1. Synthetic routes for **3–6**.

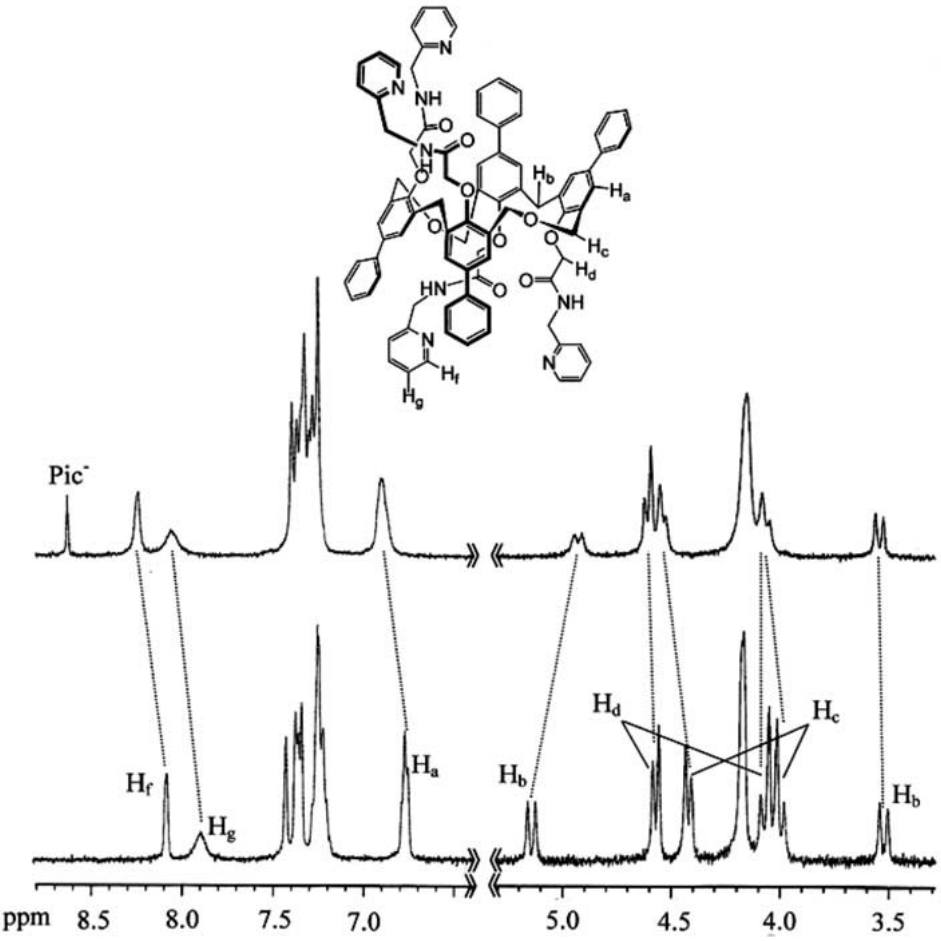


Figure 1. Silver ion induced chemical shift changes of compound **4**. To a solution of 20 mg of **4** in $CDCl_3$ was added an excess amount of silver picrate. After shaking for 10 h, the filtrate was applied for NMR spectroscopy.

Table 1. Extractability (%) of **3–6** for metal cations in two-phase picrate extraction

Compd.	Extractability (%)[a]								
	Na^+	K^+	Rb^+	Cs^+	NH_4^+	Ag^+	Sr^{2+}	Ba^{2+}	Pb^{2+}
3	16.1	15.1	4.4	3.3	1.1	5.7	5.1	4.0	8.1
4	23.8	25.2	26.3	19.3	27.6	70.1	43.1	42.4	53.7
5	2.9	20.7	9.5	20.4	7.8	15.3	29.9	35.0	16.2
6	1.1	11.2	1.6	0	0	0	0	0	0

[a]Extractability = metal ion concentration extracted into organic layer/ligand concentration used × 100. Average values were recorded from three independent experiments.

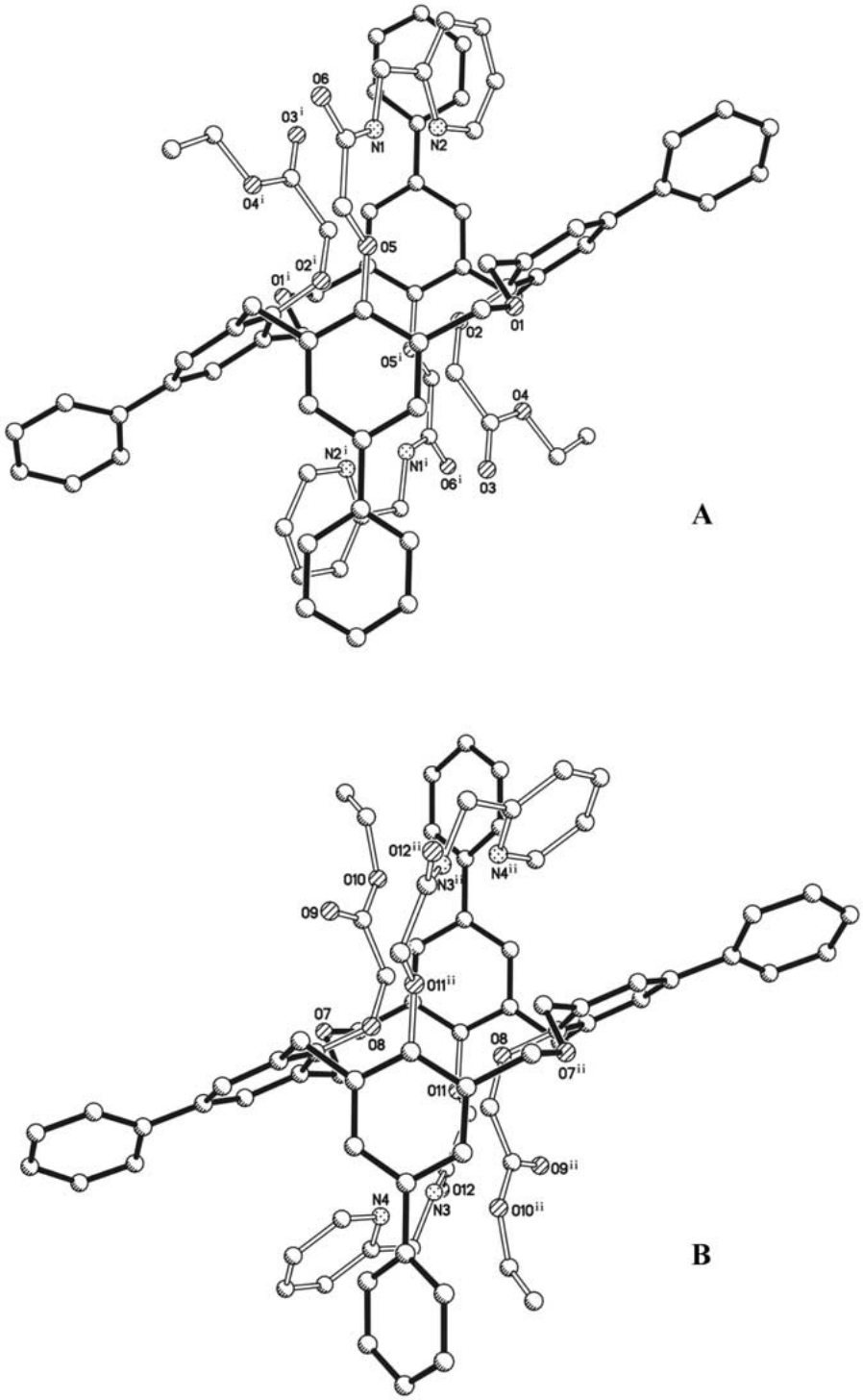


Figure 2. X-ray structures of the two molecules of **6**. For the structural comparison, each molecule is drawn in the same direction and H atoms are omitted. Symmetry code: (i) $1-x, 1-y, 1-z$; (ii) $-x, 1-y, 1-z$.

6760.8(9) Å^3, Z = 4, Dc = 1.267 g cm^{-3}, μ(Mo Kα) = 0.086 mm^{-1}, F(000) = 2728, crystal dimensions of 0.2 × 0.2 × 0.3 mm. All data were collected on a Bruker SMART diffractometer, at the Central Laboratory, Gyeongsang National University, equipped with a graphite monochromated Mo Kα (λ = 0.71073 Å) radiation source and a CCD detector. The structure was solved by a direct method and refined by full-matrix least-squares against F^2 to final R = 0.0822 and R_w = 0.2145 using 15933 independent reflections (λ_{max} = 28.29°), for all data using SHELXTL software [11]. All non-H atoms were refined with anisotropic displacement parameters. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC197374 Copies of the data can be obtained, free of charge, on application to

CCDC, 12 Union Road Cambridge CB2 1EZ, UK [Fax: +44 (0) 1223-336033 or E-mail: deposit@ccdc.cam.ac.uk].

Results and discussion

As described in Scheme 1, C-1,2-alternate homooxacalix[4]arene tetraester (**8**) was easily synthesized by the reaction of **7** with ethyl bromoacetate [8, 9]. Subsequently, amination of **8** with 50 equivalents of benzylamine, 2-aminomethylpyridine, and 3-aminomethylpyridine gave compounds **3–5** in 65, 76, and 60% yield, respectively. The use of 2 equivalents of 2-aminomethylpyridine provided disubstituted compound **6** in 38% yield.

All compounds are in the C-1,2-alternate conformation of which the nomenclature was previously designated by our research group [9]. Namely, it would be preferable to retain the 1,2-alternate designation for these conformers and to differentiate between the two possible 1,2-alternate conformers in the following manner: The 1,2-alternate conformer in which the adjacent *syn* aryl moieties are joined by a CH_2 group is designated as the C-1,2-alternate, while the 1,2-alternate conformer in which the adjacent *syn* aryl moieties are joined by a CH_2OCH_2 moiety is designated as the COC-1,2-alternate [9].

Obviously, each conformation can be identified by ^{1}H and ^{13}C NMR spectroscopy. In the 400 MHz ^{1}H NMR spectrum, for instance, the methylene protons of the $ArCH_2Ar$ bridge for **4** showed two AB doublets at δ 5.15 and δ 3.57 ($\Delta\nu = 632$ Hz) with a geminal coupling constant of 13.8 Hz. An AB pattern for the dimethylenoxy protons of $ArCH_2OCH_2Ar$ appeared at δ 4.45 and δ 4.04 ($\Delta\nu = 164$ Hz) with a geminal coupling constant of 10.92 Hz (Figure 1). The ^{13}C NMR spectrum showed a single peak from a carbonyl carbon, one peak at 73.95 ppm for the $ArCH_2O$ bridge methyleneoxy carbons and one peak at 30.90 ppm for the $ArCH_2Ar$ bridge carbons implying that two adjacent benzene rings are in a *syn* orientation. So, it is in the stable C-1,2-alternate conformation. The C-1,2-alternate conformation of **6** is unambiguously proven by single crystal X-ray structure determination. X-ray analysis of **6** reveals that there are two independent molecules A and B (Figure 2) with a centrosymmetry and both molecules show no significant difference in conformation except that of ester chains. In the crystal structure, diphenyl moieties of each molecule are not coplanar; dihedral angles between phenyl rings range from 27.2(3)° to 37.0(1)°. Both picolyl and ethyl ester units are located in same direction with C-1,2-alternate fashion which is consistent with the ^{1}H NMR results.

To obtain the metal ion affinity of the tested ligands, extractabilities of **3–6** were determined by the metal picrate extraction method. The results are listed in Table 1. Compared to benzyl substituted compound **3**, picolyl armed homooxacalixarene **4** and **5** showed rather higher extractability, deducing that the nitrogen atom of the picolyl unit may play an important role in the 3-dimensional encapsulation. Between **4** and **5**, **4** exhibited the better extractability in most metal cations and showed silver ion selectivity. Therefore, one can propose that two adjacent amide carbonyl groups coordinate the silver ion with aid of the nitrogen atom of the 2-picolyl group, giving the Ag^+ ion selectivity. To prove the above proposal, we took ^{1}H NMR spectrum of **4** in the presence and in the absence of the of Ag^+ pic^- in $CDCl_3$. As shown in Figure 1, H_f and H_g in the picolyl unit of **4** changed downfield by 0.17 and 0.18 ppm, respectively. In contrast, for **5** having 3-picolyl arm, no chemical shift change of the picolyl unit was observed, deducing that the 2-nitogen atom in **4** plays a crucial role in the metal ion complexation. Compound **6** showed low complexability due to the lack of the other amide group although a 2-picolyl unit was attached.

In consequence, it is important for us to note that in the metal ion encapsulation by the tetrahomooxacalix[4]arene tetraamide, the two adjacent *syn* amide groups in the C-1,2-alternate conformation and the additional binding unit, such as 2-picolyl group can control the metal ion binding ability. Corresponding thioamide with picolyl units are now being investigated and will be reported soon.

Acknowledgments

This work was supported by Korea Research Foundation Grant (KRF-2002-015-CP0226). We also gratefully thank KBSI in Daejon for the instrumentation support (^{1}H and ^{13}C NMR).

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