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Intramolecular hydrogen bonding effect on metal ion complexation of homooxacalix[4]arene bearing tetraamides

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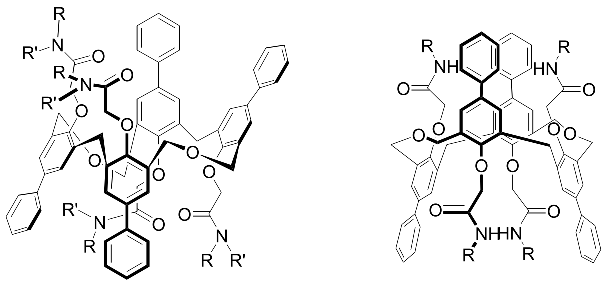
Abstract—*N*,*N*-Dipentylamido homooxacalix[4]arene (**3**) in the C-1,2-alternate conformation provided Pb^{2+} ion selectivity over other metal cations. *N*-Monopentylamido homooxacalix[4]arene in C-1,2-alternate conformation has an intramolecular hydrogen bonding, causing decrease of the metal ion complex ability. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Calixarenes have been considered as complexation hosts for both ions and molecules.[1–3] As one of the calixarene derivatives, homooxacalix[4]arenes bearing extra oxygen atoms in the macrocyclic ring have been also interesting to organic chemists because of their conformational flexibility.[4–6] Because of their synthetic difficulty, not many researchers were involved in the homooxacalix[4]arene compounds.[7–10] Masci and co-worker[11] reported that the main conformation of tetrahomodioxa-*p*-*tert*-butylcalix[4]-arene tetramethyl ether is C-1,2-alternate based on temperature-dependent NMR spectral analysis. Recently, we reported that C-1,2-alternate tetrahomodioxacalix[4]arene *N*,*N*-diethyl tetraamide (**1**) selectively encapsulates Pb^{2+} over alkali, alkaline earth, ammonium, and transition metal ions.[12] In the solid-state structure of **1**·Pb^{2+} complex, the Pb^{2+} was bound to the carbonyl oxygens of two adjacent amide substituents and an aryl–alkyl ether oxygen of one of them.[12] In addition, we reported that compound **4** having *N*-monobutyl gave a low extractability toward the Pb^{2+} ion because it is in the 1,3-alternate conformation and has intramolecular hydrogen bonding between N–H and facing oxygen atoms of the carbonyl O═C group.[13] In a continuation of the homooxacali[4]arene tetraamide research, we have investigated an influence of the conformation on the metal ion complexation. So, we herein report the synthesis of a series of tetrahomodioxa-*p*-phenylcalix[4]arene *N*-monopentyl tetraamide (**2**) and *N*,*N*-dipentyl tetraamide (**3**) in the C-1,2-alternate conformation, and *N*-monopentyl tetraamide (**5**) in the 1,3-alternate conformation along with their crystal structures.



C-1,2-alternate

	R	R'
1	C_2H_5	C_2H_5
2	C_5H_{11}	H
3	C_5H_{11}	C_5H_{11}

1,3-alternate

	R
4	C_4H_9
5	C_5H_{11}

2. Results and discussion

The synthetic routes for homooxacalix[4]amide (**2**, **3** and **5**) are described in Scheme 1. Reaction of **6** with ethyl bromoacetate gave **7** which is in the C-1,2-alternate.[14]

Addition of pentylamine in ethanol solution of **7** followed by column chromatographic separation provided the desired products **2** and **5** in moderate yields. Compound **3** was directly synthesized from the homooxacalix[4]arene **6**. Each conformation was confirmed by ^1H and ^{13}C NMR spectroscopy. For example, in the 400 MHz ^1H NMR spectrum, the methylene protons of the ArCH_2Ar bridge for

Keywords: calix[4]arenes; homooxacalixarenes; metal ion complexation.

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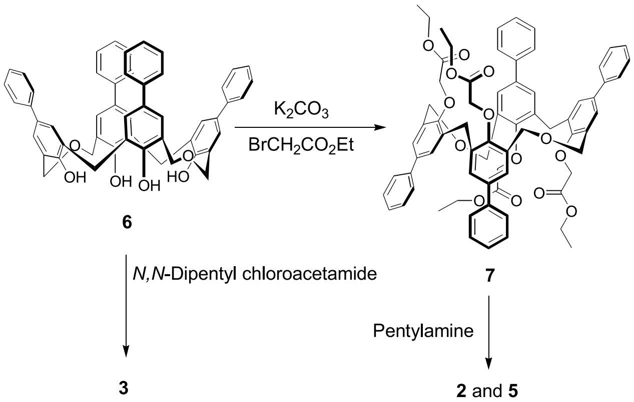

Scheme 1. Synthetic route for compounds **2**, **3** and **5**.

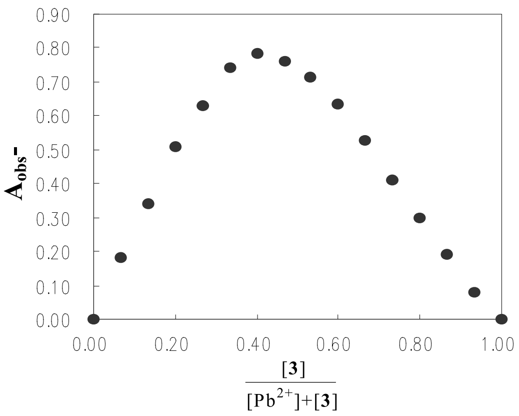

Figure 1. Job plot for complexation of **3** with Pb^{2+} ion.

2 showed two AB doublets at δ 4.91 and 3.50 ($\Delta\nu$=564 Hz) with a *geminal* coupling constant of 14.1 Hz. An AB pattern for the dimethylenoxy protons of Ar*CH*$_2$O*CH*$_2$Ar of **2** appeared at δ 4.84 and 3.95 ($\Delta\nu$=356 Hz) with a *geminal* coupling constant of 13.7 Hz. The ^{13}C NMR spectrum showed a single peak from a carbonyl carbon, one peak at 74.2 ppm for the Ar*C*H$_2$O bridge methyleneoxy carbons and one peak at 31.0 ppm for the Ar*C*H$_2$Ar bridge carbons implying that two adjacent benzene rings are in a *syn* orientation, so to speak, C-1,2-alternate conformation. On the contrary, in the case of 1,3-alternate conformer **5**, the methylene protons of the Ar*CH*$_2$Ar bridge showed single peak at δ 3.98. An AB pattern for the dimethylenoxy protons of Ar*CH*$_2$O*CH*$_2$Ar appeared at δ 3.96 and 2.68 ($\Delta\nu$=512 Hz) with a *geminal* coupling constant of 14.3 Hz. In the ^{13}C NMR spectrum a single peak at δ 37.8 from Ar*C*H$_2$Ar indicated that two adjacent benzene rings are in an *anti* orientation to suggest 1,3-alternate conformation.

To obtain an insight into the metal ion affinity of the homooxacalixarene tetraamide, extractabilities toward metal ions by **1**–**5** were determined from the metal picrate extraction method.[15] The results are listed in Table 1. C-1,2-Alternate **2** having monopentyl amide showed a poor extractability toward tested cations. In addition, both for monobutyl amide (**4**) and for monopentyl amide (**5**) which are in 1,3-alternate conformation, the cation affinity was also observed to be poor. This is obviously because they have intramolecular hydrogen bondings between N–H and facing oxygen atoms of the carbonyl O=C group.[13] Homooxacalix[4]arene dialkyl amides (**1** and **3**), however, showed a high extractability toward cations and revealed Pb^{2+} ion selectivity over other cations.

As we reported earlier, in compound **1** the cation is bound to the two carbonyl oxygens of two adjacent amide and an aryl–alkyl ether oxygen of one of them.[12] The complexation mode of **3** with metal cations can be similarly explained as done in the case of **1**. For **3**, we took Job plotting experiment to obtain the complexation ratio with $Pb^{2+}(pic^-)_2$ under conditions of invariant total concentration. As a result, **3**–Pb^{2+} complex concentration approaches a maximum when the molar fraction of [**3**]/([**3**]+[Pb^{2+}]) is about 0.4, meaning that it forms approximate 1:1.5 complex of **3** and Pb^{2+} as shown in Figure 1. Less than 1:2 complexation is presumably due to either an allosteric effect (an induced conformation change that does not favor binding of the second metal) or a metal–metal ion repulsion.

Furthermore, we have been interested in the reason for the low extractability of **2**. Is there any intramolecular hydrogen bonding between N–*H* and an oxygen atom of the adjacent carbonyl O=C group which may raise the low extractability? The answer is no, but the crystal structures of **2** and **3** can precisely explain the influence of the conformation on the extractability. Figure 2 indicates a crystal ORTEP

Table 1. Extractability (%) of **1**–**5** for metal cations in two-phase picrate extraction

Compound	Extractability (%)						
	Na^+	K^+	Rb^+	Cs^+	NH_4^+	Ag^+	Pb^{2+}
1	71.94	87.50	84.28	70.33	64.34	102.17	94.9
2	0.45	0	0	0.14	0	0	0
3	17.16	24.72	30.20	23.46	21.21	98.74	96.6
4	0	0	0	3.47	0	4.35	0
5	0.75	0.70	0.14	0.41	0.56	0.43	0.33

Extractability=metal ion concentration extracted into organic layer/ligand concentration used×100.

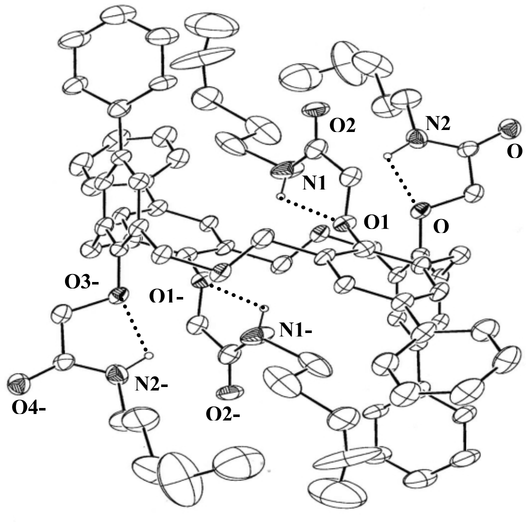

Figure 2. ORTEP drawing of **2**.

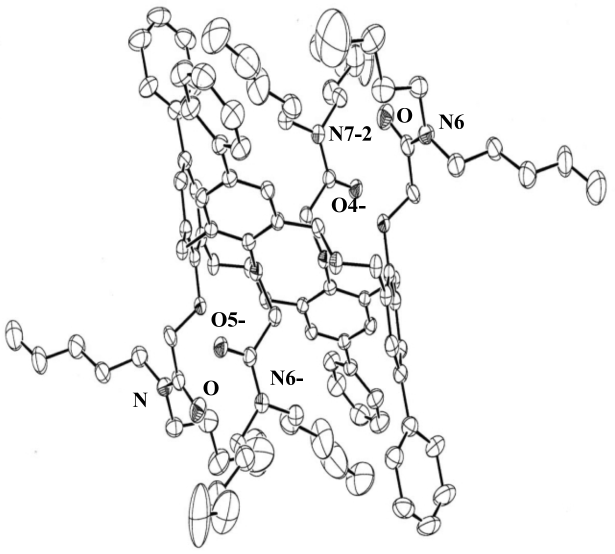

Figure 3. ORTEP drawing of **3**.

structure of compound **2**. The phenyl rings in the biphenyl units are twisted from each other with dihedral angles of 35.9(3)–39.0(3)°. From the ORTEP drawing, we observed intramolecular hydrogen bondings in O1––H–N1 and O3–H–N2 in which their bond lengths are found to be 2.195 and 2.224 Å, respectively. Their bonding angles are 115.3 and 106.6°, respectively. The rigid structure caused by this hydrogen bonding is assumed to reflect the position of two carbonyl groups which are oriented outside, resulting in a low extractability for tested metal cations. On the other hand, in the case of **3** bearing *N*,*N*-dipentylamide, two *n*-pentyl tails are stretched outward, then two oxygen atoms (O4–2 and O5) of the adjacent carbonylamides are positioned in same side to easily accept the cations. From this point of view, we also could deduce that the compound **1** showed better extractability than **3** which has a kind of steric congestion with bulkier *n*-pentyl groups when the metal cations approach to the ligand. However, concerning the Pb^{2+} ion selectivity, compound **3** were better binding partner than **1** (Fig. 3).

In conclusion, *N*,*N*-dipentylamido homooxacalix[4]arene (**3**) in the C-1,2-alternate conformation provided Pb^{2+} ion selectivity over other metal cations. However, *N*-mono-pentylamido compound **2** in C-1,2-alternate conformation has an intramolecular hydrogen bonding between N–H and oxygen atoms of a phenyloxy group, providing the low binding ability in metal ion complexation. Therefore, in the design of the homooxadioxacalix[4]arene tetraamide to optimize the metal ion affinity, *N*,*N*-dialkyl group on carboxyamide group along with C-1,2-alternate conformation should be mostly considered.

3. Experimental

3.1. Synthesis

Compounds **1**[14] and **4**[13] were prepared from the adaptation of the reported procedures.

3.1.1. 7,13,21,27-Tetraphenyl-29,30,31,32-tetrakis(pentyl-cabamoyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxa-calix[4]arene (2 and 5). To a solution of tetraester **7** (1.00 g, 0.882 mmol) in absolute ethanol (100 mL) and toluene (100 mL) was added 8.00 mL of pentylamine under Ar. After refluxing for seven days, the reaction mixture was cooled to room temperature. The precipitated solid was collected via filtration and washed with methanol to afford pure **2** (0.258 g, 22.5%) as a colorless crystalline solid. C-1,2-Alternate conformer: mp 246°C; IR (KBr): 1677.8 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.47–7.27 (m, 28H, Ar*H*), 6.82 (br, 4H, N*H*), 4.91 (d, 2H, ArCH_2Ar, *J*=14.1 Hz), 4.57 (d, 4H, OCH_2CO, *J*=10.9 Hz), 4.46 (d, 4H, OCH_2CO, *J*=10.9 Hz), 3.95 (d, 4H, ArCH_2OCH_2Ar, *J*=13.7 Hz), 4.84 (d, 4H, ArCH_2OCH_2Ar, *J*=13.7 Hz), 3.50 (d, 2H, ArCH_2Ar, *J*=14.1 Hz), 2.81 (br. q, 8H, CH_2, *J*=6.8 Hz), 1.00 (br. q, 16H, CH_2, *J*=6.8 Hz), 0.91 (m, 8H, CH_2), 0.66 (t, 12H, CH_3, *J*=6.8 Hz). ^{13}C NMR ($CDCl_3$): 168.01 (C=O), 155.18, 139.81, 137.89, 135.52, 130.15, 129.76, 129.08, 127.73, 127.06 (Ar), 74.24 (Ar*C*H_2O), 67.61 (O*C*H_2CO), 39.54 (*C*H_2), 31.03 (Ar*C*H_2Ar), 29.16, 28.92 (*C*H_2), 22.40 (*C*H_2), 14.12 (*C*H_3). Anal. Calcd for $C_{82}H_{96}O_{10}N_4$: C, 75.90; H, 7.46. Found: C, 75.72; H, 7.40. Filtrate was evaporated to dryness and the residue was triturated with MeOH. The precipitated solid was purified by recrystallization from CH_2Cl_2 and methanol to afford the 1,3-alternate **5** (580 mg, 50.7%) as colorless crystalline solid. Mp 224°C; IR (KBr): 1652.7 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46–7.24 (m, 28H, Ar*H*), 7.03 (br. t, 4H, N*H*), 4.84 (d, 4H, OCH_2CO, *J*=11.6 Hz), 4.20 (d, 4H, OCH_2CO, *J*=11.6 Hz), 3.98 (s, 4H, ArCH_2Ar), 3.96 (d, 4H, ArCH_2OCH_2Ar, *J*=14.3 Hz), 2.75 (m, 4H, CH_2), 2.68 (d, ArCH_2OCH_2Ar, *J*=14.3 Hz), 2.58 (m, 4H, CH_2), 1.17 (q, 8H, CH_2, *J*=7.2 Hz), 1.13 (m, 8H, CH_2), 1.00 (m, 8H, CH_2), 0.84 (t, 12H, CH_3, *J*=7.2 Hz). ^{13}C NMR ($CDCl_3$): 167.87 (C=O), 155.05, 140.24, 137.87, 135.36, 131.67, 130.95, 128.76, 128.68, 127.45, 127.30 (Ar), 72.12 (Ar*C*H_2O), 66.75 (O*C*H_2CO), 39.14 (*C*H_2), 37.88 (Ar*C*H_2Ar), 29.38, 29.10 (*C*H_2), 22.51 (*C*H_2), 14.34 (*C*H_3). Anal. Calcd for $C_{82}H_{96}O_{10}N_4$: C, 75.90; H, 7.46. Found: C, 75.76; H, 7.39.

3.1.2. 7,13,21,27-Tetraphenyl-29,30,31,32-tetrakis(di-pentylcabamoyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxa-calix[4]arene (3). To a solution of homooxacalix[4]arene (0.93 mg, 1.18 mmol) and K_2CO_3 (2.50 g) in dried aceto-nitrile (120 mL) was added 2.0 mL of *N*,*N*-dipentyl chloroacetamide under Ar. The reaction mixture was refluxed for four days. Solvent was evaporated to dryness and the residue was treated with dilute HCl and CH_2Cl_2. The organic layer was separated, washed with water three times and then dried with anhydrous $MgSO_4$. The oily residue obtained by the evaporation of solvent was triturated with methanol. The precipitated solid was collected to afford the desired product **3** (0.83 mg, 45.0%) as a colorless crystalline solid. C-1,2-Alternate: mp 178°C; IR (KBr): 1664 cm^{-1}; ^1H NMR ($CDCl_3$): 7.55–7.25 (m, 28H, Ar*H*), 5.42 (d, 2H, ArCH_2Ar, *J*=13.2 Hz), 4.94 (d, 4H, OCH_2CO, *J*=10.8 Hz), 4.65 (d, 4H, OCH_2CO, *J*=10.8 Hz), 4.59 (d, 4H, ArCH_2 OCH_2Ar, *J*=13.7 Hz), 4.21 (d, 4H, ArCH_2OCH_2Ar, *J*=13.7 Hz), 3.59 (d, 2H, ArCH_2Ar, *J*=13.2 Hz), 3.45 (m, 4H, CH_2), 2.80 (m, 4H, CH_2), 1.38 (quint, 8H, CH_2, *J*=7.3 Hz), 1.27 (quint, 8H, CH_2, *J*=7.3 Hz), 1.18 (m, 8H, CH_2), 0.86 (t, 12H, CH_3, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$): 168.06 (C=O),

Table 2. Crystal data for compounds **2** and **3**

	2	**3**
Empirical formula	C_{82} H_{96} N_4 O_{10}	C_{102} H_{136} N_4 O_{10}
Formula weight	1297.63	1578.14
Temperature	295(2) K	293(2) K
Wavelength	0.71073 Å	0.71069 Å
Unit cell dimensions	a=9.975(4) Å α=86.65(14)°	a=14.183(5) Å α=103.055(5)°
	b=11.684(3) Å β=80.36(2)°	b=15.081(5) Å β=96.035(5)°
	c=16.593(5) Å γ=74.92(2)°	c=11.297(5) Å γ=83.425(5)°
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
Volume	1840.7(10) Å^3	2330.6(15) Å^3
Z	1	2
Density (calculated)	1.171 g/cm^3	1.124 g/cm^3
Absorption coefficient	0.076 mm^{-1}	0.071 mm^{-1}
F(000)	696	856
Crystal size	0.16×0.14×0.12 mm^3	0.3×0.25×0.2 mm^3
Reflections collected	6875	8644
Independent reflections	6471 [R(int)=0.0796]	8187 [R(int)=0.0371]
Completeness to theta=25.00°	99.9%	99.9%
Absorption correction	None	None
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	6471/0/442	8187/3/592
Goodness-of-fit on F^2	0.969	0.934
Final R indices [I>2sigma(I)]	$R1$=0.1027, $wR2$=0.1726	$R1$=0.0739, $wR2$=0.1887
R indices (all data)	$R1$=0.3504, $wR2$=0.2694	$R1$=0.2495, $wR2$=0.2560
Extinction coefficient	0.0003(12)	0.0039(14)
Largest diff. peak and hole	0.240 and −0.176 eÅ^{-3}	0.274 and −0.297 eÅ^{-3}

157.43, 140.04, 136.01, 135.70, 129.66, 129.25, 128.71, 128.56, 126.84, 126.57 (Ar), 71.59 (ArCH_2O), 68.01 (OCH_2CO), 46.38, 45.72 (NCH_2), 33.36 (ArCH_2Ar), 29.21, 28.47, 28.36, 27.39, 22.50, 22.07 (CH_2), 14.02, 13.96 (CH_3). Anal. Calcd for $C_{102}H_{136}O_{10}N_4$: C, 77.63; H, 8.69. Found: C, 77.72; H, 8.43.

3.2. Metal picrate extraction

To determine the extractability of the ligand for a metal picrate, an aqueous solution (2.0 mL) containing 0.20 mM metal picrate and a 1,2-dichloroethane solution (2.0 mL) of the extractant (0.10 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.

3.3. Solid-state structure

Colorless crystals **2** and **3** were obtained by slow evaporation of solvent of a solution of **2** and **3** in CH_3CN–MeOH. X-Ray data were collected with the use of a Siemens P4 diffractometer equipped with a Mo X-ray tube and a graphite monochromator. All calculations were carried out with the use of SHELXTL programs.[16] The final X-ray data are given in Table 2. Crystal data were deposited with the Cambridge Crystallographic Data Centre, CCDC reference numbers 204140 (**2**) and 204139 (**3**).

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