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Hard–Soft Receptors, Tetrakis[(*N*,*N*-diethylaminocarbonyl)methoxy] thiacalix[4]arene Derivatives with *cone* and 1,3-*alternate* Conformation

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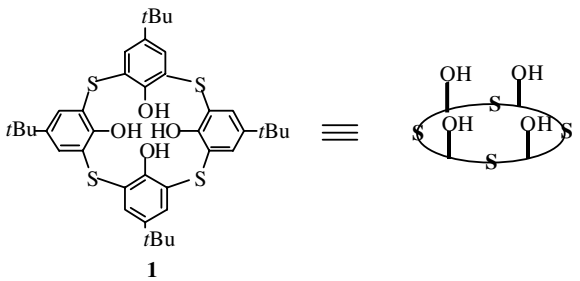
Key words: conformation, hard–soft receptors, ionophores, metal complexation, *O*-alkylation, thiacalix[4]arene

Abstract

Direct *O*-alkylation of *p-tert*-butyltetrathiacalix[4]arene with *N*,*N*-diethylchloroacetamide afforded two conformational isomers (1,3-*alternate* and *cone*) of tetrakis[(*N*,*N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene and 1,3-disubstituted bis[(*N*,*N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene, depending on the base used. The complaxation behaviors of the tetrakis isomers were assessed by ^{1}H NMR titration experiments. Evidence of 1:2 (homo- and hetero-dinuclear) complexes formation of 1,3-*alternate*-tetrakis[(*N*,*N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene with alkali (K^+ and Na^+) or transition (Ag^+) metal ions was obtained. Interestingly, it was found that the *cone*-tetrakis[(*N*,*N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene required a prior Ag^+ complexation to form 1:2 heterodinuclear complex.

Introduction

Since the thiacalix[4]arene **1** is easily accessible [1] an increasing interest on its novel properties has made this new member of the calixarene familiy [1b] popular as a building block or molecular scaffolds (Scheme 1). It is well known that conformation selective tetra-*O*-alkylation at the lower rim of all kinds of calixarenes is controlled by choosing a suitable alkali carbonate as a base [2]. In principle, the introduction of bulkier groups to the lower rim of calix[4]arene leads to the formation of four stable isomers – *cone*, *partial-cone*, 1,2-*alternate* and 1,3-*alternate*. In the case of thiacalix[4]arene, same conformational isomers are possible, however, their conformational behavior differs to a high degree from that of the classical calix[4]arene due to the presence of the sulphur atoms instead of the CH_2 groups. Previously, Lhoták *et al.* reported that tetra-*O*-alkylation of thiacalix[4]arene with simple alkyl halides leads the 1,3-*alternate* conformer as a major products [3]. Iki *et al.* studied the preparation and ionophoric properties of the four conformers of tetra-*tert*-butyltetrakis[(ethoxycarbonyl)methoxy]thiacalix[4]arene [2b]. Previously, we reported conformational studies of tetrakis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes constraining *cone* and 1,2-*alternate* conformation [4]. On the other hand, several groups have demonstrated that calix[4]aryl ester and amide derivatives serve as neutral ionophores [5]. In particular, the complexation behaviors of calix[4]arene amide derivatives have been extensively investigated due to their higher ionophoric ability to bind to alkali ion, transition ions, lanthanide ions and oxyanions than that of the ester derivatives [6a]. It is worth mentioning that the ability of amide functional group to bind either hard or soft cations provides entries to higher form of molecular behaviors such as cooperativity, allostery and regulation. It is well-known that the complexation behavior of all the calixarene family depends on the conformation of their derivatives. Recently, Lamartine *et al.* reported [7] a thiacalix[4]arene tetraamide derivative synthesized by applying the procedures established for calix[4]arene. Despite the obvious importance of thiacalix[4]arene amide derivatives no conformational studies of the direct tetra-*O*-alkylation of **1** with tertiary amides have been reported so far.



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Scheme 1.

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In this work, we report results of the conformational studies of **1** by direct *O*-alkylation with *N*,*N*-diethylchloroacetamide in the presence of different bases. The obtained complexation behaviors of the conformers (1,3-*alternate* and *cone*) with Na^+, K^+ and Ag^+ are also presented.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. NMR spectra were determined at 270MHz with a Nippon Denshi JEOL FT-270 NMR spectrometer with $SiMe_4$ as an internal reference: J-values are given in Hz. IR spectra were measured for samples as KBr pellets or a liquid film on NaCl plates in a Nipon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC. Elemental analysis: Yanaco MT-5.

Materials. 5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol **1** was prepared from *p*-*tert*-butylphenol according to the reported procedure [6b].

Synthesis

Preparation of 5,11,17,23-tetra-tert-butyl-25,27-bis-[(N,N-diethylaminocarbonyl)methoxy]-26,28-dihydroxy-2, 8,14,20-tetrathiacalix[4]arene (2)

A mixture of **1** (1.0 g, 1.38 mmol) and K_2CO_3 (4.89 g, 35.4 mmol) in dry acetone (80 mL) was heated at reflux for 1 h. Then *N,N*-diethylchloroacetamide [$ClCH_2CONEt_2$] (1.90 g, 11.38 mmol) was added and the mixture heated at reflux for 24 h under Argon. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (100 mL × 2) and washed with 1M HCl (20 mL), water (50 mL × 2), dried (Na_2SO_4). The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted $ClCH_2CONEt_2$ using a Kugelrohr apparatus. The residue was washed with MeOH to give the crude **2** (690 mg, 53%) as a white solid. Recrystallization from chloroform:ethyl acetate (1:2) gave 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(*N,N*-diethylaminocarbonyl)methoxy]-26,28-dihydroxy-2,8,14,20-tetrathiacalix[4]arene (**2**) as colorless prisms, m.p. 259–264 °C; ν_{max}(KBr)/cm^{-1} 3363, 1666; ^{1}H NMR ($CDCl_3$) $\delta = 0.78$ (18H, s, C(C*H*$_3$)$_3$), 1.25 (18H, s, C(*CH*$_3$)$_3$), 1.09–1.23 (12H, m, CH_2CH_3), 3.41–3.52 (4H, m, CONC*H*$_2$), 3.55–3.65 (4H, m, CONC*H*$_2$), 5.36 (4H, s, C*H*$_2$CON), 6.90 (4H, s, Ar–*H*), 7.64 (4H, s, Ar–*H*), 8.51 (2H, s, *OH*); ^{13}C NMR ($CDCl_3$) $\delta = 14.58$ (CH_2CH_3), 15.12 (CH_2CH_3), 32.54 (C(*C*H$_3$)$_3$), 34.72 (*C*(CH$_3$)$_3$), 40.76 (CON*C*H$_2$), 42.23 (CON*C*H$_2$), 70.22 (*C*H$_2$CON), 124.31, 129.27, 132.09, 134.92, 148.14, 157.12 (*C*Ar), 166.99 (CH$_2$*C*ON); *m*/*z*: 947.50 (M^+); Found: C, 65.67; H, 7.41. Calcd. for $C_{52}H_{70}O_6N_2S_4$ (947.39): C, 65.93; H, 7.45%.

*Preparation of 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetrakis[(N,N-diethylaminocarbonyl)]methoxy]-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-**3**)*

A mixture of **1** (1.0 g, 1.38 mmol) and Cs_2CO_3 (4.89 g, 15.0 mmol) in dry acetone (80 mL) was heated at reflux for 1 h. Then $ClCH_2CONEt_2$ (1.9 g, 11.38 mmol) was added and the mixture heated at reflux for 24 h under Argon. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (100 mL × 2) and washed with 1 M HCl (20 mL), water (50 mL × 2), dried (Na_2SO_4). The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted $ClCH_2CONEt_2$ using a Kugelrohr apparatus. The residue was washed with CH_3CN to give the crude 1,3-*alternate*-**3** (1.10g, 69%) as a white solid. Recrystallization from chloroform gave 1,3-*alternate*-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(*N,N*-diethylaminocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene, 1,3-*alternate*-**3** as colorless prisms. The spectral data are identical to those reported [7].

1,3-*alternate*-**3**: colorless prisms, m.p. 292–293 °C (lit. [7] 292.5–293 °C); ν_{max}(KBr)/cm^{-1} 1664; ^{1}H NMR ($CDCl_3$) $\delta = 0.97$–1.10 (12H, m, CH_2CH_3), 1.13–1.15 (12H, m, CH_2CH_3), 1.28 (36H, s, C(C*H*$_3$)$_3$), 3.26–3.29 (8H, m, CONC*H*$_2$), 3.34–3.39 (8H, m, CONC*H*$_2$), 4.68 (8H, s, C*H*$_2$CON), 7.53 (8H, s, Ar-*H*); ^{13}C NMR ($CDCl_3$) $\delta = 13.45$ (NCH_2CH_3), 14.88 (NCH_2CH_3), 31.63 (C(*C*H$_3$)$_3$), 34.60 (*C*(CH$_3$)$_3$), 40.38 (CON*C*H$_2$), 41.94 (CON*C*H$_2$), 69.66 (*C*H$_2$CON), 128.16, 133.43, 146.17, 158.02 (*C*Ar), 167 (CH$_2$*C*ON); *m*/*z*: 1173.60 (M^+); Found: C, 65.19; H, 8.08. Calcd. for $C_{64}H_{92}O_8N_4S_4$ (1173.90): C, 65.49; H, 7.90%.

*Preparation of 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetrakis[(N,N-diethylaminocarbonyl) methoxy]-2,8,14,20-tetrathiacalix[4]arene (cone-**3**)*

A mixture of **1** (500 mg, 0.69 mmol) and K_2CO_3 (951 mg, 6.9 mmol) in dry acetonitrile (80 mL) was heated at reflux for 1 h. Then $ClCH_2CONEt_2$ (1.03 g, 6.9 mmol) was added and the mixture heated at reflux for 36 h under Argon. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (100 mL × 2) and washed with water (50 mL × 2), dried (Na_2SO_4). The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted $ClCH_2CONEt_2$ using a Kugelrohr apparatus. The residue was washed with CH_3CN to give the crude *cone*-**3** (430 mg, 63%) as a white solid. Recrystallization from chloroform:ethylacetate (1:2) gave, *cone*-5,11,17,23-*tert*-butyl-25,26,27,28-tetrakis[(*N,N*-diethylaminocarbonyl)methoxy]-2,8,14,20-tetrathiacalix[4]arene (*cone*-**3**) as colorless prisms, m.p. 120–125 °C; ν_{max}(KBr)/cm^{-1} 1667; ^{1}H NMR ($CDCl_3$)

$\delta = 1.07$ (36H, s, C(CH_3)$_3$), 1.22–1.26 (24H, m, CH_2CH_3), 3.14–3.39 (8H, m, CH_2CH_3), 3.45–3.64 (8H, m, CONCH_2), 5.31 (8H, s, CH_2CON), 7.26 (8H, s, Ar-*H*); ^{13}C NMR ($CDCl_3$) $\delta = 12.93$ (CH_2CH_3), 14.38 (CH_2CH_3), 31.56 (C(CH_3)$_3$), 34.64 (C(CH_3)$_3$), 39.93 (CONCH_2), 41.90 (CONCH_2), 74.21(CH_2CON), 128.95, 134.25, 148.27, 157.93(*C*Ar), 167.59 (CH_2CON); Found: *m*/*z*: 1173.60 (M^+); Found: C, 65.26; H, 7.76. Calcd. for $C_{64}H_{92}O_8N_4S_4$ (1173.9): C, 65.49; H, 7.90%.

Stoichiometry of metal complexation

The method of continuous variation was employed to determine the stoichiometry of **3** metal complexes. Two-phase solvent extraction was carried out between aqueous picrates (5 mL, [metal picrate] = 2×10^{-4} M, $AgNO_3$, NaOH or KOH) and **3** (5 mL, [**3**] = 2×10^{-4} M in CH_2Cl_2). The molar ratios of the both **3** and metal picrate were varied from 0 to 1, while the total concentration was kept at several constant levels. The two-phase mixture in a glass tube immersed in a thermostated water bath at 25 °C was shaken at 300 strokes per minute for 1 h and then kept, at the same temperature, for 2 h, allowing the complete separation of the two phases. The absorbance of each solution was determined by UV spectroscopy ($\lambda = 290$ nm). Job plots were generated by plotting the extracted [Ag^+] versus the mole fraction of metal.

Determination of association constants

A solution of the receptor 1,3-*alternate*-**3** was prepared at a concentration typically on the order of 0.01 mol dm^{-3} in 1:1 (v/v) $CDCl_3$:CD_3CN. The initial ^{1}H NMR spectrum was recorded, and aliquots of cation solution ($AgSO_3CF_3$, KSO_3CF_3 and $NaClO_4$ in the same solvent mixture) were added. The solution was made such that from 1 molar equiv to 2 molar equiv was added in 20 μl. The association constant values were calculated by the integral intensity of CH_2CON methylene protons in the complex and free host molecules.

Under similar procedure the association constants for *cone*-**3** were calculated but with addition of aliquots of cation from 0–50 mM. After each addition and mixing, the change in shift of CH_2CON singlet was recorded during each titration. The result of the experiment was a plot of displacement in chemical shift as a function of the amount of added cation, which was subjected to analysis according to the literature [8].

^{1}H NMR complexation experiments

To a $CDCl_3$ solution (4×10^{-3} M) of tetradiethyl amide **3** in the NMR tube was added a CD_3CN solution (4×10^{-3} M) of $AgSO_3CF_3$, KSO_3CF_3 and $NaClO_4$. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27 °C.

The ^{1}H NMR data of the most representative complexes is given below.

1,3-*alternate*-**3**$\supset Ag^+$: δ_H ($CDCl_3$:CD_3CN, 1:1) 0.99 (12H, broaden signal, CH_2CH_3), 1.03 (12H, broaden signal, CH_2CH_3), 1.25 (18H, s, C(CH_3)$_3$), 1.34 (18H, s, C(CH_3)$_3$), 3.34 (8H, broaden signal, CONCH_2), 3.45 (8H, broaden signal, CONCH_2), 4.74 and 4.80 (8H, broaden s, CH_2CON), 7.30 (4H, s, Ar–*H*), 7.50 (4H, s, Ar–*H*).

$Ag^+\subset$1,3-*alternate*-**3**$\supset Ag^+$: δ_H ($CDCl_3$:CD_3CN, 1:1) 1.26 (36H, s, C(CH_3)$_3$), 1.31–1.33 (24H, m, CH_2CH_3), 3.32–3.41 (8H, m, CONCH_2), 3.49–3.52 (8H, m, CONCH_2), 4.92 (8H, s, CH_2CON), 7.43 (8H, s, Ar–*H*).

$Ag^+\subset$1,3-*alternate*-**3**$\supset K^+$: δ_H ($CDCl_3$:CD_3CN, 1:1) 1.22 (18H, s, C(CH_3)$_3$), 1.27 (18H, s, C(CH_3)$_3$), 1.18–1.21 (12H, m, CH_2CH_3), 1.28–1.32 (12H, m, CH_2CH_3), 3.21–3.26 (4H, m, CONCH_2), 3.31–3.36 (4H, m, CONCH_2), 3.38–3.43 (4H, m, CONCH_2), 3.49–3.54 (4H, m, CONCH_2), 4.91 (4H, s, CH_2CON), 4.98 (4H, s, CH_2CON), 7.44 (4H, s, Ar–*H*), 7.49 (4H, s, Ar–*H*).

$K^+\subset$1,3-*alternate*-**3**$\supset Na^+$: δ_H ($CDCl_3$:CD_3CN, 1:1) 1.15–1.19 (24H, m, CH_2CH_3), 1.25 (18H, s, C(CH_3)$_3$), 1.28 (18H, s, C(CH_3)$_3$), 3.21–3.26 (8H, m, CONCH_2), 3.44–3.46 (8H, m, CONCH_2), 3.44–3.46 (4H, m, CONCH_2), 3.49–3.54 (4H, m, CONCH_2), 4.98 (4H, s, CH_2CON), 5.00 (4H, s, CH_2CON), 7.46 (4H, s, Ar–*H*), 7.48 (4H, s, Ar–*H*).

cone-**3**$\supset Ag^+$: δ_H ($CDCl_3$:CD_3CN, 1:1) 1.10 (36H, s, C(CH_3)$_3$), 1.21–1.26 (24H, m, CH_2CH_3), 3.37–3.42 (16H, m, CONCH_2), 5.37 (8H, s, CH_2CON), 7.28 (8H, s, Ar–*H*).

$K^+\subset$ *cone*-**3**$\supset Ag^+$: δ_H ($CDCl_3$:CD_3CN, 1:1) 1.12 (36H, s, C(CH_3)$_3$), 1.15–1.26 (24H, m, CH_2CH_3), 3.31–3.34 (8H, m, CONCH_2), 3.45–3.48 (8H, m, CONCH_2), 5.30 (8H, s, CH_2CON), 7.44 (8H, s, Ar–*H*).

Results and discussion

Synthesis of tetrakis[(N,N-diethylaminocarbonyl) methoxy]thiacalix[4]arenes

Conformational studies, namely of tetraester derivatives of **1,** indicate that the cone conformer is obtained quite selectively in the presence of Na_2CO_3, the partial cone and 1,3-*alternate* conformers are obtained by using K_2CO_3 and Cs_2CO_3, respectively [2]. Consequently, similar conformational preference for the *O*-alkylation of **1** with *N*,*N*-diethylchloroacetamide could be expected. As shown in Table 1 the same stereoisomerical preference, as in the *O*-alkylation of **1** with ethyl bromoacetate or other functional groups, for cone and partial cone was not observed for the tetra-*O*-alkylation of **1** with *N*,*N*-diethylchloroacetamide. *O*-Alkylation in the presence of Na_2CO_3 did not afford the desired product. Only the starting compound was recovered in spite of the condition of large excess of Na_2CO_3 and alkylating reagent.

Table 1. *O*-Substitution reaction of tetraol **1** with *N,N*-diethylchloroacetamide

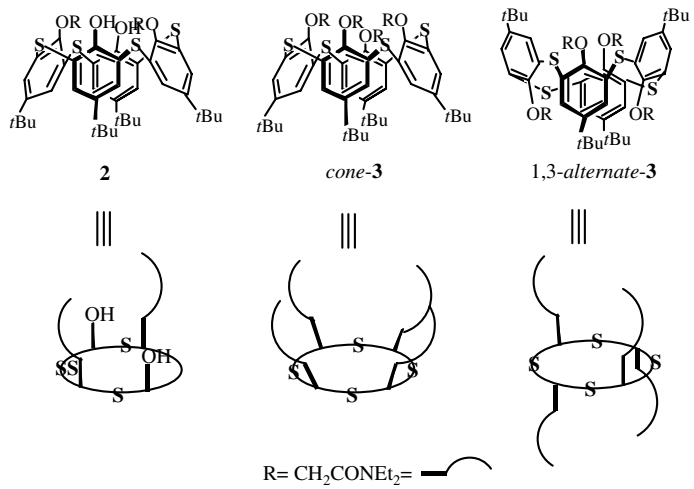
Run	Base	Solvent	Time (*t*/h)	Yield (%)[a]		*O*-Substitution
				1,3-*alternate*	*cone*	
1	Na_2CO_3	Acetone	48	0	0	–
2	Na_2CO_3	Acetonitrile	48	0	0	–
3	K_2CO_3	Acetone	36	0	0	Di[b]
4	K_2CO_3	Acetonitrile	36	0	63	Tetra
5	Cs_2CO_3	Acetone	24	69	0	Tetra
6	NaH	THF	24	0	46	Tetra

[a] The isolated yield of tetra-*O*-substitution product **3**.
[b]Di-*O*-substitution product **2** was obtained in 53% yield.

In an attempted on *O*-alkylation of **1** in the presence of K_2CO_3 under acetone reflux led to regioselective di-*O*-susbtitution to afford 1,3-disubstituted bis[(*N,N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene **2** in 53% yield. The result was conspicuous due to that until now the 1,3-dialkylation of **1** has been described only in two instances with methyl iodide [9a] and ethyl bromoacetate [9b], respectively, requiring a large excess of alkylating reagents, an equimolar quantity of K_2CO_3 (Na_2CO_3) and long reaction times (Scheme 2).

In contrast, when the reaction was carried out under the condition of CH_3CN reflux, complete tetra-*O*-substitution occurred, affording one pure stereoisomer *cone*-**3** in 63% yield. The formation of the other possible isomers was not observed. These results are opposed to that reported for calix[4]arenes [5c]. Complete tetra-*O*-alkylation also occurred in the presence NaH under THF refluxing [10], affording the same stereoisomer *cone*-**3** in 46% yield. Interestingly, the crude mixtures of both reactions showed considerable broadening in their ^{1}H NMR spectra, indicating the presence of *cone*-**3** and unknown compound A or B (50:50 ratio). In addition, the NMR patterns were quite similar to those of the 1:1 complexes of *cone*-**3** obtained upon titration with KSO_3CF_3 and $NaClO_4$. Attempted isolations by column chromatography or preparative TLC failed due to the similarity in the physical properties of these compounds. However, the present mixtures were treated with diluted hydrochloric acid to afford a pure stereoisomer *cone*-**3** in quantitative yield. It was observed accidentally that the ratio of the crude mixtures (uncomplex:complex) changed gradually in $CDCl_3$:CD_3CN (1:1) solution at room temperature and after 1 h a sharper spectra and only the signals for *cone*-**3** were observed. These findings strongly confirm the high ionophoric ability of the tetrakis[(*N,N*-diethylaminocarboyl)methoxy] derivative *cone*-**3** for K^+ and Na^+ as well as the incorporation of the metal used in the *O*-alkylation reaction as a tight complex [10] which was corroborated by the different melting points and infrared spectroscopy. Thus, IR spectrum of both *cone*-**3** complexes exhibited the carbonyl stretching band at 1658 cm^{-1} which can be compared with that of the free ligand *cone*-**3** at 1667 cm^{-1}.

On the other hand, *O*-alkylation of **1** with *N,N*-diethyliodoacetamide in the presence of K_2CO_3 has been carried out by another research group [7]. However, the structure of *cone* or 1,3-*alternate* conformation was not



Scheme 2.

confirmed due to the absence of either the CH_2 bridges, the proton signals of which are used for the conformational assignment, or another conformer.

Similar derivative was obtained when the reaction of **1** with *N*,*N*-diethylchloroacetamide was carried out in the presence of Cs_2CO_3 which led to tetra-*O*-substitution to afford 1,3-*alternate*-**3** as a major product in 69% yield, while the other possible stereoisomers (*cone*, *partial-cone* or 1,2-*alternate*) were not observed. This result is consistent with the reported preferential formation of the 1,3-*alternate* conformer in the tetra-*O*-alkylation of **1** in the presence of Cs_2CO_3.

These conformers exhibit distinct differences in their ^{1}H NMR spectra. Therefore, based on the chemical shift of the $C(CH_3)_3$, CH_2CON and Ar-*H* protons in the ^{1}H NMR spectra the two conformers of **3** were reasonably assigned to *cone* and 1,3-*alternate*. (e.g. the peak of CH_2CON protons at 5.31 and 4.68 were assigned to *cone* and 1,3-*alternate* conformers, respectively) [2b, 11].

Two-phase extraction and ^{1}H NMR titration experiments

Stoichiometry

Two-phase picrate extraction (H_2O/CH_2Cl_2) using the continuous variation method was applied to determine the stoichiometry of the 1,3-*alternate*-**3** and *cone*-**3** complexes with Na^+, K^+ and Ag^+ ions. The percents extraction for 1,3-*alternate*-**3** (Job plot) suggested the formation of 1:2 complexes with all three cations while those for *cone*-**3** indicated the formation of 1:1 complexes in all cases. Thus, the percent extractions reached maximum at 0.5 mol fraction when *cone*-**3** and Ag^+ were changed systematically. This fact clearly indicated that Ag^+ formed a 1:1 complex with *cone*-**3**, while the percent extractions reached maximum between 0.6 and 0.7 mole when systematically changing 1,3-*alternate*-**3** and Ag^+, indicating that 1,3-*alternate*-**3** forms a 1:2 complex with Ag^+. Similar results were obtained in the case of the complexes with Na^+ and K^+ ions. Typical Job plots of 1,3-*alternate*-**3** and Ag^+ is shown in Figure 1. The stoichiometries of 1,3-*alternate*-**3** and *cone*-**3** complexes with Na^+, K^+ and Ag^+ were further supported by ^{1}H NMR titration experiments [12].

Homo mono- and di-nuclear complexes of 1,3-alternate-3

Individual ^{1}H NMR titration experiments of 1,3-*alternate*-**3** and *cone*-**3** solutions with $AgSO_3CF_3$, KSO_3CF_3 and $NaClO_4$ were carried out [13]. Addition of an equiv of $AgSO_3CF_3$ into 1,3-*alternate*-**3** solution caused immediate downfield shifts for CH_2CON protons, showing slow ligand exchange on the NMR time scale [(b) in Figure 2]. The two singlets observed for such protons and for the aromatic protons suggested either the presence of two species or the interaction between the Ag^+ and the epithio function. Subsequent addition of another equiv of $AgSO_3CF_3$ into the solution containing the 1:1 1,3-*alternate*-**3**$\supset Ag^+$ (CH_2CON; $\Delta\delta = +0.09$ ppm: $K_{ass} = 1.78 \times 10^4$ M^{-1}) afforded new peaks assignable to the 1:2 $Ag^+\subset$1,3-*alternate*-**3**$\supset Ag^+$ (CH_2CON; $\Delta\delta = +0.24$ ppm: $K_{ass} = 1.38 \times 10^4$ M^{-1}) [(d) in Figure 2].

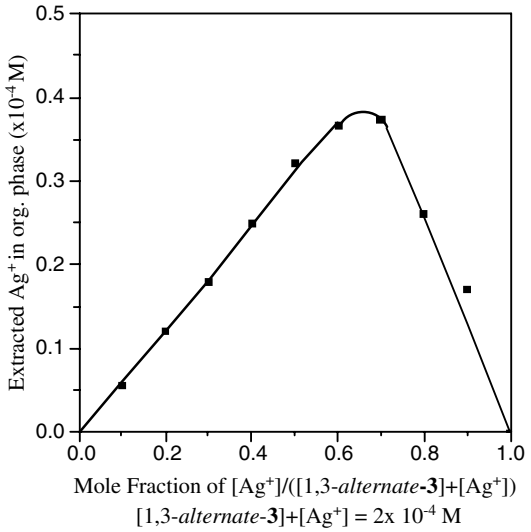


Figure 1. Job plots of the extractions of Ag^+ with host 1,3-*alternate*-**3**.

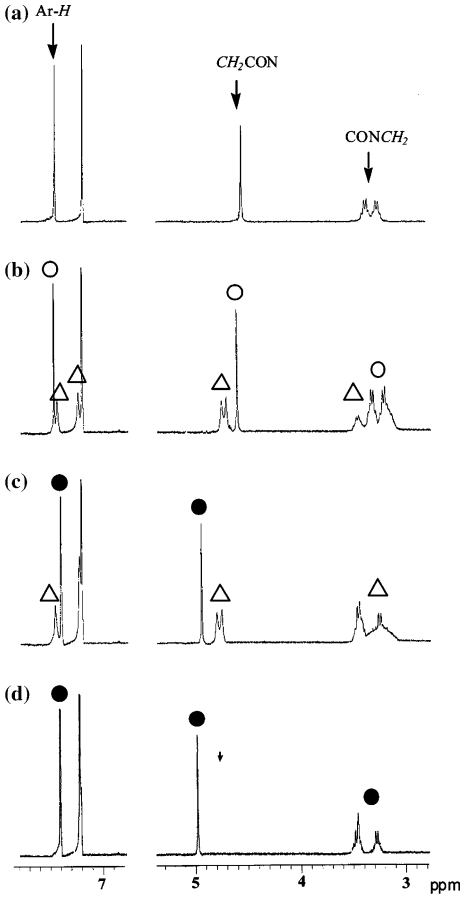


Figure 2. Partial ^{1}H NMR spectra of a 1,3-*alternate*-**3**-Ag^+ complex in $CDCl_3$:CD_3CN (1:1) (a) free ligand, (b) after 5 min in the presence of an equiv of $AgSO_3CF_3$, (c) after 5 min in the presence of 2 equiv of $AgSO_3CF_3$, (d) after 3 h in (c). Open circles, triangle and filled circles denote the signals for free, 1:1 1,3-*alternate*-**3**$\supset Ag^+$ complex and 1:2 $Ag^+\subset$1,3-*alternate*-**3**$\supset Ag^+$ complex, respectively.

Under the same experimental procedure, titration of 1,3-*alternate*-**3** solution with KSO_3CF_3 was carried out. The signals of the 1:1 1,3-*alternate*-**3**⊃K^+ (CH_2CON; $\Delta\delta = +0.15$ ppm: $K_{ass} = 8.65 \times 10^3$ M^{-1}) and 1:2 K^+⊂1,3-*alternate*-**3**⊃K^+ (CH_2CON; $\Delta\delta = +0.23$ ppm: $K_{ass} = 8.39 \times 10^3$ M^{-1}) were observed [(b) in Figure 3].

Titration of 1,3-*alternate*-**3** solution with an equiv of $NaClO_4$ did not cause immediate chemical shifts but the signals of 1:1 1,3-*alternate*-**3**⊃Na^+ (CH_2CON; $\Delta\delta = +0.09$ ppm: $K_{ass} = 2.71 \times 10^2$ M^{-1}) after 5 min were observed. Upon addition of an extra equiv of $NaClO_4$ new peaks appeared which were assignable to the 1:2 dinuclear complex, Na^+⊂1,3-*alternate*-**3**⊃Na^+ (CH_2CON; $\Delta\delta = +0.33$ ppm: $K_{ass} = 1.94 \times 10^2$ M^{-1}).

*Heterodinuclear complexes of 1,3-alternate-**3***

Titration of 1:1 1,3-*alternate*-**3**⊃Ag^+ solution with an equiv of KSO_3CF_3 afforded new peaks due to the formation of the 1:2 K^+⊂1,3-*alternate*-**3**⊃Ag^+ (CH_2CON; $\Delta\delta = +0.11$ ppm), and in the case of $NaClO_4$ the formation of 1:2 Na^+⊂1,3-*alternate*-**3**⊃Ag^+ (CH_2CON; $\Delta\delta = +0.09$ ppm) was observed. The presence of two signals for all individual protons (e.g. Ag^+⊂1,3-*alternate*-**3**⊃K^+, CH_2CON $\delta = 4.91$ and 4.98 ppm Ag^+⊂1,3-*alternate*-**3**⊃Na^+, CH_2CON $\delta =$ 4.87 and 4.89 ppm) strongly suggested the formation of heterodinuclear complexes. Similarly, the 1:2 heterodinuclear complexes Ag^+⊂1,3-*alternate*-**3**⊃K^+ (CH_2CON; $\Delta\delta = +0.29$ ppm) and Na^+⊂1,3-*alternate*-**3**⊃K^+ (CH_2CON; $\Delta\delta = +0.22$ ppm) were detected upon addition of an equiv of $AgSO_3CF_3$ and $NaClO_4$, separately, into 1,3-*alternate*-**3**⊃K^+ solution. Titration of 1:1 1,3-*alternate*-**3**⊃Na^+ solution with an equiv of $AgSO_3CF_3$ and KSO_3CF_3, separately, afforded the heterodinuclear complexes Ag^+⊂1,3-*alternate*-**3**⊃ Na^+ (CH_2CON; $\Delta\delta = +0.23$ ppm) and K^+⊂1,3-*alternate*-**3**⊃Na^+ (CH_2CON; $\Delta\delta = +0.22$ ppm), respectively.

Interestingly, the spectra of 1:2 heterodinuclear complexes obtained in the inverse titrations were indistinguishable from each other (e.g. 1,3-*alternate*-**3**⊃Ag^+ + K^+ → K^+⊂1,3-*alternate*-**3**⊃Ag^+ ← K^+⊂1,3-*alternate*-**3** + Ag^+). This fact demonstrated that the order of cation complexation played a negligible influence in the formation of the heterodinuclear complexes. It is worth mentioning that the ^{1}H NMR spectrum of the 1:2 Ag^+⊂1,3-*alternate*-**3**⊃Na^+ upon titration with an extra equiv of Ag^+ turned to that of the Ag^+⊂1,3-*alternate*-**3**⊃Ag^+ complex, suggesting the release of Na^+ and capture of Ag^+ [Figure 4]. Similarly, the K^+⊂1,3-*alternate*-**3**⊃K^+ complex was observed upon titration of K^+⊂1,3-*alternate*-**3**⊃Na^+ solution with an extra equiv of KSO_3CF_3.

Titration of either 1:2 Ag^+⊂1,3-*alternate*-**3**⊃Ag^+ or K^+⊂1,3-*alternate*-**3**⊃K^+ solutions with 5 equiv of different cation from the complex did not cause any spectral changes. The former observation provided strong experimental evidence for the existence of dinuclear complexes. In contrast, when 5 equiv of $AgSO_3CF_3$ and KSO_3CF_3 was added, separately, into the 1:2 Na^+⊂1,3-*alternate*-**3**⊃Na^+ solution new peaks appeared, which could be assigned firstly to the 1:2 Ag^+⊂1,3-*alternate*-**3**⊃Na^+ and K^+⊂1,3-*alternate*-**3**⊃Na^+ and finally to the 1:2 Ag^+⊂1,3-*alternate*-**3**⊃Ag^+ or K^+⊂1,3-*alternate*-**3**⊃K^+, respectively. These results supported the hypothesis that the Na^+ was released in the presence of Ag^+ or K^+. These findings could be explained in terms of association constants (K_{ass}). The values of K_{ass} for 1:1 or 1:2 sodium complexes are lower than those for potassium or silver complexes (e.g. $K_{ass(Na)} = 2.71 \times 10^2$ M^{-1}, $K_{ass(K)} = 7.63 \times 10^3$ M^{-1}, $K_{ass(Ag)} = 2.08 \times 10^4$ M^{-1}), due to the 1,3-*alternate* conformation.

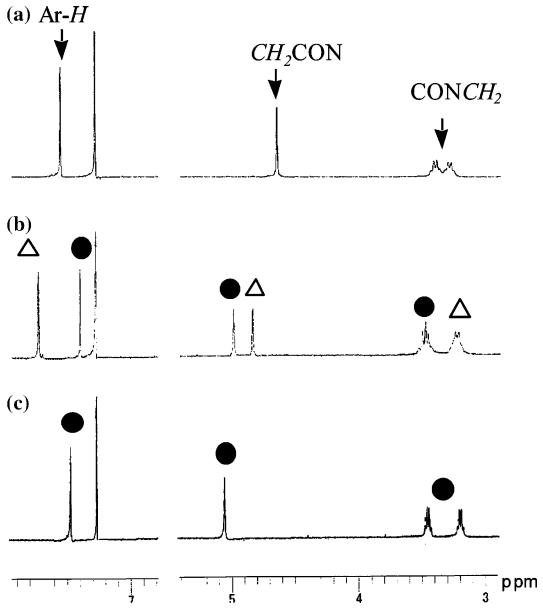


Figure 3. Partial ^{1}H NMR spectra of a 1,3-*alternate*-**3**-K^+ complex in $CDCl_3$:CD_3CN (1:1) (a) free ligand, (b) after 30 min in the presence of 2 equiv of KSO_3CF_3, (c) after 3 h in (b). Triangle and filled circles denote the signals for 1:1 1,3-*alternate*-**3**⊃K^+ complex and 1:2K^+⊂1,3-*alternate*-**3**⊃K^+ complex, respectively.

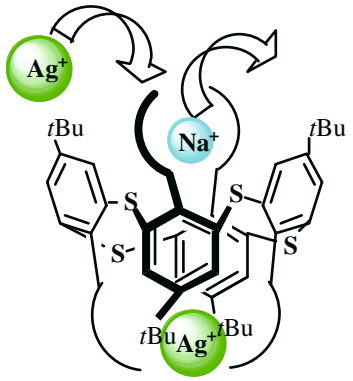


Figure 4. Competitive process in Ag^+⊂1,3-*alternate*-**3**⊃Na^+ complex with Ag^+.

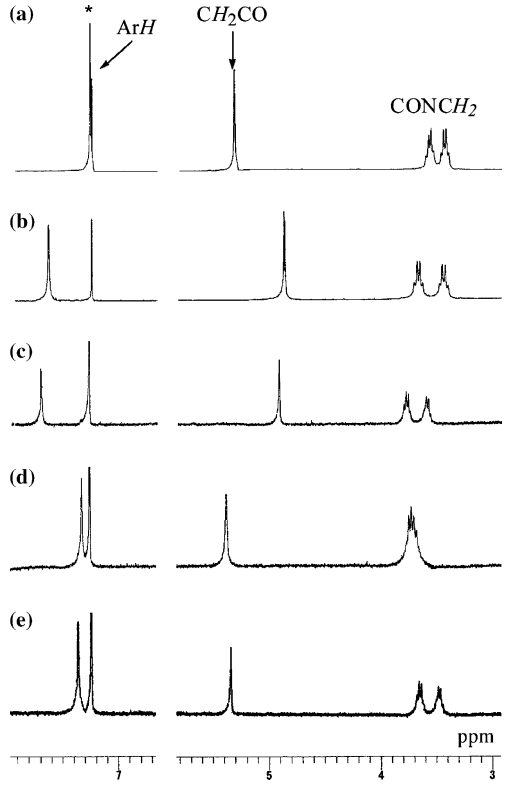


Figure 5. Partial ^{1}H NMR spectra of *cone*-**3**-metal ion complex in $CDCl_3$:CD_3CN (1:1); (a) free ligand, (b) *cone*-**3**$\supset K^+$, (c) *cone*-**3**$\supset Na^+$, (d) *cone*-**3**$\supset Ag^+$, (e) addition of KSO_3CF_3 into the *cone*-**3**$\supset Ag^+$ complex solution, $K^+\subset$*cone*-**3**$\supset Ag^+$. *Overlap with solvent signal.

Homomononuclear and heterodinuclear complexes of cone-***3***.

Upon titration of *cone*-**3** solution with an equiv of either KSO_3CF_3 or $NaClO_4$ [(b) and (c) in Figure 5], the methylene protons of the acetamide group (CH_2CON) moved −0.47 ppm (*cone*-**3**$\supset K^+$) and −0.51 ppm (*cone*-**3**$\supset Na^+$) upfield, showing slow ligand exchange on the NMR time scale. These upfield shifts could be explained by assuming that the carbonyl groups CO are towards the cation located in the interior of the hydrophobic cavity, bringing the CH_2 groups above the aromatic rings, where they experience a shielding effect. This might suggest that the expected C_{2v} symmetry [14] of *cone*-**3** in the absence of metal cation remained upon complexation of Na^+ or K^+ ions (1:1 *cone*-**3**$\supset Na^+$; $K_{ass} = 3.86 \times 10^2$ M^{-1} or 1:1 *cone*-**3**$\supset K^+$; $K_{ass} = 1.28 \times 10^4$ M^{-1} complexes). The addition of 5 equiv of K^+, Na^+ and Ag^+ into solutions of both *cone*-**3**$\supset Na^+$ and *cone*-**3**$\supset K^+$, separately, did not cause any significant chemical shifts.

Addition of an equiv of $AgSO_3CF_3$ into *cone*-**3** solution caused a small downfield shifts for all protons (Ar-*H* $\Delta\delta = +0.02$ ppm, CH_2CON $\Delta\delta = +0.06$ ppm) but interestingly, only one multiplet for the methylene protons of $CONCH_2$ was observed, being a fast ligand exchange process on the NMR time scale. No spectral changes were observed even in the presence of an excess of $AgSO_3CF_3$. Even though variable temperature experiments at low temperature in $CDCl_3$:CD_3CN (1:1) were carried out, no splitting pattern of the methylene protons of $CONCH_2$ was observed even below −60 °C. These findings confirmed the 1:1 complexes formation by *cone*-**3** with Na^+, K^+ and Ag^+ [15].

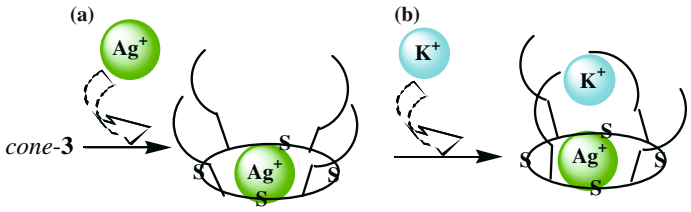
Of particular interest was the titration of *cone*-**3**$\supset Ag^+$ complex with an equiv of either K^+ or Na^+ which caused downfield shifts for Ar-*H* protons, upfield shift for CH_2CON protons and splitting of $CONCH_2$ protons [(e) in Figure 5] which could be attributable to the complexation of a second ion (K^+ or Na^+) by the amide moiety ($K^+\subset$*cone*-**3**$\supset Ag^+$ and $Na^+\subset$*cone*-**3**$\supset Ag^+$). Thus, complexation of K^+ or Na^+ led to different environment of the methylene protons of $CONCH_2$ which should be similar to that in *cone*-**3**$\subset K^+$ [(b) in Figure 5] or *cone*-**3**$\supset Na^+$ (Scheme 3).

These findings strongly suggest that two different-sized metal ions could coexist in the ionophoric cavity of *cone*-**3** ($K^+\subset$*cone*-**3**$\supset Ag^+$ or $Na^+\subset$*cone*-**3**$\supset Ag^+$) [16], even though the close proximity between them, and the participation of the epithio moiety in the complexation of Ag^+ ion [17].

Temperature dependent (TD) ^{1}H NMR studies.

Variable temperature experiments in the range of +60 to −60 °C of *cone*-**3**$\supset Ag^+$, $K^+\subset$*cone*-**3**$\supset Ag^+$ and $Na^+\subset$*cone*-**3**$\supset Ag^+$ were carried out in order to get more information about the complexation mode. In the temperature range studied, only a slight shifting and broadening of the Ar–*H* and $CONCH_2$ protons resonances when the temperature decreased and no changes upon increasing temperature, were observed in the case of *cone*-**3**$\supset Ag^+$ complex.

In contrast, the VT behavior of the CH_2CON protons of 1:2 $K^+\subset$*cone*-**3**$\supset Ag^+$ or Na^+ upon decreasing temperature showed some peculiarities. Although the line broadening made the interpretation of the spectra difficult, it was possible to draw some comments.



Scheme 3.

(1) At ambient temperature, the CH_2CON protons were seen as a broad singlet which broadened further as the temperature was decreased until it separated in two signals of different intensity in the case of $K^+\subset$*cone*-**3**$\supset Ag^+$ and equal intensity in the $Na^+\subset$*cone*-**3**$\supset Ag^+$ at −30 °C, suggesting two groups of inequivalents CH_2CON protons. (2) At −40 °C, the two signals separated from each other and below this temperature the signal broadened, resulting in the disappearance of the signal, indicating a change of the CH_2CON protons environment.

Further studies to get more inside in the complexation fashion of the heterogeneous dinuclear complexes are currently under investigation.

Conclusion

In the present work, we described the first synthesis of *cone*-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis [(*N,N*-diethylaminocarbonyl)methoxy]-2,8,14,20-tetrathiacalix [4]arene *cone*-**3** and the corresponding 1,3-*alternate*-**3** conformer as well as the 1,3-disubstituted bis[(*N,N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene **2**. The obtained evidence from ^{1}H NMR titration experiments of 1,3-*alternate*-**3** with $AgSO_3CF_3$, KSO_3CF_3 and $NaClO_4$ remarks both the complexation preferences of the 1,3-*alternate* conformation and its ability to form dinuclear complexes. The unexpected ability of *cone*-**3** to bind a second ion (K^+ or Na^+) if Ag^+ is complexed prior strongly suggests the participation of epithio moiety in the complexation of Ag^+. To the best of our knowledge, these are the first examples of the formation of heterodinuclear complexes by a thiacalix[4]arene derivative constraining *cone* conformation. The results show that both 1,3-*alternate*-**3** and *cone*-**3** are strong hard-soft donor receptors with a wide range of application as extractants. Furthermore, the present work provides some insight into the molecular design of new synthetic receptors for using in metal controlled of biomimetic systems.

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