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Novel C_{3V}-Symmetrical N_7-Hexahomotriazacalix[3]cryptand: A Highly Efficient Receptor for Halide Anions

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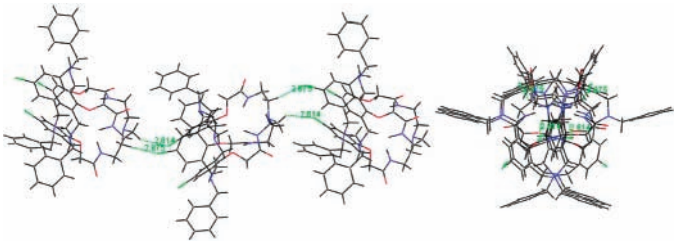
ABSTRACT



We report the synthesis of a novel C_{3V}-symmetrical N_7-hexahomotriazacalix[3]cryptand (1). Compound 1 was shown to be in a fixed cone conformation by ^{1}H NMR spectroscopy and X-ray single-crystal structure determination. Complexation studies showed that 1 is a selective receptor for halide ions. The effects of zinc metal cation on the receptor (1–Zn^{2+}) upon anion recognition are also shown.

Considerable attention has been paid to calixarenes and related compounds due to the molecular recognition properties they display.[1] The name homoazacalixarene (or azacalixarene) is currently used to indicate in a specific manner the calixarene analogues in which CH_2 groups are partly or completely replaced by CH_2NRCH_2.[2] The presence of soft nitrogen atoms in azacalixarenes is envisioned to bind soft cations such as transition metals according to the hard soft acid and base principle (HSAB) as well as other specific features such as building sophisticated receptors, metal ligand systems, etc.[2b,c] Indeed, such sophisticated ligands can be obtained by functionalization not only at the upper rim and/or lower rim, as usually done for calixarenes, but also within the macrocycle cup at the level of *N*-sidearms.[2]

Some examples have been given leading to an improvement of their ability to complex.[3] In this paper, we have

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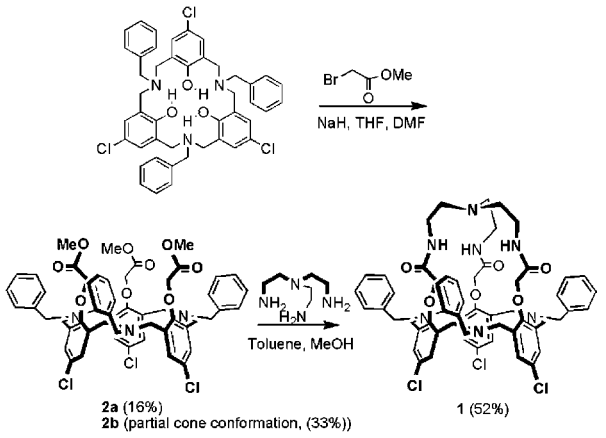
addressed the problem of complexation of anions and, more generally, of ion pairs. Current efforts aim at developing supramolecular systems that simultaneously bind both a cation and an anion. Two strategies have been presented in the literature: (1) the so-called "dual receptor strategy" involving a binary mixture of a cation-receptor and an anion-receptor[4] and (2) the so-called "ditopic receptor strategy" consisting of a single ditopic receptor with defined cation- and anion-binding sites.[5] With this in mind, we have chosen azacalix[3]arene[1a,2b,c] to elaborate a novel ditopic receptor. This choice was in part due to the fact that not only does their chemistry have a high potential to be developed for ditopic receptors but also their structural C_{3v} symmetry accompanied by a hydrophobic cavity wider than that of calix[4]arene is also able to accept large substrates.

In this paper, we report the synthesis, the conformational analysis, the X-ray crystal structure, and the binding properties of C_{3v}-symmetrical N_7-hexahomotriazacalix[3]cryptand or N_7-azacalix[3]cryptand (**1**).

Scheme 1. Preparation of N_7-Azacalix[3]cryptand (**1**)



Our first idea was to design a preorganized receptor for anion binding. N_7-Azacalix[3]cryptand (**1**) combines a C_{3v}-symmetrical *N*-benzylhexahomotriaza-*p*-chlorocalix[3]arene element and a 3-fold symmetric tren residue[6] via an *amidation* reaction. This combination result is a system that can bind anions through hydrogen bonding with primary acetamide groups. The synthesis of **1** (Scheme 1) began by the reaction of *N*-benzylhexahomotriaza-*p*-chlorocalix[3]arene[3b] with 3 equiv of $BrCH_2CO_2Me$ and 7 equiv of NaH as base in THF for 2 days. Column chromatography (silica gel, 90/10 hexane/ethyl acetate) of the crude residue gave two *N*-benzylhexahomotriaza-*p*-chlorocalix[3]tri(methyl acetate) isomers: **2a** (deep yellow oil, 16%) and **2b** (pale yellow solid, 33%). Based on ^{1}H NMR, IR, and MS spectrocopies, **2a** was shown to be in a *cone conformation* while the *partial-cone conformation* was attributed to **2b**. Compound **2a** was refluxed with 3 equiv of $N(CH_2CH_2NH_2)_3$ or tren in a 1:1 mixture of methanol/toluene for 5 days to afford N_7-azacalix-[3]cryptand (**1**) in 52% yield.

MALDI TOF MS, ^{1}H NMR, ^{13}C NMR, 2D NMR (COSY, gHSQC and gHMBC), and elemental analysis fully confirmed the structure of N_7-azacalix[3]cryptand (**1**). The cone conformation was demonstrated by ^{1}H NMR and X-ray analysis. In its ^{1}H NMR spectrum (Figure 1a), the azacalix-[3] macroring was deduced to be in cone conformation due to the presence of only one singlet at 3.63 ppm for the

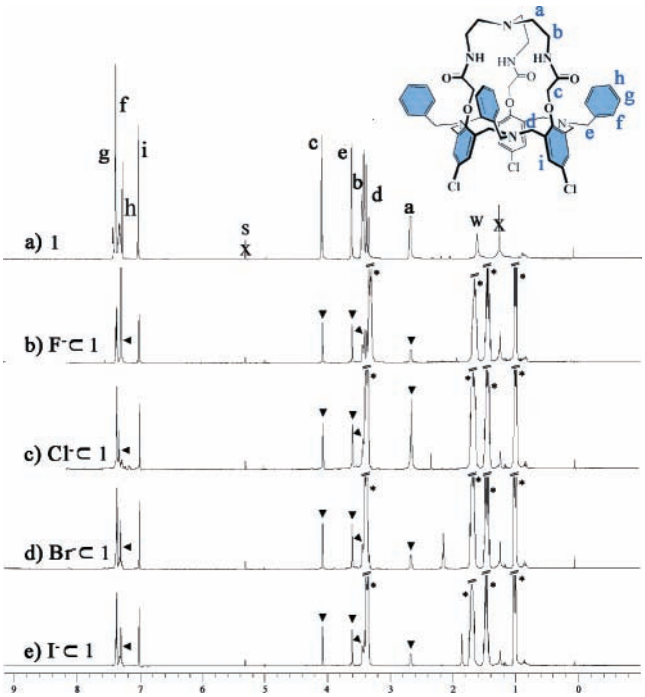


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$): (a) N_7-azacalix-[3]cryptand (**1**), (b) **1**⊃F^-, (c) **1**⊃Cl^-, (d) **1**⊃Br^-, and (e) **1**⊃I^- complexes obtained upon addition of $NBu_4^+X^-$ (10 equiv) into a $CDCl_3$ solution of **1**. ▼: signals of **1**⊃X^-. *: signals of NBu_4^+. Residual solvents and partially protonated water are labeled as "S" and "W", respectively.

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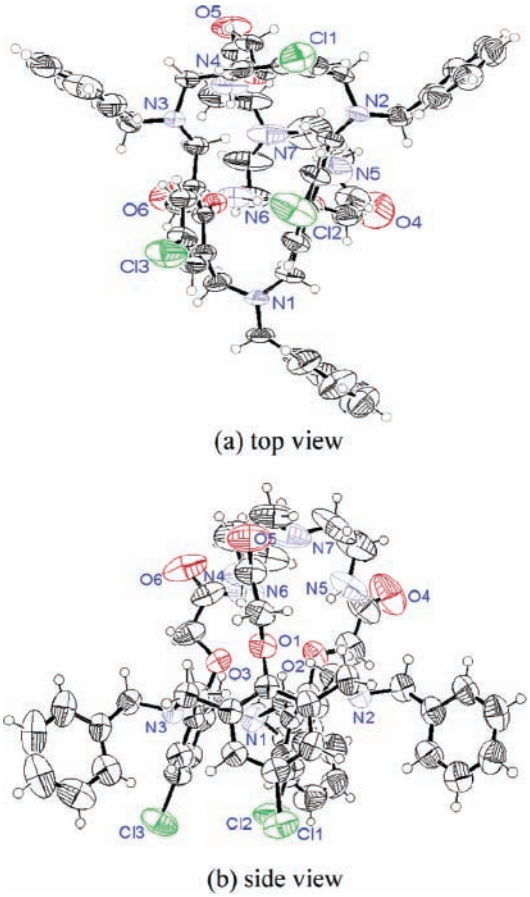

Figure 2. ORTEP drawing of N_7-azacalix[3]cryptand (**1**). The displacement ellipsoids are drawn at the 50% probability level.

ArCH_2N protons showing the retained C_{3v} symmetry of the molecule. X-ray single crystallographic analysis[7] clearly revealed that **1** was in a cone conformation (see Figure 2). They mutually interact outside the cavity to furnish a unique crytal structure stabilized by intermolecular CH/Cl hydrogen bond interactions (see Figure S11 in the Supporting Information).

The ability of **1** to include anions was investigated by ^{1}H NMR spectroscopy. $CDCl_3$ solutions of **1** were reacted with 10 equiv of tetrabutylammonium halides ($NBu_4^+X^-$). All of the resulting ^{1}H NMR spectra (see Figure 1b−e and Table S1 in the Supporting Information) displayed peaks shifts of OCH_2CO, NCH_2Ar, and NCH_2CH_2 toward downfield. This implies the formation of *endo* complexes while keeping the C_{3v} symmetry of the free ligand. Moreover, the signals of aromatic protons of benzyl moieties also displaced in the same manner, which may be due to a conformational organization.

The binding abilities of X^- by **1** were evaluated in DMSO by UV−vis spectroscopy (see Figure S1 in the Supporting Information). In all cases, hypochromic shifts were observed upon addition of $NBu_4^+X^-$ into solutions of **1**. The stoichiometries and stability constants of the complexes were refined by the SIRKO[8] program and are summarized in Table 1. It can be seen that **1** prefers to complex halide anions over CH_3COO^-, $PhCOO^-$, NO_3^-, PF_6^-, and ClO_4^- by forming 1:1 complexes.

Table 1. Stability Constants (log β)[a] of N_7-Azacalix[3]cryptand (1) Complexes with Anion in DMSO by UV−vis Titration Method (T = 25 °C, I = 0.01 M Bu_4NPF_6)

anions	log β (M^{-1})	% FA[b]
F^-	2.78 (0.01)[c]	40.80
Cl^-	4.55 (0.03)[c]	1.38
Br^-	3.97 (0.01)[c]	4.97
I^-	2.72 (0.01)[c]	43.87
NO_3^-	1.77 (0.01)[c]	89.87
ClO_4^-	undetermined	
CH_3COO^-	2.92 (0.01),[c] 6.06(0.01)[d]	0.03
$PhCOO^-$	2.36 (0.06),[c] 6.26(0.01)[d]	0.04

[a] Mean values of $n \geq 3$ independent determinations, with standard deviation σ_{n-1} on the mean in parentheses. [b] Percentage of various free halide anion at C_L, $C_A = 10^{-3}$ M. [c] 1:1 complex (AL). [d] 2:1 complex (A_2L).

Anion selectivity of **1** was obtained (as percentage of various free halide anion (% FA) (Table 1 and Figure S3 in the Supporting Information) by calculations using the Haltafall program.[9] For the halide ions, it may be concluded that **1** prefers to bind $Cl^- > Br^- > I^- > F^-$. This implies that the cavity size of receptor **1** is suitable for complexation with Cl^-. Though the NO_3^- ion (1.79 Å) has a similar size compared with the Cl^- ion (1.81 Å), the satibility constant of the NO_3^- complex is inferior to that of Cl^-. This can be explained by the ease of orientation of the anion inside the rigid cavity of receptor **1** to form hydrogen bonds with amide groups.

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(7) X-ray data were collected on a Bruker SMART CCD area detector. The crystal structure was solved by direct methods and refined by full-matrix least-squares. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined using the riding model. All calculations were performed using a crystallographic sotware package, WinGX v1.64.05.[14] Crystal data for 1: M_r = 1095.3, monoclinic, space group $P2_1/n$, a = 13.297(2) Å, b = 19.191(3) Å, c = 23.602(5) Å, β = 97.599(1)°, V = 5969.82(8)^3, Z = 4, ρ_{calc} = 1.120 g cm^{-3}, $2\theta_{max}$ = 57.4°, Mo Kα (λ = 0.71075), μ = 0.71 cm^{-1}, $\theta-\omega$ scans, T = 293(2) K, 42, 269 independent reflections, 16,815 observed reflections ($I > 3.0\sigma(I)$), 340 refined paramaters, R_1 = 0.092, R_w = 0.136, $\Delta\rho_{max}$ = 2.38 e^{-3}, $\Delta\rho_{max}$ = −2.26 e^{-3}; CCDC 292414. See the Supporting Information for crystallographic data in CIF format.

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Table 2. Stability Constants (log β')[a] of **1**·Zn^{2+} Complexes with Anion in DMSO by UV−vis Titration Method (T = 25 °C, I = 0.01 M Bu_4NPF_6)

anions	log β' (M^{-1})	% FA[b]
F^-	3.41 (0.08)[c]	15.31
Cl^-	3.58 (0.07)[c]	11.09
Br^-	4.33 (0.03)[c]	2.26
I^-	2.92 (0.05)[c]	33.94

[a] Mean values of $n \geq 3$ independent determinations, with standard deviation σ_{n-1} on the mean in parentheses. [b] Percentage of various free halide anion at C_L, $C_A = 10^{-3}$ M. [c] 1:1 complex (AL).

For CH_3COO^- and $PhCOO^-$ anions, two species of complexes (1:1 and 2:1 (anion/ligand)) were obtained leading to the lower percentages of free halide anion (% FA). This implies that the complexation may occur in an *exo* fashion.

As it was reported that the azacalix[3]arene can bind soft cations such as transition metals[2b,c] which can enhance anion binding by electrostatic force, we decided to check the effects of Zn^{2+} on anion complexation of **1**. In the presence of Zn^{2+}, hypochromic shifts increased in cases of F^-, Br^-, and I^- complexes while they decreased in the case of Cl^-, leading to incremental stability constants of halide complexation except for Cl^- (Table 2). This can be rationalized in the following manner: upon addition of Zn^{2+}, one can assume that the Zn^{2+} binds to the azacalix[3]arene part of **1** to give rise to a **1**·Zn^{2+} complex which is positively charged and thus increases the stability constants of **1**·Zn^{2+}/X^- by electrostatic interactions.[6b] In the case of Cl^-, the electronic interaction between $Zn^{2+}$and Cl^- may reduce the hydrogen bond interaction between **1** and Cl^-, which leads to a decrease of the stability constant.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (including NMR spectra and crystal structure for N_7-azacalix-[3]crytand (**1**) (CIF)). This material is available free of charge via the Internet at http://pubs.acs.org.

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