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Synthesis and complexing properties of methylated calix[4](aza)crown derivatives

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Abstract

The synthesis of methylated calix[4](aza)crowns and their complexing properties towards Co^{2+}, Ni^{2+} and Cu^{2+} are described. The crystal structure of one of those ligands, hydrogen bonded to a picric acid molecule via a water molecule, is given. © 2000 Elsevier Science Ltd. All rights reserved.

The family of *calix[4](aza)crowns* refer to molecules combining calix[4]arene elements and aza-crown units in their framework. They are constructed with aza-ethylene chains attached to the phenolic oxygen atoms of the calix via acetamido functions, which may serve as linking functions and also as chelating groups. The first 1,3-calix[4](aza)crowns were prepared by reaction of either calix dimethyl ester or calix diacid chloride with the appropriate diamine NH_2–R–NH_2 and were shown to complex divalent (Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and trivalent (Sc^{3+}, Y^{3+}, In^{3+}, Gd^{3+}, Bi^{3+}) metal cations as $[L+M]^+$ species detected by FAB-mass spectrometry.[1] The reaction of *syn* 1,3-diacid dichloride of *p-tert*-butylcalix[4]arene with various aliphatic diamines and diaza-15-crown-5 or diaza-18-crown-6 gives 1,3-capped calixarenes in cone conformation.[2] This family has been enlarged by regioselective alkylations of the two remaining phenolic OH and NH groups.[3] An anthracene-based fluorescent calix[4](aza)crown bearing a dioxo-tetraza unit in the bridge has been prepared to chelate Zn^{2+} and Ni^{2+}.[4] A calix[4](aza)crown bearing a piperazine unit in the chain has also been used to transport TcO_4^- in a double supported liquid membrane device.[5]

The aim of the present work was to obtain the calix[4](aza)crowns **3** and **4** (Scheme 1) in order to compare their complexing behavior to that of **2**, which is already known.[1]

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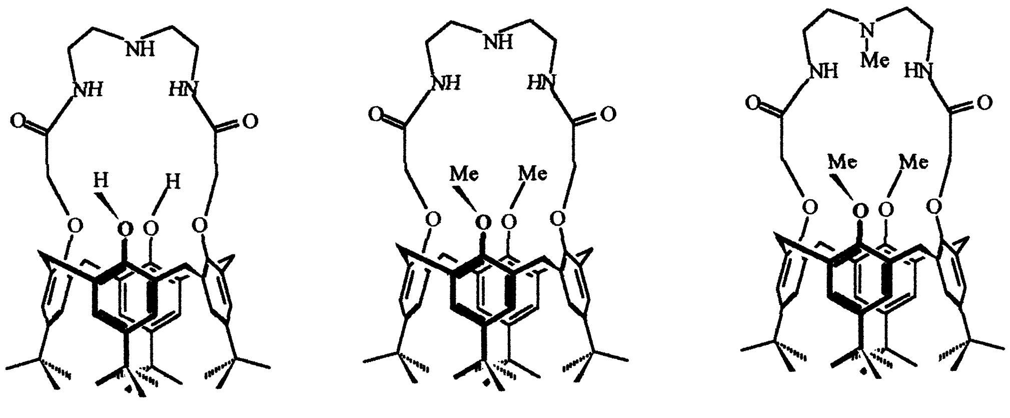
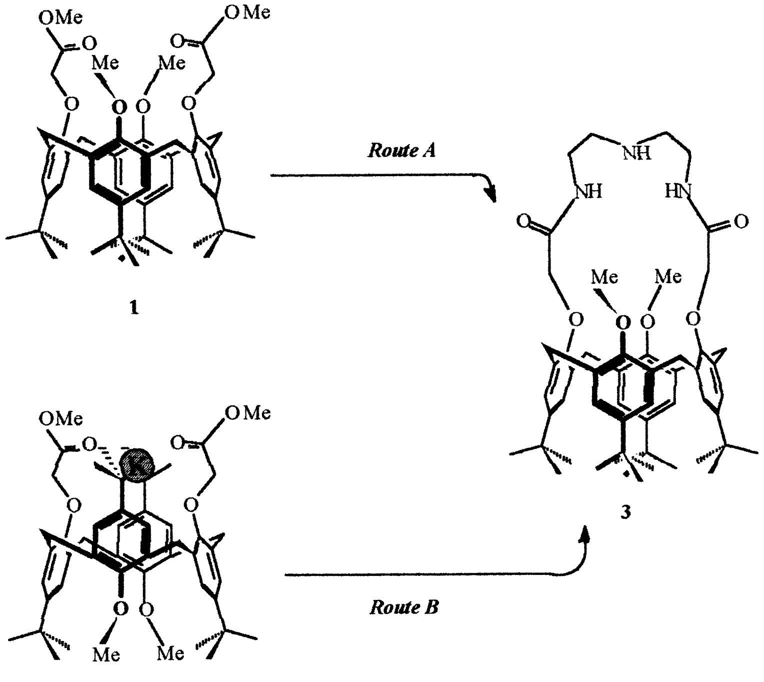


2 **3** **4**

Scheme 1.

Compound **3** was prepared according to Scheme 2. The dimethylester dimethoxy *p*-*tert*-butylcalix[4]arene **1** (route A) or its complex **1**·KI[6] (route B) was refluxed with 2 equiv. of diethylenetriamine in 1:1 methanol:toluene for 4 days.[7] Calix[4]*mono*(aza)crown **3** was produced in 72% (route A) or 19% (route B) yields. FAB(+)MS spectrometry, elemental analysis and ^{1}H NMR results were in agreement with the structures assumed. The latter gives a triplet at 7.90 ppm with $J=2.0$ Hz for the CONH function along with four singlets at 6.51 (ArH_{meta}), 4.27 (ArOCH_2), 1.35 (C(CH_3)$_3$) and 0.82 (C(CH_3)$_3$) ppm. One AB system at 4.16 and 3.20 ppm with $J=12.5$ Hz for ArCH_2Ar indicates that **3** adopts the *cone* conformation.



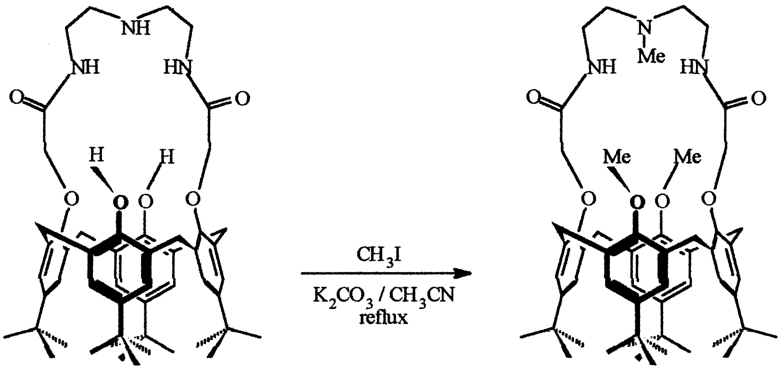
1

3

1KI

Scheme 2. Synthesis of ligand **3**

Calix[4](aza)crown **2** was reacted with 9 equiv. of CH_3I in the presence of K_2CO_3 in refluxing acetonitrile for 29 h to produce the trimethylated ligand **4** in 46% yield (Scheme 3).[7]



2 **4**

Scheme 3. Synthesis of ligand **4**

The *cone* conformation was deduced from the ^1H NMR spectrum showing one AB system at 4.22 and 3.37 ppm with $J = 13.0$ Hz for ArCH_2Ar protons. The CH_3 groups were detected as two singlets at 3.44 (ArOCH_3) and 3.30 (NCH_3) ppm. Three singlets at 1.24, 1.09 and 1.03 ppm (integration ratio 2:1:1) for $C(CH_3)_3$ and three singlets at 7.06, 7.01 and 6.89 ppm (integration ratio 1:2:1) for ArH_{meta} were also observed.

Preliminary complexation studies of **2**–**4** with Co^{2+}, Ni^{2+} and Cu^{2+} picrates were done by means of ^1H NMR. $CDCl_3$ solutions of **2**–**4** were reacted for 4 weeks with the solid picrates. For ligand **2** one singlet characteristic of picrate protons (ArH_{pic}) appeared with slight changes in its position. Because these metal ions are paramagnetic, the conclusions that no metal-extraction occurs and that picric acid is probably complexed can be drawn. A recent publication reports that the picrate extraction method for UO_2^{2+}, Cu^{2+}, Eu^{3+}, Cd^{2+}, Cr^{3+} and Pb^{2+} with calix[4]arene amides and amines as extractants is doubtful.[8] Crystallographic data confirmed the formation of a picric acid complex during extraction of $Ni(Pic)_2$.[9]

The asymmetric unit in $\mathbf{2}\cdot C_6H_3N_3O_7\cdot H_2O\cdot CH_3CN$ (**5**) is composed of one calixarene in the *cone* conformation, one water, one acetonitrile and one picric acid molecule (Fig. 1). One

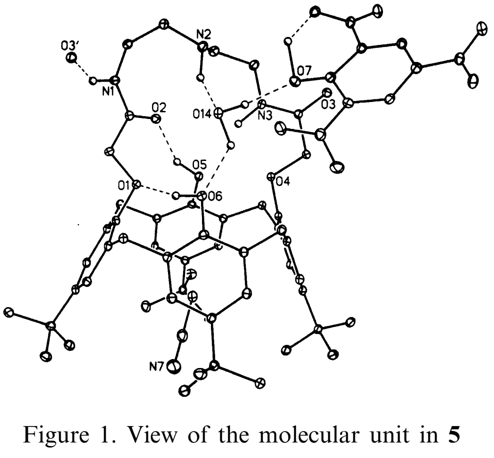


Figure 1. View of the molecular unit in **5**

phenolic proton is bound to an ether oxygen atom and the second one to the oxygen atom of an amide group. The proton of the nitrogen atom N1 points outwards and is bound to the amide oxygen atom of a neighbouring molecule. The proton of the central amine function is bound to the oxygen atom of a water molecule, which is involved in its turn in a hydrogen bond with the picric acid molecule and in another one with a phenolic oxygen atom of the calixarene. The interaction between the picric acid molecule and the calixarene is an indirect one, mediated by a water molecule. The dihedral angles between the aromatic rings of the calixarene and the mean plane defined by the four methylene bridges are 60.0(1), 59.4(1), 71.5(1) and 57.0(1)°. An acetonitrile molecule is included in the calixarene cavity. The picric acid molecule is unremarkable, with dihedral angles between the nitro groups and the aromatic ring of 29.8(5), 9.5(4) and 29.3(5)°. An example of adduct between a calix[4]arene with two amide arms on the lower rim and picric acid has been reported previously.[10] In this case, the assignment of charges on the two molecules was ambiguous, as well as the presence of intermolecular hydrogen bonds. However, the aromatic ring of picric acid being nearly parallel to one of the phenyl rings of the calixarene, with a dihedral angle of 8.6° and a minimum distance of 3.29 Å, the presence of π-stacking interactions was assumed. In the present case, such interactions are certainly present between neighbouring picric acid molecules, which are parallel to each other with a minimum distance of 3.27 Å, and possibly present between picric acid and the nearer calixarene phenolic ring, with a dihedral angle of 19.8(2)° and a shorter C···C distance of 3.440 Å.[11]

No changes are observed in the spectrum of **3** with Co^{2+} and Ni^{2+}, indicating that no extraction occurs. Cu^{2+} induces a broadening of the spectrum, in which two singlets at 9.80 and 9.10 ppm attributable to four ArH_{pic} are present. The broad singlet of CON*H* protons moves to lower fields with $\Delta\delta = +0.34$ ppm as well as the singlets of $ArOCH_3$ ($\Delta\delta = +0.07$ ppm) and $C(CH_3)_3$ *para* to ArOH ($\Delta\delta = +0.27$ ppm). The remaining part of the spectrum is almost unreadable. As an extractant, compound **3** appears to be selective for Cu^{2+} with respect to Co^{2+} and Ni^{2+}.

The spectrum of **4** is changed in the presence of the three metal ions. With Co^{2+} and Ni^{2+}, the aromatic and *p*-*tert*-butyl regions of the spectra only retain the original pattern of three singlets. The region corresponding to the bridge cannot be interpreted, probably due to the location of the metal ions in this part of the ligand. Flat singlets are observed at 9.45 (CON*H*) and 8.81 (ArH_{pic}) ppm for Co^{2+} and 9.87 (ArH_{pic}) and 9.54 (CON*H*) ppm for Ni^{2+} with an integration ratio compatible with the formation of 1:1 complexes. The spectrum with Cu^{2+} cannot be interpreted.

Several methods to immobilise the calix[4]arene conformation by *O*-substitution or by cross-linking the upper rim in order to obtain desired selectivities have already been reported.[12] We have reported herein some changes in the complexing behaviour of calix[4](aza)crown type molecules by introduction of methyl groups on the proton-ionizable atoms. Further work on competitive transport experiments with **2**–**4** as extractants is in progress.

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7. **General**: Melting points (mps) were taken in capillaries under nitrogen on a Büchi 500 apparatus. Precoated silicagel plates (Merck 60 F_{254}) were used for analytical TLC. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker SY200 spectrometer. Chemical shifts are given on δ-scale in ppm. FAB(+) mass spectra were recorded on a VG-Analytical ZAB HF. Elemental analyses were performed at the Service de Microanalyse of the Institut de Chimie de Strasbourg. Alkyl amines used are commercially available. All chemicals were reagent grade and used without further purification. Compounds **1** and **2** were prepared as described in the literature. **Preparation of 1,3-dimethoxy-*p*-*tert*-butylcalix[4](aza)*mono*crown (3)**. 1,3-dimethoxy-2,4-dimethylester-*p*-*tert*-butylcalix[4]-arene **1** (0.504 g; 0.61 mmol), triethylene diamine (0.121 g; 1.18 mmol) in 1:1 methanol:toluene (20 mL) were refluxed for 4 days. After removal of the solvents, the crude mixture was precipitated with methanol to give 1,3-dimethoxy calix[4](aza)*mono*crown (**3**) (0.375 g; 0.44 mmol) as a white solid (mp>270°C). $R_f = 0.68$ (50:50 CH_2Cl_2:acetone). ^{1}H NMR (200 MHz, $CDCl_3$): 7.90 (broad t, 2H, CON*H*), 7.16 (s, 4H, ArH_{meta}), 6.51 (broad s, 4H, ArH_{meta}), 4.27 (s, 4H, ArOCH_2), 4.16 (broad d, $J = 12.6$ Hz, 4H, ArCH_2Ar), 4.01 (broad s, 6H, ArOCH_3), 3.66 (broad m, 4H, CH_2–amide), 3.20 (broad d, $J = 12.6$ Hz, 4H, ArCH_2Ar), 2.86 (broad m, 4H, CH_2–amine), 1.35 (s, 18H, C(CH_3)$_3$), 0.82 (s, 18H, C(CH_3)$_3$). FAB(+) MS, *m*/*z* 860.6 $(M+H)^+$. Anal. calcd for $C_{54}H_{73}N_3O_6 \cdot 1.5CH_3OH$: C, 73.39; H, 8.77. Found C, 73.71; H, 8.70%. Yield 72%. When the reaction was carried out with the potassium complex **1**·KI the yield dropped to 19%. **Preparation of *N*-methyl-1,3-dimethoxy-*p*-*tert*-butylcalix[4](aza)*mono*crown (4)**. 1,3-dimethoxy-*p*-*tert*-butylcalix[4](aza)crown (**3**) (2.356 g; 2.77 mmol), K_2CO_3 (2.823 g; 20.47 mmol) in acetonitrile (200 mL) were stirred for 1 h at room temperature under N_2. Then CH_3I (3.500 g; 24.69 mmol) dissolved in acetonitrile (100 mL) was added. After refluxing for 29 h, the solvents were evaporated to dryness and the crude mixture was precipitated with methanol to give *N*-methyl-1,3-dimethoxy-*p*-*tert*-butylcalix[4](aza)*mono*crown (**4**) (1.102; 1.26 mmol) as a white solid (189–191°C). $R_f = 0.24$ (50:50 acetic acid:acetonitrile). ^{1}H NMR (200 MHz, $CDCl_3$): 9.25 (broad s, 2H, CON*H*), 7.06 (s, 2H, ArH_{meta}), 7.01 (s, 4H, ArH_{meta}), 6.89 (s, 2H, ArH_{meta}), 4.84 (s, 2H, ArOCH_2), 4.47 (s, 2H, ArOCH_2), 4.46 (s, 2H, CH_2–amine), 4.22 (d, $J = 13.0$ Hz, 4H, ArCH_2Ar), 4.05 (broad s, 4H, CH_2–amide), 3.85 (broad s, 2H, CH_2–amine), 3.44 (s, 6H, ArOCH_3), 3.37 (d, $J = 13.0$ Hz, 4H, ArCH_2Ar), 3.30 (s, 3H, NCH_3), 1.24 (s, 18H, C(CH_3)$_3$), 1.09 (s, 9H, C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$). FAB(+) MS, *m*/*z* 874.5 $(M+H)^+$. Anal. calcd for $C_{55}H_{75}N_3O_6.CH_3OH.CH_2Cl_2$: C, 64.74; H, 7.77. Found C, 64.25; H, 7.60%. Yield 46%.
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9. **Crystal structure**. The data were collected on a Nonius Kappa-CCD area detector diffractometer using graphite-monochromated Mo–Kα radiation. The structure was solved by direct methods and subsequent Fourier-difference synthesis and refined by full-matrix least-squares on F^2 with SHELXTL (Bruker AXS). The protons bound to phenolic oxygen and amine nitrogen atoms as well as those of the water and picric acid molecules were introduced as found on the Fourier difference maps whereas all other hydrogen atoms were introduced at calculated positions. All hydrogen atoms were treated as riding atoms with a displacement parameter equal to 1.2 (OH, NH, CH, CH_2) or 1.5 (CH_3) times that of the parent atom. All non-hydrogen atoms were refined anisotropically. $R1 = 0.079$, $R2w = 0.147$, $S = 1.002$ for 10 303 unique reflections ($R_{int.} = 0.14$) and 743 parameters. Crystal data have been deposited with the Cambridge Crystallographic Data Centre. **Crystal data** for $\mathbf{2} \cdot C_6H_3N_3O_7 \cdot H_2O \cdot CH_3CN$ (**5**): $C_{60}H_{77}N_7O_{14}$, $M = 1120.29$, monoclinic, space group $P2_1/c$, $a = 22.2883(10)$, $b = 12.3842(8)$, $c = 21.7519(12)$ Å, $\beta = 107.554(5)°$, $V = 5724.4(5)$ Å^3, $Z = 4$, $D_c = 1.300$ g cm^{-3}, $\mu = 0.093$ mm^{-1}, $F(000) = 2392$.
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