Pergamon

Tetrahedron Letters 42 (2001) 3595–3598

TETRAHEDRON
LETTERS

Synthesis and cation complexation studies of a new tetra(2-pyridylmethyl)amide calix[4]arene

Abdelwaheb Hamdi,[a] Rym Abidi,[a,*] Malika Trabelsi Ayadi,[a] Pierre Thuéry,[b,*] Martine Nierlich,[b]
Zouhair Asfari[c] and Jacques Vicens[c,*]

[a] *Université de Bizerte, Facultés des Sciences, 7021 Zarzouna-Bizerte, Tunisia*
[b] *CEA/Saclay, SCM (CNRS URA 331), Bât. 125, 91191 Gif-sur-Yvette, France*
[c] *Ecole Chimie Polymères Matériaux, Laboratoire de Chimie des Interactions Moléculaires Spécifiques, associé au CNRS, 25, rue Becquerel, F-67087 Strasbourg, Cédex 2, France*

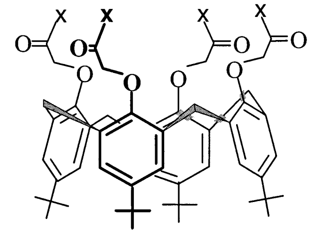
Received 29 March 2001; accepted 30 March 2001

Abstract—The synthesis of a new tetra(2-pyridylmethyl)amide calix[4]arene is reported. Its binding properties towards alkali and alkaline earth metals, transition metals and lanthanides have been determined along with the complexes stoichiometries. ^{1}H NMR investigations allowed the location of cations in the receptor to be determined. The synthesis and crystal structure of the related tetra(benzyl) derivative are also reported. © 2001 Elsevier Science Ltd. All rights reserved.

Di- or polytopic receptors are host molecules constructed with two or more structurally and energetically similar binding subunits within the same macrocyclic structure.[1] Once recognition of each binding subunit has been identified, the ability of multiple recognition and mutual effects of binding subunit occupation provide entries to higher forms of molecular behaviour such as cooperativity, allostery and regulation, as well as communication or metal transfer.[1] Calix[4]arene derivatives[2,3] can adopt four conformations: cone, partial cone, 1,2-alternate and 1,3-alternate and their complexing behaviours have been proved to depend on the conformation of the calixarene moiety. Much attention has been paid to calix[4]arenes, in the cone conformation, *O*-substituted with amide, ester or ketone functions and their complexing properties towards metal cations has been recently reviewed.[4]

As part of our work on calixarenes containing simultaneously hard and soft ion binding sites,[5,6] we report herein the synthesis of tetra(2-pyridylmethyl)amide calix[4]arene **2**. Related tetra(benzyl)amide **3** is also reported for comparison with **2**.

The four amido functions delineate a cavity consisting of four carbonyl units and four phenolic oxygens which may complex *hard* cations such as alkali metals.[4]



1 X = OCH$_3$
2 X = NH-CH$_2$-Py
3 X = NH-CH$_2$-C$_6$H$_5$

Another cavity is delineated by the attachment of the four pyridine moieties via the amido functions capable of complexing *soft* cations by the nitrogen atoms.[7] A very similar ditopic hard–soft receptor has been designed from a calix[4]arene in the cone conformation substituted with four EtS(CH$_2$)$_n$NHCOCH$_2$O- groups. ^{1}H NMR spectral studies showed that although Cd^{2+} bound to the soft binding site excludes Na$^+$ out of the hard binding site, Ag$^+$ can coexist with Na$^+$ in the ionophoric cavity.[8]

Compounds **2** and **3** were prepared by reacting 25,26,27,28-tetrakis(carboxymethoxy)calix[4]arene **1** with an excess of 2-(aminomethyl)pyridine or benzylamine in a refluxing 1:1 mixture of methanol–toluene for 10 and 8 days, respectively.[9] After evaporation of the solvents, the crude residue was precipitated with acetone to give **2** (80%) and **3** (71%). Complete alkylation and cone conformation of **2** and **3** were deduced from their ^{1}H NMR spectra in CDCl$_3$. For instance, for **2**, an AB system was found at 3.24 and 4.61 ppm with

---

* Corresponding authors. E-mail: vicens@chimie.u-strasbg.fr

PII: S0040-4039(01)00532-9

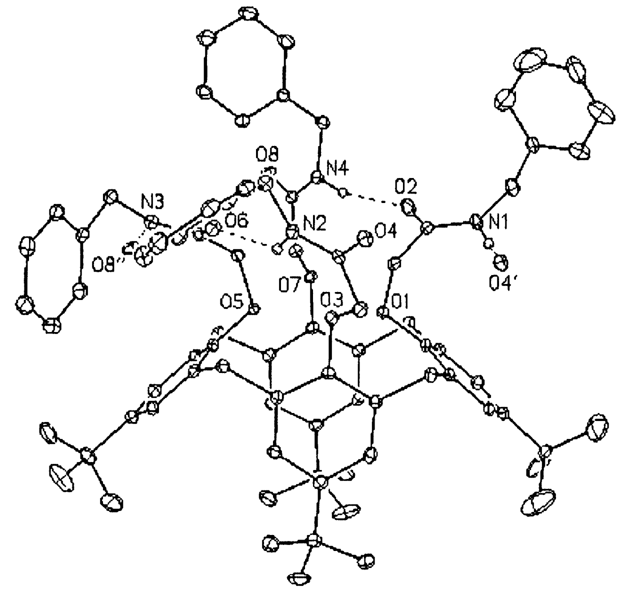


Figure 1. Crystal structure of $3{\cdot}1.5CHCl_3$. Hydrogen bonds in dashed lines. The protons of amine groups are represented as small spheres of arbitrary radii, the other protons and the solvent molecules are omitted for clarity. Symmetry codes: $' = -x, 1-y, -z$; $'' = 1-x, -y, -z$.

$J = 14.0$ Hz for the $ArCH_2Ar$ in the macroring.[9] Singlets at 1.11, 4.66 and 6.80 ppm in an integration ratio 36:8:8 were attributed to the $-C(CH_3)_3$ groups, $ArOCH_2$- and ArH_{meta} of the calix unit, respectively, showing a C_{4v} symmetry for the molecule.[9] Similar findings were made on **3**.[9] The structure of **3** was confirmed by X-ray crystallography.[10] The crystal structure of $\mathbf{3}{\cdot}1.5CHCl_3$ is represented in Fig. 1.[10]

In the solid state, molecule **3** does not possess any symmetry element. The calixarene is in a distorted cone conformation, with two opposite aromatic rings more tilted than the other ones. The dihedral angles between the aromatic rings and the mean plane defined by the four methylenic carbon atoms are 41.7(1), 87.4(1), 42.5(1) and 85.5(1)°. The four protons bound to nitrogen atoms are involved in hydrogen bonds. Two of these atoms, corresponding to N2 and N4 and to the more 'vertical' rings, are bound to the amide oxygen atoms of the neighbouring chains in the same molecule. The other two atoms, corresponding to N1 and N3, are hydrogen bonded to amide oxygen atoms pertaining to neighbouring molecules in the crystal packing.

A preliminary evaluation of the binding efficiency of **2** was carried out by solvent extraction of metal picrates into dichloromethane at 20°C under neutral conditions.[9] Alkali and alkaline earth cations were poorly extracted by **2**: Li^+ (10%), Na^+ (15%), K^+ (7%), Rb^+ (5%), Cs^+ (2%), Mg^{2+} (3%), Ca^{2+} (9%), Sr^{2+} (no extraction observed), Ba^{2+} (4%), matching percent extraction values (%*E*) already observed for related tetra methylmethylketone and tetra butylamide derivatives showing that the pyridine residues did not improve its extraction efficiency. Probably these cations are located in the hard site of **2**.[4] Soft Zn^{2+} cation was extracted in approximately the same %*E* as Na^+. To locate these cations we investigated their complexation by ^1H NMR technique. $CDCl_3$ solutions of **2** were reacted for 48 h with solid Na^+Pic^- and $Zn^{2+}(Pic^-)_2$. Singlets appeared at 8.69 and 8.76 ppm, respectively for Na^+ and Zn^{2+} in agreement with the formation of 1:1 complexes as estimated from integration ratio of the picrate proton resonance versus those for the PyH_6. For $\mathbf{2{\cdot}Na^+Pic^-}$ small Δδ shifts were observed for the signals corresponding to the pyridine moiety while a large shift was observed for the N–H triplet. We concluded Na^+ to be located in the hard 'tetraamido' cavity as already assumed. For $\mathbf{2{\cdot}Zn^{2+}(Pic^-)_2}$ larger Δδ shifts were

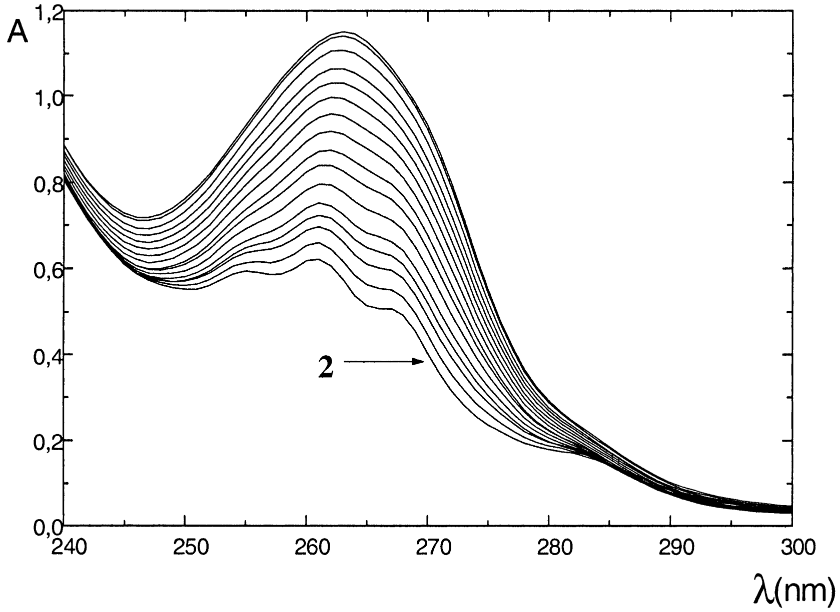


Figure 2. Changes in the UV–vis absorption spectrum of ligand **2** upon addition of $Cr(ClO_4)_2$ in acetonitrile; concentration of **2**: 4.0×10^{-5} M, $0 \leq R \leq 9$; concentration of $NEt_4ClO_4 = 0.01$ M; cuvettes of 1 cm path length.

Table 1. Stability constants in acetonitrile at 18°C

Cations	Metal:ligand **2** stoichiometries	Log β_{ij}
Li$^+$	1:1	5.47±0.10
Na$^+$	1:1	5.54±0.01
Mg^{2+}	1:1	5.56±0.01
Ca^{2+}	1:1	5.51±0.01
Sr^{2+}	1:1	4.67±0.01
Ba^{2+}	1:1	5.92±0.01
Cr^{2+}	2:1	8.14±0.01
Co^{2+}	1:2	8.90±0.01
Ni^{2+}	1:2	8.54±0.05
Cu^{2+}	2:1	9.27±0.01
Zn^{2+}	1:1	4.44±0.05
La^{3+}	1:1	3.75±0.05
Nd^{3+}	1:1	3.54±0.05
Gd^{3+}	1:1	3.79±0.05

observed for the pyridine moiety leading to the conclusion that the cation is located close to the nitrogen atoms forming the soft site. The need of the nitrogen atoms of the pyridine for complexing Zn^{2+} was shown by reacting benzyl analogue **3** in the same conditions.[9] In this case only Na$^+$Pic$^-$ was extracted giving rise to a 1:1 complex with Na$^+$ located in the hard site of **3**.[9] In separate experiments, we reacted CDCl$_3$ solutions of **2·Na$^+$Pic$^-$** with Zn^{2+}(Pic$^-$)$_2$ and of **2·Zn^{2+}(Pic$^-$)$_2$** with Na$^+$Pic$^-$. No changes were observed in the ^{1}H NMR spectra showing that a second cation is not accepted in the complex receptors.

We evaluated the thermodynamic parameters of complexation on **2** in a homogeneous medium limited to acetonitrile because of low solubility of **2** in the usual solvents. The stability constants in acetonitrile were determined by UV absorption spectrophotometry at 18°C. The procedure consisted of adding increasing amounts of metallic perchlorates to a solution of **2**. The resulting changes (see Fig. 2) were analysed by the program Letagrop–Spefo.[12,13]

The values of the corresponding stability constants (as log β_{ij}) are given in Table 1 along with the assumed stoichiometries of the complexes. 1:1 Complexes were observed for Li$^+$, Na$^+$ (no complexation was observed with K$^+$, Rb$^+$, Cs$^+$), Zn^{2+} (in agreement with extraction results), Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} (with selectivities $S_{\mathrm{Ca^{2+}/Sr^{2+}}}=7$ and $S_{\mathrm{Ba^{2+}/Sr^{2+}}}=18$, La^{3+}, Nd^{3+} and Gd^{3+} (no selectivity observed). Homobinuclear complexes **2·2Cr^{2+}(ClO$_4^-$)$_2$** and **2·2Cu^{2+}(ClO$_4^-$)$_2$** (the copper complex is 10 times more stable than the chromium one) can be assumed with a probable inclusion of two cations in both hard and soft cavities. The observation of biligand complexes with Co^{2+}(ClO$_4^-$)$_2$ and Ni^{2+}(ClO$_4^-$)$_2$ indicated a bridging of two calix units via metal linkage probably through the pyridine arms.

Future work is directed towards the synthesis of tetra-amido-type calix[4]arenes with moieties different from pyridine.

References

1. Lehn, J.-M. *Supramolecular Chemistry*, *Concepts and Perspectives*; VCH: Weinheim, 1995.
2. Gutsche, C. D. *Calixarenes Revisited*; RSC: Cambridge, 1998.
3. Böhmer, V. *Angew. Chem.*, *Int. Ed. Engl.* **1995**, *34*, 713.
4. McKervey, M. A.; Schwing-Weill, M.-J.; Arnaud-Neu, F. In *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Pergamon: Oxford, 1996; p. 537.
5. Aeungmaitrepirom, W.; Asfari, Z.; Vicens, J. *Tetrahedron Lett*. **1997**, *38*, 1907.
6. Pulpoka, B.; Asfari, Z.; Vicens, J. *J. Incl. Phenom. Mol. Recogn*. **1997**, *27*, 21.
7. Metal coordination with calixarenes appended with pyridine has been described by: (a) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem*. **1992**, *57*, 2611; (b) Regnouf-de-Vains, B.; Lamartine, R. *Tetrahedron Lett*. **1996**, *37*, 631; (c) Danil de Namor, A. F. *Coord. Chem. Rev*. **1999**, *190–192*, 283.
8. Koh, K. N.; Imada, T.; Nagasaki, T.; Shinkai, S. *Tetrahedron Lett*. **1994**, *35*, 4157.
9. **Analytical procedures**: Melting points (mps) were taken on a Büchi 500 apparatus in a capillary sealed under nitrogen. Elemental analyses were carried out at the Service de Microanalyse of the Institut de Chimie de Strasbourg. ^{1}H NMR spectra were recorded at 200 MHz on a Bruker SY 200 spectrometer. The FAB mass spectrum was obtained on a VG-Analytical ZAB apparatus. **Preparation of 2**: 25,26,27,28-Tetrakis(carboxymethoxy)-calix[4]arene **1** (1.876 g; 2.00 mmol) was reacted with an excess of 2-(aminomethyl)pyridine (5.402 g; 50 mmol) in a refluxing 1:1 mixture of methanol–toluene (66 ml) for 10 days. After evaporation of the solvents the crude residue was precipitated with acetone to give **2** in 80% yield. Mp=241–242°C. ^{1}H NMR (CDCl$_3$, δ in ppm from TMS): 8.63 (t, $J=5.5$ Hz, 4H, NH), 8.43 (d, $J=4.0$ Hz, 4H, PyH_6), 7.58 (dt,, $J=7.5$ Hz $J=4.0$ Hz, 4H, PyH_5), 7.23 (d, $J=7.5$ Hz, 4H, PyH_3), 7.09 (dd,, $J=7.5$ Hz, $J=6.5$ Hz, 4H, PyH_4), 6.80 (s, 8H, Ar$H_{\mathrm{metacalix}}$), 4.66 (s, 8H, -CH_2OAr), 4.61 (AB system, $J=14.0$ Hz, 4H, ArCH_2Ar), 4.60 (d, $J=5.5$ Hz, 8H, -CH_2Py), 3.24 (AB system, $J=14.0$ Hz, 4H, ArCH_2Ar), 1.11 (s, 36H, -C(CH_3)$_3$). FAB positive $m/z=1271.5$. Anal. calcd for $C_{76}H_{88}N_8O_8$: C, 70.24; H, 7.52. Found C, 70.58, H, 7.05. **Preparation of 3**: Similar to **2**. Calixarene **1** (1.876 g; 2.00 mmol), benzylamine (5.047 g; 50 mmol), reflux 8 days. Yield 71%. Mp>270°C. ^{1}H NMR (CDCl$_3$, δ (in ppm from TMS): 7.73 (t, $J=6.0$ Hz, 4H, NH), 7.21 (m, 20H, benzyl), 6.75 (s, 8H, Ar$H_{\mathrm{metacalix}}$), 4.38 (s, 8H, -CH_2OAr), 4.45 (d, $J=6.0$ Hz, 8H, CH_2Benz), 4.41 (AB system, $J=13.0$ Hz, 4H, ArCH_2Ar), 3.14 (AB system, $J=13.0$ Hz, 4H, ArCH_2Ar), 1.07 (s, 36H, -C(CH_3)$_3$). Anal. calcd for $C_{80}H_{92}N_4O_8$: C, 77.63; H, 7.50. Found C, 77.61, H, 7.60.

   2·Na$^+$Pic$^-$: ^{1}H NMR (CDCl$_3$, δ (in ppm from TMS): 8.69 (s, 2H, Pic$^-$), 8.38 (d, $J=5.0$ Hz, 4H, PyH_6), 8.32 (t, $J=5.5$ Hz, 4H, NH), 7.56 (t, $J=7.5$ Hz, 4H, PyH_5), 7.21 (d, $J=7.5$ Hz, 4H, PyH_3), 7.12–7.07 (m, 4H, PyH_4), 6.94 (broadening s, 8H, Ar$H_{\mathrm{metacalix}}$), 4.63 (s, 8H, –CH_2OAr), 4.49 (AB system, $J=13.0$ Hz, 4H, ArCH_2Ar), 4.57 (d, $J=5.5$ Hz, 8H, -CH_2Py), 3.27 (AB system, $J=13.0$ Hz, 4H, ArCH_2Ar), 1.09 (s, 36H, -C(CH_3)$_3$).

2·Zn^{2+}(Pic$^-$)$_2$: ^{1}H NMR (CDCl$_3$, δ (in ppm from TMS) 9.18 (broad s, 4H, N*H*), 8.76 (s, 4H, Pic$^-$), 8.48 (d, $J=4.0$ Hz, 4H, PyH_6), 7.73 (t, $J=7.5$ Hz, 4H, PyH_5), 7.37 (d, $J=9.0$ Hz, 4H, PyH_3), 7.20 (t, $J=7.5$ Hz, 4H, PyH_4), 6.67 (broadening s, 8H, Ar$H_{\text{metacalix}}$), 4.65 (broad s, 16H, -CH_2OAr and CH_2Py), 4.36 (AB system, $J=11.5$ Hz, 4H, ArCH_2Ar), 3.00 (broad s, 4H, ArCH_2Ar), 1.02 (s, 36H, -C(CH_3)$_3$).

3·Na$^+$Pic$^-$: ^{1}H NMR (CDCl$_3$, δ (in ppm from TMS): 8.21 (s, 2H, picrate) 7.73 (coales. s, 4H, N*H*), 7.21 (m, 20H, benzyl), 6.80 (coales. s, 8H, Ar$H_{\text{metacalix}}$), 4.38 (s, 8H, -CH_2OAr), 4.37 (d, $J=6.0$ Hz, 8H, CH_2Benz), 4.36 (coales. AB system, 4H, ArCH_2Ar), 3.18 (coales. AB system, 4H, ArCH_2Ar), 1.07 (s, 36H, -C(CH_3)$_3$).

10. **Crystal structure of 3·1.5CHCl$_3$**. The data were collected on a Nonius Kappa-CCD area detector diffractometer using graphite-monochromated Mo Kα radiation (0.71073 Å). The structure was solved by direct methods and subsequent Fourier-difference synthesis and refined by full-matrix least-squares on F^2 with SHELXTL.[11]No absorption correction was done. All non-hydrogen atoms were refined anisotropically. One of the chloroform molecules, located near a symmetry centre, has been affected with a 0.5 occupancy. The protons bound to nitrogen atoms were found on the Fourier-difference map and introduced as riding atoms with a displacement parameter equal to 1.2 times that of the parent atom. All other hydrogen atoms were introduced at calculated positions as riding atoms with a displacement parameter equal to 1.2 (CH, CH$_2$) or 1.5 (CH$_3$) times that of the parent atom. $R_1=0.098$, $wR_2=0.237$, $S=1.031$ for 13245 unique reflections ($R_{\text{int.}}=0.081$) and 913 parameters. Crystal data have been deposited with the Cambridge Crystallographic Data Centre, under reference CCDC 156366.

    Crystal data for **3**·1.5CHCl$_3$: $C_{81.5}H_{93.5}Cl_{4.5}N_4O_8$, $M=1416.63$, triclinic, space group P–1, $a=15.8725(11)$, $b=16.3762(6)$, $c=16.6258(11)$ Å, $\alpha=74.934(4)$, $\beta=71.591(3)$, $\gamma=72.069(4)$°, $V=3837.4(4)$ Å^3, $Z=2$, $D_c=1.226$ g cm^{-3}, $\mu=0.229$ mm^{-1}, F (000)$=1502$, $T=100(2)$ K.
11. Sheldrick, G. M. *SHELXTL*, *Version 5.1*; University of Göttingen: Germany, 1999.
12. **Extraction and complexation experiments**: The %*E* of metallic picrates (2.5×10^{-4} M) extracted from water to dichloromethane containing ligand **2** (2.5×10^{-4} M) was determined at 20°C as previously described.[13] The stability constants in acetonitrile were determined by UV absorption spectrophotometry at 18°C. The procedure consisted in adding increasing amounts of metallic perchlorates to a solution of **2** ($C_{\text{ligand}}=4\times10^{-5}$ M). The resulting changes (Table 1) were analyzed by the program Letagrop–Spefo.[13]
13. Seangprasertkij, R.; Asfari, Z.; Arnaud, F.; Weiss, J.; Vicens, J. *J. Incl. Phenom.* **1992**, *14*, 141.