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Cation- and solvent-induced conformational changes of 25,27-dimethoxy-26,28-dimethylester-*p*-*tert*-butylcalix[4]arene

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Abstract

The synthesis of 25,27-dimethoxy-26,28-dimethylacetate-*p*-*tert*-butylcalix[4]arene is presented. Complexation studies towards alkali metal cations showed selectivities for Na^+ and Li^+. Different conformations for the 1:1 complexes are detected depending on the solvent used. X-ray structures of the ligand and some complexes are given. © 2000 Elsevier Science Ltd. All rights reserved.

Calix[4]arenes are conformationally mobile in solution at room temperature and exist in a range of conformations including *the cone*, *the partial-cone*, *the 1,2-alternate and the 1,3-alternate*.[1,2] The complexing ability of a given calixarene depends on its conformation and vice versa its conformation can be induced by the presence of a given cation.[3–5] For example, the selectivity of two-phase solvent extractions of alkali metal picrates by a diester dipyridyl *p*-*tert*-butyl calix[4]arene derivative are dependent on its conformation.[6] Upon complexation with potassium picrate, mobile 1,3-dimethoxycalix[4]crown-5 was converted quantitatively into the 1,3-alternate conformation.[7] The use of potassium carbonate in *O*-alkylations of *p*-*tert*-butyl calix[4]arene gave a 2:1 complex with potassium cations and tetraamide derivative in the 1,3-alternate conformation.[8]

We present, in this letter, the synthesis of 25,27-dimethoxy-26,28-dimethylacetate-*p*-*tert*-butylcalix[4]arene **2** and complexation studies towards alkali metal cations.[9]

Compound **2** was prepared as its complex **2**.KI (pathway (i)) and as a free ligand (pathway (ii)). 1,3-Dimethyl acetate[10] **1** was reacted with 6 equiv. of CH_3I in the presence of K_2CO_3 in refluxing CH_3CN for 3 days to produce the **2**.KI complex in 64% yield.[11] Elemental analysis and

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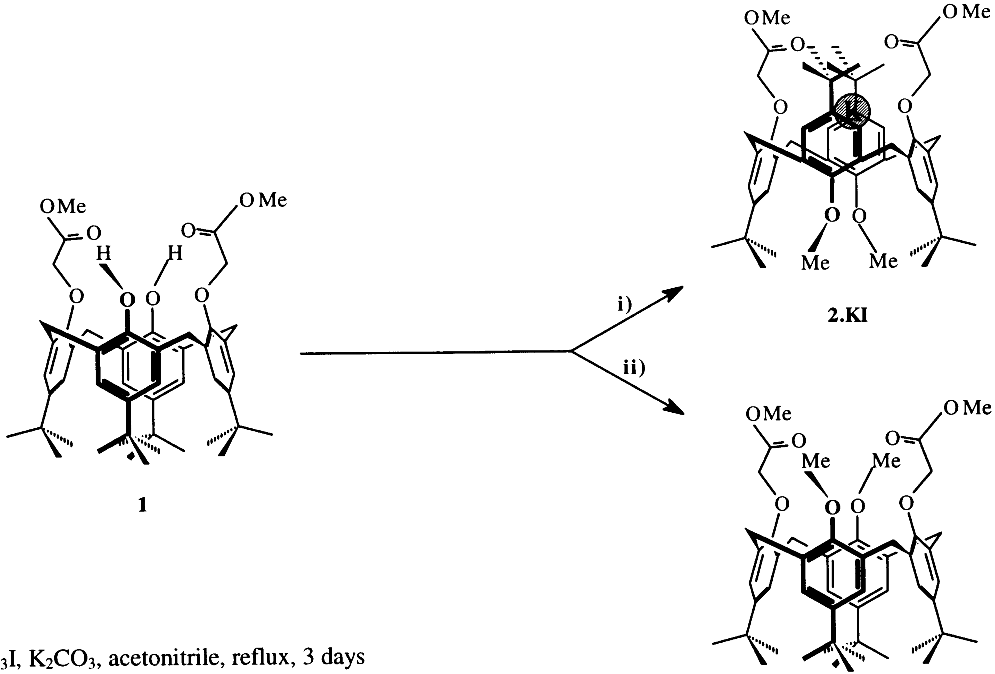
FAB(+) MS were in agreement with the structure $C_{52}H_{68}O_8KI$. The 1,3-alternate conformation was deduced from the ^1H NMR spectrum in $CDCl_3$ showing two singlets at 1.23 and 1.26 ppm in integration ratio 1:1 for $C(CH_3)_3$, one *AB* system at 3.70 and 3.80 ppm with $J_{AB}=16.5$ Hz for $ArCH_2Ar$ protons and two singlets at 7.08 and 7.15 ppm in integration ratio 1:1 for Ar***H***. A similar reaction was run with a 'work up' in acidic conditions (pathway ii)): in the final step, the organic layer was washed with 1N HCl–H_2O. Precipitation with methanol gave **2** in 67% yield.[11] Compound **2** showed broad signals in the ^1H NMR spectrum in $CDCl_3$ and was concluded to be conformationally mobile, probably due to the presence of methoxy groups allowing the oxygen-trough-the-annulus rotation.[1,2]



1

2.KI

2

i) CH_3I, K_2CO_3, acetonitrile, reflux, 3 days
ii) CH_3I, K_2CO_3, acetonitrile, reflux, 3 days, 1N HCl

To gain more information on the binding properties of **2** we investigated ^1H NMR studies on the complexation of alkali picrates M^+Pic^- ($M^+=Li^+$, Na^+, K^+ and Cs^+), $K^+NO_3{}^-$ and K^+I^- in CD_3CN.[12] All the spectra showed attributable conformations upon formation of 1:1 complexes. Compound **2** adopts a *cone conformation* with Li^+ and Na^+. This conformation is highly symmetrical because of narrow differences in the shifts of singlets attributed to $-C(CH_3)_3$. The rigidification of **2** is explained by a location of the cations in the centre of the ionophoric cavity delineated by the four oxygen phenolic atoms and the two oxygens of the carbonyl groups.[3,4] Compound **2** adopts the *1,3-alternate conformation* in the presence of K^+ whatever the counter-ion (Pic^-, $NO_3{}^-$ or I^-), showing this conformation to be only induced by K^+ during formation of 1:1 complexes. No changes in the spectrum of **2** were observed upon addition of Cs^+Pic^- with conclusion that no complexation occurred with this cation.

The extraction ability of **2** was monitored by ^1H NMR via reactions of $CDCl_3$ solutions of **2** with an excess of solid picrates at room temperature. Different picrate/ligand ratios were determined by integration of ^1H NMR spectra: 0.5 for Li^+ after 30 days and 1.0 for Na^+ after

8 days. K^+ was poorly extracted while Cs^+ was not extracted at all. This was indicative of the better extraction power of **2** towards Na^+ probably via a 1:1 complex **2**.Na^+Pic^-. These results are in agreement with Na^+ and Li^+ selectivities already observed for related *O*-substituted calix[4]arenes.[3–5] The spectrum of **2**.Na^+Pic^- presents two singlets at 1.09 and 1.25 ppm in integration ratio 3:1 for the $C(C\boldsymbol{H}_3)_3$ protons, two *AB* systems 3.36 and 4.26 ppm with $J_{AB}=15.0$ Hz and 3.51 ppm and 4.28 with $J_{AB}=12.0$ Hz in integration ratio 1:1 for the $ArC\boldsymbol{H}_2Ar$ protons, two singlets at 6.82 and 7.28 ppm and an *A*B system at 6.99 and 7.19 ppm with $J_{AB}=2.2$ Hz characteristic of aromatic protons. One singlet was observed at 3.95 ppm for $COOC\boldsymbol{H}_3$. Two singlets were found at 1.34 and 3.91 ppm for $ArOC\boldsymbol{H}_3$. It was given a *partial cone* or a *flattened partial cone conformation*. Comparison with the cone conformation of **2**.Na^+Pic^- in CD_3CN leads to the conclusion that solvent polarity[13] and/or ion-pairing and/or picrate[14] effects are inducing the conformation of **2** in the complex with Na^+.

Some structural data were obtained from the solid state.[15] The crystal structure of **2**.EtOH is isomorphous to that recently reported in the case of the ethyl ester analogous to **2**.[8] The molecule **2** in **2**.EtOH is represented in Fig. 1(a). The conformation can be described as a *partial cone*, one of the methoxy substituents (08) pointing in a direction opposite to that of the three other groups. The aromatic ring bearing the other methoxy substituent (04) is closer to the mean plane of the molecule than the two rings bearing the ester groups. The dihedral angles between the four rings and the mean plane defined by the four methylenic carbon atoms are 87.5(1), 30.9(1), 88.7(1) and 86.7(1)° for the rings associated with 01, 04, 05 and 08, respectively. This conformation is seemingly highly stable, having also been observed in the case of the ethyl ester analogous to **2**.[8]

The asymmetric unit in $[2K^+I]^-.2MeOH$ comprises a cationic core with the calixarene molecule in the *1,3-alternate conformation* and the complexed potassium ion, a non-bonding iodide ion and two methanol molecules (Fig. 1b). The dihedral angles between the four aromatic rings and the mean plane defined by the four methylenic carbon bridges are 83.1(1), 75.0(1), 81.3(1) and 78.4(1)°. The potassium ion is bonded to four oxygen atoms with distances in the range 2.621(3)–2.825(3) Å, comparable with those reported in a diamide–potassium complex.[5] This nearly square-planar coordination environment is completed by short contacts between the cation and two phenyl rings (dashed lines on the Fig. 1) with K···C distances as low as 3.199(5) Å. This was in agreement with the structure found in $CDCl_3$.

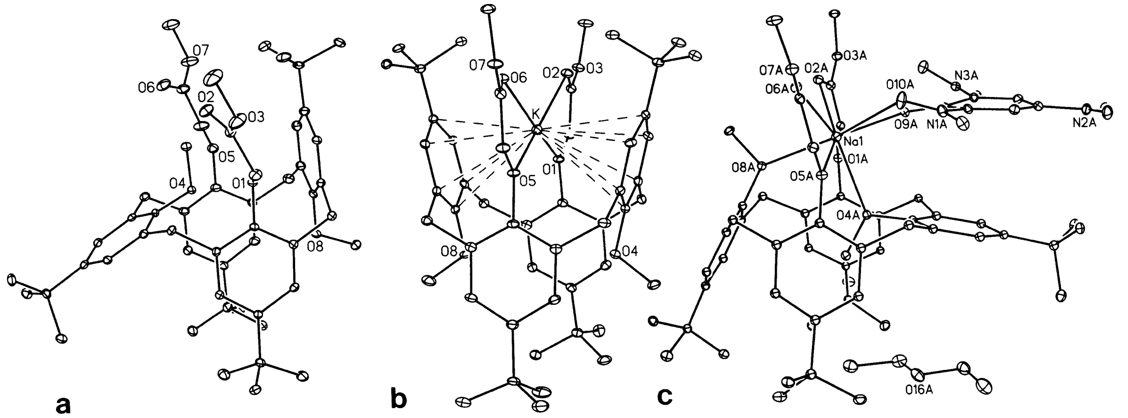


Figure 1. (a) Molecular unit of **2**.EtOH. Hydrogen atoms and solvent molecule omitted. (b) Molecular unit of $[2K^+]I^-.2MeOH$. Hydrogen atoms, solvent molecules and counter ions omitted. Cation···π interactions as dashed lines. (c) Molecule A in $[2Na^+Pic^-].Et_2O$. Hydrogen atoms omitted

The asymmetric unit in [**2**.Na^+Pic^-].Et_2O comprises two independent molecules, noted A and B, which differ mainly by the orientation of one non-bonding nitro group in the picrate ion. Molecule A is represented on Fig. 1(c). The calixarene is in a *distorted cone* or *flattened partial cone conformation*, with one of the phenolic rings close to the mean plane of the molecule [mean dihedral angles with respect to the methylenic plane in the range 64.4(1)–69.3(1)° for the three 'vertical' rings and 8.4(1)–7.8(2)° for the 'horizontal' ones (including both molecules)]. This conformation is different from those observed in the two previous compounds (compared with **2** it needs a rotation of the $ArOCH_3$ not belonging to the cone part) and approaches one of the assumed conformations in low polar $CDCl_3$ solvent. The Na^+ cation is bound to the four oxygen atoms of the ester groups and the two atoms from the methoxy substituents (Na–O distances in the range 2.426(4)–2.555(4) Å), the latter replacing the cation···π interactions present in the K^+ complex. The coordination sphere is completed by two oxygen atoms from the picrate ion: the hydroxy oxygen atom (Na–O distances 2.351(4) and 2.462(4) Å in A and B, respectively) and one from a nitro group (2.912(5) and 2.648(4) Å). The disymmetry in the complex arises from the presence of the picrate ion, which results in the peculiar arrangement of the phenolic ring closer to the mean plane, which is seemingly involved in π···π interactions with the picrate ring (dihedral angle between both rings 10.0(2)–10.3(2)°, shortest C···C distance ~3.5 Å). These π···π interactions may exist in low polar $CDCl_3$ and induce the conformation via tight ion pairs of Na^+Pic^-.

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9. A recent publication dealing with the crystal and solution structures of related 25,27-dimethoxy-26,28-diethylacetate-*p*-*tert*-butylcalix[4]arene by Duggan, P. J.; Sheahan, S. L.; Szydik, M. L. *Tetrahedron Lett.* **2000**, *41*, 3165–3168 prompted us to publish this letter.
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11. **General**: Mps, capillaries under nitrogen, Büchi 500. TLC plates silica gel 60 F_{254} Merck. ^1H NMR in $CDCl_3$, Bruker SY200 (δ in ppm), FAB(+) MS, VG-Analytical ZAB HF. Elemental analyses were performed at the Service de Microanalyse of the Institut de Chimie de Strasbourg.
    Preparation of 2.KI: **1** (4.003 g, 5.06 mmol), K_2CO_3 (4.180 g, 30.24 mmol) and CH_3CN (300 ml) were stirred for 1 h at rt under N_2. Then CH_3I (4.700 g, 33.14 mmol) was added. After refluxing for 3 days, the solvents were evaporated to dryness. The residue was dissolved in CH_2Cl_2 and precipitated with CH_3OH to give **2**.KI (2.636 g, 64%) as a white crystals. Mp 249–250°C. $R_f = 0.67$ (75/25 CH_2Cl_2–acetone).^1H NMR (200 MHz, $CDCl_3$) 7.15 (s, 4H, ArH_{meta}), 7.08 (s, 4H, ArH_{meta}), 4.58 (s, 4H, $ArOCH_2$), 3.87 (s, 6H, $COOCH_3$), 3.70 (d, $J_{AB} = 16.5$ Hz, 4H, $ArCH_2Ar$), 3.80 (d, 4H, $J_{AB} = 16.5$ Hz, $ArCH_2Ar$), 3.40 (s, 6H, $ArOCH_3$), 1.26 (s, 18H, $C(CH_3)_3$), 1.23 (s, 18H, $C(CH_3)_3$). FAB(+) MS, m/z 859.2 (M^+ of **2**+K^+). Anal. calcd for $C_{52}H_{68}O_8KI.CH_3OH$: C, 62.46; H, 7.12. Found C, 63.01; H, 7.15.

Preparation of 2: **1** (2.003 g, 2.53 mmol), K_2CO_3 (2.079 g, 15.04 mmol) and CH_3CN (150 ml) were stirred for 1 h at rt under N_2. Then CH_3I (2.290 g, 16.14 mmol) was added. After refluxing for 3 days, the solvents were evaporated to dryness and the crude mixture was solubilized in CH_2Cl_2 and acidified with 1N HCl. The organic layer was dried (Na_2SO_4) and the residue was precipitated with CH_3OH to give **2** (1.396 g, 67%) as a white solid. Mp 194–195°C. $R_f=0.60$ (75:25 CH_2Cl_2:acetone).^1H NMR (200 MHz, $CDCl_3$) 6.46–7.13 (m, 8H, $Ar\mathrm{H}_{\mathrm{meta}}$), 3.13–4.54 (m, 24H, $Ar\mathrm{OCH_2}$, $COOCH_3$, $Ar\mathrm{OCH_3}$ and $Ar\mathrm{CH_2}Ar$), 1.05 (bs, 9H, $C(CH_3)_3$), 0.82 (bs, 9H, $C(CH_3)_3$). FAB(+) MS, m/z 820.4 (M^+). Anal. calcd for $C_{52}H_{68}O_8.CH_3OH$: C, 74.60; H, 8.51. Found: C, 74.29; H, 8.40.

12. **Preparation of complexes in CD_3CN: 2.Li^+Pic^-**: **2** (0.009 g, 0.01 mmol) and Li^+Pic^- (0.003 g, 0.01 mmol) were dissolved in CD_3CN. ^1H NMR (200 MHz) 8.62 (s, 2H, H_{Pic}), 7.35 (s, 8H, $Ar\mathrm{H}_{\mathrm{meta}}$), 4.79 (s, 4H, $Ar\mathrm{OCH_2}$), 4.21 (d, $J=12.5$ Hz, 4H, $Ar\mathrm{CH_2}Ar$), 4.04 (s, 6H, $Ar\mathrm{OCH_3}$), 3.88 (s, 6H, $COOCH_3$), 3.50 (d, $J=12.5$ Hz, 4H, $Ar\mathrm{CH_2}Ar$), 1.20 (s, 18H, $C(CH_3)_3$), 1.19 (s, 18H, $C(CH_3)_3$). **2.Na^+Pic^-**: Same as for **2**.Li^+. ^1H NMR (200 MHz) 8.61 (s, 2H, H_{Pic}), 7.37 (s, 8H, $Ar\mathrm{H}_{\mathrm{meta}}$), 4.62 (s, 4H, $Ar\mathrm{OCH_2}$), 4.19 (d, $J=12.5$ Hz, 4H, $Ar\mathrm{CH_2}Ar$), 4.01 (s, 6H, $Ar\mathrm{OCH_3}$), 3.81 (s, 6H, $COOCH_3$), 3.49 (d, $J=12.5$ Hz, 4H, $Ar\mathrm{CH_2}Ar$), 1.21 (s, 18H, $C(CH_3)_3$), 1.19 (s, 18H, $C(CH_3)_3$). **2.K^+Pic^-**: Same as for **2**.Li^+. ^1H NMR (200 MHz) 8.65 (s, 2H, H_{Pic}), 7.23 (s, 4H, ArH_{meta}), 7.17 (s, 4H, ArH_{meta}), 4.55 (s, 2H, $ArOCH_2$), 3.79 (s, 6H, $COOCH_3$), 3.75 (s, 8H, $ArCH_2Ar$), 3.41 (s, 6H, $ArOCH_3$), 1.26 (s, 18H, $C(CH_3)_3$), 1.23 (s, 18H, $C(CH_3)_3$).
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15. **Crystal structure determinations**. Data were collected on a Nonius Kappa-CCD area-detector diffractometer using graphite monochromated Mo Kα radiation. The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre. **Crystal data for 2.EtOH**. $C_{54}H_{74}O_9$, $M=867.13$, monoclinic, space group $P2_1/n$, $a=9.704(1)$, $b=21.478(3)$, $c=23.708(3)$ Å, $\beta=91.751(7)°$, $V=4939(1)$ Å^3, $T=100$ K, $Z=4$, $D_c=1.166$ g cm^{-3}, $\mu=0.078$ mm^{-1}, $F(000)=1880$. 36828 reflections collected, among which 8945 unique. $R_1=0.094$ for 568 parameters. **Crystal data for [2.K^+I^-].2MeOH**. $C_{54}H_{76}IKO_{10}$, $M=1051.15$, triclinic, space group $P\bar{1}$, $a=13.279(1)$, $b=13.928(1)$, $c=15.1880(8)$ Å, $\alpha=99.152(3)$, $\beta=103.711(3)$, $\gamma=91.866(6)°$, $V=2687.0(4)$ Å^3, $T=110$ K, $Z=2$, $D_c=1.299$ g cm^{-3}, $\mu=0.727$ mm^{-1}, $F(000)=1104$. Empirical absorption correction. 20736 reflections collected, among which 9171 unique. $R_1=0.057$ for 614 parameters. **Crystal data for [2.Na^+Pic^-].Et_2O**. $C_{62}H_{80}N_3NaO_{16}$, $M=1146.28$, monoclinic, space group $P2_1/c$, $a=20.563(2)$, $b=14.639(1)$, $c=40.287(3)$ Å, $\beta=94.300(5)°$, $V=12093(2)$ Å^3, $T=100$ K, $Z=8$, $D_c=1.259$ g cm^{-3}, $\mu=0.096$ mm^{-1}, $F(000)=4896$. 82828 reflections collected, among which 22317 unique. $R_1=0.079$ for 1193 parameters.