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Synthesis of Two Calix[4]arenes in 1,3-Alternate Conformation Containing *Hard* and *Soft* Ion Binding Sites.

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Abstract: It is reported the synthesis of ligands **6** and **8** combining one calix[4]arene unit in the 1,3-alternate conformation and crown ether and aza crown ether elements. Preliminary complexations are given. © 1997 Elsevier Science Ltd. All rights reserved.

Co-receptors are polytopic receptor molecules combining two or more binding subunits within the same macropolycyclic 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 form of molecular behavior such as cooperativity, allostery and regulation, as well as communication or metal transfer.[1] Calixarenes[2] are cyclic polyphenols readily accessible and chemically transformable in a selective manner so that they are used as building blocks for larger and more sophisticated molecular assemblies with "almost (unlimited) possibilities".[3] Calix[4]arene derivatives can adopt four different conformations: *cone, partial cone, 1,2-alternate* and *1,3-alternate*, and their complexing properties have been proved to depend on the conformation of the calixarene moiety. Much attention has recently been paid to calix[4]arenes constrained to the 1,3-alternate conformation because of their structural peculiarities.[4] They present two binding sites departed on both sides of the calixarene macrocycle, which are linked to each other by a π-basic benzene tunnel.[4] This symmetrical ditopic arrangement is well-adapted for the formation of 1:1 as well as 1:2 complexes.[4,5] In the 1:1 complexes the cation (e. g. alkalis, silver, ammonium) switches from one binding site to the other through the π-basic benzene tunnel.[5,6] This "tunneling effect" has led chemists to connect several calix[4]arenes in the 1,3-alternate conformation to synthesize nano tubes.[4,7,8]

As part of our work on calix[4]-bis-crowns and related compounds[9] we report herein the synthesis of calix[4]-bis-triaza-oxa-benzo-crown, **6** and calix[4]-triaza-oxa-benzo-crown crown-6, **8**. With comparison to calix[4]-bis-crowns, **6** presents aza-crown chains able to complex *soft* metal cations while **8** contains *hard* and *soft* ion binding sites. A recent example has been published that shown a very similar calix[4]arene derivative in the 1,3-alternate conformation containing a crown ether loop and a salophene unit which is able to complex and transport a cation and an anion at the same time.[10]

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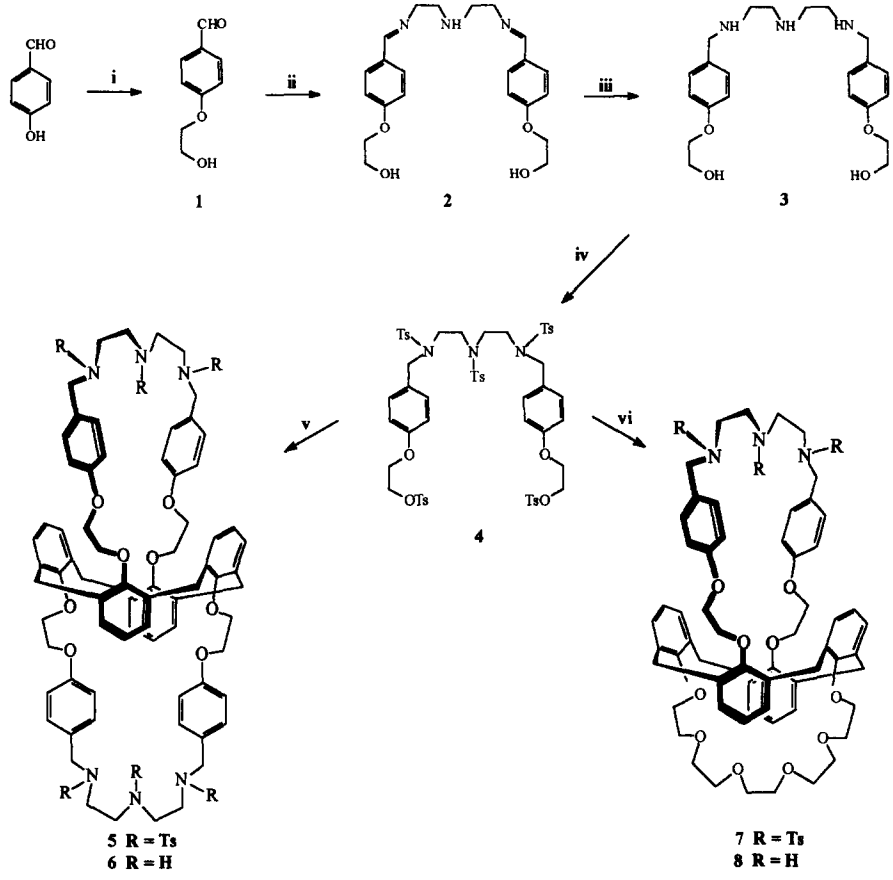
Preparation of ligands. The synthetic procedure for the preparation of **6** and **8** is illustrated in Scheme 1. 4-Hydroxybenzaldehyde was reacted with 1 equiv. of 2-chloroethanol in the presence of 1 equiv. of K_2CO_3 in refluxing acetonitrile for 4 days. The crude product was purified on silica column (eluent 1:9 acetone/CH_2Cl_2) affording 4-ethylene glycol benzaldehyde **1** as a yellow oil in 62 % yield. Condensation of **1** with 1 equiv. of diethylenetriamine in a mixture of 1:6 methanol/acetonitrile under reflux for 24 h. with a Soxhlet lead to quantitative yield of Schiff base **2**. The imine functions (N=C***H***) were deduced from the presence of a singlet at 8.19 ppm in the ^{1}H-NMR spectrum of **2**. Compound **2** was directly hydrogenated by 8 equivs of $NaBH_4$ in 1:1 THF/ethanol at rt for 36 h. After treatment with HCl in methanol and NaOH solution respectively, triamine dihydroxy **3** was extracted from CH_2Cl_2/H_2O in 65 % yield. It was identified by the presence of a ArCH_2N singlet at 3.70 ppm in the ^{1}H-NMR spectrum. The amino and hydroxyl groups of **3** were protected by tosylation reaction with 5 equivs of tosylchloride in the presence of 7 equivs of Et_3N and catalytic amounts of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 for 11 h. at rt. The penta(N,O)tosylate **4** was precipitated from acetone in 57 % yield. It was observed two singlets at 2.39 and 2.45 ppm (1:4) for the methyl of the tosyl and a singlet at 4.15 ppm for ArCH_2N in the ^{1}H-NMR spectrum of **4**.



Scheme 1. Reagents and conditions of preparation of **6** and **8**: i) $ClCH_2CH_2OH$, K_2CO_3, CH_3CN, reflux; ii) $H_2NCH_2CH_2NHCH_2CH_2NH_2$, CH_3CN/CH_3OH, reflux; iii) $NaBH_4$, THF/EtOH, rt, then HCl, then NaOH (aq); iv) TsCl, DMAP, Et_3N, CH_2Cl_2, rt; v) calix[4]arene, K_2CO_3, CH_3CN, reflux then $LiAlH_4$, THF, reflux; vi) calix[4]crown-6, Cs_2CO_3, CH_3CN, reflux then $LiAlH_4$, THF, reflux.

By a method described by us for calix[4]-bis-crowns[11], the calix[4]-bis-triazatosylate-oxa-benzo-crown, **5** was prepared by condensing calix[4]arene with 2 equivs of **4** in the presence of 20 equivs of K_2CO_3 in refluxing acetonitrile for 2 weeks. Compound **5** was eluted on silica column with 0.5:9.5 acetone/CH_2Cl_2 as eluent as a white solid in 31 % yield. N-deprotection of **5** was achieved by treatment with an excess of 100 equivs of $LiAlH_4$ in freshly distilled THF under reflux for 60 h. The residue was isolated from silica column by using a mixture of CH_2Cl_2/methanol/HCl 1N as extractant followed by sponification with NaOH to pH > 9. Extraction with CH_2Cl_2 afforded calix[4]-bis-triaza-oxa-benzo-crown **6** as a brown-yellow solid. The yield was 37 %.

Similarly calix[4]-triazatosylate-oxa-benzo-crown crown-6, **7** was prepared by capping calix[4]crown-6[12] with 1 equiv. of **4** in the presence of 3 equivs of Cs_2CO_3 in refluxing acetonitrile for 40 h. After elution of the residue on silica column with a mixture of acetone/CH_2Cl_2 (with a gradient of elution from 1:9 to bulk acetone), **7** was isolated in 24 % yield. N-deprotection of **7** was carried out as precedently for **5** and calix[4]-triaza-oxa-benzo-crown crown-6, **8** was obtained pure in 40 % yield.

Compounds **5-8** were fully characterized[13] and they were deduced to be in 1,3-alternate conformation due to the presence of a singlet of the methylene bridge protons (ArCH_2Ar) ppm in the ^{1}H-NMR spectrums at 3.94, 3.77, 3.89 and 3.88 ppm respectively.

Complexation studies. The complexation of nickel and zinc picrates by ligands **6** and **8** was monitored by ^{1}H-NMR. The complexes **8**:Ni^{2+} and **8**:Zn^{2+} were prepared by mixing ligand **8** (0.005 g, 5.03×10^{-3} mmol) and an excess of the corresponding solid metal picrates in $CDCl_3$ at rt for 48 h. and 3 h., respectively. The unreacted $Ni(Pic)_2$ and $Zn(Pic)_2$ were filtrated off before recording ^{1}H-NMR spectra.[14] We observed a singlet signal for the picrate at 8.82 and 8.84 ppm for the complexes **8**:Ni^{2+} and **8**:Zn^{2+}. The 1:1 stoichiometry of the complexes was estimated by integration of the picrate proton resonance versus those for the N***H*** signal of the ligand. The N***H*** singlet of ligand **8** shifted from 4.05 to 4.15 ppm for both complexes while the broad singlet at 3.10 ppm for the NC$\boldsymbol{H_2}$C$\boldsymbol{H_2}$ protons splitted into two singlets at 3.18 and 3.31 ppm in **8**:Ni^{2+} and into a multiplet 3.18-3.34 ppm in **8**:Zn^{2+}. We also noticed the Ar***H*** signals belonging to the triaza-oxa-benzo-crown loop to shift to strong-field from 7.50 and 6.73-6.81 ppm (overlap) to 7.48 and 6.68-6.73 ppm (overlap) in **8**:Ni^{2+} and to 7.38 and 6.66 ppm in **8**:Zn^{2+}. This was indicative that the Ni^{2+} and Zn^{2+} are probably located in the cavity of the triaza-oxa-benzo-crown and that the N-atoms are actually acting as *soft* metal coordinating sites. Although the 2:1 complex **6**:Ni^{2+} can be observed by ^{1}H-NMR through the presence of the picrate signal after mixing ligand **6** and $Ni(Pic)_2$ at rt for 48 h., we could not read its spectrum. We have been able to detect the 1:1 complex **8**:Cs^+ however we could not locate the cation. Attempts to prepare the 1:1:1 complex **8**:Zn^{2+}:Cs^+ have been unsuccessful.

Our objectives are now to prepare anionic receptors from **6** and **8**.

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13. *Analytical data of compound* **5**: (Mp 142-144 ° C) ^{1}*H-NMR* (200 MHz, $CDCl_3$): δ (ppm) 2.42 (s, 6H, CH_3), 2.48 (s, 12H, CH_3), 2.65-2.70 (m, 8H, NCH_2CH_2), 3.14-3.18 (m, 8H, NCH_2CH_2), 3.55 (t, J = 5.5 Hz, 8H, CH_2), 3.79 (t, J = 5.5 Hz, 8H, CH_2), 3.94 (s, 8H, $ArCH_2Ar$), 4.18 (s, 8H, $ArCH_2N$), 6.57 (t, J = 7.5 Hz, 4H, ArH_p-calix), 6.79 (d, J = 8.5 Hz, 8H, Ar*H*), 7.06 (d, J = 7.5 Hz, 8H, Ar*H*), 7.21-7.26 (m, 12H, ArH_m-calix, Ar*H*-tosyl), 7.37 (d, J = 8.0 Hz, 8H, Ar*H*-tosyl), 7.45 (d, J = 8.0 Hz, 4H, Ar*H*-tosyl), 7.76 (d, J = 8.0 Hz, 8H, Ar*H*-tosyl) *FAB(+) MS*: m/z 2084.6 *Anal. Found* C, 65.44; H, 5.82 *Calc. For* $C_{114}H_{118}N_6O_{20}S_6$: C, 65.68; H, 5.71.
    Analytical data of compound **6**: (Mp 74-80 ° C (dec.)): ^{1}*H-NMR* (200 MHz, $CDCl_3$): δ (ppm) 1.95 (large, s, 8H, NCH_2CH_2), 2.86 (large, s, 8H, NCH_2CH_2), 3.48-3.91 (m, 38H, CH_2, $ArCH_2N$, $ArCH_2Ar$, N*H*), 6.75-6.79 (m, 12H, Ar*H*, ArH_p-calix), 7.11-7.24 (m, 16H, Ar*H*, ArH_m-calix) *FAB(+) MS*: m/z 1159.6 *Anal. Found* C, 72.47; H, 6.93 *Calc. For* $C_{72}H_{82}N_6O_8.2CH_3OH$: C, 72.64; H, 7.41.
    Analytical data of compound **7**: (Mp 125-127 ° C) ^{1}*H-NMR* (200 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H, CH_3), 2.47 (s, 6H, CH_3), 2.63-2.68 (m, 4H, NCH_2CH_2), 3.14-3.18 (m, 4H, NCH_2CH_2), 3.33 (t, J = 5.5 Hz, 4H, CH_2), 3.44-3.53 (m, 8H, CH_2), 3.58-3.67 (m, 8H, CH_2), 3.71 (s, 4H, $Ar(OCH_2CH_2)_2OCH_2$), 3.76 (t, J = 5.5 Hz, 4H, CH_2), 3.89 (s, 8H, $ArCH_2Ar$), 4.17 (s, 4H, $ArCH_2N$), 6.53 (t, J = 7.5 Hz, 2H, ArH_p-calix), 6.79 (d, J = 8.5 Hz, 4H, Ar*H*), 6.91 (t, J = 7.5 Hz, 2H, ArH_p-calix), 7.04 (d, J = 7.5 Hz, 4H, ArH_m-calix), 7.13 (d, J = 7.5 Hz, 4H, ArH_m-calix), 7.22 (d, J = 8.5 Hz, 6H, Ar*H*, Ar*H*-tosyl), 7.36 (d, J = 8.0 Hz, 4H, Ar*H*-tosyl), 7.43 (d, J = 8.0 Hz, 2H, Ar*H*-tosyl), 7.75 (d, J = 8.0 Hz, 4H, Ar*H*-tosyl) *FAB(+) MS*: m/z 1456.5 *Anal. Found* C, 66.77; H, 5.93 *Calc. For* $C_{81}H_{89}N_3O_{16}S_3$: C, 66.78; H, 6.16.
    Analytical data of compound **8**: (Mp 56-60 ° C (dec.)) ^{1}*H-NMR* (200 MHz, $CDCl_3$): δ (ppm) 3.10 (large, s, 8H, NCH_2CH_2), 3.36-3.39 (m, 8H, CH_2), 3.47-3.54 (m, 8H, CH_2), 3.63-3.66 (m, 12H, CH_2, $Ar(OCH_2CH_2)_2OCH_2$), 3.72 (s, 4H, $ArCH_2N$), 3.88 (s, 8H, $ArCH_2Ar$), 4.05 (large, s, 3H, N*H*), 6.73-6.81 (m, 6H, Ar*H*, ArH_p-calix), 6.91 (t, J = 7.5 Hz, 2H, ArH_p-calix), 7.08 (d, J = 7.5 Hz, 4H, ArH_m-calix), 7.14 (d, J = 7.5 Hz, 4H, ArH_m-calix), 7.50 (d, J = 8.5 Hz, 4H, Ar*H*) *FAB(+) MS*: m/z 994.5 *Anal. Found* C, 60.42; H, 6.82 *Calc. For* $C_{60}H_{71}N_3O_{10}.3CH_2Cl_2$: C, 60.70; H, 6.23.
14. *Spectral data of 2:1 complex* **6:Ni^{2+}**: ^{1}*H-NMR* (200 MHz, $CDCl_3$: δ (ppm) 2.99-3.31 (broad, m, 54H, NCH_2CH_2, CH_2, $ArCH_2N$, $ArCH_2Ar$, N*H*), 6.69-6.94 (broad, m, 12H, Ar*H*, ArH_p-calix), 7.13-7.26 (broad, m, 16H, Ar*H*, ArH_m-calix), 8.84 (s, 2H, *H*pic).
    Spectral data of 1:1 complex **8:Ni^{2+}**: ^{1}*H-NMR* (200 MHz, $CDCl_3$): δ (ppm) 3.18 (large, s, 4H, NCH_2CH_2), 3.31 (large, s, 4H, NCH_2CH_2), 3.67-3.83 (m, 40H, CH_2, $ArCH_2N$, $ArCH_2Ar$), 4.15 (large, s, 3H, N*H*), 6.68-6.73 (m, 6H, Ar*H*, ArH_p-calix), 6.95 (t, J = 7.5 Hz, 2H, ArH_p-calix), 7.12 (d, J = 7.5 Hz, 4H, ArH_m-calix), 7.20 (d, J = 7.5 Hz, 4H, ArH_m-calix), 7.48 (d, J = 8.0 Hz, 4H, Ar*H*), 8.82 (s, 4H, *H*pic).
    Spectral data of 1:1 complex **8:Zn^{2+}**: ^{1}*H-NMR* (200 MHz, $CDCl_3$): δ (ppm) 3.18-3.66 (m, 36H, NCH_2CH_2, CH_2), 3.72 (s, 4H, $ArCH_2N$), 3.88 (large, s, 8H, $ArCH_2Ar$), 4.15 (large, s, 3H, N*H*), 6.66-6.89 (m, 8H, Ar*H*, ArH_p-calix), 7.70-7.15 (m, 8H, ArH_m-calix), 7.38 (d, J = 8.5 Hz, 4H, Ar*H*), 8.84 (s, 4H, *H*pic).

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