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Two novel 1,3-calix[4]azacrowns

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Abstract

Two 1,3-calix[4]azacrowns-5 in the 1,3-alternate conformation have been constructed from calix[4]arene. They formed 1:1 *endo* and 1:2 *endo–endo* complexes with NH_4^+ in $CDCl_3$. Comparison with 1,3-calix[4]-bis-crown-5 lead us to conclude a better binding by replacement of the central O atom by NH group in the crown. © 2000 Elsevier Science Ltd. All rights reserved.

Calix[4]arenes constrained to the 1,3-alternate conformation,[1,2] and more particularly, 1,3-calix[4]-bis-crowns[3] and aza-crown systems[4] have received much attention because of their structural peculiarities. They present two binding sites departed on both sides of the calixarene and are linked to each other by a π-basic benzene tunnel. This symmetrical arrangement is well adapted for the formation of 1:1 and 1:2 complexes. Interestingly, in the 1:1 complexes with 1,3-calix[4]-bis-crown-5, the cation switches from one binding site to the other through the π-basic benzene tunnel.[5] This property has recently been used to design a 'molecular syringe'.[6]

As part of our work on calix[4]azacrowns[7] we report herein the synthesis and NH_4^+ binding behavior of ligands **5** and **8** corresponding to 1,3-calix[4]-bis-crown-5 in which the central donor O atoms have been replaced once or twice by a NH group.

According to Scheme 1, calix[4]arene **1** was reacted with 2 equiv. of the tosylate of 2-(2-chloroethoxy)ethanol and 1 equiv. of K_2CO_3 in refluxing CH_3CN for 24 h. Dichlorocalix[4]arene derivative **2** was obtained pure by crystallization from Et_2O in 90% yield. Compound **2** was deduced to be in cone conformation and selectively 1,3-dialkylated due to the presence of two doublets at 3.40 and 4.45 ppm with J=13.5 Hz for the methylene protons of the ArC***H***$_2$Ar of the calix and of two triplets for the *para*-protons on the phenolic units. Condensation of **2** with 1.8 equiv. of tetraethyleneglycolditosylate with 3 equiv. of Cs_2CO_3 was achieved by refluxing CH_3CN for 24 h. The crude residue was purified on

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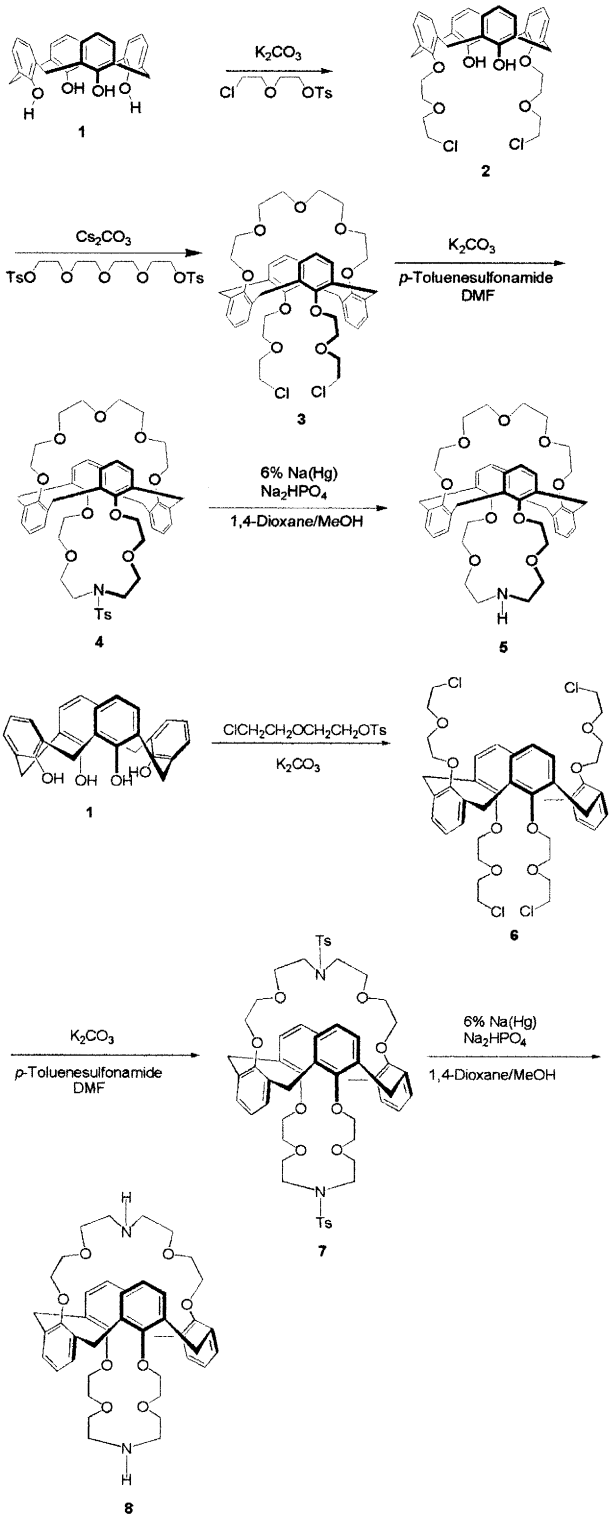

Scheme 1. Synthesis of ligands **5** and **8**

silica to afford calixcrown **3** as an oil in 73% yield. The 1,3-alternate conformation of **3** was deduced from the presence of a singlet at 3.87 ppm for the ArC***H***$_2$Ar in the calix unit. Ring-closure of dichloro **3** was performed with 1 equiv. of *p*-toluenesulfonamide by heating at 70°C in DMF for 24 h. The crude residue was chromatographed on silica to afford 1,3-calix[4]-crown-5*N*-tosyl crown-5, **4** in 24% yield. The tosyl group was removed by refluxing **4** with 6% Na(Hg) amalgam in the presence of Na_2HPO_4 in a mixture of 5:1 dioxane:methanol for 2 days. Compounds **4** and **5** were deduced to be the 1,3-alternate conformation with a singlet at 3.87 ppm for ArC***H***$_2$Ar in the calix. Calix[4]-bis-azacrown-5, **8**, was prepared in a similar way via tetrachloroethyleneglycol calix[4]-arene **6** (70% yield), double closure into 1,3-calix[4]-bis-*N,N′*-ditosyl crown-5, **7** (65% yield) and reaction with 6% Na(Hg) amalgam (52%). Compound **8** was shown to be in the 1,3-alternate conformation with a singlet at 3.88 ppm for the methylene protons ArC***H***$_2$Ar of the calix. All products were fully characterized.[8]

Complexation of $NH_4^+Pic^-$ was run to compare to results previously obtained with 1,3-calix[4]-bis-crown-5.[5,6] Ligands **5** and **8** (5–10 mg) were mixed with an excess of $NH_4^+Pic^-$ in $CDCl_3$ at rt for various times. The unreacted solid was filtrated before recording ^{1}H NMR spectra. The stoichiometries of the complexes were estimated by integration of the Ar***H***-picrate resonance vs those for the Ar***H*** aromatic signals of the calix. The 1:1 complex **5**:NH_4^+ was obtained after 1 h. The singlet signal of the picrate appeared at 8.79 ppm. The largest δ shifts were observed for the singlets of N***H*** and $OCH_2C\boldsymbol{H}_2NHC\boldsymbol{H}_2$ while the triplets corresponding to $ArOC\boldsymbol{H}_2C\boldsymbol{H}_2O$ belonging to the crown-5 remained unchanged. We concluded that NH_4^+ preferred to be in the azacrown-5. A spectrum indicating a C_{2v} symmetry, similar to the one of **5**, was obtained after 24 h. Upfield shifts of $ArOC\boldsymbol{H}_2C\boldsymbol{H}_2O$ showed that ligand **5** formed an *endo–endo* complex **5**:$2NH_4^+$. Complexes **8**:NH_4^+ and *endo–endo* **8**:$2NH_4^+$ were observed after 6 h and 24 h, respectively. These results differ from previous observations that 1,3-calix[4]-bis-crown-5 forms with NH_4^+ a 1:1 complex with *cation–ligand exchanges* and an *endo–exo* 1:2 complex[5,6] allowing us to ascertain that the modified N*H*–crown-5 displays a better binding behavior than the crown-5 does for ammonium cation. Future work will be devoted to thermodynamical studies (UV and potentiometry) to determine possible acido-basic interactions between the ligand and other different cations.

Acknowledgements

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References

1. Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713–1734 and references cited therein.
2. Asfari, Z.; Wenger, S.; Vicens, J. *Pure Appl. Chem.* **1995**, *67*, 1037–1043.
3. Asfari, Z.; Nierlich, M.; Thuéry, P.; Lamare, V.; Dozol, J.-F.; Leroy, M.; Vicens, J. *J. Anal. Quim. Int. Ed.* **1996**, *92*, 260–266.
4. Koh, K. N.; Araki, K.; Shinkai, S.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1995**, *36*, 6095–6098.
5. Wenger, S., PhD Dissertation, Strasbourg, June 1996.
6. Ikeda, A.; Tsudera, T.; Shinkai, S. *J. Org. Chem.* **1997**, *62*, 3568–3571.
7. Kim, J. S.; Ko, J. W.; Cho, M. H.; Yu, I. Y.; Shon, O. J.; Vicens, J. *J. Org. Chem*. **2000**, in press.
8. General: Mps, capillaries under nitrogen, Büchi 500, SiO_2 Merck (Art. 11567). ^{1}H NMR (δ in ppm, *J* in Hz) in $CDCl_3$, Bruker SY200 at Strasbourg and Bruker ARX-400 at Taejon. Elemental analysis, Vario EL of Elemental Analyzer and FAB^+ mass spectra, JEOL-JMS-HX 110A High Resolution Tendem Mass Spectrometry in Korea Basic Science Institute in Taejon. *Preparation of **2**.* Calix[4]arene **1** (10.02 g, 23.6 mmol), tosylate of 2-(2-chloroethoxy)ethanol (13.87 g, 49.5 mmol), K_2CO_3 (3.31 g, 23.6 mmol) and CH_3CN (200 ml) were refluxed for 24 h under N_2. The crude residue was solubilized in CH_2Cl_2 and acidified (10% aqueous HCl). The organic layer was dried ($MgSO_4$). Recrystallization from Et_2O gave **2** as a solid,

mp 174–175°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 2 H, -O*H*), 7.08 (d, *J*=7.5 Hz, 4 H, ArH_m-calix), 6.90 (d, *J*=7.5 Hz, 4 H, ArH_m-calix), 6.77 (t, *J*=7.5 Hz, 2 H, ArH_p-calix), 6.70 (t, 2 H, *J*=7.5 Hz, ArH_p-calix), 4.45 (d, *J*=13.5 Hz, 4 H, ArCH_2Ar), 4.21–4.19 (m, 4 H, ArOCH$_2CH_2$), 4.06–4.04 (m, 4 H, OCH_2CH$_2$Cl), 3.99 (t, *J*=6.5 Hz, 4 H, ArOCH_2CH$_2$), 3.75 (t, *J*=6.5 Hz, 4 H, OCH$_2CH_2$Cl), 3.40 (d, *J*=13.5 Hz, 4 H, ArCH_2Ar). FAB-MS *m/z* (M^+) calcd 634.9, found 635.2. Anal. calcd for $C_{36}H_{38}Cl_2O_6$: C, 68.03; H, 5.98. Found: C, 68.00; H, 5.95. Yield 90%. *Preparation of **3***. Compound **2** (10.08 g, 16.5 mmol), tetraethyleneglycol ditosylate (9.12 g, 18.1 mmol), Cs_2CO_3 (16.15 g, 49.5 mmol) and CH_3CN (200 ml) were refluxed for 24 h under N_2. The crude mixture was solubilized in CH_2Cl_2 and acidified (10% aqueous HCl). The organic layer was dried ($MgSO_4$). Chromatography on silica with 1:2 EtOAc:hexane as eluent gave **3** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12–7.08 (m, 8 H, ArH_m-calix), 6.93–6.86 (m, 4H, ArH_p-calix), 3.87 (s, 8H, ArCH_2Ar), 3.61–3.41 (m, 24H, -CH_2-), 3.20–3.13 (m, 8H, -CH_2-). FAB-MS *m/z* (M^+) calcd 793.2, found 793.8. Anal. calcd for $C_{44}H_{52}Cl_2O_9$: C, 55.48; H, 6.55. Found: C, 55.45; H, 6.57. Yield 73%. *Preparation of **4***. *p*-Toluenesulfonamide (0.90 g, 5.26 mmol), Cs_2CO_3 (6.54 g, 20.1 mmol) and DMF (100 ml) were heated to 70°C for 30 min. Then, compound **3** (4.04 g, 5.04 mmol) dissolved in DMF (20 ml) was added dropwise for 3 h. After refluxing for 24 h, the crude mixture was solubilized in CH_2Cl_2 and treated with 10% aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$). Chromatography on silica with 1:2 EtOAc:hexane as eluent gave **4** as a solid. mp 125–127°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J*=8.1 Hz, 2 H, Ar*H*-tosyl), 7.34 (d, *J*=8.1 Hz, 2H, Ar*H*-tosyl), 7.12 (d, *J*=7.5 Hz, 4H, ArH_m-calix), 7.05 (d, *J*=7.5 Hz, 4H, ArH_m-calix), 6.91 (t, *J*=8.7 Hz, 2H, ArH_p-calix), 6.82 (t, *J*=8.7 Hz, 2H, ArH_p-calix), 3.87 (s, 8H, Ar-CH_2-Ar), 3.63 (s, 4H, OCH_2CH_2O), 3.57 (s, 4H, OCH_2CH$_2$NH), 3.49-3.46 (m, 8H, ArOCH_2CH$_2$O), 3.34–3.28 (m, 8H, ArOCH_2CH_2O), 3.16–3.07 (m, 8 H, OCH$_2CH_2$O), 2.46 (s, 3 H, ArCH_3-tosyl). FAB-MS *m/z* (M^+) calcd 893.1, found 894.0. Anal. calcd for $C_{51}H_{59}NO_{11}S$: C, 68.53; H, 6.60. Found: C, 68.50; H, 6.63. Yield 50%. *Preparation of **5***. To a solution of dioxane (100 ml) and CH_3OH (20 ml) were added **4** (6.09 g, 6.7 mmol), Na_2HPO_4 (2.23 g, 14.76 mmol) and 6% Na(Hg) amalgam (5.00 g). The mixture refluxed for 2 days at 80°C. The crude mixture was solubilized in CH_2Cl_2 and treated with 10% aqueous Na_2HPO_4. The organic layer was dried ($MgSO_4$). Recrystallization from Et_2O gave **5** as a solid, mp 158–160°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (bs, 1 H, N*H*), 7.18 (d, *J*=7.5 Hz, 4 H, ArH_m-calix), 7.08 (s, 4 H, ArH_m-calix), 6.94 (t, *J*=7.5 Hz, 4H, ArH_p-calix), 3.90–3.84 (m, 8H, OCH_2CH_2O), 3.79 (s, 8H, Ar-CH_2-Ar), 3.65–3.63 (m, 12H, OCH_2CH$_2$NH, OCH_2CH_2O), 3.56 (t, *J*=6.5 Hz, 4H, ArOCH_2CH$_2$O-crown-5), 3.28 (t, *J*=6.5 Hz, 4H, ArOCH$_2$CH_2O-crown-5), 2.98 (s, 4H, OCH$_2CH_2$NH). FAB-MS *m/z* (M^+) calcd 739.1, found 739.5. Anal. calcd for $C_{44}H_{53}NO_9$: C, 71.44; H, 7.17. Found: C, 71.49; H, 7.15. Yield 50%. *Preparation of **6***. Same procedure as for **2** with calix[4]arene **1** (5.04 g, 11.7 mmol), tosylate of 2-(2-chloroethoxy)ethanol (13.13 g, 47.1 mmol), K_2CO_3 (8.13 g, 58.8 mmol) and CH_3CN (100 ml), reflux 24 h, N_2. Recrystallization from (4:1) Et_2O:hexane gave **6** a solid, mp 149–151°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07–6.99 (m, 8H, ArH_m-calix), 6.79–6.67 (m, 4H, ArH_p-calix), 3.77–3.62 (m, 40H, ArCH_2Ar, OCH_2CH_2O, OCH_2CH_2Cl). FAB-MS *m/z* (M^+) calcd 721.77, found 722.60. Anal. calcd for $C_{42}H_{50}Cl_2O_6$: C, 69.83; H, 6.93. Found: C, 69.71; H, 6.96. Yield 70%. *Preparation of **7***. Same procedure as for **4** with *p*-toluenesulfonamide (2.11 g, 12.3 mmol), K_2CO_3 (0.96 g, 6.95 mmol), DMF (60 ml), **6** (5.00 g, 5.88 mmol), reflux 24 h, N_2. Silica column (1:8 EtOAc:hexane) provided **7** as a solid, mp 148–151°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J*=8.0 Hz, 4H, Ar*H*-tosyl), 7.33 (d, *J*=8.0 Hz, 4H, Ar*H*-tosyl), 7.05 (d, *J*=8.6 Hz, 8H, ArH_m-calix), 6.82 (t, *J*=8.3 Hz, 4H, ArH_p-calix), 3.80 (dd, *J*=15.8 Hz, *J*=9.5 Hz, 8H, ArCH_2Ar), 3.53–3.24 (m, 20H, OCH_2CH_2O), 3.06 (bs, 4H, OCH$_2$CH_2NCH_2), 2.46 (s, 6H, ArCH_3-tosyl). FAB-MS *m/z* (M^+) calcd 819.2, found 820.3. Anal. calcd for $C_{49}H_{57}NO_8S$: C, 71.79; H, 6.96. Found: C, 71.52; H, 6.94. Yield 65%. *Preparation of **8***. Same procedure as for **5** with 5:1 dioxane:CH_3OH (150 ml), **7** (3.02 g, 2.86 mmol), 6% Na(Hg) (5.00 g) and Na_2HPO_4 (0.85 g, 6.0 mmol) reflux 2 days, 80°C. Recrystallization from Et_2O gave **8** as a solid, mp 185–188°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J*=8.4 Hz, 8H, ArH_m-calix), 6.82 (t, *J*=8.3 Hz, 4H, ArH_p-calix), 3.88 (s, 8H, ArCH_2Ar), 3.67–3.46 (m, 24H, OCH_2CH_2O), 2.81 (s, 8H, OCH$_2CH_2$NCH_2), 1.76 (bs, 2H, N*H*). FAB-MS *m/z* (M^+) calcd. 738.9, found 739.1. Anal. calcd for $C_{44}H_{54}N_2O_8$: C, 71.5; H, 7.31. Found: C, 71.51; H, 7.33. Yield 52%. *Spectral data of the 1:1 complex* **5**:NH_4^+: ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.45 (bs, 1H, N*H*), 8.79 (s, 2H, Ar*H*-picrate), 7.31 (d, *J*=7.5 Hz, 4H, ArH_m-calix), 7.21 (s, 4H, ArH_m-calix), 7.14–6.92 (m, 4H, ArH_p-calix), 3.96–3.84 (m, 8H, OCH_2CH$_2$NH, OCH_2CH_2O), 3.77 (s, 8H, Ar-CH_2-Ar), 3.54 (t, *J*=6.5 Hz, 4H, ArOCH_2CH$_2$O), 3.26 (t, *J*=6.5 Hz, 4H, ArOCH$_2CH_2$O), 3.06 (s, 4H, OCH$_2CH_2$NHCH_2). *Spectral data of the 1:2 complex* **5**:2NH_4^+: ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.39 (bs, 1H, NH), 8.78 (s, 4H, Ar*H*-picrate), 7.32 (d, *J*=7.5 Hz, 4H, ArH_m-calix), 7.21 (s, *J*=7.5 Hz, 4H, ArH_m-calix), 6.98 (t, *J*=7.5 Hz, 4H, ArH_p-calix), 3.96–3.46 (m, 20H, OCH_2CH$_2$NH, OCH_2CH_2O, ArOCH_2CH_2O), 3.79 (s, 8H, Ar-CH_2-Ar), 3.06 (broad s, 4H, OCH$_2CH_2$NHCH_2). *Spectral data of the 1:1 complex* **8**:NH_4^+: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.87 (s, 2H, Ar*H*-picrate), 7.24 (d, *J*=7.5 Hz, 4H, ArH_m-calix), 7.20 (d, *J*=7.5 Hz, 4H, ArH_m-calix), 7.00 (t, *J*=7.5 Hz, 2H, ArH_p-calix), 6.89 (d, *J*=7.5 Hz, 2H, ArH_p-calix), 4.63–2.81 (m, 24H, -CH_2-), 3.75 (s, 8H, ArCH_2Ar), 3.15–2.70 (m, 8H, OCH$_2CH_2$NHCH_2), 1.74 (bs, 2H, N*H*). *Spectral data of the 1:2 complex* **8**:2NH_4^+: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.86 (s, 4H, Ar*H*-picrate), 7.33 (bd, 8H, ArH_m-calix), 7.09 (bt, 4H, ArH_p-calix), 4.84 (bs, 8H, OCH_2CH_2O), 3.93–3.50 (bm, 24H, ArCH_2Ar, OCH_2CH_2O), 2.82 (bs, 8H, OCH$_2CH_2$NCH_2), 1.67 (bs, 2H, N*H*).