



Pergamon

Tetrahedron Letters 41 (2000) 3345–3348

TETRAHEDRON
LETTERS

Two novel 1,3-calix[4]azacrowns

Jong Seung Kim,^{a,*} Won Ku Lee,^a Kwanghyun No,^b Zouhair Asfari^c and Jacques Vicens^{c,*}

^aDepartment of Chemistry, Konyang University, Nonsan 320-711, South Korea

^bDepartment of Chemistry, Sookmyung Women's University, Seoul 140-742, South Korea

^cEcole Chimie Polymères Matériaux, Laboratoire de Chimie des Interactions Moléculaires Spécifiques, associé au C.N.R.S.,
25 rue Becquerel F-67087 Strasbourg, France

Received 20 December 1999; accepted 2 March 2000

Abstract

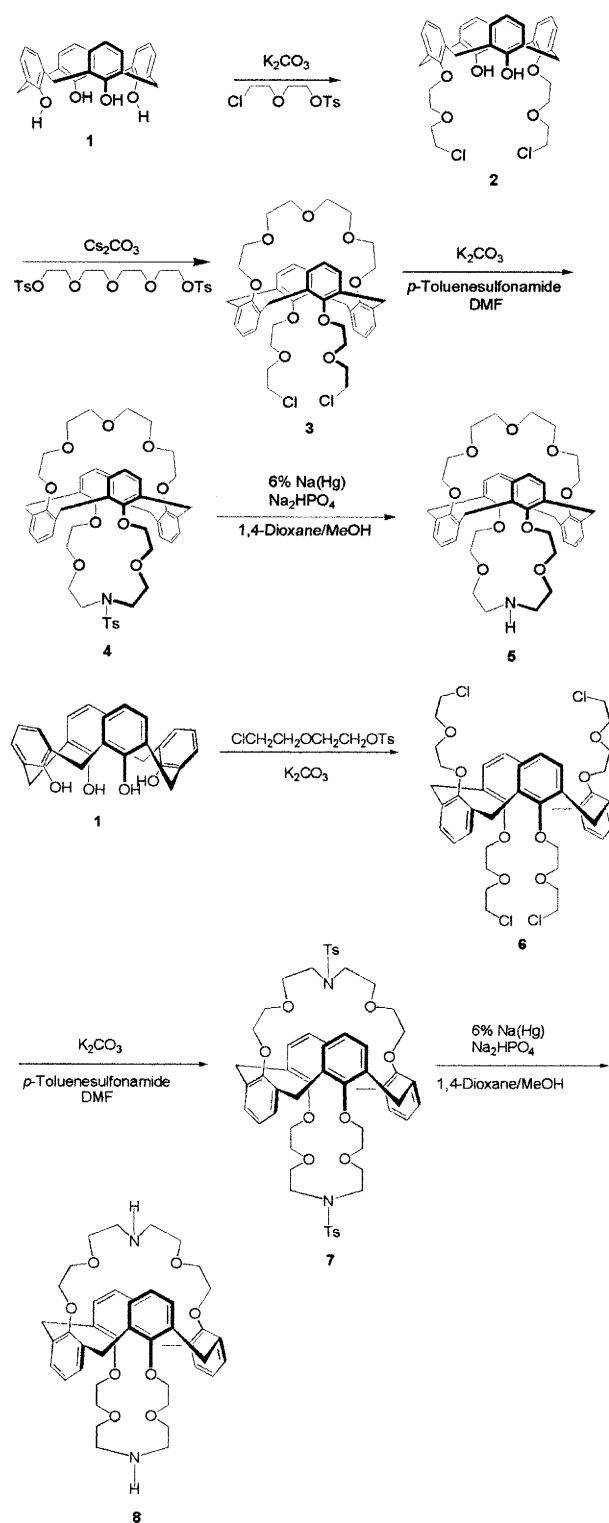
Two 1,3-calix[4]azacrowns-5 in the 1,3-alternate conformation have been constructed from calix[4]arene. They formed 1:1 *endo* and 1:2 *endo-endo* complexes with NH_4^+ in CDCl_3 . Comparison with 1,3-calix[4]-bis-crown-5 lead us to conclude a better binding by replacement of the central O atom by NH 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-crowns³ and aza-crown systems⁴ 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]azacrowns⁷ 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 ArCH_2Ar 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

* Corresponding authors. Fax: [82]4617335240/[33](0)388136932; e-mail: jongskim@kytis.konyang.ac.kr (J. S. Kim), vicens@chimie.u-strasbg.fr (J. Vicens)

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 ArCH_2Ar 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 ArCH_2Ar 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 ArCH_2Ar of the calix. All products were fully characterized.⁸

Complexation of $\text{NH}_4^+\text{Pic}^-$ 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 $\text{NH}_4^+\text{Pic}^-$ in CDCl_3 at rt for various times. The unreacted solid was filtrated before recording ^1H NMR spectra. The stoichiometries of the complexes were estimated by integration of the ArH -picrate resonance vs those for the ArH 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 NH and $\text{OCH}_2\text{CH}_2\text{NHCH}_2$ while the triplets corresponding to $\text{ArOCH}_2\text{CH}_2\text{O}$ 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 $\text{ArOCH}_2\text{CH}_2\text{O}$ 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 NH -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

This research was fully supported by the Korea Research Foundation (BSRI Grant No. 1999-015-DP0203).

References

- Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, 97, 1713–1734 and references cited therein.
- Asfari, Z.; Wenger, S.; Vicens, J. *Pure Appl. Chem.* **1995**, 67, 1037–1043.
- Asfari, Z.; Nierlich, M.; Thuéry, P.; Lamare, V.; Dozol, J.-F.; Leroy, M.; Vicens, J. *J. Anal. Quim. Int. Ed.* **1996**, 92, 260–266.
- Koh, K. N.; Araki, K.; Shinkai, S.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1995**, 36, 6095–6098.
- Wenger, S., PhD Dissertation, Strasbourg, June 1996.
- Ikeda, A.; Tsudera, T.; Shinkai, S. *J. Org. Chem.* **1997**, 62, 3568–3571.
- Kim, J. S.; Ko, J. W.; Cho, M. H.; Yu, I. Y.; Shon, O. J.; Vicens, J. *J. Org. Chem.* **2000**, in press.
- General: Mps, capillaries under nitrogen, Büchi 500, SiO_2 Merck (Art. 11567). ^1H 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 Tandem 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. ^1H NMR (400 MHz, CDCl_3): δ 7.34 (s, 2 H, -OH), 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, $\text{ArOCH}_2\text{CH}_2$), 4.06–4.04 (m, 4 H, $\text{OCH}_2\text{CH}_2\text{Cl}$), 3.99 (t, $J=6.5$ Hz, 4 H, $\text{ArOCH}_2\text{CH}_2$), 3.75 (t, $J=6.5$ Hz, 4 H, $\text{OCH}_2\text{CH}_2\text{Cl}$), 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 $\text{C}_{36}\text{H}_{38}\text{Cl}_2\text{O}_6$: 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. ^1H 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 $\text{C}_{44}\text{H}_{52}\text{Cl}_2\text{O}_9$: 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. ^1H NMR (400 MHz, CDCl_3): δ 7.74 (d, $J=8.1$ Hz, 2 H, ArH -tosyl), 7.34 (d, $J=8.1$ Hz, 2H, ArH -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, $\text{Ar-CH}_2\text{-Ar}$), 3.63 (s, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.57 (s, 4H, $\text{OCH}_2\text{CH}_2\text{NH}$), 3.49–3.46 (m, 8H, $\text{ArOCH}_2\text{CH}_2\text{O}$), 3.34–3.28 (m, 8H, $\text{ArOCH}_2\text{CH}_2\text{O}$), 3.16–3.07 (m, 8 H, $\text{OCH}_2\text{CH}_2\text{O}$), 2.46 (s, 3 H, ArCH_3 -tosyl). FAB-MS m/z (M^+) calcd 893.1, found 894.0. Anal. calcd for $\text{C}_{51}\text{H}_{59}\text{NO}_{11}\text{S}$: 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. ^1H NMR (400 MHz, CDCl_3): δ 9.45 (bs, 1 H, NH), 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, $\text{OCH}_2\text{CH}_2\text{O}$), 3.79 (s, 8H, $\text{Ar-CH}_2\text{-Ar}$), 3.65–3.63 (m, 12H, $\text{OCH}_2\text{CH}_2\text{NH}$, $\text{OCH}_2\text{CH}_2\text{O}$), 3.56 (t, $J=6.5$ Hz, 4H, $\text{ArOCH}_2\text{CH}_2\text{O-crown-5}$), 3.28 (t, $J=6.5$ Hz, 4H, $\text{ArOCH}_2\text{CH}_2\text{O-crown-5}$), 2.98 (s, 4H, $\text{OCH}_2\text{CH}_2\text{NH}$). FAB-MS m/z (M^+) calcd 739.1, found 739.5. Anal. calcd for $\text{C}_{44}\text{H}_{53}\text{NO}_9$: 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** as a solid, mp 149–151°C. ^1H 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 , $\text{OCH}_2\text{CH}_2\text{O}$, $\text{OCH}_2\text{CH}_2\text{Cl}$). FAB-MS m/z (M^+) calcd 721.77, found 722.60. Anal. calcd for $\text{C}_{42}\text{H}_{50}\text{Cl}_2\text{O}_6$: 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. ^1H NMR (400 MHz, CDCl_3): δ 7.73 (d, $J=8.0$ Hz, 4H, ArH -tosyl), 7.33 (d, $J=8.0$ Hz, 4H, ArH -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, $\text{OCH}_2\text{CH}_2\text{O}$), 3.06 (bs, 4H, $\text{OCH}_2\text{CH}_2\text{NCH}_2$), 2.46 (s, 6H, ArCH_3 -tosyl). FAB-MS m/z (M^+) calcd 819.2, found 820.3. Anal. calcd for $\text{C}_{49}\text{H}_{57}\text{NO}_8\text{S}$: 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. ^1H 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, $\text{OCH}_2\text{CH}_2\text{O}$), 2.81 (s, 8H, $\text{OCH}_2\text{CH}_2\text{NCH}_2$), 1.76 (bs, 2H, NH). FAB-MS m/z (M^+) calcd. 738.9, found 739.1. Anal. calcd for $\text{C}_{44}\text{H}_{54}\text{N}_2\text{O}_8$: C, 71.5; H, 7.31. Found: C, 71.51; H, 7.33. Yield 52%. *Spectral data of the 1:1 complex 5:NH₄⁺*: ^1H NMR (200 MHz, CDCl_3): δ 9.45 (bs, 1H, NH), 8.79 (s, 2H, ArH -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, $\text{OCH}_2\text{CH}_2\text{NH}$, $\text{OCH}_2\text{CH}_2\text{O}$), 3.77 (s, 8H, $\text{Ar-CH}_2\text{-Ar}$), 3.54 (t, $J=6.5$ Hz, 4H, $\text{ArOCH}_2\text{CH}_2\text{O}$), 3.26 (t, $J=6.5$ Hz, 4H, $\text{ArOCH}_2\text{CH}_2\text{O}$), 3.06 (s, 4H, $\text{OCH}_2\text{CH}_2\text{NHCH}_2$). *Spectral data of the 1:2 complex 5:2NH₄⁺*: ^1H NMR (200 MHz, CDCl_3): δ 10.39 (bs, 1H, NH), 8.78 (s, 4H, ArH -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, $\text{OCH}_2\text{CH}_2\text{NH}$, $\text{OCH}_2\text{CH}_2\text{O}$, $\text{ArOCH}_2\text{CH}_2\text{O}$), 3.79 (s, 8H, $\text{Ar-CH}_2\text{-Ar}$), 3.06 (broad s, 4H, $\text{OCH}_2\text{CH}_2\text{NHCH}_2$). *Spectral data of the 1:1 complex 8:NH₄⁺*: ^1H NMR (200 MHz, CDCl_3): δ 8.87 (s, 2H, ArH -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, $\text{OCH}_2\text{CH}_2\text{NHCH}_2$), 1.74 (bs, 2H, NH). *Spectral data of the 1:2 complex 8:2NH₄⁺*: ^1H NMR (200 MHz, CDCl_3): δ 8.86 (s, 4H, ArH -picrate), 7.33 (bd, 8H, ArH_m -calix), 7.09 (bt, 4H, ArH_p -calix), 4.84 (bs, 8H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.93–3.50 (bm, 24H, ArCH_2Ar , $\text{OCH}_2\text{CH}_2\text{O}$), 2.82 (bs, 8H, $\text{OCH}_2\text{CH}_2\text{NCH}_2$), 1.67 (bs, 2H, NH).