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Synthesis of 1,3-alternate calix[4]-cyclen-benzo-crown-6 as a hard–soft receptor

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Abstract

1,3-Alternate calix[4]-cyclen-benzo-crown-6 incorporating a cyclen subunit on one side and a benzo-crown-6 on the other side of the calix[4]arene framework has been synthesized. Preliminary complexation studies of this macropolycycle with cesium and zinc picrate salts have been carried out by means of proton nuclear magnetic resonance spectroscopy. © 2000 Elsevier Science Ltd. All rights reserved.

Calixarenes, calix[4]arene in particular, show their versatility as building-blocks in supramolecular chemistry due to their ease of synthesis and well-defined structures.[1–5] Furthermore, the 1,3-alternate calix[4]arene framework is of interest to the chemist because it provides two cavities, symmetric or asymmetric, on each side of calix[4]arene platform.[1–4] Since the first double-bridge calix[4]arene in the 1,3-alternate conformation, 1,3-*p*-*tert*-butylcalix[4]-bis-crown-ether-5,[6] many 1,3-alternate calix[4]arene derivatives, i.e. 1,3-calix[4]-bis-crown-ethers[7–9] and crown-ethers with phenylene[9] or pyridine[10] units have been prepared. In order to enhance stability and selectivity by increasing the number of coordination sites, the diaza-crown ether moiety was introduced onto a 1,3-alternate calix[4]arene.[11] This 1,3-calix[4]-bis-cryptand can form dinuclear complexes with Na^+, K^+ and Rb^+ and shows the oscillation of NH_4^+ through the π-basic benzene tunnel of the calix[4]arene framework[12] as found in 1,3-calix[4]-bis-crown-5.[13,14] Many 1,3-alternate calix[4]arene building-blocks incorporating different cavities have also been synthesized. The calix[4]-uranylsalophen-crown-6 containing one anion loop and one cation cavity on each side of 1,3-alternate calix[4]arene can simultaneously transport both a cation and an anion, CsCl and $CsNO_3$, through a liquid membrane.[15] The 1,3-alternate calix[4]-cryptand[2,2]-crown-6[16] can form heterobinuclear complexes with Na^+, K^+ and Cs^+ in which Na^+ and K^+ are complexed in the cryptand cavity, whereas Cs^+ is bound in the crown ether loop.[12]

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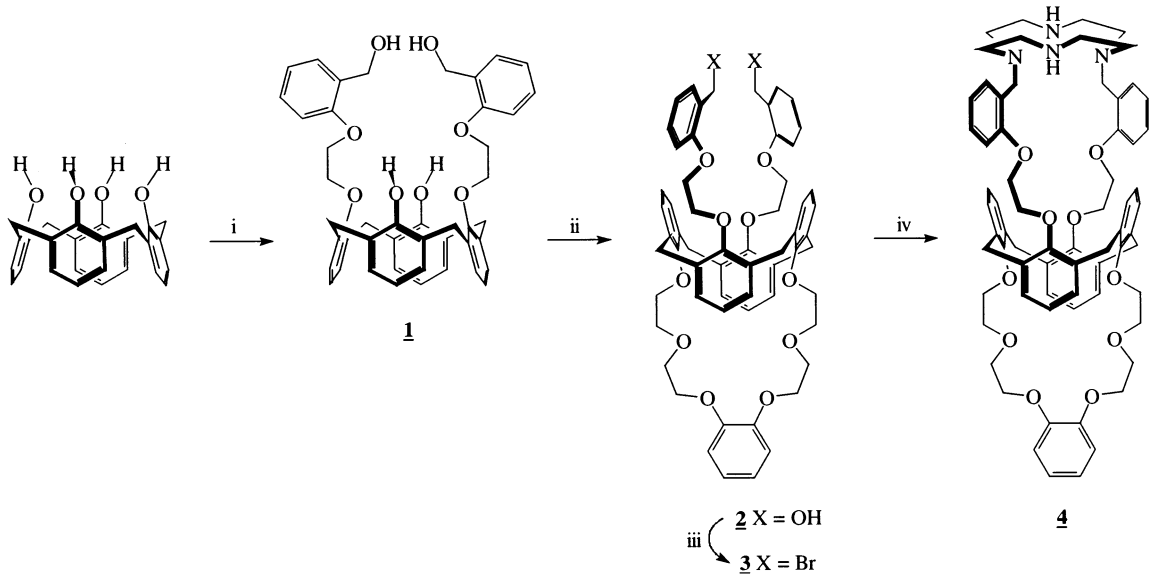
Moreover, this ligand can act as '*hard–soft*' receptor due to its '*soft*' cavity, cryptand, which can bind soft metal ions, Ni^{2+} and Zn^{2+}, and '*hard*' binding site, crown ether loop, which can accommodate hard metal ions such as Cs^{+}.[17]

These observations led us to synthesize 1,3- alternate calix[4]-cyclen-benzo crown-6 **4** consisting of 1,4,7,11-tetraazacyclododecane or '*cyclen*', which can form high stable transition-metal[18] and lanthanide[19] complexes and a benzo-crown ether subunit which can complex Cs^{+} ions selectivity,[9] linking on each side of calix[4]arene in 1,3-conformation. This novel heteroditopic ligand is aimed to be an approach to a '*hard–soft*' receptor,[20] which could bind hard and soft metal ions strongly and selectively and to act as molecular sensors and/or catalysts capable of detecting or catalysing redox action on guest species.[21,22]

The synthesis of **4**, shown in Scheme 1, began with preparation of 2-(2-bromoethoxy)benzyl alcohol[23] by reaction of 2-hydroxybenzyl alcohol with 1,2-dibromoethane according to the literature.[16] 1,3-*Distal* disubstitution of the calix[4]arene was carried out by substitution with 3 equiv. of 2-(2-bromoethoxy)benzyl alcohol in refluxing acetonitrile in the presence of an excess Na_2CO_3 as base for 7 days. After precipitation with hexane, calix[4]-di-2-ethoxybenzyl alcohol **1**[24] was obtained as a white solid in 53%. Compound **1** existed in a cone conformation due to the presence of two AB-systems at 4.36 and 3.42 ppm with a coupling constant of 13.0 Hz in the ^{1}H NMR spectrum. Bridging of **1** was achieved by refluxing **1** with 1 equiv. of 1,2-bis-(diethylene glycol tosyl)benzene[25] in a suspension of 10 equiv. of K_2CO_3 in acetonitrile for 3 days. Calix[4]-di-2-ethoxy-benzyl alcohol-benzo-crown-6 **2**[26] was eluted from a silica gel column as a white solid in 98% using 95:5 CH_2Cl_2/EtOAc as eluent. The conversion of hydroxy groups of **2** to bromide groups was accomplished by treating **2** with PBr_3 in the presence of pyridine in dichloromethane at 0°C for 10 min to give calix[4]-di-2-ethoxy-benzyl bromide-benzo-crown-6 **3**[27] as a white solid in quantitative yield. The condensation of compound **3** with cyclen began



Scheme 1. Synthetic pathway to 1,3-alternate calix[4]-cyclen-benzo-crown-6 **4**. *Reagents and conditions*: (i) 2-(2-bromoethoxy)benzyl alcohol, Na_2CO_3, CH_3CN, reflux 7 days, 53%; (ii) 1,2-bis-(diethylene glycol tosyl)benzene, K_2CO_3, CH_3CN, reflux 3 days, 98%; (iii) PBr_3, pyridine, CH_2Cl_2, 0°C 10 min, quantitative yield; (iv) cyclen·$2H_2SO_4$, NaOEt, CH_3CN, EtOH, H_2O, reflux 24 h, 10%

with the generation of cyclen in situ by treatment of cyclen·$2H_2SO_4$[28] dissolved in a minimum quantity of water with ethanolic NaOEt. 1 Equiv. of **3** dissolved in acetonitrile was added and the reaction mixture refluxed for 24 h. Calix[4]-cyclen-benzo-crown-6 **4**[29] was obtained as a white solid in 10% after purification by alumina chromatography using 75:25 CH_2Cl_2:acetone as eluent. The compounds **2**, **3** and **4** were in the 1,3-alternate conformation indicated by the presence of a singlet for the methylene bridge protons (Ar–CH_2–Ar) at 3.81, 3.82 and 3.79 ppm, respectively, in the ^{1}H NMR spectra.

Preliminary complexation studies of **4** with cesium picrate (Cs^+Pic^-), and zinc picrate ($Zn^{2+}Pic^-_2$) were carried out by means of ^{1}H NMR spectroscopy. The stoichiometry of the complexes was estimated by comparing the integration of the picrate protons versus those of glycolic ethylene protons (OCH_2) of the ligand. Compound **4** was dissolved in $CDCl_3$ at the concentration of 3×10^{-3} mol L^{-1} and solid picrate salts were added into each tube. After addition, the clear solution turned yellow which indicated the formation of complexes. With the cesium picrate, the 1:1 (Cs^+:**4**) complex was obtained after 2 weeks. The singlet for the picrate protons was observed at 8.78 ppm and that for benzo-crown protons shifted from 6.97 ppm in the ligand to 6.87 ppm in the complex. Moreover, the signal for the glycolic ethylene protons of benzo-crown loop dislocated from a multiplet at 3.79–3.72 ppm to a singlet at 3.99 ppm. The results suggest that cesium ion probably resides in the benzo-crown cavity and the formation of cation-π interaction with the phenylene unit occurred as found in the calix[4]-bis-benzo-crown-6.[30] For complexation with zinc picrate, the 1:1 (Zn^{2+}:**4**) complex was achieved after 3 weeks of reaction. The singlet for the picrate protons appeared at 8.74 ppm. We observed that the doublet and the triplet of Ar*H* of **4** at 7.48 ($J=6.2$ Hz) and 7.16 ($J=7.2$ Hz) ppm, respectively, shifted to a multiplet at 7.38–7.29 ppm. We also noticed the migration of doublet of H_2CNHCH_2 protons from 2.82 ($J=9.0$ Hz) ppm to be a broad signal at 3.23 ppm. This implies the Zn^{2+} was coordinating to the cyclen subunit. Such an upfield shift has already been observed in tris(Zn^{II}–cyclen)complex.[31]

Further studies of the complexation properties of **4** are currently under investigation and will be presented in due course. Our complexation project will concentrate on showing evidence of heterobinuclear complexes and investigation of binding constants toward alkali and transition metal ions.

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References

1. In *Calixarenes-A Versatile Class of Macrocyclic Compounds*; Vicens, J.; Böhmer, V. Eds.; Kluwer Academic Publishers: Dordrecht, 1991.
2. In *Calixarenes and Related Hosts-Comprehensive Supramolecular Chemistry*; Pochini, A.; Ungaro, R.; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Executive Eds.; Lehn, J.-M., Chairman of the Editorial Board; Elsevier Science Ltd., 1996.

3. Lhotak, P.; Shinkai, S. *Syn. Org. Chem. Jpn.* **1995**, *53*, 963–974.
4. Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–745.
5. van Loon, J.-D.; Verboom, W.; Reinhoudt, D. N. *Org. Prep. Proced. Int.* **1992**, *24*, 437–462.
6. Ghidini, E.; Ugozzoli, F.; Ungaro, R.; Harkema, S.; El-Fadl, A. A.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1990**, *112*, 6979–6985.
7. Asfari, Z.; Wenger, S.; Vicens, J. *Supramol. Sci.* **1994**, *1*, 103–110.
8. Asfari, Z.; Wenger, S.; Vicens, J. *Pure Appl. Chem.* **1995**, *67*, 1037–1043.
9. Asfari, Z.; Bressot, C.; Vicens, J.; Hill, V.; Dozol, J.-F.; Rouquette, H.; Eymard, S.; Lamare, V.; Tournois, B. *Anal. Chem.* **1995**, *67*, 3133–3139.
10. Xue, G.-P.; Bradshaw, J. S.; Su, N.; Krakowiak, K. E.; Sauvage, P. B.; Izatt, R. M. *J. Het. Chem.* **2000**, *37*, 1–4.
11. Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1996**, *37*, 8747–8750.
12. Pulpoka, B. *Thèse de Doctorat de l'Université Louis Pasteur*, 1997 and references cited therein.
13. Koh, K. N.; Araki, K.; Shinkai, S.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1995**, *36*, 6095–6098.
14. Pérez-Aldermar, J. A.; Abraham, H.; Sanchez, C.; Rissanen, K.; Prados, P.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1009–1011.
15. Rudkevich, D. M.; Mercer-Chalmers, J. D.; Verboom, W.; Ungaro, R.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 6124–6125.
16. Pulpoka, B.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **1996**, *37*, 6315–6318.
17. Pulpoka, B.; Asfari, Z.; Vicens, J. unpublished results.
18. Poon, C. K.; Che, C. M. *Inorg. Chem.* **1981**, *20*, 1640–1643.
19. Parker, D. *Chem. Soc. Rev.* **1990**, *19*, 271–291.
20. van Veggel, F. C. J. M.; Harkema, S.; Bos, M.; Verboom, W.; van Stveren, C. J.; Gerritsma, G. J.; Reinhoudt, D. N. *Inorg. Chem.* **1989**, *28*, 1133–1148.
21. Beer, P. D.; Chen, Z.; Goulden, A. J.; Grieve, A.; Hesek, D.; Szemes, F.; Wear, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1269–1271.
22. Beer, P. D.; Hesek, D.; Kingston, J. E.; Smith, D. K.; Stokes, S. E.; Drew, M. G. B. *Organometallics* **1995**, *14*, 3288–3295.
23. Analytical data for 2-(2-bromoethoxy)benzyl alcohol: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.30–7.20 (m, 2H, Ar*H*), 6.95 (t, $J=6.4$ Hz, 1H, Ar*H*), 6.80 (d, $J=8.0$ Hz, 1H, Ar*H*), 4.68 (s, 2H, ArCH_2), 4.28 (t, $J=5.7$ Hz, 2H, ArOCH_2), 3.64 (t, $J=5.7$ Hz, 2H, ArOCH_2), 2.95 (s, 1H, $ArCH_2OH$). Anal. found C, 46.82; H, 4.72. Calcd for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80.
24. Analytical data for compound **1**: (mp 213–214°C) ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 8.87 (s, 2H, ArO*H*), 7.31 (dd, $J=7.3$, 1.7 Hz, 2H, Ar*H*), 7.14 (dt, $J=7.8$, 1.7 Hz, 2H, Ar*H*), 7.05 (d, $J=7.6$ Hz, 4H, Ar*H*), 7.00 (d, $J=8.7$ Hz, 4H, Ar*H*), 6.94 (dt, $J=7.9$, 0.9 Hz, 2H, Ar*H*), 6.82 (t, $J=7.5$ Hz, 2H, Ar*H*), 6.70–6.60 (m, 4H, Ar*H*), 4.62 (d, $J=6.8$ Hz, 4H, ArCH_2), 4.36 (d (AB-system), $J=13.0$ Hz, 4H, ArCH_2Ar), 4.33 (bs, 8H, ArOCH_2), 3.42 (d (AB-system), $J=13.0$ Hz, 4H, ArCH_2Ar). Anal. found C, 75.56; H, 6.11. Calcd for $C_{46}H_{44}O_8$: C, 76.22; H, 6.12.
25. Preparation procedure of 1,2-bis-(diethylene glycol tosyl)benzene see: Abidi, R.; Asfari, Z.; Harrowfield, J. M.; Nauman, V.; Sobolev, A. N.; Vicens, J. *Anales de Quimica Int. Ed.* **1996**, *92*, 51–56. Analytical data: ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.75 (d, $J=8.3$ Hz, 4H, Ar*H*), 7.26 (d, $J=7.9$ Hz, 4H, Ar*H*), 6.86 (d, $J=2.0$ Hz, 4H, Ar*H*), 4.14 (t, $J=4.7$ Hz, 4H, OCH_2), 4.03 (t, $J=4.7$ Hz, 4H, OCH_2), 3.77–3.71 (m, 8H, OCH_2), 2.37 (s, 6H, ArCH_3). Anal. found C, 56.45; H, 5.73; S, 10.52. Calcd for $C_{28}H_{34}O_{10}S_2$: C, 56.55; H, 5.76 S, 10.78.
26. Analytical data for compound **2**: (Mp 72–73°C) ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.32 (dd, $J=7.3$, 1.4 Hz, 2H, Ar*H*), 7.21 (dt, $J=7.3$, 1.6 Hz, 2H, Ar*H*), 7.10 (d, $J=7.6$ Hz, 4H, Ar*H*), 7.05 (d, $J=7.6$ Hz, 4H, Ar*H*), 6.99 (s, 4H, Ar*H*), 6.96 (t, $J=7.3$ Hz, 2H, Ar*H*), 6.76–6.69 (m, 6H, Ar*H*), 4.66 (s, 4H, ArCH_2OH), 4.17–4.10 (m, 4H, ArOCH_2), 3.81 (s, 8H, ArCH_2Ar), 3.77–3.72 (m, 12H, OCH_2), 3.61 (d, $J=4.6$ Hz, 4H, OCH_2), 3.54 (d, $J=4.6$ Hz, 4H, OCH_2), 2.63 (s, 2H, CH_2OH). Anal. found C, 73.65; H, 6.53. Calcd for $C_{60}H_{62}O_{12}$: C, 73.90; H, 6.41.
27. Analytical data for compound **3**: (mp 66–67°C) ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.34 (dd, $J=7.4$, 1.3 Hz, 2H, Ar*H*), 7.18 (dt, $J=7.8$, 1.3 Hz, 2H, Ar*H*), 7.08 (d, $J=7.5$ Hz, 8H, Ar*H*), 6.98 (s, 4H, Ar*H*), 6.89 (t, $J=7.4$ Hz, 2H, Ar*H*), 6.74–6.66 (m, 6H, Ar*H*), 4.53 (s, 4H, ArCH_2Br), 4.13 (t, $J=5.0$ Hz, 4H, ArOCH_2), 3.89–3.83 (m, 8H, ArOCH_2), 3.82 (s, 8H, ArCH_2Ar), 3.71 (t, $J=4.9$ Hz, 4H, OCH_2), 3.64–3.54 (m, 8H, OCH_2). Anal. found C, 65.89; H, 6.06. Calcd for $C_{60}H_{60}Br_2O_{10}$: C, 65.46; H, 5.49.
28. Preparation procedure of cyclen·$2H_2SO_4$ see: Atkin, J. T.; Richman, J. E.; Oettle, W. F. *Org. Synth*, **1978**, *58*, 86–98.

29. Analytical data for compound **4**: (mp 190–200°C (dec.)) ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.48 (d, $J=6.2$ Hz, 2H, Ar*H*), 7.16 (t, $J=7.2$ Hz, 2H, Ar*H*), 7.07 (d, $J=7.8$ Hz, 4H, Ar*H*), 7.03 (d, $J=8.4$ Hz, 4H, Ar*H*), 6.97 (s, 4H, Ar*H*), 6.92 (t, $J=6.9$ Hz, 2H, Ar*H*), 6.82–6.70 (m, 6H, Ar*H*), 4.13 (t, $J=4.8$ Hz, 4H, ArOCH_2), 3.79 (s, 8H, ArCH_2Ar), 3.79–3.72 (m, 20H, NCH_2 and OCH_2), 3.63–3.53 (m, 8H, ArCH_2N and OCH_2), 3.54 (t, $J=5.5$ Hz, 4H, OCH_2), 2.82 (d, $J=9.0$ Hz, 8H, HNCH_2). Anal. found C, 71.32; H, 6.95. Calcd for $C_{68}H_{78}N_4O_{10}$. 2 H_2O: C, 71.18; H, 7.20. ES(+)-MS, m/z 1110.30 (M^+).
30. Thuéry, P.; Nierlich, M.; Bressot, C.; Lamare, V.; Dozol, J. F.; Asfari, Z.; Vicens, J. *J. Inc. Phenom., Mol. Recogn.* **1995**, *23*, 111–118.
31. Kimura, E.; Aoki, S.; Koike, T.; Shiro, M. *J. Am. Chem. Soc.* **1997**, *119*, 3068–3076.