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Aza crown ether calix[4]arenes containing cation and anion binding sites: effects of metal ions towards anion binding ability

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Abstract—Tripodal aza crown ether calix[4]arenes containing both cation and anion binding sites (**5a** and **5b**) have been synthesized. The X-ray analysis shows that **5a** forms a self-threaded rotaxane-like structure in the solid state. ^{1}H NMR titrations of the two ligands with various halide anions indicate that **5a** and **5b** can form complexes with Br^- and I^- but not F^-. However, both compounds form more stable complexes with I^- than with Br^- in the presence of Bu_4N^+. The presence of K^+ enhances the binding ability of **5a** towards Br^-. © 2001 Elsevier Science Ltd. All rights reserved.

Molecular recognition of abiotic anions by synthetic receptors has received increasing attention in the past few years according to recent reviews written by Beer and Gale.[1] Many receptors have been used successfully as sensors for anions.[2] Recently, synthetic receptors containing two individual recognition sites for a cation and an anion have attracted chemists' attention. Applications of such receptors may be found in metal-controlled anion sensing devices. Reinhoudt and co-workers have elegantly demonstrated that a calix[4]arene derivative with cation binding ester groups on the lower rim and anion binding ureas on the upper rim can efficiently bind Cl^- only in the presence of Na^+.[3] Beer and coworkers have synthesized a number of ditopic receptors that can undergo selective ion pair recognition.[4]

In 1997, polyaza crown ether derivatives of *p*-*tert*-butylcalix[4]arene were synthesized in our lab. The ammonium derivatives were found to form complexes with CO_3^{2-}, NO_3^-, AsO_2^- and Cl^- to a different extent using electrostatic interactions.[5] We are interested in constructing a three dimensional anion receptor by combining the calix[4]arene framework with tris(2-amino)ethylamine, **tren** and glycolic chains to obtain compounds that have both a cation and an anion binding site in the same molecule. This compound may have great potential to bind a metal ion and an anion cooperatively and selectively.

Tripodal aza crown ether calix[4]arenes, **5a** and **5b**, were synthesized according to the procedure shown in Scheme 1. Substitution reactions of *p*-*tert*-butylcalix[4]arene with 3.0 equiv. of 2-(2′-bromoethoxy)benzaldehyde, **1a**, and 4-(2′-bromoethoxy)benzaldehyde, **1b**, respectively, were carried out in the presence of a base to produce trialdehyde precursors, **3a** and **3b**, for preparing the tripodal amine capped calix[4]arene. The synthesis of **3a** was reported previously in acetonitrile using K_2CO_3 as base. This reaction gave only 6% yield of the desired trialdehyde derivative.[6] Furthermore, substitution reactions using K_2CO_3 always gave the dialdehyde derivatives, **2a** and **2b**, in high yields.[7] Since then, a number of bases and solvents have been employed to optimize the yields of the desired products. However, it was found that in the presence of strong bases such as NaH and KOH the aldehydes underwent Cannizzaro reactions and gave both alcohol and carboxylic acid derivatives instead.[8] Finally, we found that reactions using BaO in DMF gave higher yields of trialdehyde calix[4]arenes, **3a**[6] (21%) and **3b**[9] (46%), than those of dialdehyde calix[4]arenes, **2a** (20%) and **2b** (2%). It should be noted that the yield of **3b** was

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Keywords: aza crown; calix[4]arene; anion binding; proton NMR titration.

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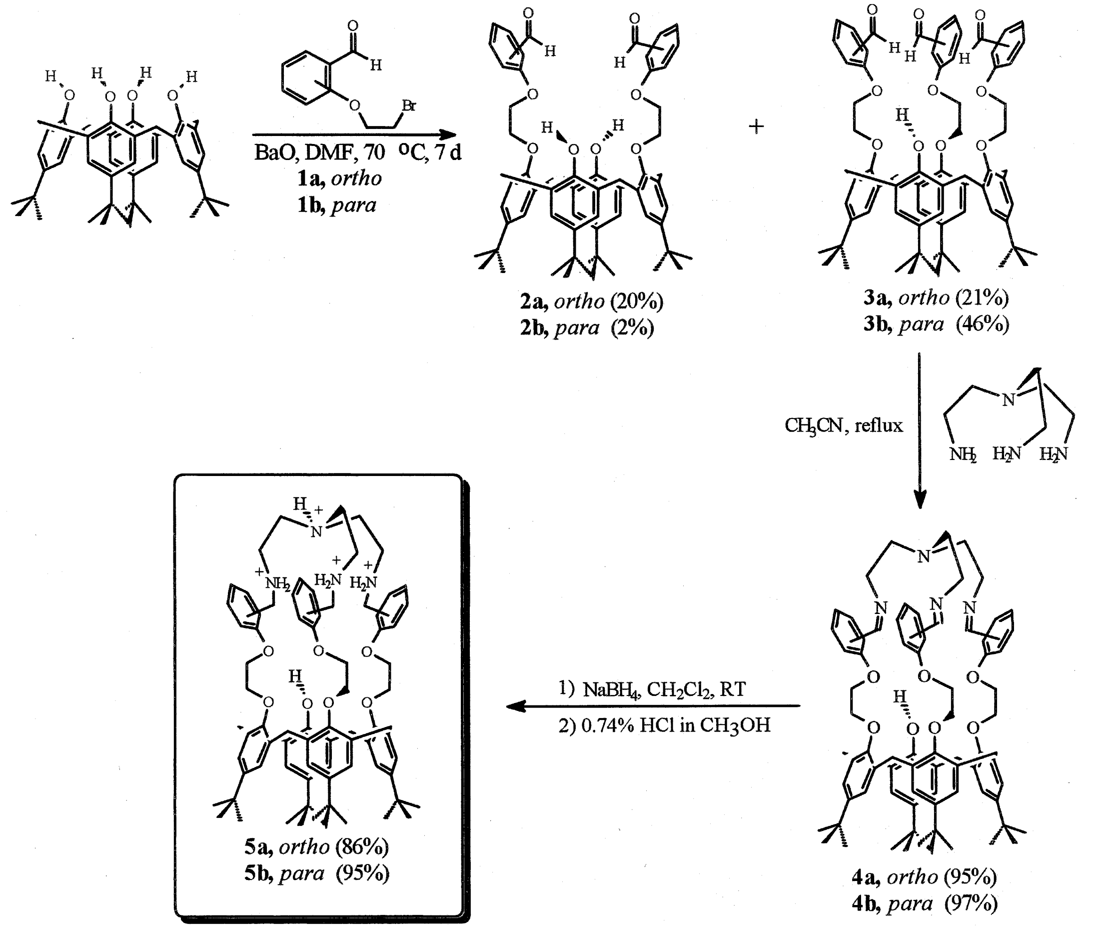


Scheme 1. Synthetic procedure of compounds **5a** and **5b**.

twice as much as that of **3a** probably due to the less steric hindrance of the *para* isomer facilitating the substitution reaction. Compounds **2** and **3** were separated by silica-gel chromatography using CH_2Cl_2 as eluent. Condensation reactions of **3a** and **3b** with 1.1 equiv. of tris(2-amino)ethylamine in acetronitrile precipitated the imine or Schiff base products, **4a**[6] (95%) and **4b**[10] (97%). Reduction of **4a** and **4b** by 20 equiv. of $NaBH_4$ and subsequent acidification with HCl/CH_3OH (0.74% v/v) yielded the desired tripodal ammonium derivatives, **5a**[6] (86%) and **5b**[11] (95%). The ^1H NMR spectra of compounds **3b**–**5b** possessed four sets of doublets due to the methylene bridge protons on the calix[4]arene moiety suggesting the existence of the cone conformation.

The solid state structure of compound **5a** has been determined by X-ray crystallography (Fig. 1).[12] The calix[4]arene unit is in a pinched cone conformation. One of the ethoxy benzyl chains connecting to the **tren** unit threads through the cavity of the other two ethoxy benzyl chains. This structure resembles a self-threaded rotaxane derivatised from two homooxacalix[3]arenes.[13] Recently, Vicens and colleagues have also reported a similar structure of tripodal calix[4](azo)crowns.[14]

Although suitable crystals of **5b** for X-ray analysis could not be obtained, the ^1H NMR spectrum of **5b** suggests a more symmetrical orientation of the glycolic chains.[11] Both **5a** and **5b** possess N_4-tripodal ammonium units for binding anions and O_6-crown ether cavities for binding alkali cations. However, the N_4-tripodal ammonium cavity of the *para* isomer, **5b**, should have more space than that of the *ortho* isomer, **5a**. This leads to the different selectivity of **5a** and **5b** towards various anions.

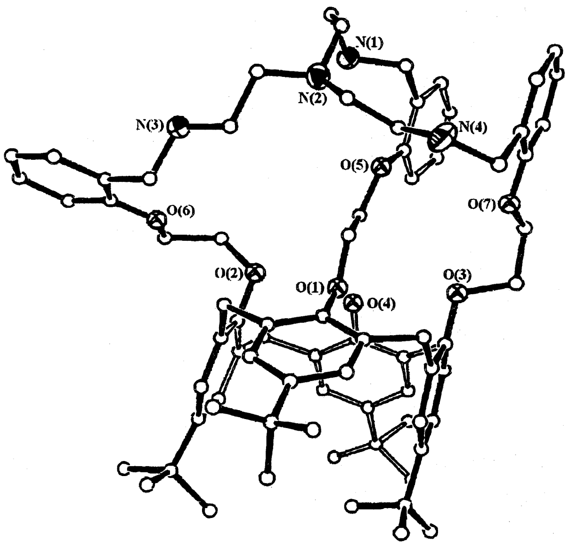


Figure 1. Crystal structure of **5a**. Hydrogen atoms are omitted for clarity.

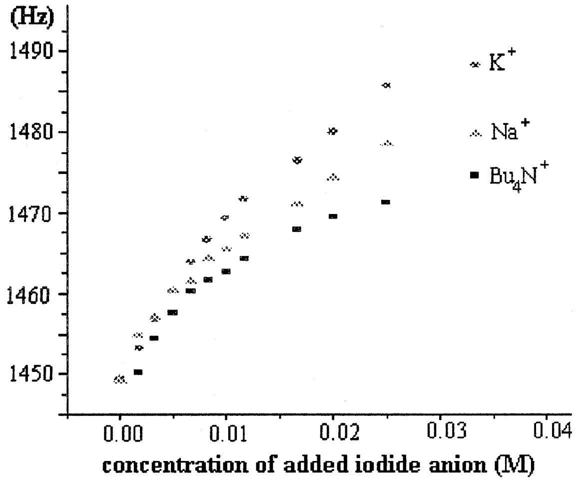


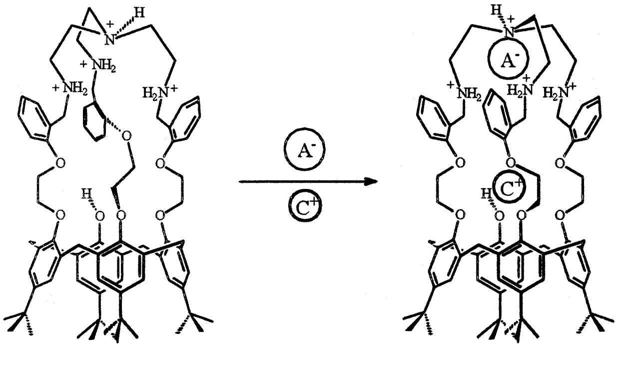
Figure 2. Titration curves of **5b** with I$^-$ in the presence of Bu$_4$N$^+$, Na$^+$ and K$^+$.

Table 1. Association constants of ligands **5a** and **5b** towards Br$^-$ and I$^-$ in the presence of various countercations[a]

Metal	Anion	K_{assoc} (M^{-1})	
		5a	**5b**
None[b]	Br$^-$	84.2	76.5
Na$^+$	Br$^-$	58.6	53.0
K$^+$	Br$^-$	120.1	34.9
None[b]	I$^-$	108.9	137.9
Na$^+$	I$^-$	77.2	57.3
K$^+$	I$^-$	103.3	66.3

[a] All experiments were carried out at 298 K, errors estimated to be less than 15%.

[b] Using Bu$_4$N$^+$ as countercation.



Scheme 2. A metal ion can possibly induce the structural reformation of **5a** to bind an anion more efficiently.

^{1}H NMR (200 MHz) titrations were employed in complexation studies of **5a** and **5b** towards halide anions (F$^-$, Br$^-$ and I$^-$) in the presence of various countercations.[15] It was found that no displacement of any proton signals of **5a** and **5b** occurred upon addition of F$^-$. This result indicates that **5a** and **5b** do not form complexes with F$^-$. Addition of Br$^-$ and I$^-$ to **5a** and **5b**, however, resulted in the displacement of signals due to -OArCH$_2$NH_2^+- and –OArHCH$_2$-. The plot showing the relationship between chemical shifts of the signal due to –OArHCH$_2$- and concentrations of iodide anion is depicted in Fig. 2. Job plot analysis indicates that **5a** and **5b** bind Br$^-$ and I$^-$ in a 1:1 ligand/anion ratio. Association constants of **5a** and **5b** towards Br$^-$ and I$^-$ in the presence of various countercations such as Bu$_4$N$^+$, Na$^+$ and K$^+$ calculated by the program EQNMR[16] are collected in Table 1.

The result implies that the tripodal ammonium cavities of **5a** and **5b** are not suitable for binding F$^-$. With Bu$_4$N$^+$ as countercation, **5a** and **5b** can form more stable complexes with I$^-$. However, the stability of **5b** towards I$^-$ is higher than **5a**. This signifies that the cavity of **5b** is more suitable for binding a big anion such as I$^-$. In the presence of K$^+$, **5a** shows an increase in binding affinity towards Br$^-$ by nearly 1.5 fold. On the other hand, Na$^+$ does not show any enhancement in the anion binding ability of **5a**. The result suggests that the crown ether unit of **5a** prefers binding K$^+$ over Na$^+$. A similar crown ether cavity found in a biscalix[4]arene in which two molecules of calix[4]arene are linked by four glycolic units has been reported to bind K$^+$ selectively.[17] From the crystal structure of **5a**, it is also possible that an alkali metal ion can coordinate to the crown ether unit and induce the structural reorganization of **5a** to be more appropriate for binding anions (Scheme 2). Interestingly, the binding ability of **5b** towards Br$^-$ and I$^-$ decreases in the presence of Na$^+$ and K$^+$. An observation in which the presence of alkali metal ions decreases the anion binding ability of **5a** and **5b** can be rationalized in terms of the binding competition. Alkali metal ions (Na$^+$ or K$^+$) that cannot fit into the cavity size of the crown ether unit in **5a** or **5b** retain alkali metal–anion pairs and compete in binding with the tripodal ammonium unit of the ligands.

In summary, we have synthesized two tripodal aza crown ether calix[4]arenes, **5a** and **5b**, and shown that both can bind Br$^-$ and I$^-$ to a different extent depending on countercations. We are currently investigating the complexation of **5a** and **5b** towards other anions and also preparing new ion pair receptors for better understanding of such cooperative behavior and for possible applications in metal ion-controlled anion extraction.

Supplementary material

Crystallographic data for **5a** are available upon request from the Cambridge Crystallographic Data Base (CCDC 165241).

Acknowledgements

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References

1. (a) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 486; (b) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79.
2. Anslyn, E. V. *Curr. Opin. Chem. Biol.* **1999**, *3*, 740.
3. Scheerder, J.; van Duynhoven, J. P. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1090.
4. (a) Redman, J. E.; Beer, P. D.; Dent, S. W.; Drew, M. G. B. *Chem. Commun.* **1998**, 231; (b) Beer, P. D.; Hopkins, P. K.; McKinney, J. D. *Chem. Commun.* **1999**, 253; (c) Cooper, J. B.; Drew, M. G. B.; Beer, P. D. *J. Chem. Soc., Dalton Trans.* **2000**, 2721.
5. Rojsajjakul, T.; Veravong, S.; Tumcharern, G.; Seangprasertkij-Magee, R.; Tuntulani, T. *Tetrahedron* **1997**, *53*, 4669.
6. Tuntulani, T.; Ruangpornvisuti, V.; Tantikunwattana, N.; Ngampaiboonsombut, O.; Seangprasertkij-Magee, R.; Asfari, Z.; Vicens, J. *Tetrahderon Lett.* **1997**, *38*, 3985.
7. (a) Seangprasertkij, R.; Asfari, Z.; Arnaud, F.; Vicens, J. *J. Org. Chem.* **1994**, *59*, 1741; (b) Navakun, K.; Tuntulani, T.; Ruangpornvisuti, V. *J. Incl. Phenom.* **2000**, *38*, 113.
8. Sukwattanasinitt, M.; Rojanathanes, R.; Tuntulani, T.; Ruangpornvisuti, V., accepted for publication in *Science Asia*.
9. Compound **3b**: ^{1}H NMR spectrum (500 MHz, $\mathrm{CDCl_3}$): δ 9.76 and 9.68 (s each, 2H and 1H, -Ar(C=O)H), 7.57 and 7.43 (d each, $J_{H-H}=8.7$ Hz, 4H and 2H, -OArH_a), 7.19 (s, 2H, HOArH), 7.14 (s, 2H, ROArH), 6.70 and 6.63 (d each, $J_{H-H}=8.7$ Hz, 4H and 2H, -OArH_b), 6.54 (s, 4H, ROArH), 5.40 (s, 1H, HOAr), 4.86 (m, 2H, OCH_2CH$_2$O), 4.45 and 3.32 (d each, $J_{H-H}=12.4$ Hz, 4H each, ArCH_AH_BAr), 4.28 (m, 2H, OCH$_2$CH_2O), 4.13 (s, 8H, OCH_2CH_2O), 1.36 (s, 18H, HOAr-*t*-$\mathrm{C_4H_9}$ and ROAr-*t*-$\mathrm{C_4H_9}$), 0.82 (s, 18H, ROAr-*t*-$\mathrm{C_4H_9}$). FAB MS (*m*/*z*): 1092.5. Anal. calcd for **3b** ($\mathrm{C_{77}H_{80}O_{10}}$): C, 77.99; H, 7.37%. Found: C, 77.91; H, 7.52%.
10. Compound **4b**: ^{1}H NMR spectrum (500 MHz, $\mathrm{CDCl_3}$): δ 8.07 and 7.86 (s each, 1H and 2H, -CH=N), 7.38 (d, $J_{H-H}=8.7$ Hz, 4H, -OArH_a), 7.20 (s, 2H, HOArH), 7.18 (s, 2H, ROArH), 6.73 (d, $J_{H-H}=8.7$ Hz, 4H, -OArH_b), 6.62 (d, $J_{H-H}=2.4$ Hz, 2H, ROArH_a), 6.52 (d, $J_{H-H}=2.4$ Hz, 2H, ROArH_b), 6.32 (s, 1H, HOAr), 6.13 (d, $J_{H-H}=8.8$ Hz, 2H, ROArH), 6.02 (d, $J_{H-H}=8.8$ Hz, 2H, ROArH), 4.92 and 3.32 (d each, $J_{H-H}=13.0$ Hz, 4H, ArCH_AH_BAr), 4.56 (m, 2H, OCH_2CH$_2$O), 4.33 and 3.23 (d each, $J_{H-H}=13.0$ Hz, 4H, ArCH_AH_BAr), 4.28–4.02 (m, 10H, OCH_2CH_2O), 3.74 (m, 4H, CH=NCH_2CH$_2$N), 3.64 (m, 2H, CH=N CH_2CH$_2$N), 2.83 (m, 4H, CH=NCH$_2$CH_2N), 2.59 (m, 2H, CH=NCH$_2$ CH_2N), 1.39 (s, 9H, HOAr-*t*-C$_4H_9$), 1.36 (s, 9H, ROAr-*t*-C$_4H_9$), 0.83 (s, 18H, ROAr-*t*-C$_4H_9$). Anal. calcd for **4b** ($\mathrm{C_{77}H_{92}N_4O_7}$): C, 78.01; H, 7.82; N, 4.73%. Found: C, 77.95; H, 7.66; N, 4.77%.
11. Compound **5b**: ^{1}H NMR spectrum (500 MHz, $\mathrm{CDCl_3}$): δ 8.71 and 8.23 (s each, broad, 4H and 2H, ArCH$_2$NH_2^+Cl$^-$), 7.79 (d, $J_{H-H}=8.6$ Hz, 4H, -OArH_a), 7.36 (d, $J_{H-H}=8.5$ Hz, 2H, -OArH_a), 7.14 (s, 2H, HOArH), 7.10 (s, 2H, ROArH), 6.92 (d, $J_{H-H}=8.7$ Hz, 4H, -OArH_b), 6.54 (m, 6H, ROArH and -OArH_b), 6.12 (s, 1H, HOAr), 4.56 and 3.30 (d each, $J_{H-H}=13.3$ Hz, 4H, ArCH_AH_BAr), 4.55-4.40 (m, 14H, OCH_2CH_2O, ArCH_2N and ArCH_AH_BAr), 4.20–3.98 (m, 6H, OCH_2CH_2O, ArCH_2N), 3.70 (s, br, 2H, NCH$_2$CH_2N), 3.41–3.10 (m, 10H, NCH_2CH_2N), 3.25 (d, $J_{H-H}=13.0$ Hz, 2H, ArCH_AH_BAr), 1.34 (s, 9H, HOAr-*t*-$\mathrm{C_4H_9}$), 1.32 (s, 9H, ROAr-*t*-$\mathrm{C_4H_9}$), 0.82 (s, 18H, ROAr-*t*-$\mathrm{C_4H_9}$). Anal. calcd for **5b** ($\mathrm{C_{77}H_{102}N_4O_7Cl_4}$): C, 69.15; H, 7.69; N, 4.19%. Found: C, 69.19; H, 7.76; N, 4.16%.
12. Crystal data for **5a**, $\mathrm{C_{77}H_{102}N_4O_7Cl_2(OH)_2\cdot(CH_3OH)(H_2O)_2}$, M = 1368.7, monoclicnic, space group $C2/c$, $Z=8$, $a=43.6552$ (14), $b=15.9085$ (5), $c=25.1856$ (7) Å, $\beta=109.4630$ (10)°, $V=16491.6$ (9) Å^3, $D_c=1.119$ g cm^{3-}, 23606 unique data, $R1=0.1355$, $wR2=0.3402$.
13. Zhong, Z.; Ikeda, A.; Shinkai, S. *J. Am. Chem. Soc.* **1999**, *121*, 11906.
14. Oueslati, I.; Abidi, R.; Amri, H.; Thuéry, P.; Nierlich, M.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **2001**, *42*, 1685.
15. A solution of **5a** (0.0250 M) and a solution of **5b** (0.0083 M) in DMSO-d_6 and in a mixture of $\mathrm{CDCl_3}$ and $\mathrm{CD_3OD}$, respectively, were prepared. To a solution of a ligand in each NMR tube was added 0.0–4.0 equiv. of 0.1 M anion salts. Spectra were recorded every 24 h until the complexation reached the equilibrium. The result of the experiment was a plot of displacement in chemical shift as a function of the amount of added anion. The program EQNMR was then used to analyse the resulting titration curves and calculate stability constant values for 1:1 anion complexes in M^{-1}. Titration experiments were repeated twice with at least 12 data points for each anion.
16. Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311.
17. Schmitt, P.; Beer, P. D.; Drew, M. G. B.; Sheen, P. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1840.