Pergamon

Tetrahedron Letters, Vol. 38, No. 22, pp. 3985-3988, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00738-7

# Synthesis of the Tripodal-Amine Capped Benzo Crown *p-tert*-Butylcalix[4]arene and Its Host-Guest Chemistry

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***Abstract***: The tripodal-amine capped benzo crown *p-tert*-butylcalix[4]arene (**6**) was synthesised. The basicity of the nitrogen donors in **6** based on the protonation constants was measured by potentiometric titration. The complexation studies of **6** with Zn(II) ions were also carried out by $^1$H NMR spectroscopy.
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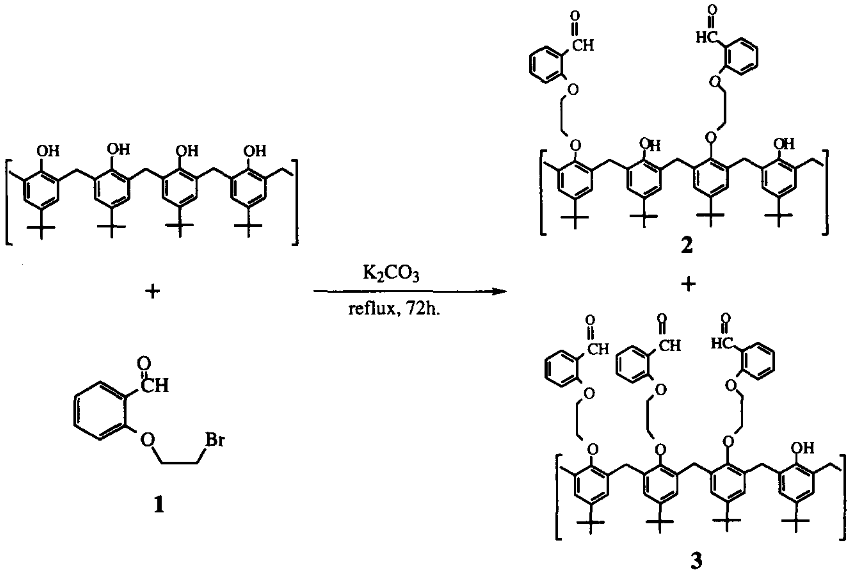
One of the most important types of macrocyclic compounds that plays a very important role in host-guest chemistry is the cage molecules such as cryptands.[1] They possess three dimensional structures which enhance the ability to encapsulate metal ions and anions.[2-4] *p-tert*-Butylcalix[4]arene has been shown to be an important starting building block for host-guest chemistry because it can be chemically modified at the phenolic oxygens (lower rim) and at the para-positions (upper rim). The chemical modifications associated with the conformational properties lead to a large variety of fascinating receptors.[5-7] It is of interest to combine the calix[4]arene framework with the cage constructing unit such as tris(2-amino)ethylamine, **tren**, to synthesise a compound that has great potential to bind metal ions and anions. We report herein the preparation of the tripodal-amine capped benzo crown *p-tert*-butylcalix[4]arene (**6**). To our knowledge, this is the first **tren** capped benzo crown *p-tert*-butylcalix[4]arene that has been synthesised. The compound **6** is a heterotopic receptor containing both the $N_4$ cage and the crown ether like units. It can, therefore, possibly exhibit appealing host-guest chemistry with metal ions and anions. The preliminary complexation studies of **6** with Zn(II) salts are also described.

The compound **6** can be prepared from the substitution reaction of calix[4]arene with 2.7 equiv. of 2[(1-formyl-2-phenyl)oxy]ethylbromide,[8] **1**, in the presence of $K_2CO_3$ in acetonitrile. The reaction under the condition shown in eq. 1 yielded dialdehyde calix[4]arene, **2** (50%) and trialdehyde calix[4]arene, **3** (6%). The compounds **2** and **3** were separated by silica gel chromatography using $CH_2Cl_2$ as an eluent. The compound **3** was characterised by spectroscopy and elemental analysis.[9] $^1$H NMR spectrum of **2** shows (C=O)-*H* signals at 9.75 and 10.41 ppm in 1:2 integral ratio. Interestingly, signals in the methyl region corresponding to methyl protons on *tert*-butyl groups exhibit complicated patterns suggesting that the calix[4]arene framework is not rigid in the solution. Condensation reaction of **3** with 1.1 equiv. of tris(2-amino)ethylamine in acetronitrile precipitated an imine or Schiff base product, **4** (46%) which was characterised by spectroscopy.[10] The signals due to (C=O)-*H* protons disappear, and the signals due to RN=C*H* protons display at 8.82 and 8.92 ppm in the

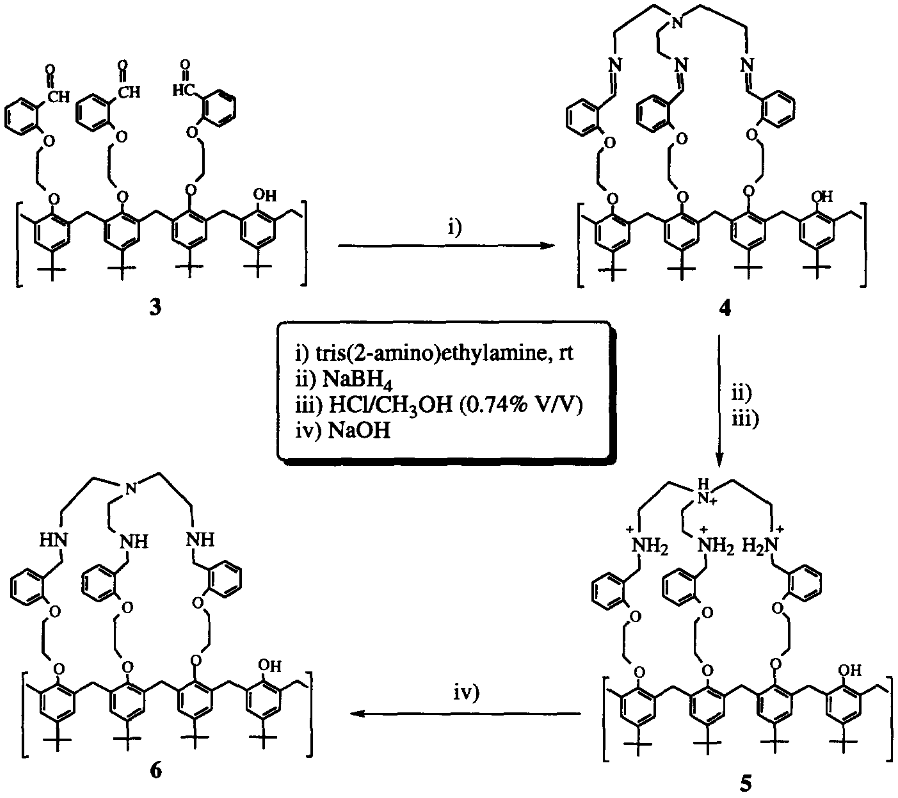
$^1H$ NMR spectrum of **4**. The methyl proton signals exhibits only three singlet lines at 1.35, 1.22 and 0.73 ppm in 1:1:2 ratio, respectively indicating that the molecule possesses the cone conformation. It also implies that the structure of **4** is more rigid than that of **3** when capped with the **tren** unit. Hydrogenation of **4** by 20 equiv. of $NaBH_4$ and subsequently acidifying with $HCl/CH_3OH$ (0.74% v/v) yielded an ammonium derivative, **5** (86%) which shows very broad signals in $^1H$ NMR spectrum due to the effect of positive charges. There are signals due to $R\text{-}NH_2^+\text{-}R$ and $R_3NH^+$ appear at 8.55, 9.55 and 10.02 ppm; however, the integral ratio cannot be estimated. Due to the mechanism of FAB MS, the mass spectrum of **5** shows a strong signal at m/z 1191.7 corresponding to molecular weight of the neutralised species **6**. Nevertheless, elemental analysis suggests the existence of **5**.[11] Neutralisation of **5** with NaOH in methanol provided the neutral tripodal-amine capped benzo crown calix[4]arene, **6** (46%). $^1H$ NMR spectrum (400 MHz) of **6** suggests a rigid cone conformation of the calix[4]arene unit observed from 3 singlet signals due to *t*-butyl protons at 0.86, 1.39 and 1.41 ppm and 4 doublet signals (J = 13 Hz) due to the bridging methylene protons on the calix[4]arene unit identified by a COSY experiment at 3.23, 3.37, 4.45 and 4.85 ppm.[12]



(1)

The ligand **6** possesses both nitrogen donors and oxygen donors. It can possibly accommodate metal ions and anions in the cavity of amine nitrogen donors or phenolic oxygen donors. We have examined the basicity of the nitrogen donors by determining protonation constants of **6** in 0.01 M methanolic solution of tetramethylammonium chloride at 25 °C with potentiometric titration. The titrations were carried out four times at the pH range of 2.968-12.030. The first, second, third and fourth protonation constants of **6** obtained from computer evaluation of the potentiometric titration data are $\log K_1 = 11.80 \pm 0.05$, $\log K_2 = 10.88 \pm 0.09$, $\log K_3 = 7.75 \pm 0.10$ and $\log K_4 = 4.97 \pm 0.12$, respectively.[13] The first two values are higher than the protonation constants of **tren** and bis-**tren** reported by Martell and Lehn by approximately an order of magnitude.[14]

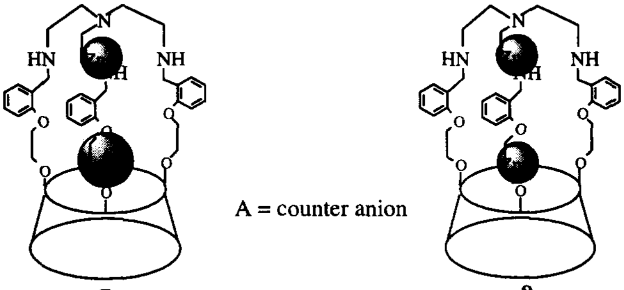
The ligand **6** shows selectivity towards metal ions and anions. Complexation of Zn(II) ions with the ligand **6** can be studied by $^1H$ NMR titration experiments.[15] The possible structures of Zn(II)-**6** complexes, deduced from the NMR data and the previous studies on similar calix[4]arene derivatives, are illustrated in Scheme 2.[16,17] Although the signals due to the $RNCH_2CH_2NR$ are broad when **6** forms complex with Zn(II) ions, we can observe the displacement of signals due to $\text{Ar-}t\text{-C(C}H_3)_3$ (a) and $t\text{-C(CH}_3)_3\text{Ar-}H$ (b) on the calix[4]arene framework. In the $ZnBr_2$ case, signals (a) and (b) shift downfield (2-10 Hz) with respect to the free ligand **6** upon increasing mole ratio of $ZnBr_2$. The plot between mole ratio of $ZnBr_2$:**6** and the magnitude of displacement reveals a 1:1 complex formation. One Zn(II) ion may reside in the cavity of the amine nitrogen donors while one of $Br^-$ ions may be induced into the cavity of phenolic oxygen, Scheme 2 (**7**). The calix[4]arene framework must adjust the cavity to enclathrate a $Br^-$ ion. This results in the displacement of protons (a) and (b). Curve fitting by iteration technique has been applied to calculate the stability constant for $ZnBr_2$-**6**: log K = 2.58.[16] In addition, we have isolated the $ZnBr_2$-**6** complex and characterised it by elemental analysis: anal. cald. (found) for $C_{77}H_{98}N_4O_7ZnBr_2$: C, 65.28 (65.44); H, 6.97 (6.60); N, 3.95 (3.68).[18] The result thus agrees with the proposed 1:1 structure. $^1H$ NMR titration of **6** with $Zn(NO_3)_2$ also gives the displacement of protons (a) and (b); however, the displacement does not proceed in the same direction. In addition, we observe that the methyl protons signals of *tert*-butyl groups are very complicated suggesting the existence of more than one species in the NMR solution.[19] Another possible species is the 2:1 complex in which two Zn(II) ions reside in **6**; one Zn(II) ion must reside in the amine nitrogen cavity while the other is in the phenolic oxygen cavity, Scheme 2 (**8**).[17]



i) tris(2-amino)ethylamine, rt
ii) $NaBH_4$
iii) $HCl/CH_3OH$ (0.74% V/V)
iv) NaOH

**Scheme 1.** Preparation method for the compound **6**.

This preliminary study, therefore, indicates the selectivity of the ligand **6** towards a metal and anions. Further studies of the complexation of **6** with other zinc salts by NMR spectroscopy are currently under investigation. Future work will also be focused on elucidation of the structures of Zn(II)-**6** complexes by X-ray crystallography.



**7** **8**

**Scheme 2**. Possible structures of Zn(II)-**6** complexes.

## Acknowledgements

We thank Prof. Yodhathai Thebtaranonth for the permission to access 400 MHz NMR spectrometer at the National Center for Genetic Engineering and Biotechnology. The Thailand Research Fund is also gratefully acknowledged for financial support.

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9. Anal. Cald. for **3** ($C_{71}H_{80}O_{10}$): C, 77.99; H, 7.37. Found: C, 78.11; H, 7.17. $^1$H NMR (δ ppm, $CDCl_3$, 200 MHz): 0.8-1.5 (36H, m, -ArC(C$H_3$)$_3$); 3.25 and 4.22 (4H each, m, ArC$H_AH_B$Ar); 4.16, 4.42 and 4.92 (12H, m, -OC$H_2$C$H_2$O-); 5.20 (1H, s, ArO*H*); 6.32-7.85 (20H, m, aromatic protons); 9.75 and 10.41 (1H and 2H, s each, -Ar(C=O)*H*). FAB MS (m/z): 1092.5.
10. Anal. Cald. for **4**•$H_2O$ ($C_{77}H_{94}N_4O_8$): C, 76.84; H, 7.87; N, 4.65. Found: C, 76.70; H, 7.61; N, 4.24. $^1$H NMR (δ ppm, $CDCl_3$, 200 MHz): 0.73, 1.22 and 1.35 (18H, 9H, 9H, s each, ROArC(C$H_3$)$_3$ and HOArC(C$H_3$)$_3$); 3.32, 3.53, 4.32 and 4.35 (2H each, d (J = 13 Hz), ArC$H_AH_B$Ar); 2.85 (12H, b, m, -NC$H_2$C$H_2$N-); 4.03, 4.50 and 5.15 (12H, m, -OC$H_2$C$H_2$O); 5.30 (1H, s, -ArO*H*); 6.42-7.90 (20H, m, aromatic protons); 8.82 and 8.92 (1H and 2H, s each, -C*H*=N-). FAB MS (m/z): 1185.7.
11. Anal. Cald. for **5**•4$H_2O$($C_{77}H_{110}N_4Cl_4O_{11}$): C, 65.69; H, 8.44; N, 3.78. Found: C, 65.61; H, 7.87; N, 3.97. FAB MS (m/z): 1191.7.
12. Anal. Cald. for **6** ($C_{77}H_{98}N_4O_7$): C, 77.61; H, 8.29; N, 4.70. Found: C, 77.57; H, 7.85; N, 4.32. $^1$H NMR (δ ppm, $CDCl_3$, 400 MHz): 0.86, 1.39 and 1.41 (18H, 9H, 9H, s each, ROArC(C$H_3$)$_3$ and HOArC(C$H_3$)$_3$); 1.99-2.66 (12H, b, m, RNC$H_2$C$H_2$NR); 3.23, 3.37, 4.45 and 4.85 (2H each, d (J = 13 Hz), ArC$H_AH_B$Ar); 3.75 and 4.18 (4H and 2H, d (J = 14 Hz), ArC$H_2$NR); 3.86, 4.03, 4.32 and 4.98 (12H, m, -OC$H_2$C$H_2$O-); 5.20 (1H, s, -ArO*H*); 6.25, 6.93, 7.15 and 7.47 (12H, m, -Ar*H*OC$H_2$-); 6.56 and 7.20 (4H, each, s, *t*-C($CH_3$)$_3$Ar*H*C$H_2$-). FAB MS (m/z): 1191.7.
13. The protonation constants of **6** were estimated by the Superquad computer program: Gans, P.; Sabatini, A.; Vacca, A. *J. Chem. Soc., Dalton Trans.* **1985**, 1195. The deprotonation constant of methanol at 25 °C was calculated to be $\log K = -16.7$.
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15. Typically, the ligand **6** (0.036 g, 0.030 mmol) was dissolved in $CDCl_3$ (2.40 mL) and placed into 6 NMR tubes (0.40 mL each). Zinc salts (0.053 mmol) in $CD_3OD$ (1 mL) were then added to the ligand solution in each tube by varying the ratio of Zn(II):**6** from 0.5:1 to 3:1.
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18. A methanolic solution (5 mL) of $ZnBr_2$ (0.020 g, 0.088 mmol) was added into a stirred $CH_2Cl_2$ solution (5 mL) of **6** (0.100g, 0.084 mmol). The reaction was allowed to stir at room temperature for 48 h. White solids precipitated from the reaction. The solvent volume was subsequently reduced, and white solids were separated by filtration and washed with diethylether. (0.061 g, 51%).
19. The proton signals due to *tert*-butyl groups appear at 0.53, 0.60, 0.65, 0.67, 1.03, 1.13, 1.17 and 1.19 ppm.

(*Received in UK* 26 *March* 1997; *accepted* 18 *April* 1997)