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# Synthesis of 1,3-Alternate Calix[4]-*bis*-Cryptand as a Cylindrical Macro*penta*cyclic Receptor

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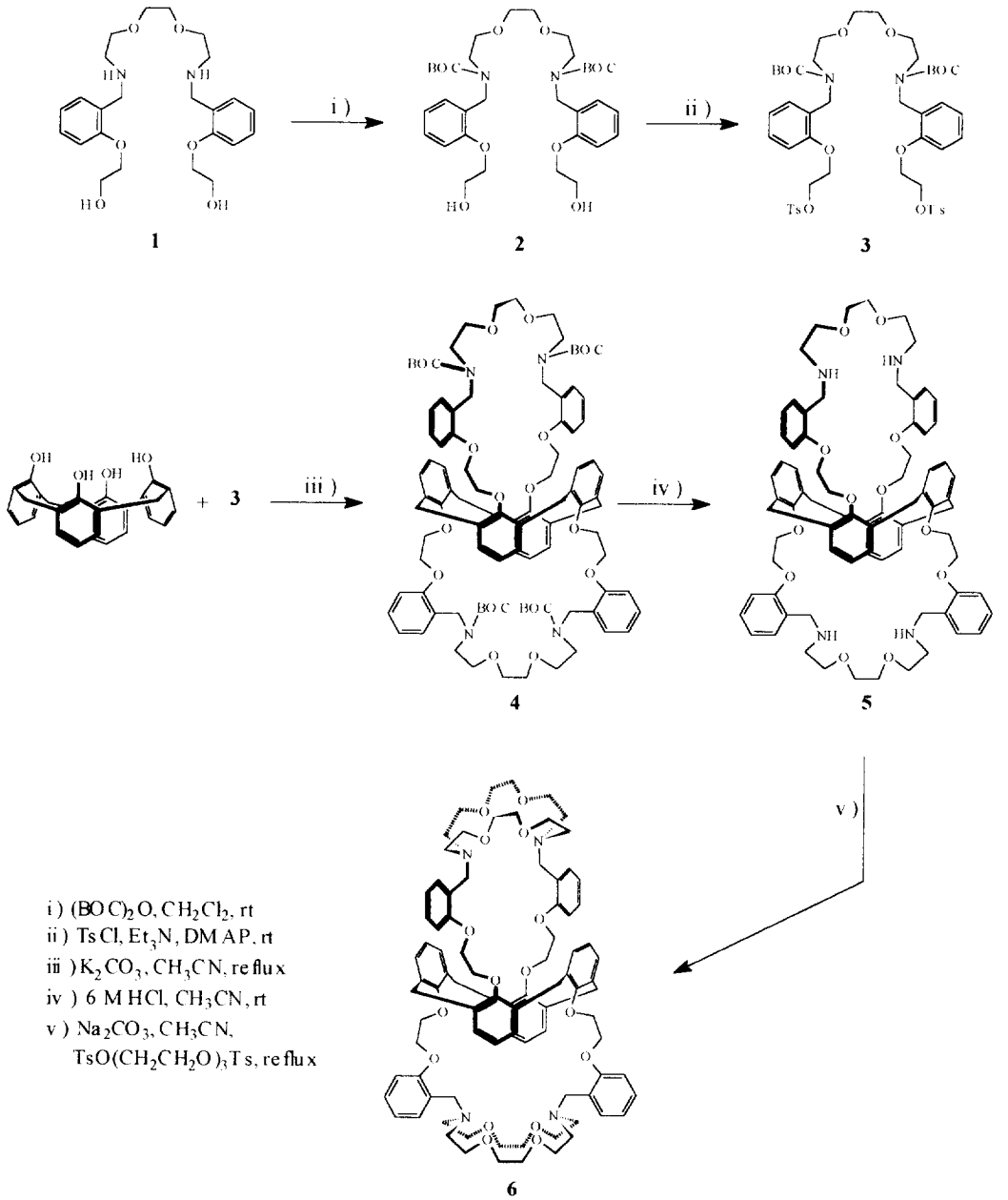
**Abstract**: Cylindrical calix[4]-*bis*-cryptand, calix[4]arene incorporating one diaza-tetraoxa-macrocyclic [18]-$N_2O_4$ subunit on each side of 1,3-alternate calix[4]arene framework, has been synthesized. The complexations of some alkali and ammonium cations by this macropentacycle have been studied by means of proton nuclear magnetic resonance spectroscopy. Copyright © 1996 Published by Elsevier Science Ltd

Cylindrical macrotricyclic cryptands refers to cryptand-type ligands consisting of two diaza-crown ether elements linked by two bridges to maintain the whole structure.[1] They present three cavities : two lateral circular cavities and one central cavity.[2] Their interest resides in their well-defined structures, their easy modification at the level of ring sizes and coordination sites to lead to high stable and selective complexes.[3] Most of former works have been focused on the complexation of ammonium cation, and especially *bis*-alkyl ammonium cations.[4,5] The other fascinating property of cylindrical macrotricyclic cryptands is to operate as an ion-channel in which intramolecular cation exchange can take place between the two diaza-crown ether cavities.[6] On the other hand a very similar ion oscillation has been shown to occur between the two metal-binding sites through the π-basic benzene tunnel of calix[4]arene derivatives in 1,3-alternate conformation.[7] For example $Na^+$, $K^+$, $Rb^+$, $Cs^+$, and $NH_4^+$ have been shown to oscillate from one crown ether loop to the other one through π-basic tube of 1,3-calix[4]-*bis*-crown-5 in 1,3-alternate conformation.[8] Similar findings were observed for $NH_4^+$ with a 1,3-calix[4]-*bis*-(N,O)-crown.[9]

These observations lead us to synthesize 1,3-calix[4]-*bis*-cryptand **6** similar to cylindrical macrotricyclic cryptands and consisting of two diaza-tetraoxa-crown ether subunits [18]-$N_2O_4$ linked on each side of calix[4]arene in 1,3-alternate conformation. This novel cylindrical macro*penta*cyclic cryptand is waited for being an approach to synthetic *'nano-tube'* through the occurrence of π-cation interactions similar to those found during the transport and permeation of cationic species in living systems.[10] Two recent examples of such an approach involving calix[4]arenes in 1,3-alternate conformation have been reported.[11,12]

The synthesis of **8**, shown in Scheme 1, began by the N-protection[13] of diamine dihydroxy **1**[14] with 2.5 equiv. of di-*tert*-butyl dicarbonate ($(BOC)_2O$) in dichloromethane at room temperature for 24 h., leading to di(N-BOC) dihydroxy **2** in 93% yield after purification on silicagel column by using 95:5 $CH_2Cl_2/CH_3OH$ as eluent. The tosylation of compound **2** was carried out with 2.5 equiv. of tosylchloride in the presence of 3.0 equiv. of triethylamine and a catalytic quantity of 4-dimethylaminopyridine (DMAP)[15] in dichloromethane for 4 h. The residue was purified on silicagel column by using 97:3 $CH_2Cl_2/CH_3OH$ as eluent to give di(N-BOC) ditosylate **3** as a transparent oil in 91% yield. By the conventional one-pot method




1 2 3 4 5 6

**Scheme 1**. Synthetic pathway to 1,3-alternate calix[4]-*bis*-cryptand **6**.

calix[4]-*bis*-crown,[9] the calix[4]-*bis*-di(N-BOC dioxa-benzo) crown **4**[16] was prepared by condensation of calix[4]arene with 2 equiv. of **3** in the presence of 20 equiv. of $K_2CO_3$ in the refluxing acetonitrile for 2 weeks. Compound **4** was eluted on silicagel column with 60:32:8 $CH_2Cl_2$:hexane:acetone as a white solid in 32% yield. The N-deprotection[13] of **4** was achieved by the treatment of compound **4** with 240 equiv. of 6M HCl in methanol at room temperature for 3 days.[13] The residue was dissolved in dichloromethane and neutralized with the sodium carbonate solution. After purification on the alumina column chromatography with 90:10 $CH_2Cl_2$:$CH_3OH$ as eluent, calix[4]-*bis*-di(azaoxa-benzo) crown **5**[17] was obtained as a white solid in 87% yield. N-cyclocondensation to [18]-$N_2O_4$ subunits[14] was performed by reacting **5** with 2 equiv. of triethylene glycol ditosylate in the presence of 47 equiv. of $Na_2CO_3$ in refluxing acetonitrile for 3 days. The residue was purified by alumina chromatography using 97:3 $CH_2Cl_2$:$CH_3OH$ as eluent to provide calix[4]-*bis*-cryptand **6**[18] as a white solid in 14% yield. **4**, **5** and **6** were deduced to be in 1,3-alternate conformation by the presence of a singlet of the methylene bridge protons (Ar-C*H*$_2$-Ar) at 3.60 3.66 and 3.61 ppm respectively.

Preliminary complexation studies of calix[4]-*bis*-cryptand **6** with sodium picrate ($Na^+Pic^-$), potassium picrate ($K^+Pic^-$), and ammonium picrate ($NH_4^+Pic^-$) were analyzed by means of proton nuclear magnetic resonance spectroscopy ($^1$H-NMR). The stoichiometry of the complexes was estimated by integration of the picrate protons resonance versus those for the NC*H*$_2$CH$_2$ of [18]-$N_2O_4$ subunits. The 1:1 sodium complex was achieved by reacting a 3 x $10^{-3}$ mol.L$^{-1}$ $CDCl_3$ solution of **6** with 1 equiv. of sodium picrate during 24 h. We observed the singlet of picrate protons at 8.75 ppm. We also observed the dd at 7.58 ppm ($J$ = 7.5, 1.5 Hz) of Ar*H* of **6** to be split into two doublets with same integration of protons at 7.57 ppm ($J$ = 6.0 Hz) and 7.40 ppm ($J$ = 7.0 Hz) corresponding probably to a location of sodium ion near by the [18]-$N_2O_4$ unit while the other one remained empty. This was confirmed by a split of the triplet of NC*H*$_2$CH$_2$ protons of the free ligand **6** from 2.98 ppm ($J$ = 6.0 Hz) into two broad signals at 2.97 ppm (corresponding to the empty cavity) and at 2.73 ppm (corresponding to the occupied cavity). The reaction of solution of **6** with an excess sodium picrate gave 1:2 ligand:metal complex in about 15 min. We observed the singlet of picrate protons at 8.73 ppm and the shifts of the dd of Ar*H* at 7.40 ppm (t, $J$ = 7.0 Hz) and of NC*H*$_2$CH$_2$ protons at 2.73 ppm (broad signal). This implied that the sodium to be located in both cavities of [18]-$N_2O_4$ subunits in a symmetrical manner leading to an *endo-endo*[1,2] binuclear complex. In the presence of an excess of potassium picrate, the 1:1 complex was obtained after 12 h. of reaction. The singlet of picrate protons was found at 8.74 ppm. Similar findings as for 1:1 sodium complex were assumed on the structure of the complex with the dd of Ar*H* at 7.56 ppm (d, $J$ = 5.5 Hz; corresponding to the empty cavity). Furthermore, NC*H*$_2$CH$_2$ protons were found at 2.97 ppm (broad signal) and 2.67 ppm (broad signal) corresponding to the empty and occupied cavities respectively. When 1:1 potassium complex was reacted with an excess potassium picrate, 1:2 potassium complex was detected after 2 days. We observed the singlet of picrate protons at 8.72 ppm and the shifts of Ar*H* from 7.56 ppm (d, $J$ = 5.5 Hz) to 7.36 ppm (t, $J$ = 7.5 Hz) and of NC*H*$_2$CH$_2$ signal from 2.97 ppm (s(br)) to 2.68 ppm. We concluded the 1:2 complex to be an *endo-endo* dinuclear complex as observed in the case of 1:2 sodium complex. The 1:1 ammonium complex was obtained by reacting the solution of **6** with 1 equiv. of solid ammonium picrate after 4 days. The singlet of picrate protons was found at 8.77 ppm. The dd of Ar*H* signal disappeared and a coalescence of all peaks was observed. We concluded that the ammonium ion probably oscillated between the [18]-$N_2O_4$ subunits. This phenomena might correspond to an inter- and/or intramolecular metal exchange between two identical cavities.[6,8,19] When the solution of **6** reacted with an excess of ammonium picrate, the 1:2 ammonium complex was obtained within 15 min. The picrate protons resonance was found at 8.76 ppm and, by comparison to the spectrum of 1:1 complex, the 1:2 complex spectrum was more symmetrical and more defined. This suggested that the ammonium cations were located in the cavities as proposed in the cases of sodium and potassium complexes. FAB (+) MS spectra of all the 1:1 complexes gave m/z = 1499.3 ($M+Na^+$) showed that this complex was probably more stable.

Further studies of the complexation properties of **6** are currently under investigation and will be presented in due course. Our objectives include : a.) showing evidence of inter- and/or intramolecular metal-ligand exchange by variable temperature experiments; b.) studying the complexation of neutral molecules; and c.) preparing 1,3-alternate calix[4]-*bis*-cryptands with variable size to provide new selective cation receptors.

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16. Analytical data of compound **4** : (Mp 94 - 95 °C) $^1$H-NMR (200 MHz, $CDCl_3$) : δ (ppm) 7.26 (t, *J*= 7.0 Hz, 4H, Ar*H*), 7.12 - 6.89 (m, 20H, Ar*H*), 6.60 (t, *J*= 6.0 Hz, 4H, Ar*H*), 4.73 (d, *J*= 8.0 Hz, 8H, ArC$H_2$N), 4.29 (s(br), 8H, ArOC$H_2$), 4.11 (s(br), 8H, ArOCH$_2$C$H_2$), 3.60 (s, 8H, ArC$H_2$Ar), 3.45 (s, 8H, NCH$_2$C$H_2$), 3.36 (s, 8H, NCH$_2$CH$_2$OC$H_2$), 3.18 - 3.06 (m, 8H, N C$H_2$CH$_2$), 1.48 (s, 18H, C(CH$_3$)$_3$), 1.35 (s, 18H, C(CH$_3$)$_3$). *Anal. Found* C, 69.86; H, 7.25. *Calc.* For $C_{96}H_{120}N_4O_{20}$: C, 69.88; H, 7.33.
17. Analytical data of compound **5** : (Mp 68 - 69 °C) $^1$H-NMR (200 MHz, $CDCl_3$) : δ (ppm) 7.39 (dd, *J*= 6.0, 1.6 Hz, 4H, Ar*H*), 7.25 (t, *J*= 8.0 Hz, 4H, Ar*H*), 7.14 (d, *J*= 7.5 Hz, 8H, Ar*H*), 6.97 (t, *J*= 7.0 Hz, 4H, Ar*H*), 6.91 (d, *J*= 8.0 Hz, 4H, Ar*H*), 6.67 (t, *J*= 7.5 Hz, 4H, Ar*H*), 4.19 (m, 8H, ArOC$H_2$), 4.07 (m, 8H, ArOCH$_2$C$H_2$), 4.00 (s, 8H, ArC$H_2$N), 3.66 (s, 8H, ArC$H_2$Ar), 3.46 (t, *J*= 5.5 Hz, 8H, NCH$_2$C$H_2$), 3.34 (s, 8H, NCH$_2$CH$_2$OC$H_2$), 2.79 (t, *J*= 5.5 Hz, 8H, N C$H_2$CH$_2$), 1.92 (s, 4H, N*H*). *Anal. Found* C, 72.84; H, 6.96. *Calc.* For $C_{76}H_{88}N_4O_{12}$: C, 73.05; H, 7.10.
18. Analytical data of compound **6** : (Mp 101 - 102 °C) $^1$H-NMR (200 MHz, $CDCl_3$) : δ 7.58 (dd, *J*= 7.5, 1.5 Hz, 4H, Ar*H*), 7.25 - 7.19 (m, 10H, Ar*H*), 6.99 (t, *J*= 7.0 Hz, 4H, Ar*H*), 6.90 (d, *J*= 8.0 Hz, 4H, Ar*H*), 6.75 (t, *J*= 7.5 Hz, 4H, Ar*H*), 4.29 (m, 8H, ArOC$H_2$), 4.16 (m, 8H, ArOCH$_2$C$H_2$), 4.05 (s, 8H, ArC$H_2$N), 3.64 - 3.54 (m, 16H, NCH$_2$C$H_2$), 3.61 (s, 8H, ArC$H_2$Ar)3.45 (s, 8H, NCH$_2$CH$_2$OC$H_2$), 2.98 (t, *J*= 6.0 Hz, 8H, N C$H_2$CH$_2$) *Anal. Found* C, 69.42; H, 6.94. *Calc.* For $C_{88}H_{108}N_4O_{16}$ . $0.5CH_2Cl_2$.$0.5H_2O$.: C, 69.51; H, 7.25; FAB (+) MS, m/z 1477.3 (M+H$^+$)
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