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## Synthesis of 1,3-Alternate Calix[4]-bis-Cryptand as a Cylindrical Macropentacyclic 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.<sup>1</sup> They present three cavities : two lateral circular cavities and one central cavity.<sup>2</sup> 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.<sup>3</sup> Most of former works have been focused on the complexation of ammonium cation, and especially *bis*-alkyl ammonium cations.<sup>4,5</sup> 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.<sup>6</sup> On the other hand a very similar ion oscillation has been shown to occur between the two metal-binding sites through the  $\pi$ -basic benzene tunnel of calix[4]arene derivatives in 1,3-alternate conformation.<sup>7</sup> For example Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup>, Cs<sup>+</sup>, and NH4<sup>+</sup> have been shown to oscillate from one crown ether loop to the other one through  $\pi$ -basic tube of 1,3-calix[4]-*bis*-crown-5 in 1,3-alternate conformation.<sup>8</sup> Similar findings were observed for NH4<sup>+</sup> with a 1,3-calix[4]-*bis*-(N,O)-crown.<sup>9</sup>

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<sub>2</sub>O<sub>4</sub> linked on each side of calix[4]arene in 1,3-alternate conformation. This novel cylindrical macropentacyclic cryptand is waited for being an approach to synthetic 'nano-tube' through the occurrence of  $\pi$ -cation interactions similar to those found during the transport and permeation of cationic species in living systems.<sup>10</sup> Two recent examples of such an approach involving calix[4]arenes in 1,3-alternate conformation have been reported.<sup>11,12</sup>

The synthesis of **8**, shown in Scheme 1, began by the N-protection<sup>13</sup> of diamine dihydroxy 1<sup>14</sup> with 2.5 equiv. of di-*tert*-butyl dicarbonate ((BOC)<sub>2</sub>O) 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<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 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)<sup>15</sup> in dichloromethane for 4 h. The residue was purified on silicagel column by using 97:3 CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH as eluent to give di(N-BOC) ditosylate **3** as a transparent oil in 91% yield. By the conventional one-pot method



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

calix[4]-*bis*-crown,<sup>9</sup> 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<sub>2</sub>CO<sub>3</sub> in the refluxing acetonitrile for 2 weeks. Compound 4 was eluted on silicagel column with 60:32:8 CH<sub>2</sub>Cl<sub>2</sub>:hexane:acetone as a white solid in 32% yield. The N-deprotection<sup>13</sup> of 4 was achieved by the treatment of compound 4 with 240 equiv. of 6M HCl in methanol at room temperature for 3 days.<sup>13</sup> The residue was dissolved in dichloromethane and neutralized with the sodium carbonate solution. After purification on the alumina column chromatography with 90:10 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH as eluent, calix[4]-*bis*-di(azaoxa-benzo) crown 5<sup>17</sup> was obtained as a white solid in 87% yield. N-cyclocondensation to [18]-N<sub>2</sub>O<sub>4</sub> subunits<sup>14</sup> was performed by reacting 5 with 2 equiv. of triethylene glycol ditosylate in the presence of 47 equiv. of Na<sub>2</sub>CO<sub>3</sub> in refluxing acetonitrile for 3 days. The residue was purified by alumina chromatography using 97:3 CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>OH as eluent to provide calix[4]-*bis*-dige protons (Ar-CH<sub>2</sub>-Ar) at 3.60 3.66 and 3.61 ppm respectively.

Preliminary complexation studies of calix[4]-bis-cryptand 6 with sodium picrate (Na<sup>+</sup>Pic<sup>-</sup>), potassium picrate ( $K^+Pic^-$ ), and ammonium picrate ( $NH_4^+Pic^-$ ) were analyzed by means of proton nuclear magnetic resonance spectroscopy (<sup>1</sup>H-NMR). The stoichiometry of the complexes was estimated by integration of the picrate protons resonance versus those for the NCH<sub>2</sub>CH<sub>2</sub> of [18]-N<sub>2</sub>O<sub>4</sub> subunits. The 1:1 sodium complex was achieved by reacting a 3 x  $10^{-3}$  mol.L<sup>-1</sup> CDCl<sub>3</sub> 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 ArH 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<sub>2</sub>O<sub>4</sub> unit while the other one remained empty. This was confirmed by a split of the triplet of  $NCH_2CH_2$  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 ArH at 7.40 ppm (t, J = 7.0 Hz) and of NCH<sub>2</sub>CH<sub>2</sub> protons at 2.73 ppm (broad signal). This implied that the sodium to be located in both cavities of [18]-N<sub>2</sub>O<sub>4</sub> subunits in a symmetrical manner leading to an endo-endo<sup>1.2</sup> 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 ArH at 7.56 ppm (d, J = 5.5 Hz; corresponding to the empty cavity). Furthermore, NCH<sub>2</sub>CH<sub>2</sub> 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 ArH from 7.56 ppm (d, J = 5.5 Hz) to 7.36 ppm (t, J = 7.5 Hz) and of NCH<sub>2</sub>CH<sub>2</sub> 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 ArH signal disappeared and a coalescence of all peaks was observed. We concluded that the ammonium ion probably oscillated between the [18]-N2O4 subunits. This phenomena might correspond to an interand/or intramolecular metal exchange between two identical cavities.<sup>6,8,19</sup> 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<sup>+</sup>) 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 metalligand 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 :  $(Mp \ 94 95 \ ^{\circ}C)^{-1}$ H-NMR (200 MHz, CDCl<sub>3</sub>) :  $\delta$  (ppm) 7.26 (t, J= 7.0 Hz, 4H, ArH), 7.12 6.89 (m, 20H, ArH), 6.60 (t, J= 6.0 Hz, 4H, ArH), 4.73 (d, J= 8.0 Hz, 8H, ArCH<sub>2</sub>N), 4.29 (s(br), 8H, ArOCH<sub>2</sub>), 4.11 (s(br), 8H, ArOCH<sub>2</sub>CH<sub>2</sub>), 3.60 (s, 8H, ArCH<sub>2</sub>Ar), 3.45 (s, 8H, NCH<sub>2</sub>CH<sub>2</sub>), 3.36 (s, 8H, NCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>), 3.18 3.06 (m, 8H, N CH<sub>2</sub>CH<sub>2</sub>), 1.48 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>), 1.35 (s, 18H, C(CH<sub>3</sub>)<sub>3</sub>). Anal. Found C, 69.86; H, 7.25. Calc. For C<sub>96</sub>H<sub>120</sub>N<sub>4</sub>O<sub>20</sub>: C, 69.88; H, 7.33.
- 17. Analytical data of compound 5 :  $(Mp \ 68 69 \ ^{\circ}C)^{-1}$ H-NMR (200 MHz, CDCl<sub>3</sub>) :  $\delta$  (ppm) 7.39 (dd, J = 6.0, 1.6 Hz, 4H, ArH), 7.25 (t, J = 8.0 Hz, 4H, ArH), 7.14 (d, J = 7.5 Hz, 8H, ArH), 6.97 (t, J = 7.0 Hz, 4H, ArH), 6.91 (d, J = 8.0 Hz, 4H, ArH), 6.67 (t, J = 7.5 Hz, 4H, ArH), 4.19 (m, 8H, ArOCH<sub>2</sub>), 4.07 (m, 8H, ArOCH<sub>2</sub>CH<sub>2</sub>), 4.00 (s, 8H, ArCH<sub>2</sub>N), 3.66 (s, 8H, ArCH<sub>2</sub>Ar), 3.46 (t, J = 5.5 Hz, 8H, NCH<sub>2</sub>CH<sub>2</sub>), 3.34 (s, 8H, NCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>), 2.79 (t, J = 5.5 Hz, 8H, N CH<sub>2</sub>CH<sub>2</sub>), 1.92 (s, 4H, NH). Anal. Found C, 72.84; H, 6.96. Calc. For C<sub>76</sub>H<sub>88</sub>N<sub>4</sub>O<sub>12</sub>: C, 73.05; H, 7.10.
- 18. Analytical data of compound 6 : (Mp 101 102 °C) <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) :  $\delta$  7.58 (dd, J= 7.5, 1.5 Hz, 4H, ArH), 7.25 7.19 (m, 10H, ArH), 6.99 (t, J= 7.0 Hz, 4H, ArH), 6.90 (d, J : 8.0 Hz, 4H, ArH), 6.75 (t, J= 7.5 Hz, 4H, ArH), 4.29 (m, 8H, ArOCH<sub>2</sub>), 4.16 (m, 8H, ArOCH<sub>2</sub>CH<sub>2</sub>), 4.05 (s, 8H, ArCH<sub>2</sub>N), 3.64 3.54 (m, 16H, NCH<sub>2</sub>CH<sub>2</sub>), 3.61 (s, 8H, ArCH<sub>2</sub>Ar)3.45 (s, 8H, NCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>), 2.98 (t, J= 6.0 Hz, 8H, N CH<sub>2</sub>CH<sub>2</sub>) Anal. Found C, 69.42; H, 6.94. Calc. For C<sub>88</sub>H<sub>108</sub>N<sub>4</sub>O<sub>16</sub> . 0.5CH<sub>2</sub>Cl<sub>2</sub>.0.5H<sub>2</sub>O.: C, 69.51; H, 7.25; FAB (+) MS, m/z 1477.3 (M+H<sup>+</sup>)
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