Synthesis of a New Stable Peristatic Chiral Pseudocryptand for Simultaneous Binding of Boron and Sodium

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A new selective molecular receptor, borocryptate, based on the combination of the 15 membered ring diazatrioxa core and two saligenin units as binding sites for boron has been described. The resulting peristatic chiral compound is stable in air and easily converted to polynuclear complex, Na-borocryptate, without using an inert atmosphere.

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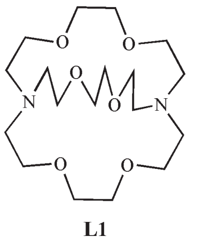
Introduction.

Since the discovery of cryptands, in particular the [2.2.2] macrobicyclic ligand **L1**, some 30 years ago by Dietrich, Lehn and Sauvage [1] and of the crown ethers by Pedersen [2] an exciting new field of research named supramolecular chemistry has opened to inorganic, organic and physical chemists [3-5]. Whereas at the outset much attention was focused on the selective binding of monoatomic alkaline and alkaline-earth metal cations, very rapidly considerable achievements were reported with regard to the recognition of molecular cations [6].

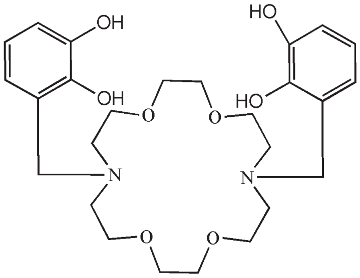
Many aspects of supramolecular chemistry remain to be developed, for example new materials based on self assembly may be targeted by using weak interactions [7]. On the other hand, the design and synthesis of bi-nuclear complexes have been extensively studied over the past three decades [7]. In these complexes, intrinsic molecular properties such as magnetic coupling, redox activity and optical features may be tuned with remarkable precision [8]. Although at an earlier period many homo- and heterobinuclear complexes reported were essentially of the same type, *i.e.* two alkaline or two transition metal cations, only recently considerable afford has been invested in the synthesis of heterobinuclear complexes possessing both a hard alkaline or alkaline-earth and soft transition metal cations [9]. Inspiring from structural aspects of boromycin [10] and aplasmomycin [11], natural antibiotics bearing a spiroborate group and of cryptands, Hosseini and co-workers have embarked upon a program dealing with the design and synthesis of polynucleating ligands.

Their approach to the design of binucleating receptor was based on the combination of a macrocyclic framework and two bidentate dianionic ligands. Using preorganised cores, such as diaza-macrocyclic, bi- and polynucleating ligands bearing bidentate catechol units have been prepared [12]. For the macrocyclic core, a diazamacrocyclic ring was chosen because of its ability to bind hard cations. For this reason, Hosseini and co-workers have designed a new family of artificial receptor for alkaline metal cations [12a]. Compounds in which two catechol units were interconnected by polyethylene glycol spacers have been also reported [13].

However, during the preparation of borocryptand, it was observed that if oxygen was not completely removed, the reaction afforded a pink precipitate that resulting from the oxidation of the catechol moieties prior to binding of boron. Probably this is due to the strong basicity of its macrocyclic core promoting an intramolecular proton transfer from catechol moieties to the tertiary amino groups and thus generating the catecholate ammonium zwitter ion, which is extremely sensitive to oxidation and hence should be stored in the absence of oxygen.



L1



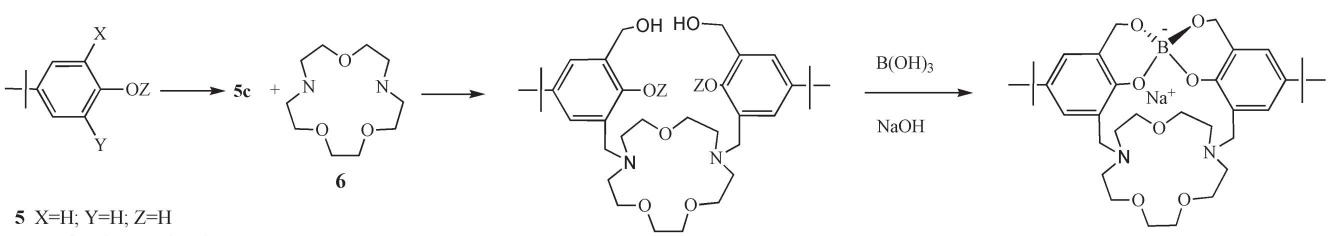
L2

Therefore, to prevent the oxidation of the ligand **L2** complexation must be carried out under inert atmosphere, such as argon [14].

Results and Discussion.

In the present contribution a new sodium receptor based on the combination of the 15 membered ring diazatrioxa macrocyclic core and two saligenin units instead of [2.2] macrocyclic cores and catechol moieties in **L2** was designed **(3-B, Na)**. The saligenin moieties provide binding sites for boron as catechol, but it also makes the ligand more stable against air oxidation. The sodium borocryptant synthesis was prepared as shown in Scheme 1. In the **L2** ligand, one of the two phenolic hydroxyl groups is converted to saligenin in the case of **L3**. Replacement of catechol units, acting as binding sites for boron, with saligenin moieties contributes to the stability of **L3** over **L2** against air oxidation.

Scheme 1



5 X=H; Y=H; Z=H
5a X=CH$_2$OH; Y=CH$_2$OH; Z=H
5b X=CH$_2$OH; Y=CH$_2$OH; Z=Bn
5c X=CH$_2$OH; Y=CH$_2$Cl; Z=Bn
5d X=CH$_2$Cl; Y=CH$_2$Cl; Z=Bn

6

L3 Z=H
L4 Z=Bn

(3-B, Na)

The free ligand **L3** was converted to **(3-B, Na)** complex without using inert atmosphere. The binding ability of receptor **L3** towards boron and sodium was achieved by treating the free ligand **L3** with 1 eq. of NaOH and 1 eq. of B(OH)$_3$ in H$_2$O/EtOH mixture at room temperature affording the **(3-B, Na)** complex as a white precipitate which was filtered and recrystallised from methanol. The **(3-B, Na)** complex was perfectly stable towards oxidation and could be stored in the presence of oxygen. The structure of **L3** was determined by ^{1}H and ^{13}C NMR spectroscopy in CDCl$_3$. For the complex **(3-B, Na)** all ^{1}H and ^{13}C signals were assigned based on a ^{1}H-^{13}C NMR correlation experiment (Figure 1). Comparison of the ^{1}H and ^{13}C NMR spectra of free ligand **L3** and its complex produces surprising results, not only in chemical shifts but also in the number of signals. Based on this observations, the proton and carbon chemical shift for the alkali metal complexes of type **(3-B, Na)** were strongly depend on the nature of the cation [12b]. ^{1}H NMR of ligand **L3** gave signals at 1.16 ppm as a singlet, 2.63-2.68 ppm as a triplet, 2.72-274 ppm

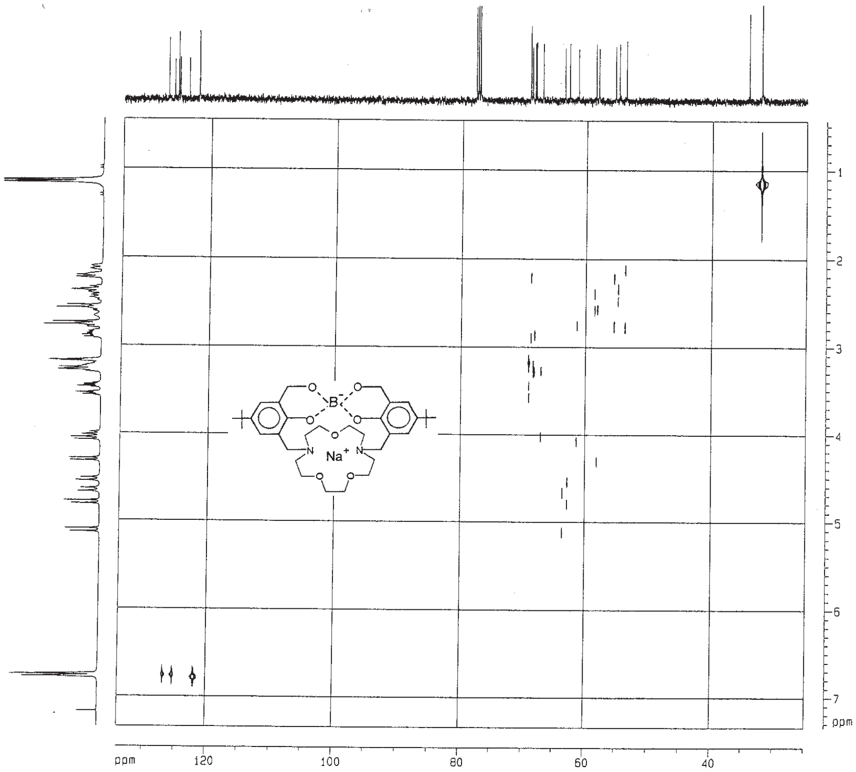


Figure 1. ^{1}H-^{13}C corelation spectra of (3-B, Na).

as a triplet, 3.65 ppm as a singlet, 4.56 ppm as a singlet, corresponding to tertiary butyl groups, CH_2N, CH_2O, $PhCH_2N$, $PhCH_2O$ protons, respectively (Figure 2). Upon complexation, tertiary butyl groups appear at 1.24 and 1.27

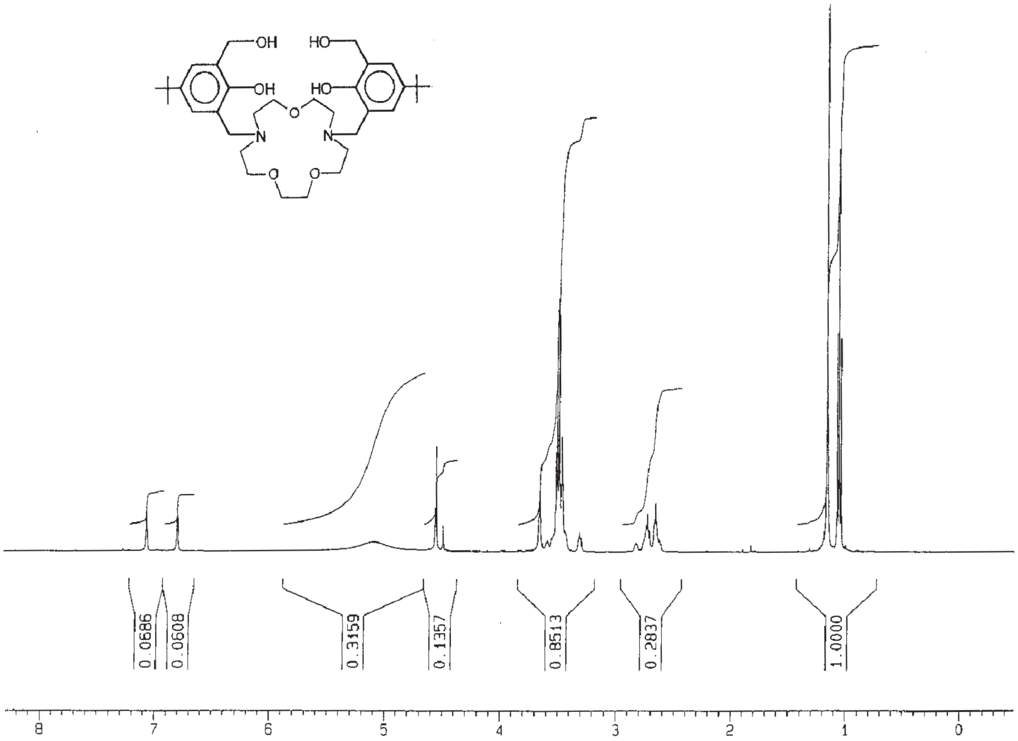


Figure 2. ${}^1H$ NMR spectra of L3.

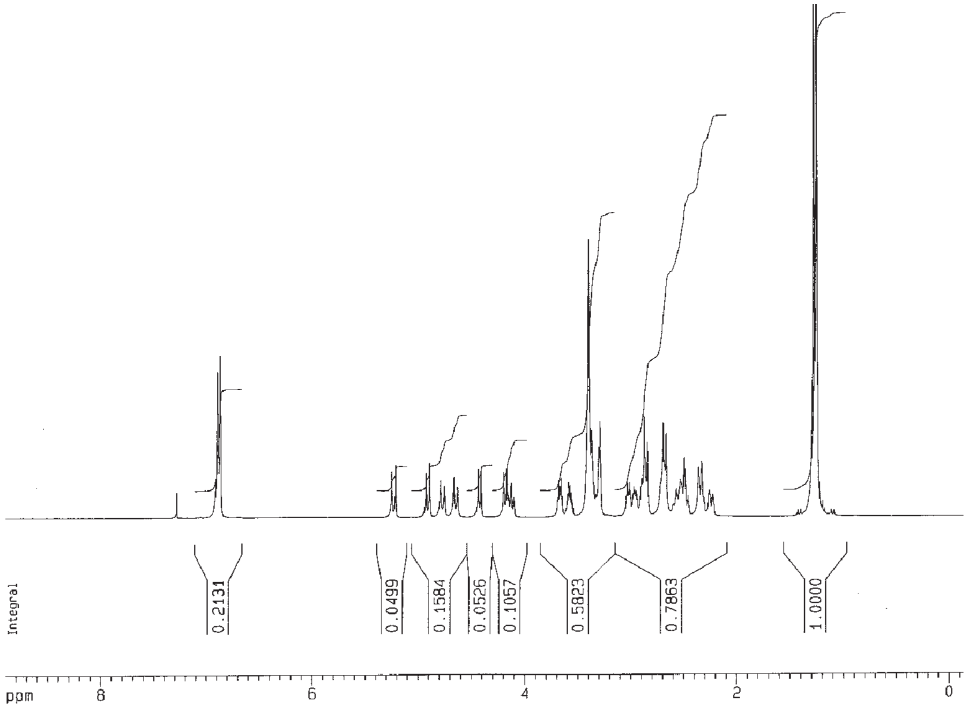


Figure 3. ${}^1H$ NMR spectra of (3-B, Na) (Doubled peaks were shown in spectrum).

ppm as two singlets while both $PhCH_2N$ and $PhCH_2O$ peaks appears as AB quartets. And also OCH_2CH_2O protons gave a multiplet at 3.46-3.50 ppm (Figure 3).

As to ^{13}C NMR spectra, the free ligand **L3** gave 9 and 6 peaks for aliphatic and aromatic region but in **(3-B, Na)** complex, 18 and 12 peaks were observed respectively, *i.e*, the number of carbon peaks in free ligand **L3** doubled upon complexation with Na^+.

This observation might be explained in terms of tetrahedral nature of boron complex resulted in a peristatic chiral [12c,15] structure. Schematic representation of *R* and *S* enantiomers obtained upon complexation of boron in tetrahedral geometry by the ligand **(3-B, Na)** is shown in Figure 4.

In summary, high yield synthesis of **L3** that is very stable against air oxidation based on the macrocyclic backbone bearing two saligenin units was achieved. The binding ability of **L3** towards both boron and sodium cation was analysed by NMR spectroscopy.

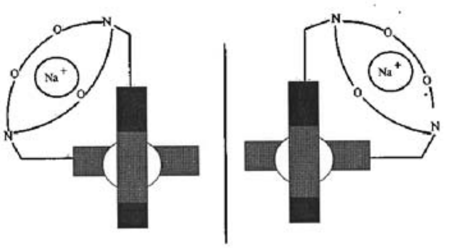


Figure 4. Schematic representation of both *R* and *S* enantiomers obtained upon complexation of boron in tetrahedral coordination geometry by the ligand **(3-B, Na)**.

EXPERIMENTAL

General Information.

The ^1H nmr spectra were obtained at 400 MHz on a BRUKER DPX-400 High Performance Digital FT-NMR in $CDCl_3$ with TMS as the internal standard. The ^{13}C nmr spectra were obtained at 100 MHz on a BRUKER DPX-400 High Performance Digital FT-NMR. The elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. Infrared spectra were recorded on a MIDAC-FTIR Model 1700 Spectrophotometer. Melting points were determined with a GALLENKAMP Model apparatus with open capillaries. Mass spectra data were recorded with an AGILENT 1100 MSD spectrometer.

4-*tert*-Butyl-2,6-Dihydroxymethyl Phenol (**5a**).

Tert-butyl phenol **5** was converted to the **5a** according to the literature method [16]. *Tert*-butyl phenol **5** (24 g, 0.16 mol), 40% aqueous formaldehyde (24 g, 0.32 mol) and 2% aqueous NaOH (320 g, 0.16 mol) was stirred at 30-40 °C for 30-50 hours. Then 25% of H_2SO_4 solution (31.32 g, 0.16 mol) was added to the mixture. The resulting organic phase was extracted with ethers (3 x 50 mL). The ethers extract was dried over Na_2SO_4 and solvent was evaporated with rotary evaporator. The product crystallised from ether-petroleum ether mixture to give as a white crystals of **5a** (25.2 g, 75%), mp 75-75.5°C. ir: ν 3401, 3308, 3068, 3034, 2956, 2874, 1606, 1486, 1463, 1363, 1264, 1216, 1064, 1011, 870 cm^{-1}.

Anal. Calcd for: $C_{12}H_{28}O_3$; C, 68.57; H, 8.57. Found: C, 68.48; H, 8.41.

4-*tert*-Butyl-2,6-Dihydroxymethyl Phenyl Benzyl Ether (**5b**).

4-*tert*-Butyl-2,6-dihydroxy-methyl phenol **5a** (17 g, 0.081 mol) was dissolved in absolute ethanol and then K_2CO_3 (11.18 g, 0.081 mol) was added to the mixture. Benzylchloride (10.24 g, 0.081 mol) was added dropwise to the solution. The mixture was refluxed for 18 hours. Then, the mixture was filtered and ethanol was evaporated. The product crystallised from ether-petrolium ether mixture, to give as a white crystals of **5b** (17g, 70%), mp 98-100°C. ir: ν 3551, 3460, 3275, 3063, 3034, 2950, 2903, 2865, 1606, 1482, 1454, 1381, 1361, 1301, 1240, 1199, 1118, 1062, 1011, 886, 739, 700 cm^{-1}.

Anal. Calcd. For: $C_{19}H_{24}O_3$; C, 75.97; H, 8.05. Found: C, 76.18; H, 8.15.

4-*tert*-Butyl-2-hydroxymethyl-6-Chloromethyl Phenyl Benzyl Ether (**5c**).

A solution of 4-*tert*-butyl-2,6-dihydroxymethyl phenyl benzyl ether **5b** (16.75 g, 0.056 mol) and pyridine (4.74 g, 0.06 mol) in absolute benzene (350 mL), was stirred with reflux. Thionyl chloride (6.64 g, 0.056 mol) was added to the solution dropwise in three hours and then left for 16 hours with reflux. The mixture was cooled to the room temperature and filtered. After then, 1.5 mL concentrated hydrochloric acid and 25 mL water was added. The resulting organic phase was washed with water. The benzene extract was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel eluted with petrolium ether/ether (2:1). After column chromatography the product recrystallised from ether-petrolium ether to give as a white crystal of **5c** (9.4 g, 50%), mp 77-77.5 °C; ir: ν 3579, 3486, 3029, 2960, 2898, 2875, 1584, 1476, 1454, 1385, 1362, 1268, 1256, 1204, 1113, 979, 886, 733, 694, 633 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.38 (s, 9H); 1.92 (bs, 1H); 4.71 (s, 2H); 4.74 (s, 2H); 5.07 (s, 2H); 7.44-7.53 (m, 7H); ^{13}C nmr ($CDCl_3$): δ 31.81, 34.94, 41.85, 61.77, 73.39, 127.63, 128.24, 128.48, 128.82, 129.12, 130.90, 134.32, 137.40, 148.36, 153.29 ppm.

Anal. Calcd. for: $C_{19}H_{23}O_2Cl$: C, 71.59; H, 7.22; found: C, 71.57; H, 7.35.

Second product recrystallised from ether-petrolium ether to give as a white crystal of 4-*tert*-butyl-2,6-dichloromethyl phenyl benzyl ether **5d**, mp 80-82 °C. ir: ν 3095, 3068,3038, 2964, 2867, 1500, 1481, 1465, 1455, 1381, 1364, 1270, 1210, 1108, 982, 891, 781, 696, 637 cm^{-1}; ^1H nmr ($CDCl_3$):δ 1.38 (s, 9H); 4.69 (s, 4H); 5.14 (s, 2H); 7.28-7.58 (m, 7H); ^{13}C nmr ($CDCl_3$): δ 31.73, 34.93, 41.72, 77.58, 128.78, 129.09, 129.36, 131.32,137.34, 148.53, 153.53 ppm.

Anal. Calcd. For: $C_{19}H_{22}OCl_2$; C, 64.59; H, 6.23. Found: C, 64.52; H, 6.28.

Saligenin Armed Diaza-15-Cr-5 Derivative L3 (Pseudocryptand).

Commercially available diaza-15-Cr-5 (**6**) (1.0 g, 45.87 mmol) and 4-*tert*-butyl-2-hydroxymethyl-6-chloromethyl phenyl benzyl ether **5c** (4.64 g, 45.87 mmol) in the presence of Et_3N was dissolved in toluene (75 mL). The mixture was stirred at 80-85 °C for

16 hours. Then mixture was cooled and filtered. After the evaporation the crude product was obtained as an oil of L4 (3.26 g, 91%). This crude residue was directly debenzylated with Pd/C in dry ethanol- ethyl acetate mixture. The compound L3 was obtained as a colourless liquid in almost quantitative yield. ^{1}H nmr ($CDCl_3$): δ 1.16 (s, 18H); 2.65-2.75 (m, 8H); 3.46-3.67 (m, 16H); 4.56 (s, 4H); 4.66 (bs, 4H); 7.07 (dd, 4H); ^{13}C nmr ($CDCl_3$): δ 18.40, 31.87, 34.21, 54.55, 54.67, 57.77, 59.74, 61.98, 68.50, 69.11, 70.77, 124.84, 125.00, 125.18, 127.45, 141.77, 153.65 ppm.

Anal. Calcd. for: $C_{34}H_{56}N_2O_7$; C,67.55; H, 9.27; N, 4.64. Found: C, 67.42; H, 9.34; N, 4.58.

Sodium Borocryptate (**3-B, Na**).

The benzyl protected ligand L4 was debenzylated as described in literature [17]. A mixture of L4 (3.26 g, 4.17 mmol) and 0.25 g of preequilibrated 10% palladium/carbon in 75 ml ethanol/ethylacetate (2:1) was hydrogenated at room temperature and atmospheric pressure. Hydrogen absorption ceased after the uptake to afford L3. The free L3 (2.51 g, 4.17 mmol) dissolved in ethanol and treated with 1 eq. of NaOH and 1 eq. of $B(OH)_3$ in H_2O/EtOH mixture at room temperature affording the (3-B, Na) complex as a precipitate which was filtered and recrystallised from methanol. The compound (3-B, Na) was obtained as a white crystal in almost quantitative yield, mp 310 °C decomposed. MS: m/z (M^++1, 633.4) ir: ν 3384, 2952, 2870, 2825, 1613, 1485, 1365, 1281, 1263, 1219, 1112, 1040, 1007, 935, 884, 791, 643, 620 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.24 (s, 9H); 1.27 (s, 9H); 2.33-3.03 (m, 8H); 3.28-4.12 (m, 12H); 3.52 (dd, 2H); 3.55 (dd, 2H); 4.78 (dd, 2H); 5.00 (dd, 2H); 6.87 (dd, 4H); ^{13}C nmr ($CDCl_3$): δ 32.11, 34.12, 34.15, 50.79, 53.71, 54.85, 55.57, 58.18, 58.51, 61.38, 62.81, 63.62, 67.18, 67.28, 68.40, 68.76, 69.05, 69.20, 121.95, 122.05, 123.63, 125.03, 125.32, 125.38, 125.87, 126.92, 139.53, 139.69, 152.78, 152.90 ppm.

Anal. Calcd. for: $C_{34}H_{52}N_2O_7BNa$; C, 64.35; H, 8.20; N, 4.42. Found: C, 64.12; H, 8.37; N, 4.34.

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