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Borocryptands : Synthesis and Structural Analysis of a Lithium Borocryptate

Frédéric Bockstahl[a], Ernest Graf[a], Mir Wais Hosseini*[a], Dominique Suhr[a], André De Cian[b], Jean Fischer[b]

[a]Laboratoire de Chimie de Coordination Organique, [b]Laboratoire de Cristallochimie et Chimie Structurale, associé au CNRS, Université Louis Pasteur, Institut Le Bel, 4, rue Blaise Pascal, F-67000 Strasbourg, France

Abstract: A new lithium receptor based on the combination of the [11] macrocyclic core and two catechol units was designed and prepared. The binding ability of the ligand towards boron and lithium was demonstrated in solution by NMR and in the solid state by an X-ray analysis of the lithiumborocryptate.
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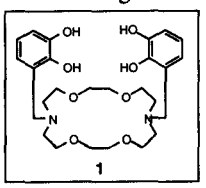
Due to the role played by lithium in science, medicine and technology,[1] the design of Li-selective complexing agent is still an active area of research. The complexation of lithium by a variety of synthetic receptor molecules has been investigated.[2] Among many structural features screened, cryptands[3] and spherands[4] appeared to be the most appropriate and selective receptors for lithium. Based on structural aspects of boromycin[5] and aplasmomycin[6], natural antibiotics bearing a spiroborate group, and of cryptands, we have designed a new family of artificial receptors for alkaline metal cations.[7-10] The early design of borocryptand was based on the double functionalisation, at both nitrogen centres, of the [22] macrocyclic core by two catechol units[7] leading thus to the receptor molecule **1**. The simultaneous binding of boron and alkaline metal[8,9] as well as ammonium[10] cations leading to metalloborocryptates has been demonstrated both in solution and in the solid state. As a consequence of the size of its cavity, the binding ability of the borocryptand $(\mathbf{1}\text{-B})^-$, generated by treatment of **1** with boric acid, was extremely high for K^+ and rather low for Li^+ cations. In order to obtain the reverse selectivity sequence the ligand **2** was designed. In the present contribution we report the synthesis of compound **2** and of its Li^+-borocryptate as well as a solid state structural analysis of the latter.



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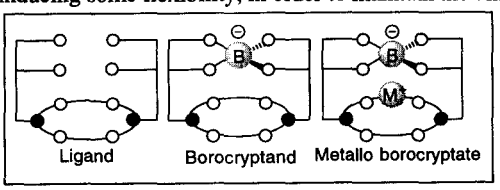
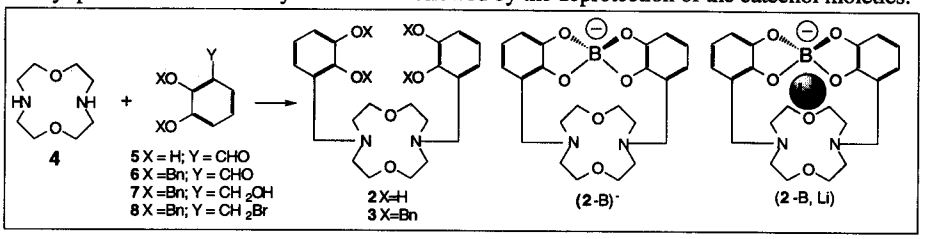
The design of **2** as a precursor of a selective lithium receptor is based on the shrinking of the size of the cavity of the borocryptand. This may be achieved, while maintaining the catechol moieties as the boron binding sites, by the use of the [1,1] macrocycle **4** in stead of the [22] macrocycle as in the case of the **1**. Although inducing some flexibility, in order to maintain the binding ability of the nitrogen atoms, the linkage between the catechols and the macrocyclic core was achieved by methylene groups. Due to the presence of the same potential coordinating sites (N_2O_4), the anionic borocryptand $(\mathbf{2}\text{-B})^-$ may be regarded as an analogue of the neutral [211] cryptand.[11] Compounds in which two catechol units were interconnected by polyethylene glycol spacers have been also reported.[12]



Fax: 33 388 41 62 66, E-mail: hosseini@chimie.u-strasbg.fr

The synthesis of compound **2** was achieved by condensing the commercially available [1,1] macrocycle **4** with the benzyl protected bromomethyl catechol **8** followed by the deprotection of the catechol moieties.



Treatment of **5** with benzyl bromide in EtOH in the presence of K_2CO_3 afforded the protected aldehyde **6** in quantitative yield.[13] The latter was first reduced to the benzyl alcohol **7** by treatment with $LiAlH_4$ in THF[14] in 80 % yield and then converted in 98 % yield into the bromomethyl **8** by treatment with PBr_3 in THF.[14] The condensation of **8** with **4** in the presence of Et_3N in toluene afforded, after chromatography (Al_2O_3, CH_2Cl_2/MeOH : 98/2), the protected compound **3** as a colourless liquid in almost quantitative yield. The final product **2** was obtained by catalytic hydrogenation (Pd/C/EtOAc) of **3** in 92 % yield. The latter, probably due to the strong basic nature of its macrocyclic core promoting an intramolecular proton transfer from the catechol moieties to the tertiary amino groups and thus generating the catecholate ammonium zwitterion, was found to be extremely sensitive to oxidation and should be stored in the absence of oxygen.

Compound **2** may also be regarded as a binucleating ligand capable of binding two different cations. The binding by **2** of boron should lead to the negatively charged borocryptand **(2,B)**$^-$, a complex of the Böeseken type [15] found in boromycin[5] and in aplasmomycin[6]. This complex possessing a preorganised and suitable cavity should bind in its turn Li^+ cation affording thus the neutral lithium borocryptate **(2-B, Li)**. The binding ability of receptor **2** towards boron and lithium was indeed demonstrated by treating under argon the free ligand **2** with 1 eq of LiOH and 1 eq of $B(OH)_3$ in H_2O/EtOH mixture at room temperature affording the **(2-B, Li)** complex as a precipitate which was filtered and recrystallised from CH_2Cl_2/*i*Pr-ether mixture. The **(2-B, Li)** complex was perfectly stable towards oxidation and could be stored in the presence of oxygen. However, during the preparation of the latter, it was observed that if oxygen was not completely removed, the reaction afforded a pink precipitate resulting from the oxidation of the catechol moieties prior to the binding of boron. In the solid state, the inclusive nature of the **(2-B, Li)** borocryptate was demonstrated by an X-ray study of the crystals obtained from a CH_2Cl_2/*i*Pr-ether mixture.[16] As expected because of the tetrahedral coordination around boron, both R and S isomers are present in the unit cell (Fig. 1). The presence of enantiomers in solution has been previously demonstrated in the case of metalloborocryptates based on **1** by enantiomeric differentiation using NMR studies in chiral liquid crystalline phase.[17]

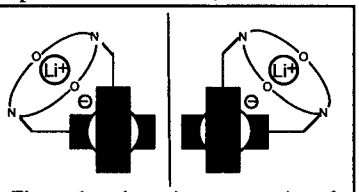


Figure 1 : schematic representation of both R and S enantiomers obtained upon complexation of boron in a tetrahedral coordination geometry by the ligand **2**.

The X-ray analysis of the racemate revealed the following features (Fig. 2): i) Li^+ is located within the cavity formed by the negatively charged **(2-B)**$^-$ borocryptand; ii) the coordination geometry around boron is tetrahedral with an average O-B-O angles of 109.5° with an average B-O distance of *ca* 1.48 Å; iii) both lone pairs of the two nitrogen atoms are oriented towards the interior of the cavity (in, in conformation) with an average N-Li^+ distance and a N-K^+-N angle of *ca* 2.39 Å and 133.4° respectively. iv) among the six oxygen atoms present in **2**, only four of them composed of the two ether junctions and two borate oxygen atoms are localised within a bonding distance of Li^+ (average B-O distance of ca 2.11 Å); v) in the **(2-B, Li)** complex, Li^+

is surrounded by four oxygen and two nitrogen atoms and the coordination polyhedron around Li^+ is irregular. Hexacoordination and distorted coordination sphere are not unusual for lithium[18]; vi) in comparison with the ([211], Li^+, Br^-) cryptate[19], for which average Li^+-O and Li^+-N distances of *ca* 2.13 Å and 2.29 Å respectively are obtained, in the case of (**2**-B, Li) complex, whereas the average Li^+-O distance of *ca* 2.11 Å is about the same, the average Li^+-N distance of *ca* 2.39 Å is significantly shorter.

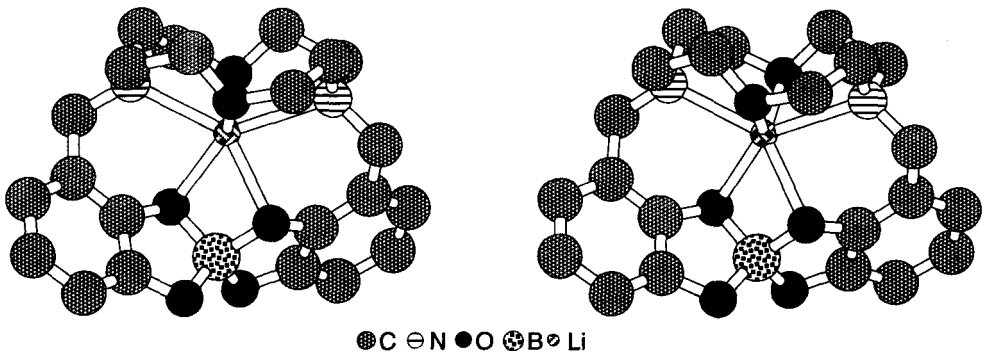


Figure 2 : Solide state structure of (**2**-B,Li) complex (stereoview of an arbitary isomer). For the sake of clarity, hydrogen atoms are not presented. Selected bond distances and angles : average B-O distance = 1.48 Å, average Li-N distance = 2.39 Å, average Li-O distance = 2.11 Å, average OBO angle 109.48°.

In solution, the binding ability of **2** towards boron and lithium cations was studied by ^1H- and ^{13}C-, ^7Li and ^{11}B-NMR spectroscopy in CD_2Cl_2. Whereas for the parent ligand **2** in the 2-4.5 ppm region two triplets at 3.12 and at 3.68 ppm for CH_2N and CH_2O respectively and one singlet at 4.18 ppm for the benzylic CH_2N protons were observed, for the Li-complex, dramatic changes occurred. In particular, the benzylic CH_2N protons gave rise to an AB quartet (Fig. 3). The presence of boron was established by ^{11}B-NMR (160 MHz, CD_2Cl_2, 25 °C) which revealed the presence of a signal at 16.21 ppm, whereas the presence of lithium was demonstrated by ^7Li-NMR (194 MHz, CD_2Cl_2, 25 °C) which showed a unique signal at -1.31 ppm. Since the proton chemical shift values for the (**2**-B, M) complexes were strongly dependent on the nature of the cation, binding of Na^+ was studied in DMSO by competition experiments which revealed that the binding affinity of $(\mathbf{2}\text{-B})^-$ was at least an order of magnitude higher for Li^+ than for Na^+.

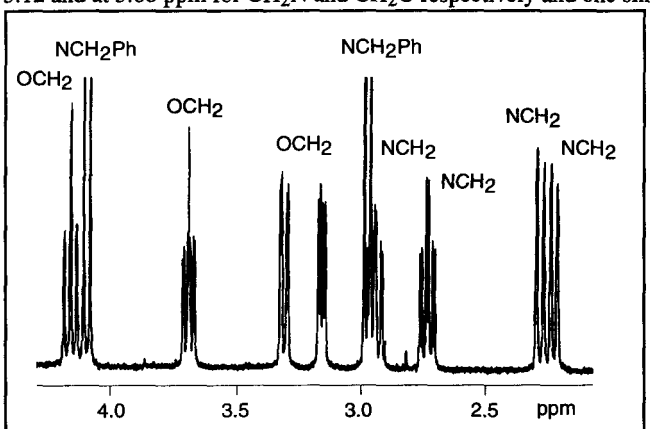


Figure 3 : selected region (2-4.5 ppm) of the ^1H-NMR (500 MHz, CD_2Cl_2, 25 °C) spectrum of (**2**-B, Li) complex. The signal assignement was based on two-dimensional NMR experiments.

In summary, high yield syntheses of **2** based on the [11] macrocyclic backbone bearing two catechol units was achieved. The binding ability of **2** towards both boron and lithium cations was established in solution by NMR spectroscopy and in the solid state by an X-ray study demonstrating the inclusive nature of the complex.

The use of the (**2**-B)$^-$ cryptand as lithium carrier is under current investigation. The enantiomeric differentiation by NMR of the (**2**-B, Li^+) complex in chiral liquid crystalline phase is under study.

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16. *X-ray data for* (**2**-B, Li) : $C_{23}H_{28}N_2O_6LiBCl_2$, M = 517.15, monoclinic, a = 13.610(5), b = 13.165(5), c = 15.113(7) Å, β = 113.13(1)°, U = 2490.0 $Å^3$, space group $P2_1/c$, Z = 4, Dc = 1.38 gcm^{-3}, μ(Cu-Kα) = 2.722 cm^{-1}, crystal dimensions 0.30x0.25x0.10 mm. Data were measured at 193K on a Philips PW1100 diffractometer with graphite monochromated Cu-Kα radiation. The structure was solved by direct methods and refined anisotropically using absorption corrected data to give R = 0.046, Rw = 0.066 for 2218 independent observed reflections [$|F_o| > 3\sigma(|F_o|$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
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