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Cryptands revisited
Design, synthesis, complexation behaviour and structural analysis of borocryptands

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Contents

Abstract

A new family of abiotic receptor molecules of the cryptand type (borocryptands) was designed by combining structural features of naturally occurring antibiotics such as boromycin and aplasmomycin and cryptands. Their binding ability towards alkaline metal cations was established both in solution and in the solid state. The binding ability of borocryptands was further expanded to the molecular recognition of NH_4^+ cationic molecule. Finally, enantiomeric differentiation of chiral borocryptates using NMR spectroscopy in a liquid crystalline medium was achieved. The chirality at the substrate, observed for the first time, was described as being induced by the structure of the receptor and mediated by the peristatic chirality of the cavity to the complexed substrate. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Alkaline metals; Borocryptand; Boron compounds; Chirality; Cryptand; Receptor

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1. Introduction

Since the discovery of the crown ethers by Pedersen [1,2] and of cryptands, in particular the [222] macrobicyclic ligand, by Lehn and coworkers [3,4], great efforts by inorganic, organic and physical chemists dealing with the design and binding ability of a large variety of synthetic host molecules have been reported [5–7]. Whereas at the outset much attention was focused on the selective binding of spherical alkaline and alkaline-earth monoatomic cations, considerable achievements have now been reported on the recognition of molecular cations [8–12].

The early design of cryptands [3,4,13,14] consisted in the construction of cage molecules able to bind cationic substrates within their cavity, thus leading to cryptates. Since the [222] cryptand is neutral, for the sake of charge neutrality, the cation cryptate is accompanied by a counter anion (Fig. 1). In order to overcome the problem associated with the presence of the counter anion, one can design cryptands bearing a negative charge within their framework. This design principle is found in boron containing antibiotics. Indeed, boromycin [Fig. 2(a)], an antibiotic produced

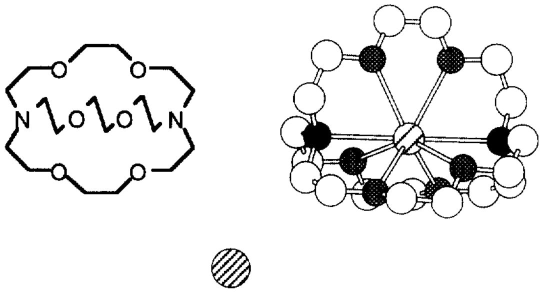
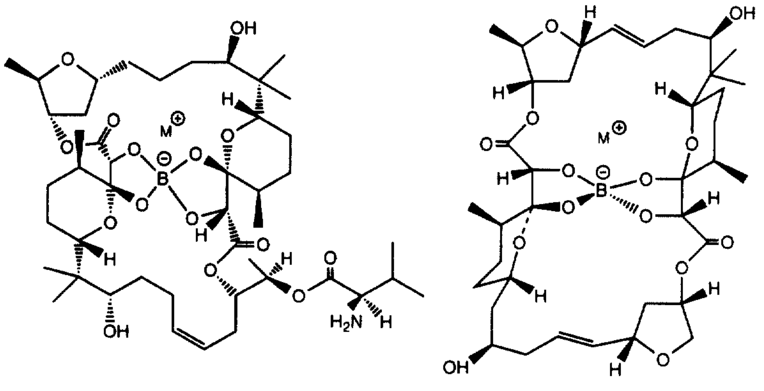


Fig. 1. Solid-state structure of (222) KI cryptate [15]. For the sake of clarity, hydrogen atoms are not presented.



a) b)

Fig. 2. Chemical formula of metal complexes of (a) boromycin and (b) aplasmomycin.

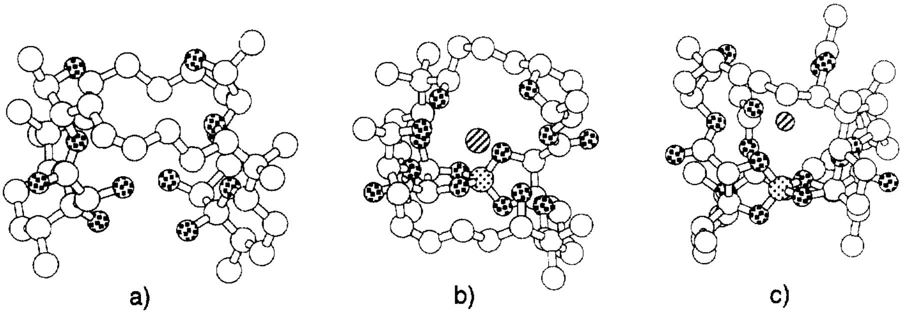


Fig. 3. Solid-state structure of boromycin: (a) free ligand; (b) boron and rubidium complex and (c) of boron and sodium complex of aplasmomycin. For the sake of clarity, hydrogen atoms are not presented.

by *Streptomyces antibioticus*, is the first known natural product containing a boron atom. The organic core of boromycin may be regarded as a tetradentate polyhydroxy macrolide capable of binding boron and presenting a molecular cleft bearing oxygen atoms. The first report on boromycin, isolated by Hütter et al., appeared in 1961 [16]. Later on, the structure of both the boron free *des*-valine-boromycin [17] [Fig. 3(a)] and of its boron and rubidium complex [Fig. 3(b)] have been elucidated by X-ray crystallography [18]. Aplasmomycin [Fig. 2(b)], produced by *Streptomyces griseus*, is another antibiotic containing a boron atom [19]. Its structure differs from boromycin by having two chemically identical subunits surrounding the borate complex. The solid state structure of sodium aplasmomycin complex [Fig. 3(c)] was also investigated [20]. When analysing both antibiotics in the spirit of coordination chemistry, both boromycin and aplasmomycin may be regarded as binucleating ligands.

The design and synthesis of binuclear complexes have been extensively studied over the past 20 years [21–23]. In these complexes, intrinsic molecular properties such as magnetic coupling, redox activity and optical features can be tuned with remarkable precision [24,25]. Although at an earlier period many homo- and heterobinuclear complexes reported were dealing essentially with the same type of metals, i.e. two alkaline or two transition metal cations, only recently has considerable effort been invested in the synthesis of heterobinuclear complexes engaging both hard alkaline or alkaline-earth and soft transition metal cations [26].

2. Design of borocryptands

Inspired by structural and chemical features of the above mentioned naturally occurring antibiotics and those of cryptands, our approach to the design of macrocyclic binucleating receptors **1**–**3** (Fig. 4) was based on the combination of a macrocyclic framework with tuneable size and two bidentate dianionic ligands [27,28]. For the preorganised macrocyclic core, the 12-membered ring diazadioxa **28** [13,14] and 18-membered ring diazatetraoxa macrocycle **8** [13,14] were considered because

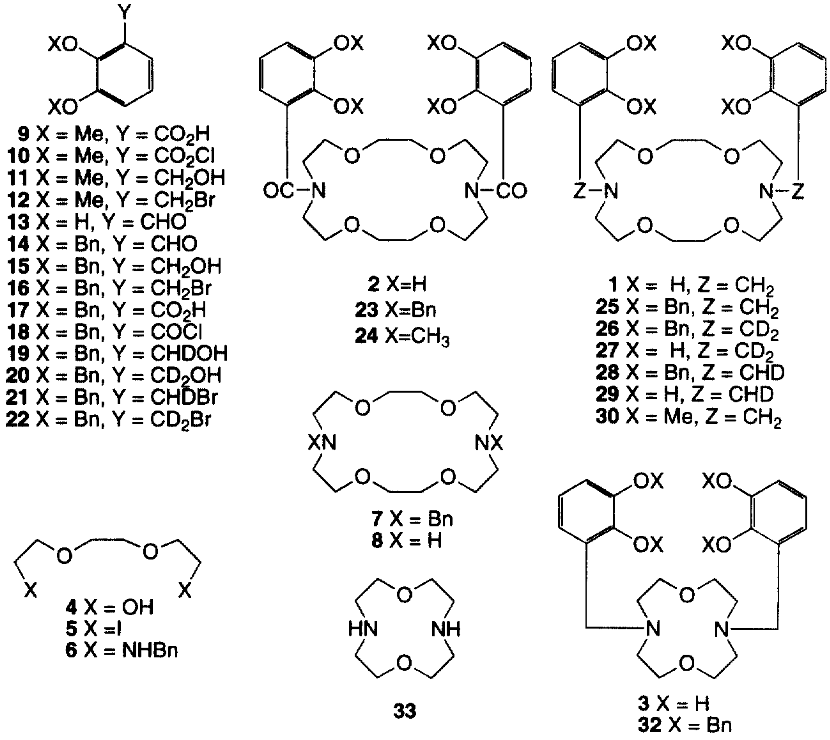


Fig. 4. Synthetic scheme for the preparation of ligands **1**–**3**.

of their ability to bind hard cations. A similar concept has been reported previously for podands and coronands bearing two catechol units linked by polyethylene glycol chains [29]. Combinations of amines and catechol affording analogues of siderophores have been studied extensively [30–36].

By analogy (Fig. 5) with boromycin and aplasmomycin, the macrocyclic moiety of the synthetic analogues should act as the cleft of oxygen atoms observed for the natural antibiotics. On the other hand, the glycol units present in the natural compounds can be replaced by bidentate ligands such as catechol, well known to bind transition metal cations. The linkage of the catechol moieties to the macrocyclic core could be achieved either using an amide bond or a methylene group. In the former case, the CO linkages impose rigidity and, thus, preorganise the receptor, but on the other hand strongly reduce the binding properties of the nitrogen atoms of the macrocyclic moiety, whereas in the latter case, the CH_2 groups should preserve the complexation ability of the two nitrogen atoms of the macrocycle but would render the ligand more flexible and, thus, less preorganised.

Due to the dianionic nature of the pendant catechols, in principle, the choice of appropriate oxidation states for both hard and soft metals, and their combination, should lead to neutral complexes (Fig. 6). It is worth noting that for receptors **1**–**3**, the binding of the transition metal M^{2+} or M^{3+} by the two catechol units would

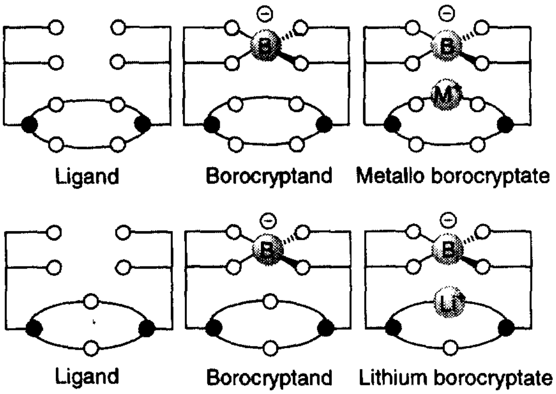


Fig. 5. Schematic representations of the free ligands **1** and **3**, and of their borocryptands and borocryptates.

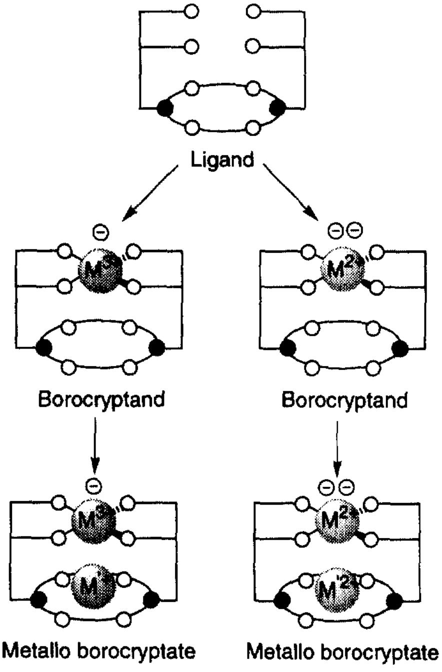


Fig. 6. Schematic representations of the formation of neutral inclusion complexes engaging the ligand **1** and (M^{3+}, M'^{+}) or (M^{2+}, M'^{2+}) couples.

lead to mono- or dianionic pseudo-cryptands, respectively, with enhanced binding ability towards the second metal cation M'^{+} or M'^{2+}. Dealing with the coordination geometry around the transition metal cation, ligands **1**–**3** should in principle accommodate both square planar and tetrahedral geometries. In order to obtain neutral complexes, all three ligands **1**–**3** were designed to bind simultaneously a combination of (M'^{+}, M^{3+}) or (M'^{2+}, M^{2+}) cations. For the ligands **1** and **2**, in the first combination, alkaline metal mono cations (Li^{+}, Na^{+}, K^{+}, Rb^{+}, Cs^{+}), complexed within the macrocyclic core of the ligand, can be combined with M^{3+} cations such as B^{3+} and Al^{3+} coordinated to pendant catechol units. For the second combination, alkaline-earth dications (Be^{2+}, Mg^{2+}, Ca^{2+}, Ba^{2+}) and dicationic transition metals such as Ni^{2+}, Cu^{2+}, Zn^{2+} can be associated. In the case of ligand **3**, combinations such as Li^{+} and B^{3+} or Al^{3+} might be expected.

Compounds **1**–**3** can also be regarded as binucleating ligands capable of binding two cations (Fig. 5). Indeed, the binding by X^{4-} (X=**1**–**3**) of a main group element Y (Y=B^{3+} or Al^{3+}) leads to the negatively charged pseudo-cryptand (X^{4-}, Y^{3+}), a complex of the Böeseken type [37]. In turn, this complex binds an alkaline cation M^{+} affording the neutral pseudo-cryptate (X^{4-}, Y^{3+}, M^{+}). The driving force for the formation of these complexes is attractive charge–charge and charge–dipole interactions.

3. Synthesis of borocryptands

The synthetic strategy for the preparation of **1** and **2** was based on the coupling of either the acyl chloride or bromomethyl derivatives of protected catechol with the diazatetraoxa macrocycle **8** (Fig. 4) [27]. The synthesis of the latter was achieved in four steps starting from the commercially available 1,2-bis(2-chloroethoxy)ethane **4** following published procedures [38]. Compound **4** was first transformed into the diiodo compound **5**. The latter was condensed with benzylamine to give the protected diamino compound **6**. Condensation of the latter with the diiodo **5** afforded the protected macrocycle **7** which was deprotected by catalytic hydrogenation (H_2/Pd/C) affording the desired compound **8**.

In a first attempt to prepare **1** and **2**, the methyl-protected catechols **10** and **12** were used [27]. For the preparation of **2**, commercially available 2,3-dimethoxybenzoic acid **9** was converted into acid chloride **10** by treatment with $SOCl_2$ [39]. Reaction of the latter with **8** in dry THF in the presence of Et_3N afforded the desired compound **24**. For the synthesis of **1**, alcohol **11** was first transformed into its bromo derivative **12** by treatment with Br_2 in the presence of PPh_3 in DMF [40]. Condensation of **12** with **8** in CH_2Cl_2 at −5 °C afforded **30**. Unfortunately for both final compounds **24** and **30**, the removal of the methyl protective groups using the standard BBr_3 method [41,42] was unsuccessful. Finally, using PPh_2Li [43] as specific deprotecting agent, both compounds **1** and **2** could be obtained. However, since the purification of the desired compounds in the final step appeared to be rather tedious, the route using the benzyl protecting group (Bn) was investigated. Treatment of 2,3-dihydroxybenzaldehyde **13** with benzyl bromide in EtOH in the presence of K_2CO_3 afforded the protected aldehyde **14** in quantitative yield. The latter was the common intermediate for the synthesis of the benzyl bromide **16** and the acyl chloride **18**. Indeed, oxidation [44] at RT of **14** by $NaClO_2$ in the presence of H_2NSO_3H in a 1/1 acetone/water mixture afforded acid **17**, which was further converted into its acyl chloride **18** by treatment with $SOCl_2$ in DMF [44]. Aldehyde

14 was reduced to the benzyl alcohol **15** by treatment with $LiAlH_4$ in THF [45]. The latter was converted into bromomethyl **17** by treatment with PBr_3 in THF [45]. Condensation of **18** with **8** in the presence of Et_3N in toluene afforded protected product **23**. Reaction of **16** with **8** in the presence of Et_3N in toluene afforded **25**. Final products **1** and **2** were obtained by catalytic (Pd/C) hydrogenation of **23** and **25**, respectively.

Dealing with the synthesis of deuterated compounds **27** and **29**, again the common starting material was the protected aldehyde **14**. Reduction of the latter using $LiAlD_4$ afforded monodeuterated alcohol **19**, whereas the reduction of the acid **17** using the same agent gave dideuterated **20**. Both alcohols **19** and **20** were first brominated, affording compounds **21** and **22**. Following the same procedure as for macrocycle **1**, ligands **27** and **29** were obtained [46].

The amide containing ligand **2** was soluble in DMSO and in alkaline water and rather insoluble in $CHCl_3$, whereas amine-containing receptor **1** was soluble in organic solvents such as CH_2Cl_2, $CHCl_3$, DMF and CH_3CN and in both acidic and alkaline water solutions.

The synthesis of compound **3** was achieved by condensing the commercially available [1, 1] macrocycle **33** with benzyl-protected bromomethyl catechol **6** followed by the deprotection of the catechol moieties [28]. Compound **3**, because of an intramolecular proton transfer from the catechol moieties to the tertiary amino groups, thus generating the catecholate ammonium zwitterion, was found to be extremely sensitive to oxidation.

4. Binding of alkaline metal cations by borocryptand 1 [47]

Treatment of **1** in EtOH with 1 equiv. $B(OH)_3$ and 1 equiv. MOH (M = Li, Na, K, Rb, Cs) in H_2O at room temperature leads exclusively to the formation of the ($\mathbf{1}^{4-}$, B^{3+}, M^+) complexes. A single recrystallisation of the raw material affords the pure binuclear complex. The ($\mathbf{1}^{4-}$, B^{3+}, M^+) complexes were found to be chemically stable even in a solvolyzing solvent such as CD_3OD or H_2O. No alteration of their ^1H spectrum was detected over a several week period.

The binding ability of ($\mathbf{1}^{4-}$, B^{3+}) towards alkaline cations was studied by ^1H NMR spectroscopy in $CDCl_3$ and in CD_3OD. Since the chemical shift values appeared to be strongly dependent on the nature of the cation complexed in the cavity, the binding studies could be conveniently monitored by NMR. Furthermore, the binding ability of ($\mathbf{1}^{4-}$, B^{3+}) towards alkaline cations was also studied by ^{23}Na NMR spectroscopy which revealed in CD_3OD a slow exchange process between the free and the complexed Na^+ at 25 °C ($T_c = 55$ °C, $K_c = 2.7 \times 10^3\ s^{-1}$, $\Delta G^{\#} = 15.5$ kcal mol^{-1}).

Based on competition experiments, followed by ^1H and ^{23}Na NMR spectroscopy, the binding constant for the ($\mathbf{1}^{4-}$, B^{3+}, K^+) complex was estimated to be ca. $10^{12.5}$ mol l^{-1} in methanol. This value appeared to be the highest ever observed for a potassium synthetic complexing agent. Selectivity factors between K^+ and both Na^+ and Cs^+ cations greater than 10^3 and 10^2, respectively, were determined. The

(1^{4-}, B^{3+}, K^+) complex was also shown to be more stable by a factor of 10^2 than the ([222], K^+) complex.

5. Solid state structural analysis of borocryptates [15]

In the crystalline phase, the free ligand **1** [Fig. 7(a)] and its (1^{4-}, B^{3+}, M^+) complexes with $M^+ = K^+$ [Fig. 7(b)], Rb^+ [Fig. 7(c)], Cs^+ [Fig. 7(d)] were studied by X-ray diffraction methods which confirmed the proposed structures. In all three cases, as expected because of the tetrahedral coordination around boron, both R and S isomers were present in the unit cell (Fig. 8). The cation M^+ (K^+, Rb^+, Cs^+) was indeed located within the cavity formed by the negatively charged borocryptand (1^{4-}, B^{3+}).

For each complex, the lone pairs of both nitrogen atoms were oriented towards the interior of the cavity (in, in conformation). The N–N distances of ca. 6.27 Å were almost the same for all three complexes. The observed average distance of ca.

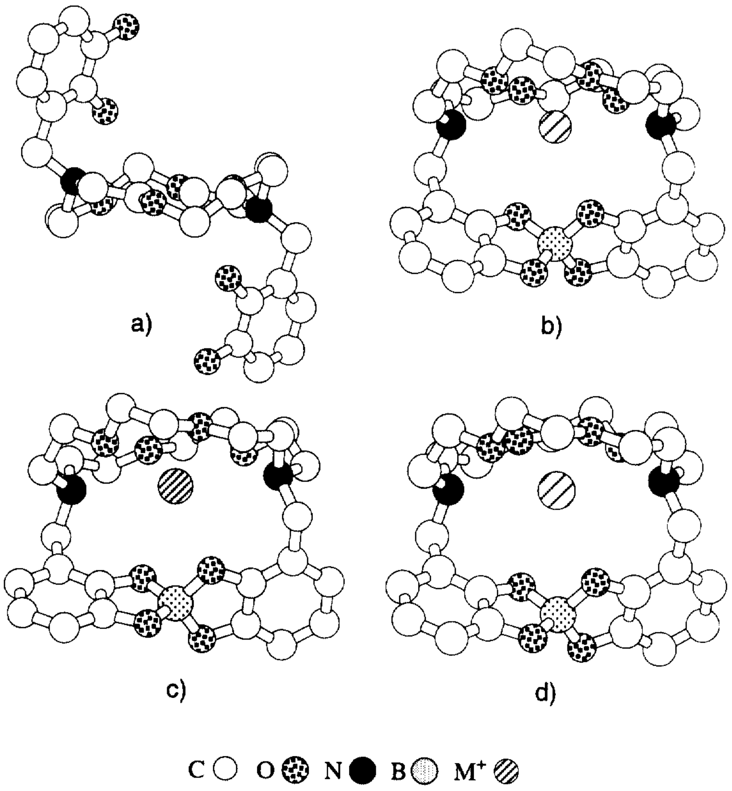


Fig. 7. Solid state structure of (1^{4-}, B^{3+}, M^+) complex (arbitrary isomer). (a) Free ligand; (b) $M = K^+$; (c) $M = Rb^+$; (d) $M = Cs^+$. For the sake of clarity, hydrogen atoms are not presented.

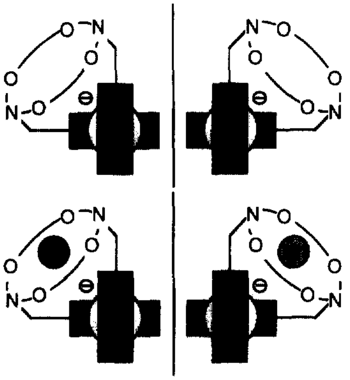


Fig. 8. Schematic representation of chirality due to the spiroborate junction in the borocryptand **1**.

6.27 Å was longer than the N–N distances of 5.75 Å, ca. 6.00 Å and ca. 6.06 Å observed for ([222], K^+), ([222], Rb^+) and ([222], Cs^+) complexes, respectively [48]. The cation M^+ was almost located at equal distances from the two bridgehead nitrogen atoms. In marked contrast with the ([222], M^+) cryptate, for ($\mathbf{1}^{4-}$, B^{3+}, M^+) the N–M^+ distance varies only slightly from an average distance of ca. 3.15 Å. This distance is considerably longer than the N–M^+ distances of 2.87 Å, ca. 3.00 Å and ca. 3.03 Å observed for ([222], K^+), ([222], Rb^+) and ([222], Cs^+) complexes, respectively [48].

Among the eight oxygen atoms present in ($\mathbf{1}^{4-}$, B^{3+}, M^+) complexes, only six of them composed of the four ether junctions and two borate oxygen atoms were localised within a bonding distance of M^+ (average distance ca. 2.82 Å for K^+, ca. 2.89 Å for Rb^+, ca. 2.98 Å for Cs^+). For all three complexes the metal cation M^+ is surrounded by six oxygen and two nitrogen atoms with irregular coordination polyhedrons around M^+. In contrast with the ([222], M^+) complexes in which the cation, located almost in the centre of the cage, interacts with all heteroatoms, in the case of ($\mathbf{1}^{4-}$, B^{3+}, M^+), the average M^+–O distances were considerably shorter than the average M^+–N distances. This was an indication of stronger attractive interactions between the metal cation and oxygen atoms within bonding distances than with the two nitrogen atoms. Whereas for ([222], M^+) complexes, the N–M–N angle was almost 180°, in the case of ($\mathbf{1}^{4-}$, B^{3+}, M^+), this value dropped from 177° for K^+ to 176° for Rb^+ and to 174° for Cs^+.

The coordination geometry around boron was indeed tetrahedral. The B–O distances were close to 1.48 Å. The O–B–O angles, due to the rather rigid structure of the catecholate units, varied from 104° to 114°, indicating a slight deformation of the tetrahedron, whereas the average values for all three structures remained almost identical.

As expected, the increase in the average M–O distance from 2.82 Å for K^+ to 2.89 Å for Rb^+ and to 2.98 Å for Cs^+ paralleled the enhancement of the ionic radii of the alkaline cations.

6. Lithium borocryptate [28]

Due to the role played by lithium in science, medicine and technology [49], the design of a Li-selective complexing agent is still an active area of research. Complexation of lithium by a variety of synthetic receptor molecules has been investigated [50]. Among many structural features screened, cryptands [7–11] and spherands [6,8–11] appeared to be the most appropriate and selective receptors for lithium. As presented above, the early design of borocryptand was based on the double functionalisation, at both nitrogen centres, of the [2,2] macrocyclic core by two catechol units leading to the receptor molecule **1**. As a consequence of the size of its cavity, the binding ability of the borocryptand ($\mathbf{1}^{4-}$, B^{3+}) appeared to be extremely high for K^+ and rather low for Li^+. In order to obtain the reverse selectivity sequence, ligand **3** was prepared (Fig. 4). The design of **3** as a precursor of a selective lithium receptor is based on shrinking the size of the borocryptand cavity. This can be achieved, while maintaining the catechol moieties as the boron binding sites, by the use of the [1,1] macrocycle **28** instead of the [2,2] macrocycle **8** present in **1** (Fig. 5). 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 ($\mathbf{3}^{4-}$, B^{3+}) can be regarded as an analogue of the neutral [211] cryptand which has been shown to form a stable inclusion complex with lithium (Fig. 9).

The ($\mathbf{3}^{4-}$, B^{3+}, Li^+) complex was obtained as a precipitate upon treatment, under argon, of free ligand **3** with 1 equiv. LiOH and 1 equiv. $B(OH)_3$ in an H_2O/EtOH mixture at room temperature. The pure ($\mathbf{3}^{4-}$, B^{3+}, Li^+) complex, obtained by recrystallisation from CH_2Cl_2/*i*Pr–ether mixture, was stable towards oxidation and could be stored in the presence of oxygen.

The binding ability of **3** towards boron and lithium cations was studied by ^1H and ^{13}C, ^7Li and ^{11}B NMR spectroscopy in CD_2Cl_2. The presence of boron was established by ^{11}B NMR which revealed the presence of a signal at 16.21 ppm, whereas the presence of lithium was demonstrated by ^7Li NMR which showed a unique signal at −1.31 ppm. Since the proton chemical shift values for the ($\mathbf{3}^{4-}$, B^{3+}, Li^+) complexes were strongly dependent on the nature of the cation,

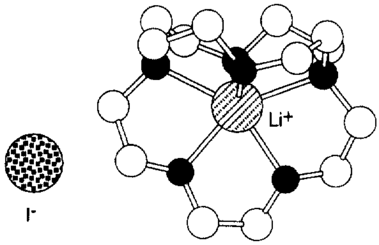


Fig. 9. Solid state structure of (211) LiI cryptate [51]. For the sake of clarity, hydrogen atoms are not presented.

complexation of Na^+ was studied in DMSO by competition experiments which revealed that the binding affinity of (3^{4-}, B^{3+}) was at least an order of magnitude higher for Li^+ than for Na^+.

In the solid state, the inclusive nature of the (3^{4-}, B^{3+}, Li^+) borocryptate was demonstrated by an X-ray study (Fig. 10). As expected because of the tetrahedral coordination around boron, both R and S isomers (Fig. 8) were present in the unit cell. The X-ray analysis of the racemate revealed the following features: (i) Li^+ is located within the cavity formed by the negatively charged (3^{4-}, B^{3+}, Li^+) borocryptand; (ii) the coordination geometry around boron was tetrahedral with an average O–B–O angle of 109.5° and an average B–O distance of ca. 1.48 Å; (iii) both lone pairs of the two nitrogen atoms were oriented towards the interior of the cavity (in, in conformation) with an average N–Li^+ distance and N–K^+–N angle of ca. 2.39 Å and 133.4°, respectively; (iv) among the six oxygen atoms present in (3^{4-}, B^{3+}), only four of them composed of the two ether junctions and two borate oxygen atoms were localised within bonding distances of Li^+ (average B–O distance of ca. 2.11 Å); (v) Li^+ was surrounded by four oxygen and two nitrogen atoms and the coordination polyhedron around Li^+ was irregular — hexacoordination and distorted coordination sphere are not unusual for lithium [51]; (vi) in comparison with the ([211], Li^+, I^-) cryptate [52], 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 (3^{4-}, B^{3+}, Li^+) complex, whereas the average Li^+–O distance of ca. 2.11 Å was about the same, the average Li^+–N distance of ca. 2.39 Å was significantly shorter.

7. Ammonium borocryptate [53]

Due to the fundamental importance of ammonium cations in living organisms, molecular recognition of these organic cations has been widely investigated over the past 25 years [54,55]. Although many thermodynamic measurements are available for ammonium complexes [50], only few structural data in the solid state have been reported. In particular, only a small number of structural analyses dealing with the binding of the simplest ammonium cation, i.e. NH_4^+, by crown ethers [56–61], macrobicyclic [62] and macrotricyclic [63,64] cryptands and by antibiotics such as

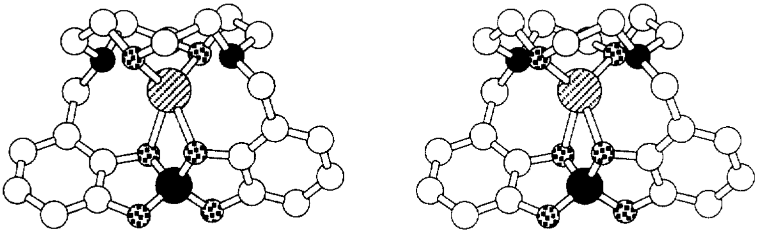


Fig. 10. Solid state structure of (3^{4-}, B^{3+}, Li^+) complex (stereo view of an arbitrary isomer). For the sake of clarity, hydrogen atoms are not presented. Selected bond distances and angles: average B–O distance 1.48 Å, average Li–N distance 2.39 Å, average Li–O distance 2.11 Å, average OBO angle 109.48°.

nonactin [65] and tetranactin [66] have been published. It is worth noting that all of the above mentioned ligands, except the crown ether bearing a *p*-nitrophenate moiety [59] are neutral ligands and the complexation of the cation is associated with the presence of a counter anion.

Treatment of **1** in EtOH with 1 equiv. $B(OH)_3$ and 1 equiv. aqueous NH_3 in an H_2O/EtOH mixture at room temperature leads exclusively to the formation of the ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) complex. A single recrystallization of the raw material affords the pure complex. The complex ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) was shown to be chemically stable. Indeed, even in a solvolyzing solvent such as CD_3OH or H_2O, no alteration of its ^1H spectrum was detected over several weeks [53].

In solution, the presence of boron was again confirmed by ^{11}B NMR spectroscopy which showed a single signal at 12.68 ppm. In $CDCl_3$ and in CD_3OD the binding features of ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) were also studied using ^1H NMR spectroscopy by monitoring spectral changes induced upon addition of alkaline cations to a solution of the ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) complex. Competition experiments between ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) and Na^+ in CD_3OD revealed a selectivity of ca. 40 in favour of NH_4^+. On the other hand, addition of 1.1 equiv. KI to a CD_3OD solution of ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) caused the complete removal of NH_4^+ and its substitution by K^+, indicating a much higher affinity for the latter. Dealing with NH_4^+ vs. Cs^+, the same type of competition experiments revealed a selectivity factor of ca. 100 in favour of NH_4^+. Finally, competition experiments in $CDCl_3$ with [222] cryptand indicated that ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) was more stable than the ([222], NH_4^+) cryptate by at least three orders of magnitude. In CD_3OD the following selectivity sequence $K^+ \gg NH_4^+ > Na^+ = Cs^+$ for cation binding was observed.

In the solid state, the inclusive nature of the NH_4^+ complex ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) was demonstrated by an X-ray study (Fig. 11). Again, as expected because of the tetrahedral coordination around boron, both R and S isomers were present in the unit cell (Fig. 8). The X-ray analysis of the racemate revealed the following features: (i) a slightly deformed tetrahedral geometry around boron with OBO angles varying from 104.2° to 112.9° (average 109.5°) and an average B–O distance of ca. 1.47 Å; (ii) since all four protons around the nitrogen atom of the substrate were localised, the bond distance analysis revealed that the substrate was indeed the NH_4^+ cation. The coordination geometry around the nitrogen atom of the substrate was a distorted

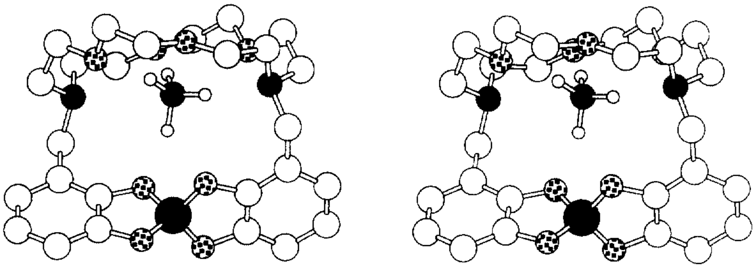


Fig. 11. Solid state structure of ($\mathit{1}^{4-}$, B^{3+}, NH_4^+) complex (stereo view of an arbitrary isomer). For the sake of clarity, hydrogen atoms, except those belonging to the substrate, are not presented.

tetrahedron with an average N–H distance of ca. 1.07 Å and an average HNH angle of ca. 109.6° (HNH angle values varied from 103.2° to 122.4°); (iii) both lone pairs of the two bridgehead nitrogen atoms are oriented towards the interior of the cavity (in, in conformation); (iv) the NH_4^+ cation is located within the cavity formed by the negatively charged cryptand; (v) the nitrogen atom of the NH_4^+ cation is located almost at equal distances from the two bridgehead nitrogen atoms ($N1–N^+$ and $N10–N^+$ 3.126 Å and 3.072 Å, respectively, $N–N^+–N$ angle 178°); (vi) in the complex (*1*$^{4-}$, B^{3+}, NH_4^+), the NH_4^+ cation is surrounded by three oxygen atoms (average $N^+–O$ distance of ca. 2.87 Å, average N^+HO angle of ca. 165.6°) and one nitrogen atom ($N^+–N$ distance of 3.07 Å, N^+HN angle of 166.5°) leading to tetrahedral coordination around the molecular cation. Thus, as in the case of the ([222], NH_4^+) complex, the eight oxygen atoms present in (*1*$^{4-}$, B^{3+}, NH_4^+), only three of them composed of the two ether junctions and one borate oxygen atom, were localised within a bonding distance of NH_4^+.

8. Peristatic chirality of borocryptates [67]

For more than a century, chemists have been continuously dealing with chirality, which appears to be one of the most subtle aspects of chemistry [68]. On the one hand, synthetic chemists use their skill to prepare chemical objects presenting either established [69] or new types of chirality [70]. On the other hand, physical chemists develop methods allowing us to measure chirality. Amongst the various physical methods allowing us to study chirality, NMR spectroscopy appears to be one of the most useful techniques [71]. In particular, NMR spectroscopy in oriented nematic phases has been shown to be a powerful method for differentiation of enantiomers [72–75].

With respect to chirality, the binding of boron by **1** with a tetrahedral coordination geometry affords the chiral borocryptand (**1**$^{4-}$, B^{3+}) (Fig. 8). The latter, upon complexation of the alkali metal cations, leads to chiral cryptates (**1**$^{4-}$, B^{3+}, M^+). As stated above, the X-ray analysis of K^+, Rb^+, Cs^+ and NH_4^+ complexes revealed the presence of both R and S enantiomers as a racemic mixture in the solid state. For the free cryptand (**1**$^{4-}$, B^{3+}) the chirality of the enantiomorphic type (R and S) is inherent to its structural connectivity pattern, whereas for the labile and exchangeable complexed alkali metal cation the chirality is imposed by the chiral cavity of the receptor through non-covalent interactions and is therefore not inherent and can be described as peristatic chirality [76] (peristasis = environment).

For the chiral borocryptate (**1**$^{4-}$, B^{3+}, M^+), the receptor part (**1**$^{4-}$, B^{3+}) contains, in addition to the more classical ^1H and ^{13}C NMR active nuclei, both ^{10}B ($I=3$) and ^{11}B ($I=3/2$) possessing quadrupolar moments. The complexed alkaline metal cations, also being NMR active and possessing a quadrupolar moment, can be studied by the same technique.

Enantiomeric differentiation of chiral molecules has been demonstrated using NMR spectroscopy in oriented chiral liquid crystals [72], in particular in a poly(γ-benzyl-L-glutamate) (PBLG)/CH_2Cl_2 (11–12% w/w) mixture [73] forming cholesteric lyotropic mesophases [74]. Based on reported results for aminoacids, the enantiomeric differentiation for the (1^{4-}, B^{3+}, M^{+}) complexes could be studied in a poly(γ-benzyl-L-glutamate) (PBLG)/CH_2Cl_2 (11–12% w/w) mixture, both at the level of the receptor (1^{4-}, B^{3+}) and the substrate by combining the NMR data collected for the receptor (^{10}B, ^{11}B) and for the cationic substrates (^{133}Cs and ^{14}N) [67].

The ^{10}B NMR ($I=3$) spectrum of the (1^{4-}, B^{3+}, Cs^{+}) complex [Fig. 12(a)] could be decomposed as two sets of signals [Fig. 12(b) and (c)] with a 1/1 ratio as expected for a racemic mixture. The two distinct signals were due to both enantiomers. For one of the enantiomers [Fig. 12(b)], the signal was a broad singlet, while the signal for the other enantiomer appeared as a sextet with values of 221.6 Hz and 73.3 Hz for the quadrupolar splitting (ν_Q) and $\Delta n_{1/2}$, respectively [Fig. 12(c)].

The (1^{4-}, B^{3+}, Cs^{+}) complex was also studied by ^{11}B NMR ($I=3/2$). Again, the observed spectrum [Fig. 12(d)] could be decomposed as a broad signal [Fig. 12(e)] and a triplet with $\nu_Q=503.2$ Hz and $\Delta\nu_{1/2}=48.7$ Hz [Fig. 2(f)].

Interestingly, when investigating the (1^{4-}, B^{3+}, Cs^{+}) complex by ^{133}Cs NMR ($I=7/2$), the observed spectrum [Fig. 12(g)] was also composed of two sets of signals corresponding to both enantiomers. The spectrum could be decomposed as two septets, one with a small quadrupolar splitting constant ($\nu_{Q1}=73.0$ Hz, $\Delta\nu_{1/2}=$

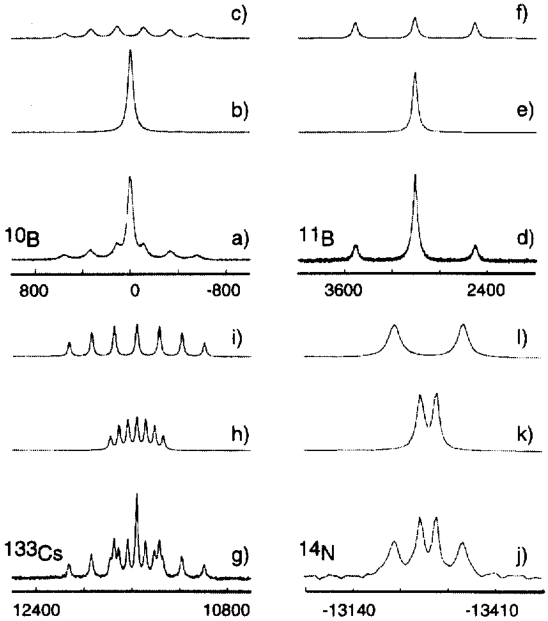


Fig. 12. NMR spectra of (1^{4-}, B^{3+}, Cs^{+}) complex in chiral liquid crystalline solvent: ^{10}B (53.73 MHz) observed (a), decomposed signals for both enantiomers (b, c); ^{11}B (160.42 MHz) observed (d), decomposed signals for both enantiomers (e, f); ^{133}Cs (65.58 MHz) observed (g), decomposed signals for both enantiomers (h, i); ^{14}N (36.12 MHz) observed (j), decomposed signals for both enantiomers (k, l).

25.0 Hz) [Fig. 12(h)] and one with a larger quadrupolar splitting constant ($\nu_{Q2}=188.2$ Hz, $\Delta\nu_{1/2}=28.7$ Hz) [Fig. 12(i)].

As stated above, the binding ability of ($\mathbf{1}^{4-}$, B^{3+}) towards molecular cations such as NH_4^+ has been established previously by an X-ray study [17]. The (1^{4-}, B^{3+}, NH_4^+) complex was investigated by ^{10}B, ^{11}B and ^{14}N NMR. For ^{10}B, NMR observations were similar to those obtained for the ($\mathbf{1}^{4-}$, B^{3+}, Cs^+) complex ($\nu_{Q1}=120.0$ Hz, $\Delta\nu_{1/2}=55.1$ Hz). However, for ^{11}B the observed spectrum appeared to be a superimposition of two triplets of the same ratio with $\nu_{Q1}=66.7$ Hz and $\nu_{Q2}=293.2$ Hz corresponding to both enantiomers.

For ^{14}N NMR ($I=1$), probably due to the unsymmetrical environment around the two bridgehead nitrogen atoms leading to large quadrupolar interactions, the amino groups could not be observed. However, the signal for the symmetrical NH_4^+ substrate could be observed [Fig. 12(j)] as a superimposition of two doublets with a 1/1 ratio [Fig. 12(k)Fig. 12(l)]. Again, the two enantiomers were differentiated by a large ($\nu_{Q1}=128.7$ Hz, $\Delta\nu_{1/2}=18.0$ Hz) and a small ($\nu_{Q2}=30.7$ Hz, $\Delta\nu_{1/2}=6.0$ Hz) quadrupolar splitting constant.

Although enantiomeric differentiation of chiral molecules based on NMR studies in liquid crystalline medium was elegantly demonstrated by Courtieu and coworkers [72,73] using different NMR probes carried both by the receptor and by the substrate, we were able to detect for the first time, on different locations of the complex molecule, the chirality of the ensemble. Based on our observations, we described the observed chirality at the cationic site as induced by the spiroborate junction and mediated by the peristatic chirality of the cavity.

9. Conclusion

Based on structural features of naturally occurring antibiotics such as boromycin and aplasmomycin and cryptands, a new family of abiotic receptor molecules named borocryptands was designed. The binding ability of borocryptands towards alkaline metal cations was established in solution by various NMR studies and in the solid state by X-ray diffraction. To our knowledge, both the estimated binding constant of ca. $10^{12.5}$ mol l^{-1} for the potassium borocryptate in methanol and the selectivity factor between K^+ and both Na^+ and Cs^+ cations greater than 10^3 and 10^2, respectively, were the highest values obtained this far for artificial K^+ receptors. Following the same path, upon tuning the size of the cavity of the borocryptand by using a smaller macrocyclic unit, a lithium selective complexing agent was obtained. The binding ability of borocryptands was further expanded to the molecular recognition of NH_4^+ cationic molecule. The following selectivity sequence of $NH_4^+ > Na^+ > Cs^+$ in CD_3OD could be established. The NH_4^+ inclusion borocryptate appeared to be more stable, by at least three orders of magnitude, than the ([222], NH_4^+) complex. Finally, enantiomeric differentiation of chiral borocryptates using NMR spectroscopy in liquid crystalline medium was achieved using different NMR probes localised both on the receptor and on the substrate. The chirality at the substrate, observed for the first time, was described as being induced by the structure of the receptor and mediated by the peristatic chirality of the cavity to the complexed substrate.

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