Pergamon

Tetrahedron Letters 39 (1998) 3501-3504

TETRAHEDRON
LETTERS

Deuterium Labelled Borocryptands : Synthesis, Structural Analysis and Binding Studies

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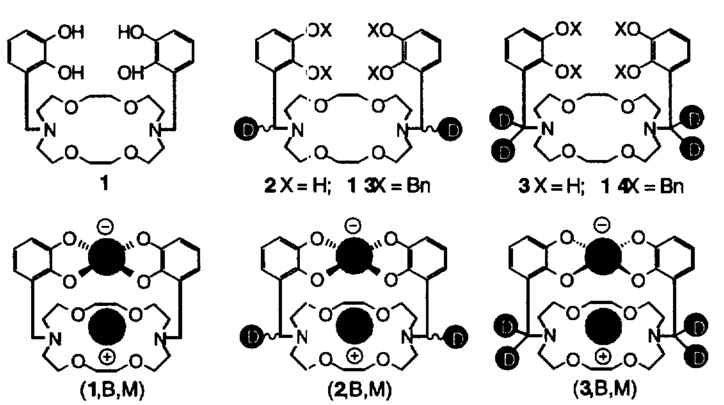
Received 24 February 1998; accepted 17 March 1998

Abstract: High yield syntheses of two new deuterium labelled compound **2** and **3** based on the [22] macrocyclic backbone bearing two catechol units was achieved. The solid state structure of the tetradeuterated compound **3** was elucidated by X-ray diffraction methods. The binding ability of **2** and **3** towards both boron and alkaline metal cations was established in solution by ^{1}H-, ^{2}D- and ^{11}B-NMR spectroscopy.

Boromycin[1a], aplasmomycin[1b], borophycin[1c] and tartrolon[1d] form a rather intriguing class of naturally occurring antibiotics. These compounds upon binding a boron atom forme a spiroborate junction bearing thus a negatively charged cavity capable of complexing alkaline metal cations. The nature of some of the inclusive complexes has been demonstrated in the solid state by X-ray analysis.[1c, 2]

Based on a combination of structural and functional features of boromycin[1a] and of cryptands[3], we have designed borocryptands as a new class of receptors for alkaline metal cations.[4-8] These ligands are based on polyaza-polyoxa macrocyclic cores of variable size bearing two bidentate catecholate units. Polyethyleneglycols[9], macrocyclic polyaza compounds[10], calix[4]arene[11] and porphyrins[12] bearing catechol units have been reported.



Scheme 1

The simultaneous binding of B and alkaline metal [5-7] as well as ammonium[8] cations by receptors such as **1** was demonstrated both in solution and in the solid state (scheme 1). The borocryptand resulting from the binding of B(III) by **1** appeared to be the most powerful synthetic complexing agent for potassium.[5] As expected, and previously observed in the solid state, upon binding, in the tetrahedral coordination geometry, of B by both catechol units of **1** and analogues a racemic mixture of R and S isomers are obtained.[5-8] It is worth noting that whereas the free cryptands (X,B)$^-$; X = **1-3**

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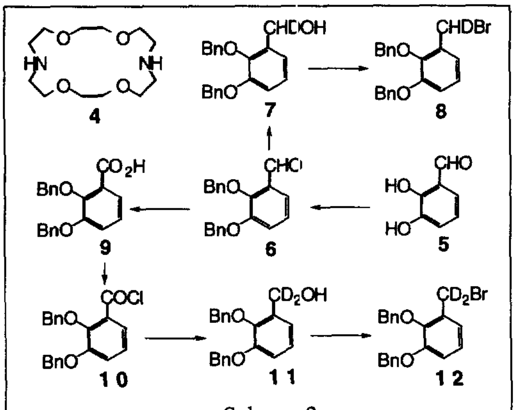
PII: S0040-4039(98)00610-8

possess an inherent chirality, for the labile and exchangeable complexed alkali metal cations, the chirality is of the peristatic (peristasis = environment)[13] type since it is imposed by the chiral cavity of the receptor through non covalent interactions. This type of chirality has been recently demonstrated in solution by enantiomeric differentiation using NMR studies on quadrupolar nuclei in chiral liquid crystalline phase.[14] In order to further investigate this type of chirality as well as complexation processes by NMR, the synthesis of the di- (compound **2**) and tetra-deuterated (compound **3**) and their binding ability were studied. In terms of synthetic ease, the most appropriate centres to introduce deuterium atoms within the backbone of the ligand **1** appeared to be the benzylic positions. The deuteration could be achieved using $LiAlD_4$ by the reduction of either the aldehyde **6** or the acylchloride **10** derivatives of the protected catechol. In the case of the ligand **2**, the introduction of isotopic chirality at both benzylic positions may be also of interest for further investigation. The synthetic strategy for the preparation of **2** and **3** was based on the coupling of deuterium labelled compounds **8** and **12** with the diazatetraoxa macrocycle **4** (scheme 2). The latter was prepared in four steps following published procedures.[15] Treatment of 2,3-benzaldehyde **5** with benzyl bromide in EtOH in the presence of K_2CO_3 afforded the protected aldehyde **6** in quantitative yield.[16] The latter was the common intermediate for the synthesis of both **2** and **3**. Upon direct treatment of the aldehyde **6** by $LiAlD_4$ in THF, the monodeuterated **7** was obtained in 78 % yield as a mixture of enantiomers. The latter was converted in 92 % yield into **8** by treatment with PBr_3 in THF.[17] On the other hand, the oxidation[16] at r. t. of **6** by $NaClO_2$ in the presence of H_2NSO_3H in a 1/1 acetone/water mixture afforded the acid **9** in 90 % yield. The latter was first activated by treatment with $(COCl)_2$ affording the acylchloride **10** in 94 % yield and then converted in 50 % yield into the deuterated hydroxymethyl **11** by treatment with $LiAlD_4$ in THF under conditions described for $LiAlH_4$.[17] **11** was converted in 82 % yield into the labelled bromomethyl **12** by treatment with PBr_3 in THF.[17] The condensation of **8** with the macrocycle **4** in toluene in the presence of Et_3N afforded the compounds **13** as a mixture of diastereoisomers in 90 % yield, whereas the reaction of **12** with **4**, under the same conditions, afforded **14** in 90% yield. The final products **2** (obtained as a mixture of diastereoisomers) and **3** were obtained by catalytic (Pd/C) hydrogenation of **13** and **14** in 64 % and 60 % yields respectively.



Scheme 2

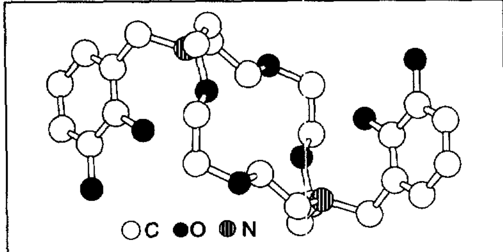


Figure 1. X-ray structure of **3**, for clarity, H atoms are not presented

The structure of the free ligand **3** was studied in the solid state by X-diffraction methods which confirmed the proposed connectivity pattern (Fig. 1).[18] Due to the rather poor preorganisation of the ligand, the two catechol units in trans configuration were localised bellow and above to the mean plane of the macrocycle.

The binding ability of receptors **2** and **3** towards boron and alkaline metal cations was demonstrated by treating under argon either the free ligand **2** or **3** with 1 eq of MOH and 1 eq of $B(OH)_3$ in H_2O/EtOH mixture at room temperature affording after crystallisation the pure (X,B,M) complexes. The formation of (X,B,M) complexes with X = **2** (mixture of diastereoisomers) or **3** (mixture of enantiomers) and M = Na^+, K^+ and Cs^+ was studied in chloroform by NMR spectroscopy using various nuclei such as ^1H and ^2D and ^{11}B.

Dealing with ^1H-NMR (300 MHz, $CDCl_3$, 25 °C) studies, for all free compounds **1-3** the observed spectra were rather simple. For (X,B,M) complexes, because of the tetrahedral coordination of both catechols around B(III), all protons became diastereotopic and the observed spectra were fairly complicated. However, in the case of the ligand **1** all signals were assigned using bidimensional NMR experiments.[5] Whereas for all (**1**,B,M) complexes the benzylic CH_2N protons gave rise to an AB quartet at 2.54 and 4.39 ppm (Fig. 2 top), for (**2**,B,M) complexes only two singlets at 4.37 and 2.51 ppm were observed (Fig. 2 middle). Obviously no proton signals corresponding to the benzylic positions were observed for (**3**,B,M) complexes (Fig. 2 bottom). As expected, for (**2**,B,M) complexes, the binding process could be studied following the CHD proton signals as a function of the nature of the complexed alkaline metal cation (Fig. 3). When comparing the Na^+, K^+ and Cs^+ complexes, the largest shifts were obtained for the potassium complex. Dealing with ^2D-NMR (76.77 MHz, $CHCl_3$, 25 °C), whereas for both compounds **2** and **3** a unique signal at *ca* 3.8 ppm was observed, for the (X,B,M) with X =**2** or **3** and M = Na^+, K^+, Cs^+, again due to the coordination of boron by the catechol units in a tetrahedral geometry, all deuterium atoms became diastereotopic and thus two signals were obtained (Fig. 4). The ^2D δ values, as for the ^1H signals, were dependant upon the nature of the complexed cation (see figure 4 for compound **3**). Finally, the presence of boron in both (**2**,B,M) and (**3**,B,M) complexes was established by ^{11}B-NMR (160 MHz, $CDCl_3$, 25 °C) which revealed the presence of a unique signal around 14.5 ppm. The effect of the nature of the complexed cation on the chemical shift of the signal was marginal.

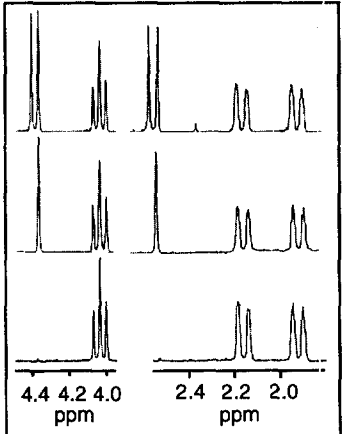


Figure 2 : ^1H-NMR ($CHCl_3$) selected regions for (X, B,K) complexes: X = **1** (top), X = **2** (middle), X = **3** (bottom)

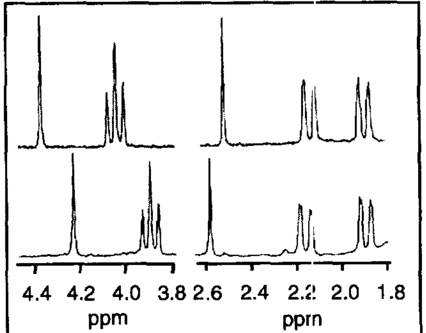


Figure 3 : ^1H-NMR ($CHCl_3$) selected regions, (**2**, B,M) complexes: M =K^+ (top), M = Cs^+ (bottom)

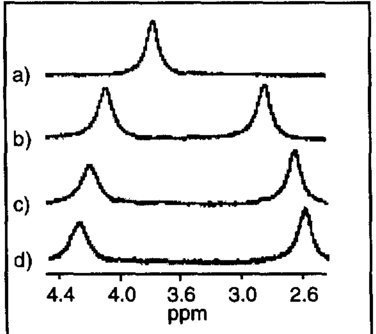


Figure 4 : ^2D-NMR ($CHCl_3$) : free **3** (a), Na^+(b), K^+(c) and Cs^+ (d) complexes

In summary, high yield syntheses of deuterium labelled compound **2** and **3** based on the [22] macrocyclic backbone bearing two catechol units was achieved. The solid state structure of the tetradeuterated compound 3 was elucidated by X-ray diffraction methods. The binding ability of **2** and **3** towards both boron and alkaline metal cations was established in solution by ^1H-, ^2D- and ^{11}B-NMR spectroscopy. The enantiomeric differentiation by ^2D- and ^{10}B- as well as ^{11}B-NMR of the (2-B, M) and of (2-B, M) complexes in chiral liquid crystalline phase is under study.

Acknowledgement: We thank the CNRS and the Institut Universitaire de France for financial support.

References and notes

1. a) Hütter, R., Keller-Schierlein, W., Knüsel, F., Prelog, V., Rodgers, G. C., Sutter, P., Vogel, G., Voser, W., Zähner, H., *Helv. Chim. Acta*, **1967**, *50*, 1533-1539; b) Okazaki, T., Kitahara, T., Okami, Y., *J. Antibiotics*, **1975**, *28*, 176-184; Stout, T. J., Clardy, J., Pathirana, I. C., Fenical, W., *Tetrahedron*, **1991**, *47*, 3511-3520; Hemscheidt, T., Puglisi, M. P., Larsen, L. K., Patterson, R. E., Moore, R. E., Rios, J. L., *J. Org. Chem.*, **1994**, *59*, 3467-3471; Schummer, D., Irschik, H., Reichenbach, H., Höfle, G., *Liebigs Ann. Chem.*, **1994**, 283-289.
2. Dunitz, J. D., Hawley, D. M., Miklos, D., White, D. N. J., Berlin, Y., Marusic, R., Prelog, V., *Helv. Chim. Acta*, **1971**, *54*, 1709-1713; Marsh, W., Dunitz, J. D., White, D. N. J., *Helv. Chim. Acta*, **1974**, *57*, 10-17.
3. Dietrich, B., Viout, P., Lehn, J.-M. in *Macrocyclic Chemistry*, VCH, Weinheim, **1993**.
4. Graf, E., Hosseini, M. W., Ruppert, R., *Terahedron Lett.*, **1994**, *35*, 7779-7782.
5. Graf, E., Hosseini, M. W., Ruppert, R., Kyritsakas, N., De Cian, A., Fischer, J., Estournès, Taulelle, F. C., *Angew. Chem., Int. Ed. Engl.*, **1995**, *34*, 1115-1117.
6. Graf, E., Hosseini, M. W., De Cian, A., Fischer, J., *Bull. Soc. Chim. Fr.*, **1996**, *133*, 743-748.
7. Bockstahl, F., Graf, E., Hosseini, M. W., Suhr, D., De Cian, A., Fischer, J., *Terahedron Lett.*, **1997**, *38*, 7539-7542.
8. Graf, E., Hosseini, M. W., Ruppert, R., De Cian, A., Fischer, J., *J. C. S., Chem. Comm.*, **1995**, 1505-1506.
9. Weitl, F. L., Raymond, K. N., *J. Am. Chem. Soc.* **1980**, *102*, 2289-2293; Raymond, K. N.; Müller, G.; Matzanke, B. F., *Topics Current Chem.* **1984**, *123*, 49-102.
10. Mislin, G.; Graf, E.; Hosseini, M. W., *Tetrahedron Lett.* **1996**, *37*, 4503-4506.
11. Drexler, C., Hosseini, M. W. , De Cian, A., Fischer, J., *Tetrahedron Lett.* **1997**, *38*, 2993-2996; Drexler, C., Hosseini, M. W. , Planeix, J.-M., Stupka, G., De Cian, A., Fischer, J., *J. C. S., Chem. Comm.*, **1998**, in press.
12. Kobuke, Y., Sumida, Y., Hayashi, M., Ogoshi, H., *Angew. Chem. Int. Ed. Engl.***1991**, *30*, 1496-1498.
13. Mislow, K., Raban, M., *Topics Stereochem.*, **1967**, *1*, 1-38.
14. Graf, E., Graff, R., Hosseini, M. W., C. Huguenard, Taulelle, F. C., *J. C. S., Chem. Comm.*, **1997**, 1459-1460.
15. Gatto, V. J. , Miller, S. R. , Gokel, G. W. *Organic Synthesis*, **1989**, *68*, 227-233.
16. Rastetter, W. H., Erickson, T. J. , Venuti, M. C., *J. Org. Chem.* **1981**, *46*, 3579-3590.
17. Marchand, B. Benezra, C. *J. Med. Chem.* **1982**, *25*, 650-653.
18. *X-ray data for* **3** : $C_{28}H_{40}N_2O_9$, M = 548.6, triclinic, a = 7.498(0), b = 7.573(0), c = 13.417(0) Å, α = 89.42(2)°, β = 89.35(2)°, γ = 79.84(2)°, U = 749.8 Å^3, space group P-1, Z = 1, Dc = 1.215 gcm^{-3}, μ(Mo-Kα) = 0.847 cm^{-1}, crystal dimensions 0.25x0.25x0.30 mm. Data were measured at 293K on a Philips PW1100 diffractometer with graphite monochromated Mo-Kα radiation. The structure was solved by direct methods and refined anisotropically using absorption corrected data to give R = 0.054, Rw = 0.077 for 1512 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.