Pergamon

Tetrahedron Letters, Vol. 35, No. 42, pp. 7779-7782, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01719-0

Synthesis of Macrocyclic Ditopic Receptors Designed for Simultaneous Binding of Alkaline and Transition Metal Cations

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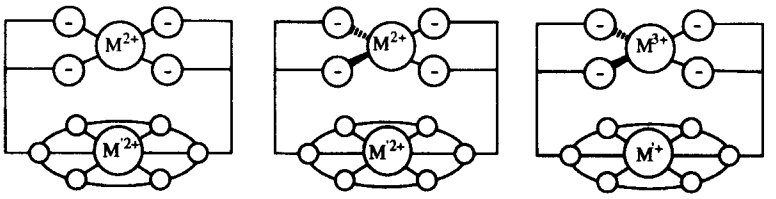
Abstract: The synthesis of diazatetraoxacyclooctadecane derivatives bearing two catechol groups was achieved in good yield. The binucleating ligands were designed to bind both soft and hard cations simultaneously.

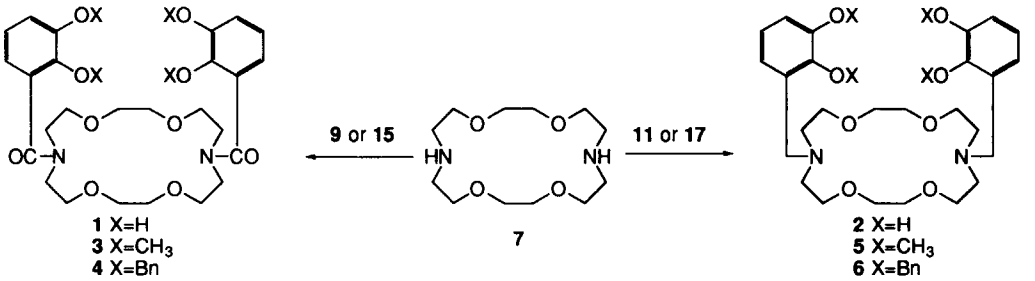
The design and synthesis of binuclear complexes have been extensively studied over the past twenty years.[1] In these complexes, intrinsic molecular properties such as magnetic coupling, redox activity and optical features may be tuned with remarkable precision.[2] Although at an earlier period many homo- and hetero-binuclear complexes reported were essentially of the same type, *i.e.* two alkaline or two transition metal cations, only recently considerable effort has been invested in the synthesis of heterobinuclear complexes possessing both a hard alkaline or alkaline-earth and a soft transition metal cations.[3]

Our approach to the design of a binucleating receptor was based on the combination of a macrocyclic framework and two bidentate dianionic ligands. For the macrocyclic core, the 18 membered ring diazatetraoxa compound **7** [4a] was chosen because its ability to bind hard cations has been previously demonstrated [4b]. As for the bidentate ligand, catechol derivatives seemed to be suitable for binding transition metal cations. The linkage of the latter to the macrocycle may be realised either using an amide bond (**1**) or a methylene group (**2**). In the former, 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. In the latter case, the CH_2 groups would preserve the complexation ability of the macrocycle but the ligand is more flexible and, thus, less preorganised. For **1** and **2**, it is worth noting that the binding of the transition metal (M^{2+}or M^{3+}) by the two catechol units leads to mono- or di-anionic pseudo cryptands with enhanced binding ability towards the second hard cation (M'^{+} or M'^{2+}). Due to the dianionic nature of the pendant catechols, the choice of appropriate oxidation states for both hard and soft metals, and their combination, should lead to neutral complexes (see scheme). Dealing with the coordination geometry around the transition metal cation, both ligands **1** and **2** should accommodate a square planar or tetrahedral geometry. Nevertheless, based on CPK models, the more rigid compound **1** may show some preferences for a tetrahedral geometry. The ligands **1** and **2** were designed to bind

simultaneously Na^+, K^+, or Ca^{2+}, Ba^{2+} within their macrocyclic core and Ni^{2+}, Cu^{2+}, Zn^{2+} by the two pendant catechol units. Furthermore, the binding of a B^{3+} cation by both catecholate dianions would lead to a borate ester bearing one negative charge which should increase the binding affinity of the macrocyclic core for mono charged cations such as Na^+ or K^+, thus leading to a neutral complex. The formation of a borate ester leading to molecular clefts bearing oxygen atoms has been found in antibiotics such as boromycin.[5] Recently, the same concept has been applied to increase the binding ability of macrocyclic crown ether receptors bearing two endocyclic catecholate moieties.[6] The macrocycle **7** bearing two pendant bipyridine derivatives, and its ability to bind both transition and alkaline metal cations were described.[7] Triaza- and tetraaza-macrocycles bearing three and four pendant catecholate units have also been previously reported.[8] We report here the synthesis of the new ditopic macrocyclic ligands **1** and **2** bearing two catechol units.

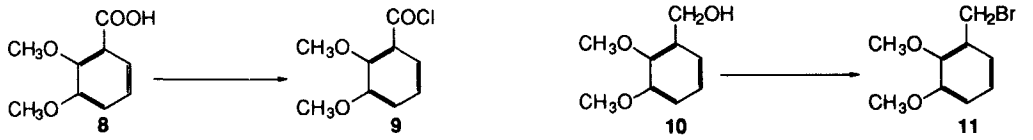


The synthetic strategy for the preparation of **1** and **2** was based on the coupling of either the acyl chloride or bromomethyl derivatives of protected catechol with the diazatetraoxa macrocycle **7**. The synthesis of the latter was achieved in 4 steps starting from the commercially available 1,2-bis(2-chloroethoxy)ethane following published procedures.[9]

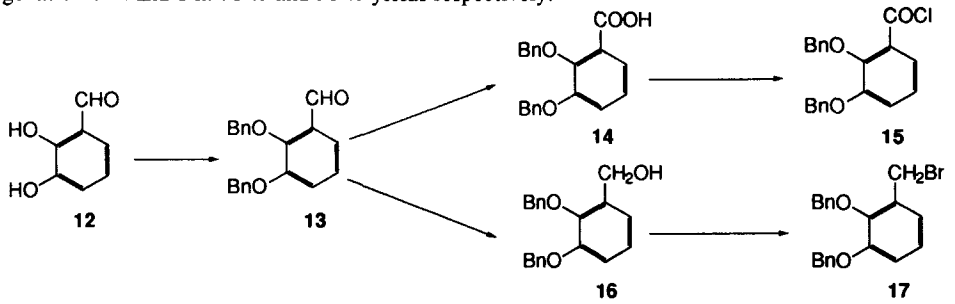


In a first attempt to prepare **1** and **2**, the methyl-protected catechols **9** and **11** were used. For the preparation of **1**, commercially available 2,3-dimethoxybenzoic acid **8** was converted into the acid chloride **9** by treatment with $SOCl_2$.[10] The reaction of the latter with **7** in dry THF in the presence of Et_3N afforded the desired compound **3** (95 %).[11] For the synthesis of **2**, commercially available **10** was first transformed into its bromo derivative **11** in 71 % yield by treatment with Br_2 in the presence of PPh_3 in DMF.[12] Condensation of **11** with **7** in CH_2Cl_2 at -5 °C afforded **5** in 62 % yield.[13] Unfortunately, we were unable to remove the methyl protective group in the final compounds using the standard BBr_3 method.[14] A systematic investigation of the reaction conditions (effect of temperature, concentration and reaction time) did not lead to **1** and **2**. Indeed, the non-specificity of BBr_3 leads to the opening of the macrocyclic moiety of both **3** and **5**. Nevertheless, using a specific deprotecting agent such as PPh_2Li,[15] we succeeded in preparing compounds **1** and **2**. However, since the purification of the desired compounds in the final step appeared to be rather tedious, the route using the

benzyl protective group (Bn) was investigated. Treatment of 2,3-benzaldehyde **12** with benzyl bromide in EtOH in the presence of K_2CO_3 afforded the the protected aldehyde **13** in quantitative yield.[16] The latter was the



common intermediate for the synthesis of the acyl chloride **15** and the benzyl bromide **17**. Indeed, oxidation[16] at r. t. of **13** by $NaClO_2$ in the presence of H_2NSO_3H in a 1/1 acetone/water mixture afforded the acid **14**, which was further converted into its acyl chloride **15** by treatment with $SOCl_2$ in DMF.[16] The same aldehyde **13** was reduced in 80 % yield to the benzyl alcohol **16** by treatment with $LiAlH_4$ in THF.[17] The latter was converted in 98 % yield into the bromomethyl **17** by treatment with PBr_3 in THF.[17] Condensation of **15** with **7** in the presence of Et_3N in toluene afforded product **4** (67 %).[18] Reaction of **17** with **7** in the presence of Et_3N in toluene afforded **6** (88 %).[19] The final products **1**[20] and **2**[21] were obtained by catalytic (Pd/C) hydrogenation of **4** and **6** in 70 % and 90 % yields respectively.



In summary, high yield syntheses of **1** and **2** composed of a macrocyclic backbone bearing two catechol units were achieved. The amide containing **1** was soluble in DMSO and in alkaline water and rather insoluble in $CHCl_3$. Whereas, the amine containing **2** was soluble in organic solvents such as CH_2Cl_2, $CHCl_3$, DMF and CH_3CN and in both acidic and alkaline water solutions.

Preliminary results obtained by NMR spectroscopy for ligand **2** indicated that the latter indeed binds simultaneously the boron cation by its catechol units and potassium by its macrocyclic moiety. The binding properties of both **1** and **2** towards alkaline and transition metal cations are under current investigation and will be reported elsewhere.

Acknowledgement: We thank Institut Universitaire de France (IUF), CNRS, DRET and CEA-LETI for financial support.

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11. Compound **3**: In a dry 250 ml flask, **7** (1 g, 3.82 mmol) and Et_3N (1.33 ml, 9.55 mmol) were stirred under argon in dry THF (50 ml) at r. t. To the mixture, compound **9** (1.68 g, 8.4 mmol) in dry THF (40 ml) was added dropwise (1 h.) and stirring was further continued for 24 h. The reaction mixture was filtered and the solvent removed. The residue was taken in CH_2Cl_2 (100 ml) and washed twice with aqueous HCl solution (50 ml, 10 %). The organic layer was dried ($MgSO_4$) and evaporated to dryness; **3** (2.17 g, 96 %) was obtained as an oil after chromatography (SiO_2, CH_2Cl_2/MeOH). ^1H (200 MHz, $CDCl_3$, 25 °C): δ(ppm): 3.41-3.86 (m, 36H, OCH_3, OCH_2, NCH_2), 6.74-7.10 (m, 6H, Arom.); ^{13}C (50.32 MHz, $CDCl_3$, 25 °C): δ(ppm): 45.9, 49.4 (NCH_2), 55.8, 61.5, 69.6, 70.0, 70.5 (OCH_2, OCH_3), 112.7, 118.8, 124.7, 131.9, 144.6, 152.6 (Arom.), 169.2 (CO); FAB $^+$ (*meta*-nitrobenzylalcohol matrix) m/z 591.2 (MH^+, 75%); Found: C 60.90, H 7.41, N 4.68; calc. for $C_{30}H_{42}N_2O_{10}$: C 61.00, H 7.16, N 4.72.
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13. Compound **5**: In a dry 100 ml flask, **7** (1 g, 3.82 mmol) and Et_3N (5.5 ml, 39.5 mmol) were stirred under argon in dry CH_2Cl_2 (30 ml) at -8 °C. To the mixture, **11** (1.80 g, 7.79 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise (20 min.) and stirring was further continued at r. t. for 16 h. The reaction mixture was washed twice with aqueous NEt_4OH solution (30 ml, pH 10). The organic layer was dried ($MgSO_4$) and evaporated to dryness; **5** (0.42 g, 20 %) was obtained as a white solid after chromatography (Al_2O_3, AcOEt/Hexane). M. p. 85 °C; ^1H (200 MHz, $CDCl_3$, 25 °C): δ(ppm): 2.84 (t, J=5.4 Hz, 8H, NCH_2), 3.57-3.83 (m, 20H, OCH_2, NCH_2Ph), 3.83-3.86 (2s, 12H, OCH_3), 6.80-7.05 (m, 6H, arom.); ^{13}C (50.32 MHz, $CDCl_3$, 25 °C) δ(ppm): 53.5, 53.9 (NCH_2), 55.5, 60.5 (OCH_3), 69.9, 70.5 (OCH_2), 111.0, 122.4, 123.5, 133.1, 147.5, 152.5 (arom.); Found: C 65.06, H 8.62, N 5.21; calc. for $C_{30}H_{46}N_2O_8$: C 64.04, H 8.24, N 4.98.
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18. Compound **4**: In a dry 100 ml flask, **7** (1.3 g, 4.95 mmol) and Et_3N (1.5 ml, 10.8 mmol) were stirred under argon in dry toluene (30 ml) at r.t.. To the mixture, **15** (3.5 g, 9.92 mmol) in dry toluene (30 ml) was added dropwise (15 min.) and stirring was further continued at r. t. for 2 h. The reaction mixture was filtered and the solvent removed. The solid residue was dissolved in CH_2Cl_2 (100 ml) and washed twice with NaOH solution (100 ml, 2.5 N). The organic layer was dried ($MgSO_4$) and evaporated to dryness affording the pure **4** (4.28 g, 97 %) as a white solid. M. p. 136-138 °C; ^1H (200 MHz, $CDCl_3$, 25 °C): δ(ppm) : 3.31-3.68 (m, 24H, OCH_2, NCH_2); 4.88-5.22 (m, 8H, OCH_2Ph); 6.81-7.07 (m, 6H, arom.); 7.27-7.42 (m, 20H, arom.); ^{13}C (50.32 MHz, $CDCl_3$, 25 °C) δ(ppm): 46.2, 49.6 (NCH_2); 69.5, 70.1, 70.4, 70.9, 75.9 (OCH_2, OCH_2Ph); 114.8, 119.4, 124.9, 127.6, 128.0, 128.2, 128.4, 128.6, 128.7, 132.8, 136.7, 137.7, 144.3, 152.1 (arom.); 169.4 (CO); Found: C 72.40, H 6.70; calc. for $C_{54}H_{58}N_2O_{10}$: C 72.46, H 6.53.
19. Compound **6**: In a dry 100 ml flask, **7** (0.95 g, 3.62 mmol) and Et_3N (3 ml, 21.5 mmol) were stirred under argon in dry toluene (30 ml) at r. t.. To the mixture, **17** (3.0 g, 7.83 mmol) in dry toluene (40 ml) was added dropwise (30 min.) and stirring was further continued at r. t. for 16 h. The reaction mixture was filtered and the solvent removed; **6** (2.42 g, 78 %) was obtained as a white solid after chromatography (Al_2O_3, CH_2Cl_2). M. p. 77-78 °C; ^1H (200.32 MHz, $CDCl_3$, 25 °C): δ(ppm) : 2,77 (t, J=5,5 Hz, 8H, NCH_2); 3,55 (m, 20H, OCH_2, NCH_2Ph), 5,02, 5,12 (2s, 8H, OCH_2Ph), 6,85-7,10 (m, 6H, CH, arom.), 7,31-7,44 (m, 20H, Bn); ^{13}C (50.32 MHz, $CDCl_3$, 25 °C) δ(ppm): 54 (NCH_2, NCH_2Ph); 70.1, 70.8, 71.0, 75.1, (OCH_2, OCH_2Ph), 113.0, 123.0, 123.9, 127.6, 128.0, 128.4, 128.6, 134.2, 137.2, 138.1, 147.2, 152.0 (Arom.); Found: C 75.04, H 7.42, N 3.20; calc. for $C_{54}H_{62}N_2O_8$: C 74.80, H 7.21, N 3.23.
20. Compound **1**: In a 200 ml autoclave **4** (1 g, 1.13 mmol) and Pd/C catalyst (50 mg, 10 %) were stirred at r. t. in a mixture of EtOH (30 ml) and AcOEt (15 ml). The autoclave was filled with H_2 (5 atm.) and stirring was continued for 6 h. The catalyst was filtered and washed with hot EtOH (5 x 100 ml). The filtrate and washes were combined. Evaporation to dryness left the pure compound **1** (0.38 g, 67 %) as a white solid. M. P. 214-219 °C; ^1H (200 MHz, DMSO, 25 °C): δ(ppm) : 3.34-3.60 (m, 24H, NCH_2, OCH_2), 6.47-6.78 (m, 6H, Ph), 8.87, 9.60 (2s, 4H, OH); ^{13}C (50.32 MHz, D_2O, OH^-, 25 °C) δ(ppm): 49.3, 52.2 (NCH_2); 70.9, 71.9, 72.3 (OCH_2); 115.7, 116.5, 119.4, 126.9, 157.2, 160.6 (arom.); 179.4 (CO); Found: C 58.39, H 6.59; calc. for $C_{26}H_{34}N_2O_{10}$: C 58.42, H 6.41.
21. Compound **2**: In a 100 ml flask, **6** (0.68 g, 7.84 mmol) and Pd/C catalyst (40 mg, 10 %) were stirred at r. t. in a mixture of EtOH (30 ml) and AcOEt (15 ml). The flask was filled with H_2 (1 atm.) and stirring was continued for 7 h. The catalyst was filtered and washed with hot EtOH (5 x 50 ml). The filtrate and washes were combined. Evaporation to dryness left the pure compound **2** (0.35 g, 88 %) as a white solid. M. p. 128-129 °C; ^1H (200 MHz, $CDCl_3$, 25 °C): δ(ppm) 2.82 (t, J=5,2 Hz, 8H, NCH_2) 3.61-3.69 (m, 16H, OCH_2), 3.81 (s, 4H, NCH_2Ph); 6.50-6.88 (m, 6H, Arom.); 7.92 (br. s, 4H, OH); (50.32 MHz, $CDCl_3$, 25 °C) δ(ppm): 54.6 (NCH_2); 58.7 (NCH_2Ph), 69.2, 70.9 (OCH_2), 114.3, 119.3, 119.6, 122.5, 144.8, 145.1 (Arom.); Found: C 61.92, H 7.68; calc. for $C_{26}H_{38}N_2O_8$: C 61.64, H 7.56.

(*Received in France* 22 *July* 1994; *accepted* 27 *August* 1994)