A Template Synthesis of Polyamine Macrocycles Containing the 1,1′-Bis(2-phenol) Function

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The synthesis of two new polyamine macrocycles, each bearing the 1,1′-bis(2-phenol) group as an integral part of the cyclic framework, is reported. The ligands were obtained by template reactions using a cadmium(II) complex of the suitable polyamine condensed with 3,3′-diformyl-1,1′-bis(2-phenol), followed by selective reduction of the two imine bonds and demetallation in acidic medium.

Introduction

Macrocyclic polyamines continue to be of great interest in coordination chemistry. The importance of these compounds is due to the role they play as polyprotic bases, multidentate ligands and important biological substances.[1−5] Metal coordination by polyazamacrocycles has been widely investigated in the design of selective complexing agents, ionophores and catalysts.[6−8] These compounds have also recently been used to mimic the active center of important metal-containing enzymes.[9,10] Moreover, polyamine macrocycles constitute an excellent starting point for studies of the molecular recognition of different kinds of substrates: protonated species of polyazamacrocycles or metal complexes of them are in fact efficient receptors for many different substrates.[11,12] In this field, one of the aims of synthetic design is to modify a polyaza-cycloalkane skeleton with a [3k]aneN_k structure by inserting one or more groups into the cyclic ligand, thus producing inhomogeneity in the macrocycle.[13] This approach changes the coordination parameters of the ligands and allows the peculiar properties of the inserted group to be exploited.

1,1′-Bis(2-phenol) is an interesting chromophore which can act as a ligand for metal ions; however, no examples of its coordination properties toward metal cations and only very few examples of it as an integral part of macrocyclic ligands, have been reported.[14−16] Moreover, it can be present in solution in anionic form; for this reason, polyamine macrocycles containing this function have the capability to show, at the same time, an internal separation of positive (polyammonium groups) and negative (phenolate groups) charges depending on the pH values in aqueous solution. Thus they could be used as receptors for substrates such as amino acids.

To extend our knowledge of these compounds, we synthesized two new polyamine ligands **L1** and **L2** in which one 1,1′-bis(2-phenol) moiety is an integral part of the macrocycle (Figure 1).

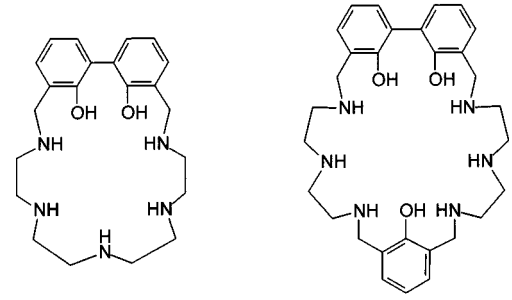

Figure 1. Ligands

Results and Discussion

One of the most important problems connected with 1,1′-bis(2-phenol) is its instability during the deprotection of the protected macrocycles obtained. To avoid this problem, we synthesized 3,3′-diformyl-1,1′-bis(2-phenol) using a slightly modified version of the synthesis reported in the literature,[17] and cyclized it with the Cd^{II} complex of a suitable linear polyamine containing two terminal primary amine groups. To do this, in the case of **L2**, we had previously synthesized the new polyamine ligand **5**. The open ligand **5** has coordination properties which merit investigation in their own right, but it also constitutes a new building block with which to obtain macrocycles, as in the present study. Compound **5** contains two triamine subunits linked together by the phenol group which can also act as a

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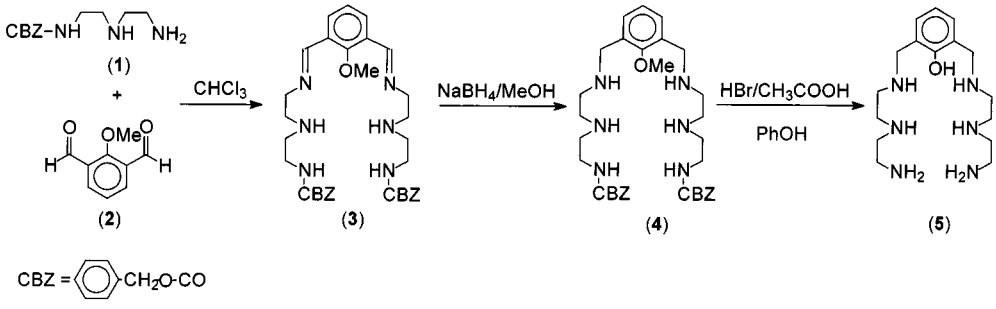
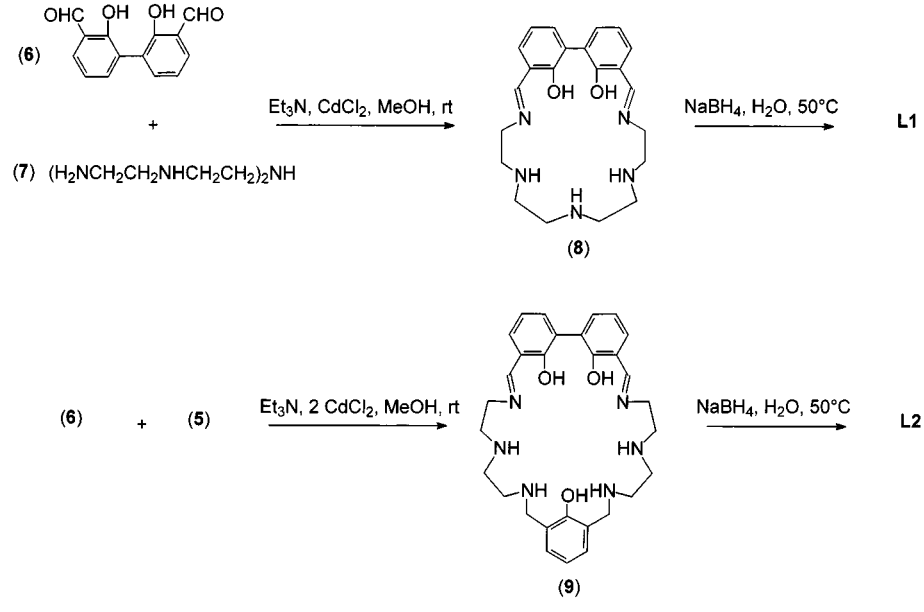
complexing agent and a chromogenic group. The procedure shown in Scheme 1 was followed to obtain **5**, whereas **1** and **2** were synthesized as previously reported.[18,19] The reaction of **1** with **2**, carried out in chloroform solution, gives the imine derivative **3** as a yellow solid. The two imine functions were reduced with $NaBH_4$ in methanol to give **4** as a white solid after extraction of the crude solid mixture with $CHCl_3$. The methyl and benzyloxycarbonyl protecting groups of **4** were both removed by treatment with 33% HBr in acetic acid in the presence of phenol. The deprotection reaction gave **5** as a hexahydrobromide salt, which was used without further purification. The reactions carried out to obtain **L1** and **L2** were performed as shown in Scheme 2, by treating 3,3′-diformyl-1,1′-bis(2-phenol) (**6**) with the appropriate, previously prepared, cadmium(II) complex of the open polyamines **5** and **7**, in methanol solution in the presence of triethylamine. While the mononuclear complex of **7** was used in this template reaction, better results were achieved using a binuclear cadmium(II) complex of **5**, obtaining the imine-macrocycle complexes of **8** and **9**, respectively, as their cadmium complexes. The imine functions of the macrocyclic complexes were reduced with $NaBH_4$ in water and, after workup in acidic solution to dissociate the metal complexes, the macrocycles **L1** and **L2** were obtained as their hydrochloride salts. In a typical cyclization reaction, **6** (1 mmol) in methanol (100 cm^3) was added dropwise over a period of 5 h to a preformed complex of **7** (1 mmol) in methanol (100 cm^3) containing two equivalents of Et_3N. The mixture was stirred for a further 12 h, after which time the yellow precipitate formed (**8**·Cd) was filtered off, washed with methanol and dried (yield 67%). The cadmium complex of **8** (1 mmol) was reacted with an excess of $NaBH_4$ (10 mmol) in water (50 cm^3) at 50 °C for 12 h. The mixture was cooled to room temperature and 3 M HCl was added up to strongly acid pH. The insoluble part was filtered off, the solution concentrated under vacuum and ethanol was added until complete precipitation of a white solid, which was recrystallized from $EtOH/H_2O$ to give **L1** as its pentahydrochloride salt (yield 72%). All compounds showed the expected spectroscopic properties and satisfactory elemental analyses and mass spectra were obtained.[20]

In conclusion, we obtained two new polyamine-macrocycles, **L1** and **L2**, each containing the 1,1′-bis(2-phenol) moiety as an integral part of the macrocycles. This was possible using a template reaction, which requires a cadmium complex of a suitable open polyamine with two terminal primary amines and 3,3′-diformyl-1,1′-bis(2-phenol) as cycling reagents. The ligands were obtained in good yield after



Scheme 1



Scheme 2

the reduction of the imine functions and dissociation of the cadmium complexes and represent new receptors for use in coordination and molecular recognition chemistry. Moreover, to obtain **L2**, we synthesized the new molecule **5**, another new ligand which can be used as a building block to obtain new macrocycles from the synthetic pathway described for **L2**, by substituting **6** with a different diformyl reagent.

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[20] **3:** Yield 94%. ^{1}H NMR ($CDCl_3$, 25° C): δ = 2.39 (t, 4 H), 3.27 (m, 8 H), 3.84 (m, 7 H), 7.48(t, 1 H), 7.88(d, 2 H), 8.62 (s, 2 H). FT-IR: $\tilde{\nu}$ = 1635 (HC=N), 1706 (C=O) cm^{-1}. $C_{33}H_{42}N_6O_5$ (602.7): calcd. C 65.76, H 7.02, N 13.94; found C 65.9, H 6.9, N 14.0. **4:** Yield 76%. ^{1}H NMR (D_2O, pH = 2, 25° C): δ = 3.18 (t, 4 H), 3.41 (m, 12 H), 3.80 (s, 3 H), 4.34 (s, 4 H), 5.03 (s, 4 H), 7.29 (t, 1 H), 7.34 (m, 10 H), 7.52 (d, 2 H). ^{13}C NMR: δ = 38.2, 44.3, 44.4, 47.9, 49.5, 64.2, 68.6, 126.0, 127.4, 129.2, 129.8, 130.1, 134.7, 137.4, 158.7, 159.9. $C_{33}H_{46}N_6O_5$ (606.8): calcd. C 65.32, H 7.64, N 13.85; found C 65.2, H 7.6, N 13.7. **5·6HBr:** Yield 72%. ^{1}H NMR (D_2O, pH = 2, 25° C): δ = 3.32 (t, 4 H), 3.41 (t, 4 H) 3.48 (m, 8 H), 4.32 (s, 4 H), 7.02 (t, 1 H), 7.41 (d, 2 H). ^{13}C NMR: δ = 36.6, 43.8, 44.8, 45.9, 48.6, 121.0, 123.6, 135.2, 155.0. MS (ESI): *m/z* = 325 [M + H$^+$]. $C_{16}H_{38}Br_6N_6O$ (809.9): calcd. C 23.73, H 4.73, N 10.38; found C 23.7, H 4.7, N 10.3. **8·Cd:** Yield 67%. FT-IR: $\tilde{\nu}$ = 1635 (HC=N) cm^{-1}. $C_{22}H_{27}CdN_5O_2$ (505.9): calcd. C 52.23, H 5.38, N 13.84; found C 52.4, H 5.5, N 13.8. **9·Cd_2Br_2:** Yield 58%. FT-IR: $\tilde{\nu}$ = 1639 (HC=N) cm^{-1}. $C_{30}H_{36}Br_2Cd_2N_6O_3$ (913.3): calcd. C 39.45, H 3.97, N 9.20; found C 39.2, H 4.1, N 9.0. **L1·3HCl:** Yield 72%. ^{1}H NMR (D_2O, pH 2, 25° C): δ = 3.38 (m, 8 H), 3.53 (m, 8 H), 4.35 (s, 4 H), 7.06 (d, 2 H), 7.29 (d, 2 H) 7.39 (d, 2 H). ^{13}C NMR: δ = 44.0, 44.8, 45.0, 45.2, 49.0, 119.7, 122.7, 126.0, 133.4, 135.0, 153.8. MS (ESI): *m/z* = 400 [M + H$^+$], 510 [M·3HCl + H$^+$]. $C_{22}H_{36}Cl_3N_5O_2$ (508.9): calcd. C 51.92, H 7.13, N 13.76; found C 51.9, H 7.1, N 13.8. **L2·6HCl:** Yield 73%. ^{1}H NMR (D_2O, pH 2, 25 °C): δ = 3.52 (m, 16 H), 4.36 (s, 4 H), 7.07 (m, 3 H), 7.30 (d, 2 H), 7.41 (d, 2 H), 7.45 (d, 2 H). ^{13}C NMR: δ = 43.7, 43.8, 44.8, 48.5, 49.0, 119.6, 120.9, 122.7, 123.4, 125.9, 133.4, 134.9, 135.1, 153.6, 154.9. MS (ESI): *m/z* = 535 [M + H$^+$]. $C_{30}H_{48}Cl_6N_6O_3$ (753.5): calcd. C 47.82, H 6.42, N 11.15; found C 47.7, H 6.5, N 11.1.

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