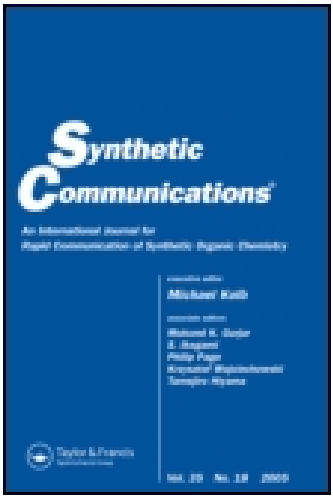

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A New Synthesis of Macrotricyclic Ligand Based on 1,4,8,11-Tetraazacyclotetradecane

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A NEW SYNTHESIS OF MACROTRICYCLIC LIGAND BASED ON 1,4,8,11-TETRAAZACYCLOTETRADECANE

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Abstract: A convenient five-step synthesis of a cylindrical macrotricyclic ligand containing two cyclam units linked together by two m-xylyl bridges is reported starting from "trans"dioxocyclam as diprotected macrocycle.

First macrocycles containing donor atoms have been reported many years ago and more than thousands of oxygen-, sulfur-, or nitrogen-based crown ethers have been prepared and characterized[1]. In order to improve the selectivity for given guests, some more preorganized supramolecules such as cryptands have been synthesized. Among them are cylindrical macrotricyclic molecules which contain two macrocyclic receptor sites linked together through two bridges[2-5]. Such

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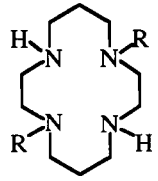
compounds are defined by three cavities : two lateral cavities corresponding to the macrocycles and a central cavity. *A priori* these ligands are able to coordinate two metal ions, leading to the formation of dinuclear cryptates. In such complexes, the two metal centres are constrained to be close to each other, inducing metal-metal interactions which may change the electrochemical, electronic, and magnetic properties when compared to those of their mononuclear analogues. These properties may be monitored by the distance between the two metallic centres, which depends on the size of the cavity of the macrocycles and the length of the bridges.

The study of these bimetallic species is of major interest for both applied and academic purposes. When the distance between two transition metal ions is in the range 4-6 Å, small guest molecules like dioxygen should be able to interact simultaneously with the two metallic centres. Such supramolecules may act as catalysts, dioxygen carriers or biomimetic models. For example, dicobalt cofacial bisporphyrins show high affinity towards dioxygen and act as efficient catalysts for the four electron reduction of dioxygen to water[6,7].

Most of the macrotricycle ligands described in the literature are formed by porphyrin units or macrocycles containing both N and O or S atoms. The synthesis of face-to-face porphyrins is not trivial. Crown-ethers show high affinity for alkali, alkaline-earth, and lanthanide ions but their corresponding transition metal complexes are less stable than those obtained in polyazamacrocycle series[8]. Recently, three cylindrical macrotricycles based on tetraazacycloalkanes have been reported by our group. One of them contains two cyclen (1,4,7,10-tetraazacyclododecane) units[9] while the two others are formed by two cyclam (1,4,8,11-tetraazacyclotetradecane) rings[10,11]. It has to be noted that the two latter compounds are N-functionalized.

In this paper, we report a five step synthesis of a cylindrical macrotricyclic compound containing two cyclams bridged by two m-xylyl units.

The synthesis of the aimed compound involves the use of a "trans" diprotected cyclam as starting material. The tosyl and tertbutyloxycarbonyl (Boc) protective groups can be used but during the preparation of protected macrocycle, a mixture of mono-, tri-, and of the two diprotected isomers ("cis" and "trans") is obtained. The separation by chromatography is laborious and for example the "trans" -ditosyl- and -diBoc-cyclams are obtained respectively in 30% [12]and 25%[11] yields.



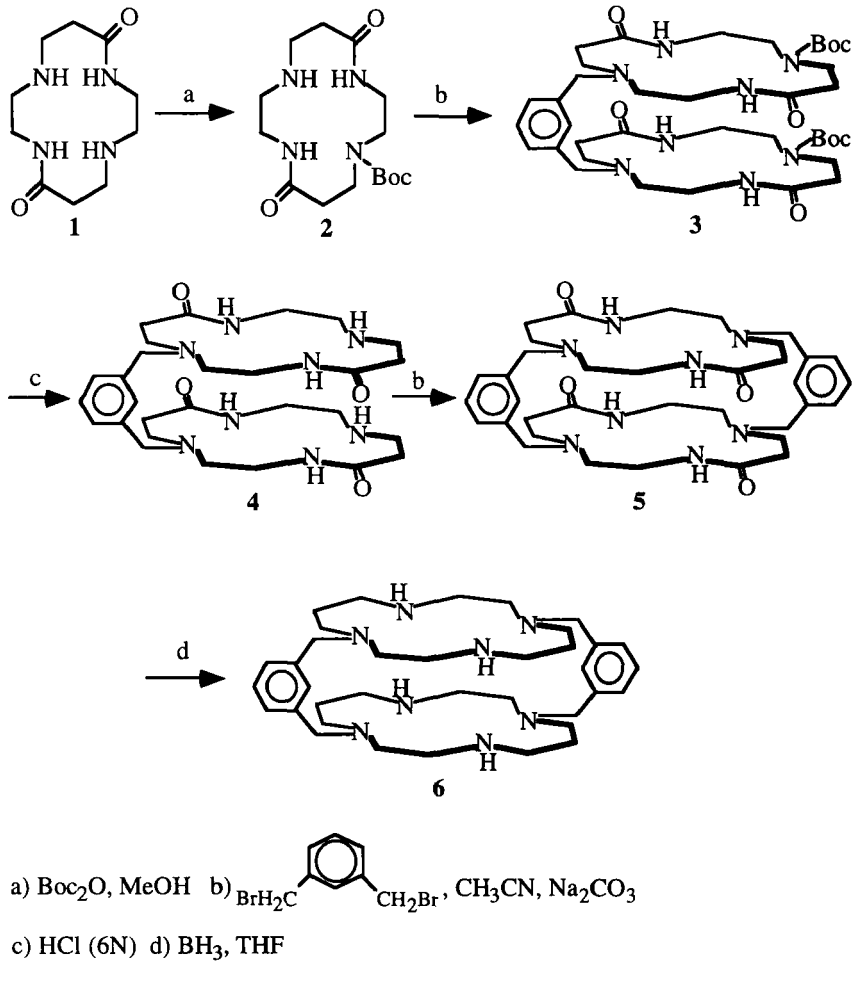
R = Ts, Boc

We have decided to use the dioxocyclam **1** (1,4,8,11-tetraazacyclotetradecane-5,12-dione) which contains two amide moieties in "trans" positions and can be considered as an "autodiprotected" cyclam (Scheme). This compound is prepared according to a previous procedure[13] in a poor yield but the synthesis proceeds from very usual materials and without any solvent.

Moreover, an univocal way for the synthesis of the desired macrotricycle implies the protection of one of the two remaining secondary amine sites of the previous "trans"dioxocyclam. The removal of this second protective group may occur without removing of the first one.

The reaction scheme is as follows :

Scheme



a) Boc_2O, MeOH b) BrH_2C CH_2Br, CH_3CN, Na_2CO_3

c) HCl (6N) d) BH_3, THF

Firstly, the protected dioxocyclam **2** is obtained in 49% yield using the Boc protective group. Then this compound is allowed to react with 0.5 eq. of α,α'-dibromo-m-xylene in acetonitrile, leading to the bridged bismacrocycle **3** in 86% yield. The removal of Boc groups by a concentrated hydrochloric acid solution affords the biscyclam **4** in 90% yield. The obtention of the macrotricycle **5** is

achieved in 75% yield by reacting 1 eq. of dibromo-m-xylene with a highly diluted solution of **4** in acetonitrile. In a final step, the aimed cylindrical macrotricycle **6** is nearly quantitatively obtained by reduction of **5** with borane in refluxing THF. The overall yield of this synthesis is close to 27%. All the intermediates and the final compound have been characterized by ^{1}H, ^{13}C NMR spectroscopies and microanalysis.

In conclusion, we report in this paper a convenient five step synthesis of a symmetrical macrotricycle starting from dioxocyclam, which is more easily accessible than the other "trans"diprotected cyclams already described. Moreover, this procedure may be applied for the synthesis of unsymmetrical macrocycles by using two different linkers. The metallation of the obtained macrotricycle and the determination of the distance between the two metallic centres by ESR spectroscopy and molecular mechanics calculations[14] are now in progress.

Experimental Section

The starting 1,4,8,11-tetraazacyclotetradecane-5,12-dione **1** was prepared as previously described[13]. The procedure involves reaction of methyl acrylate with ethylenediamine without solvent. During the reaction, the temperature was maintained below to 45 °C. The compound was recrystallized in water. All other chemicals were commercial derivatives and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in D_2O or $CDCl_3$ at 200 MHz on a Bruker AC200 spectrometer of the "Centre de Spectroscopie Moléculaire de l'Université de Bourgogne". All chemical shifts were referenced to tetramethylsilane or trimethylsilane sodium propionate as internal standards. Microanalyses were

performed by the "Service Central d'Analyse du Centre National de la Recherche Scientifique", Vernaison, France.

1-tert-butyloxycarbonyl-1,4,8,11-tetraazacyclotetradecane-5,12-dione (**2**)

The 1,4,8,11-tetraazacyclotetradecane-5,12-dione (6.0 g ; 26.3 mmol) was dissolved in methanol (3 L) and a solution of di-tert-butyl dicarbonate (5.2 g ; 23.8 mmol) in methanol was slowly added under stirring. After 24 h the solvent was evaporated and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 80:20) (m = 3.8 g ; yield = 49%).

^1H NMR ($CDCl_3$) δ (ppm) : 1.16 (s, 9H), 2.05 (t, 2H), 2.34 (t, 2H), 2.46 (t, 2H), 2.61 (t, 2H), 3.13 (m, 8H), 6.43 (m, 1H), 8.21 (m, 1H), 8.98 (m, 1H).

^{13}C NMR ($CDCl_3$) δ (ppm) : 28.6, 36.0, 36.7, 38.2, 38.9, 45.0, 45.1, 48.8, 48.9, 80.4, 157.4, 171.9, 172.7.

Anal calc for $C_{15}H_{28}O_4N_4$: C, 54.88 ; H, 8.84 ; N, 16.85. Found : C, 54.86 ; H, 8.59 ; N, 17.06.

1,1'-m-Xylylbis(8-tert-butyloxycarbonyl-1,4,8,11-tetraazacyclotetradecane-5,12-dione) (**3**)

α, α'-dibromo-m-xylene (1.2 g, 4.56 mmol) was dissolved in dry acetonitrile (50 mL) and added to a solution of the monoprotected macrocycle **2** (3 g, 9.13 mmol) in the same solvent (100 mL) and in presence of anhydrous sodium carbonate (3 g). The resulting mixture was refluxed for 24 h. Then the solid was filtered off and the solvent evaporated. After purification by chromatography on silica gel (CH_2Cl_2/MeOH 90:10), the title compound was obtained (m = 2.98 g ; yield = 86%).

^1H NMR ($CDCl_3$) δ (ppm) : 1.43 (s, 18H), 2.26 (t, 4H), 2.41 (t, 4H), 2.55 (t, 4H), 2.68 (t, 4H), 3.33-3.43 (m, 16H), 3.57 (s, 4H), 6.50 (m, 2H), 7.14-7.36

(m, 4H), 7.77 (m, 2H).

^{13}C NMR ($CDCl_3$) δ (ppm) : 29.1, 34.8, 38.0, 40.4, 46.6, 49.0, 51.2, 53.2, 59.1, 81.2, 129.3, 129.5, 131.7, 138.5, 157.8, 172.2, 173.3.

Anal calc for $C_{38}H_{62}O_8N_8$. $1H_2O$: C, 58.74 ; H, 8.30 ; N, 14.42. Found : C, 58.57 ; H, 8.29 ; N, 14.25.

1,1'-m-Xylylbis (1,4,8,11-tetraazacyclotetradecane-5,12-dione) (**4**)

The bridged bismacrocycle **3** (2.5 g, 3.29 mmol) was dissolved in a hydrochloric acid solution (100 mL of a 6M solution). The mixture was stirred at room temperature for 1 h and after the gas evolution ceased, the solution was concentrated. The residue was then purified on an ion-exchange resin DOWEX 1X8-100 (m = 1.65 g ; yield = 90%).

^1H NMR (D_2O) δ (ppm) : 2.49 (m), 2.78-2.85 (m), 2.95 (m), 3.07 (m), 3.37 (m), 3.80 (s), 7.22-7.43 (m).

^{13}C NMR (D_2O) δ (ppm) : 30.7, 34.8, 31.8, 38.5, 38.9, 45.0, 49.6, 52.2, 57.9, 61.2, 133.1, 133.5, 135.6, 136.5, 177.1, 177.9.

Anal calc for $C_{28}H_{46}O_4N_8$. $3\ H_2O$: C, 54.88 ; H, 8.55 ; N, 18.29. Found : C, 55.15 ; H, 8.86 ; N, 18.10.

1,1',8,8'-m-Xylylbis (1,4,8,11-tetraazacyclotetradecane-5,12-dione) (**5**)

The bridged bismacrocycle **4** (1.65 g, 2.95 mmol) was refluxed with stirring in dry acetonitrile (1 L) in presence of anhydrous sodium carbonate (2 g). A solution of α, α'-dibromo-m-xylene (0.78 g, 2.95 mmol) in the same solvent (10 mL) was then added during 24 h. Then the solid was filtered off and the solvent evaporated. After purification by chromatography on silica gel (CH_2Cl_2/MeOH 95:5), the title compound was obtained (m =1.47 g ; yield = 75%).

^1H NMR ($CDCl_3$) δ (ppm) : 1.93-2.33 (m), 2.65-3.10 (m), 3.23 (d), 3.48-3.61

(m), 3.95 (d), 7.16-7.36 (m), 8.51 (m), 8.77 (m).

^{13}C NMR ($CDCl_3$) δ (ppm) : 32.5, 37.5, 48.2, 53.4, 60.7, 129.6, 129.9, 132.4, 137.9, 172.8.

Anal calc for $C_{36}H_{52}O_4N_8$. 1 H_2O : C, 63.69 ; H, 8.02 ; N, 16.51. Found : C, 63.55 ; H, 7.86 ; N, 16.09.

1,1',8,8'-m-Xylylbis (1,4,8,11-tetraazacyclotetradecane) (**6**)

The macrotricycle **5** (0.5 g, 0.76 mmol) was reduced under argon with a large excess of refluxing THF solution of diborane (15 mL of an 1M solution) for 24 h. The solvent was evaporated and the residue was refluxed in a hydrochloric acid solution (30 mL of a 3M solution). After evaporation the residue was then purified on an ion-exchange resin DOWEX 1X8-100 (m = 0.43 g ; yield = 94%).

^1H NMR ($CDCl_3$) δ (ppm) : 1.64 (m), 1.97-2.15 (m), 3.90 (m), 6.96 (d), 7.14 (t), 7.39 (s).

^{13}C NMR ($CDCl_3$) δ (ppm) : 26.3, 48.0, 51.6, 52.2, 53.8, 56.6, 128.0, 130.5, 132.5, 137.2.

Anal calc for $C_{36}H_{60}N_8$: C, 71.48 ; H, 10.00 ; N, 18.52. Found : C, 71.33 ; H, 10.20 ; N, 18.36.

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