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A Two-Step Synthesis of New Macrobicyclic Aza-Ligands Starting from "Trans"Dioxocyclam as Diprotected Macrocycle

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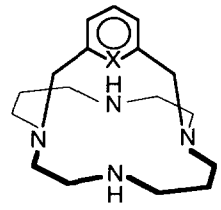
Abstract : A rapid and convenient synthesis of two small aza-cryptands containing a 1,4,8,11-tetraazacyclotetradecane backbone is reported. This strategy can be applied to the preparation of many other aza-cages by varying the nature of the cross linker. Moreover, the two remaining secondary amine sites may allow the functionalization of these ligands or their grafting on a polymer.

The design and synthesis of new macrocyclic polyamine ligands are of current interest because they form stable complexes with transition element and heavy metal ions[1]. The cavity size and the shape of host molecule, as well as the number and nature of the N-substituents may be tuned in order to improve the coordination properties and the selectivity for specific guests. The chelating properties of such compounds allow their use in various domains such as purification of waste waters[2], magnetic resonance imaging[3] or selective coordination of dioxygen from air[4].

Some highly preorganized molecules such as macrobicycles based on tetraazacycloalkanes have already been synthesized, most of which are based on 1,4,7,10-tetraazacyclododecane (cyclen)[5]. These aza-cages behave as proton sponges and interact strongly with small cations such as Li^+. Analogous 1,4,8,11-tetraazacyclotetradecane (cyclam) derivatives are very rare. Moreover, the four nitrogen atoms of the few compounds already reported[6,7] are substituted and no further functionalization can occur. To our knowledge, only a macrobicycle containing a cyclam unit bearing two secondary amine sites has been recently obtained by Weisman et al.[8]. The strategy used involves the preparation of tetraamines which have nonadjacent nitrogens bridged by ethylene. However, the synthesis of systems containing different cross-linkers cannot be performed using this method.

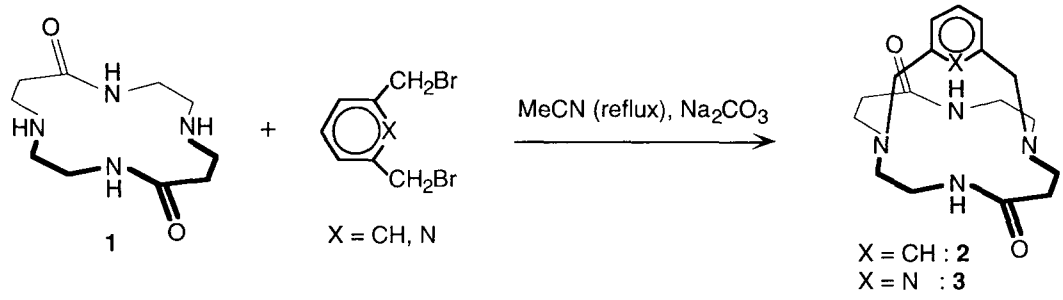


X = CH, N

Figure 1

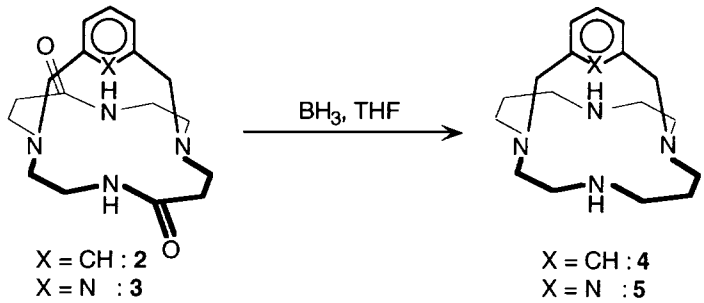
A versatile synthesis of the aimed macrobicycles (Figure 1) implies the use of a "trans"diprotected cyclam as starting material. Various conditions are required for the protection reaction : the preparation of the diprotected cyclam needs to be a straightforward, single step reaction and the protective group must be removed without affecting the bridge arm. In this regard, some protective groups have already been used in macrocycle series such as tosyl or tertiobutyloxycarbonyl groups. However, contrary to that of cyclen[9], the selective "trans" disubstitution of cyclam cannot be performed and the separation of the desired diprotected macrocycle from the mixture of the formed isomers is laborious[6].

In a previous communication[10], we have reported the synthesis of a cylindrical macrotricycle using 1,4,8,11-tetraazacyclotetradecane-5,12-dione as precursor. The synthesis proceeds as previously described from methylacrylate and ethylenediamine and requires no solvent[11]. The desired compound precipitates among the other products of the reaction, and is isolated by filtration and recrystallized in water. Despite the poor yield of this synthesis, this preparation is attractive from the standpoint that the two starting materials are commercially available, no solvent is necessary, and the "transautodiprotected" cyclam can be prepared on a large scale.



Scheme 1 : Synthesis of dioxomacrobicycles

The condensation of the "trans"dioxocyclam with a biselectrophilic reagent was realized by a slow addition of α,α'-dibromo-m-xylene in acetonitrile to a suspension of one equivalent of "trans"dioxocyclam **1** in a large volume of refluxing acetonitrile (5 mmol for 1 l of solvent) containing an excess of sodium carbonate (Scheme 1). The mixture was refluxed for four days, after which the solvent was evaporated and the resulting solid purified by silica gel chromatography (CH_2Cl_2/MeOH). Compound **2** was obtained as a colorless solid in 90% yield. A similar procedure starting from 2,6-dibromomethylpyridine yielded the dioxomacrobicycle **3** (84%). The dioxomacrobicycles **2** and **3** can be reduced to give the targeted compounds (Scheme 2). A large excess (10 eq.) of an 1M solution of borane in THF was slowly added to a suspension of the dioxomacrobicycle in dry THF at 0 °C. The mixture was gradually allowed to reach the room temperature and then refluxed for one day. The excess of borane was hydrolyzed with a mixture of water and methanol and then, after evaporation of the solvents, the residue was refluxed in a 3M hydrochloric acid solution. Treatment of the solution by addition of a concentrated NaOH solution (6M) afforded the monoprotonated macrobicycle **4** as a yellowish sticky oil in 61% yield. The same extraction sequence applied to the macrobicycle **5** afforded only traces of the aimed compound. However, product work-up of the aqueous phase on an ion-exchange resin DOWEX® 1X8-100 gave the diprotonated species of **5** in 53% yield. All the macrobicycles have been characterized by ^1H and ^{13}C NMR and by EI mass spectrometry. Satisfactory spectral data and elemental analysis have been obtained[12-15]. It is interesting to note the presence of two doublets near 3.5-4.0 ppm in the ^1H NMR spectrum for ligands **3**, **4**, and **5**. These signals can be attributed to the diastereotopic protons of the two equivalent methylene groups of the bridge arm.



Scheme 2 : Reduction of dioxomacrobicycles

The problem encountered for the extraction of the macrobicycles from aqueous alkaline phase (particularly the one containing the pyridine moiety) show that these cryptands are very strong bases. The basicity properties of these cryptands and their binding ability towards transition metal ions are currently under investigation. A structural study based on the X-ray crystallographic data and molecular mechanics calculations is also in progress.

In this paper, we report a direct two-step synthesis of two new macrobicycles containing cyclam moieties starting from 1,4,8,11-tetraazacyclotetradecane-5,12-dione which is a very accessible "transautodiprotected" cyclam. The introduction of a bridge arm may improve the rigidity and thus the selectivity of the ligand. Moreover, the steric hindrance of one side of the macrocycle is able to enhance the stability of the oxygenated Co(II) complex by limiting its degradation generally observed in solution. The procedure used here may be applied for the synthesis of a large variety of new cryptands by varying the nature of the biselectrophilic reagent. Different bridge arms containing aromatic moieties as well as aliphatic chains of variable length may be linked to the macrocycle. One or several donor atoms can be present on these cross-linkers in order to complete the coordination sphere around the metal. Finally, the two remaining secondary amine sites may allow further functionalization of these ligands or their immobilization within a polymer matrix.

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12. dioxomacrobicycle **2** : δH ($CDCl_3$) : 2.14 (2H, m); 2.36 (2H, m); 2.62 (2H, m); 2.82 (2H, m); 3.00 (4H, m); 3.10 (2H, m); 3.42 (2H, m); 3.63 (4H, s); 6.35 (2H, bs); 6.88 (2H, d, 7.0 Hz); 7.07 (1H, dd, 7.0 and 8.1 Hz); 8.20 (1H, s). $\delta^{13}C$ ($CDCl_3$) : 37.9; 39.5; 54.4; 56.6; 60.9; 125.1; 128.1; 132.0; 142.6; 173.7. Found : C. 64.91; H. 7.96; N. 16.93; O. 9.72. $C_{18}H_{26}N_4O_2$ requires : C. 65.41; H. 7.94; N. 16.96; O. 9.69.
13. dioxomacrobicycle **3** : δH ($CDCl_3$) : 2.26 (4H, m); 2.44 (2H, m); 2.78 (4H, m); 2.94 (2H, m); 3.13 (2H, m); 3.30 (2H, m); 3.71 (2H, d, 17.0 Hz); 3.90 (2H, d, 17.0 Hz); 6.97 (2H, d, 8.0 Hz); 7.54 (2H, t, 8.0 Hz); 9.64 (2H, bs). $\delta^{13}C$ ($CDCl_3$) : 34.6; 37.7; 51.0; 54.8; 58.3; 120.1; 137.9; 158.7; 172.0. Found : C. 61.16; H. 7.78; N. 21.02; O. 9.96. $C_{17}H_{25}N_5O_2$ requires : C. 61.59; H. 7.61; N. 21.14; O. 9.66.
14. macrobicycle **4** : δH ($CDCl_3$) : 1.50 (2H, m); 1.96 (2H, m); 2.13 (2H, t, 10.2 Hz); 2.40 (2H, td, 12.2 Hz and 2.4 Hz); 2.56 (6H, m); 2.94 (4H, m); 3.06 (2H, m); 3.54 (2H, d, 15.0 Hz); 3.65 (2H, d, 15.0 Hz); 6.99 (2H, d, 7.5 Hz); 7.14 (1H, t, 7.5 Hz); 8.21 (1H, s). $\delta^{13}C$ ($CDCl_3$) : 27.5; 49.4; 52.1; 54.3; 60.0; 60.9; 124.5; 127.6; 132.7; 143.7. Found : C. 65.38; H. 9.64; N. 16.46. $C_{18}H_{30}N_4$, HCl requires : C. 63.86; H. 9.24; N. 16.56.
15. macrobicycle **5** : δH ($CDCl_3$) : 1.3-1.9 (4H, m); 2.3-2.7 (16H, m); 3.52 (2H, d, 16.3 Hz); 3.95 (2H, d, 16.3 Hz); 6.88 (2H, d, 7.6 Hz); 7.44 (1H, t, 7.6 Hz). $\delta^{13}C$ ($CDCl_3$) : 27.8; 49.9; 51.6; 55.9; 56.5; 57.8; 120.4; 137.6; 158.0. Found : C. 54.46; H. 8.62; N. 18.11. $C_{17}H_{29}N_5$, 2 HCl requires : C. 54.37; H. 8.33; N. 18.66.

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