COMMUNICATION

# Convenient synthesis of new tetraazamacrocycle-based macrobicycles

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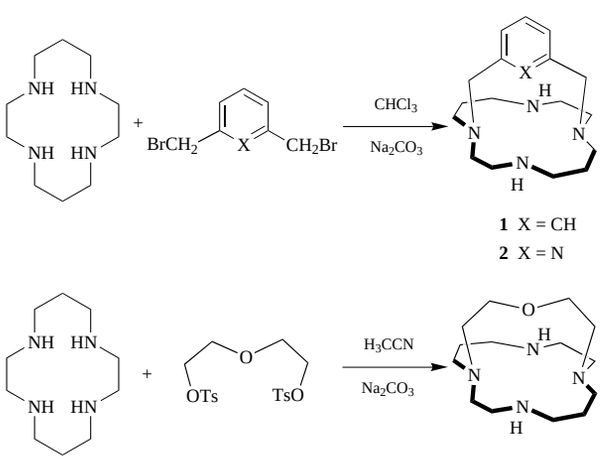
**New macrobicyclic cryptands are synthesized according to a one-step procedure starting from a non-protected tetraazamacrocycle (cyclam).**

The coordination chemistry of polyazamacrocycles such as porphyrins or saturated tetraazamacrocycles has been extensively studied in solution[1–6] as well as in the solid state.[7] The coordination properties depend upon the design of the macrocyclic receptor and the chelating ring which can be adjusted in order to selectively coordinate anions,[8] transition metals[8] and heavy metals.[9] Moreover, the careful design of the macrocyclic ligand should favour the coordination of small molecules such as dioxygen on the central metal.[10–12] Macropolycyclic ligands[13] are known to provide suitable frameworks for many receptor sites and delineate cavities into which a substrate can penetrate to form inclusion complexes.[14–16] Various studies concerning cage-type tetraazamacrobicycles[17–21] have shown the influence of the cavity size selectivity towards alkali, alkaline earth and ammonium ions when such systems are used as selective receptors. The synthesis of new macrobicyclic polyamines is of fundamental interest because they can exhibit unusual basicity, redox behaviour and coordination chemistry; these compounds need to be studied in order to prepare selective receptors, molecular carriers and catalysts.

In all the previous studies, the cross-bridging of cyclam (1,4,8,11-tetraazacyclotetradecane) to form a macrobicyclic tetraamine (Scheme 1) involves the synthesis of a *trans*-diprotected macrocycle. The first cyclam-based macrobicycle synthesis was reported by Weisman and co-workers[22,23] and more recently, new synthetic pathways were elaborated to obtain a large range of ligands starting from the 1,7-dimethyl-1,4,7,10-tetraazacyclododecane macrocycle[17–21] (cyclen = 1,4,7,10-tetraazacyclododecane). However, such derivatives have been prepared according to a multistep reaction scheme and the yields of these syntheses are generally low. These low yields are mainly due to the use of *trans*-diprotected tetraazamacrocycles (tosyl,[24] methyl or *tert*-butoxycarbonyl groups[25,26]) as intermediates. Recently, we have described a two step synthesis of spherical macrobicyclic[27] and cylindrical macrotricyclic[28] ligands starting from dioxomacrocycles to avoid the use of the usual protecting groups.




**Scheme 1**

We describe herein the synthesis of new cyclam-based macrobicyclic ligands in a one pot procedure starting from non-protected cyclam. The macrobicyclic ligands were prepared by condensation of cyclam with a bis-electrophilic aromatic or aliphatic spacer in high dilution conditions (3–5 mmol $l^{-1}$) as shown in Scheme 1. The reagents were rapidly mixed together in stoichiometric amounts and the reaction occurred in the presence of anhydrous sodium carbonate. Chloroform was chosen as solvent when α,α′-dibromo-*m*-xylene and 2,6-bis-(bromomethyl)pyridine were the cross-linkers and the reaction was followed at room temperature for 14 h. However, these reaction conditions did not provide the desired macrobicyclic ligand when cyclam was reacted with diethylene glycol ditosylate (ditoluene-*p*-sulfonate). Ligand **3** was thus obtained using high dilution conditions by condensing cyclam in refluxing acetonitrile with the ditosylate compound which is added over a period of 15 h. Compounds **1** and **3** have been purified on an alumina column followed by a basic aqueous washing (pH 12) to give the cryptands in the non-protonated form. The elemental analyses ‡ are those of the monohydrated free ligands and the reaction yields are in the 30–37% range. However, the microanalytical data ‡ of ligand **2** correspond to the monoprotonated form (yield 17%). The comparison of the $^1$H NMR spectra § of cyclam and cage-tetraazamacrocycles demonstrates that the cage compounds possess a lower symmetry. In partic-

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‡ Microanalytical data: for **1**, Calc. for $C_{18}H_{30}N_4 \cdot H_2O$: C, 67.5; H, 10.0; N, 17.5. Found: C, 68.2; H, 9.9; N, 17.4%. For **2**, Calc. for $C_{17}H_{29}N_5 \cdot HBr$: C, 53.1; H, 7.8; N, 18.2. Found: C, 53.5; H, 7.9; N, 18.0%. For **3**, Calc. for $C_{14}H_{30}N_4O \cdot H_2O$: C, 58.3; H, 11.1; N, 19.4. Found: C, 58.1; H, 11.0; N, 19.1%.

§ NMR data: $^1$H NMR data, $\delta_H$(200 MHz, $SiMe_4$, $CDCl_3$) for **1**, 1.52 (m, $\beta_N$-$CH_2$, 2H), 1.9–3.3 (m, $\alpha_N$-$CH_2$, 18H), 3.57 (d, Ar$CH_2$, 2H, *J* 15), 3.67 (d, Ar$CH_2$, 2H, *J* 15), 6.97 (d, Ar, 2H), 7.15 (dd, Ar, 2H), 8.45 (s, Ar, 1H). For **2**, 1.71 (m, $\beta_N$-$CH_2$, 2H), 2.08 (m, $\beta_N$-$CH_2$, 2H), 2.5–3.1 (m, $\alpha_N$-$CH_2$, 16H), 3.55 (d, Ar$CH_2$, 2H, *J* 16.3), 4.04 (d, Ar$CH_2$, 2H, *J* 16.3), 6.94 (d, Ar, 2H), 7.49 (dd, Ar, 1H). For **3**, 1.51 (m, $\beta_N$-$CH_2$, 2H), 1.73 (m, $\beta_N$-$CH_2$, 2H), 2.1–2.8 (m, $\alpha_N$-$CH_2$, 20H), 3.34 (ddd, $\alpha_O$-$CH_2$, 2H), 3.50 (ddd, $\alpha_O$-$CH_2$, 2H). $^{13}$C NMR $\delta_C$(50 MHz, $CDCl_3$) for **1**, 26.2 ($\beta_N$-$CH_2$), 49.3, 51.6, 52.5, 59.2 ($\alpha_N$-$CH_2$), 60.5 (Ar$CH_2$), 124.4, 128.3, 131.3, 143.8 (Ar). For **2**, 25.6 ($\beta_N$-$CH_2$), 48.6, 50.3, 54.1, 55.0 ($\alpha_N$-$CH_2$), 56.5 (Ar$CH_2$), 120.1, 137.3, 156.7 (Ar). For **3**, 27.2 ($\beta_N$-$CH_2$), 49.2, 52.4, 54.7, 55.4, 59.0 ($\alpha_N$-$CH_2$), 69.1 ($\alpha_O$-$CH_2$).

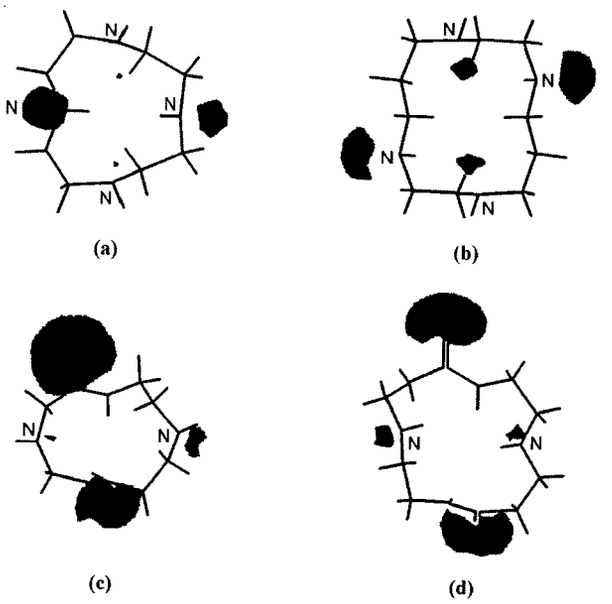


**Fig. 1** Negative molecular electrostatic potentials of (a) cyclen, (b) cyclam, (c) dioxocyclen and (d) dioxocyclam

ular, the $^1$H NMR spectra of macrobicycles **1**–**3** reveal that each α-$CH_2$ proton site appears as multiplets due to the low symmetry of the macrobicyclic ligands and the rigidity of the structural arrangement. These spectral features are mainly observed for the methylenic sites of xylenyl and pyridinyl spacers which give two doublets, and also for the ether fragment which appears as a doublet of doublets. The rigidity of the macrobicyclic framework should be validated by a crystallographic study. Moreover, the reaction conditions described here are also an efficient way to synthesize the macrobicycles in the cyclen series and a new ligand was obtained using an eight carbon aliphatic spacer.¶

In order to explain the selectivity of the reaction, a molecular modelling study has been carried out and the molecular electrostatic potentials of cyclam and cyclen were determined. Indeed, many indices of reactivity like atomic charges, bond orders, free valences, frontier electron orbital densities, fukui functions and molecular electrostatic potentials[29] (MEP) have been introduced in recent years in order to understand and predict the nature of the products of chemical reactions. In particular, MEP is a real physical property which can be either determined experimentally by X-ray diffraction methods or calculated from the wave functions. One of the first applications of the MEP was to determine a reactivity map in order to predict the sites of electrophilic attack on a molecule. The lowest energy conformers of the macrocycles have been selected using molecular mechanics and molecular dynamics (CVFF force field, DISCOVER module of the MSI Molecular Modeling Package on a Silicon Graphics Indigo2 workstation),[30] and their respective MEPs have been obtained from single point density functional theory (DFT) calculations. The COSMO[30] program has been used to estimate the solvent effect using a continuum model approach. In the present study we have plotted the MEP to localize the more electronegative sites of cyclam and cyclen. The location of the negative MEPs reported in Fig. 1 (a), (b) and (d) clearly indicates that electrophilic attack on the macrocycles, which have nearly equivalent values of negative MEP, would take place on the two nitrogens in a *trans* position favouring the formation of a macrobicycle. Moreover, the validity of the DFT method for exploring the reactivity of the compounds was demonstrated for the dioxocyclen and dioxocyclam derivatives which exhibit totally different reactivities from each other. Fig. 1 (c) shows that the values of the negative MEPs on the *trans* nitrogen atoms are very different which should favour the formation of a bis-macrocycle at the first stage of the reaction. It is important to notice that the large negative MEPs shown on Fig. 1 (c) and (d) correspond to carbonyl groups and are associated with the lone pairs of oxygen atoms. Indeed, the experimental results fit with the negative MEPs of the two dioxomacrocycles [Fig. 1 (c) and (d)], and a macrotricycle is formed with dioxocyclen[28] while only a macrobicycle is obtained for dioxocyclam.[27]

In summary, we have described a new one-step synthesis of a macrobicyclic ligand series using non-protected cyclam as starting material. To our knowledge, it is the most convenient synthetic procedure to date for the preparation of a spherical macrobicycle. This method can be used to prepare a large variety of macrobicycles by changing the spacer size or the hydrophobic character. It is also important to note that it is possible to vary the nature of the spacer atom (nitrogen or oxygen) which coordinates the metal ion in the macrocyclic cavity. This synthetic pathway is of major interest because it is possible to obtain many different ligands which are able to coordinate selectively transition, alkali or heavy metals. The adequate design of the ligand can also favour the coordination of dioxygen or nitrogen on the central metal.

## Experimental

The $^1$H and $^{13}$C NMR spectra were recorded at 200 MHz on a Bruker AC 200 spectrometer at the Centre de Spectroscopie Moléculaire de l'Université de Bourgogne. For $^1$H NMR chemical shifts are referenced to internal TMS and for $^{13}$C NMR they are referenced to $CDCl_3$ at 77.7 ppm. *J* Values are given in Hz. Microanalyses were performed on an EA 1108 CHNS Fisons instrument.

Cyclam[31,32] and cyclen[33] were synthesized following literature procedures. All other chemicals (Acros or Aldrich) were used as received without further purification.

### Ligand 1

Cyclam (7.00 g, 35 mmol) was dissolved in 3.5 l of chloroform in the presence of 9.3 g of anhydrous sodium carbonate. A 500 ml chloroform solution of α,α′-dibromo-*m*-xylene (12.7 g, 48.1 mmol) was added dropwise over 12 h and the mixture was stirred at room temperature for a further 24 h. The solvent was evaporated and the oily residue was purified on an alumina column ($CH_2Cl_2$–MeOH 97:3). After evaporation of solvents, the product was dissolved in 200 ml of chloroform and washed with 50 ml of 1 M aqueous KOH. The organic phase was dried over magnesium sulfate and evaporated to give **1** as the monohydrate (4.1 g, 37%).

### Ligand 2

The above procedure was applied to 2 g of cyclam (10 mmol), 2.8 g of 2,6-bis(bromomethyl)pyridine (10.5 mmol) and 2.7 g of anhydrous sodium carbonate to give after purification on alumina ($CH_2Cl_2$–MeOH 95:5) compound **2** as a monoprotonated salt (530 mg, 17%).

### Ligand 3

The procedure described for **1** was applied to 2 g of cyclam (10 mmol), 4.5 g of diethylene glycol ditosylate (11 mmol) and 2.7 g of anhydrous sodium carbonate in refluxing acetonitrile as solvent. After purification on alumina ($CH_2Cl_2$–MeOH 97:3) and washing with aqueous base (KOH, 1 M), the product was obtained as an oil (860 mg, 30%).

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