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# A powerful route to *C*-functionalised tetraazamacrocycles†

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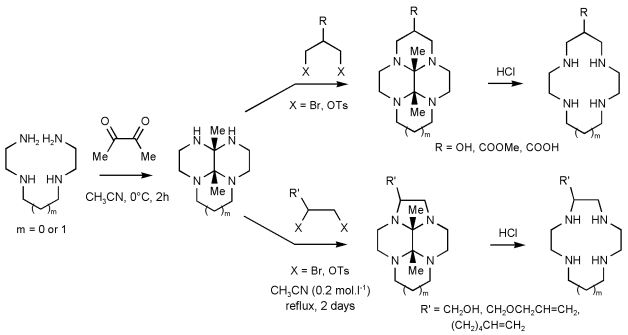
**The bisaminal template approach represents a powerful synthetic tool for the preparation of various *C*-functionalised tetraazacycloalkanes which are efficient precursors of bifunctional chelating agents.**

Macrocyclic polyamines, especially tetraazacycloalkanes such as cyclam or cyclen and their derivatives, have known a growing interest in the last two decades owing to their ligating properties.[1,2] The total or selective *N*-functionalisation of the four secondary amine functions of the macrocyclic core allows tuning of the coordinating properties of the ligand. This versatility makes possible the use of cyclic tetraamines in various fields of applications such as molecular recognition, catalysis, purification of liquids, or medicinal purposes. For instance, cyclen is the most common building block for the preparation of a large family of lanthanide complexes used as MRI contrast agents.[3] More and more applications involve macrocycles containing two different kinds of functional groups, called bifunctional chelating agents.[4] Indeed, the affinity and the selectivity towards a given guest might be enhanced by a fine tuning of the ligand design, but also new properties may result from the presence of the second function, *e.g.* an increased lipophilicity by addition of a long chain. Furthermore, the immobilisation of the ligand on a solid support or an antibody can be achieved by using an appropriate spacer arm. Radionuclide complexes linked to antibodies may be used in radioimmunotherapy. Grafting on a solid support is recommended to avoid the loss of the ligand in solution when extracting metal ions from waste waters. Such macrocycle-bound materials can be also used in heterogeneous catalysis. Many different strategies have been developed for the preparation of selectively *N*-functionalised tetraazacycloalkanes, including cyclisation of *N*-functionalised precursors or protection/deprotection sequences.[5] Another way to prepare bifunctional chelating agents is to attach one functional group on the carbon skeleton. One advantage of this approach is to preserve the reactivity of the four secondary amines which can be further functionalised with various coordinating groups. The synthesis of such *C*-functionalised macrocycles implies the use of *C*-functionalised precursors prior to cyclisation. The most frequently used procedures for the synthesis of *C*-functionalised cyclens are based on the Richman and Atkins cyclisation, involving *p*-toluenesulfonyl protecting groups.[6] These methods are not atom-economic and the deprotection step requires harsh conditions. The condensation of the linear tetraamine with substituted malonic esters allows the preparation of various *C*-functionalised cyclams.[7] However, reaction times are very long, yields are often poor, and borane is needed for the reduction of the diamide intermediate. These drawbacks prompted us to investigate new and clever ways to synthesize such compounds.

Undoubtedly, the 'bisaminal route' emerged as one of the most powerful synthetic tools in the field of tetraazacycloalkane chemistry over the past few years. The tricyclic derivative formed by the action of an α-dicarbonylated species on the linear tetraamine undergoes cyclisation in high yield. The bisaminal template is easily removed, more especially when butanedione is used. Improved syntheses of cyclen and cyclam have been achieved in this way.[8] At last, we have described a highly selective method for the preparation of *N*-functionalised tetraazacycloalkanes.[9]

In this paper, we wish to report a general route for the synthesis of *C*-functionalised cyclens, cyclams and [13]aneN4 using the bisaminal template approach. The synthetic pathway is shown in Scheme 1.‡ The protected *C*-functionalised macrocycles were obtained following a 'one-pot' procedure by reaction of the suitable biselectrophile with the tricyclic bisaminal derivative. Indeed, the intermediate obtained by reaction of butanedione with the desired tetraamine, *i.e.* triethylenetetraamine or *N*,*N*′-bis(2-aminoethyl)-1,3-propanediamine, was not isolated. We have used many different dihalogenated or ditosylated propane or ethane derivatives, bearing a wide range of functions such as alcohol, ester, or vinyl groups. Removal of the bisaminal bridge was nearly quantitatively achieved in an acidic medium. Even quite fragile functional groups may survive the mild deprotection conditions. For instance, the ester group can be either preserved or converted in the carboxylic acid depending on the experimental conditions. Numerous *C*-functionalised macrocycles have been obtained in cyclen, cyclam and the [13]aneN4 series, thus demonstrating the versatility of the method.[12] Cyclam derivatives have been synthesized in overall yields ranging from 71 to 87%, starting from the linear tetraamine. Despite the lower yields obtained in cyclen and the [13]aneN4 series (20 to 52%), the two-step procedure described herein represents a very efficient alternative to the methods already devised for the synthesis of *C*-functionalised cyclens.

The structure of the tetraprotonated form of the new 1,4,8,11-tetrazacyclododecan-6-ol (**1**) (*m* = 1, R = OH) is shown in Fig. 1. According to Dale's nomenclature,[1,13] the macrocycle adopts a (3,4,3,4)-A conformation, the four nitrogen atoms being located on the corners of a square. When ethane derivatives are used in the cyclisation step, the bisaminal cyclens and [13]aneN4 thus obtained contain three chiral carbon atoms. The *cis*-configuration of the two methyl groups on the aminal carbon atoms is fixed but there are still eight possible stereoisomers which are four pairs of enantiomers. All these isomers are formed, as evidenced by the presence of eight signals in the methyl region of the $^{13}C$ NMR spectra. The structure of one *anti*-isomer diprotonated form of the 9b,9c-dimethyldecahydro-2a,4a,7a,9a-tetraazacyclopenta[cd]phenalen-1-yl)-methanol (**2**) (bisaminal intermediate in which *m* = 1, R′ = $CH_2OH$) is represented in Fig. 2. It has to be noted that the two protonations occur on the two adjacent nitrogen atoms N1 and N2. This protonation sequence is not usual, since the second protona-




**Scheme 1**

† Electronic supplementary information (ESI) available: synthesis and spectroscopic data of different *C*-functionalised macrocycles. See http://www.rsc.org/suppdata/cc/b3/b315285e/

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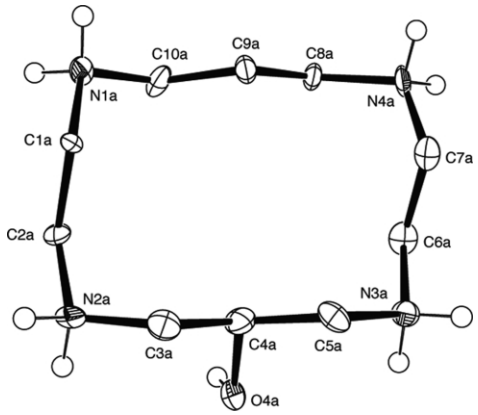


**Fig. 1** ORTEP[15] view of the tetraprotonated form of tetrazacyclododecan-6-ol (**1**) in position A, showing thermal ellipsoids at the 50% probability level. H-atoms are omitted for clarity, except those bonded to nitrogen and oxygen atoms which are represented by spheres of arbitrary radii.

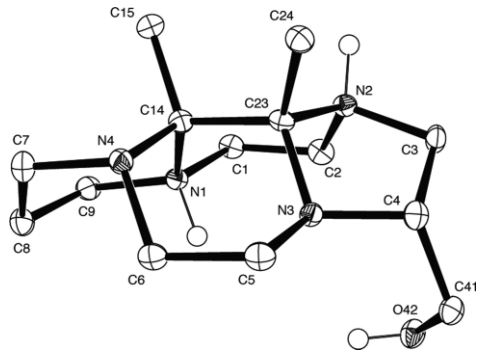


**Fig. 2** ORTEP[15] view of one *anti*-steroisomer diprotonated form of 9b,9c-dimethyldecahydro-2a,4a,7a,9a-tetraazacyclopenta[cd]phenalen-1-yl)methanol (**2**), showing thermal ellipsoids at the 50% probability level. H-atoms are omitted for clarity, except those bonded to nitrogen and oxygen atoms which are represented by spheres of arbitrary radii.

tion usually takes place on the *trans*-nitrogen atom in such compounds.[14]

The bisaminal template approach has proved to be a powerful route towards a wide variety of *C*-functionalised tetraazacycloalkanes. Owing to the large interest in such precursors of bifunctional chelating agents, the two-step, convenient procedure reported here is of major importance. Indeed, the absence of high dilution techniques, long reaction times, drastic deprotection conditions, tedious chromatographic work-up, or the production of large amounts of wastes, makes it a very attractive method for the synthesis of *C*-functionalised macrocycles on a multigram scale. We are currently working on the *N*-functionalisation of such macrocycles as well as on the development of new methods for grafting on a solid support the bifunctional chelators thus obtained. The study of the coordination properties of these compounds is also underway.

## Notes and references

‡ *Typical experimental procedure*: to a solution of tetraamine in acetonitrile (*ca.* 0.20 M) cooled to 4 °C was added dropwise one equivalent of butanedione. After completion of the reaction (4 h) the solution was heated under reflux, and five equivalents of potassium carbonate and a solution of one equivalent of the biselectrophilic agent in acetonitrile were added. After 48 h, the mixture was filtered over a pad of celite, the filtrate was evaporated and the residue was chromatographed over an alumina plug using dichloromethane as eluent. The residual oil was dissolved in ethanol (*ca.* 0.10 M) and 2 mL of 37% HCl per mmol of bisaminal adduct were added. The mixture was heated at 60 °C for 48 h. The white precipitate formed was filtered off, washed with cold ethanol and then diethyl ether to yield the fully protonated *C*-functionalised macrocycle.

High-quality colourless single-crystals of **1** and **2** were grown from water and ethanol, respectively. The crystal structures were solved using direct methods[10] and the refinements were carried out by full-matrix least squares on $F^2$.[11] Anisotropic thermal parameters were used for non-hydrogen atoms (for **1** they were refined using rigid-bond restraints). Hydrogens were located by Fourier synthesis and placed at calculated positions using a riding model, except those bonded to the nitrogen and oxygen atoms (N1, N2, O42) in **2** and those belonging to the water molecules in **1** which were refined. In both crystal structures hydrogens were refined with a global isotropic thermal factor.

*Crystal data*: for $C_{10}H_{28}N_4O^{4+}\cdot 4(NO_3)^-\cdot 2H_2O$ (**1**): $M$ = 504.44, monoclinic, space group $P\,2_1$, $a$ = 8.415(1), $b$ = 10.176(1), $c$ = 12.718(1) Å, $\beta$ = 91.284(5)°, $U$ = 1088.8(2) Å$^3$, $Z$ = 2, $T$ = 115(2) K, $D_c$ = 1.539 g cm$^{-3}$, $\lambda$(Mo-K$\alpha$) = 0.71069 Å, $\mu$(Mo-K$\alpha$) = 0.143 mm$^{-1}$, 4168 reflections collected, 4168 unique. The maximum and minimum residual electron densities are 0.223 and −0.225 e Å$^{-3}$. The final agreement factors are $R(F)$ = 0.0458 and 0.0585, and $wR(F^2)$ = 0.1021 and 0.1089, for $I > 2\sigma(I)$ and all data, respectively. The cation is found disordered occupying two positions A/B. Except for the OH group, the A/B positions are related to each other by a pseudo $C_i$ symmetry element placed at the centre of the molecule. Thus, pairs of related A/B atoms which belong to the macrocycle moiety were constrained to share the same site in the cation. The site occupation factors corresponding to the atoms in A and B positions are 0.61(1) and 0.39(1), respectively. The C–O(H) bond distance is longer in A than in B [1.412(5) and 1.353(5) Å, respectively] due to the different hydrogen-bonding patterns associated with the cation in these two positions. In order to investigate the absolute structure, Friedel pairs were not merged (merging the 4168 collected reflections leads to 2150 unique reflections and $R_{int}$ = 0.0250). At the convergence, the Flack parameter is 0(2), the estimated standard deviation indicating that the absolute structure can not be unambiguously determined, as expected from the small anomalous dispersion corrections for C, N and O when using Mo-radiation.

For $C_{14}H_{28}N_4O^{2+}\cdot 2Cl^-$ (**2**): $M$ = 339.30, monoclinic, $P\,2_1/c$, $a$ = 8.295(1), $b$ = 15.365(1), $c$ = 12.826(1) Å, $\beta$ = 102.37(1)°, $U$ = 1596.8(3) Å$^3$, $Z$ = 4, $T$ = 115(2) K, $D_c$ = 1.411 g cm$^{-3}$, $\lambda$(Mo-K$\alpha$) = 0.71069 Å, $\mu$(Mo-K$\alpha$) = 0.412 mm$^{-1}$, 6805 reflections collected, 3634 unique ($R_{int}$ = 0.0507). The maximum and minimum residual electron densities are 0.320 and −0.328 e Å$^{-3}$. The final agreement factors are $R(F)$ = 0.0422 and 0.0818, and $wR(F^2)$ = 0.0845 and 0.0969, for $I > 2\sigma(I)$ and all data, respectively. CCDC 225247 and 225248. See http://www.rsc.org/suppdata/cc/b3/b315285e/ for crystallographic data in .cif or other electronic format.


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