An easy route towards regioselectively difunctionalized cyclens and new cryptands

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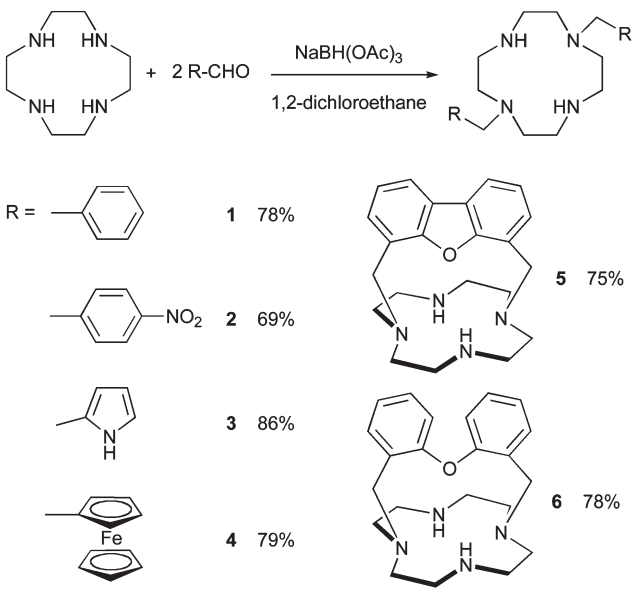
Reductive amination of various aldehydes with cyclen represents a very convenient method for the synthesis of a wide range of 1,7-difunctionalized cyclens, as well as new cryptands.

Functionalized tetraazacycloalkanes continue to see growing interest, since they represent a class of chelating agents able to form stable complexes with a large variety of metal ions, ranging from transition metals to lanthanides and other heavy metals.[1] The affinity towards a given ion may be tuned by varying the size of the macrocyclic ring, and by changing the number and the nature of the pendant coordinating arms. Cyclen derivatives are probably the most extensively studied macrocyclic polyamines, mainly because of the wide use of some of their complexes in medical applications. Indeed, Gd(III) chelates are well known as magnetic resonance imaging (MRI) contrast agents,[2] and radioactive metal (^{64}Cu, ^{111}In, ^{90}Y) complexes have been studied for both diagnostic and therapeutic purposes.[3] Macrocycles incorporating Eu(III) and Tb(III) have been used as fluorescent probes and labels,[4] and some cyclen metal complexes have also been used in molecular recognition and catalysis.[5] All these applications require fine tuning of the chelating properties of the ligand, the tuning of other properties such as their hydrophilic/hydrophobic character, and even the addition of an appropriate linker to attach the macrocycle to the antibody. This can be achieved by mixing different pendant arms, leading to so-called bifunctional chelating agents (BCAs). The synthesis of such BCAs, and also the preparation of cryptands or other macropolycycles, has attracted increasing interest, and many different synthetic methods for the selective functionalization of tetraazacycloalkanes have been devised.[6] Indeed, cyclen tetrafunctionalization is straightforward[7] but partial functionalization of the macrocycle is more tricky. Monofunctionalized cyclens can be obtained by using a large excess of the starting macrocyclic tetraamine or through the triBoc cyclen.[8] More recently, the bisaminal route proved to be a very convenient way to functionalize cyclens directly from a linear precursor.[9] However, selective difunctionalization of cyclen is still difficult to achieve and only a few methods have been reported.[6,10]

Reductive amination of carbonyl derivatives is a convenient method for the N-alkylation of amines. In such reactions, the reducing agent must be selective enough to reduce the imine or iminium species formed *in situ*, without reacting with the starting aldehyde. Among the different reducing agents, sodium tetraacetoxyborohydride ($NaBH(OAc)_3$) has been widely used.[11] Surprisingly, this method has rarely been applied to the N-functionalization of cyclic polyamines. Bradshaw *et al.* have used this tool for appending quinoline arms onto azacrowns.[12] A mono-N-functionalized cyclen has been synthesized by reductive amination, but poor selectivity in the formation of the mono- over the di-N-functionalized derivative was observed.[13] More recently, the tetraalkylation of cyclen has been carried out by reductive amination under high pressure conditions.[14]

In this paper, we report a new route for the synthesis of selectively 1,7-difunctionalized cyclens by reacting two equivalents of various aldehydes with cyclen under reductive amination conditions, *i.e.* in the presence of 2.8 equimolar amounts of $NaBH(OAc)_3$ as reductant in 1,2-dichloroethane (0.02 M) at room temperature (Scheme 1).† Under such conditions, the *trans*-difunctionalized compound is highly predominant, as shown by the NMR spectra of the crude products. This selectivity has been attributed to steric effects.[13] However, the reaction of cyclen with two equivalents of benzyl bromide in the same solvent, at the same concentration and in the presence of potassium carbonate gives a mixture of mono-, di-, tri- and even tetra-N-benzylated macrocycles. Benzylcyclen, treated according to the conditions described above (2 equivalents of benzaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane), yields the tribenzylated cyclen as the main product, while it has been reported that full N-alkylation can be achieved by running the reductive amination at high pressure.[14] All these experiments prove that further functionalization of disubstituted



Scheme 1

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cyclen is possible, and that the excellent selectivity is certainly due to reasons other than a steric one. One may suggest the formation of a bisaminal species, which is then reduced to give the difunctionalized macrocycle, according to our observations in cyclam series. Attempts to isolate the bisaminal adducts, expected from the reaction of cyclen with two equivalents of various aldehydes, failed in the absence of reducing agent. Under such conditions, only the monoaminal compound was formed. In our opinion, the reaction proceeds through the *in situ*-reduction of a bisiminium species formed at an earlier stage. In order to minimize the electrostatic repulsion between the two positive charges of the iminium groups, the reaction takes place on the two nitrogens in *trans* positions. The exceptional selectivity observed could result from these interactions.

The few examples shown in Scheme 1 illustrate the scope of the method. Any kind of aldehyde can be used *a priori*. All these macrocycles are new compounds except **1**, which is prepared straightforwardly according to this procedure. Among these compounds, 1,7-bis(ferrocenylmethyl)cyclen (**4**) is of particular interest. Indeed, ferrocene has been widely used as a redox active moiety attached to various host molecules for the electrochemical detection of guest binding. Ferrocene units have been appended to the periphery of crown ethers or cyclam in various ways.[15] To our knowledge, there is only one report in the literature describing a cyclen that has been N-functionalized by one ferrocenylmethyl unit.[16] No cyclen derivative containing two organometallic moieties has been prepared until now. The crystal structure of compound **4** has been solved, and an ORTEP[17] view is shown in Fig. 1.‡ This compound has a crystallographically imposed two-fold symmetry.

Moreover, an exceptional selectivity was also observed when reacting cyclen with dialdehydes, thus providing a very straightforward route towards three-dimensional macropolycycles. For instance, new cryptands **5** and **6**, bearing a dibenzofuran and a diphenylether handle, respectively, can be prepared by a very convenient one-pot procedure in 75–78% yield. The [1 + 1] condensation of cyclen and dialdehyde has been evidenced by mass spectrometry and X-ray diffraction. The only discrepancy between cryptands **5** and **6** is the presence of a C–C bond between the two phenyl groups, which makes the handle planar in **5**. Consequently, these two compounds adopt different geometries both in the solid state and in solution, as shown by their NMR spectra. Indeed, the two protons of each methylene group of the handle in compound **6** are diastereotopic and appear as an AB system in the ^{1}H NMR spectrum, either at room temperature or at 200 K, proving that the cryptand exhibits C_2 symmetry, similar to that observed in the solid state for the corresponding Cu(II) complex (Fig. 2).‡ In

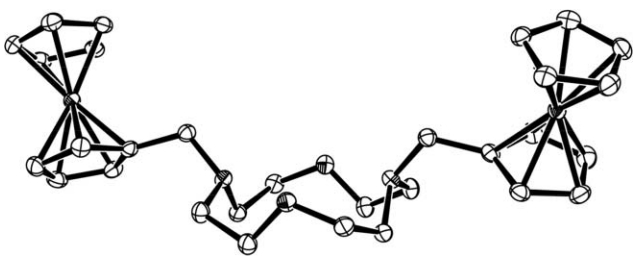

Fig. 1 ORTEP[17] view of **4** showing thermal ellipsoids at a 50% probability level. Hydrogen atoms are omitted for clarity.

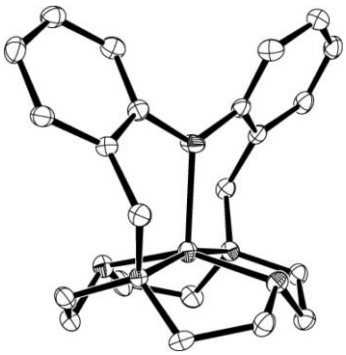

Fig. 2 ORTEP[17] view of the Cu(II) complex of **6** showing thermal ellipsoids at a 50% probability level. Hydrogen atoms are omitted for clarity.

contrast, the ^{1}H NMR spectrum of the cryptand incorporating the rigid dibenzofuran unit, recorded at room temperature, shows only one singlet for the protons of the methylene groups linking the dibenzofuran to the cyclen. This singlet splits into two doublets upon lowering the temperature (Fig. 3). This feature can be attributed to a swinging motion of the handle that occurs rapidly at room temperature on the NMR time scale and considerably more slowly at 200 K. This structural study suggests that these two cryptands should possess very different ligating properties.

The method described herein is a powerful tool for the synthesis of 1,7-difunctionalized cyclens and cryptands incorporating a cyclen unit. The reaction is highly regioselective and represents a very convenient alternative to previously described methods for the preparation of known compounds. Moreover, the use of aldehydes, instead of the halogenated compounds commonly used for the alkylation of cyclic polyamines by nucleophilic substitution, allows access to new ligands. *Ansa*-cyclens, cryptands which are usually obtained through tedious multi-step syntheses, implying

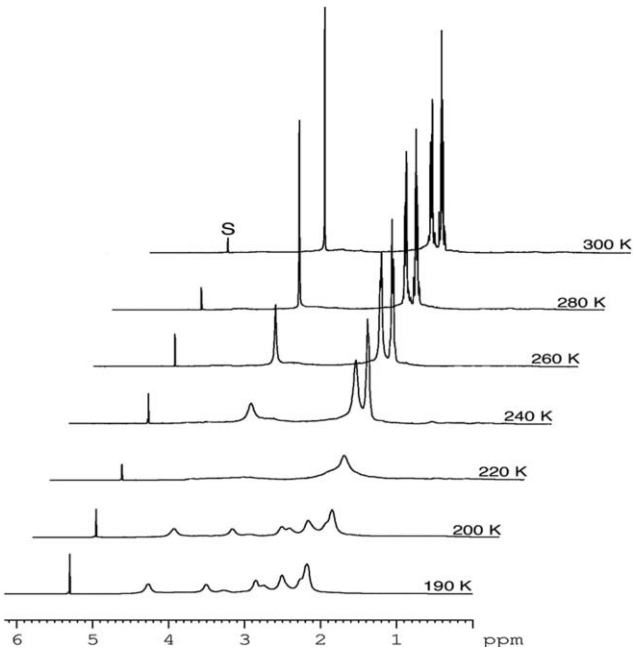

Fig. 3 0–6 ppm region of the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **5**, recorded between 300 and 190 K (S = solvent).

protection/deprotection sequences, can be prepared in high yields by an one-pot reaction using dialdehydes as starting materials. The coordination properties of these new ligands are currently being investigated and will be discussed in forthcoming papers.

Notes and references

† *Typical experimental procedure*. Synthesis of 1,7-bis(ferrocenylmethyl)-1,4,7,10-tetraazacyclododecane (**4**).

A solution of ferrocenecarboxaldehyde (1.39 g, 6.51 mmol) in 1,2-dichloroethane (50 cm^3) was added dropwise to a stirred solution of 1,4,7,10-tetraazacyclododecane (cyclen) (0.56 g, 3.3 mmol) and fresh sodium triacetoxyborohydride (1.93 g, 9.12 mmol) in 1,2-dichloroethane (100 cm^3). The solution was stirred at room temperature under an atmosphere of nitrogen for 24 h. The reaction mixture was quenched by the addition of a 1M NaOH solution (150 cm^3), and the product extracted with chloroform (3 × 100 cm^3). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the compound as a brown oil. The oil was washed with cyclohexane and the product obtained as a brown solid, m.p. 206–208 °C (1.46 g, 79%). δ_H(500 MHz, $CDCl_3$): 2.50–2.52 (10 H, m), 2.55–2.56 (8 H, m), 3.52 (4 H, s), 4.09–4.10 (14 H, m) and 4.12–4.13 (4 H, m); δ_C(125 MHz, $CDCl_3$): 46.3, 51.8, 55.4, 68.8, 69.2, 70.7 and 83.9; *m/z* (MALDI-TOF) 568.61.

‡ High quality yellow single crystals of **4** and violet single crystals of **6** were grown from THF and acetonitrile, respectively. Both crystal structures were solved using direct methods,[18] and the refinement was carried out by full-matrix least-squares on F^2.[19] Anisotropic thermal parameters were used for non-hydrogen atoms. Hydrogens were located by Fourier synthesis and placed at calculated positions using a riding model, except for that bonded to the nitrogen atom N2 in **4**, for which the positional parameters were refined, and those bonded to the nitrogen atoms in **6**, which were refined then placed at the mean N–H distances observed from neutron diffraction experiments (1.01 Å).[20] In both crystal structures, all hydrogens were refined with a global isotropic thermal factor.

Crystal data for $C_{30}H_{40}Fe_2N_4$ (**4**): M = 568.36, monoclinic, space group $C2/c$, a = 19.8821(4), b = 12.4231(3), c = 10.8980(3) Å, β = 102.466(1)°, U = 2628.3(1) $Å^3$, Z = 4, T = 115(2) K, D_c = 1.436 g cm^{-3}, λ(Mo-Kα) = 0.71069 Å, μ(Mo-Kα) = 1.131 mm^{-1}, 5717 reflections collected, 3025 unique (R_{int} = 0.0312). The maximum and minimum residual electron densities were 0.336 and −0.320 e $Å^{-3}$. The final agreement factors were $R(F)$ = 0.0324 and 0.0560, and w$R(F^2)$ = 0.0714 and 0.0783 for $I > 2\sigma(I)$ and all data, respectively. A half of the molecular unit belongs to the asymmetric unit. CCDC 619209.

Crystal data for $C_{22}H_{30}Cl_2CuN_4O_9$ (**6**): M = 628.94, monoclinic, space group $P2_1/n$, a = 12.1266(2), b = 13.4493(3), c = 15.1931(3) Å, β = 94.260(1)°, U = 2471.06(8) $Å^3$, Z = 4, T = 115(2) K, D_c = 1.691 g cm^{-3}, λ(Mo-Kα) = 0.71069 Å, μ(Mo-Kα) = 1.162 mm^{-1}, 10890 reflections collected, 5676 unique (R_{int} = 0.0442). The maximum and minimum electron densities were 0.599 and −0.724 e $Å^{-3}$. The final agreement factors were $R(F)$ = 0.0447 and 0.0776, and w$R(F^2)$ = 0.1004 and 0.1117 for $I > 2\sigma(I)$ and all data, respectively. CCDC 619210.

For crystallographic data in CIF or other electronic format see DOI: 10.1039/b612293k

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