RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

RSC Advances

PAPER

A [Two-Steps / One Week] Synthesis of *C*-Functionalized Homocyclens and Cyclams. Application to the Preparation of Conjugable BCAs without Chelating Properties Alteration

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Nathalie Camus,[a] Zakaria Halime,[a] Nathalie Le Bris,[a] Hélène Bernard,[a] Maryline Beyler,[a] Carlos Platas-Iglesias[b] and Raphael Tripier[a,*]

A versatile and efficient bisaminal template approach for the synthesis of cyclam and [13]aneN4 (homocyclen) bifunctional chelating agents (BCAs) bearing a hydroxyethyl function as *C*-appended group is presented. The synthesis is rapid (two steps/one week) and does not require fastidious protection-deprotection steps or chromatographic purification. Another reactional route and alternative work-up give access to their oxo-cyclam and oxo-homocyclen analogues. The procedure consists of the cyclization of the preorganized tetraamine 1,4,8,11-tetraazaundecane, in its *cis*-butanedione-bisaminal form, with an α,β-unsaturated lactone to provide the tetracyclic oxo-intermediate whose bisaminal bridge can be easily removed and/or its amide function reduced under mild conditions. Furthermore, the synthetic route was successfully applied to the synthesis of teta and trita BCAs analogues starting from the linear tetramine 1,4,7,10-tetraazadecane. Additionally, the appended alcohol function of various cyclam and homocyclen based ligands were converted into their ethylamine function following a very convenient procedure. Finally, preliminary analytical and complexation studies highlight that the supplementary hydroxyethyl *C*-appended chain has only a low impact on the acid-base behaviour and copper(II) or zinc(II) coordination properties of the macrocycle.

Introduction

The growing interest in the applications of tetraazacycloalkanes such as cyclam, homocyclen ([13]aneN4) and cyclen is related to their well-documented exceptional coordination properties toward numerous metal ions (Figure 1).[1] The presence of four secondary amino functions allows the *N*-functionalization of the macrocycle with various coordinating groups leading to a large panel of powerful ligands for applications in various fields, especially for medical purposes.[2] Among the different appended functions introduced on the macrocyclic skeleton, acetate functions have been the more intensively used since they fulfill the criteria for a good and specific complexation of numerous metallic cations.[3] For copper (II) ions, cyclam and homocyclen bearing acetate arms are commonly used despite a significant decrease of their thermodynamic properties (when compared to the free macrocycle) and preferred to cyclen derivatives since they lead to chelates combining a fast complexation, a high selectivity, a good thermodynamic stability and an appreciable kinetic inertness. They have been then widely used in numerous applications as in medical imaging for positrons emission tomography (PET)[4] or radio immunotherapy (RIT)[5] where a good combination of physicochemical properties is required.

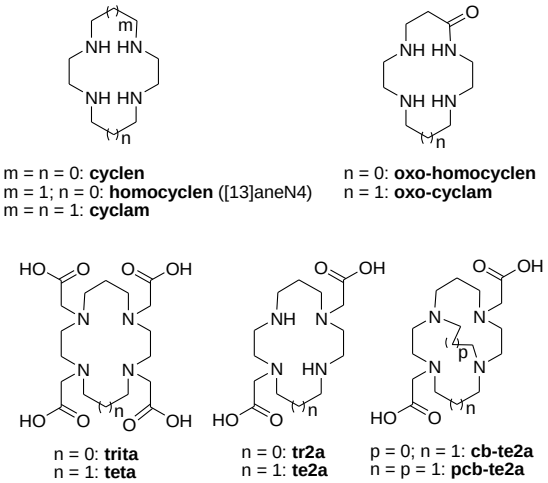


Fig.1 Ligands discussed in this work.

Thereby *N*-functionalized cyclams such as teta[6], te2a[7] and, to a lesser extent, the [13]aneN4 analogue trita[8] attracted the attention of numerous research groups. Similar derivatives such as the constrained macrocycles cb-te2a[9] and pcb-te2a[10], whose synthesis requires prior di-*N*-protection of the macrocycles, are also highly

[a] *Université de Brest, UMR-CNRS 6521 / SFR148 ScInBioS UFR Sciences et Techniques, 6 Avenue Victor le Gorgeu, C.S. 93837, 29238 Brest, France.*
[b] *Grupo QUICOOR, Centro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química Fundamental, Universidade da Coruña, Campus da Zapateira, Rúa da Fraga 10, 15008 A Coruña, Spain.*

Electronic Supplementary Information (ESI) available: [^{1}H, ^{13}C NMR, MS and HRMS, IR spectra and microanalysis. Cif files of **4, 5** and **10**. Numerical documentation of the theoretical calculations. Comparative figures of structures are presented in Fig. 7]. See DOI: 10.1039/x0xx00000x

desirable (Figure 1). Moreover, amide derivatives namely oxo-cyclam or oxo-homocyclen have also been investigated and used for their interesting coordinating properties not only with copper(II) but also with technetium(III).[11] Indeed, even if oxo-macrocycles were first known as protected precursors of selectively *N*-functionalized macrocycles,[12] their chelating properties due to their particular acid-base properties make them very attractive ligands.[13]

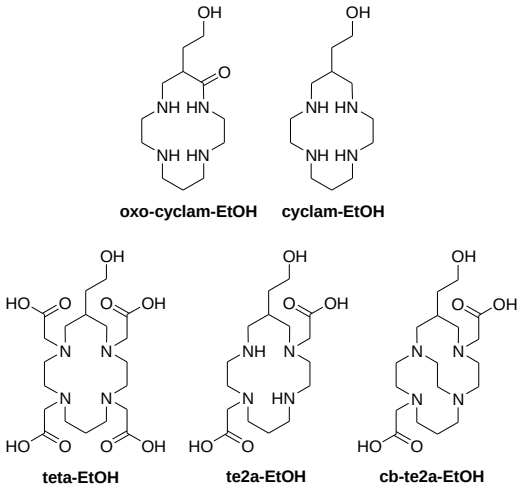


Fig. 2 BCAs discussed in this work.

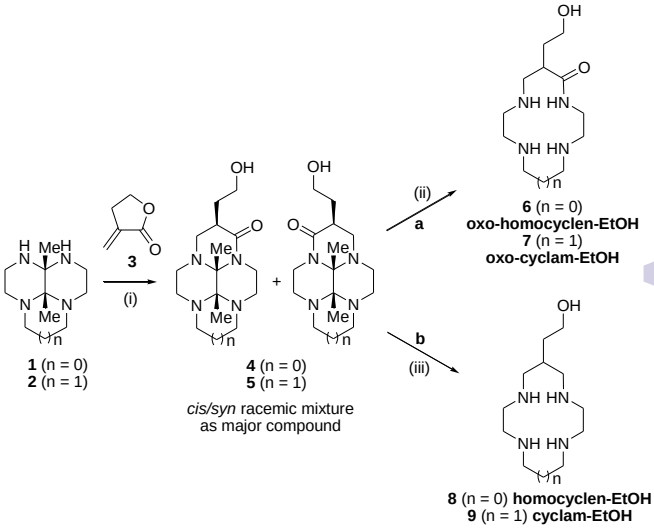
The use of the glyoxal as a template agent for the cyclization process is very useful especially for the preparation of specifically mono- and di-protected BCAs since the bisaminal bridge also acts as a protecting group. However, this methodology is less effective for the synthesis of *C*-functionalized oxo-cyclams or cyclams because it requires multi-steps of *N*-benzylation and *N*-debenzylation sequences; additionally, this synthetic route is restricted to cyclam derivatives only and cannot be extended to homocyclen derivatives.

In this paper we describe a complementary bisaminal approach for the synthesis of the oxo-cyclam-EtOH and cyclam-EtOH BCAs as the result of a rapid (two steps/one week) and powerful synthesis that involves butanedione-bisaminals already used for the preparation of tetraazamacrocycles and their functionalized analogues.[18] The procedure consists of the cyclization of the preorganized tetraamine 1,4,8,11-tetraazaundecane, in its *cis*-butanedione-bisaminal form, with α-methylene-γ-butyrolactone to provide the oxo-cyclam-butanedione-EtOH intermediate whose bisaminal bridge, unlike glyoxal-bisaminals bridge, can easily be removed under mild conditions. Furthermore, our synthetic route was also successfully extended to the linear tetramine 1,4,7,10-tetraazadecane for the synthesis of oxo- and "naked" homocyclen-EtOH precursors of new BCAs. Moreover, in order to show the potential of *C*-functionalized chetales bearing EtOH appended function as conjugable BCAs, in some of our compounds this function was converted into "$EtNH_2$" function which is more suitable for coupling reactions with biomolecules such as small peptides and antibodies for example.

Finally, we present a preliminary study of the complexation behaviour of cyclam-EtOH toward Cu^{2+} and Zn^{2+} in order to evaluate the influence of the coupling function on the coordinating properties compared to cyclam. The acid-base properties as well as stability constants with metallic ions were determined using potentiometric titrations.

Results and discussion

Synthesis of oxo- and "naked" homocyclen and cyclam *C*-EtOH. The synthesis consists of the cyclization of butanedione-bisaminals **1** and **2** obtained in there *cis*-stereoisomers from the corresponding linear tetraamine, respectively 1,4,7,10-tetraazadecane and 1,4,8,11-tetraazaundecane,[18] with the commercially available α-methylene-γ-butyrolactone **3**. This cyclization step involves an aza-Michael addition followed by a nucleophilic addition-elimination performed in methanol as a conventional solvent for Michael-type reactions. The major isolated product is the *cis/syn* diastereoisomer as a racemic mixture (Scheme 1). Trace amounts of the *cis/anti* diastereoisomer may be detected by ^{13}C NMR analysis of the crude product. Compounds **4** and **5** were isolated after recrystallization in 45% and 68% yield, respectively. The significantly lower yield obtained for compound **4** compared to **5** can be attributed to a relatively lower stability of the starting bisaminal **1**, which contains an internal five-membered cycle when bisaminal **2** contains only six-membered rings .[19]



Scheme 1 Reagents and conditions: (i) CH_3OH, 40 °C, 5 d (n = 0: 45%; n = 1: 68%); (ii) HCl 3 M, rt, 30 min; ion exchange resin (n = 0: 83%; n = 1: 85%); (iii) BH_3·THF (4 equiv.), THF, N_2, reflux, 1.5 d; HCl 3 M, reflux, 1 h; ion exchange resin (n = 0: 85%; n = 1: 80%).

Single crystals suitable for X-ray diffraction analysis were obtained for both intermediates **4** and **5** (Figure 3). The crystal data (Table 4 in experimental section) confirm that the molecules retain their *cis* configuration during the cyclization step and reveal the *syn*-position of the chain with respect to the bisaminal bridge. A comparison of the X-ray structure of **5** to that reported previously for the glyoxal-bisaminal analogue shows that both molecules present relatively similar geometries, indicating that the presence of methyl groups in **5** has a relatively low impact on the overall conformation of the macrocyclic fragment. The main difference between the two geometries is related to the H-C-C-H and H_3C-C-C-CH_3 dihedral

angles of the bisaminal bridge. The H-C-C-H angle in the glyoxal-bisaminal derivative amounts to 48.2º, while the corresponding H_3C-C-C-CH_3 dihedral angle in **5** is 50.2º. The slightly more open dihedral angle observed for **5** is obviously the result of the steric hindrance created by the presence of the two vicinal methyl groups.

Density functional theory (DFT) calculations performed at the TPSSh/6-311(d,p) level on **5** confirmed that the *cis/syn*-stereoisomer is more stable than the *cis/anti* one by 60.2 kJ·mol^{-1}. This suggests that the cyclization step proceeds under thermodynamic control, as previously showed for glyoxal-bisaminal intermediates where the energy difference was found to be considerably lower (23.3 kJ·mol^{-1}). So, the introduction of the two methyl groups on the bisaminal bridge provokes a very important stabilization of the *cis/syn* isomer. This stabilization of the *cis/syn*-stereoisomer can be related to the lower steric hindrance experienced of the vicinal methyl groups in the *cis/syn* than in the *cis/anti* isomers, as the H_3C-C-C-CH_3 dihedral angles calculated are 48.7º and 45.0º, respectively.

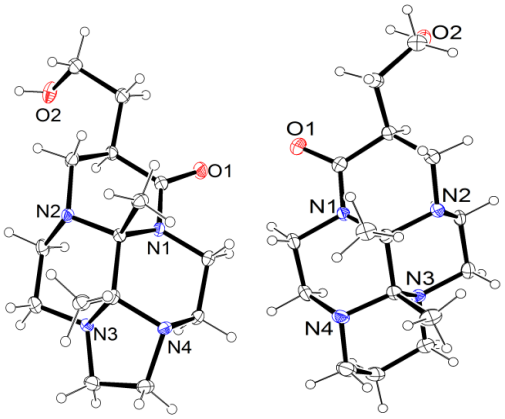


Fig. 3 Views of the crystal structures of **4** (left) and **5** (right). The ORTEP plots are at the 30% probability level.

The cyclized bisaminals **4** and **5** can be engaged in two different pathways. The first one consists of the deprotection of the bisaminal butanedione-bridge by treatment in a soft acidic medium at room temperature, which leads to oxo-homocyclen-EtOH **6** and oxo-cyclam-EtOH **7**, as free bases with about 85% yield (Scheme 1, route **a**); the amide group was not hydrolyzed under these mild experimental conditions. The second pathway involves the initial reduction of the amide group of **4** and **5** by BH_3·THF, followed by an acidic hydrolysis, to give rise to homocyclen-EtOH **8** and cyclam-EtOH **9** with nearly 85% as free bases (Scheme 1, route **b**). It should be noted that the amide group cannot be reduced by $NaBH_4$ in contrast with the previous results reported for glyoxal-derivatives.[20]

Theoretical studies were conducted on oxo-cyclam-EtOH bisaminals of butanedione and glyoxal, respectively **5** and **5'**, in order to rationalize their reactivity towards *N*-alkylation reactions and reducing agents. The molecular electrostatic potential calculated on the molecular surface of **5** defined by the 0.001 electrons·bohr^{-3} contour of the electronic density is compared to that previously reported[17] for **5'** (Figure 4). The most negative electrostatic potential is located on the oxygen atoms of the hydroxyl groups of both compounds, but a significant negative electrostatic potential is also located at N2 and N4 on the convex side of the molecule. However, the presence of methyl substituents in the bisaminal group of **5** clearly causes steric hindrance around N2 and N4, thereby precluding *N*-alkylation reactions to occur. These methyl groups also hinder the carbon atom of the carbonyl group on the convex side of the molecule, which explains the lack of reactivity of **5** towards reducing agents such as $NaBH_4$.

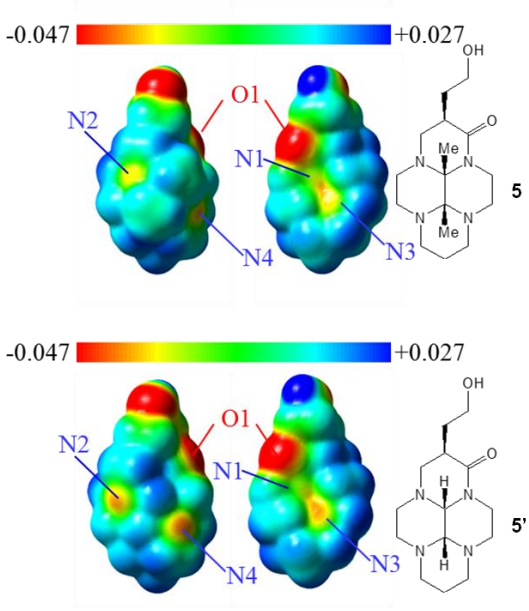


Fig. 4 Computed TPSSh/6-311G(d,p) electrostatic potentials (hartree) of **5** (bottom) and **5'** (top) on the molecular surfaces defined by the 0.001 electrons·bohr^{-3} contour of the electronic density. Convex sides are represented on the left and concave ones on the right.

To our knowledge, *C*-functionalized oxo-homocyclen **6** and "naked" homocyclen **8** are original and one can note that they have not been obtained by the glyoxal route because of the multiple stereoisomers (*gem/vic* and *cis/trans*) of the bisaminal obtained from the condensation of the starting linear tetramine with glyoxal.[21] Moreover, this strategy constitutes an efficient alternative to the glyoxal-bisaminal approach for the synthesis of *C*-functionalized cyclam derivatives **7** and **9**, because the experimental procedure is significantly faster: **7** is obtained in 6 days *vs* 10 days, whereas **9** is synthesized in only 2 steps and 7 days *vs* 5 steps and 24 days; furthermore, overall yields are higher and the synthesis described here for a 1 g scale has also been optimized to form 30 g of final macrocyclic compounds. Nevertheless, the two methods are complementary since the glyoxal approach is necessary for the synthesis of reinforced *C*-functionalized cyclam derivatives such as cb-te2a-EtOH.

Although a conjugation of these BCAs *"C*-EtOH" to a biomolecule is conceivable, through an ester or an ether bond for example, achieving *C*-functionalized macrocycle derivatives directly conjugable on biovectors (peptides or antibodies…) is a synthetic challenge that prompted us to modify the hydroxyl function into a

primary amino function *C*-EtNH$_2$, either from bisaminal intermediates or tetra-*N*-alkylated derivatives.

Synthesis of oxo-cyclam-EtNH$_2$ and cyclam-EtNH$_2$ by modification of the "*C*-EtOH" function. Here we describe the procedure for the synthesis of the oxo-cyclam-EtNH$_2$ and cyclam-EtNH$_2$ BCAs which could also be applied to the synthesis of the homocyclen analogues *C*-EtNH$_2$. The modification of the hydroxyl group was carried out starting from the bisaminal **5** in which the four nitrogen atoms of the macrocycle are protected by the bisaminal bridge. In a first step, **5** was treated with methanesulfonylchloride in dry dichloromethane with an excess of trimethylamine (Scheme 2). Surprisingly, the chloride derivative **10** was isolated instead of the expected mesylate derivative. One can assume that the carbon atom in the α position of the mesylate is particularly reactive and undergoes a nucleophilic substitution with the chloride ions released in the medium during the formation of the intermediate sulfene. Single crystals suitable for X-ray diffraction analysis were obtained for this chloro derivative **10** (Figure 5 and Table 4 in experimental section for data).

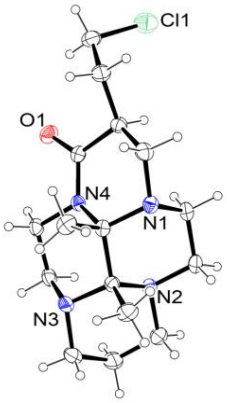
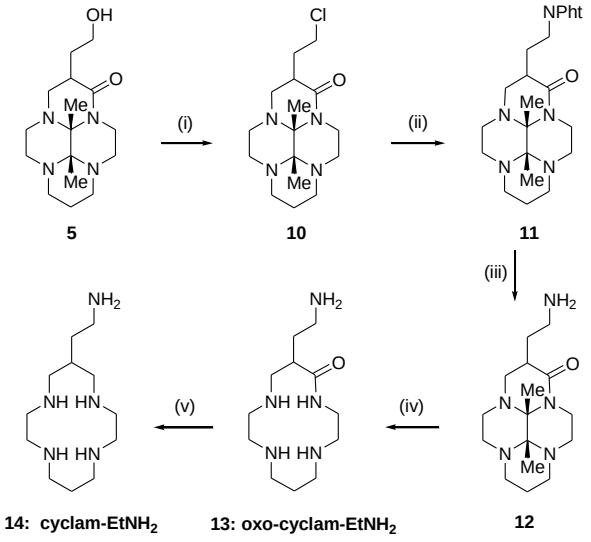


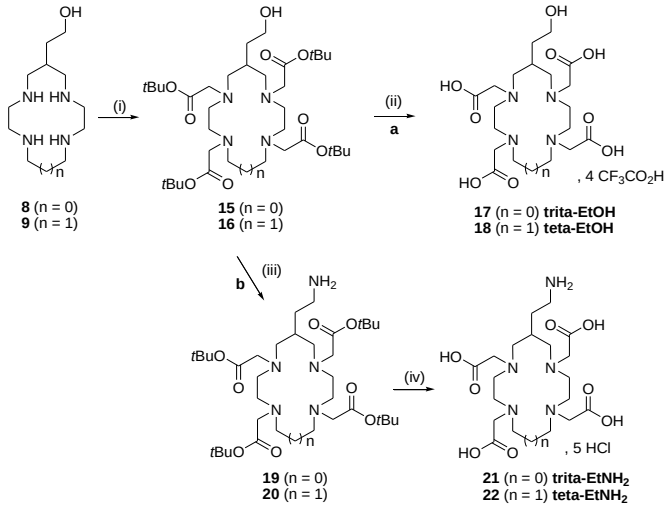
Fig. 5 View of the crystal structures of **10**. The ORTEP plot is at the 30% probability level.

In the next step, according to Gabriel synthesis of primary amines the addition of potassium phthalimide on **10** in refluxing toluene led to the phthalimide derivative **11** with 90% yield (54% from **5**). The overall yield of **11** is improved (82% from **5**) when the substitution with phthalimide is directly carried out with the crude mixture of **10**. The treatment of **11** with aqueous hydrazine in refluxing ethanol led to **12**, "EtNH$_2$" analogue of **5**, with 92% yield. Then, removal of the bisaminal bridge of **12** was achieved in an aqueous acidic medium containing 2,4-dinitrophenylhydrazine to prevent the reaction of free butanedione with the primary amino function of the chain. Oxo-cyclam-EtNH$_2$ **13** was obtained with 95% yield. Finally, the amide function of **13** was reduced using BH$_3$·THF to give cyclam-EtNH$_2$ **14** with 70%. One can note that, unlike for the synthesis of cyclam-EtOH **9,** for compound **14** the removal of bisaminal bridge can be performed prior to the reduction of amide function.



Scheme 2 Reagents and conditions: (i) Methanesulfonyl chloride (1.2 equiv.), Et_3N (2.5 equiv.), CH_2Cl_2, -14 °C, 4 h then rt, 2 h, 60%; (ii) Potassium phthalimide (4 equiv.), toluene, reflux, 18 h, 90%; (iii) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 4 h, 92%; (iv) HCl / 2,4-DNPH, rt, 30 min; ion exchange resin, 95%. (v) $BH_3{\cdot}THF$ (4 equiv.), THF, N_2, reflux, 7 d; HCl 3 M, reflux, 1 h; ion exchange resin, 70%.

Synthesis of tetraacetate derivatives. The syntheses were carried out starting from macrocycles-EtOH because of the inertness of the hydroxyl group in the conditions of *N*-alkylation reactions. The four secondary amine functions of homocyclen-EtOH **8** and cyclam-EtOH **9** were alkylated, as previously described,[17] in the presence of exactly four equivalents of *t*-butylbromoacetate in acetonitrile and an excess of potassium carbonate to give **15** and **16** with approximately 85% yield (Scheme 3). These tetra-*N*-alkylated compounds were engaged in two different pathways. The first one consists of the deprotection of the *tert*-butyl ester groups by treatment with trifluoroacetic acid in dichloromethane at room temperature, which allows to prevent the formation of lactone derivatives due to the reaction of the hydroxyl group with one of the pendant carboxylic acid arms (Scheme 3, route **a**). The BCAs teta-EtOH **17** and trita-EtOH **18** were obtained here very quickly and with quantitative yields. The second pathway consists of a Gabriel reaction, similar to that used for compound **5**, with a slight excess of methanesulfonyl chloride in presence of triethylamine (Scheme 3, route **b**). Because of their relative instability, the crude mesylated intermediates were directly reacted with an excess of potassium phthalimide in toluene at reflux for 18 hours to give phthalimide intermediates, which were treated with hydrazine hydrate in ethanol to give compounds **19** and **20** with overall yields of about 85%. If necessary, the phthalimide intermediates can be isolated after purification using silica-gel chromatography ($CHCl_3$/MeOH, 100:0-94:6) with respectively 70% and 75% yield. Finally, the hydrolysis of *t*-butyl esters was performed according to a classical treatment with aqueous hydrochloric acid under reflux to lead quantitatively to the new BCAs **21** and **22**.



Scheme 3 Reagents and conditions: (i) *t*-Butylbromoacetate (4 equiv), K_2CO_3, CH_3CN, 80 °C, 2 d, (n = 0: 90%; n = 1: 84%); (ii) TFA, CH_2Cl_2, rt, 24 h, quantitative yields; (iii) Methanesulfonyl chloride (1.2 equiv.), Et_3N (2.5 equiv.), CH_2Cl_2, -14 °C, 4 h then rt, 2 h; Potassium phthalimide (4 equiv), toluene, reflux, 18 h ; $NH_2NH_2{\cdot}H_2O$ (6 equiv.), EtOH, reflux, 4 h, (n = 0: 86%; n = 1: 83%); (iv) HCl 3 M, reflux, 18 h, quantitative yields.

Acid-base properties of cyclam-EtOH and thermodynamic stability of the Cu^{2+} and Zn^{2+}. The *C*-functionalization of azamacrocycles is now recognized as one of the most efficient techniques to obtain their BCAs analogues while avoiding any critical loss of their coordination properties. Although this point is crucial for *in vivo* evaluation of ligands in the perspective of radiopharmaceutical applications, to our knowledge, no real physico-chemical study was reported to assess the effect of *C*-alkylation on the properties of the chelates. Only comparisons of *in vivo* and *in vitro* inertness of ligands and their grafted analogues on biovectors (peptides, antibodies…) have been described.[22] The eventual effect of the *C*-appended group can be investigated by assessing the acid-base and/or coordination properties of the ligands with metallic cations. Thus, we decided to investigate the protonation constants of cyclam-EtOH and to determine the thermodynamic stability of the corresponding Cu^{2+} and Zn^{2+} chelates. The cyclam-EtOH was selected for this study as the most representative example for two reasons: i) unlike $EtNH_2$, the hydroxyl function is relatively inert in the pH range of the study (2-12), ii) The choice of a "naked" cyclam for a first investigation was more convenient because it is easier to study compared to teta-like ligands such as **17** and **18** where the presence of both coordinated and non-coordinated acetate functions in Cu^{2+} and Zn^{2+} complexes can add a significant complexity to this study.

Potentiometric titrations in aqueous solutions were conducted at 25.0 ºC with ionic strength adjusted to 0.10 M using KNO_3. The stepwise constants (log K_i^H) and overall protonation constants (log β_i^H) of cyclam-EtOH are collected in Table 1, together with literature values for cyclam.[23] In a first view, the acid-base properties of both ligands are comparable, considering that the third and fourth protonation constants of cyclam-EtOH could not be determined because of the detection limit of the electrode. Indeed, the equilibrium constants characterizing the first and second protonation processes are very similar, showing that the supplementary *C*-appended chain has no effect on the protonation pattern of the azamacrocyclic backbone.

Table 1 Protonation constants of cyclam-EtOH and cyclam.[a,b]

Equilibrium quotient	cyclam-EtOH[c] log β_{H_iL} / log K_{H_iL}	cyclam[d] log β_{H_iL} / log K_{H_iL}
[HL]/[L][H]	11.16 11.16(1)	11.54 11.54
$[H_2L]/[HL][H]$	21.31 10.14(2)	21.89 10.35
$[H_3L]/[H_2L][H]$	– –	24.32 2.43
$[H_4L]/[H_3L][H]$	– –	26.29 1.97

[a]Charges are omitted for clarity; [b]Values in parentheses are standard deviations in the last significant digit; [c] 25.0 ºC, *I* = 0.1 M in KNO_3; [d] 20.0°C, I= 0.1 M in KNO_3 , refs [23] and [24].

Table 2 Stepwise (log K_{MH_iL}) and overall (log β_{MH_iL}) stability constants determined for the complexes of Cu^{2+} and Zn^{2+} with cyclam-EtOH and cyclam.[a,b]

	Equilibrium	cyclam-EtOH[c] log β_{MH_iL} / log K_{MH_iL}	cyclam log β_{MH_iL} / log K_{MH_iL}
Cu^{2+}	[ML]/[M][L]	23.6 23.6(1)	26.51[d] 26.51
	[MHL]/[ML][H]	26.6 2.9(1)	– –
	[ML]/[MLOH][H]	12.8 -10.8(2)	– –
	pCu	**19.5**	**20.4**
Zn^{2+}	[ML]/[M][L]	14.7[e] 14.7(1)	15.34[f] 15.34
	[ML]/[MLOH][H]	6.0 -8.7(1)	– –
	$[MLOH]/[ML(OH)_2][H]$	-3.9 -12.7 (2)	– –
	pZn	**9.2**	**9.2**

[a]Charges are omitted for clarity; [b]Values in parentheses are standard deviations in the last significant digit; [c]"out-of-cell" titrations, 25.0 ºC, *I* = 0.10 M (KNO_3), Na_2H_2edta solution; *d* "out-of-cell" titrations, 25.0 ºC, *I* = 0.10 M (KNO_3), K_2H_2edta solution, ref [25]; [e]"out-of-cell" titrations, 25.0 ºC, *I* = 0.10 M (KNO_3), f 25.0 ºC, *I* = 0.5 M in KNO_3, ref [26].

The stability constants of the Cu^{2+} and Zn^{2+} complexes with cyclam-EtOH were determined by means of potentiometric titrations in aqueous solutions. Indeed, in numerous applications Zn^{2+} is frequently considered as one of the most important competitors for Cu^{2+} and generally exhibits similar coordination properties. For instance, as Zn^{2+} is readily available in the biologic media, BCAs must present an important affinity for Cu^{2+} but must also preser an important selectivity over Zn^{2+}. The complexe of cyclam-EtOH with Cu^{2+} is formed very quickly at low pH, with almost no free metal ion found above pH 2. Consequently, for this complex it w s not possible to determine the stability constants by direc potentiometry. Instead, "out of cell" competition titration wi H_4edta (ethylenediaminetetracetic acid) was used to determine t stability constant of the [Cu(cyclam-EtOH)] complex. On th

contrary, complexation process with Zn^{2+} was very slow at low pH. Thus "out of cell" titration was also performed in the case of Zn^{2+} order this time to overcome the slow complexation kinetics. Stepwise (log K_{MH_iL}) and overall (log β_{MH_iL}) stability constants determined for both cations are reported in Table 2, while copper(II) and zinc(II) speciation diagrams in the presence of cyclam-EtOH are presented in Figure 6.

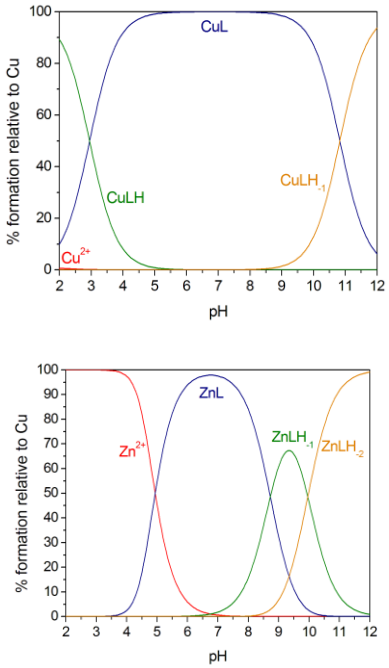


Fig. 6 Copper(II) and zinc(II) speciation diagrams in the presence of Cyclam-EtOH. $[M^{2+}]_{tot} = [L]_{tot} = 10^{-3}$ M.

In a first view, cyclam-EtOH presents very high complexation constants with copper(II) and a moderate affinity for zinc(II). The speciation diagram obtained for the Cu^{2+} complex shows that the metal ion is in the complexes form nearly in the whole pH domain from 2 to 12, a very slight dissociation only occurring at very acidic pH values. The Zn^{2+} complex is, as expected, less stable, with dissociation occurring just below pH ~ 7. The logK_{ML} values reported in the literature for the Cu^{2+} and Zn^{2+} complexes of cyclam differ significantly from those reported here for Cyclam-EtOH, particularly in the case of Cu^{2+}. This might be related to the different speciation models used to analyze the titration data and to the different ionic strengths used for the two sets of data. However, the difference could be also explained in terms of possible distortions of the functionalized carbon subunit in solution. A more accurate assessment of the complexation efficiency of the ligands can be made by determining the respective pM values (-log $[M]_{free}$), which take into account the difference in basicity of the ligands and the full set of stability constants for each system. Table 2 also presents the pM values determined at physiological pH for all complexes from the previously discussed constants. The obtained pM values show that the stability of the complex of Cu^{2+} with cyclam is only one log unit higher than those of cyclam-EtOH (pM = 19.5 *vs* pM 20.4). Even more interestingly, the complexes of Zn^{2+} with both ligands have the exact same pM (pM = 9.2). Thus, these values demonstrate that the *C*-alkylated cyclam derivative preserves the coordination properties and the selectivity for copper(II) over zinc(II) of the parent chelator.

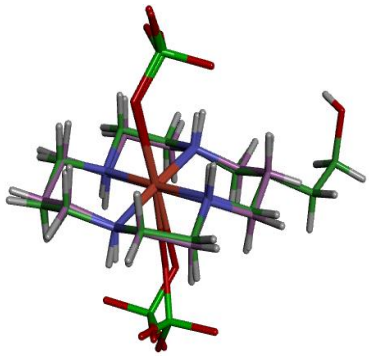


Fig. 7 Superposition of the X-ray crystal structures of $[Cu(cyclam\text{-}EtOH)](ClO_4)_2$[15] (green) and $[Cu(cyclam)](ClO_4)_2$ (purple).[25]

These results are in full agreement with the work reported in our previous paper,[17] where we presented the X-ray structure of $[Cu(cyclam\text{-}EtOH)](ClO_4)_2$, in which a *trans-III* conformation and a distorted octahedral geometry similar to that reported for $[Cu(cyclam)](ClO_4)_2$[27] were observed. Indeed, for these two complexes, according to the Cu-N and Cu-O bond lengths values (Table 3), Cu^{2+} is strongly coordinated by the four nitrogen atoms of the macrocycle, which define the equatorial plane, and more weakly by two oxygen atoms of two perchlorate anions in apical position. A superposition of the two structures (Figure 7) clearly confirms that the *C*-functionalization does not have a significant influence on the geometry of the Cu^{2+} complex (see in ESI for atoms numbering and comparison of the separated structures).

Table 3 Experimental (X-ray) bond lengths (Å)[a] and angles (°)[a] of the metal coordination environment in $[Cu(cyclam\text{-}EtOH)](ClO_4)_2$ and $[Cu(cyclam)](ClO_4)_2$. See figures for labeling.

Bond lenghts (Å) / Angles (°)	$[Cu(cyclam\text{-}EtOH)](ClO_4)_2$	$[Cu(cyclam)](ClO_4)_2$[b]
Cu-N1	2.0313(18)	2.02(2)
Cu-N4	2.0072(18)	2.02(2)
Cu-O1	2.51 (4)	2.57(4)
N1-Cu-N4	86.23(7)	86.0(2)
N4-Cu-N8 (or N1')	93.55(7)	94.0(2)
O1-Cu-N1	93.73(1)	85.4(2)
O1-Cu-N4	94.13(6)	92.4(2)
O1-Cu-N8 (or N1')	85.69(4)	94.6(2)
O1-Cu-N11 (or N4')	86.38(3)	87.6(2)

[a]Values in parentheses are standard deviations in the last significant digit. [b]Ref [27]

Conclusion

Because of the importance of cyclam or [13]aneN4 based BCAs in applications such as nuclear medicine, the development of new synthetic procedures to quickly and efficiently obtain new *C*-functionalized macrocycle derivatives is a great challenge.

The butanedione "route" reported here lead to *C*-functionalized cyclam or homocyclen bearing a hydroxyethyl function with good yields in only two steps and one week which is a significant advantage in comparison to our previously reported glyoxal methodology. This strategy also gives access to the corresponding oxo-cyclam and oxo-homocyclen analogues in a similar manner. The method is very efficient and could easily be scaled up. Moreover teta-EtOH and trita-EtOH were easily obtained by the direct *N*-functionalization by acetate functions of the *C*-EtOH cyclam and homocyclen backbones, respectively.

An additional procedure based on the Gabriel synthesis was finally performed to substitute the hydroxyethyl function by an aminoethyl one, more suitable for a subsequent conjugation to biovectors. This route gives access to the three different types of ligands presented here: "naked", oxo and tetraacetate-macrocycles.

Preliminary acid-base and thermodynamic studies of the Cu^{2+} and Zn^{2+} complexes with cyclam-EtOH by means of potentiometric titrations were conducted in order to evaluate the influence of the *C*-EtOH group on the physico-chemical properties of the chelating moiety of the BCA. Results showed a very similar behaviour to those of cyclam in particular for the preservation of the selective complexation of copper(II) over zinc(II).

This synthetic strategy constitutes a powerful alternative and a complementary procedure to obtain *C*-functionalized cyclams and related derivatives (homocyclens and oxo-macrocycles) without alteration of their coordination properties toward Cu^{2+}. Such BCAs can then be safely used in nuclear medicine applications and could also be useful for other purposes (catalysis, bioprobes…). Current works are in progress to study the physico-chemical properties of new ligands prepared according to this methodology, as well as their use as components of new radiopharmaceuticals.

Experimental Section

Materials and Methods. Bisaminals **1**, **2**[18] and [Cu(cyclam-OH)]$(ClO_4)_2$[17] were synthesized as previously described. 2D NMR ^{1}H-^{1}H homonuclear, ^{1}H-^{13}C and ^{1}H-^{15}N heteronuclear correlations and homonuclear decoupling experiments were used for assignment of the ^{1}H and ^{13}C signals. The δ scales are relative to TMS (^{1}H, ^{13}C) and CH_3NO_2 (^{15}N). The signals are indicated as follows: chemical shift, intensity, multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; m, multiplet; q, quartet), coupling constants *J* in hertz (Hz), assignment: Hα, Cα and Hβ, Cβ correspond to CH or CH_2 located in alpha or beta position respectively of considered nitrogen atom; Am, Ar and Ph are the abbreviations used for aminal, aromatic and phenyl respectively). All analytical spectra and data are given in Supplementary Information.

General procedure for the synthesis of 4 and 5.

A solution of α-methylene-γ-butyrolactone **3** (1.5 equiv.) in MeOH (50 mL) was added dropwise to a solution of 10.00 g of compound **1** (50.94 mmol) or **2** (47.60 mmol) in MeOH (200 mL). The solution was stirred at 45 °C for 5 d. The solvent was evaporated under reduced pressure. An aqueous solution of NaOH was added (75 mL, 3 M) and the solution was stirred at rt overnight. The product was extracted with $CHCl_3$ (5 × 120 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure. For compound **4**, the resulting yellow oil was crystallized in refluxed Et_2O to give off white crystals (6.75 g, 45%), m.p. 84-86 °C. For compound **5**, the resulting residue was recrystallized in a mixture of toluene/hexane 1:1 (60 mL) to give off white crystals (9.00 g, 68%), m.p. 134-136 °C.

Oxo-homocyclen-butanedione-EtOH (**4**) *(cis/syn diastereoisomer).* IR: $\tilde{\nu}$ = 3355 (O-H, weak, broad), 1619 (NH-*C*=*O*, strong, sharp) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): *δ* = 4.75 (br s, 1H, O*H*), 4.35 (dt, *J* = 13.5, 3.0 Hz, 1H), 3.80-3.70 (m, 1H), 3.70-3.60 (m, 1H), 3.30-3.10 (m, 4H), 2.95-2.80 (m, 5H), 2.75-2.60 (m, 3H), 2.60-2.55 (m, 1H), 2.50-2.40 (m, 1H), 1.95-1.85 (m, 1H), 1.61 (s, 3H, C*H*$_3$), 1.50-1.40 (m, 1H), 1.16 ppm (s, 3H, C*H*$_3$). ^{13}C Jmod NMR (100 MHz, $CDCl_3$, 25 °C, TMS): *δ* = 172.5 (*C*O), [78.2, 74.6] (N-*C*(CH$_3$)-N), [61.6, 50.6, 50.1, 48.9, 47.3, 45.8, 43.9, 37.8] (*C*H$_2$-α-N, *C*H$_2$-α-OH), 34.2 (*C*H-β-N), 32.8 (*C*H$_2$-β-OH), [25.9, 12.9] ppm (*C*H$_3$). MS (MALDI-TOF, matrix: dithranol): *m/z* 295.12 [M+H]$^+$. Elemental analysis calcd (%) for $C_{15}H_{26}N_4O_2{\cdot}0.9H_2O$: C 58.00, H 9.02, N 18.04, found: C 57.76, H 9.29, N 18.06.

Oxo-cyclam-butanedione-EtOH (**5**). IR: $\tilde{\nu}$ = 3371 cm^{-1} (O-H, weak, broad), 1610 cm^{-1} (C=O, strong, sharp). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): *δ* = 4.31 (d, *J* = 13.0 Hz, 1H), 3.80-3.65 (m, 2H), 3.65-3.55 (m, 1H), 3.28-3.12 (m, 3H), 2.90-2.70 (m, 3H), 2.70-2.55 (m, 3H), 2.55-2.45 (m, 2H), 2.35-2.30 (m, 2H), 2.30-2.15 (m, 1H), 1.95-1.80 (m, 1H), 1.63 (s, 3H, C*H*$_3$), 1.58-1.48 (m, 1H), 1.30 (s, 3H, C*H*$_3$), 1.18-1.10 (m, 1H). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): *cis/syn* diastereoisomer *δ* = 173.4 (*C*O), [75.9, 73.1] (N-*C*(CH$_3$)-N), [61.0, 50.7, 49.2, 48.8, 46.6, 45.9, 43.5, 38.5] (*C*H$_2$-α-N, *C*H$_2$-α-OH), 33.4 (*C*H-β-N), 32.5 (*C*H$_2$-β-OH), 24.9 (*C*H$_3$), 17.6 (*C*H$_2$-β-N), 10.9 ppm (*C*H$_3$); chemical shifts of the c*is/anti* diastereoisomer are not attributed. MS (MALDI-TOF, matrix: dithranol): *m/z* 309.14 [M+H]$^+$. Elemental analysis calcd (%) for $C_{16}H_{28}N_4O_2$: C 62.31, H 9.15, N 18.17, O 10.38; found: C 62.12, H 9.17, N 18.18, O 10.41.

General procedure for the synthesis of oxo-macrocycles-EtOH 6 and 7.

Compounds **6** and **7** were prepared by dissolving respectively 500 mg of compounds **4** (1.70 mmol) and **5** (1.62 mmol) in aqueous HCl (5.0 mL, 3M). The mixtures were stirred at rt for 30 min. An extraction with $CHCl_3$ (5 × 15 mL) was performed to eliminate organic impurities. Then the aqueous layers were subjected to an anion exchange resin (AG 3-X4A, 200-400 mesh) to yield the derivatives **6** (360 mg, 85%) and **7** (346 mg, 83%) as yellow oils.

Oxo-homocyclen-EtOH:
12-(2-hydroxyethyl)-1,4,7,10-tetraazacyclotridecan-11-one **(6).**
IR: $\tilde{\nu}$ = 3275 cm^{-1} (O-H, weak, broad), 1640 cm^{-1} (NH-*C*=*O*, strong, sharp), 1545 cm^{-1} (CO-*N*-*H*, strong, sharp). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): *δ* = 8.52 (br s, 1H, CO-N*H*), 3.64 (t, J = 6.0 Hz, 2H), 3.55-3.45 (m, 1H), 3.30 (br s, 4H, CH$_2$-N*H*-CH$_2$, O*H*), 3.15-3.05 (m, 1H), 2.90-2.70 (m, 10H), 2.70-2.60 (m, 2H), 2.60-2.55 (m, 1H), 1.95-1.85 (m, 1H), 1.70-1.55 (m, 1H). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): *δ* = 176,0 (*C*O), [60.4, 51.6, 47.2, 47.0, 46.78, 46.76, 45.5] (*C*H$_2$-α-N, *C*H$_2$-α-OH), 43.7 (*C*H-β-N), [39.4, 32.8] (*C*H$_2$-α-N, *C*H$_2$-β-

OH). HRMS (ESI) *m/z* calcd for $C_{11}H_{25}N_4O_2^+$ $[M+H]^+$ 245.1972, found: 245.1975.

Oxo-cyclam-EtOH:

***6-(2-hydroxyethyl)-1,4,8,11-tetraazacyclotetradecan-5-one* (7)**. IR: $\tilde{\nu}$ = 3269 cm^{-1} (O-H, weak, broad), 1648 (NH-*C*=*O*, strong, sharp), 1554 cm^{-1} (CO-*N*-*H*, strong, sharp). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 8,50 (br s, 1H, CO-N*H*), 4.00 (br s, 4H, CH_2-N*H*-CH_2, CH_2O*H*), 3.70-3.55 (m, 3H), 3.15-3.05 (m, 1H), 3.05-2.90 (m, 2H), 2.90-2.60 (m, 11H), 2.00-1.85 (m, 1H), 1.85-1.75 (m, 1H), 1.75-1.65 (m, 1H), 1.65-1.55 ppm (m, 1H). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = 176,0 (*C*O), [60.2, 51.0, 50.4, 49.8, 48.73, 48.65, 46.4] (*C*H_2-α-N, *C*H_2-α-OH), 43.5 (*C*H-β-N), [38.2, 33.1] (*C*H_2-α-N, *C*H_2-β-OH), 26.3 ppm (*C*H_2-β-N). HRMS (ESI) *m/z* calcd for $C_{12}H_{27}N_4O_2^+$ $[M+H]^+$ 259.2129, found: 259.2133.

General procedure for the synthesis of macrocycles-EtOH 8 and 9.
A solution of BH_3·THF (1.0 M, 4 equiv) was added dropwise to a solution of 3.00 g of compounds **4** (10.16 mmol) and **5** (9.73 mmol) in distilled THF (50 mL) under nitrogen atmosphere. The solution was stirred at rt for 1 h and then refluxed for 1.5 d. After cooling down to rt, EtOH was added to the solution to eliminate the excess of borane. The mixture was evaporated under reduced pressure. HCl (40 mL, 3 M) was added to the residue and the solution was refluxed for 1 h. After cooling down to rt, a first extraction with $CHCl_3$ (5 × 75 mL) was performed to eliminate organic impurities and the aqueous layer was evaporated under reduced pressure. MeOH (50 mL) was added to the residue and the resulting solution was immediately evaporated to eliminate methyl borate. This last operation was repeated three times. The brown residue was washed with warm EtOH to dissolve organic impurities. The white residue was filtered, dried under vacuum to give **8** or **9** as hydrochloride salts. In order to obtain the free base, the solid was dissolved in the minimum amount of distilled water and the solution was subjected to an anion exchange resin workup (AG 3-X4A, 200-400 mesh). Compound **9** was obtained as a white powder (1.90 g, 80%, m.p. 129-131 °C). For compound **8** the yellow oil obtained was crystallized from ethyl acetate to give an off white powder (1.99 g, 85%, m.p. 79-81 °C).

Homocyclen-EtOH:

***2-(1,4,7,10-tetraazacyclotridecan-12-yl)ethanol* (8).** ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): 3.63 (t, *J* = 6.0 Hz, 2H, CH_2OH), 2.95-2.40 (m, 17H), 2.40-1.80 (m, 5H), 1.75-1.40 ppm (m, 2H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [59.2, 53.0, 48.5, 47.4, 46.8] (*C*H_2-α-N, *C*H_2-α-OH), 36.1 (*C*H-β-N), 34.8 ppm (*C*H_2-β-OH). MS (MALDI-TOF, matrix: dithranol): *m/z* 231.08 $[M+H]^+$. Elemental analysis calcd (%) for $C_{11}H_{26}N_4O\cdot0.2H_2O$: C 56.47, H 11.37, N 23.95, found: C 56.67, H 11.53, N 23.82.

Cyclam-EtOH:

***2-(1,4,8,11-tetraazacyclotetradecan-6-yl)ethanol* (9).** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.50-3.30 (m, 2H), 3.10-1.85 (m, 21H), 1.80-1.65 (m, 1H), 1.55-1.40 (m, 2H), 1.40-1.30 ppm (m, 2H). ^{13}C Jmod NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = [59.0, 53.6, 49.9, 48.64, 48.61] (*C*H_2-α-N, *C*H_2-α-OH), 36.0 (*C*H-β-N), 35.2 (*C*H_2-β-OH), 29.0 ppm (*C*H_2-β-N). MS (MALDI-TOF, matrix: dithranol): *m/z* 245.17 $[M+H]^+$. Elemental analysis calcd (%) for $C_{12}H_{28}N_4O$: C 58.98, H 11.55, N 22.93, O 6.55, found: C 58.68, H 11.64, N 23.10, O 6.81.

Reactional sequence from oxo-cyclam-butanedione-EtOH 5 to cyclam-EtNH_2 14.

***Oxo-cyclam-butanedione-EtCl* (10)**. To a solution of compound **5** (1.10g, 3.57 mmol) and distilled triethylamine (1.24 mL, 8.93 mmol) in distilled CH_2Cl_2 (20 mL) at -10 °C methanesulfonyl chloride (550 µL, 7.14 mmol) was added dropwise. The mixture was stirred at the same temperature for 1 h and then warmed up to rt. The progress of the reaction was monitored by TLC (silica, $CHCl_3$/MeOH 94:6) and after the reaction was complete (~ 6 h), it was quenched by the addition of a saturated solution of $NaHCO_3$ (15 mL). The mixture was then extracted with CH_2Cl_2 (5 × 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a brown residue which was recrystallized in a mixture of hexane/ethyl acetate 1:1 (15 mL). Compound **10** was obtained as an off white powder (1.35 g, 60%). m.p. 123-125 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.40-4.10 (m, 1H), 3.90-3.65 (m, 3H), 3.40-3.10 (m, 3H), 3.00-2.80 (m, 3H), 2.80-2.50 (m, 5H), 2.50-2.20 (m, 3H), 1.80-1.60 (m, 2H), 1.57 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.30-1.10 ppm (m, 1H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.0 (*C*O), [75.7, 73.0] (N-*C*(CH_3)-N), [50.1, 49.2, 48.8, 46.6, 46.0, 43.5, 43.3, 38.3, 32.9] (*C*H_2-α-N, *C*H_2-α-Cl, *C*H_2-β-Cl), 31.6 (*C*H-β-N), [24.7, 10.8] (*C*H_3), 17.5 ppm (*C*H_2-β-N). HRMS (ESI) *m/z* calcd for $C_{16}H_{28}ClN_4O^+$ $[M+H]^+$ 327.1946, found: 327.1947.

***Oxo-cyclam-butanedione-EtPht* (11)**. The **crude mixture** of compound **10** was dissolved in toluene (25 mL) and potassium phtalimide (2.66 g, 14.48 mmol) was added. The mixture was stirred at reflux for 18 h and then filtered after cooling down to rt to eliminate the excess of potassium phtalimide. The filtrate was evaporated under reduced pressure to give a brown solid which was washed with EtOH (3 × 10 mL). Compound **11** was obtained as an off white powder (2.44 g, 82%). m.p. 201-203 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.75-7.65 (m, 2H, C*H*-Ar), 7.65-7.55 (m, 2H, CH-Ar), 4.22-4.10 (m, 1H), 3.80-3.50 (m, 3H), 3.25-3.05 (m, 3H), 3.05-2.90 (m, 1H), 2.80-2.40 (m, 7H), 2.40-2.00 (m, 4H), 1.50-1.35 (m, 1H), 1.42 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.10-1.00 ppm (m, 1H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.9 (*C*O-Amide), 168.0 (*C*O-Phtalimide), [133.8, 122.9] (*C*H-Ar), 131.9 (*C*-Ar), [75.8, 73.1] (N-*C*(CH_3)-N), [50.4, 49.4, 48.9, 46.7, 46.0, 43.7, 38.5, 36.1] (*C*H_2-α-N, *C*H_2-α-N-Phtalimide), 32.3 (*C*H-β-N), 29.3 (*C*H_2-β-N-Phtalimide), [24.8, 10.9] (*C*H_3), 17.7 ppm (*C*H_2-β-N). HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_5O_3^+$ $[M+H]^+$ 438.2500, found: 438.2501.

***Oxo-cyclam-butanedione-EtNH_2* (12)**. Compound **11** (500 mg, 1.14 mmol) was dissolved in a mixture of hydrazine monohydrate (330 µL, 64% in water, 6.84 mmol) and EtOH (20 mL). The solution was stirred at reflux for 4h and then EtOH was evaporated under reduced pressure. The white residue obtained was dissolved in an aqueous solution of NaOH (10 mL, 3M) and the organic compound was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give **12** as a yellow oil (290 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.35-4.15 (m, 1H), 3.70-3.50 (m, 1H), 3.20-3.05 (m, 3H), 2.90-2.35 (m, 9H), 2.35-1.80 (m, 7H), 1.5[illegible]-

1.30 (m, 1H), 1.42 (s, 3H, C*H*$_3$), 1.24 (s, 3H, C*H*$_3$), 1.20-1.00 ppm (m, 1H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 172,2 (*C*O), [75.3, 72.9] (N-*C*(CH_3)-N), [50.0, 48.6, 45.8, 43.4, 39.5, 38.0, 33.5] (*C*H_2-α-N, *C*H_2-α-NH_2, *C*H_2-β-NH_2), 31.7 (*C*H-β-N), [24.4, 10.6] (*CH*$_3$), 17.4 ppm (*C*H_2-β-N). HRMS (ESI) *m/z* calcd for $C_{16}H_{30}N_5O^+$ $[M+H]^+$ 308.2445, found: 308.2444.

Oxo-cyclam-EtNH$_2$:

***6-(2-aminoethyl)-1,4,8,11-tetraazacyclotetradecan-5-one* (13)**.

Compound **12** (3.00 g, 9.76 mmol) was dissolved in 40 mL of an hydrochloric (2.0 M) solution of 2,4-DNPH (5.0 M). The mixture was stirred at rt for 30 min. The light yellow precipitate was eliminated by filtration. An extraction of the filtrate with $CHCl_3$ (5 × 70 mL) was performed to eliminate organic impurities and the aqueous layer was subjected to an anion exchange resin (AG 3-X4A, 200-400 mesh). The combined aqueous phases were evaporated under reduced pressure to give **13** as a yellow oil (2.40 g, 95%). IR: $\nu^{\sim}$ = 1634 (NH-*C*=*O*, strong, sharp), 1557 (CO-*N*-*H*, strong, sharp) cm^{-1}. ^{1}H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 3.80-3.60 (m, 1H), 3.20-2.70 (m, 15H), 2.70-2.50 (m, 2H), 2.00-1.70 ppm (m, 4H). ^{13}C Jmod NMR (75 MHz, D_2O, 25 °C, TMS): δ = 179,1 (*C*O), [52.0, 51.4, 51.1, 50.9, 49.4, 47.8] (*C*H_2-α-N), 46.3 (*C*H-β-N), [40.6, 40.5, 30.3] (*C*H_2-α-N), 27.2 ppm (*C*H_2-β-N). HRMS (ESI) *m/z* calcd for $C_{12}H_{28}N_5O^+$ $[M+H]^+$ 258.2288, found: 258.2294.

Cyclam-EtNH$_2$:

***2-(1,4,8,11-tetraazacyclotetradecan-6-yl)ethanamine* (14)**.

A solution of BH_3·THF (110 mL, 1.0 M) was added dropwise to a solution of **13** (2.80 g, 10.89 mmol) in distilled THF (50 mL) under nitrogen atmosphere. The suspension was stirred at rt for 1 h and then refluxed for 7 days. After cooling down to rt, EtOH was added to the solution to eliminate the excess of borane. The mixture was evaporated under reduced pressure. HCl (40 mL, 3 M) was added to the residue and the solution was refluxed for 1 h. After cooling down to rt, a first extraction with $CHCl_3$ (5 × 75 mL) was performed to eliminate organic impurities and the aqueous layer was evaporated under reduced pressure. MeOH (50 mL) was added to the residue and the resulting solution was immediately evaporated to eliminate methyl borate. This operation was repeated three times. The brown residue was rinsed with warm EtOH to dissolve organic impurities. The white residue was filtered, dried under vacuum to give **14** as the hydrochloride salt. In order to obtain the free base, the solid was dissolved in the minimum of distilled water and the solution was subjected to an anion exchange resin workup (AG 3-X4A, 200-400 mesh). Compound **14** was obtained as a white powder (1.90 g, 70%). ^{13}C Jmod NMR (75 MHz, D_2O, 25 °C, TMS): δ = [55.7, 50.6, 49.7, 49.5, 41.2] (*C*H_2-α-N), 37.3 (*C*H-β-N), 36.6 (*C*H_2-β-NH_2), 29.3 ppm (*C*H_2-β-NH). HRMS (ESI) *m/z* calcd for $C_{12}H_{30}N_5^+$ $[M+H]^+$ 244.2496, found: 244.2493.

Synthesis of tetraacetate derivatives from macrocycles-EtOH 8 and 9.

General procedure for the synthesis of the intermediates 15 and 16.

A solution of *tert*-butyl bromoacetate (4 equiv.) in distilled CH_3CN (5 mL) was added dropwise to a suspension of 1.00 g of homocyclen-EtOH **8** (4.34 mmol) or cyclam-EtOH **9** (4.09 mmol) and K_2CO_3 (8 equiv.) in distilled CH_3CN (35 mL) heated to 80 °C. The suspension was stirred at the same temperature for 2 d and then cooled down to rt and filtered. After the removal of the solvent under vacuum, the residue was dissolved in $CHCl_3$ (15 mL). The organic fraction was washed with a solution of NaOH (3M, 2 × 15 mL), dried over $MgSO_4$, filtrated and evaporated under reduced pressure to give **15** as a yellow oil (2.68 g, 90%) and **16** as a yellow oil (2.40 g, 84%). If necessary, the compounds can be purified by aluminium oxide gel chromatography ($CHCl_3$/MeOH, 100:0-94:6).

tritatBu-EtOH:

***2-(1,4,7,10-Tetra(2-tert-butoxy-2-oxoethyl)-1,4,7,10-tetraazacyclotridecan-12-yl)ethanol* (15)**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.70-3.50 (m, 2H), 3.40-3.10 (m, 8H), 3.00-2.55 (m, 13H), 2.40-2.15 (m, 2H), 2.05-1.85 (m, 1H), 1.60-1.10 ppm (m, 40H). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = [170.9, 170.4] (*C*O), [80.9, 80.7] (*C*$(CH_3)_3$), [61.5, 59.7, 58.4, 55.5, 51.8, 51.6, 50.0] (*C*H_2-α-N, *C*H_2-α-OH), 37.8 (*C*H_2-β-OH), 36.4 (*C*H-β-N), 28.1 ppm (C(*C*H_3)$_3$ × 2). HRMS (ESI) *m/z* calcd for $C_{35}H_{67}N_4O_9^+$ $[M+H]^+$: 687.4903, found: 687.4898.

tetatBu-EtOH:

***2-(1,4,8,11-Tetra(2-tert-butoxy-2-oxoethyl)-1,4,8,11-tetraazacyclotetradecan-6-yl)ethanol* (16)**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.70-3.60 (m, 2H), 3.40-3.10 (m, 8H), 2.90-2.50 (m, 13H), 2.40-2.10 (m, 3H), 1.90-1.70 (m, 1H), 1.70-1.35 (m, 5H), 1.45 (s, 18H, C*H*$_3$), 1.44 ppm (s, 18H, C*H*$_3$). ^{13}C Jmod NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ = [170.7, 170.3] (*C*O), [81.0, 80.6] (*C*$(CH_3)_3$), [61.1, 60.3, 57.6, 56.7, 51.7, 51.0, 50.9] (*C*H_2-α-N, *C*H_2-α-OH), 37.6 (*C*H_2-β-OH), 36.0 (*C*H-β-N), 28.1 (C(*C*H_3)$_3$ × 2), 25.4 ppm (*C*H_2-β-N). HRMS (ESI) *m/z* calcd for $C_{36}H_{69}N_4O_9^+$ $[M+H]^+$: 701.5059, found: 701.5059.

General procedure for the synthesis of intermediates 17 and 18.

Compound **15** or **16** (0.43 mmol) were dissolved in a mixture of anhydrous CH_2Cl_2/TFA 1:1 (15 mL). The solution was stirred at room temperature for 36 h, and then the solvent was evaporated under reduced pressure at room temperature to give brown oil, which was lyophilized. Compounds **17** and **18** were obtained as off white solids (quantitative yields).

trita-EtOH:

***12-Aminoethyl-1,4,7,10-tetraazacyclotridecane-1,4,7,10-tetra acetic acid, tetratrifluoroacetic acid* (17)**. ^{13}C Jmod NMR (75 MHz, D_2O, 25 °C, TMS): δ = [174.5, 174.4] (*C*O), [63.5, 62.2, 58.0, 57.8, 56.4, 55.1, 54.9] (*C*H_2-α-N, *C*H_2-α-OH), 36.7 (*C*H_2-β-OH), 31.6 ppm (*C*H-β-N).

teta-EtOH:

***6-hydroxyethyl-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra acetic acid, tetratrifluoroacetic acid* (18).** ^{1}H NMR (300 MHz, D_2O, 25 °C, TMS): δ = 4.20-3.75 (m, 2H), 3.75-3.50 (m, 6H), 3.50-2.50 (m, 18H), 2.25-2.10 (m, 1H), 2,10-1,85 (m, 1H), 1,85-1,60 (m, 1H), 1,50-1,30 ppm (m, 2H). ^{13}C Jmod NMR (125 MHz, D_2O, 50 °C, TMS): δ = [172.2, 171.5] (*C*O), 162.5 (q, $^2J_{CF}$ = 36.3 Hz, *C*F_3CO_2H), 116.5 (q, $^1J_{CF}$ = 288.6 Hz, *C*F_3CO_2H), [62.1, 59.1, 55.6 (× 2), 55.5, 51.4, 50.8] (*C*H_2-α-N, *C*H_2-α-OH), 33.1 (*C*H_2-β-OH), 29.5 (*C*H-β-N), 20.8 ppm (*C*H_2-β-

N). (HRMS (ESI) m/z calcd for $C_{20}H_{37}N_4O_9^+$ $[M+H]^+$: 477.2555; found: 477.2560.

General procedure for the synthesis of the intermediates 19 and 20.

To a solution of 550 mg of compound **15** (0.80 mmol) or **16** (0.78 mmol) and distilled triethylamine (2.5 equiv.) in distilled CH_2Cl_2 (15 mL) at -10 °C was slowly added methanesulfonyl chloride (1.2 equiv.). The mixture was stirred at the same temperature for 1 h and then warmed up to rt. The progress of the reaction was monitored by TLC (silica gel, $CHCl_3$/MeOH 94:6) (~ 6 h), the solvent was evaporated under reduced pressure at 25 °C. The resulting residue was dissolved again in toluene (15 mL) and potassium phtalimide (4 equiv) was added. The mixture was stirred at reflux for 18 h and then filtered after cooling down to rt. The filtrate was evaporated under reduced pressure to give a yellow residue which was dissolved in a mixture of hydrazine monohydrate (64% in water, 6 equiv.) and EtOH (10 mL). The solution was stirred at reflux for 4 h and then EtOH was evaporated under reduced pressure. The yellow residue obtained was dissolved in an aqueous solution of NaOH (8 mL, 3 M) and the organic compound was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic fractions were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give **19** (470 mg, 86%) and **20** (450 mg, 83%) as yellow oils.

tritatBuEtNH$_2$:

***2-(1,4,7,10-Tetra(2-tert-butoxy-2-oxoethyl)-1,4,7,10-tetraazacyclo tridecan-12-yl)ethanamine* (19)**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.35-3.15 (m, 8H), 2.90-2.50 (m, 17H), 2.50-2.30 (m, 2H), 2.25-1.85 (br s, 2H), 1.60-1.40 (m, 2H), 1.40 (s, 36H, C*H$_3$*), 1.25-1.15 ppm (m, 1H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [171.20, 171.16] (*C*O), [80.77, 80.73] (*C*$(CH_3)_3$), [58.6, 58.3, 56.3, 52.4, 51.6, 50.8, 40.2, 36.6] (*C*H$_2$-α-N, *C*H$_2$-α-NH$_2$, *C*H$_2$-β-NH$_2$), 35.1 (*C*H-β-N), 28.3 ppm (*C*H$_3$ × 2). HRMS (ESI) *m/z* calcd for $C_{35}H_{68}N_5O_8^+$ $[M+H]^+$ 686.5072, found: 686.5076.

tetatBuEtNH$_2$:

***2-(1,4,8,11-Tetra(2-tert-butoxy-2-oxoethyl)-1,4,8,11-tetraazacyclo tetradecan-6-yl)ethanamine* (20)**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.40-3.10 (m, 8H), 2.90-2.40 (m, 14H), 1.90-1.35 (m, 8H), 1.45 (s, 36H, C*H$_3$*), 1.35-1.15 ppm (m, 3H). ^{13}C Jmod NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = [171.1, 171.0] (*C*O), 80.6 (× 2) (*C*$(CH_3)_3$), [58.9, 57.6, 57.1, 51.9, 51.3, 40.2, 36.5] (*C*H$_2$-α-N, *C*H$_2$-α-NH$_2$, *C*H$_2$-β-NH$_2$), 35.2 (*C*H-β-N), 28.2 (× 2) (*C*H$_3$), 25.5 ppm (*C*H$_2$-β-N). HRMS (ESI) *m/z* calcd for $C_{36}H_{70}N_5O_8^+$ $[M+H]^+$ 700.5219, found: 700.5210.

General procedure for the synthesis of compounds 21 and 22.

Compounds **21** and **22** were prepared by dissolving respectively 300 mg of compounds **19** (0.44 mmol) and **20** (0.43 mmol) in aqueous HCl (10.0 mL, 6M) and the mixtures were stirred at reflux overnight. The solutions were evaporated under reduced pressure to give quantitatively **21** (280 mg) and **22** (310 mg) as white powders.

trita-EtNH$_2$:

***12-Aminoethyl-1,4,7,10-tetraazacyclotridecane-1,4,7,10-tetra acetic acid, pentahydrochloric acid* (21)**. ^{1}H NMR (300 MHz, D_2O, 60 °C, TMS) : δ = 4.30-3.20 (m, 30H), 2.80-2.50 (m, 1H), 2.10-1.80 ppm (m, 2H). ^{13}C Jmod NMR (75 MHz, D_2O, 60 °C, TMS): δ = [174.1, 173.9] (*C*O), [63.3, 57.4, 56.6 (× 2), 54.6, 54.3, 40.2] (*C*H$_2$-α-N, *C*H$_2$-α-NH$_2$), 31.91 (*C*H-β-N), 31.86 ppm (*C*H$_2$-β-NH$_2$). HRMS (ESI) *m/z* calcd for $C_{19}H_{36}N_5O_8^+$ $[M+H]^+$ 462.2558, found: 462.2561.

teta-EtNH$_2$:

***6-Aminoethyl-1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetra acetic acid, pentahydrochloric acid* (22)**. ^{1}H NMR (300 MHz, D_2O, 25 °C, TMS) : δ = 4.20-3.50 (m, 9H), 3.50-3.10 (m, 14H), 3.10-2.70 (m, 7H), 2.15-1.75 (m, 3H), 1.75-1.40 ppm (m, 2H). ^{13}C Jmod NMR (75 MHz, D_2O, 25 °C, TMS): δ = [174.4, 172.4] (*C*O), [63.0, 57.7 (× 2), 56.3, 52.4, 52.1, 39.4] (*C*H$_2$-α-N, *C*H$_2$-α-NH$_2$), 32.2 (*C*H-β-N), 30.6 (*C*H$_2$-β-NH$_2$), 22.0 ppm (*C*H$_2$-β-N). Elemental analysis calcd (%) for $C_{20}H_{37}N_5O_8{\cdot}5HCl{\cdot}3.4H_2O$: C 33.41, H 6.84, N 9.74, found: C 33.14, H 6.45, N 9.81.

Computational methods. All calculations were performed employing DFT within the hybrid meta generalized gradient approximation (hybrid meta-GGA), with the TPSSh exchange-correlation functional,[28] and the Gaussian 09 package (Revision A.02).[29] Full geometry optimizations of **5** and **19** were performed *in vacuo* by using the standard 6-311G(d,p) basis set. No symmetry constraints have been imposed during the optimizations. The default values for the integration grid ("fine") and the SCF energy convergence criteria (10^{-8}) were used. The stationary points found on the potential energy surfaces as a result of the geometry optimizations have been tested to represent energy minima rather than saddle points via frequency analysis. Relative free energies of the *cis*/*syn* and *cis*/*anti* isomers of **9** include non-potential energy contributions (zero point energies and thermal terms) obtained from frequency analysis. The electrostatic potential *V*(r) that the electrons and nuclei create at any point **r** in the surrounding space was calculated at the TPSSh/6-311G(d,p) level according to eq. 1:

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r'-r|} \quad (1)$$

where *Z* is the charge on nucleus A, located at R_A, and ρ(r) is the electron density of the molecule.

X-ray diffraction measurements. Single-crystal X-ray diffraction data were collected with graphite-monochromatized MoK_α radiation (λ = 0.71073). Crystal data and structure refinement details are given in Table 4. Unit-cell determination and data reduction, including interframe scaling, Lorentz, polarization, empirical absorption and detector sensitivity corrections, were carried out using attached programs of Crysalis software (Oxford Diffraction).[30] Structures were solved by direct methods and refined by full matrix least squares method on F^2 with the SHELXL[31] suite of programs. The hydrogen atoms were identified at the last step and refined under geometrical restraints and isotropic U-constraints. CCDC 1412260-1412262 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 4 X-Ray crystal data collection and refinement details of organic compounds.

Compound	4	5	10
formula	$C_{15}H_{26}N_4O_2$	$C_{16}H_{28}N_4O_2$	$C_{16}H_{27}ClN_4O$
MW	294.40	308.42	326.87
crystal system	Monoclinic	Monoclinic	Orthorhombic
space group	$P2_1/n$	$P2_1/n$	$Pna2_1$
T/K	170(2)	170(2)	297(2)
a/Å	11.7908(8)	5.9879(5)	19.2249(8)
b/Å	10.4516(8)	19.2936(13)	13.6646(5)
c/Å	12.3326(8)	13.5403(9)	6.0897(2)
α/deg	90	90	90
β/deg	97.971(6)	90.795(7)	90
γ/deg	90	90	90
v/Å^3	1505.10(18)	1564.1(2)	1599.77(10)
F(000)	640	672	704
Z	4	4	4
λ, Å (MoK$_\alpha$)	0.71073	0.71073	0.71073
D_{calc}/g cm^{-3}	1.299	1.310	1.357
μ/mm^{-1}	0.088	0.088	0.247
θ range/deg	2.97 to 25.68	3.19 to 28,27	3.16 to 28.27
R_{int}	0.0622	0.0925	0.0282
reflns collect	10760	13412	13686
unique reflns	2854	3861	2980
GOF on F^2	0.805	0.846	1.010
R_1[a]	0.0383	0.0534	0.0428
wR_2 (all data)[b]	0.0701	0.0886	0.1020
Largest diff peak and hole /eÅ^{-3}	0.156 and -0.162	0.201 and -0.183	0.314 and -0.136

[a] $R1 = \sum \big| |F_0| - |Fc| \big| / \sum |F_0|$. [b] $wR2 = \{\sum[w(|F_0|^2 - |Fc|^2)^2] / \sum[w(F_0^4)]\}^{1/2}$

Potentiometric studies. All experiments were carried out in aqueous solutions thermostated at 25.0 ± 0.1 ºC under inert atmosphere. Protonation and complexation titrations were performed in a glass-jacketed titration cell, using a Metrohm 702 SM Titrino titration stand connected to a Metrohm 6.0233.100 combined glass electrode. Competition titrations were performed using different samples of 2 mL solutions at various pH and incubated at 25 °C. Titrants were KOH solutions prepared at *ca.* 0.1 M from a commercial ampoule of analytical grade, and their accurate concentration was obtained by titration of a standard HNO_3 solution. Ligand solutions were prepared at *ca.* 2×10^{-3} M, and the Cu^{2+} and Zn^{2+} solutions were prepared from analytical grade chloride salts and standardized by complexometric titrations with edta (ethylenediaminetetraacetic acid). Sample solutions for titration contained approximately 0.05 mmol of ligand in a volume of 30 mL where the ionic strength was kept at 0.10 M using KNO_3 as background electrolyte. In complexation titrations metal cations were added at 0.9 equiv. of the ligand amount, while in competition titrations Cu^{2+} was added at 1 equiv. and edta was added at 1.6 equiv. as a competitor ligand. The electromotive force of the sample solutions was measured after calibration of the electrode by titration of a standard HNO_3 solution at 2×10^{-3} M. The $[H^+]$ of the solutions was determined by measurement of the electromotive force of the cell, $E = E^{o'} + Q \log [H^+] + E_j$. The term pH is defined as $-\log [H^+]$. $E^{o'}$ and Q were determined by titrating a solution of known hydrogen-ion concentration at the same ionic strength. The liquid-junction potential, E_j, was found to be negligible under the experimental conditions used. A value of $K_w = [H^+][OH^-]$ equal to $10^{-13.778}$ was taken from the literature for our ionic strength conditions.[33] The protonation constants of H_4edta and the thermodynamic stability constants of its copper(II) complex used in competition titration refinements were taken from the literature.[34] Each titration consisted of 100–150 equilibrium points in the range of pH 2.0–11.5, and at least two replicate titrations were performed for each particular system. The potentiometric data were refined with the Hyperquad software,[35] and speciation diagrams were plotted using the Hyss software.[36] The overall equilibrium constants β_i^H and $\beta_{M_mH_hL_l}$ are defined by $\beta_{M_mH_hL_l} = [M_mH_hL_l]/[M]^m[H]^h[L]^l$ and $\beta_{MH_{-1}L} = \beta_{ML(OH)} \times K_w$. Differences, in log units, between the values of protonated (or hydrolysed) and non-protonated constants provide the stepwise (log K) reaction constants (being $K_{M_mH_hL_l} = [M_mH_hL_l]/[M_mH_{h-1}L_l][H]$). The errors quoted are the standard deviations of the overall stability constants calculated by the fitting program from all the experimental data for each system.

Acknowledgements

R.T. acknowledges the Région Bretagne (VALITEP program), the Ministère de l'Enseignement Supérieur et de la Recherche, the Centre National de la Recherche Scientifique and specially the financial support from the Région Bretagne and the ANR program αRIT/βPET France. R.T. also thanks the "Service Commun" of NMR facilities of the University of Brest. Authors also thank Fréderic Boschetti for the starting tetraamine. C. P.-I. acknowledges Centro de Supercomputación de Galicia (CESGA) for providing the computer facilities.

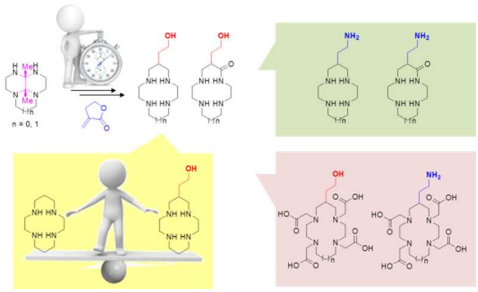
Notes and references

1 a) R. M. Izatt, K. Pawlak, J. S. Bradshaw, *Chem. Rev.* 1995, **95**, 2529; b) R. Delgado, V. Felix, L. M. P. Lima, D. W. Price, *Dalton Transactions*, 2007, **26**, 2734.
2 R. Lewis, S. J. Archibald, *Coord. Chem. Rev.,* 2010, **254***,* 1686.
3 a) T. J. Wadas, E. H. Wong, G. R. Weisman, C. J. Anderson, *Chem. Rev.*, 2010, **110**, 2858. b) E. W. Price, C. Orvig, *Chem. Soc. Rev.*, 2014, **43**, 260. c) D. Brasse, A. Nonat, *Dalton Trans.*, 2015, **44**, 4845.
4 C. F. Ramogida, C. Orvig, *Chem. Commun.,* 2013, **49**, 4720.
5 M. W. Brechbiel, *Dalton Trans.*, 2007, 1918.
6 R. Delgado, J. J. R. Fraústo da Silva, *Talanta,* 1982, **29**, 815.
7 D. N. Pandya, J. Y. Kim, J. C. Park, H. Lee, P. B. Phapale, W. Kwak, T. H. Choi, G. J. Cheon, Y.-R. Yoon, J. Yoo, *Chem. Commun.,* 2010, **46**, 3517.
8 R. Ruloff, E. Toth, R. Scopelliti, R. Tripier, H. Handel, A. E. Merbach, Chem. Commun., 2002, 2630.
9 K. J. Heroux, K. S. Woodin, D. J. Tranchemontagne, P. C. B. Widger, E. Southwick, E. H. Wong, G. R. Weisman, S. A. Tomellini, T. J. Wadas, C. J. Anderson, S. Kassel, J. A. Golen, A. L. Rheingold, *Dalton Trans.,* 2007, 2150.
10 N. D. Pandya, A. V. Dale, J. Y. Kim, H. Lee, Y. S. Ha, G. I. An, J. Yoo, *Bioconjugate Chem.*, 2012, **23**, 330.
11 a) F. Riche, M. Vidal, C. Bolzati, L. Uccelli, A. Marchi, A. Duatti, *Inorg. Chem. Acta,* 1995, **231**, 147. b) F. Riche, R. Pasquali, A. Duatti, M. Vidal, *Appl. Radiat. Iso.,* 1992, **43**, 438.
12 E. Kimura, A. Sakonaka, T. Yatsunami, M. Kodama, *J. Chem. Soc.* 1981, **103**, 3041; b) D. A. Tomalia, L. R. Wilson, U.S. patent, 1985, US4517122; c) M. Achmatowicz, L. S. Hegedus, *J. Org. Chem*., 2003, **68**(16), 6435.
13 a) J. W. Krajewski, P. Gluzinski, R. A. Kolinski, A. Kemme, A. Mishnev, *Pol. J. Chem.,* 1994, **68**, 703. b) F. Bellouard, F. Chuburu, N. Kervarec, L. Toupet, S. Triki, Y. Le Mest, H. Handel, *J. Chem. Soc., Perkin Trans. 1,* 1999, 3499; c) X. Sun,

J. Kim, A. E. Martell, M. J. Welch, C. J. Anderson, *Nucl. Med. Biol.*, 2004, 1051.
14 B. M. Zeglis, J. S. Lewis, *Dalton Trans.*, 2011, **40**, 6168.
15 a) I. Tabuschi, Y. Taniguchi, H. Kato, *Tetrahedron Lett.,* 1977, **12**, 1049; b) E. Kimura, T. Koike, R. Machida, R. Nagai, M. Kodama, *Inorg. Chem.,* 1984, **23**, 4181; c) E. Kimura, T. Koike, M. Takahashi, *J. Chem. Soc., Chem. Commun*., 1985, 385. d) E. Kimura, T. Koike, H. Nada, Y. Iitaka, *J. Chem. Soc., Chem. Commun*., 1986, 1322; e) J. R. Morphy, D. Parker, R. Kataky, M. A. W. Eaton, A. T. Millican, R. Alexander, A. Harrison, C. Walker, *J. Chem. Soc., Perkin Trans. 2*, 1990, 573; f) P. Moreau, M. Tinkl, M. Tsukazaki, P. S. Bury, E. J. Griffen, V. Snieckus, R. B. Maharajh, C. S. Kwok, V. V. Somayaji, Z. Peng, T. R. Sykes, A. A. Noujaim, *Synthesis*, 1997, 1010; g) J. P. L. Cox, K. J. Jankowski, R. Kataky, D. Parker, N. R. A. Beeley, B. A. Boyce, M. A. W. Eaton, K. Millar, A. T. Millican, A. Harrison and C. Walker , *J. Chem. Soc., Chem. Commun*., 1989, 797.
16 a) P. Désogère, C. Bernhard, C. Goze, M.-J.; Penouilh, Y. Rousselin, F. Denat, *Eur. J. Org. Chem.* 2013, 1538; b) F. Boschetti, F. Denat, E. Espinosa, J.-M. Lagrange, R. Guilard, *Chem. Commun.,* 2004, 588; c) E. A. Lewis, C.C. Allan, R. W. Boyle, S. J. Archibald, *Tetrahedron Lett.,* 2004, 45, 3059.
17 a) R. Tripier, N. Camus, World Patent, 2013, WO 2013072491 A1. b) N. Camus, Z. Halime, N. Le Bris, H. Bernard, C. Platas-Iglesias, R. Tripier, *J. Org. Chem.*, 2014, 1885.
18 G. Hervé, H. Bernard, N. Le Bris, J. J. Yaouanc, H. Handel, *Tetrahedron Lett.,* 1998, **39**, 6861.
19 R. Tripier, J.- M. Lagrange, E. Espinosa, F. Denat, R. Guilard, *Chem. Commun.*, 2001, 2728.
20 H. Handel, H. Bernard, M. Antoine, *Int. Appl.* 2002, WO 02/06209.
21 G. Hervé, H. Bernard, N. Le Bris, M. Le Baccon, J. J. Yaouanc, H. Handel, *Tetrahedron Lett.,* 1999, **40**, 2517 ; b) F. Chuburu, R. Tripier, M. Le Baccon, H. Handel, *Eur. J. Org. Chem*., 2003, 1050.
22 C. A. Boswell, C. A. S Regino, K. E. Baidoo, K. J. Wong. A. Bimb, H. Xu, D. E. Milenic, J. A. Kelley, C. C. Lai, M. W. Brechbiel, *Bioconjugate Chem.,* 2008, **19**, 1476.
23 E. Suet, A. Laouenan, *Talanta*, 1986, **33**, 721.
24 E. Suet, A. Laouenan, H. Handel, R. Guglielmetti, *Helv. Chim. Acta*, 1984, **67**, 441.
25 Y. Moriguchi, M. Hashimoto, K. Sakata, *Fukuoka Kyoiku Daigaku Kiyo, Dai-3-bunsatsu: Sugaku, Rika, Gijutsuka Hen*, 1990, 43.
26 M. Micheloni, P. Paoletti, *Inorg. Chim. Acta*, 1980, **43**, 109.
27 P. A. Tasker, L. Sklar, *J. Cryst. Mol. Struct.,* 1975, **5**, 329.
28 J. M. Tao, J. P. Perdew, V. N. Staroverov, G. E. Scuseria, *Phys. Rev. Lett.,* 2003, **91**, 146401.
29 Gaussian 09, Revision A.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, Jr. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian Inc., Wallingford CT, 2009.
30 Crysalis software system, version 1.171.28 cycle4 beta; Oxford Diffraction Ltd.: Abingdon, U.K., 2005.
31 SHELX; G. M. Sheldrick, *Acta Crystallogr.,* 2008, A64, 112.
32 P. K. Glasoe, F. A. Long, *J. Phys. Chem.,* 1960, 188.
33 R.F. Jameson, M.F. Wilson, *J. Chem. Soc. Dalton Trans.,* 1972. 2607.
34 R. Delgado, M. C. Figueira, S. Quintino, *Talanta,* 1997, **45**, 451.
35 P. Gans, A. Sabatini, A. Vacca, *Talanta,* 1996**, 43**, 1739.
36 L. Alderighi, P. Gans, A. Ienco, D. Peters, A. Sabatini, A. Vacca *Coord. Chem. Rev.,* 1999**, 184**, 311.

A [Two-Steps / One Week] Synthesis of *C*-Functionalized Homocyclens and Cyclams. Application to the Preparation of Conjugable BCAs without Chelating Properties Alteration

Nathalie Camus, Zakaria Halime, Nathalie Le Bris, Hélène Bernard, Maryline Beyler, Carlos Platas-Iglesias and Raphaël Tripier*



An efficient synthesis of *C*-functionalized tetraazamacrocycles is presented together with a coordination investigation showing that macrocycles kept their coordination properties.