

Bis-aminals: efficient tools for bis-macrocycle synthesis

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Tetraazamacrocyclic bis-aminals prove to be excellent tools for the synthesis of symmetrical, dissymmetrical or functionalized bis-tetraazamacrocycles. The key feature of the process is the separation of insoluble mono- or bis-quaternary ammonium salts from solution during the course of the alkylation reaction.

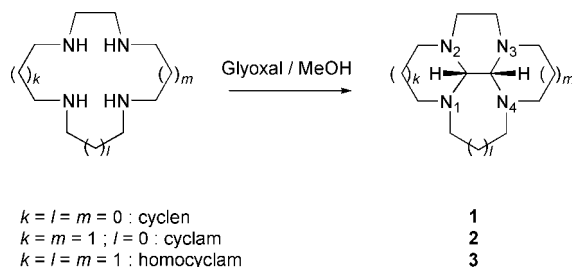
Macrocyclic saturated tetraamines constitute versatile ligands whose high binding affinity for transition metals is now well documented.¹ Their complexation ability can be modulated by ligand functionalization and derivatives with tailored properties can be synthesized.² Among these derivatives, bis-macrocycles represent noteworthy examples. In particular, bis-cyclams were described as a new class of antiviral agents that exhibit potent inhibitory effects on HIV-1 and HIV-2 replication along with high selectivity.³

From a chemical point of view, their synthesis requires a subsequent mono-N alkylation of the starting macrocycle and the methods previously reported have been based either on classical temporary techniques^{4–6} or on the use of triprotected groups.^{7–10} Recently, new methods using an amination intermediate have been developed for cyclen¹¹ and cyclam¹² mono-N functionalization. But surprisingly, to our knowledge no extension of this route to bis-tetraazamacrocycles has been developed.

In this paper, we report on a new strategy for the synthesis of symmetrical and dissymmetrical bis-tetraazamacrocycles and propose an extension to functionalized bis-tetraazamacrocycles.

Results and discussion

Macrocyclic bis-aminals, synthesized from the condensation of glyoxal with tetraazamacrocycles such as cyclen, cyclam or homocyclam, have been known for more than twenty years.¹³ When the reaction is carried out in methanol, compounds **1**, **2** and **3** are obtained quantitatively (Scheme 1). Their respective structures are characterized by a maximum of six-membered



Scheme 1

fused rings and the *cis* configuration of the central two-carbon bridge is revealed by the temperature-dependent ¹³C NMR spectrum. The *cis* isomers are indeed known to exhibit exchange phenomena whereas the more rigid *trans* isomers do not allow such a process.¹⁴

As a result of the *cis* configuration, the bis-aminals possess a folded geometry that governs nitrogen reactivity. Thus, for bis-aminal **2** the nitrogen atoms whose lone pairs are directed towards the convex side of the molecular structure are stronger nucleophiles.^{12,15} AM1 molecular orbital calculations of bis-aminals **1**, **2** and **3** are in favor of this analysis since whatever the macrocycle, N₂ and N₄ lone pairs directed towards the concave fold were involved in amination bridge bonds; on the other hand, the lone pairs that pointed out from the convex side remained localized on N₁ and N₃ (Fig. 1). Therefore, the action of an electrophile on bis-aminals leads to N₁ functionalization and these adducts can further be alkylated on the opposing N₃ atom to obtain a diquat salt^{11b,12} (Scheme 2). Significant results on the mono-N₁ and di-N₁,N₃ alkylation of cyclen glyoxal and cyclam glyoxal are gathered in Table 1.

The comparison of bis-aminal reactivity is complicated by the more or less complete precipitation of the ammonium salts under experimental conditions. The above-mentioned results highlight the higher reactivity of cyclen glyoxal due to its more constrained topology and thus to the better accessibility of the corresponding nitrogen lone pairs. However, di-N₁,N₃ alkylation of **1** and **2** can be reached providing that, with non activated electrophiles, the reaction is allowed to run over longer times.

The precipitation of the monoalkylated cationic products allows one to selectively synthesize mono-N alkylated compounds; it constitutes the key feature of the process.^{11b} Furthermore, control of this step enabled us to use the bis-aminal as an intermediate for bis-macrocycle synthesis, all the more so as deprotection of compounds **1** and **3** in hydrazine monohydrate¹⁶ and compound **2** in hydroxylamine¹⁷ is easy to achieve.

When bis-electrophiles and molecules that possess two alkylation sites are involved, the main drawback arises from the side reaction consisting of oligomer formation. In the synthesis of symmetrical bis-tetraazamacrocycles, the best results were obtained on running the reaction in CH₃CN: in this

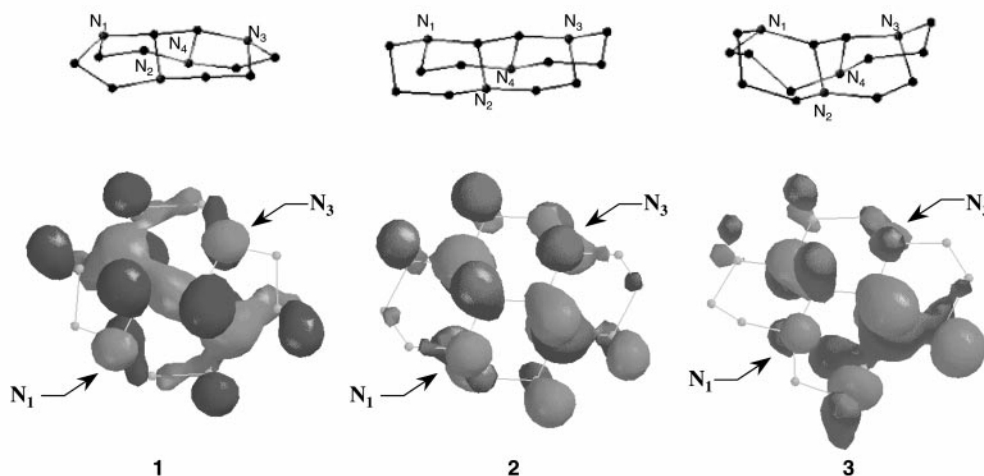
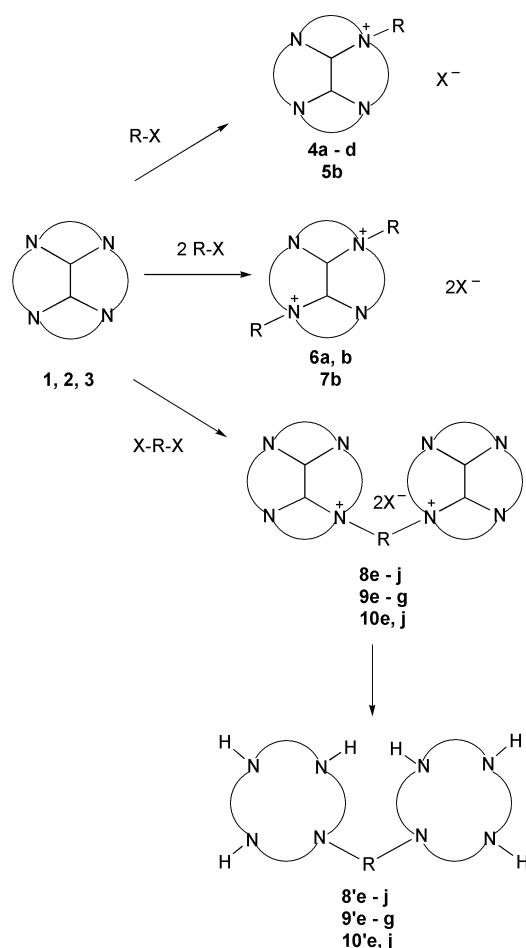


Fig. 1 Calculated AM1 geometries and molecular orbitals of compounds 1, 2 and 3.



Scheme 2

solvent, the protected bis-macrocyclic salts precipitate as soon as formed, which avoids the formation of polymers (Table 2).

Due to the chirality of aminal carbons and ammonium nitrogens, several stereoisomers were expected for protected bis-macrocycles. Moreover, for homocyclam, its lower symmetry leads to three potential structures, **10e₁**, **10e₂** and **10e₃**, for the corresponding disalt (Scheme 3). The simplicity of the ¹³C NMR spectrum suggested the existence of a symmetrical form such as **10e₁** or **10e₂**. Resolution of the X-ray structure for single crystals of the corresponding deprotected bis-macrocyclic indicated that the disalt obtained had structure **10e₁** (Fig. 2).

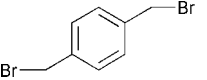
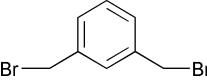
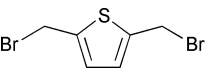
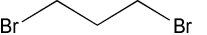
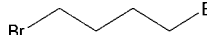
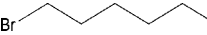
The preparation of dissymmetrical bis-tetraazamacrocycles implies additional constraints that make their synthesis tricky. The first attack of the electrophile by one of its ends must be controlled prior to the introduction of the second macrocycle. The use of bis-electrophiles that bear two functions of well differentiated reactivities was previously proposed.⁷ Bis-aminals offer an alternative solution: symmetrical bis-electrophiles can indeed be used, which requires that the anchoring of the link on the first macrocycle be controlled. This means that the reactive mono-N salt has to be rapidly isolated. This can be done in an appropriate solvent in which the solubility of this monosalt is low. Salts **11e** and **11f** were found to precipitate in THF or benzene and were subsequently isolated by filtration.¹⁸ In a second step, dissymmetrical bis-tetraazamacrocycles were obtained after partial solubilization of the mono-salts **11** in CH₃CN in the presence of a slight excess of the second macrocyclic aminal (Scheme 4). This strategy is very successful on condition that, in the first step, the less reactive bis-aminal is allowed to react with the bis-electrophile; if not, oligomers are mainly obtained.

Finally, this strategy can be extended to obtain bis-macrocycles with additional pendant arms: for example the scorioid bis-macrocyclic **13'** was obtained from compound **4d**

Table 1 Synthesis of mono-N₁ and di-N₁,N₃ alkylated cyclen and cyclam glyoxals at room temperature

Bis-aminal	RX	Stoichiometry bis-aminal : RX	Solvent	Reaction time	Product	Yield (%)	Ref.
1	CH ₃ I	1 : 1	THF	3 h	4a	97	This work
1	CH ₃ I	1 : 1	Toluene	1 h	4a	98	11b
1	CH ₃ I	1 : 2.5	CH ₃ CN	24 h	6a	90	This work
1	C ₆ H ₅ CH ₂ Br	1 : 1	THF	3 h	4b	96	This work
1	C ₆ H ₅ CH ₂ Br	1 : 2.5	CH ₃ CN	24 h	6b	98	This work
1	CH ₃ CH ₂ CH ₂ CH ₂ Br	1 : 1	THF	10 days	4c	65	This work
1	N-(3-Bromopropyl) phthalimide	1 : 2.1	CH ₃ CN	3 d	4d	75	This work
2	C ₆ H ₅ CH ₂ Br	1 : 2	CH ₃ CN	2 h	5b	90	12
2	C ₆ H ₅ CH ₂ Br	1 : 6	CH ₃ CN	3 weeks	7b	73	12

Table 2 Bis-macrocyclic salt syntheses carried out in CH₃CN at room temperature

XXR		Bis-aminal	Reaction time/days	Product	Yield (%)
	e	1	1	8e	97
		2	7	9e	100
		3	7	10e	80
	f	1	1	8f	90
		2^a	7	9f	85
	g	1	1	8g	95
		2	7	9g	95
	h	1	7	8h	80
	i	1	7	8i	78
	j	1	7	8j	75
		2	22	9j	^b
		3	22	10j	88

^a In CH₃CN–THF (1 : 1). ^b See Experimental.

after reaction with α,α' -dibromo-*p*-xylene and deprotection with hydrazine monohydrate (Scheme 5).

Conclusion

According to the nature of the solvent, the alkylation reaction can be orientated either to an unequivocal mono-N alkylation or to a specific di-N₁,N₃ alkylation. The choice of the solvent constitutes the key feature of the process. The high-yield syntheses of bis-macrocycles reported here are not only the straightforward outcome of these considerations, but also demonstrate the powerful utility of bis-aminals. This synthesis

pathway is easy to run, quasi-quantitative and for these reasons constitutes an attractive alternative to the previously published methods. Furthermore, the control of the mono-N alkylation allows the design of more sophisticated bis-macrocycles or of bis-macrocycles possessing two cavities of different sizes.

Experimental

General

All ¹H and ¹³C NMR spectra were recorded on Bruker AC300 and Bruker AMX400 spectrometers (respectively 75.47 and 100.62 MHz for ¹³C). Chemical shifts are given downfield from external TMS. Elemental analysis were performed at the Centre de Microanalyses du CNRS (Gif sur Yvette). All the reactions were run using freshly distilled and dry solvents.

Molecular modelling was performed with Spartan¹⁹ software on a Silicon Graphics station. Trial structures of compounds **1**, **2** and **3** were generated and a conformational search was made to find the global minimum of each surface. Semi-empirical calculations were then performed, geometries

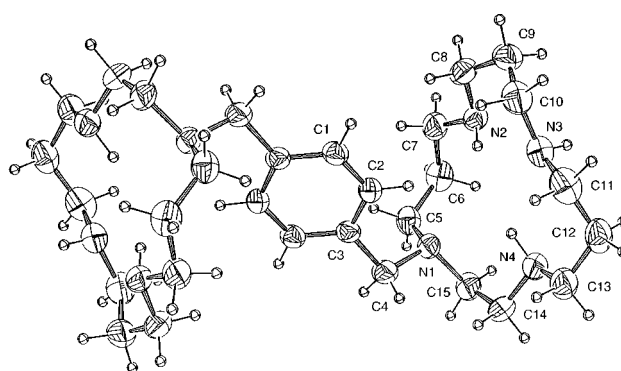
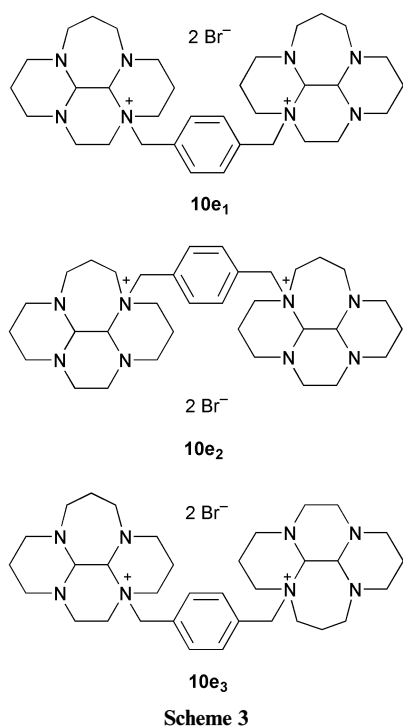
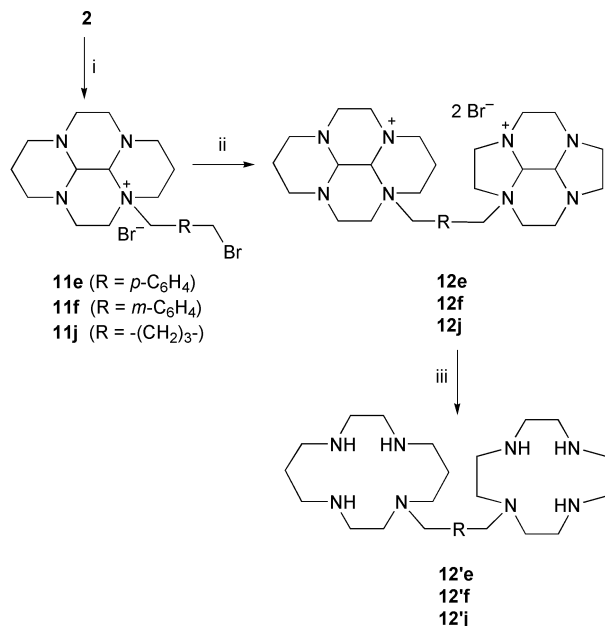


Fig. 2 Crystal structure of compound **10'e** with crystallographic numbering scheme.



Scheme 4 e: (i) α,α' -Dibromo-*p*-xylene in THF at RT; (ii) **1** in CH₃CN at RT; (iii) H₂NOH in ethanol. f: (i) α,α' -Dibromo-*m*-xylene in toluene at RT; (ii) **1** in CH₃CN at RT; (iii) H₂NOH in ethanol. j: (i) 1,5-Dibromopentane in CH₃CN at RT; (ii) **1** in CH₃CN at RT; (iii) H₂NOH in ethanol.

were fully optimized and minima characterized by the number of negative eigenvalues (none) of the Hessian matrix.

Synthesis of the monomeric starting materials

Bis-aminal 1, 2, 3 syntheses. A methanolic solution of 25 mmol of glyoxal (40% aqueous) was added dropwise, between -5 and 0°C , to a cooled methanolic solution of 25 mmol of the tetraazamacrocyclic (cyclen, cyclam or homocyclam). The mixture was stirred for 3 h at room temperature. After solvent evaporation, the residue was dissolved in Et₂O and the solution filtered to remove polymers. After evaporation of the

solvent, bis-aminals were isolated as white solids and used as such in the following steps.

Bis-aminal 1: *perhydro-2a,4a,6a,8a-tetraazacyclopenta[*f,g*]acenaphthylene (cyclen glyoxal)*. 95% yield, mp = 94°C , ^{13}C NMR(CDCl₃): δ 77.5 (C_{aminal}), 51.1, 50.3 (CH₂N).

Bis-aminal 2: *cis-3a,5a,8a,10a-tetraazaperhydropyrene (cyclam glyoxal)*. 89% yield, mp = 82°C , ^{13}C NMR (CDCl₃): δ 77.1 (C_{aminal}), 56.0, 54.3, 52.4, 44.7 (CH₂N), 19.6 (CH₂CH₂N).

Bis-aminal 3: *perhydro-3a,5a,8a,11a-tetraazacyclohepta[*d,e,f*]phenanthrene (homocyclam glyoxal)*. 90% yield, mp = 74°C , ^{13}C NMR (CDCl₃): δ 80.6 (C_{aminal}), 55.6, 54.6, 49.6, 49.4 (CH₂N), 22.7, 20.5 (CH₂CH₂N).

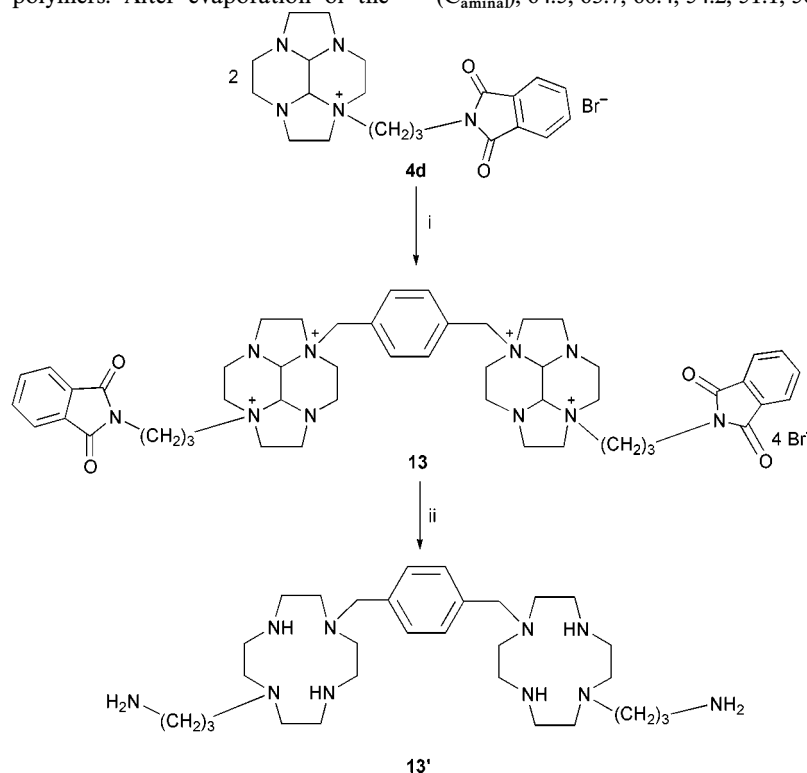
Syntheses of mono-N₁ and di-N₁,N₃ alkylated cyclen and cyclam glyoxals. Compounds **4a–d** and **6a, b** were synthesized according to a slightly modified Lukeš procedure.¹¹ Spectroscopic data and elemental analysis of derivatives **4a–c** and **6a, b** were in good agreement with the previously reported data.¹¹

Compound 4d. To a stirred solution of 970 mg of bis-aminal **1** (5 mmol) dissolved in 5 ml of dry acetonitrile, a solution of 2.8 g (10.5 mmol) of *N*-(3-bromopropyl)phthalimide in 10 ml of dry acetonitrile was added. The mixture was stirred at room temperature for 3 days. The precipitate was collected by filtration, washed with acetonitrile and dried *in vacuo*, giving **4d** (75%) as a white powder. ^{13}C NMR (D₂O): δ 173.0 (CO), 137.7, 133.9, 126.3 (C_{ar}), 86.8, 74.5 (C_{aminal}), 65.0, 59.9, 58.6, 54.1, 51.2, 51.0, 50.6, 50.4, 46.5 (CH₂N), 37.6 (N⁺CH₂CH₂CH₂N), 25.2 (N⁺CH₂CH₂CH₂N).

Typical procedure for symmetrical bis-macrocyclic syntheses

Bis-salts 8, 9 and 10. Due to the chirality of aminal carbons and ammonium nitrogens, several stereoisomers can be observed. Consequently, the signal splitting is indicated in italics.

Compound 8e. α,α' -Dibromo-*p*-xylene (5 mmol) was added to a stirred solution of cyclen glyoxal **1** (11 mmol) in dry acetonitrile (20 ml). The mixture was stirred at room temperature for 24 h. The precipitate was collected by filtration, washed with acetonitrile and dried *in vacuo*, giving **8e** (98%) as a white powder. ^{13}C NMR (D₂O): δ 136.4, 132.6 (C_{ar}), 85.9, 74.5 (C_{aminal}), 64.5, 63.7, 60.4, 54.2, 51.1, 50.9, 50.4, 46.6 (CH₂N).



Scheme 5 (i) α,α' -Dibromo-*p*-xylene in DMF at RT; (ii) H₂NNH₂, H₂O reflux overnight.

Compound 8f. White powder (90%). ^{13}C NMR (D_2O): δ 138.9, 138.2, 133.8, 131.5 (C_{ar}), 86.0, 85.9, 74.5 (C_{aminal}), 64.3, 63.7, 59.9, 59.8, 54.2, 51.2, 51.1, 50.4, 46.6 (CH_2N).

Compound 8g. White powder (95%). ^{13}C NMR (D_2O): δ 138.1, 135.0, (C_{ar}), 85.6, 74.4 (C_{aminal}), 65.2, 60.1, 58.4, 54.2, 51.2, 51.0, 50.7, 50.5, 46.4 (CH_2N).

Compound 8h. White powder (80%). ^{13}C NMR (D_2O): δ 87.2, 74.4 (C_{aminal}), 65.2, 60.2, 60.1, 57.1, 54.1, 51.2, 51.0, 50.6, 50.4, 46.5 (CH_2N), 21.0, ($\text{CH}_2\text{CH}_2\text{CH}_2$).

Compound 8i. White powder (78%). ^{13}C NMR (D_2O): δ 84.6, 72.4 (C_{aminal}), 62.9, 58.0, 57.8, 52.0, 49.1, 48.9, 48.5, 48.3, 44.4 (CH_2N), 20.8 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$).

Compound 8j. White powder (75%). ^{13}C NMR (D_2O): δ 86.6, 74.5 (C_{aminal}), 65.0, 60.7, 59.8, 54.1, 51.3, 51.1, 50.6, 50.5, 46.6 (CH_2N), 25.8 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 25.3 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$).

Compound 9e. White powder (100%). ^{13}C NMR (D_2O): δ 137.0, 131.5 (C_{ar}), 85.2, 72.3 (C_{aminal}), 64.5, 62.9, 56.8, 56.1, 54.8, 54.2, 51.4, 49.4, 44.8 (CH_2N), 21.3, 20.9 (NCH_2CH_2).

Compound 9f. White powder (85%). ^{13}C NMR (D_2O): δ 140.6, 138.6, 133.2, 129.9 (C_{ar}), 84.9, 72.3 (C_{aminal}), 64.6, 62.7, 56.7, 56.2, 54.7, 54.2, 51.7, 49.4, 44.8 (CH_2N), 21.2, 20.8 (NCH_2CH_2).

Compound 9g. White powder (95%). ^{13}C NMR (D_2O): δ 138.9, 133.8 (C_{ar}), 84.8, 72.3 (C_{aminal}), 63.1, 59.4, 56.7, 56.1, 54.8, 54.2, 51.6, 49.3, 44.8 (CH_2N), 21.4, 20.9 (NCH_2CH_2).

Compound 9j. The low reactivity of cyclam glyoxal 2 towards 1,5-dibromopentane leads after evaporation of the solvent to the sole monosalt **11j** (*vide infra*).

Compound 10e. White powder (80%). ^{13}C NMR (D_2O): δ 136.7, 132.4 (C_{ar}), 86.0, 85.9, 78.2 (C_{aminal}), 65.9, 59.7, 57.9, 55.5, 54.5, 53.7, 53.4, 53.3, 49.0, 45.4 (CH_2N), 31.1, 25.0, 22.2 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$).

Compound 10j. Soluble in CH_3CN , this compound was isolated by evaporation of the solvent. The resulting solid was washed with THF and dried *in vacuo*. White powder (88%). ^{13}C NMR (D_2O): δ 87.1, 77.5 (C_{aminal}), 63.2, 60.2, 57.9, 55.6, 54.9, 53.5, 52.3, 49.3, 45.5 (CH_2N), 31.8, 25.0, 22.3 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 25.8 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 23.3 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$).

Bis-salts deprotection: bis-macrocycles 8',9',10'

Representative deprotection procedure in hydrazine monohydrate. Compound **8** or **10** (4.6 mmol) and 20 ml of hydrazine monohydrate were heated at 120 °C overnight. After cooling, the solid was filtered, dissolved in ethanol and the solvent was rotary evaporated. The solid was recrystallized in acetone and precipitated as the hydrochloride salt for elemental analysis and NMR spectra.

1-[4-(1,4,7,10-Tetraazacyclododecan-1-ylmethyl)benzyl]-1,4,7,10-tetraazacyclododecane (8'e). White crystals (91%). ^{13}C NMR (D_2O): δ 136.6, 133.8 (C_{ar}), 59.7, 51.1, 46.7, 45.1 (CH_2N). $\text{C}_{24}\text{H}_{46}\text{N}_8 \cdot 6\text{HCl} \cdot 3\text{H}_2\text{O}$ (719.49): calc. C 40.06, H 8.13, N 15.57, Cl 29.57; found C 39.39, H 7.87, N 15.22, Cl 29.46%.

1-[3-(1,4,7,10-Tetraazacyclododecan-1-ylmethyl)benzyl]-1,4,7,10-tetraazacyclododecane (8'f). White crystals (85%). ^{13}C NMR (D_2O): δ 137.6, 135.1, 133.0, 132.4 (C_{ar}), 59.6, 50.8, 46.9, 44.9, 44.8 (CH_2N). $\text{C}_{24}\text{H}_{46}\text{N}_8 \cdot 7\text{HCl} \cdot 4\text{H}_2\text{O}$ (773.96): calc. C 37.24, H 7.94, N 14.48, Cl 32.06; found C 37.27, H 7.67, N 14.04, Cl 31.94%.

1-[5-(1,4,7,10-Tetraazacyclododecan-1-ylmethyl)-2-thienyl]-methyl-1,4,7,10-tetraazacyclododecane (8'g). White crystals (90%). ^{13}C NMR (D_2O): δ 139.7, 132.2, (C_{ar}), 53.2, 50.1, 47.0, 45.0, 44.6 (CH_2N). $\text{C}_{22}\text{H}_{44}\text{N}_8\text{S} \cdot 6\text{HCl} \cdot 4\text{H}_2\text{O}$ (743.53): calc. C 35.54, H 7.86, N 15.07, S 4.31, Cl 28.61; found C 35.82, H 7.59, N 15.04, S 4.37, Cl 28.40%.

1-[3-(1,4,7,10-Tetraazacyclododecan-1-yl)propyl]-1,4,7,10-tetraazacyclododecane (8'h). White crystals (68%). ^{13}C NMR

(D_2O): δ 53.9, 51.6, 46.5, 45.2, (CH_2N), 20.7 ($\text{CH}_2\text{CH}_2\text{CH}_2$). $\text{C}_{19}\text{H}_{44}\text{N}_8 \cdot 6\text{HCl} \cdot 4\text{H}_2\text{O}$ (675.43): calc. C 33.79, H 8.66, N 16.59, Cl 31.49; found C 33.51, H 8.62, N 16.44, Cl 31.28%.

1-[4-(1,4,7,10-Tetraazacyclododecan-1-yl)butyl]-1,4,7,10-tetraazacyclododecane (8'i). White crystals (72%). ^{13}C NMR (D_2O): δ 56.8, 52.3, 46.6, 45.8, 45.3 (CH_2N), 23.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$). $\text{C}_{20}\text{H}_{46}\text{N}_8 \cdot 7\text{HCl} \cdot 5\text{H}_2\text{O}$ (743.93): calc. C 32.29, H 8.54, N 15.06, Cl 33.36; found C 32.12, H 8.47, N 14.71, Cl 33.20%.

1-[5-(1,4,7,10-Tetraazacyclododecan-1-yl)pentyl]-1,4,7,10-tetraazacyclododecane (8'j). White crystals (81%). ^{13}C NMR (D_2O): δ 57.9, 53.0, 46.4, 46.2, 45.3 (CH_2N), 28.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 25.7 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$). $\text{C}_{21}\text{H}_{48}\text{N}_8 \cdot 6\text{HCl} \cdot 3\text{H}_2\text{O}$ (685.47): calc. C 36.80, H 8.82, N 16.35, Cl 31.03; found C 36.56, H 8.86, N 16.24, Cl 30.86%.

1-[4-(1,4,8,12-Tetraazacyclopentadecan-1-ylmethyl)benzyl]-1,4,8,12-tetraazacyclopentadecane (10'e). White crystals (93%). ^{13}C NMR (D_2O): δ 135.0, 133.5, (C_{ar}), 61.8, 51.7, 48.9, 45.7, 44.9, 44.7, 44.3, 41.7 (CH_2N), 23.1, 22.7, 22.0 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$). $\text{C}_{30}\text{H}_{58}\text{N}_8 \cdot 6\text{HCl} \cdot 4\text{H}_2\text{O}$ (821.66): calc. C 43.85, H 8.83, N 13.64, Cl 25.89; found C 44.02, H 8.82, N 13.72, Cl 26.01%.

1-[5-(1,4,8,12-Tetraazacyclopentadecan-1-yl)pentyl]-1,4,8,12-tetraazacyclopentadecane (10'f). White crystals (95%). ^{13}C NMR (D_2O): δ 58.5, 52.2, 49.5, 45.9, 45.0, 44.9, 44.5, 41.8, (CH_2N), 23.2, 22.8, 22.1 ($\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$), 26.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 25.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$). $\text{C}_{27}\text{H}_{60}\text{N}_8 \cdot 6\text{HCl} \cdot 4\text{H}_2\text{O}$ (787.64): calc. C 41.17, H 9.47, N 14.23, Cl 27.01; found C 41.33, H 9.44, N 14.32, Cl 27.11%.

Representative deprotection procedure with hydroxylamine.

Bis-cyclam **9** (1.4 mmol) was dissolved in 20 ml of dry ethanol with 3 g of hydroxylamine hydrochloride and 2.9 g of sodium ethoxide. The mixture was refluxed under nitrogen for 4 h. After cooling, the solvent was evaporated, the resulting solid was dissolved in 10 ml of 10 M NaOH and extracted four times with chloroform. The combined organic phases were evaporated and dropwise addition of an HCl-ethanol solution induced precipitation of the hydrochloride salt. Acetone was then added to complete precipitation. After standing in a refrigerator overnight, a white solid was filtered off, washed with acetone and dried *in vacuo*.

1-[4-(1,4,8,11-Tetraazacyclotetradecan-1-ylmethyl)benzyl]-1,4,8,11-tetraazacyclotetradecane (9'e). White crystals (93%). ^{13}C NMR (D_2O): δ 135.0, 133.5 (C_{ar}), 61.4, 50.5, 47.2, 44.0, 43.8, 40.4, 39.9 (CH_2N), 21.4, 20.9 (NCH_2CH_2). $\text{C}_{28}\text{H}_{54}\text{N}_8 \cdot 6\text{HCl} \cdot 4\text{H}_2\text{O}$ (793.61): calc. C 42.38, H 8.64, N 14.12, Cl 26.80; found C 42.06, H 8.70, N 14.02, Cl 26.63%.

1-[3-(1,4,8,11-Tetraazacyclotetradecan-1-ylmethyl)benzyl]-1,4,8,11-tetraazacyclotetradecane (9'f). White crystals (91%). ^{13}C NMR (D_2O): δ 136.6, 136.1, 133.7, 132.3 (C_{ar}), 61.6, 50.5, 47.2, 44.3, 43.7, 40.4, 40.3, 39.8 (CH_2N), 21.3, 20.8 (NCH_2CH_2). $\text{C}_{28}\text{H}_{54}\text{N}_8 \cdot 6\text{HCl} \cdot 4\text{H}_2\text{O}$ (793.61): calc. C 42.38, H 8.64, N 14.12, Cl 26.80; found C 42.23, H 8.64, N 14.08, Cl 26.69%.

1-[5-(1,4,8,11-Tetraazacyclotetradecan-1-ylmethyl)-2-thienyl]methyl-1,4,8,11-tetraazacyclotetradecane (9'g). White crystals (88%). ^{13}C NMR (D_2O): δ 136.5, 136.0, (C_{ar}), 55.2, 50.5, 47.4, 44.4, 44.1, 44.0, 40.8, 40.6, 40.5 (CH_2N), 21.6, 21.5 (NCH_2CH_2). $\text{C}_{26}\text{H}_{52}\text{N}_8\text{S} \cdot 6\text{HCl} \cdot 3\text{H}_2\text{O}$ (781.62): calc. C 39.95, H 8.25, N 14.34, S 4.10, Cl 27.21; found C 39.53, H 8.27, N 14.17, S 4.13, Cl 26.98%.

Dissymmetrical bis-macrocyclic syntheses

Monosalts 11. **Compound 11e.** A solution of α,α' -dibromo-*p*-xylene (1.18 g) in 10 ml of dry THF was added dropwise to a THF solution of cyclam glyoxal **2** (1 g, 15 ml) and the mixture was stirred for 10 days at room temperature. The precipitate was filtered off, washed with dry THF and dried *in vacuo*. White solid (87%). ^{13}C NMR (CDCl_3): δ 139.9, 134.1, 129.3, 126.5 (C_{ar}), 80.9, 69.5 (C_{aminal}), 60.1, 58.2, 54.2, 54.1, 52.0,

49.0, 46.6, 42.5 (CH₂N), 32.3 (CH₂Br), 19.1, 18.7, (NCH₂CH₂CH₂N).

Compound 11f. A solution of α,α' -dibromo-*m*-xylene (1.18 g) in 10 ml of dry toluene was added dropwise to a toluene solution of **2** (1 g, 10 ml) and the mixture was stirred for 10 days at room temperature. The precipitate was filtered off, washed with dry toluene and dried *in vacuo*. White solid (59%). ¹³C NMR (CDCl₃): δ 138.7, 133.7, 133.5, 131.2, 129.4, 126.9 (C_{ar}), 81.1, 69.6 (C_{aminal}), 60.2, 58.3, 54.3, 54.0, 51.9, 48.8, 46.6, 42.4 (CH₂N), 32.4 (CH₂Br), 19.0, 18.7, (NCH₂CH₂CH₂N).

Compound 11j. A solution of cyclam glyoxal **2** (2 g) and 1.2 ml of 1,5-dibromopentane in 10 ml of dry acetonitrile was stirred for 3 weeks at room temperature. The solvent was rotary evaporated and the residue was washed three times with diethyl ether. White solid (29%). ¹³C NMR (CDCl₃): δ 85.2, 72.2 (C_{aminal}), 63.1, 62.2, 56.7, 56.1, 54.9, 54.1, 51.3, 49.1, 44.8, (CH₂N), 37.1 (CH₂Br), 34.2 (CH₂CH₂Br), 27.2 (CH₂CH₂CH₂Br), 22.6 (CH₂CH₂CH₂CH₂Br), 21.4, 20.9 (NCH₂CH₂CH₂N).

Dissymmetrical bis-salts 12. To a suspension of compound **11e** or **11f** (1.41 g) in 10 ml of dry acetonitrile, 0.65 g of bis-aminal **1** was added and the mixture was stirred for 5 days at room temperature. The precipitate was filtered and washed with acetonitrile and dried *in vacuo*. White solids **12e** or **12f** were obtained.

Due to the chirality of aminal carbons and ammonium nitrogens, several stereoisomers can be observed. Consequently, the signal splitting is indicated in italics.

Compound 12e. (86%). ¹³C NMR (D₂O): δ 137.3, 136.2, 132.6, 131.5 (C_{ar}), 85.9, 85.2, 74.5, 72.3 (C_{aminal}), 64.5, 64.4, 63.5, 63.0, 60.0, 56.8, 56.2, 54.8, 54.2, 51.4, 51.2, 51.1, 50.5, 49.4, 46.6, 44.8 (CH₂N), 21.3, 20.9 (NCH₂CH₂CH₂N).

Compound 12f. (91%). ¹³C NMR (D₂O): δ 139.8, 138.6, 137.9, 133.5, 131.0, 130.1 (C_{ar}), 85.9, 85.7, 85.1, 74.4, 72.2 (C_{aminal}), 64.6, 64.2, 63.5, 62.7, 60.0, 59.7, 56.7, 56.1, 54.7, 54.1, 51.4, 51.1, 51.0, 50.4, 49.4, 46.6, 44.7 (CH₂N), 21.2, 20.8 (NCH₂CH₂CH₂N).

Compound 12j. To a solution of compound **11j** (1.0 g) in 10 ml of dry acetonitrile, 0.5 g of bis-aminal **1** was added and the mixture was stirred for 10 days at room temperature. The solvent was rotary evaporated and the residue was washed three times with diethyl ether. White solid (84%). ¹³C NMR (D₂O): δ 86.5, 85.2, 74.5, 72.1 (C_{aminal}), 65.0, 63.2, 62.0, 60.7, 59.8, 56.6, 56.1, 54.9, 54.2, 54.1, 51.4, 51.3, 50.9, 50.6, 50.4, 49.1, 46.5, 44.8 (CH₂N), 25.8, 25.3, 23.2 (NCH₂CH₂CH₂CH₂CH₂N), 21.2, 20.8 (NCH₂CH₂CH₂N).

Bis-salt deprotection: bis-macrocycles 12'. Compounds **12e**, **12f** and **12j** were deprotected with an ethanolic solution of hydroxylamine, as previously described. The corresponding compounds **12'** were isolated as hydrochloride salts.

1-[4-(1,4,7,10-Tetraazacyclododecan-1-ylmethyl)benzyl]-1,4,8,11-tetraazacyclotetradecane (12'e). White solid (92%). ¹³C NMR (D₂O): δ 140.0, 134.3, 134.0, 131.0, (C_{ar}), 61.9, 59.0, 50.5, 50.2, 47.0, 44.9, 44.6, 44.1, 43.6, 40.0, 39.5 (CH₂N), 21.2, 20.6 (NCH₂CH₂CH₂N). C₂₆H₅₀N₈ · 6HCl · 5H₂O (783.57): calc. C 39.85, H 8.49, N 14.30, Cl 27.15; found C 40.23, H 8.44, N 14.40, Cl 27.31%.

1-[3-(1,4,7,10-Tetraazacyclododecan-1-ylmethyl)benzyl]-1,4,8,11-tetraazacyclotetradecane (12'f). White solid (89%). ¹³C NMR (D₂O): δ 138.2, 135.6, 133.8, 133.0, 132.3, 131.6, (C_{ar}), 62.0, 59.3, 50.6, 50.2, 46.8, 45.3, 45.0, 44.0, 43.5, 39.9, 39.4 (CH₂N), 21.1, 20.6 (NCH₂CH₂CH₂N). C₂₆H₅₀N₈ · 7HCl · 3H₂O (784.00): calc. C 39.83, H 8.10, N 14.29, Cl 31.65; found C 40.33, H 8.24, N 14.40, Cl 30.82%.

1-[5-(1,4,7,10-Tetraazacyclododecan-1-yl)pentyl]-1,4,8,11-tetraazacyclotetradecane (12'j). White solid (87%). ¹³C NMR (D₂O): δ 59.4, 58.4, 54.1, 50.6, 47.3, 46.9, 46.4, 45.8, 44.1, 43.6, 40.1, 39.4, (CH₂N), 26.3, 25.6 (NCH₂CH₂CH₂CH₂CH₂N),

21.2, 20.8 (NCH₂CH₂CH₂N). C₂₃H₅₂N₈ · 6HCl · 3H₂O (713.52): calc. C 38.72, H 9.04, N 15.70, Cl 29.81; found C 38.41, H 9.10, N 15.58, Cl 29.60%.

Synthesis of the functionalized bis-macrocycle 13'

Compound 13. A solution of 650 mg (2.38 mmol) of α,α' -dibromo-*p*-xylene in 50 ml of dry DMF was added dropwise to a suspension of 2.2 g of **4d** (4.76 mmol) in 100 ml of dry DMF. The mixture was stirred at room temperature for 2 weeks. The solvent was evaporated, 10 ml of dry acetonitrile were added to the residue and the mixture was stirred for several minutes. The precipitate was collected by filtration, washed with acetonitrile and dried *in vacuo*, giving **13** (85%). ¹³C NMR (D₂O): δ 173.0 (CO), 137.7, 136.6, 134.1, 134.0, 132.1, 126.3 (C_{ar}), 81.6, 80.4 (C_{aminal}), 64.5, 63.9, 63.1, 58.4, 58.2, 49.1, 48.8, 45.5, 45.3, 37.6 (NCH₂), 25.1 (CH₂CH₂CH₂).

Deprotection of 13 to give 3-[7-(4-{7-(3-aminopropyl)-1,4,7,10-tetraazacyclododecan-1-yl}methyl)benzyl]-1,4,7,10-tetraazacyclododecan-1-yl]propylamine (13'). Compound **13** (2.4 g, 2 mmol) and 6 ml of hydrazine monohydrate were heated at 120 °C for 5 h. After cooling, the solid was filtered off, dissolved in ethanol and the solvent was evaporated. The resulting oil was dissolved in 10 ml ethanol and 10 ml concentrated HCl were added dropwise. Acetone was then added to complete precipitation. After standing in a refrigerator overnight, a white solid was filtered off, washed with acetone and dried *in vacuo*. White solid (82%). ¹³C NMR (D₂O): δ 137.4, 133.4 (C_{ar}), 58.6, 51.9, 49.8, 49.6, 45.4, 45.3, 40.4 (NCH₂), 23.9 (CH₂CH₂CH₂). C₃₀H₆₀N₁₀ · 7HCl · 2H₂O (852.12): calc. C 42.29, H 8.40, N 16.44, Cl 29.12; found C 42.41, H 8.31, N 16.35, Cl 29.52%.

Crystal structure determination of 10'e

The structure is presented in Fig. 2. Monocrystals of compound **10'e** were isolated by recrystallization from dry acetone: C₃₀H₅₈N₈, *M* = 530.84, triclinic, *P*1 (no. 2), *a* = 8.7740(5), *b* = 9.4790(5), *c* = 18.8510(7) Å, α = 80.211(2), β = 82.197(2), γ = 67.030(3)°, *U* = 816.41(8) Å³, *Z* = 1, *D*_x = 1.080 Mg m⁻³, λ (Mo-K α) = 0.71073 Å, μ = 0.66 cm⁻¹, *F*(000) = 294, *T* = 290 K. The sample was studied on a NONIUS Kappa CCD with graphite monochromated Mo-K α radiation. The cell parameters are obtained with Denzo and Scalepack²⁰ with 10 frames (ϕ rotation: 1° per frame). The data collection²¹ gave 3798 integrated reflections. The data reduction with Denzo and Scalepack²⁰ led to 3724 independent reflections (2191 with *I* > 2.0 σ (*I*)). The structure was solved with SIR-97,²² which reveals all the non-hydrogen atoms of the compound and the solvent. After anisotropic refinement, the hydrogen atoms were found with a Fourier difference map. The whole structure was refined with SHELXL97²³ by the full-matrix least-square techniques (use of *F* square magnitude; *x*, *y*, *z*, β_{ij} for C and N atoms and riding mode for H atoms; calc. $w = 1/[\sigma^2(F_o^2) + (0.104 P)^2 + 0.073 P]$ where $P = (F_o^2 + 2 F_c^2)/3$ with the resulting *R* = 0.0613, *R*_w = 0.174.

Atomic scattering factors were taken from ref. 24. ORTEP views were realized with PLATON98.²⁵ All the calculations were performed on a Pentium NT Server computer.

CCDC reference number 166637. See <http://www.rsc.org/suppdata/nj/b1/b103995b/> for crystallographic data in CIF or other electronic format.

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