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Phenylglyoxal for polyamines modification and cyclam synthesis

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Abstract—The bis-aminals obtained by tetraamine and phenylglyoxal condensation display various behaviours such as equilibrium between different configurations, rearrangements that lead to lactam derivatives, or amine deprotection. Our investigations about them were focused on three different linear amines, and then extended to polyazacycloalkanes cyclen and cyclam. Cyclam was also synthesised with the bis-aminals issued from condensation of linear polyamines with phenylglyoxal. The lactam derivatives described here were moreover, employed for the mono-*N*-functionalisation of tetraamines by phenyl-acetic acid group.

1. Introduction

Over the last years, the complexation chemistry of cyclen (1,4,7,10-tetraazacyclododecane), cyclam (1,4,8,11-tetraazacyclotetradecane) and especially of their functionalised derivatives has been extensively studied. This ensues mainly from their strong ligating ability towards a wide range of cations including lanthanide ions.[1,2] Cyclen and cyclam have taken up a dominant position in biomedical applications and research as evidenced by the common use of their complexes as contrast agents in magnetic resonance imaging, luminescent probes or in radioimmunotherapy.[3,4]

From a synthetic point of view, cyclisation and mono-*N*-functionalisation are challenging steps in the chemistry of linear or cyclic polyamines; among the recently proposed solutions, bis-aminals have proved their efficiency as tools in polyazacycloalkanes syntheses or modifications.[5–8] They are easily prepared by condensation of an α-dicarbonyl derivative with the suitable linear or cyclic tetraamine. The control of the ensuing *N*-alkylation steps is decisive in the preparation of functionalised macrocycles. However, the subsequent reaction of an electrophile with such protected tetraamines often leads to unexpected adducts, and different behaviours have been reported. As a matter of fact, depending on the nature of the involved reactants, even the simple protonation of the bis-aminal results in amine deprotection, equilibrium between different configurations of the bis-aminals, or gives rise to more complicated rearrangements leading to lactam derivatives.[9–13]

Here, we demonstrate that, by comparison with other α-dicarbonyl derivatives, phenylglyoxal can induce all these behaviours. Thus, this compound constitutes a good model for gaining insight into these reaction mechanisms. From a synthetic point of view, we provide evidence of the usefulness of phenylglyoxal as protection in the synthesis of cyclam and describe an easy route to linear and cyclic mono-*N*-alkylated polyamines.

2. Results and discussion

Bis-aminals are easily obtained by condensation of an α-dicarbonyl reagent on a linear or cyclic tetraamine. In theory, this condensation reaction results in multiple stereoisomers according to the *vic*/*gem* insertion of the dicarbonyl reagent and *cis*/*trans* configuration of the resulting bis-aminal bridge. In practice, few stereoisomers are obtained; in addition, we previously showed that their configuration is governed by kinetic and thermodynamic factors.[14] The formation of a first six-membered diiminium cycle is the driving force of the reaction. Furthermore, compared to the ketone function, the aldehyde moiety reacts faster with a secondary amine function, whereas the latter shows a higher affinity for primary amine. The formation of two different six-membered diiminium intermediates, i.e. central and lateral, explains the reaction process as follows: two secondary amines are involved in the former, whereas, a secondary and a primary amines are both implicated in the latter. For linear polyamines **1**–**3**, depending on the nature (central vs lateral) of the intermediate diiminium and further to nucleophilic amine attacks, its evolution leads to *cis* and/or *trans* bis-aminals as follows:[14] with the lateral diiminium, the corresponding bis-aminals, indeed, exhibits a *gem cis* configuration. With the central one, the corresponding bis-aminal are generally obtained as a

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mixture of *cis* and *trans* isomers and their proportion is governed by the kinetics of successive nucleophilic attacks provide that no isomerisation process modifies their respective abundance.

The products obtained here by condensation of phenylglyoxal hydrate with linear or cyclic tetraamines were in good agreement with the previously established model (Scheme 1).

Reactions proceeded as described in Scheme 1 with very good yields. For **1a**–**5a** bis-aminals, the *vic*/*gem* configuration was identified from ^{13}C NMR data, and the recognition of *cis*/*trans* isomers was deduced from the temperature-dependent spectra since, the *cis* bis-aminal junction presents a fluxional behaviour whereas, the *trans* one remains rigid. The location of the benzyl group on the bis-aminal bridge for **1a** and **2a** was elucidated with the help of HMQC, HMBC and COSY NMR sequences when required. With amines **1**–**2**, only the isomers **1a**-*cis*–**2a**-*cis* were obtained. On the other hand, the use of amine **3** resulted in a mixture of **3a**-*cis* and **3a**-*trans* isomers.

In the case of the cyclic tetraamines **4**–**5**, the key feature of the reaction was again the formation of a first six-membered diiminium ring. Consequently, the corresponding tetracyclic bis-aminals **4a**–**5a** issued from its evolution exhibited a systematic *cis* configuration of the bis-aminal bridge. One should note that, when cyclam was involved in the reaction, **5b** was always formed at trace level even though the reaction was performed at 0°C (see below).

As regards to the mixture of compounds **3a**, the first bis-aminal formed was the **3a**-*cis* isomer, which rapidly evolved to the more stable isomer **3a**-*trans* (Δ=24.45 kJ mol^{-1}, Figs. 1 and 2). As the *cis* isomer was stable in anhydrous ethanol and isomerised further to water addition, this process was certainly catalysed by water from phenylglyoxal hydrate. The ^{13}C NMR spectrum of **3a**-*trans* was remarkable since, at room temperature, it displayed six carbon signals for the phenyl group, which is consistent with a slowed rotation; at higher temperature the rotation was fast, four signals were, therefore, observed on NMR spectra. Molecular modelling of **3a**-*cis* and **3a**-*trans* compounds (Figs. 1 and 2) showed that the bis-aminal bridge substituents were respectively, in axial–equatorial (**3a**-*cis*) and equatorial–equatorial (**3a**-*trans*) positions with a

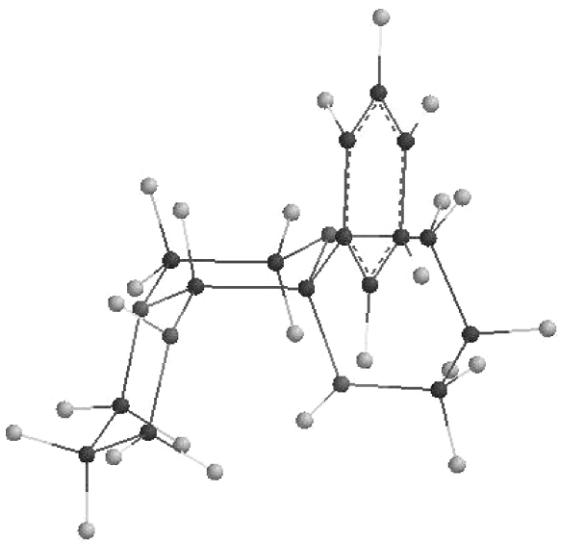
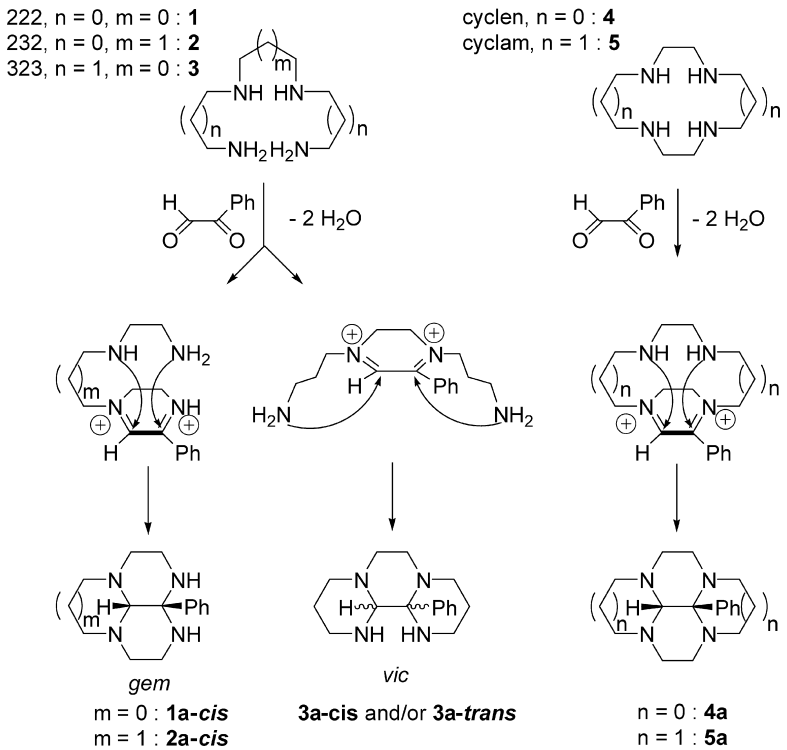


Figure 1. AM1 geometry and energy of formation for **3a**-*cis*, E=242.94 kJ mol^{-1}.



Scheme 1. Synthesis of tri- and tetra-cyclic bis-aminals **1a**–**5a** formation mechanism.

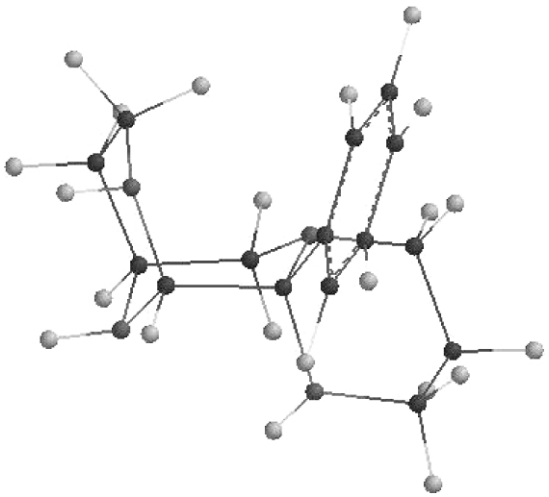


Figure 2. AM1 geometry and energy of formation for **3a**-*trans*, E=218.49 kJ mol^{-1}.

phenyl group in equatorial position. These geometries evidenced severe intramolecular strains likely responsible for the benzyl group slowed rotation.

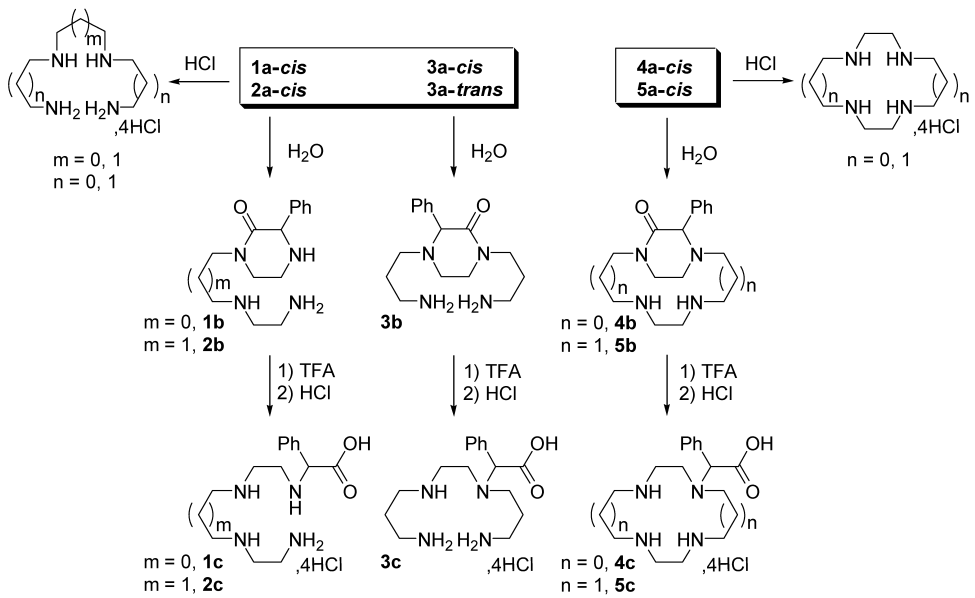
Under more rigorous conditions (Scheme 2) such as boiling water for instance, **1a**–**5a** gave the corresponding lactams derivatives **1b**–**3b** and **4b**–**5b** in good yields. An intermediate amidinium ion is undoubtedly involved in the bis-aminal hydrolysis: it was identified by mass spectrometry and NMR investigation with evidence for **2a**-*cis* bis-aminal. Phenylglyoxal condensation with linear or cyclic tetraamines in boiling water gave directly the lactam, which showed as being the end-product of the hydrolysis process.

Finally, the acidic hydrolysis (HCl 6 M) of linear and cyclic tetramines–phenylglyoxal adducts **1a**–**5a** regenerated the starting polyamine **1**–**5** in good yields (Scheme 2).

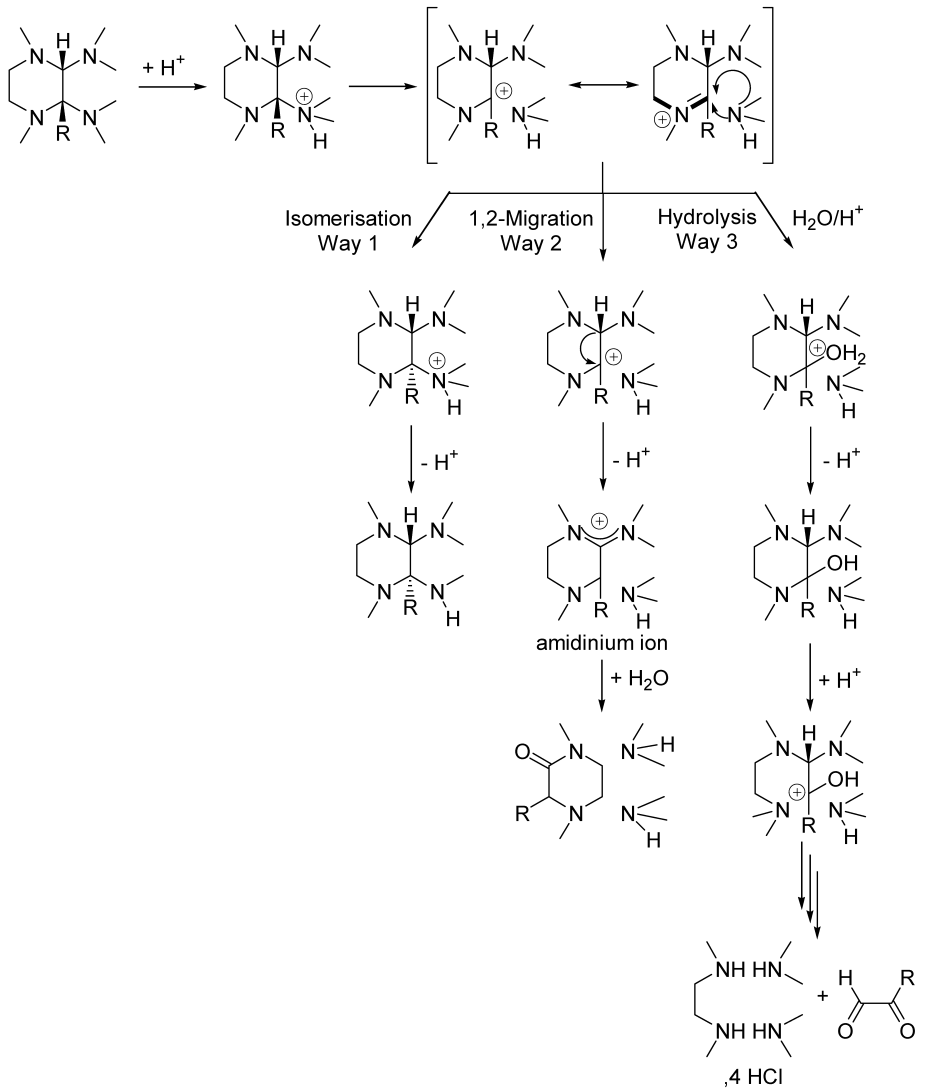
All these processes have a factor in common: water. Concerning the reaction mechanisms depicted on Scheme 3, the protonation of the benzylic secondary amine function followed with C–N bond cleavage constitutes the first common step of all subsequent evolutions; the amine function is, indeed, released further to the formation of the imidium intermediate. Scheme 3 evidences the three ways this cation can evolve: (i) way 1 shows that the repetition of this opening–locking sequence corresponds to an equilibration reaction which leads to the thermodynamically more stable bis-aminal; (ii) in way 2, the migration of a hydrogen atom leads to an amidinium species whose hydrolysis generates the lactam adduct; (iii) way 3 takes place in acidic medium where the fast opening of the first C–N aminal bond followed by the cleavage of the second one produces the bis-amidinium intermediate whose further hydrolysis regenerates the tetraamine as a polyammonium salt together with phenylglyoxal.

From a synthetic point of view, the treatment of lactams **1b**–**3b** or bicyclic lactams **4b**–**5b** in refluxing trifluoroacetic acid/water solution overnight gave the expected corresponding amino-acid salts, which were easily converted into their chlorohydrate salts, **1c**–**3c** and **4c**–**5c**, respectively (Scheme 2). This reaction provides one with an easy-to-use route to phenyl-acetic acids derivatives of linear or cyclic polyamines; moreover, this new and interesting example of mono-*N*-alkylation makes this type of alkylation far less tedious than by using the classical methods.[15]

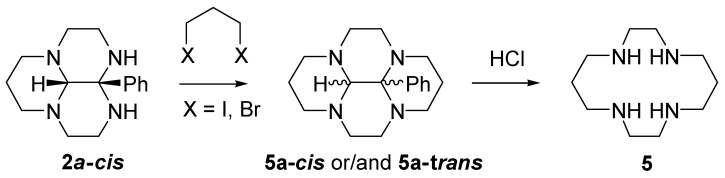
In addition, because of its easy removal, the bis-aminal bridge is advantageously used as template in the synthesis of cyclen or cyclam structures. Unfortunately, all attempts to obtain cyclen from **1a**-*cis* failed; cyclam–phenylglyoxal was, however, prepared in good yields by reaction of **2a**-*cis* with the corresponding biselectrophile, here dibromopropane (Scheme 4). Surprisingly, a 50/50 mixture of the two isomers **5a**-*cis* and **5a**-*trans* of the cyclam phenylglyoxal was obtained. Both the stability of **2a**-*cis* isomer in the



Scheme 2. From bis-aminals to lactam derivatives. Mono-phenyl acetic acid alkylation and bis-aminals deprotection.



Scheme 3. General scheme of the three processes.



Scheme 4. Cyclam synthesis by cyclisation of bis-aminal **2a**-*cis*.

medium before biselectrophile addition and the lack of equilibrium for the end-products indicate that the isomerisation process takes place during the early step of cyclisation. In this process, the biselectrophile acts as the proton: the opening of the first formed ammonium ion gives again an iminium ion along with a free secondary amine function; consequently, an isomerisation likely occurs before the cyclisation. When the cyclisation reaction was performed at room temperature with diiodopropane, a single product was isolated and characterised as the **5a**-*cis* bis-aminal, which highlights the important role of reaction temperature in the isomerisation process. Isomers **5a**-*cis* and/or **5a**-*trans* were very easily hydrolysed in acidic medium, and cyclam was recovered in good yield. Starting from the tetramine **2**, this three-step procedure constitutes a new, easy-to-run and attractive synthesis of cyclam.

3. Conclusion

In contrast to other dicarbonyl compounds like glyoxal, phenylglyoxal allows a large range of behaviours for the ensuing bis-aminals. A first electrophilic attack is at the origin of *cis*/*trans* configuration rearrangements, lactam derivative formations or polyamine deprotections. In addition, the study reported here opens an alternative

route to mono-functionalised polyamines from linear or cyclic tetraamine and constitutes an attractive pathway to cyclam.[16–19]

4. Experimental

4.1. General information

Polyamine triethylenetetraamine **1** (222), *N*,*N*′-bis-(2-aminoethyl)-1,3-propanediamine **2** (232) and *N*,*N*′-bis-(3-aminopropyl)ethylenediamine **3** (323), 1,4,7,10-tetraazacyclotetradecane **4** (cyclen) and 1,4,8,11-tetraazacyclotetradecane **5** (cyclam) were used as starting compounds.

Molecular modelling was performed with the Spartan[20] software on a Silicon Graphics station. Trial structures of the compounds **3a**-*cis* and **3a**-*trans*, were generated and a conformational search was made to find the global minimum of each surface. Semi-empirical calculations was then accomplished, geometries were fully optimised and minima characterised by the number of negative eigenvalues (none) of the Hessian matrix.

4.2. General procedure for the tricyclic bis-aminals 1a–3a synthesis

A solution of phenylglyoxal monohydrate (2 mmol) in absolute ethanol (10 mL) was slowly added to a solution of the convenient linear amine (2 mmol) in absolute ethanol (10 mL) at room temperature under vigorous stirring. After 5 h, solvent was evaporated to give quantitatively the desired compound.

4.2.1. Compound 1a-*cis*. The title compound was quantitatively obtained as a yellow oil. ^{13}C NMR ($CDCl_3$, 100 MHz, 245 K): δ (ppm) 41.3, 48.8, 48.9, 49.0, 68.8, 78.5, 125.9, 127.1, 127.9, 143.9. ESI-MS (MeOH): *m*/*z* 183.3, $[M+H]^+$. Anal. calcd for $C_9H_{18}N_4$: C, 59.31; H, 9.95; N, 30.74%; found: C, 59.34; H, 9.90; N, 30.85%.

4.2.2. Compound 2a-*cis*. The title compound was quantitatively synthesised as a yellow oil. ^{13}C NMR ($CDCl_3$, 100 MHz, 218 K): δ (ppm) 19.0, 39.5, 42.1, 44.2, 52.6, 54.7, 56.3, 68.5, 78.5, 125.5, 127.1, 128.2, 143.6. ESI-MS (MeOH): *m*/*z* 259.4, $[M+H]^+$. Anal. calcd for $C_{15}H_{22}N_4$: C, 69.73; H, 8.58; N, 21.69%; found: C, 69.88; H, 8.49; N, 21.76%.

4.2.3. Compound 2a Amidinium ion derivative. ^{13}C NMR ($CDCl_3$, 100 MHz, 218 K): δ (ppm) 36.8, 48.2, 49.3, 72.4, 126.9, 129.1, 138.7, 162.4. ESI-MS (MeOH): *m*/*z* 257.3, $[M]^+$.

4.2.4. Compound 3a-*cis*. ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K): δ (ppm) 24.9, 29.9, 39.9, 43.4, 44.0, 46.3, 52.4, 53.6, 81.7, 87.5, 126.6, 126.9, 127.5, 128.5, 130.3, 140.5. ESI-MS (MeOH): *m*/*z* 273.4, $[M+H]^+$.

4.2.5. Compound 3a-*trans*. The title compound was quantitatively obtained as a yellow oil. ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K): δ (ppm) 17.7, 26.4, 40.0, 44.5, 45.0, 47.4, 54.1, 55.2, 74.8, 83.6, 126.6, 126.9, 127.5, 128.5, 130.3, 141.5. ESI-MS (MeOH): *m*/*z* 273.4, $[M+H]^+$. Anal. calcd for $C_{16}H_{24}N_4$: C, 70.55; H, 8.88; N, 20.57%; found: C, 70.71; H, 8.78; N, 20.63%.

4.3. General procedure for tetracyclic bis-aminals 4a-*cis* and 5a-*cis* synthesis from the convenient tetraazamacrocycle

A solution of phenylglyoxal monohydrate (2 mmol) in absolute ethanol (10 mL) was slowly added to a solution of the convenient tetraazamacrocycle (2 mmol) in absolute ethanol (10 mL) at room temperature and under vigorous stirring. After one-week stirring for cyclen **4**, 4 h for cyclam **5**, solvent was evaporated to give the desired compound. When required, the unreacted macrocycle was precipitated with diethyl ether (yield for **4a**-*cis*: 60%, **5a**-*cis*: 95%).

4.3.1. Compound 4a-*cis*. The title compound was obtained as a yellow oil. ^{13}C NMR ($CDCl_3$, 100 MHz, 320 K): δ (ppm) 44.2, 46.1, 49.1, 51.2, 78.4, 79.4, 127.1, 127.8, 128.5, 128.7, 137.3, 145.5. ESI-MS (MeOH): *m*/*z* 271.4, $[M+H]^+$. Anal. calcd for $C_{16}H_{22}N_4$: C, 71.08; H, 8.20; N, 20.72%; found: C, 70.92; H, 8.31; N, 20.74%.

4.3.2. Compound 5a-*cis*. The title compound was obtained as a yellow solid. ^{13}C NMR ($CDCl_3$, 100 MHz, 320 K): δ (ppm) 18.3, 18.4, 47.3, 48.5, 49.7, 51.2, 74.2, 83.5, 125.1, 126.2, 127.3, 129.3, 138.6, 144.6. ESI-MS (MeOH): *m*/*z* 299.5, $[M+H]^+$.

4.4. General procedure for tetracyclic bis-aminals 5a-*cis* and/or 5a-*trans* synthesis from tricyclic bis-aminal 2a-*cis*

A solution of 1,3-dibromopropane (2 mmol) in freshly distilled acetonitrile (25 mL) was added dropwise to a refluxing mixture of **2a**-*cis* (2 mmol), freshly distilled acetonitrile (50 mL) and dried K_2CO_3 (20 mmol) under vigorous stirring. After 2 days, the solution was filtered and the solvent evaporated to give a brown oil, which was added to toluene (10 mL) to precipitate polymers. Toluene phase was separated, then evaporated to give a mixture of **5a**-*cis* and **5a**-*trans* in 48% yield.

When the same synthesis procedure was performed with diiodopropane (2 mmol) at room temperature and for 3 days, **5a**-*cis* was obtained as the unique compound (yield: 50%).

4.4.1. Compound 5a-*cis*. ^{13}C NMR see before. Anal. calcd for $C_{18}H_{26}N_4$: C, 72.44; H, 8.78; N, 18.77%; found: C, 72.49; H, 8.71; N, 18.81%.

4.4.2. Compound 5a-*trans*. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 19.7, 22.2, 43.0, 45.1, 49.7, 56.2, 66.4, 80.96, 121.4, 127.7, 128.1, 128.9, 129.4, 130.2. ESI-MS (MeOH): *m*/*z* 299.5, $[M+H]^+$.

4.5. General procedure for lactams 1b–3b synthesis from the convenient linear amine

A solution of phenylglyoxal monohydrate (2 mmol) in distilled water (10 mL) was slowly added to a solution of the convenient linear amine (2 mmol) in distilled water (10 mL)

at room temperature under vigorous stirring. After 2 h, water was evaporated to give quantitatively the desired compounds.

4.6. General procedure for lactams 1b–3b synthesis from bis-aminals 1a–3a

A solution of the convenient tricyclic bis-aminal in boiling water was vigorously stirred. After 2 days, solvent was evaporated to give the desired compound.

4.6.1. Compound 1b. The title compound was quantitatively synthesised as a yellow oil. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 41.6, 41.7, 47.2, 47.6, 49.2, 51.5, 64.4, 128.2, 128.9, 129.6, 140.6, 169.7. ESI-MS (MeOH): *m/z* 263.2, $[M+H]^+$. Anal. calcd for $C_{14}H_{22}N_4O$: C, 64.09; H, 8.45; N, 21.36%; found: C, 64.29; H, 8.27; N, 21.48%. IR (CH_2Cl_2): ν_{CO}=1690 cm^{-1}.

4.6.2. Compound 2b. The title compound was quantitatively obtained as a yellow oil. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 26.6, 40.9, 41.0, 44.2, 45.8, 47.5, 51.9, 63.5, 127.9, 128.6, 128.7, 140.5, 169.0. ESI-MS (MeOH): *m/z* 277.4, $[M+H]^+$. Anal. calcd for $C_{15}H_{24}N_4O$: C, 65.19; H, 8.75; N, 20.27%; found: C, 65.32; H, 8.61; N, 20.46%. IR (CH_2Cl_2): ν_{CO}=1690 cm^{-1}.

4.6.3. Compound 3b. The title compound was quantitatively obtained as a yellow oil. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 29.3, 29.6, 37.9, 39.0, 43.0, 45.3, 45.9, 50.9, 70.7, 126.7, 127.4, 128.1, 139.0, 167.5. ESI-MS (MeOH): *m/z* 291.3, $[M+H]^+$. Anal. calcd for $C_{16}H_{26}N_4O$: C, 66.17; H, 9.02; N, 19.29%; found: C, 66.46; H, 9.32; N, 19.19%. IR (CH_2Cl_2): ν_{CO}=1690 cm^{-1}.

4.6.4. Lactam 4b synthesis. A solution of phenylglyoxal monohydrate (2 mmol) in DMF/H_2O (9/1, 10 mL) was slowly added to a solution of cyclen (2 mmol) in refluxing DMF/H_2O (9/1, 10 mL) under vigorous stirring. After one night, solvents were evaporated, 20 mL of distilled water were added to the brown residue, then the mixture was washed with dichloromethane (5×30 mL). The aqueous phases were combined and evaporated to give the desired compound (yield: 60%) **4b** in yellow oil form. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 43.4, 44.3, 46.0, 46.2, 46.4, 47.9, 48.5, 49.8, 50.6, 127.2, 128.6, 129.6, 137.1, 172.5. ESI-MS (MeOH): *m/z* 289.4, $[M+H]^+$. Anal. calcd for $C_{16}H_{24}N_4O$: C, 66.64; H, 8.39; N, 19.43%; found: C, 66.71; H, 8.21; N, 19.58%. IR (CH_2Cl_2): ν_{CO}=1690 cm^{-1}.

4.6.5. Lactam 5b synthesis. Same procedure as the one followed for **5a**-*cis* from cyclam with a 2-days reflux, or 1-night reflux, in H_2O (yield: 100%). **5b** was produced as a yellow solid. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 24.6, 25.5, 35.4, 38.4, 46.4, 47.7, 48.7×2, 49.4, 50.4, 52.65, 67.9, 126.3, 126.7, 128.7, 133.1, 167.5. ESI-MS (MeOH): *m/z* 317.3, $[M+H]^+$. Anal. calcd for $C_{18}H_{28}N_4O$: C, 68.32; H, 8.92; N, 17.71%; found: C, 68.59; H, 9.18; N, 17.49%. IR (KBr): ν_{CO}=1690 cm^{-1}.

4.7. General procedure for mono-phenyl-acetic acid derivatives 1c–5c synthesis

A solution of lactam (2 mmol) **1b**–**5b** in aqueous TFA (6 M, 10 mL) solution was refluxed overnight under vigorous stirring. After solvent evaporation, a brown solid was obtained and added to an aqueous hydrochloride solution (6 M, 10 mL) and refluxed during 2 h. Then, the solvent was evaporated to give quantitatively the desired compound.

4.7.1. Compound 1c. The title compound is obtained as a brown powder. ^{13}C NMR (D_2O, 100 MHz): δ (ppm) 38.2, 41.8, 56.5, 57.0, 57.4, 58.6, 63.0, 129.8, 132.1, 132.3, 134.2, 169.2. Anal. calcd for $C_{14}H_{28}N_4O_2Cl_4$, $2H_2O$: C, 36.38; H, 6.98; N, 12.12%; found: C, 36.00; H, 7.09; N, 12.33%. IR (KBr): ν_{CO}=1710 cm^{-1}.

4.7.2. Compound 2c. The title compound was obtained as a brown powder. ^{13}C NMR (D_2O, 100 MHz): δ (ppm) 26.2, 38.4, 41.5, 46.5, 47.15, 47.6, 48.5, 62.6, 132.5, 132.6, 133.5, 134.1, 168.4. Anal. calcd for $C_{15}H_{30}N_4O_2Cl_4$, $3H_2O$: C, 35.17; H, 7.48; N, 10.94%; found: C, 34.98; H, 7.59; N, 11.11%. IR (KBr): ν_{CO}=1710 cm^{-1}.

4.7.3. Compound 3c. The title compound was obtained as a brown powder. ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 24.0, 26.6, 38.7, 39.4, 45.05×2, 47.0, 53.8, 71.8, 131.7, 132.3, 132.7, 136.1, 167.0. Anal. calcd for $C_{16}H_{32}N_4O_2Cl_4$, $4H_2O$: C, 36.51; H, 7.66; N, 10.64%; found: C, 36.32; H, 7.49; N, 10.44%. IR (KBr): ν_{CO}=1710 cm^{-1}.

4.7.4. Compound 4c. The title compound was obtained as a yellow powder. ^{13}C NMR (D_2O, 100 MHz): δ (ppm) 37.5, 43.7, 47.5, 55.6, 60.8, 130.1, 131.6, 132.4, 136.1, 168.8. Anal. calcd for $C_{16}H_{30}N_4O_2Cl_4$, $2H_2O$: C, 39.36; H, 7.02; N, 11.47%; found: C, 39.07; H, 7.04; N, 11.33%. IR (KBr): ν_{CO}=1710 cm^{-1}.

4.7.5. Compound 5c. The title compound was obtained as a yellow powder. ^{13}C NMR (D_2O, 100 MHz): δ (ppm) 21.9, 25.2, 43.6, 43.8, 44.1, 44.3, 44.4, 46.2, 46.7, 53.9, 67.3, 132.7, 133.1, 134.1, 139.2, 166.8. Anal. calcd for $C_{18}H_{34}N_4O_2Cl_4$, $2H_2O$: C, 40.46; H, 7.55; N, 10.49%; found: C, 40.69; H, 7.68; N, 10.20%. IR (KBr): ν_{CO}=1710 cm^{-1}.

4.8. General procedure for 1a–5a hydrolysis

Bis-aminals derivatives (2 mmol) were placed in an aqueous solution of hydrochloric acid (10 mL, 6 M) at 70°C for 2 h under vigorous stirring. After solvent evaporation, NaOH (4N) was added to the product obtained as a brown powder and the solution was extracted with CH_2Cl_2 (3×30 mL). The organic phases were dried with $MgSO_4$, filtered and evaporated to give the desired compound (which was purified by crystallisation in CH_3CN for azamacrocycles) (Yields obtained starting from: **1a**-*cis*: 80%, **2a**-*cis*: 84%, **3a**-*cis*: 90%, **5a**-*cis*, 70%, **5a**-*cis*/*trans*: 72%).

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