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Stereochemistry of the intermediates in the synthesis of 1,4,7,10-tetraazacyclododecane from triethylenetetramine, glyoxal and diethyl oxalate

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Abstract—The equilibrium and rearrangement phenomena encountered in two steps for the synthesis of 1,4,7,10-tetraazacyclododecane from triethylenetetramine, glyoxal and diethyl oxalate were studied and elucidated after the development of two micellar electrokinetic chromatographic (MEKC) methods. The latter were able to separate: (i) the four bis-aminals (**2**–**5**) obtained from the condensation of triethylenetetramine with glyoxal; (ii) the four diones (**6**–**9**) derived from the reaction of the bis-aminals with diethyl oxalate, whose solid state structures were determined by single crystal X-ray diffraction. The three not yet reported diones (**6**, **7** and **9**) were synthesised by taking advantage of both the reaction conditions and the use of a particular catalyst (MeONa). A plausible reaction mechanism, as well as a discussion of the solid state structures, is presented.

1. Introduction

Within the past two decades, the importance of 1,4,7,10-tetraazacyclododecane (cyclen, **1**) has continuously grown since it became an intermediate for the synthesis of chelating agents, which found applications in diagnostics and therapeutics.[1] In particular, the complexes of such ligands with paramagnetic metal ions, like the gadolinium ion, are largely used as magnetic resonance imaging (MRI) contrast agents.[2] Accordingly, a series of synthetic routes to cyclen appeared in the literature[3–12] and we wish to report here some recent findings regarding one of those synthetic paths.[4–7,9]

2. Results and discussion

The reaction of triethylenetetramine with glyoxal affords a mixture of four bis-aminals, i.e., *cis*-octahydro-3*H*,6*H*-2*a*,5,6,8*a*-tetraazacenaphthylene (**2**), *trans*-octahydro-3*H*,6*H*-2*a*,5,6,8*a*-tetraazacenaphthylene (**3**), *cis*-decahydro-diimidazo-[1,2-a:2′,1′-*c*]pyrazine (**4**) and *trans*-decahydro-diimidazo-[1,2-a:2′,1′-*c*]pyrazine (**5**).[6,7,10] By amidation with diethyl oxalate (DEO), the related mixture containing *cis*-octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene 1,2-dione (**6**), *trans*-octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene 1,2-dione (**7**), *cis*-octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene 3,4-dione (**8**) and *trans*-octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]acenaphthylene 3,4-dione (**9**) is obtained.[6] The subsequent reduction of the amide carbonyls, followed by removal of the central bridging moieties of compounds **10** and **11**, leads to **1** (see Scheme 1).[6,7]

The composition of the mixture containing **2**–**5** was at first determined by means of NMR studies, which were in accordance with those reported in the literature,[10,13] and showed that **2**, the thermodynamically favoured product, was predominant in reactions carried out in water at 5 °C in the presence of $Ca(OH)_2$ (Bracco procedure)[5,6] while **5**, the kinetically favoured product, was the major component working in EtOH at rt (Nycomed procedure).[7] By means of GC analysis,[5,6] we could detect the couple of compounds **2**+**3** and **4**+**5** but we did not make further efforts to find the conditions that are able to separate them. Indeed, we could not exclude that the harsh conditions used for the GC analysis might affect the composition of the mixture, as it is known[10,13] that isomerisation may occur. Accordingly, a micellar electrokinetic chromatographic (MEKC) method was developed to allow the separation of the four isomers and their quantification. Analytical results, obtained using

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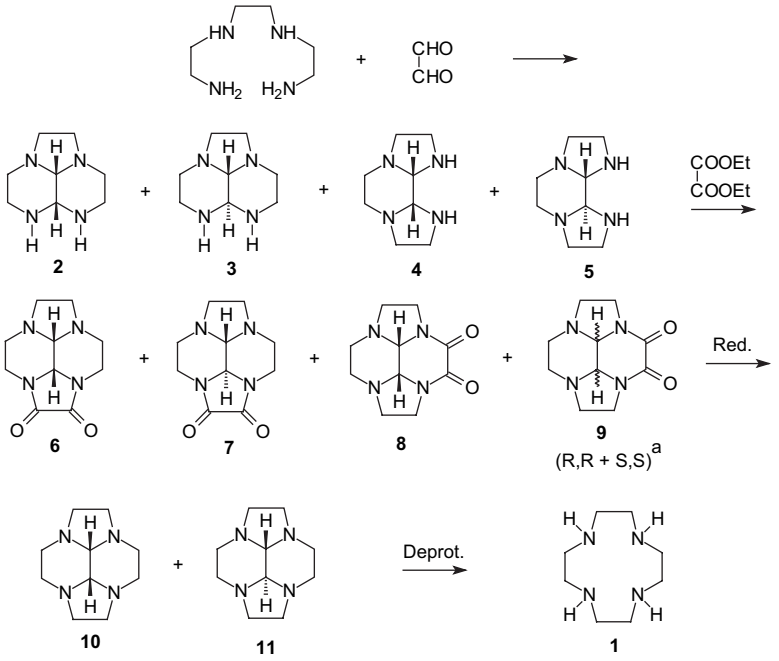


Scheme 1. [a]Both enantiomers of **9** are present in the solid state, as crystallised in an achiral space group.

both synthetic procedures for the preparation of **2–5** mixtures, are reported in Table 1.

As partly anticipated, the composition of the mixtures greatly depends on the reaction conditions. In particular: (i) in water at 5 °C in the presence of $Ca(OH)_2$,[5,6] **2** is formed as the main component, followed by **5**. Compound **3** is present in low percentage, while **4** only appears in a late reaction stage (entries 1–4); (ii) in EtOH at rt,[7] **5** is largely predominant along with **4** while **2** and **3**, which were derived from an isomerisation, are formed in small percentages only after the work up (entries 5 and 6). These results confirm those obtained from NMR studies and reported in the literature.[13]

We subsequently checked the stability of the mixtures obtained with the Bracco procedure,[5,6] especially under the reaction conditions used in the following step (reflux in EtOH, without or with a catalyst). The results are summarised in Table 2.

In particular: (i) the mixture stored at rt changed its composition over time: the content of the trans isomers increased whereas the content of the cis isomers decreased (entry 3 vs entry 1); (ii) heating at reflux a solution in EtOH led to an increase in the content of **3** and a decrease in the content of **2** while no significant change in the content of the other isomers was observed (entry 2 vs entry 1); (iii) heating at reflux a solution in EtOH, in the presence of MeONa, had almost no influence on the composition of the mixture (entry 4 vs entry 3).

Later on, we reacted mixtures having different compositions in each of the **2–5** isomers with DEO in EtOH under the conditions reported in Section 4. As we observed that compounds **4** and **5** were more reactive than **2** and **3**, we took advantage of this peculiarity for the preparation of pure **8** and **9**. Indeed, the reactions were performed, without or with MeONa, using about half of theoretical DEO. The latter preferentially reacted with **4** and **5** affording mixtures enriched with **8** and **9** from which the isolation of the products resulted easier. The work up of the different reaction mixtures allowed us to obtain pure **6**, **7**, **8** and **9** as crystals suitable for the determination of the solid state structure by single crystal X-ray diffraction (the structure of **8** was already reported in the literature[9]). After a MEKC method for the separation of each of the four isomers was devised, we were able to follow the amidation reaction, which was performed using the mixture reported in Table 1, entry 4, without or with a catalyst. Quite interestingly, even in the

Table 1. Percentages of the mixture containing **2–5** determined by MEKC

Entry[a]	2	3	4	5
1[b]	74.8	4.5	—[c]	20.7
2[d]	77.0	4.4	—[c]	18.6
3[e]	71.3	4.0	7.0	17.7
4[f]	70.2	5.9	6.0	17.9
5[b]	—[c]	—[c]	12.3	87.6
6[f]	6.6	5.7	11.9	75.8

[a] Entries 1–4: prepared according to Bracco procedure;[5,6] entries 5 and 6: prepared according to Nycomed procedure.[7]
[b] Reaction (0.5 h).
[c] Not detected.
[d] Reaction (2 h).
[e] Reaction (18 h).
[f] Isolated product.

Table 2. Percentages of the mixture containing **2–5** determined by MEKC

Entry	2	3	4	5
1[a]	70.2	5.9	6.0	17.9
2[b]	63.2	13.0	6.2	17.6
3[c]	68.8	9.6	2.6	19.0
4[d]	67.9	10.2	2.4	19.5

[a] Starting material.
[b] Mixture of entry 1 heated for 10 h in EtOH at reflux.
[c] Mixture of entry 1 reanalysed after one month at rt.
[d] Mixture of entry 3 heated for 10 h in EtOH at reflux in the presence of MeONa (1 mol equiv).

Table 3. Percentages of the mixture[a] containing **6–9** determined by MEKC

Entry	Time (h)[b]	Conversion (%)	6	7	8	9
1[c]	24	75	64.1	—[d]	35.9	—[d]
2[e]	6	91	76.3	—[d]	23.7	—[d]
3[f]	1	95	61.5	16.4	3.4	18.7

[a] Prepared starting from the mixture reported in Table 1, entry 4.
[b] Reflux time of a 12.5% ethanol solution containing DEO (3 mol equiv for the reaction of entry 1; 2 mol equiv for the reactions of entries 2 and 3).
[c] Without catalyst.
[d] Not detected.
[e] Catalysed by 2-pyridinol (0.5 mol equiv).
[f] Catalysed by MeONa (1 mol equiv).

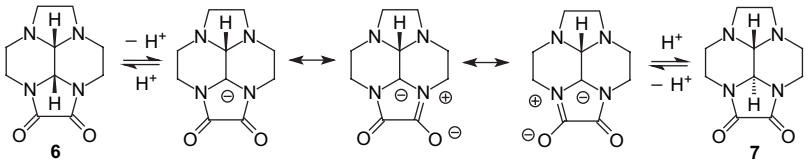
reactions performed with an excess of DEO (2–3 mol equiv) or in neat DEO, no oligomers were found. This clearly indicates that the monoamidated intermediate, which we could not detect, undergoes a rapid cyclisation reaction leading to compounds **6–9** instead of being attached by the amino groups of other molecules.

Some significant results, obtained from the same starting material, are reported in Table 3 while other un-tabulated data will be mentioned in the following discussion.

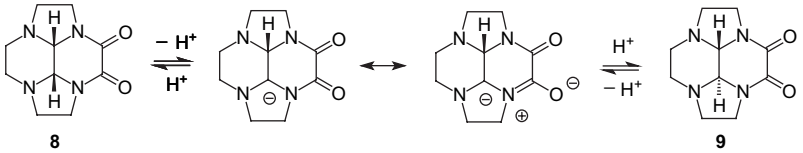
In the uncatalysed and in the 2-pyridinol catalysed reactions,[14] only the *cis* bis-aminals **6** and **8** were obtained (Table 3, entries 1 and 2). When a 95% pure *cis* bis-aminal **2** was reacted at rt, the related cis compound **6** was obtained. This is in disagreement with a previous report[9] asserting that **2** does not react at rt and that only polymers are formed upon heating. Indeed, in our experiment the conversion to **6** increased after heating at reflux. When pure, isolated *trans* bis-aminal **3** was reacted, the cis compound **6** was exclusively obtained. It was already reported in the literature[9] that *trans* bis-aminal **5** was quantitatively transformed into the *cis* diamide **8** as a consequence of an initial isomerisation of **5** into **4** before reacting with DEO. Our data confirmed that assumption and we think that the analogous isomerisation of **3** into **2** takes place, leading to **6**.

The results obtained in the presence of MeONa deserve some comments. The catalytic effect of MeONa could be explained by the in situ generation of dimethyl oxalate that might be more reactive than the corresponding diethyl ester. Such a mechanism was ruled out when we used dimethyl in place of diethyl oxalate and we obtained very similar results. Alternatively, generation of a more nucleophilic species through deprotonation assisted by the catalyst could occur. However, a complete transfer of a proton from the bis-aminals to the catalyst should be difficult because the bis-aminals are very weak acids. Therefore, we can suppose that MeONa assists the cleavage of hydrogen ion from the tetrahedral intermediate. Moreover, using NaOMe, along with **6** and **8**, the trans compounds **7** and **9** were also formed, while these compounds were absent in the reaction run in the absence of NaOMe (Table 3, entry 3 vs entries 1 and 2). As a preliminary assumption, MeONa could play a role in determining the stereochemical configuration of the acylation products in three different ways, as it could: (i) catalyse the interconversion of the mixtures containing **2–5**; (ii) catalyse the interconversion of the mixtures containing **6–9**; (iii) change the stereochemical course of the uncatalysed acylation. Quite interestingly, the percentage of **9** was well related to the content of trans isomer **5** in the starting material while the content of **7** resulted considerably higher than that of **3** (Table 3, entry 3 vs Table 1, entry 4). However, the reaction of pure **3** in the presence of MeONa initially afforded a 1:4 mixture of **6** and **7**, which upon heating, was transformed into a 4:1 mixture of **6** and **7**. Both **6** and **7** proved to be stable in refluxing EtOH but, when they were individually dissolved in EtOH containing MeONa, again a 4:1 mixture of **6** and **7** was obtained. Compound **8** proved to be stable in refluxing EtOH and the addition of MeONa afforded only 3% of **9**, along with residual **8** and degradation products. Considering that MeONa: (i) practically does not affect the composition of the **2–5** mixture (Table 2, entry 4); (ii) promotes the interconversion between **6** and **7**; (iii) has nearly no effect on the transformation of **8** into **9**, we propose that the interconversion between **6** and **7** occurs through an assisted deprotonation of the ethinic carbon atom (see Scheme 2). The intermediate carbanion is stabilised by: (i) the field effect[15] associated with the ylide-type system of the carbanion and the positively charged nitrogen of the dipolar form of the amide function; (ii) the resonance effect, between two equivalent structures, which share the carbanion.

Once applied to **8**, the same mechanism would involve the same field effect between the carbanion and the dipolar structure but, although in this case there are two equivalent ethinic hydrogen atoms, the absence of the resonance effect decreases the acidity of such hydrogens (see Scheme 3).



Scheme 2.



Scheme 3.

Accordingly, the stereochemical stability of **8** and **9** to MeONa is higher in comparison with that of **6** and **7**.

Therefore, in the noncatalysed reaction (Table 3, entry 1) only compounds **6** and **8** are formed because there is enough time for the isomerisation of **3** and **5** into **2** and **4**, respectively, to occur. In the presence of 2-pyridinol (Table 3, entry 2) the reaction, although accelerated, is still sufficiently slow to permit the isomerisation. When the amidation is performed in the presence of MeONa (Table 3, entry 3), **7** can be formed from **3** and from a partial inversion of configuration of **6** according to the mechanism depicted in Scheme 2, while **9** could be the consequence of the catalytic effect of MeONa, which makes the amidation of **5** faster than its stereoisomerisation into **4**. Indeed, the content of **9** (18.7%) is very similar to that (17.7%) of **5** in the starting material.

As previously mentioned, crystals of **6**, **7**, **8** and **9** were obtained and, by means of single crystal X-ray diffraction, their solid state structures were determined. The structure of compound **8** resulted isomorphous and isostructural with the already published structure,[9] thus our data will not be reported and those already known for **8**[9] will be taken into account for comparative purposes.

Bond distances and angles are those expected for this kind of molecules. Concerning the overall geometry of compounds **6–9**, both the trans isomers, **7** and **9**, show a more regular shape with respect to the cis ones (**6** and **8**). Indeed, in compound **7** (Fig. 1) a pseudo-symmetry plane passing through the C9–C10 bond and perpendicular to the mean plane defined by all the nonhydrogen atoms can be recognised, while in **9** a twofold pseudo-symmetry axis, bisecting bonds C1–C2, C5–C6 and C9–C10 is present (Fig. 2).

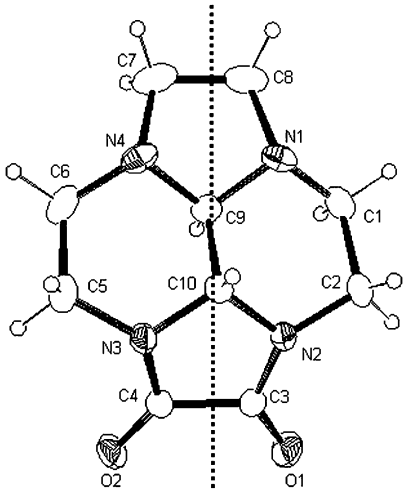


Figure 1. ORTEP3 view of compound **7**. The pseudo-symmetry plane is represented by the dotted line.

Obviously, the overall shape of molecules **6–9** results from the relative arrangement of the four condensed cycles A–D (see Scheme 4) and from their intrinsic symmetry, or better from their conformations. These latter results are summarised in Table 4.

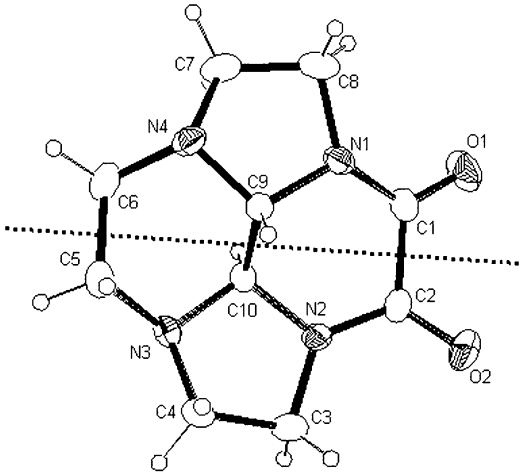
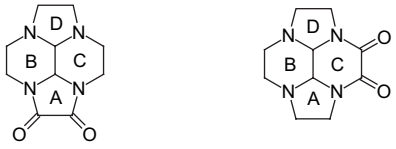


Figure 2. ORTEP3 view of compound **9**. The twofold pseudo-symmetry axis is represented by the dotted line.



Scheme 4.

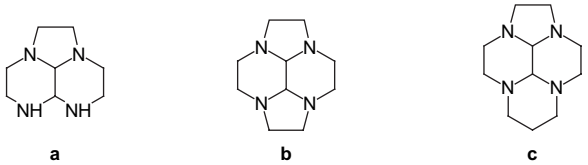
Table 4. Conformations of the four condensed rings in **6**, **7**, **8** and **9**

Ring	**6**	**7**	**8**[9]	**9**
A	Planar	Planar	Envelope	Envelope
B	Twist	Chair	Chair	Twist
C	Twist	Chair	Twist	Twist
D	Envelope	Envelope	Envelope	Envelope

Given the hybridisation of C3, C4, N2 and N3, the five-membered ring labelled 'A' is planar in compounds **6** and **7**, while in compounds **8** and **9** (where only N2 is sp^2) it show an envelope conformation. Ring D shows the same conformation (envelope) in all the four isomers.

The six-membered rings, B and C, have the same conformation in compounds **6** and **9** (twist), and in compound **7** (chair). In compound **8** the two six-membered rings show a chair (B) and a twist (C) conformation.

For comparative purposes a search for the solid state structures of fragments shown in Scheme 5 was performed in the Cambridge Structural Database (CSD, v. 5.26).[16] However, the very small number of entries prevents from any statistical analysis. In addition, because all the deposited molecules show a cis junction between the six-membered rings, retrieved data will be compared only with **6** and **8**.



Scheme 5.

Fragments **a** (one entry),[17] **b** (four entries)[18] and **c** (one entry)[19] show an almost identical 3D arrangement of the common rings as provided by the root mean square value (RMS, calculated using all the carbon and nitrogen atoms) that ranges between 0.054 and 0.152 Å. In all cases the five- and six-membered rings have envelope and chair conformations, respectively. Accordingly, the cis junction of three (**a** fragment) and four rings (**b** and **c** fragments) does not influence the conformational behaviour of these fully saturated rings. In the cis isomer **6** the conformation of both the six-membered cycles differs either from that (chair) observed in the retrieved solid state structures (**a**–**c** type) or from that (still of chair type) expected for six-membered rings having one sp^2 atom (N2 and N3). On the contrary, both the smaller rings (A and D) have the expected conformation.

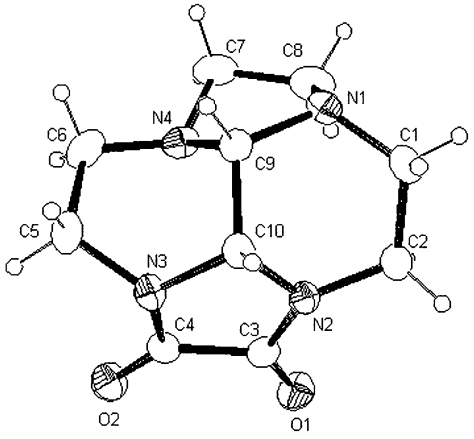


Figure 3. ORTEP3 view of compound **6**.

In compound **8** all the four fused rings show the expected conformations (twist for the C ring due to the presence of four sp^2 atoms). Thus, concerning the cis isomers, **6** and **8**, the introduction of sp^2 atoms in the smaller ring (A in **6** vs C in **8**) causes a more significant 3D rearrangement in the nearby rings (B and C in **6** vs A, B and D in **8**). However, this cannot be the unique reason for such distortion, as provided by the 'regular' (not distorted with respect to that expected) geometry of the four condensed rings in **7**. Accordingly, also the six-membered rings' junction plays an important role.

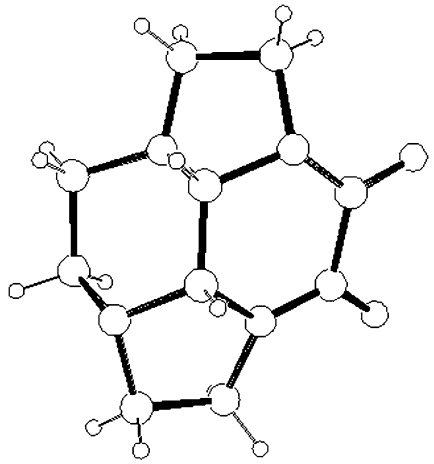


Figure 4. PLUTO view of compound **8** (the atomic coordinates are those reported in the literature.[9] The atom labelling is consistent with the other solid state structures reported here).

3. Conclusion

trans Bis-aminals **3** and **5** can isomerise into their corresponding cis isomers **2** and **4**, which in turn can be transformed, by reaction with DEO in EtOH without catalyst or in the presence of 2-pyridinol, into the related *cis* diamides **6** and **8**. When the amidation is performed in the presence of MeONa, the so far unknown *trans* diamides **7** and **9** are formed. Diamide **7** can be derived from both amidation of bis-aminal **3** and the partial inversion of configuration of the *cis* diamide **6** according to the mechanism described in Scheme 2, while **9** could be the consequence of the catalytic effect of MeONa, which makes the amidation faster than the stereoisomerisation of **5** into **4**.

The comparison of the solid state structures of compounds **6** and **8** with those of similar cis fragments deposited in the Cambridge Structural Database evidenced that the introduction of sp^2 atoms in a five-membered ring (**6**), instead of in the six-membered one (**8**), causes a significant 3D rearrangement in the nearby rings. However, also the six-membered rings' junction should play an important role in determining the rings' conformation, given the regular (i.e., not distorted with respect to the expected one) geometry of the four condensed rings in **7**.

4. Experimental

4.1. General

All reagents and solvents, obtained from commercial sources, were used without further purification. MeONa was used as a 1 M solution obtained by dissolution of sodium in MeOH. Melting points (°C, uncorrected) were measured with a Büchi 510 instrument. IR spectra were recorded on a Perkin–Elmer 882 spectrophotometer, using potassium bromide disks. MS spectra were acquired on a TSQ700 ThermoFinnigan Spectrometer using CH_3OH as the solvent. ^1H and ^{13}C NMR spectra were recorded at 298 K in $CDCl_3$ at 400.13 and 100.61 MHz, respectively, with a Bruker DRX 400 spectrometer. In order to have a complete assignment of the structures, 2D spectra were recorded using ^1H–^1H COSY45, HMQC and HMBC standard pulse sequences. The chemical shifts are given in δ units (ppm) relative to TMS (δ=0). For the assignment, see the numeration of the atoms in the related ORTEP figures. Elemental analyses were carried out at the Redox Laboratories (Monza, Milano, Italy).

4.2. Micellar electrokinetic chromatography (MEKC)

Analyses were performed on a Hewlett–Packard 3D Capillary Electrophoresis System equipped with an autosampler, column thermostat set at 15 °C and diode array detector set at 200 nm. A hydrodynamic injection of a 1–2 mg/mL solution into a fused silica capillary column (50 μm inner diameter) 80.5 cm long was used and a voltage of 30 kV was applied. For the analyses of the mixtures containing **2**–**5**

we used: (i) injection: 50 mbar, 5 s; (ii) electrolyte: 30 mM sodium borate buffer at pH 9.3, 0.3 mM EDTA, 20 mM sodium dodecyl sulfate (SDS), 1% MeOH. For the analyses of the mixtures containing **6–9** we used: (i) injection: 50 mbar, 3 s; (ii) electrolyte: 50 mM sodium borate buffer at pH 8.1, 0.3 mM EDTA, 180 mM sodium dodecyl sulfate (SDS), 1% MeOH.

4.3. Synthetic methods

4.3.1. *cis*-Octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]-acenaphthylene 1,2-dione (6). A solution of bis-aminals having the composition described in Table 1, entry 4 (21 g; 0.125 mol) in EtOH (160 mL) was treated with MeONa (6.75 g; 0.125 mol) and DEO (36.5 g; 0.25 mol). After 2 h at reflux under nitrogen atmosphere, the mixture was cooled to 30 °C and 37% HCl (12.3 g; 0.125 mol) was dropped in. The precipitated hydrochloride was filtered, washed with EtOH (3×20 mL), dissolved in water (80 mL), and then the solution was neutralized with Na_2CO_3 (6.9 g; 0.065 mol) and taken to dryness. The residue was boiled with MeOH (55 mL), the suspension was filtered and the clear solution was left at rt for 24 h. The crystalline precipitate was filtered, washed with MeOH (10 mL) and dried to afford **6** (7.5 g; 27%). Mp 158–160 °C. IR (KBr) ν 1429, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (ddd, 2H, J=2.2, 5.7, 10.3 Hz: 6, 1), 2.73 (m, 2H: 7, 8), 2.95 (m, 4H: 7, 8, 6, 1), 3.11 (ddd, 2H, J=5.7, 10.0, 13.9 Hz: 5, 2), 3.64 (d, 1H, J=4.6 Hz: 9), 4.20 (ddd, 2H, J=2.2, 6.4, 13.9 Hz: 5, 2), 5.17 (d, 1H, J=4.6 Hz: 10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.0 (5, 2), 48.0 (6, 1), 50.4 (7, 8), 65.4 (10), 74.8 (9), 160.0 (4, 3); MS *m*/*z* (ESI) 223 $(M+H)^+$, 245 $(M+Na)^+$; Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.02; H, 6.39; N, 25.18.

4.3.2. *trans*-Octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]-acenaphthylene 1,2-dione (7). The mother liquor obtained from the filtrate of the hydrochloride used for the preparation of **6** was evaporated to dryness and the residue was purified by silica gel chromatography (6:3:1 $CHCl_3$/CH_3OH/25% NH_4OH). The fractions enriched with the desired compound were combined and evaporated to dryness, then the residue was crystallised three times from methanol to afford **7** (1.5 g; 5.4%). Mp 258–260 °C. IR (KBr) ν 1442, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, 1H, J=6.2 Hz: 9), 2.33 (m, 2H: 6, 1), 2.46 (m, 2H: 7, 8), 3.22 (dd, 2H, J=4.7, 10. 9 Hz: 6, 1), 3.38 (m, 4H: 7, 8, 5, 2), 4.22 (d, 1H, J=6.2 Hz: 10), 4.28 (dd, 2H, J=3.1, 14.1 Hz: 5, 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.2 (5, 2), 50.8 (7, 8), 52.3 (6, 1), 67.0 (10), 92.8 (9), 157.5 (4, 3); MS *m*/*z* (ESI) 223 $(M+H)^+$, 245 $(M+Na)^+$; Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.97; H, 6.41; N, 25.15.

4.3.3. *cis*-Octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent[*fg*]-acenaphthylene 3,4-dione (8). A solution of bis-aminals having the composition reported in Table 1, entry 6 (30 g; 0.178 mol) in EtOH (225 mL) was treated with DEO (13 g; 0.089 mol) and heated at reflux for 18 h under nitrogen atmosphere. After addition of further DEO (2.6 g; 0.018 mol) and heating for 4 h at reflux, the solid, which spontaneously precipitated was filtered after cooling the suspension to rt. The product was crystallised from MeOH (270 mL) to afford **8** (6.2 g; 26%). Mp 255–257 °C (lit.[9] 252 °C). IR (KBr) ν 1458, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (see the atom numbers in the ORTEP view of the parent compound **9**) δ 2.60 (m, 2H: 5, 6), 2.76 (m, 4H: 4, 7, 5, 6), 3.12 (m, 2H: 4, 7), 3.45 (m, 2H: 3, 8), 3.89 (m, 2H: 3, 8), 4.13 (s, 2H: 9, 10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.5 (3, 8), 47.1 (5, 6), 49.7 (4, 7), 69.8 (9, 10), 157.6 (1, 2); MS *m*/*z* (ESI) 223 $(M+H)^+$, 245 $(M+Na)^+$; Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.95; H, 6.40; N, 25.12.

4.3.4. *trans*-Octahydro-2*a*,4*a*,6*a*,8*a*-tetraazacyclopent-[*fg*]acenaphthylene 3,4-dione (9). A solution of bis-aminals having the composition reported in Table 1, entry 6 (5.5 g; 0.033 mol) in EtOH (80 mL) was treated with MeONa (0.88 g; 0.0163 mol) and DEO (2.38 g; 0.0163 mol). After heating at reflux for 8 h under nitrogen atmosphere, the reaction mixture was concentrated to 20 g. The suspension thus obtained was filtered and the solid was crystallised from MeOH (10 mL) to afford **9** (0.5 g; 13.8%). Mp 255–256 °C. IR (KBr) ν 1433, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.71 (ddd, 2H, J=6.5, 8.7, 10.2 Hz: 4, 7), 2.90 (m, 2H: 5, 6), 3.38 (m, 4H: 4, 7, 5, 6), 3.49 (ddd, 2H, J=5.9, 10.2, 11.6 Hz: 3, 8), 4.20 (ddd, 2H, J=0.7, 6.5, 11.6 Hz: 3, 8), 4.42 (s, 2H: 9, 10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.6 (3, 8), 49.9 (5, 6), 53.3 (4, 7), 71.8 (9, 10), 156.9 (1, 2); MS *m*/*z* (ESI) 223 $(M+H)^+$, 245 $(M+Na)^+$; Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.88; H, 6.44; N, 24.98.

4.4. X-ray crystallographic study

Cell parameters and intensity data for compounds **6**, **7**, **8** and **9** were obtained on a Siemens P4 diffractometer, using graphite monochromated Cu Kα radiation (λ=1.54180 Å). Cell parameters were determined by least squares fitting of 25 centered reflections. The intensities of three standard reflections were measured every 60 min to check the stability of the diffractometer and the decay of the crystals. Intensity data were corrected for Lorentz and polarisation effects, an absorption correction was applied once the structures were solved by using the Walker and Stuart method.[20] Structures were solved using the SIR-97[21] program and subsequently refined by the full-matrix least squares program SHELX-97.[22] Given that the solid state structure of compound **8** was found to be isomorphous and isostructural with the already published structure,[9] our X-ray data will not be published. The hydrogen atoms of compounds **6**, **7** and **9** were introduced in calculated position and their coordinates refined in agreement with those of the linked atoms. All the nonhydrogen atoms were refined anisotropically. Atomic scattering factors and anomalous dispersion corrections for all the atoms were taken from the literature.[23] The molecular plots were produced by the ORTEP3 program[24] and the ORTEP views of compounds **6**, **7** and **9**, along with a PLUTO view of compound **8**, are detailed in Figures 1–4. Crystal parameters and structure refinement data for **6**, **7** and **9** are resumed in Table 5.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Structural Data Centre as supplementary publication numbers CCDC 292972, CCDC 292973 and CCDC 292974.

Table 5. Crystal data and refinement parameters of compounds **6**, **7** and **9**

	6	**7**	**9**
Empirical formula	$C_{10}H_{14}N_4O_2$	$C_{10}H_{14}N_4O_2$	$C_{10}H_{14}N_4O_2$
Formula weight	222.25	222.25	222.25
T (K)	293	293	293
λ (Å)	1.54180	1.54180	1.54180
Crystal system, space group	Orthorhombic, $P2_1cn$	Triclinic, P-1	Orthorhombic, $P2_1nb$
Unit cell dimensions (Å, °)	a=5.906(1)	a=7.868(5), α=111.190(5)	a=7.373(2)
	b=11.550(1)	b=8.735(5), β=95.210(5)	b=8.768(1)
	c=14.871(3)	c=9.543(5), γ=112.060(5)	c=15.934(3)
Volume (Å^3)	1014.4(3)	546.9(5)	1030.1(4)
Z, d_{calcd} (g/cm^3)	4, 1.455	2, 1.350	4, 1.433
μ (mm^{-1})	0.871	0.807	0.857
2θ range for data collection (°)	9.5–130.0	10.0–130.0	11.0–130.0
Reflections collected/unique	1274/902	1936/1574	1299/917
	[R(int)=0.0246]	[R(int)=0.0354]	[R(int)=0.0295]
Data/restraints/parameters	902/1/147	1574/0/155	917/1/147
Final R indices [$I>2\sigma(I)$]	$R1$=0.0467, $wR2$=0.1162	$R1$=0.0512, $wR2$=0.1255	$R1$=0.0424, $wR2$=0.1087
R indices (all data)	$R1$=0.0468, $wR2$=0.1163	$R1$=0.0521, $wR2$=0.1265	$R1$=0.0427, $wR2$=0.1089

4.5. Cambridge structural database

For comparative purposes crystal data of compounds containing fragments **a–c** (Scheme 5) were retrieved in the Cambridge Structural Database (v. 5.26).[16] Given the low number of entries featuring fragments **a–c**, no filters were turned on, except that only entries having 3D coordinates have been considered.

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