Synthesis and NMR characterisation of new cyclam–glyoxal diamides

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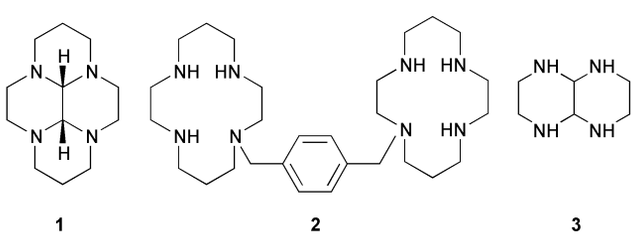
New cyclam–glyoxal diamides were synthesised by reaction of 1,4,5,8-tetraazadecalin with two equivalents of methyl acrylate. The configuration of the four stereoisomers obtained was assigned using NMR tools.

Introduction

As regards their applications in organic synthesis, glyoxal and butanedione[1] have been successfully used for the direct construction of tetraazamacrocycles like cyclen, cyclam and homocyclen. † In these routes, the dicarbonyl compound, which generates bis-aminal derivatives, acts as a rigidifying agent of the linear tetraamine and the macrocycles are obtained after a cyclisation step followed by a deprotection. Furthermore, the synthesis of mono-N alkylated derivatives of these macrocycles requires protection methods based either on classical temporary techniques or on the use of triprotecting groups. Recently, new methods using a *cis* bis-aminal intermediate have been developed for tetraazamacrocycle mono-N-functionalisation.[2]

So, owing to the cost of cyclam and potential of its derivatives, new routes to *cis* cyclam–glyoxal **1** are of high interest (Fig. 1). In particular, bis-cyclams are described as a new class



1 **2** **3**

Fig. 1 Cyclam–glyoxal, derivative and precursor.

of antiviral agent that exhibits potent inhibitory effects on HIV-1 and HIV-2 replication along with high selectivity.[3] Thus a new route to compound **2** using *cis* cyclam–glyoxal[4] as intermediate has been proposed.

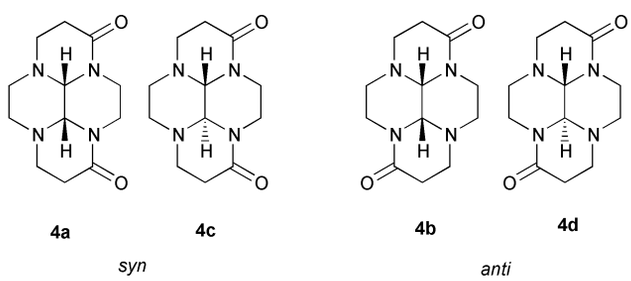
1,4,5,8-Tetraazadecalin ‡ **3**[5] is easily obtained from ethylenediamine and aqueous glyoxal; its use as a building block for the synthesis of cyclen and cyclam[6,7] has been recently described. Further to our studies on the reactivity of bis-aminal we observed that a double cyclisation occurs when 1,4,5,8-tetraazadecalin is condensed with methyl acrylate. This cyclisation results from a combination of a Michael-type reaction with a nucleophilic addition of an amine on an ester to lead to new dioxo-derivatives that are precursors of cyclam–glyoxal.

In this paper we describe the condensation of methyl acrylate on 1,4,5,8-tetraazadecalin and the structure determination of the reaction adducts. As usual in the chemistry of bis-aminals of polyamines the assignment of the relative configurations remains a non-trivial exercise. It was achieved thanks to the NMR tools, *e.g.* 2D sequences: HMBC, HMQC, ^{1}H–^{15}N correlations and variable temperature processes.

Results and discussion

NMR assignments

When 1,4,5,8-tetraazadecalin was allowed to react with methyl acrylate in methanol, the reaction led to a mixture of stereoisomers. The ^{13}C-NMR spectrum showed four signals in the carbonyl resonance area: they correspond to four products **4a**, **4b**, **4c**, **4d** (Fig. 2) in a 20 :16 : 35 : 29 ratio which depends on



4a **4c** **4b** **4d**

syn *anti*

Fig. 2 Stereoisomers of cyclam–glyoxal diamide.

reaction conditions. The compounds were separated by chromatography and recrystallisation and we never observed any equilibrium between the four products. At room temperature, the ^{13}C-NMR spectrum of each fraction presented six lines that corresponded to one carbonyl, one aminal and four cyclic carbon signals, respectively. The spectra can be related to the four possible structures shown in Fig. 2.

Moreover, as it is well known that the starting material **3** has a *trans* configuration,[5] an isomerisation process obviously took place during the reaction. This, however, raises a question: which spectrum corresponds to which compound?

As a matter of fact, all the four configurations seem to present, at least in their planar representations, symmetries which make pairs of carbons equivalent. However, numerous works[1,8] have shown that, in related situations involving bis-aminals of linear or cyclic tetraamines, this situation is reached in two cases: (i) when the junction corresponds to a *trans* configuration, hence the system is rigid and the equivalence is true, and (ii) when the junction is *cis*, the molecule is therefore labile. The scrambling process implies simultaneous nitrogen atom inversion and conformational exchange. Only an average

† The IUPAC names for cyclen, cyclam and homocyclen are 1,4,7,10-tetraazacyclododecane, 1,4,8,11-tetraazacyclotetradecane and 1,4,8,11-tetraazacyclotridecane.
‡ The IUPAC name for decalin is decahydronaphthalene.

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Table 1 HMQC correlation data ($^1J_{^1H-^{13}C}$)

4a		4b		4c		4d	
δ^1H (ppm)	δ^{13}C (ppm)	δ^1H (ppm)	δ^{13}C (ppm)	δ^1H (ppm)	δ^{13}C (ppm)	δ^1H (ppm)	δ^{13}C (ppm)
2.38; 2.71	28.6	2.17; 2.70	27.7	2.41; 2.66	32.5	2.42; 2.71	32.5
3.45; 4.05	38.8	2.79; 4.44	39.6	2.67; 4.62	38.9	2.89; 4.62	39.5
2.49; 3.00	47.3	2.54; 3.02	43.4	2.60; 2.90	48.8	2.57; 2.91	49.2
2.85; 3.12	49.8	3.11; 3.23	49.4	2.70; 2.89	52.2	2.44; 2.90	51.7
4.45	70.2	4.38	70.1	3.27	77.3	3.22	78.0
	168.2		169.2		167.2		167.5

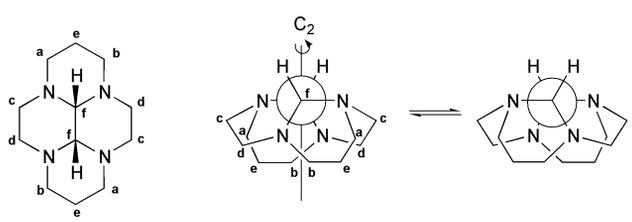
Table 2 HMBC correlation data (^2J, $^3J_{^1H-^{13}C}$)

4a		4b		4c		4d	
δ^1H (ppm)	δ^{13}C (ppm)	δ^1H (ppm)	δ^{13}C (ppm)	δ^1H (ppm)	δ^{13}C (ppm)	δ^1H (ppm)	δ^{13}C (ppm)
2.38	49.8; 168.2	2.17	49.4; 169.2	2.41	48.8; 167.2	2.42	49.2; 67.5
2.71	49.8; 168.2	2.70	49.4; 169.2	2.66	48.8; 167.2	2.71	49.2; 167.5
3.45	38.8; 168.2	2.79	43.4	2.67	38.9; 77.3	2.89	51.7; 78.0; 67.5
4.05	38.8; 70.2; 168.2	4.44	43.4; 70.1; 169.2	4.62	38.9; 77.3; 167.2	4.62	51.7; 78.0; 167.5
2.49	47.3; 49.8; 70.2	2.54	39.6; 49.4; 70.1	2.60	32.5; 77.3	2.57	32.5; 78.0; 167.5
3.00	47.3; 49.8; 70.2	3.02	39.6; 49.4; 70.1	2.90	32.5; 52.2; 77.3	2.91	32.5; 51.7; 167.5
2.85	28.6; 47.3; 70.2; 168.2	3.11	27.7; 43.4; 70.1; 169.2	2.70	52.2; 77.3	2.44	39.5; 49.2; 78.0
3.12	28.6; 47.3; 70.2; 168.2	3.23	27.7; 43.4; 70.1; 169.2	2.89	48.8	2.90	29.5
4.45	47.3; 49.8; 70.2 (w); 168.2 (w)	4.38	43.4; 70.1; 169.2	3.27	48.8; 52.2; 77.3	3.22	49.2; 51.7; 78.0

Table 3 HMBC ^{1}H–^{15}N correlation data (^2J, $^3J_{^1H-^{15}N}$)

4a		4b		4c		4d	
δ^1H (ppm)	δ^{15}N (ppm)	δ^1H (ppm)	δ^{15}N (ppm)	δ^1H (ppm)	δ^{15}N (ppm)	δ^1H (ppm)	δ^{15}N (ppm)
2.38	−340.4	2.17	−266.0 (w); −342.1	2.41	−332.0	2.42	−261.8 (w); −333.1
2.71	−264.0 (w)	4.44	−342.1	4.62	−262.8	2.71	−333.1 (w)
3.45	−264.0	2.54	−266.0	2.89	−262.8; −332.0	4.62	−261.8; −333.1
4.05	−264.0	3.11	−342.1	3.27		2.57	−333.1
2.49	−340.4	3.23	−342.1			2.91	−333.1 (w)
3.00	−340.4	4.38	−266.0; −342.1 (w)			2.44	−261.8
3.12	−340.4					2.90	−331.1(w)
4.45	−340.4; −264.0						

spectrum is observed at high temperature when the exchange process is fast. Therefore, the behaviour of *cis* cyclam–glyoxal is typical:[9] the spectrum shows six lines at low temperature. This phenomenon is due to the presence of a permanent symmetry axis that makes pairs of carbon atoms equivalent (Scheme 1).



Scheme 1

Moreover, the molecule is chiral and, therefore, exists as a pair of enantiomers. At high temperature (370 K), the spectrum shows only four lines as a consequence of a fast exchange between two enantiomeric forms: an average spectrum is observed above the coalescence temperature (345 K).

Thus, a variable temperature ^{13}C-NMR study should permit the *trans* configurations to be distinguished from the *cis* ones. Unfortunately only compound **4a** presented a temperature-dependent spectrum, which made the determination of the configurations more complicated. The entire analysis using impulse sequences: HMQC (Table 1), HMBC (Table 2), and ^{1}H–^{15}N correlation (Table 3) was necessary to achieve the identification.

The *cis* and *trans* configurations were deduced by BH_3–SMe_2 reduction of the four compounds which quantitatively led to *cis*[9] or *trans*[10] cyclam–glyoxal.

Compound 4a. The ^{1}H–^{13}C correlation (HMQC) at room temperature showed that two protons correlate with each methylene carbon. It is in agreement with the diastereotopic situation of the two vicinal hydrogen atoms which are never exchanged by any symmetry operation. The two carbons in the β position are not bound to nitrogen atoms; they appear at higher field (28.6 ppm). The aminal carbons bear a single hydrogen atom and so are shifted to 70.2 ppm. The HMBC correlation performed at room temperature showed the $^2J_{C-H}$ and $^3J_{C-H}$ couplings. The adjacent carbon to C_β was then easily identified: two correlation spots corresponding to the protons attributed to the carbons at 49.8 ppm are observed for 28.6 ppm. Furthermore, a coupling is observed between the protons borne by the carbons at 47.3 ppm, the ones at 49.8 ppm, and the aminal ones at 70.2 ppm. Finally, because of the lack of coupling between the protons borne by the carbons of the ethylenediamine bridges (47.3 and 38.8 ppm), the compound **4a** obviously has a *syn* structure. This conclusion is corroborated by the examination of the ^{1}H–^{15}N correlation: first the hydrogen atoms situated on C_β, on the aminal carbon and on the carbon at 38.8 ppm, show couplings with the amide nitrogen (−340.4 ppm) and, secondly, the protons assigned to the aminal carbon as well as those borne by the carbons at 47.3 and 49.8 ppm show couplings with the sp^3 amine nitrogen (−264.0 ppm).

The ^{13}C-NMR spectrum recorded at 193 K (Fig. 3, spectrum

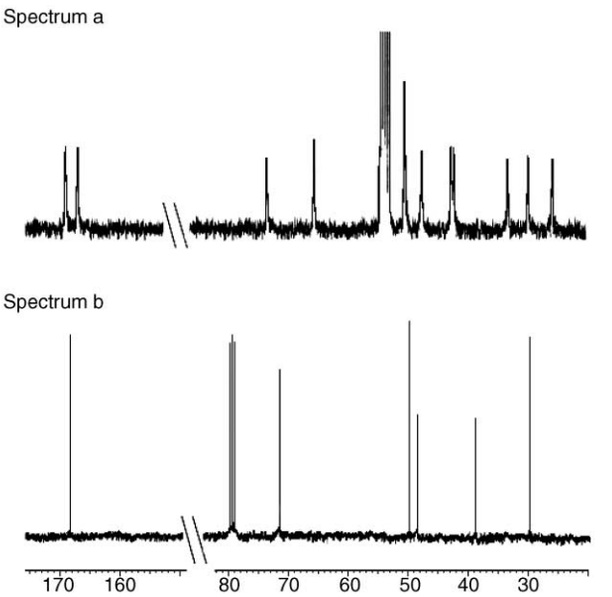
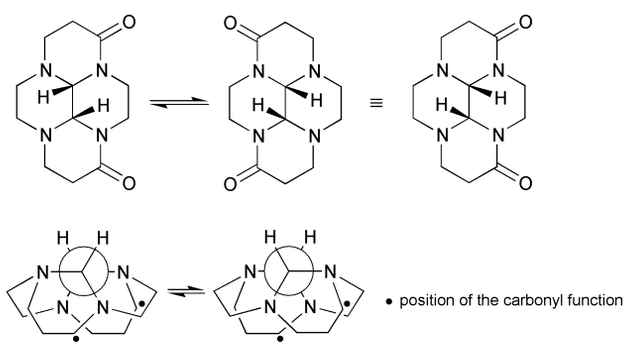


Fig. 3 Carbon 13 NMR spectra of **4a**. Spectrum a: 193 K, CD_2Cl_2, 75.468 MHz. Spectrum b: 298 K, $CDCl_3$, 75.468 MHz.

a) presented the twelve signals expected for an entirely unsymmetrical and subsequently chiral molecule. At room temperature (Fig. 3, spectrum b), six lines were observed: they correspond to the mean spectrum in which carbon atoms exchange, two by two, their situations.

This behaviour is the consequence of the dynamic equivalence induced by the equilibrium between the two enantiomers (Scheme 2). It clearly indicates a *cis* configuration of the



Scheme 2

junction in which, for instance, the two carbons bearing two aminal hydrogen atoms in nearly axial and equatorial positions exchange their situations. This situation corresponds to a dynamic racemate.

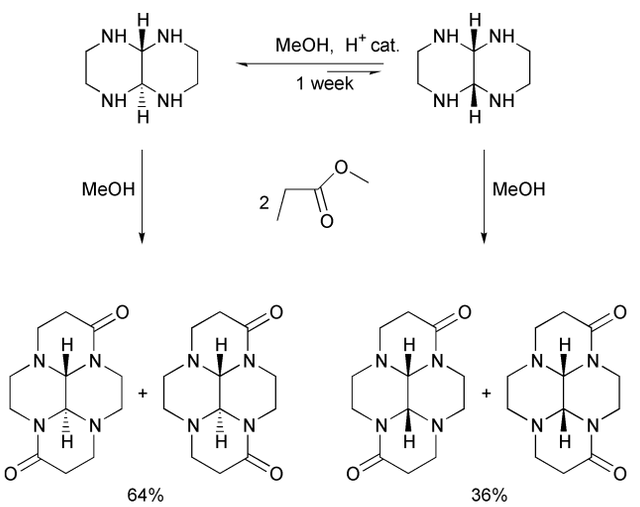
Compound 4b. The results of the 2D experiments and particularly the coupling observed (HMBC) between the protons borne by the carbons of the ethylenediamine bridges (43.4 and 39.6 ppm), are in good agreement with an *anti* structure. This *cis*-configuration does not exhibit any exchange behaviour in variable temperature NMR spectroscopy. Even at 193 K neither the beginning of any coalescence phenomenon nor the widening of signals was detected. The molecule is chiral and presents a C_2 axis, however an exchange between the two enantiomers cannot be simply obtained by nitrogen and cycle exchange but would also necessitate the breaking of several bonds; consequently, and whatever the temperature, the racemate is always characterised by six signals.

Compounds 4c and 4d. For the last two isomers the same procedure using a ^{13}C NMR variable temperature process was performed. It confirmed that **4c** and **4d** did not show any coalescence phenomenon since they were of *trans* configuration. The complete structure of the two compounds was established from 2D experiments.

Isomerisation process

Once the structure of the four diamides had been established, a new question arose: what is the origin of the *cis* configurations?

Fuchs *et al.* have noticed that very little of the *cis* configuration was obtained from the *trans*-1,4,5,8-tetraazadecalin when stirred in water for one week.[11] In methanol and under acid catalysis we observed that the amount of the *cis* form increased to 34% over the same period. The equilibrium had certainly been reached as three weeks later the proportions had not varied. Moreover, this result is in agreement with the total amount (36%) of the *cis* diamides (Scheme 3).



Scheme 3

Conclusion

In this paper, we provided evidence of the slow isomerisation of *trans*-tetraazadecalin, which is probably the origin of the unexpected formation of *cis* diamides. The configuration of the four stereoisomers was assigned and a *cis* bis-aminal (**4b**) whose NMR spectrum does not depend on the temperature was picked out. It is noteworthy that, in comparison to *cis* cyclam–glyoxal and from the point of view of the exchange process, the introduction of the two oxygen atoms results in great modification of the molecule symmetry and consequently of its dynamic NMR spectrum. Thus, *cis* cyclam–glyoxal, on the one hand, possesses a C_2 axis which makes pairs of ring carbons equivalent, and, on the other hand, is able to exchange its two enantiomeric forms by nitrogen and cycle inversion. Two supplementary pairs of carbons exchange their situation. In consequence, when increasing temperature, the number of the observed signals in ^{13}C-NMR spectroscopy changes from six to four. Compound **4a** does not possess any element of symmetry, and its ^{13}C-NMR spectrum presents twelve lines at low temperature; as the two enantiomeric forms also equilibrate by nitrogen and ring inversion the situation of the carbons is still exchanged in pairs and, consequently, six lines are observed at high temperature. Compound **4b** possesses only C_2 symmetry, however the two enantiomers do not equilibrate and six signals are always observed.

Experimental

1,4,5,8-Tetraazadecalin was easily obtained from ethylenediamine and glyoxal according to the method described by Fuchs *et al.*[5] in 50% yield. ^{13}C-NMR (D_2O, 75.468 MHz, 298 K, ppm): 75.5 N–*C*–N, 47.2 C_α–N.

Synthesis of the four isomers

1,4,5,8-Tetraazadecalin was dissolved in 100 mL of absolute methanol. Four equivalents of methyl acrylate were added and the solution was stirred for ten days. MeOH was then evaporated and the residue was dried under vacuum. A mixture of the four isomers was obtained in a 20 : 16 : 29 : 35 ratio with 100% yield.

Separation of the four isomers

One of the isomers (**4c**) was isolated by crystallisation of the crude product in CH_3CN. Column chromatography on Al_2O_3 was then run with CH_3CN–CH_2Cl_2–isopropylamine 55 : 33 : 11% as eluant. The fractions obtained were then purified by crystallisation in CH_3CN. The four isomers were obtained in the following proportions: **4c** 35%, **4d** 29%, **4a** 20%, **4b** 16%.

^{13}C-NMR ($CDCl_3$, 100.613 MHz, 298 K, ppm): **4a**: 167.9 *C*O, 69.8 N–*C*–N, 49.4 C_α–N, 46.9 C_α–N, 38.4 C_α–N, 28.4 C_β–N; **4b**: 169.25 *C*O, 70.15 N–*C*–N, 49.4 C_α–N, 43.41 C_α–N, 39.67 C_α–N, 27.76 C_β–N; **4c**: 166.9 *C*O, 77.2 N–*C*–N, 52.2 C_α–N, 48.9 C_α–N, 38.9 C_α–N, 32.5 C_β–N; **4d**: 166.44 *C*O, 78.29 N–*C*–N, 52.04 C_α–N, 49.48 C_α–N, 39.73 C_α–N, 32.89 C_β–N.

Reduction of the diamides by BH_3–SMe_2

The desired isomer was dissolved in dry THF (30 mL), an excess of BH_3–SMe_2 ($\frac{5}{3}$ equivalents) was added and the mixture was refluxed overnight under nitrogen. After cooling, the unreacted BH_3–SMe_2 was destroyed by slow addition of methanol. The solution was then evaporated to leave a white solid taken up in 6 M aqueous HCl (30 mL) and refluxed overnight. After cooling, the pH was raised to 14 with NaOH pellets and the solution was extracted with $CHCl_3$ (3 × 40 mL). The organic phase was dried on K_2CO_3, the solvent was evaporated and cyclam–glyoxal was isolated in 80% yield. Compounds **4a** and **4b** give *cis* cyclam–glyoxal whereas **4c** and **4d** give *trans* cyclam–glyoxal.

NMR spectral studies

Variable temperature ^{13}C-NMR spectra were recorded in CD_2Cl_2 on an AC 300 BRUKER spectrometer equipped with a QNP 5 mm probehead, operating at 75.468 MHz with a 30° tip angle (3 μs) and a 2 s recycle delay. Chemical shifts are reported in ppm relative to TMS as internal reference for ^{1}H and ^{13}C, and to CH_3NO_2 as external reference for ^{15}N.

2D NMR spectra were recorded in $CDCl_3$ at 298 K on a DRX Avance 500 BRUKER spectrometer equipped with an indirect triple TBI ^{1}H{BB}^{13}C 5 mm probehead. Heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple band coherence (HMBC) ^{1}H–^{13}C with a 60 ms mixing-time, and heteronuclear multiple band coherence (HMBC) ^{1}H–^{15}N with a mixing-time of 60 and 100 ms were performed according to standard pulse sequences and were employed to assign signals. For example, in an HMQC experiment the raw data set consisted of 1024(F2) × 700(F1) complex data points zero-filled to 1k in the F1 dimension prior to Fourier transform with a spectral width of 17000 and 3546 Hz in the F1 and F2 dimensions respectively.

Acknowledgements

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