Condensation of Glyoxal with Triethylenetetraamine; Isomerization and Cyclization

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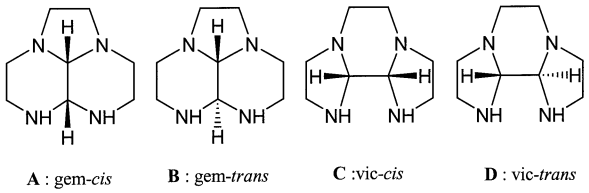
The condensation of triethylenetetraamine with glyoxal leads to the formation of four stereoisomers **A**, **B**, **C**, **D**. **A** is the thermodynamic product and **D** the kinetic one. These four compounds exhibit equilibrium and isomerization phenomena which are the key-feature of this cyclen synthesis.

The synthesis and study of 1,4,7,10-tetraazacyclododecane (cyclen) has attracted considerable attention owing to its remarkable complexing properties, which have allowed one to find medicinal applications of its derivatives.[1] In a previous paper we described a new route to cyclen from the key intermediate bis-aminal obtained by condensation of triethylenetetraamine with aqueous glyoxal.[2] We found that this reaction led to the four configurations depicted in Scheme 1.



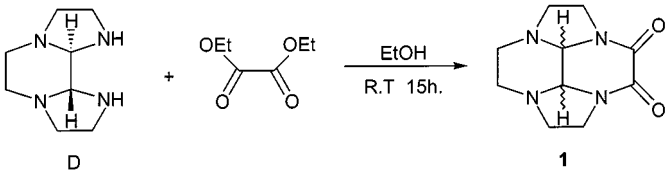
Scheme 1. Bis-aminals (222)-glyoxal

We also showed that an irreversible isomerization occurred when the mixture of the four isomers was heated in ethanol in the presence of a small amount of water, leading mainly to the thermodynamic product **A** which presented a *gem* configuration favorable to its cyclization with 1,2-dibromoethane.[2] Isomer **D** was identified as the kinetic product, the major compound obtained when the reaction was performed at relatively low temperature (−10°C). We reported that the *vic* configuration of **D** was not favorable to its cyclization with 1,2-dibromoethane. This condensation leads to polymers. So, prior to the addition of reactant, an isomerization to **A** is necessary. We also noticed that isomer **B** was always present in small amounts, less than 10%, and that isomer **C** never exceeded 20%.

We wish to report here new investigations on the isomerization process and another synthesis of cyclen.

Starting from the crude mixture of the four isomers, obtained after glyoxal condensation of triethylenetetraamine in ethanol at −10°C, we observed that only one product crystallized in 75% yield from a tetrahydrofuran/pentane solution. Its vicinal configuration was unambiguously established on the basis of its ^{13}C NMR spectrum, which exhibited only one kind of aminal carbon. The *trans* relation between the two aminal hydrogen atoms was deduced from temperature-dependent ^{13}C NMR studies. As no exchange phenomena were observed, we could deduce that this compound was rigid and totally symmetric; consequently, it corresponded to the isomer **D**. On the other hand, its diastereoisomeric *vic*-structure with a *cis*-configuration, the isomer **C**, was conformationally labile and exhibited exchange phenomena.[2][3] At low temperature, the ^{13}C NMR spectrum of **C** showed a set of eight signals indicating an unsymmetrical configuration.

In order to extend the field of applications of these intermediates, we explored the cyclization reaction with other reactants such as diesters, and, more particularly, the diethyloxalate.[4] When diethyloxalate was added to a solution of the bis-aminal **A** in ethanol at room temperature, no cyclization reaction occurred; when the mixture was heated for several hours only polymeric products were obtained. However, at room temperature, we observed a reaction with the recristallized bis-aminal **D** leading to compound **1** in 60% yield (Scheme 2).



Scheme 2. Condensation of **D** with diethyl oxalate

The structure of this unique reaction product was established from an X-ray analysis (Figure 1). Surprisingly the ORTEP-type plots showed that **1** has two hydrogen atoms in a *cis*-configuration. So, we wondered whether compound **1** resulted from a rearrangement process occurring during the reaction course, or alternatively, from a previous isomerization of **D**. To get an answer to this question we studied the behavior of **D** in solution.

In a first experiment, the isolated isomer **D** was allowed to stand in absolute ethanol at room temperature overnight. No isomerization occurred. The same experiment was carried out in 95° ethyl alcohol; a **D** → **C** transformation in a

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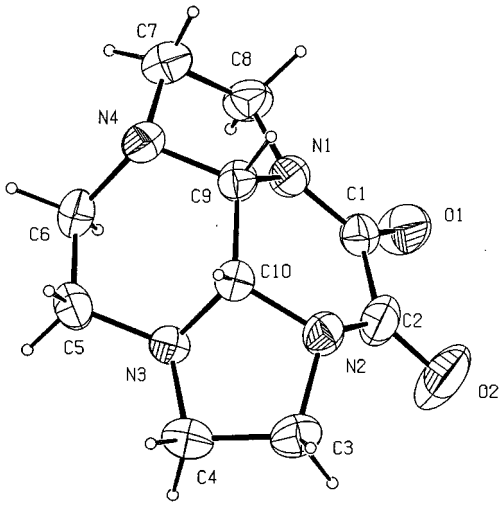


Figure 1. Molecular structure of compound **1**in the crystal

80:20 ratio was reached in fifteen hours, although **A** was not formed. In another experiment, **D** was refluxed for several hours in absolute ethanol, and the **D** → **C** transformation was observed in the same proportion. After adding a few drops of water and heating the mixture overnight, compound **A** was obtained as the major isomer (75%).

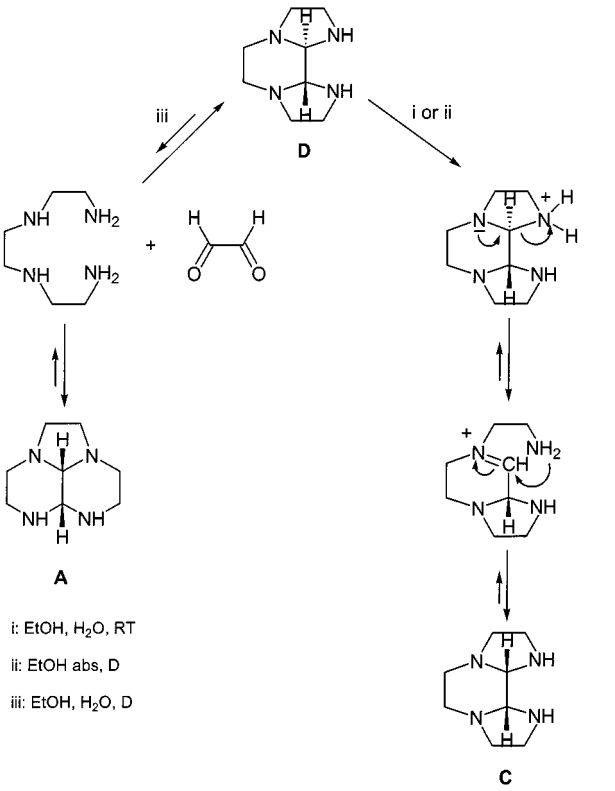
The constancy of the **D/C** ratio indicated an equilibrium between these two isomers. These results highlighted the importance of water catalysis in the isomerization process. In fact, two steps have to be considered: the first one was rather fast in the presence of water and occurred at room temperature leading to an equilibrium between **D** and **C**; the second one, corresponding to the formation of **A**, required heating and water catalysis. This configuration corresponds to the most stable product, which contains a maximum number of six-membered rings. In anhydrous conditions at room temperature, the formation of **A** was not observed and the **D** ⇌ **C** equilibrium was slowed. When starting from isomer **A**, no condensation with diethyloxalate occurred; so, one can deduce that this second step is not reversible or must be extremely slow.

The fact that water was not required for the **D** ⇌ **C** equilibrium could be explained by an intramolecular rearrangement involving an iminium ion as intermediate[5] and facilitated in protic medium by a proton transfer as depicted in Scheme 3.

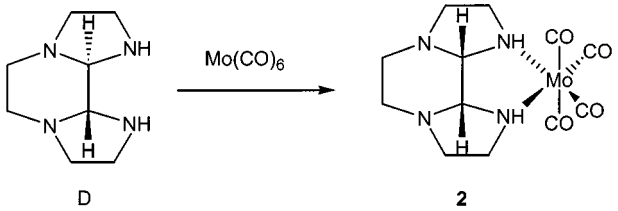
The formation of compound **A** is probably the consequence of glyoxal release by bis-aminal. We noticed that the **A/B** ratio remained constant, which is indicative of a possible equilibrium between **A** and **B**.

So, the condensation of **D** with diethyloxalate in ethanol displaced the **D** ⇌ **C** equilibrium and the cyclization product **1** was obtained in good yield. An analogous isomerization was observed when **D** was allowed to react with molybdenum hexacarbonyl in n-dibutyl ether at 140°C. Under these conditions, the complex **2** was isolated in 75% yield (Scheme 4).

The IR spectrum of **2** was consistent with the presence of a *cis*-$M(CO)_4$ moiety since the four expected ν(CO)



Scheme 3. Isomerization process



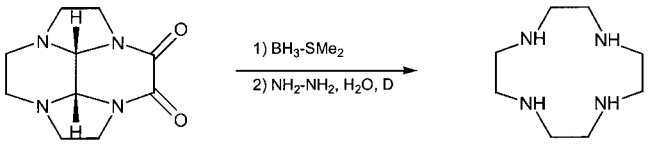
Scheme 4. Complexation of **D** with $Mo(CO)_6$

bands ($2A_1 + B_1 + B_2$) for a structure possessing a local C_{2v} symmetry were observed. All the carbon atoms were identified by ^{13}C NMR spectroscopy. This was consistent with the unsymmetrical *cis*-configuration of bis-aminal rigidified by its coordination to the metal. The four distinct signals of equivalent intensity observed between 200 and 225 ppm were attributed to the four carbonyls of the complex.[6] Consequently, the **D** ⇌ **C** equilibrium occurred upon warming, even in a strictly anhydrous medium, to give a configuration more favorable to the metal coordination. Isomer **A** did not react under these drastic experimental conditions: no reaction occurred and the reactants were entirely recovered. Moreover, this indicated that the (**D** ⇌ **C**) → **A** transformation was not reversible.

Among the four configurations, only **C** and **A** gave rise to a cyclic adduct, the first one with diethyloxalate and molybdenum hexacarbonyl and the second one with dibromo derivatives, respectively, while isomers **D** and **B**, both totally rigid, were unreactive or led to polymers. This behavior can be explained by the good fitting between the substrate and the reactive. Indeed, **C** and **A** had in common flexible and

adaptable conformations. One can assume that the template effect induced by the formation of the bis-aminal in a *cis*-configuration maintained the two secondary nitrogens in a configuration favorable to a cyclization process while preserving the adaptability required for a further intramolecular reaction.

Acid hydrolysis of compound **1** led to rearrangement products; dioxocyclen and further cyclens were not obtained this way. However, the reduction of the two amide functions gave easily the previously described cyclen-glyoxal adduct,[8] which was subsequently treated with hydrazine monohydrate to give the cyclen deprotection as previously described (Scheme 5).[2]



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Scheme 5. Reduction of **1** and deprotection

In summary, the synthesis of the bis-aminal triethylenetetraamine-glyoxal involved both thermodynamic and kinetic phenomena leading to the formation of four isomers. The isomer **D**, the kinetic compound, was obtained as the major component of the mixture when the reaction was controlled. Concerning thermodynamics, we have seen the important part played by water and/or heating in the product transformations. Cyclen was obtained through a controlled isomerization process.

The advantage of this method lies in the easy purification of the intermediate. No by-products are obtained in the two next steps (reduction and deprotection). Thus, this reaction sequence constitutes a clean and facile new route to cyclen.

Experimental Section

All the NMR spectra were recorded with a Bruker AC 300 (^{13}C: 100.62 MHz, ^{1}H: 300 MHz) or with a Bruker Advance DRX 400 (^{13}C: 75.47 MHz, ^{1}H: 400 MHz) spectrometer. Chemical shifts δ (in ppm) are given relative to the solvent. IR spectra were recorded with a Perkin-Elmer 1430 spectrometer. High Resolution Mass spectra were recorded with ZabSpecETOF EI + VG analytical spectrometer. Elemental analyses were carried out by the Centre de Microanalyses du CNRS de Lyon, France.

Typical Procedure for the Synthesis of Bis-aminals [(222)-glyoxal]: Triethylenetetraamine (2.00 g, 13.69 mmol) was dissolved in ethanol (30 mL + 2 drops of glacial acetic acid). The resulting solution was cooled to −10°C and a cooled solution of glyoxal (40% in water, 1.98 g, 13.69 mmol) in ethanol was added dropwise. After completion of the reaction (2 h), an excess of K_2CO_3 was added. Filtration and solvent evaporation under reduced pressure gave a clear oil, which was taken up in toluene (20 mL). The mixture was allowed to stand 15 min and then polymers were eliminated by filtration. The filtrate was evaporated and the procedure repeated twice to give pure bis-aminal in 90% yield (2.08 g) as a mixture of the four isomers. Recrystallization of **D** from tetrahydrofuran/pentane yielded white crystals in 75% (1.55 g). − ^{13}C NMR ([D_8]toluene, 75 MHz, 373 K): isomer **A**: δ = 42.9, 51.1, 51.3 (CH_2-α-N), 66.9, 77.8 (N*C*N). Isomer **B**: δ = 45.7, 50.5, 51.3 (CH_2-α-N), 71.7, 88.9 (N*C*N). Isomer **C**: δ = 43.8, 48.8, 51.0 (CH_2-α-N), 77.2 (N-*C*-N). Isomer **D**: δ = 44.4, 48.8, 51.9 (CH_2-α-N), 80.4 (N-*C*-N).

Typical Procedure for the Synthesis of 1: The recrystallized vic-*trans* isomer **D** (700 mg., 4.1 mmol) was dissolved in ethanol (20 mL) and diethyloxalate (557 μL, 4.1 mmol) added. A white precipitate was formed, then filtered after completion of the reaction (15 h) and dried in vacuo to give pure **1** in 60% yield (450 mg), m.p = 252°C. − ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K): δ = 4.12 (N-C*H*-C*H*-N): 4.12 ppm (s). − ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K): δ = 44.4, 47.0, 49.6 (*C*H_2-α-N); 69.7 (N-*C*-N), 157.5 (*C*O). − $C_{10}H_{14}N_4O_2$: calcd. C 54.05, H 6.30, N 25.22; found: C 53.81, H 6.52, N 25.43. − HRMS *m*/*z* = 223.1195 $[M + H]^+$.

Crystallographic data (excluding structure factors) were deposited with the Cambridge Crystal Data Centre as supplementary publication no. CCDC-118129. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK. [Fax: (internat.) + 44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

Typical Procedure for the Synthesis of 2: Complexation was carried out under a nitrogen atmosphere using standard Schlenk techniques. Solvents were freshly distilled from an appropriate desiccant (P_2O_5 for Bu_2O, CaH_2 for hexane). Sublimed $Mo(CO)_6$ (290 mg, 1.1 mmol) and bis-aminal **D** (168 mg, 1.00 mmol) were heated under reflux (142°C) in *n*-dibutyl ether (20 mL) for 3 h, while occasionally returning the sublimed $Mo(CO)_6$ to the reaction solution by scraping the condenser walls. A yellow precipitate was formed during the reaction. After cooling to room temperature, the solid was separated, washed with hexane (3 × 20 mL) and then dried in vacuo at 50°C to yield 2 in 75%. − IR (CH_2Cl_2): 2000 (w), 1880 (s, sh), 1865 (vs), 1827 (m) ν(CO) cm^{-1}. − ^{13}C NMR ([D_6]DMSO, 75 MHz, 298 K): δ = 47.5, 48.0, 48.3, 51.7, 54.2, 54.6 (*C*H_2-α-N), 73.8, 82.0 (N-*C*-N), 206.5, 207.6, 220.7, 222.0 (*C*O).

Reduction of 1, Hydrolysis and Deprotection: To a mixture of **1** in THF (30 mL) was added an excess of BH_3·SMe_2 (5/3 equivalents) and the mixture refluxed for 48 h. After cooling, the unreacted BH_3·SMe_2 was destroyed by slow addition of methanol, and the solution evaporated to leave a white solid. This was taken up in 10% aqueous HCl (30 mL) and refluxed overnight. After cooling, the pH was raised to 14 with NaOH pellets and the product extracted with CH_2Cl_2 (3 × 30 mL). After drying ($MgSO_4$) and solvent evaporation, the well-known cyclen-glyoxal was isolated in 60% yield. The deprotection step of cyclen-glyoxal was achieved by refluxing in hydrazine monohydrate as described elsewhere.[2] − ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K): δ = 50.0, 50.7 (*C*H_2-α-N), 78.8 (N-*C*-N).

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