Pergamon

Tetrahedron Letters 40 (1999) 2517–2520

TETRAHEDRON LETTERS

# Condensation of glyoxal with triethylenetetraamine. Stereochemistry, cyclization and deprotection.

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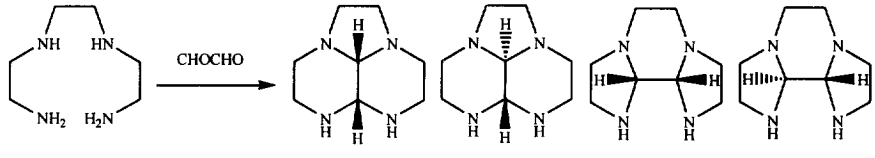
Received 22 December 1998; accepted 2 February 1999

***Abstract***: A mixture of bis-aminal isomers was obtained from aqueous glyoxal-triethylenetetraamine condensation. The irreversible isomerization of the species was observed and a new synthesis of cyclen proposed.


**Keywords**: Glyoxal, triethylenetetraamine, bis-aminal, cyclen.

Tetraazacyclododecane, or cyclen, well-known for its complexing properties,[1] is the key-intermediate in the preparation of magnetic resonance contrast agents for medical imaging.[2] The most investigated compound at this time is 1,4,7,10-tetraazacyclotetradecane-1,4,7,10 tetraacetate, designed as DOTA, which forms an extremely stable complex with gadolinium III used for clinical purpose.[3] Thus, a new route to cyclen affords a high interest. As a matter of fact, in the two past years, two patents proposed a new approach of the synthesis of this macrocycle.[4,5] Both had the first step in common which consists in the condensation of aqueous glyoxal with triethylenetetraamine to get a rigid intermediate further cyclized and deprotected to lead to cyclen.

Theoretically, the condensation of glyoxal with this tetraamine will result in one or several of the four stereoisomers depicted hereafter:




**A** : Gem-*cis* **B** : Gem-*trans* **C** : Vic-*cis* **D** : Vic-*trans*

This reaction has been reported in 1981 by Jazwinski and Kolinski.[6] They described the formation, in limited yield, of the gem-*cis* isomer together with traces of the gem-*trans* bis-aminal when the synthesis was performed in water. However, the Nycomed patent mentioned the obtention of a gem-compound in absolute ethanol at room temperature.[4] Furthermore, the Bracco patent described a synthesis carried out in water at 5°C in the presence of calcium hydroxide leading to a vicinal compound.[5] In both cases the configuration was not specified.

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0040-4039/99/$ - see front matter 
*PII:* S0040-4039(99)00260-9

In a previous paper, we described a new route to cyclen based on a very close principle, but where butanedione replaced glyoxal.[7] Prospecting simultaneously the synthesis with glyoxal we observed that the use of this rigidifying reagent aroused some questions. In this paper, we wish to report new interpretations about the condensation step of aqueous glyoxal with triethylenetetraamine and about cyclization and macrocycle release processes.

Best yields were obtained when glyoxal (40% in water) was slowly added to a solution of the tetraamine in acetonitrile at 0°C. We observed the very fast and quasi-quantitative formation of a mixture composed of the four isomers described above. The $^{13}$C-NMR spectrum of the crude reaction products in range of aminal-type carbons (**Figure 1, spectrum a**) indicates the typical composition of the mixture obtained according to the procedure described here.[8]

The two geminated structures, **A** or **B**, can be easily distinguished from the vicinal ones, **C** or **D,** using symmetry criteria. So, two peaks referred to aminal-type carbons for each of the two gem-compounds whereas each of the two vic-structures presented only one peak. The identification of *cis* and *trans* configurations required an additional study. Taking the relative intensities of the peaks into account, the observation of temperature-dependent changes on the spectrum in the range of the N-$\underline{C}H_2$ signals enabled us to attribute unambiguously the *cis* or *trans* configurations to each of the four stereoisomers. Thus, the three N-$\underline{C}H_2$ associated with the two aminal peaks of compound **A** gave rise to a coalescence phenomenon as did the three signals associated with the compound **C**. This result is consistent with conformationally labile *cis*-fused cycles. The two other sets of three signals associated to **B** and **D** respectively, did not exhibit exchange phenomenon indicating a rigid *trans* configuration of these isomers.

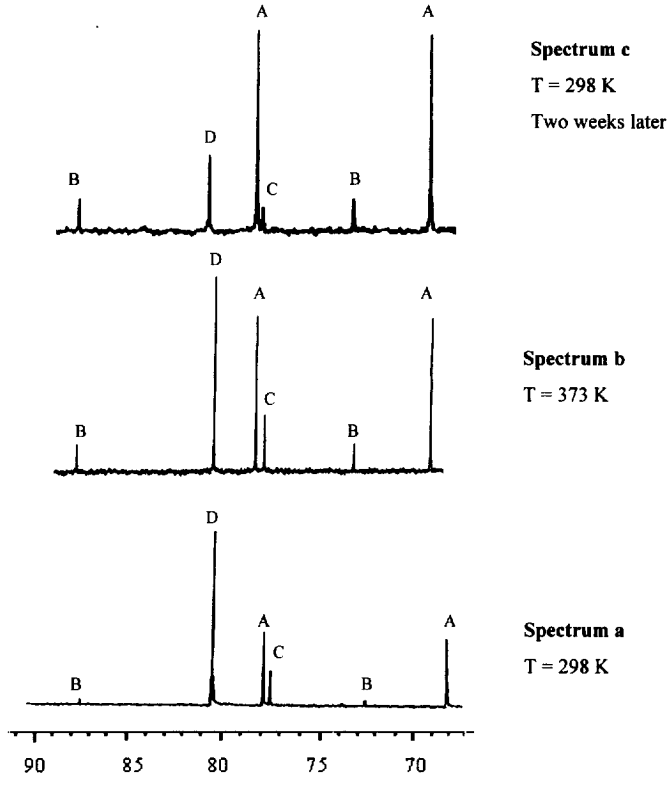
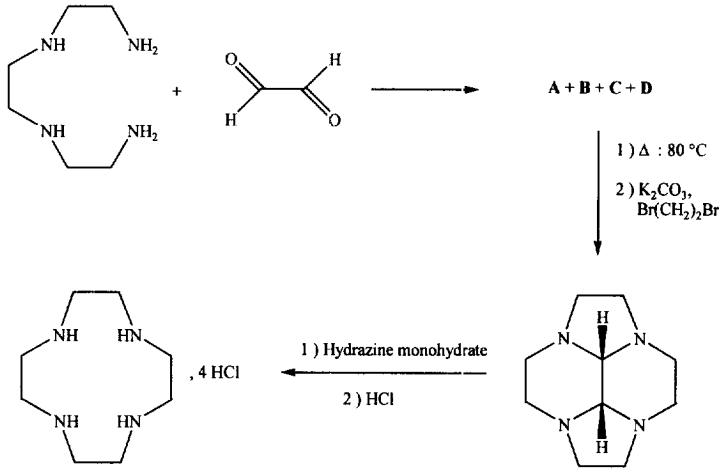



**Figure 1:** Aminal-type carbon of the isomers mixture.

In addition, when rising temperature, we noticed an irreversible isomerization of the species (**Figure 1, spectrum b**). Back to room temperature, the mixture still evolved slowly (**Figure 1, spectrum c**). The measurement of signals relative intensity suggested that the vic-*trans* (**D**) structure was isomerized into gem-*cis* (**A**), and that the vic-*cis* (**C**) structure led to the gem-*trans* (**B**) compound. This isomerization, which was rather fast at 80°C, is certainly catalyzed by traces of water. Thus, the kinetics was greatly slowed when the experiment was performed with products recristallized in hexane and carefully dried. Water would open the cycle[9] to lead to the most thermodynamically stable compounds, *i.e.* the ones with a maximum of six-membered cycles. The equilibrium between these two compounds should not be excluded but it was not established with certitude from the NMR-study.

The cyclization of this isomer mixture by dibromoethane in acetonitrile is also surprising. Indeed, the recristallized and carefully dried bis-aminals mainly led to polymers. This observation is in agreement with our previous results on butanedione: we had noticed that the gem-configuration was more favourable to cyclization than the vicinal one.[7] Traces of water and prolonged heating before the addition of bis-electrophile highly improved the reaction yield, the cyclen-glyoxal synthesized being exclusively in *cis* configuration [10, 11] (**scheme 1**).




**Scheme 1** : Synthesis of cyclen

The fast and complete deprotection easily achieved in acid medium with butanedione derivative was far more difficult with the cyclen-glyoxal adduct. We did not notice any acid hydrolysis.[4, 10, 12] The other methods proposed involving the use of hydroxylamine or oxidation gave poor yields.[4, 5]

We propose here an efficient alternative: the cyclen-glyoxal previously synthesized was treated with an excess of hydrazine monohydrate for 20 hours at 100°C. The reactant in excess was evaporated and the residue taken up in chloroform and cooled. After filtration of the precipitated polyazine and evaporation of the solvent, the cyclen was quantitatively obtained. Finally, this tetraazamacrocycle was recovered in the tetrachlorhydrate form as previously described.[13]

In summary, the slow vic→gem isomerization of the glyoxal-rigidified tetraamine is the key-feature of this cyclen synthesis. Considering this point, this route constitutes an interesting alternative to the classical Richman and Atkins cyclization.[14]

**References and Notes.**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8. **Typical procedure for bis-aminal synthesis.** Triethylenetetraamine (2 g, 13.69 mmol) was solubilized in acetonitrile (30 mL). The resulting solution was cooled to 0°C. Glyoxal (40% in water, 1.98 g, 13.69 mmol) was also solubilized in acetonitrile (30 mL) and added dropwise to the amine in solution. Once the addition was achieved (15 min), the reaction mixture was allowed to stand for two hours at room temperature. Solvent evaporation under reduced pressure gave a clear oil, which could be either recristallized in hexane (yield: 90%) or used as such in the next steps. ***Selected data***: $^{13}$C NMR ( Toluene-$d^8$, 75 MHz, 373 K): isomer **A**: 66.9, 77.8 (N<u>C</u>N); 42.9, 51.1, 51.3 ($CH_2$-α-N). Isomer **B**: 71.7, 88.9 (N<u>C</u>N); 45.7, 50.5, 51.3 ($CH_2$-α-N). Isomer **C**: 77.2 (N<u>C</u>N); 43.8, 48.8, 51.0 ($CH_2$-α-N). Isomer **D**: 80.4 (N<u>C</u>N); 44.4, 48.8, 51.9 ($CH_2$-α-N).
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11. The oil was taken up into acetonitrile (40 mL), then water (2 mL) was added. The resulting solution was kept 12 hours at 80°C prior to the addition of $K_2CO_3$ in excess (13 g) and dibromoethane (1,1 eq., 1.3 mL). The mixture was allowed to react 12 hours, then the base was filtered, washed with $CH_2Cl_2$ (2 × 10 mL) and solvents evaporated in vacuo leading to a powder consisting of the desired compound in mixture with polymers. The residue was solubilized in the minimum volume of dichloromethane and the polymers were precipitated with hexane. After filtration and solvent evaporation, the resulting *cis* cyclen-glyoxal was either purified by chromatography or used as such in the following step, (yield: 50 %). **Selected data:** $^{13}$C NMR ( $CDCl_3$, 75 MHz, 298 K): 76.8 (N<u>C</u>N); 49.6, 50.4 ($CH_2$-α-N).
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