The Unexpected Conversion of 1,5,8,12-Tetraazadodecane-Glyoxal Bisaminal into Its Amidinium Salt in an Acidic Medium

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Keywords: Bisaminals / Amines / Nitrogen heterocycles / Amides

When refluxed in aqueous hydrochloric acid solution, 1,5,8,12-tetraazadodecane-glyoxal bisaminal is quantitatively converted into its amidinium salt, which is a lactam precursor. The mechanism of this unexpected reaction is discussed.

Introduction

Owing to its recognised applications in medical imaging, 1,4,7,10-tetraazacyclododecane (cyclen) has gained a preponderant position among tetraazamacrocycles.[1] The complex of its 1,4,7,10-tetraacetate derivative (DOTA) with the gadolinium(III) ion (DOTAREM®) is a well-known MRI contrast agent and was one of the first compounds available for this purpose. The recently proposed new generation ligands of this type have different functionalities on the nitrogen atoms, therefore the mono *N*-substitution of cyclen is an important step for the synthesis of these chelating agents.[2]

Bisaminals of cyclic tetraamines have proven to be efficient protection tools for the synthesis of mono *N*-alkylated ligands: when the reaction is applied to cyclen, it consists of an alkylation of cyclen-glyoxal **1a** followed by treatment of the resulting quaternary ammonium salt to release the free mono *N*-alkylated cyclen.[3,4] Hydrolysis by treatment with an aqueous sodium hydroxide solution or refluxing in hydrazine hydrate usually gives good results. Recently, an unexpected reaction involving the glyoxal-protected cyclen **1a** was described in a Bracco SPA patent:[5] the hydrolysis of this compound between pH 5 and 9 led to the lactam **1b**, which was easily converted into cyclen monoacetate **1c** (Figure 1).

Bisaminals of linear tetraamines have been used successfully for the synthesis of cyclic adducts.[6] The formation of the intermediate is easily achieved by direct reaction of the tetraamine with a dicarbonyl compound. This reaction is usually reversible and a simple acidic hydrolysis allows the recovery of the starting material.[7] However, we observed that a lactam was also isolated when the bisaminal **2** was treated with aqueous hydrochloric acid (Figure 2).

In this paper we describe the isolation and characterization of new intermediates involved in the formation of the lactam resulting from **2**; the observation of the reversibility of these reactions allowed us to propose a mechanism for this sequence.

Results and Discussion

Compound **2** is easily obtained by the condensation of aqueous glyoxal with *N*,*N*′-bis(3-aminopropyl)ethylenediamine in ethanol solution as described previously.[8] When **2** was hydrolysed in a strongly acidic medium (11 M HCl) the reaction led to a unique product, **3**, which is stable under these conditions. The ^{13}C NMR spectrum of this compound is significantly different from the one expected for the deprotected linear tetraamine. In fact, ten different peaks are observed and, among them, one corresponds to an sp^2 carbon. The whole structure was established by NMR correlation sequences (HMBC ^1H-^{15}N, HMBC ^1H-^{13}C, TOSCY ^1H-^1H, HMQC ^1H-^{13}C).

The first significant structural information was gained from the HMBC ^1H-^{15}N correlation (Table 1, compound **3**), which shows two nitrogen atoms of similar nature and possessing a marked sp^2 character. They appear at $\delta = -267$ and -273 ppm relative to nitromethane as external reference. Furthermore, the other two nitrogen atoms resonate at $\delta = -350$ and -335 ppm, which indicates their sp^3 character. The single signal at $\delta = 4.41$ ppm, integrating for two protons, provided us with further important information as it correlates with all the nitrogen atoms except the

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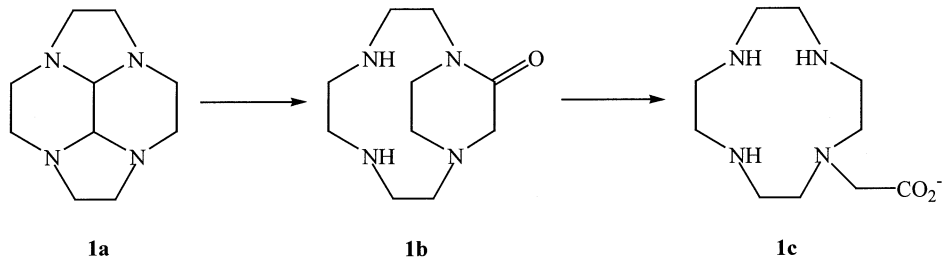

Figure 1. Hydrolysis of glyoxal-protected cyclen to cyclen monoacetate

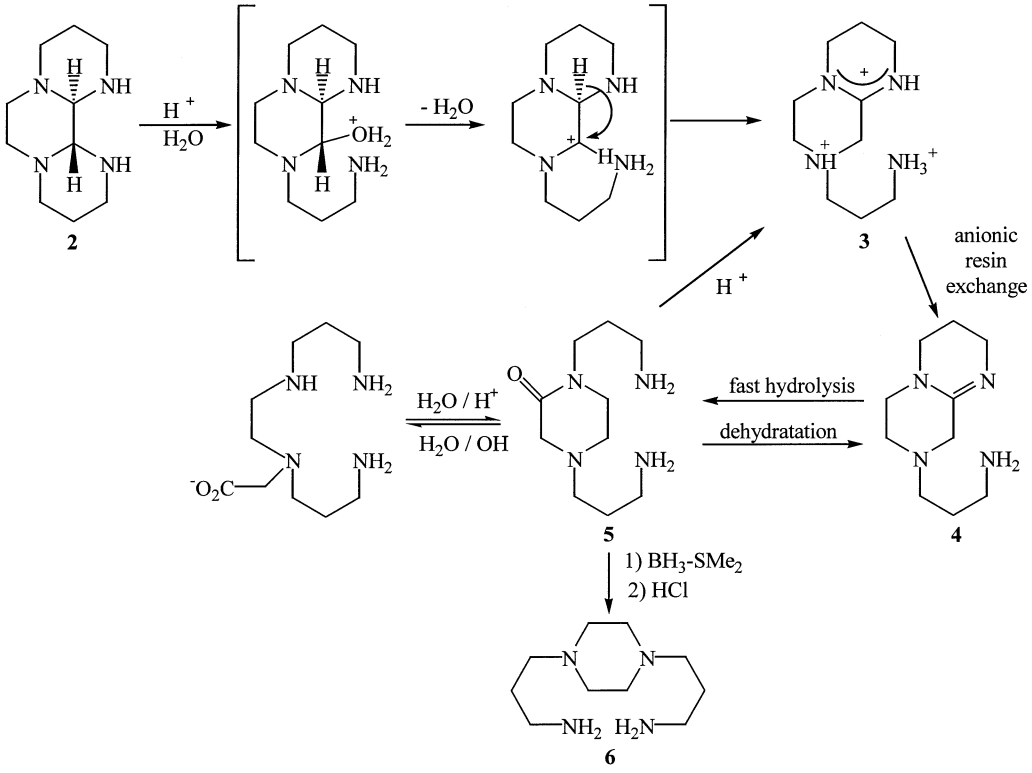

Figure 2. Hydrolysis sequence of compound **2**

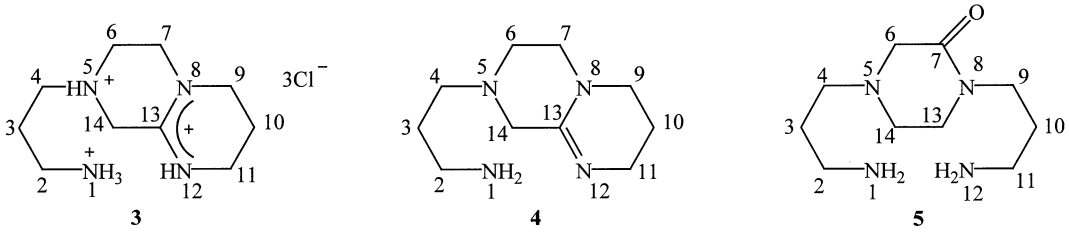

Figure 3. Atom numbering of compounds **3**−**5**

one at $\delta = -350$ ppm; these observations are consistent with the lack of a bond between the C^{14} and N^{1} atoms. The other correlations are consistent with the amidinium ion **3** depicted in Figure 2.

This structure was corroborated by the TOCSY ^{1}H-^{1}H sequence (Table 2), which highlighted the interaction of the protons borne by the carbon atoms C^{14} and C^{11}. This result implies a bond between C^{13} and N^{12}.

Table 1. HMBC ^{1}H-^{15}N spectroscopic data for compounds **3**−**5**

3		**4**		**5**	
δ^{1}_{H} ppm (C)	δ^{15}_{N} ppm (N)	δ^{1}_{H} ppm (C)	δ^{15}_{N} ppm (N)	δ^{1}_{H} ppm (C)	δ^{15}_{N} ppm (N)
2.05 (10)	−267 (8); −273 (12)	1.53 (3)	−340 (5); −360 (1)	1.26 (3)	−361 (1); −343 (5)
2.12 (3)	−335 (5); −350 (1)	1.77 (10)	−190 (12); −300 (8)	1.32 (10)	−362 (12); −265 (8)
3.07 (2)	−273	2.32 (4)	−300	2.08 (4)	−362; −265
3.26 (4)	−267	2.52 (6)	−360	2.30 (11, 14)	−361
3.40 (11)	−267; −335	2.65 (2)	−190; −300; −340	2.37 (2)	−343; −265
3.53 (9)	−267; −335	2.94 (14)	−300; −340	2.73 (6)	−343; −265
3.55 (6)	−267; −273; −335	2.99 (7)	−300	2.94 (13)	−265
3.75 (7)		3.01 (9)		3.09 (9)	
4.41 (14)		3.23 (11)			

Table 2. TOCSY ^{1}H-^{1}H spectroscopic data for compound **3**

3	
δ^{1}_{H} ppm (C)	δ^{1}_{H} ppm
2.05 (10)	3.4; 3.53; 4.41(w)
2.12 (3)	3.07; 3.26
3.07 (2)	2.12; 3.26
3.26 (4)	2.12; 3.07
3.40 (11)	2.05; 3.53; 4.41
3.53 (9)	2.05; 3.40
3.55 (6)	3.75; 4.41
3.75 (7)	3.55; 4.41
4.41 (14)	2.05(w); 3.40; 3.55; 3.75

Passing **3** through an anionic exchange resin-packed column gave the expected dehydrochlorinated amidine **4**, which readily evolved to another product **5** (subsequently identified as an amide). The analysis of the NMR sequences is in agreement with the structures **4** and **5** (Table 1 3 4).

The free amidine **4** can also be prepared quantitatively by dehydration of the amide by stirring and refluxing a mixture of **5** and alumina in toluene in a Dean−Stark apparatus. Confirmation of the structures of **4** and **5** was obtained upon their reduction by $BH_3{\cdot}SMe_2$, which led to the well-known and commercially available piperazine derivative **6** (Figure 2).[9]

A probable mechanism for the formation of the amide during the hydrolysis sequence is proposed in Figure 2. Normally, complete hydrolysis of the bisaminal to the free tetraamine results from the first acid-catalysed attack of the two aminal carbons by two molecules of water. The formation of the amidinium salt implies the breaking of a single

Table 3. HMQC correlation data (^{1}J,^{1}H-^{13}C) spectroscopic data for compounds **3**−**5**

3		**4**		**5**	
δ^{1}_{H} ppm	δ^{13}_{C} ppm (C)	δ^{1}_{H} ppm	δ^{13}_{C} ppm (C)	δ^{1}_{H} ppm	δ^{13}_{C} ppm (C)
2.05	20.7 (10)	1.53	30.4 (3)	1.26	30.3 (3)
2.12	24.6 (3)	1.77	21.2 (10)	1.32	30.3 (10)
3.07	39.2 (2)	2.32	55.5 (4)	2.08	55.3 (4)
3.26	56.6 (4)	2.52	50.9 (6)	2.30	38.9 (11)
3.40	41.1 (11)	2.65	40.3 (2)	2.30	49.8 (14)
3.53	50.3 (9)	2.94	57.9 (14)	2.37	40.2 (2)
3.55	50.8 (6)	2.99	49.1 (7)	2.73	57.4 (6)
3.75	48 (7)	3.01	46.9 (9)	2.94	46.3 (13)
4.41	51.3 (14)	3.23	43.3 (11)	3.09	43.3 (9)
	155.3 (13)		152.6 (13)		167.1 (7)

Table 4. HMBC ^{1}H-^{13}C spectroscopic data for compounds **3**−**5**

3		**4**		**5**	
δ^{1}_{H} ppm	δ^{13}_{C} ppm	δ^{1}_{H} ppm	δ^{13}_{C} ppm	δ^{1}_{H} ppm	δ^{13}_{C} ppm
2.05	41.1; 50.3	1.53	40.3; 55.5	1.26	40.3; 55.3
2.12	39.2; 56.6	1.77	43.3; 46.9	1.32	38.9; 43.3
3.07	24.6; 56.6	2.32	30.4; 40.3; 50.9; 57.9	2.08	30.3; 40.2; 49.8; 57.3
3.26	24.6; 39.2; 50.8; 51.3	2.52	49.1; 55.5; 57.9	2.30	30.3; 43.3; 46.3; 55.3; 57.3
3.40	20.7; 50.3	2.65	30.4; 55.5	2.37	30.3; 55.3;
3.53	20.7; 41.1; 155	2.94	50.9; 55.5; 152.7	2.73	49.8; 55.3; 167.1
3.55	48	2.99	46.9; 50.9; 152.7	2.94	49.8; 167.1
3.75	50.8; 155	3.01	21.2; 43.3; 49.1; 152.7	3.09	30.3; 38.9; 46.3; 167.1
4.41	50.8; 56.6; 155	3.23	21.2; 46.9; 152.7		

bis-aminal bridge with production of a cation and migration of a hydrogen aminal atom. The amidinium salt **3** is remarkably stable in acidic medium; however, after dehydrochlorination the resulting amidine **4** is rapidly hydrolysed into the six-membered lactam **5**. This reaction is reversible and the amidinium salt **3** is easily regenerated in acidic medium. However, the expected corresponding amino acid sodium salt was detected after treatment of **5** with alkaline medium. This end compound, which is difficult to isolate, rapidly converts into the lactam **5** and the amidinium salt **3** in acidic medium.

When hydrolysis of **2** was performed in dilute acidic solution, we noticed that the reaction was slower; formation of the free tetraamine was never observed. To the best of our knowledge this behaviour is unique among the other bisaminals formed by the condensation of linear tetraamines and glyoxal. Although the corresponding amidinium salt was not identified, the previously mentioned hydrolysis of cyclen-glyoxal is probably the consequence of a similar mechanism.

Further investigations concerning the extension of this reaction to bisaminals formed from other α-dicarbonyl compounds are in progress.

Experimental Section

General: All reagents were of commercial quality and solvents were dried using standard procedures. Elemental analyses were performed at the Service de Microanalyse, CNRS, 91198 Gif sur Yvette, France and at the Service Central d'Analyse, CNRS, B. P. 22, 69390 Vernaison, France.

NMR Spectral Studies

2D NMR spectra were recorded in $CDCl_3$ (compounds **4** and **5**) or D_2O (compound **3**) at 298 K on a DRX Avance 500 Bruker spectrometer equipped with an indirect triple TBI $^1H\{BB\}^{13}C$ 5 mm probehead operating at 500.13 MHz for ^1H, 125.77 MHz for ^{13}C and 50.68 MHz for ^{15}N. Heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple band coherence (HMBC; 60 ms mixing time) ^1H-^{13}C and heteronuclear multiple band coherence (HMBC; mixing time of 60 and 100 ms) ^1H-^{15}N spectra were recorded using standard pulse sequences. For example, in a typical HMBC experiment the raw data set consisted of $512(F_2) \times 233(F_1)$ complex data points zero-filled to 512 in the F_1 dimension prior to Fourier transform, with a spectral width of 19490 and 1498 Hz in the F_1 and F_2 dimensions, respectively.[10] The atom labelling of compounds **3**−**5** is shown in Figure 3.

Procedure for the Synthesis of 3: Compound **2** (0.98 g, 5 mmol) was added to 10 mL of 11 M hydrochloric acid and the reaction mixture was stirred for 2 h. After evaporation of the solvent a brown oil was obtained. Absolute ethanol (10 mL) was then added and removed under vacuum. This operation was repeated several times until a hygroscopic white solid was isolated. The solid was then filtered off and washed with small amounts of absolute ethanol; compound **3** (1.14 g, 3.75 mmol) was isolated in 75% yield. NMR spectroscopic data are gathered in Table 1−4

Procedure for the Preparation of 5: Compound **3**, dissolved in a minimum of water, was passed through a column packed with anionic exchange resin Amberlyst A-26 (3 g of resin for 1 g of chlorohydrate). A mixture of free amidine **4** and amide **5** was obtained, which converted into amide **5**, isolated in 93% yield, after evaporation of the water. NMR spectroscopic data are gathered in Tables 1, 3 and 4. $C_{10}H_{22}N_4O$ (214): calcd. C 56.07, H 10.28, N 26.17; found C 56.00, H 10.27, N 26.27.

Procedure for the Preparation of 4: Compound **5** (0.214 g, 1 mmol) was dissolved in a minimum of water. Alumina (10 mmol) and toluene (50 mL) were then added. The mixture was refluxed for 48 h and a Dean−Stark trap was used to collect the water. After cooling, the suspension was filtered and the solid was repeatedly washed with a mixture of dichloromethane and methanol (9:1). The solvents were evaporated to give **4** (0.141 g, 0.72 mmol) in 72% yield. NMR spectroscopic data are gathered in Tables 1, 3 and 4.

Procedure for the Preparation of 6 from 5: An excess of $BH_3{\cdot}SMe_2$ (2 mmol) was added to a solution of **5** (1 mmol) in 20 mL of THF. The mixture was refluxed under a nitrogen atmosphere for 48 h. After cooling, the unchanged $BH_3{\cdot}SMe_2$ was destroyed by slow addition of methanol, and the solvents then evaporated to yield a white solid. This solid was taken up in 10% aqueous HCl (20 mL) and refluxed overnight. After cooling, the pH was raised to 14 with NaOH pellets and the product extracted with CH_2Cl_2 (3×20 mL). After drying ($MgSO_4$) and solvent evaporation, the well-known and commercially available piperazine derivative **6** was isolated in 80% yield. ^{13}C NMR (100.61 MHz, $CDCl_3$, 298 K): δ = 56.2, 53.0; 40.5 (8 C_α−N), 30.2 (2 C_β−N) ppm.

Acknowledgments

We are grateful to the Région Bretagne for financial support.

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Received September 12, 2002
[O02510]