Synthesis of three dissymmetrical pentaamines *via* bisaminals of linear tetraamines

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Bisaminals of linear tetraamines were selectively *N*-monofunctionalised with acrylonitrile in a Michael-type addition giving rise, after reduction, to three open-chain dissymmetrical pentaamines, bearing a new aminopropyl group on one terminal nitrogen atom.

Keywords: tetraamine, pentaamine, bisaminal, *N*-monofunctionalisation, Michael-type addition

Natural polyamines are widely distributed in the nature in various bacteria, plants and animals. They play an important role in the regulation of the growth of cells, their proliferation and differentiation.[1-5] Among the polyamines, diamines, triamines and tetraamines have been much studied.[6-9] Pentaamines are also known in nature: for instance, some of them have been found in thermophile bacteria[5,10] or in spider venom;[11,12] however, the knowledge of the chemistry of this class of molecules is rather poor and they are relatively rarely mentioned in the literature in spite of their biological importance. Some symmetrical pentaamines, like TEPA (tetraethylenepentaamine), were also proposed for numerous industrial applications as antifouling agents, textile or asphalt additives, and corrosion inhibitors.[13,14] The known routes to this class of compounds often consist in tedious multi-step processes or in statistical methods giving rise to complex mixtures of polyamines of various lengths.[15-18] Note that almost all published works concern mainly symmetrical pentaamines. On the other hand, the isolation of natural polyamines is difficult and an easy access to new pentaamines would be useful to have at one's disposal new building blocks for derivatives for medicinal purposes and giving the opportunity to undertake studies on their biological properties.[19,20]

Over the last years, bisaminals of cyclic and linear tetraamines have been extensively studied and they have enabled the synthesis and selective *N*-alkylations of tetraaazamacrocycles.[21-26] In a previous paper, we reported the use of linear tetraamine bisaminals as successful tools for the *N*-monoalkylation of tetraamines.[27]

We now report a facile route to three dissymmetrical open-chain pentaamines, 1,4,7,10,14-pentaazatetradecane, 1,4,8,11,15-pentaazapentadecane and 1,5,8,12,16-pentaazahexadecane, *via* a selective *N*-monofunctionalisation of linear tetraamine bisaminals involving acrylonitrile in a Michael-type addition. To our knowledge, the first two pentaamines are new[3] and the last one has been mentioned in several patents but no efficient synthesis was described.[28]

Results and discussion

Bisaminals **1** (mixture of isomers), **2** (*gem-trans*) and **3** (*vic-trans*) used in this study were previously described;[27,29] they are synthesised by the condensation of aqueous glyoxal with the suitable linear tetraamines, 1,4,7,10-tetraazadecane, 1,4,8,11-tetraazaundecane and 1,5,8,12-tetraazadodecane, denoted in the literature as **222**, **232** and **323** respectively (Scheme 1).

A first consequence of the protection of the tetraamine in the bisaminal derivative is the transformation of the secondary amino groups of the linear tetraamine into tertiary amines, making them unreactive in a Michael-type addition. The two primary amino groups, now secondary in the rigidified intermediate, are the only ones able to react with the electrophile, and the main distinctive feature is certainly that this reaction is very selective. As previously observed,[27] the functionalisation of the first nitrogen atom reduces the accessibility of the second one and thus considerably limits its reactivity. Even in presence of a large excess of acrylonitrile, the *N*-monofunctionalised adduct is obtained cleanly, whatever the configuration of the starting bisaminal.

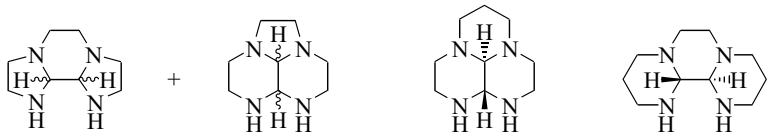
Typically, bisaminals **1**–**3** were allowed to react with acrylonitrile, in ethanol. This reaction, which was rather slow, required an excess of electrophile which reacted in part with ethanol. After evaporation, the reduction of the nitrile function was easily performed using Raney-type alloy (Ni–Al), in an ethanolic solution of sodium hydroxide, according to a previously described procedure.[30] The deprotection step was achieved quantitatively after refluxing the crude products in hydrazine hydrate for 2 hours.[27] Pentaamines were purified by precipitation of their corresponding hydrochloride salts. Free pentaamines **4**–**6** were isolated by the action of potassium carbonate in refluxing acetonitrile or, after treatment with strongly basic anion-exchange resin (Scheme 2, Table 1).

Intermediate compounds **1a** and **1b**, formed from bisaminal **1**, were obtained as a mixture of isomers. Nitrile

Table 1

Bisaminal	Ratio[a] mono: di	Pentaamine	Yield/%
1	95: 5	**4**[b]	48
2	97: 3	**5**[b]	60
3	90:10	**6**[c]	58

[a]Ratio determinated on the basis of NMR spectra, before purification. [b]Reaction conducted at 50 °C for 18 h. [c] Reaction conducted under reflux for 24 h.



1 : *vic*-(*cis* + *trans)* + *gem*-(*cis* + *trans*) **2** : *gem-trans* **3** : *vic-trans*

Scheme 1

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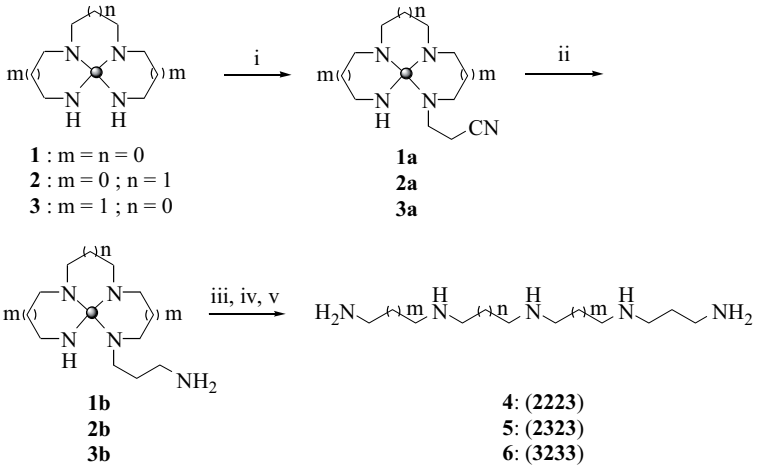

Scheme 2 Reagents and conditions: i, CH_2 =CH–CN (excess), EtOH, Δ; ii, Ni–Al, OH^-, Δ; iii, $N_2H_4.H_2O$, Δ; iv, HCl, EtOH; v, K_2CO_3, CH_3CN, Δ or Amberlyst A-26.

compounds **2a** and **3a,** respectively formed from bisaminals **2** and **3,** and corresponding reduced amino intermediates **2b** and **3b**, were identified by ^{13}C NMR spectroscopy. The three pentaamines **4** (**2223**), **5** (**2323**) and **6** (**3233**) were fully characterised.

The results presented in Table 1 bring to the fore the fact that bisaminals **1** and **2** have a similar behaviour towards acrylonitrile and lead to quasi-univocal monofunctionalisation. On the other hand, bisaminal **3** is less reactive and only 15 % of the starting material has reacted when the synthesis is carried out in the conditions described for bisaminals **1** and **2**. However, a good result is obtained when the mixture is kept under reflux for 24 hours. The higher reaction temperature and the greater distance between the two reactive nitrogen atoms in bisaminal **3** is probably responsible for the little loss of selectivity. Overall, pentaamines **4**, **5** and **6** are obtained in satisfactory overall yields.

In conclusion, the conversion of a linear tetraamine in a rigid bisaminal intermediate constitutes an efficient method for discrimination of the two terminal amino groups. The reaction of one of the secondary nitrogen atoms in the bisaminal by a Michael-type process with acrylonitrile, gives rise to new dissymmetrical pentaamines difficult to obtain by other means. Moreover, the new protected pentaamino intermediates could certainly be useful as building blocks for further reactions. Compounds **4**, **5** and **6** are under investigation as candidates for use as antifouling agents.

Experimental

General information

All reagents were of commercially quality and solvents were dried using standard procedures. ^1H and ^{13}C NMR spectra were recorded with a DX Avance 400 Bruker spectrometer. Bisaminals **1**–**3** were synthesised as previously described.[27,29] Elemental analyses were performed at the Service de Microanalyse of the CNRS (Gif sur Yvette, France).

Typical procedure for the synthesis of pentaamines **4**–**6**

Acrylonitrile (1.65 ml, 25 mmol for bisaminals **1** and **2**, 3.30 ml, 50 mmol for **3**) was added to a solution of bisaminal (5 mmol) in absolute EtOH (15 ml). The resulting mixture was stirred, at 50 °C for 18 h for compounds **1** and **2,** and under reflux for 24 h for bisaminal **3**. After cooling, the solvent and the excess of acrylonitrile were removed under reduced pressure. Intermediates **1a**, **2a** and **3a** are pure enough to be used as it in the next step. The oily residue of the crude aminonitrile was dissolved in EtOH (15 ml). Raney-type alloy (Al–Ni 50/50) (1.3 g) was introduced into the flask and then a solution of sodium hydroxide (4 mol l^{-1}) was slowly added. The solution was stirred at 50 °C for 1 h and after cooling, the solid was filtered through celite and then the solvent was removed under a vacuum. The protected pentaamine was used without further purification in the next step. The crude mixture was dissolved in hydrazine hydrate (10 ml) and the solution was refluxed for 2 h. Excess hydrazine was removed *in vacuo* and the residual oil was taken up with $CHCl_3$ (20 ml); insoluble polyhydrazones were eliminated by filtration. After evaporation, the crude product was stirred in 4 M hydrochloric solution (5 ml) for 3 h at room temperature. The solution was reduced to half under a vacuum and absolute ethanol (20 ml) was added. The precipitate was washed with cold EtOH (3 × 20 ml) and finally dried. The pentaamine hydrochloride was dissolved in the minimum amount of water (2 ml) and liberated on an Amberlyst A-26 anion-exchange resin. The basic aqueous solution was evaporated to dryness. Alternatively, the pentaamine hydrochloride was treated by potassium carbonate (10 equiv) in refluxing dry acetonitrile for 2 h. The solid was filtered and the solvent was removed under a vacuum. The pure pentaamine was obtained as colourless oil.

Spectroscopic data of intermediate compounds **2a, 2b, 3a, 3b** *and pentaamines* **4–6**

(**2a**): ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 15.1, 23.3 (C_β–N),42.4, 46.6, 49.7, 51.8, 53.1, 53.3, 55.2 (C_α–N), 74.4, 86.5 (N–*C*–N) ppm.

(**3a**): ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 17.1, 18.2, 24.6 (C_β–N), 41.5, 43.2, 49.5, 50.5, 52.0, 53.7, 54.2 (C_α–N), 75.0, 81.2 (N–*C*–N) ppm.

(**2b**): ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 23.7, 29.4 (C_β–N), 39.8 (C_α–NH_2), 42.7, 49.1, 49.7, 52.4, 53.6, 53.8, 55.5 (C_α–N), 75.4, 87.1 (N–*C*–N) ppm.

(**3b**): ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 14.8, 18.6, 25.4 (C_β–N), 39.3 (C_α–NH_2), 42.2, 44.1, 49.0, 52.0, 53.0, 53.6, 55.3 (C_α–N), 75.6, 82.2 (N–*C*–N) ppm.

1,4,7,10,14-pentaazatetradecane (**4**): ^1H NMR (400.13 MHz, $CDCl_3$, 25 °C): δ = 1.14 (m, 2H, $C_\beta H$–N), 2.18–2.39 (m, 16H, $C_\alpha H$–N) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 33.8 (C_β–N), 40.3, 41.7 (C_α–NH_2), 47.6, 49.2, 49.3 (3C), 52.4 (C_α–N) ppm. (**4**).5HCl: ^{13}C NMR (100.62 MHz, D_2O, 25 °C): δ = 26.4 (C_β–N), 38.8, 39.4 (C_α–NH_2), 46.3, 46.9 (2C), 47.3 (3C) (C_α–N) ppm. $C_9H_{30}Cl_5N_5$ (385.6): calcd. C 28.0, H 7.8, N 18.2; found C 27.95, H 8.05, N 18.2.

1,4,8,11,15-pentaazapentadecane (**5**): ^1H NMR (400.13 MHz, $CDCl_3$, 25 °C): δ = 1.63 (m, 2H, $C_\beta H$–N), 1.69 (m, 2H, $C_\beta H$–N) 2.63–2.83 (m, 16H, C_αH–N) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 29.9, 33.4 (C_β–N), 39.9, 41.2 (C_α–NH_2), 47.2, 47.7 (2C), 49.0 (2C), 52.1 (C_α–N) ppm. (**5**).5HCl: ^{13}C NMR (100.62 MHz, D_2O, 25 °C): δ = 25.8, 26.4 (C_β–N), 38.4, 39.4 (C_α–NH_2), 46.0 (2C), 47.1, 47.7 (2C), 47.9 (C_α–N) ppm. $C_{10}H_{32}Cl_5N_5$ (399.7): calcd. C 30.05, H 8.1, N 17.5; found C 29.9, H 7.9, N 17.3.

1,5,8,12,16-pentaazahexadecane (**6**): ^1H NMR (400.13 MHz, $CDCl_3$, 25 °C): δ = 1.32–1.40 (m, 6H, $C_\beta H$–N), 2.33–2.48 (m, 16H, $C_\alpha H$–N) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 29.7, 33.1 (2C) (C_β–N), 39.8 (2C) (C_α–NH_2), 47.1, 47.2, 47.7, 47.8, 48.9 (2C) (C_α–N) ppm. (**6**).5HCl: ^{13}C NMR (100.62 MHz, D_2O, 25 °C): δ = 25.2 (2C), 26.2 (C_β–N), 38.3, 38.4 (C_α–NH_2), 47.6, 47.8, 49.1 (2C), 52.1, 52.4 (C_α–N) ppm. $C_{11}H_{34}Cl_5N_5$ (413.7): calcd. C 31.9, H 8.3, N 16.9; found C 31.7, H 8.1, N 17.1.

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