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# Selective mono-N-alkylation of triethylenetetraamine. A new versatile route to polylinear aza-ligands

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ABSTRACT

A new route to triethylenetetraamine selective mono-N-alkylation on secondary nitrogen atom using simultaneously bisaminal and diamide protections is presented and applied to the synthesis of poly-linear aza-ligands.

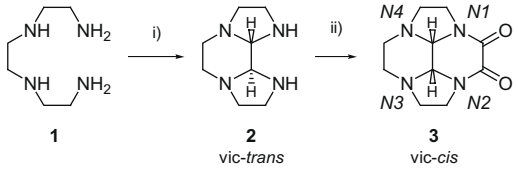


Macrocyclic saturated polyamines constitute versatile ligands whose coordination properties are now well documented.[1] They are the center of interest of numerous research groups in the fields of organic, inorganic, applied chemistry[2] or medical applications.[3] The relatively rigid architecture of azamacrocyclic ligands imposes a coordination geometry on the metal ion and forms metal complexes with high thermodynamic stability and kinetic inertness. In contrast, linear ligands are more flexible and are then able to encapsulate the ion in a way that achieves an optimal match between the requirements of both anionic and cationic species, at the price of somewhat lower thermodynamical stability and higher kinetic lability than those of cyclic homologs.[1] As reported for tetraazacycloalkanes, the selective N-alkylation of linear tetraamines allows a large pannel of applications as biomolecule or solid support coupling. Another idea aims in the formation of polytopic ligands. In general, tetraamines properties are obviously maintained in their dimeric or trimeric analogs, which present moreover several coordination centers.[4,5]

The known routes for the efficient selective N-alkylation of linear polyamines often consist in tedious multistep processes;[6] for instance, very few examples of selective mono-N-alkylation of the primary amine of triethylenetetraamine **1** have been described.[7] The bisaminal tool, initially used as template agent of linear tetraamines for tetraazacycloalkanes synthesis,[8] was afterwards successfully employed as temporary protecting agent for the mono-N-alkylation of cyclic tetraamine[9] and of terminal amine functions of linear tetraamines.[10] Moreover, the bisaminal tool is not suitable to the selective mono-N-alkylation of tetraamines by one of the secondary amine functions, which remains tricky to perform.

It was previously shown that the reaction of triethylenetetraamine **1** with glyoxal affords a mixture of bisaminal derivatives depending on the relative position/configuration of the bisaminal function (gem-cis, gem-trans, vic-cis, and vic-trans, see in Supplementary data).[8] The vic-trans derivative isolated in a 75% yield proved to be the most suitable for condensation of the diester agent (70% yield, Scheme 1). The intermediate **3** obtained as its vic-cis isomer in a very good yield was previously used for cyclen synthesis.[11] Moreover, it presents similarities with the so-called 'autoprotected' macrocycles possessing unreactive amide functions in their ring which proved to be interesting intermediates for the selective alkylation of tetraazacycloalkanes.[12] We found indeed that **3** combines advantageously the two kinds of protections (bisaminal and autoprotection) previously cited and enables to control the selective mono-N-alkylation of the azamacrocycle.

As established from its computer-generated model that fits well to the observed ORTEP structure[11] (Fig. 1), the synthesized bisaminal diamide **3** presents at the same time two non-reactive amide functions (*N1*, *N2*) and a bent cis-configuration, which induce a discrimination between the two remaining nitrogen atoms. As a matter of fact, the *N4* atom possesses its lone pairs directed toward the convex side of the molecular structure while the lone pair of *N3* is located on the concave side of the bisaminal. Consequently *N4* atom exhibits a much more marked nucleophilic character as already mentioned for cyclenglyoxal.[9] AM1 molecular orbital calculations on **3** are in favor of this analysis: *N3* lone pair is involved in the aminal bridge bonds while the *N4* lone pair stays localized on the nitrogen atom. Since *N1,N2* were locked by the amide functions, only *N4* remains ready for further alkylation (Fig. 1, top). Then, the formation of the monoammonium salt is univocal: the




1 2 vic-*trans* 3 vic-*cis*

**Scheme 1.** Synthesis of **3**: (i) glyoxal, (ii) diethyloxalate.

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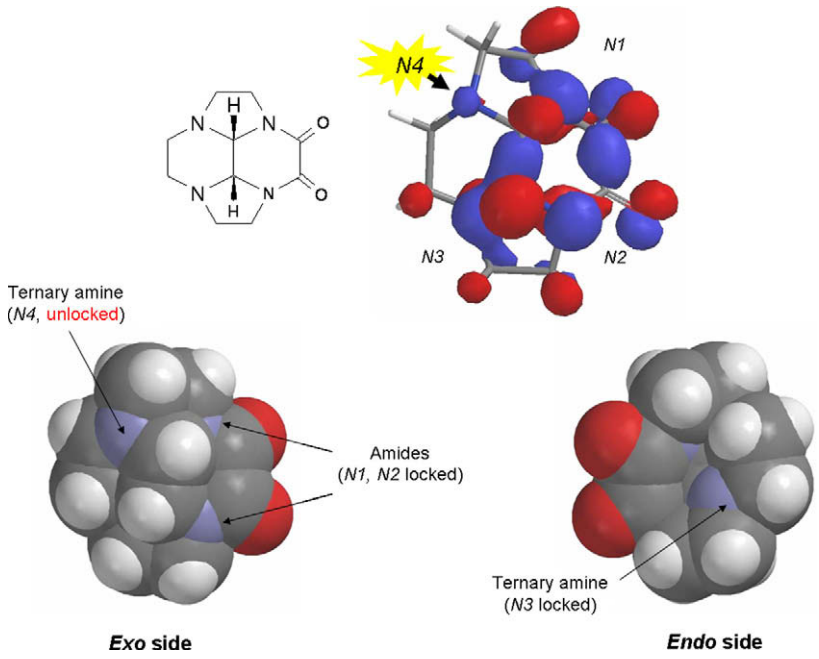
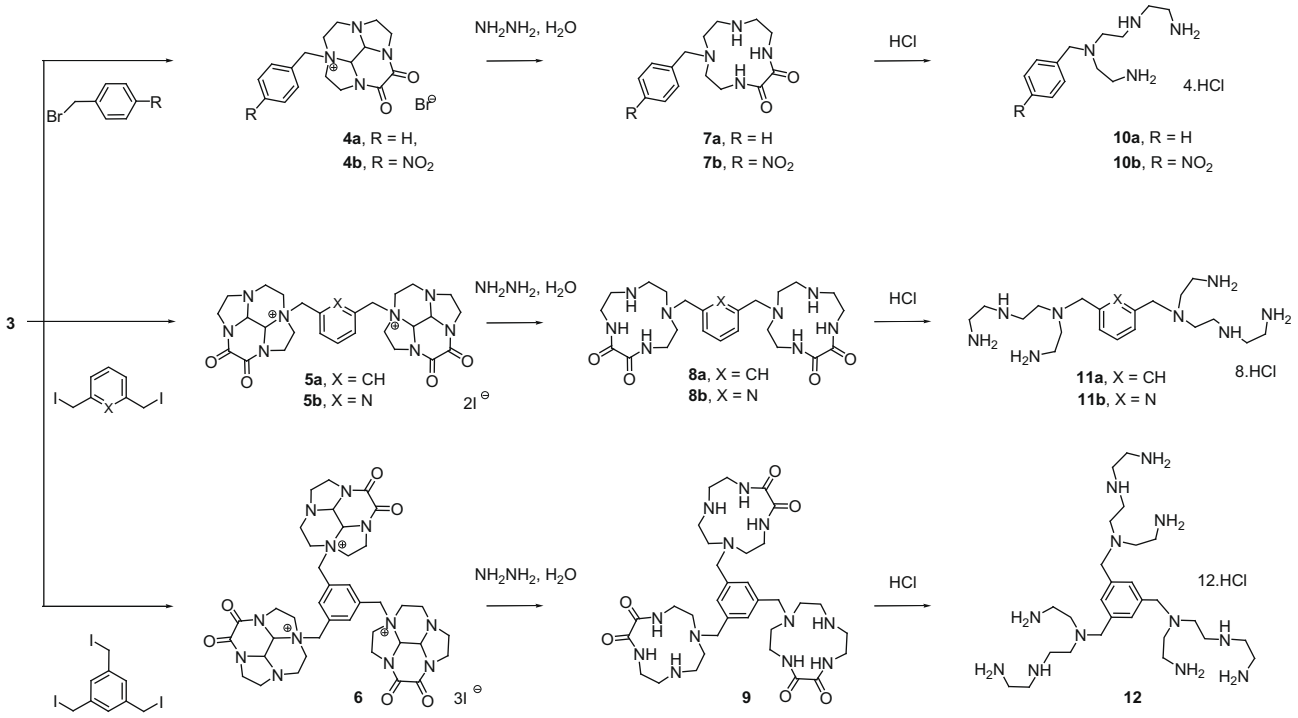



**Figure 1.** AM1 molecular orbital calculations and computer-generated model of **3** vic-cis derivative.

reaction of one equivalent of an electrophile with **3** leads to the corresponding mono-alkylated derivative without any special precautions. The use of an excess of electrophile leads to the same result.

In a typical experiment (Scheme 2), the synthesis starts with the preparation of the ammonium salts **4a–b** using benzyl bromide (or 1-bromomethyl-4-nitrobenzene) as the electrophile. The reaction is performed at room temperature in chloroform and the protected adduct (monoammonium salt) precipitates as soon as it is formed (70% yields). Crystallization of **4a** from water afforded suitable crystals for X-ray diffraction studies. The obtained structure (Fig. 2) unambiguously shows the vic-cis-configuration of the bisaminal derivative and the alkylation on the *exo*-side of the tetraamine skeleton.

It is noteworthy that the alkylation also takes place with one of the minor isomers of **3,** the gem-cis derivative, isolated as presented in the literature.[13] AM1 molecular orbital calculations on the gem-cis isomer of **3** indicate that here again the *N3* lone pair is involved in the aminal bridge bonds while the *N4* lone pair stays localized on the nitrogen atom (Fig. 3). The selective alkylation per-




**Scheme 2.** From cyclic to linear polyamines; overview of the synthetic ways.

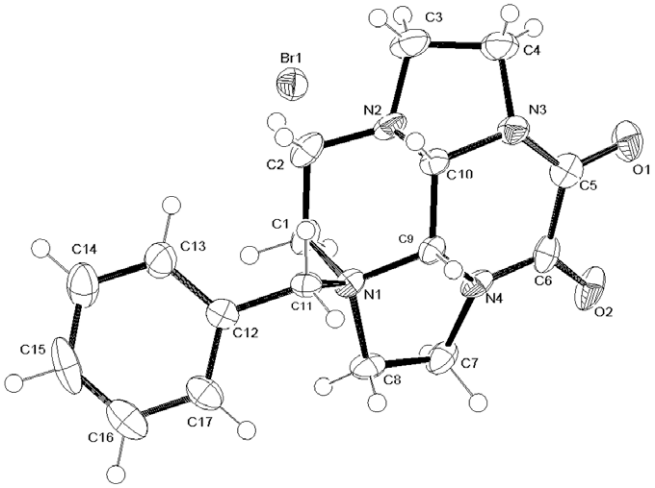



**Figure 2.** X-ray structures of **4a**, ORTEP view, 50% probability ellipsoids.

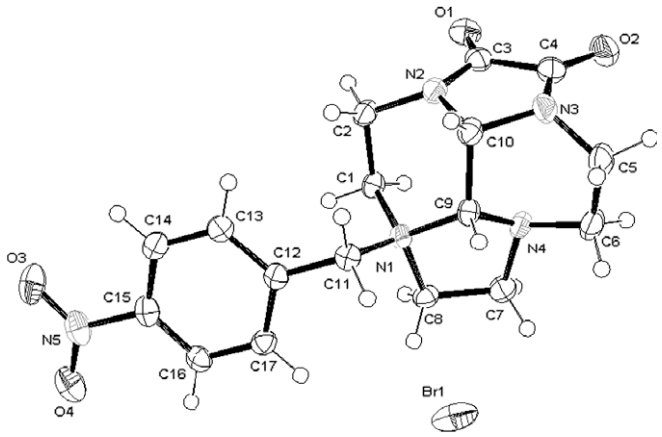



**Figure 4.** X-ray structures of **4b′**, ORTEP view, 50% probability ellipsoids.

formed under the same conditions leads to **4b′** in similar yield. X-ray diffraction studies made on crystals obtained by water evaporation and structure of **4b′** (Fig. 4) clearly highlight the nature of this ammonium salt.

The deprotection of **4a**, **4b–b′** ammonium salts was performed in hydrazine monohydrate as previously described,[9] leading to the free diamide ligands in good yield (**7a–b**: 78%). One can note the particular inertness of the amide functions in respect to the hydrazinolyzis workup.

At this point, the reduction of the amide functions could be considered to obtain mono-alkylated cyclen and derivatives, but we found that the synthetic pathway presented here implies no real advantage compared with the existing route, based on cyclenglyoxal as the intermediate.[9] However, after removing the amide functions the reaction leads selectively to N-functionalized triethylenetetraamine: the hydrolysis of the diamides was achieved in acidic medium (HCl 8 N, 80 °C) to give linear polyamines **10a–b**, in quantitative yields (X-ray structure in Fig. 5).

The reaction conditions were extended in order to obtain dimeric and trimeric derivatives, playing on the type of alkylating agents (bis- or tris-electrophile) and the stoichiometry of the reagents (electrophile/compound **3** 1:2 or 1:3, respectively) to yield dimeric derivatives using 1,3-bis(iodomethyl)benzene or 2,6-bis-bromomethyl-pyridine and a trimeric derivative using the 1,3,5-tris(iodomethyl)benzene.

It is noteworthy that the alkylation of **3,** and consequently the formation of the monoammonium salt, lead to racemic diastereoisomers. Therefore, the formation of the diammonium or triammonium salts **5ab–6**, consists in the formation of several possible configurations. The diammonium salt is constituted by a mixture of racemic and *meso* diastereoisomers, possessing, respectively, a *C*2 axis and a plane of symmetry, while the triammonium salt is composed of a mixture of two racemic diastereoisomers: the first one containing no element of symmetry and the second one possessing a C3 axis as the unique symmetry element. Thus, this situation results in complex NMR $^{13}C/^{1}H$ spectra for **5ab** and **6**, due to the coexistence of multiple configurations. The presence of the differently linked isomers has no impact on the end products obtained in good yields (**8a**: 73%, **8b**: 71%, **9**: 71%).

The preparation of monomeric compounds **10a–b** is very easy-to-run and shows the suitability of our method to functionalize selectively one of the secondary amines of triethylenetetraamine **1** (neither high dilution conditions nor chromatography workup or fastidious deprotection step were needed). Bipodal **11ab** and tripodal **12** polyamines constitute interesting ligands for further coordination investigations with cationic or anionic guests based, respectively, on their high number of functionalizable amines[4] or their protonation[5] potentials. According to the nature of both tetraamine and linker, they also can prefigure the building blocks of new generation of podands.

In conclusion, taking simultaneously advantage of two well-known protecting strategies of tetraazacycloalkanes we report here a very efficient route to the triethylenetetraamine selective mono-N-alkylation in high yields and no restricting reaction conditions (neither high dilution conditions nor chromatography workup or fastidious deprotection step were needed). The scope of this method now remains to be extended to other tetraamines and quaternizing agents. This strategy was applied to the synthesis of two new kinds of podal ligands with very attractive potentialities in coordination or applied chemistry. Investigations are now in

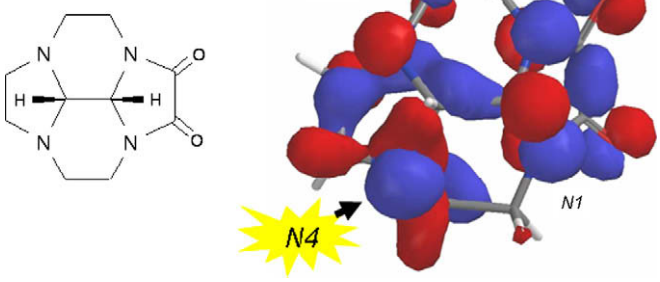



**Figure 3.** AM1 molecular orbital calculations on **3** gem-cis derivative.

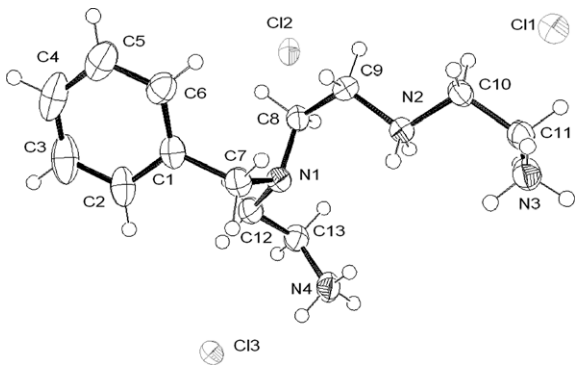



**Figure 5.** X-ray structure of **10a**, ORTEP view, 50% probability ellipsoids.

progress to further develop these compounds as receptors in host-guest processes as we have recently done with their cyclic analogs.[5,14]

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## Supplementary data

Compound **2** isomers, experimental procedure, $^{1}H$, $^{13}C$ NMR data, X-ray analytical data. CCDC references numbers: **4a** CCDC 653285, **4b′** CCDC 653286, **10a** CCDC 653287. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.088.

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