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## A Convenient Synthesis of Bis-Tetraazamacrocycles

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**Abstract:** Bis-tetraazacyclotetradecanes (bis-cyclam) are readily prepared with fairly good yields in a one step procedure from non-protected cyclam. The synthesis involves a selective addition of cyclam on bis-acrylamides in chloroform in the presence of one equivalent of *p*-toluenesulfonic acid.

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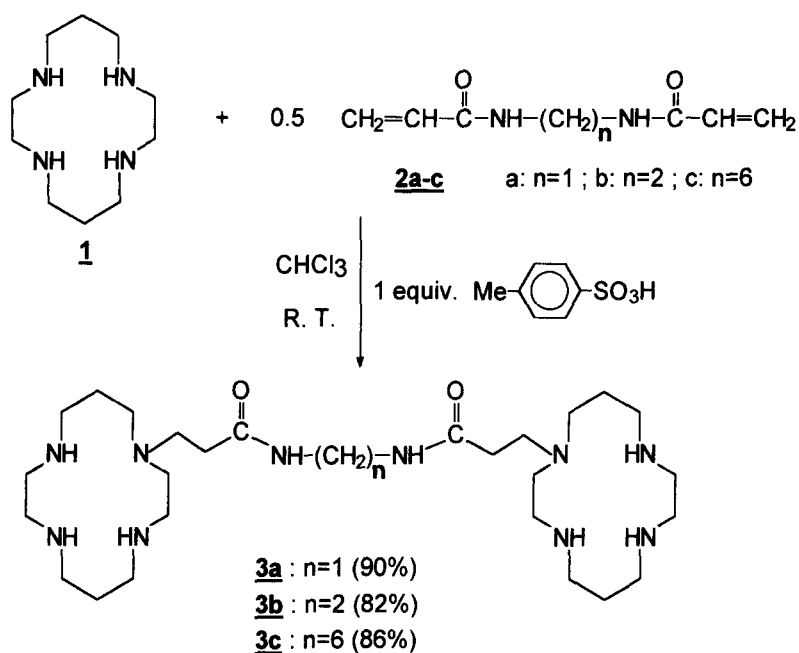
Chelating ligands based on polyazamacrocycles have received a considerable attention over the last two decades since they find numerous applications such as selective complexation and extraction of metallic cations as well as contrast agents and radiochemical agents.<sup>1-3</sup> Dinucleating ligands containing two macrocycles connected by a bridge starting either from a nitrogen or a carbon atom, have been developed for a variety of practical and fundamental purposes. For example, binuclear metal complexes of bismacrocycles have been used to study the cooperative interaction of the two metallic sites<sup>4-6</sup> as well as models in selective protein recognition.<sup>7</sup> More recently, it has been reported that bis-cyclam derivatives exhibit potent and selective inhibition of human immunodeficiency virus (HIV-1 and HIV-2) replication with a unique mechanism of action.<sup>8</sup> Bis-tetraazamacrocycles bridged by a chain between two nitrogen atoms have been synthesized by multi-step protection-functionalization-deprotection schemes using selectively triprotected compounds in which only one nitrogen atom is available for substitution either by alkylation or acylation.<sup>4-10</sup> Tosyl and *t*-butyloxycarbonyl (Boc) protecting groups have been mainly used.<sup>4-9</sup> The overall yields of these multi-step synthesis are most often limited by the preparation and the purification of the triprotected macrocycles and in some cases by the deprotection step.

In this paper we report an expeditious one-step synthesis of bis-tetraazacyclotetradecanes (bis-cyclam), possessing various inter-ring distances, via nucleophilic addition of unprotected cyclam on commercially available or easily prepared bis-acrylamides. Addition of **1** or other azamacrocycles on Michael acceptors have been used to prepare tetra-N-substituted macrocycles<sup>11</sup> or monoalkylated macrocycles using an excess

of free base **1**,<sup>12</sup> but to the best of our knowledge, such reactions have never been used for the synthesis of bis-macrocycles.

Thus, cyclam **1** (1.1 equiv) readily reacts with methylene, ethylene or hexamethylene bis-acrylamide **2a-c** (0.5 equiv.), (Scheme).<sup>13</sup> The reaction, performed at room temperature in chloroform in the presence of one equivalent of p-toluenesulfonic acid (TosOH), specifically affords the bis-macrocycles **3a-c**. The slight excess of cyclam is easily precipitated upon addition of acetonitrile and the bis-macrocycles **3** are purified by flash chromatography and isolated with fairly good yields ranging from 80 to 90%.<sup>14</sup>

#### Scheme



The reaction is highly selective since using these experimental conditions we do not observe the formation of di- or poly-substituted cyclam derivatives or cyclisation products. The presence of one equivalent of non-aqueous acid (TosOH) and the non-polar medium may account for the remarkable specificity of these nucleophilic additions for the production of bis-macrocycles **3a-c**. In these reactions, we take profit of the unusual protonation constants of tetraazamacrocycles like **1** (pK<sub>i</sub> = 11.6, 10.6, 1.6 and 2.4)<sup>15</sup> which exhibit only two basic nitrogen atoms. Consequently, in the presence of one equivalent of acid TosOH, the starting base cyclam is monoprotonated thus leaving only one nucleophilic nitrogen atom available for Michael addition. Furthermore, the monoalkylated cages resulting from the addition on an acrylamide residue are even more readily protonated. A protonated structure where the proton is tightly associated with the tetraaza framework through hydrogen bonding may account for the poor nucleophilicity

of the remaining secondary nitrogens atoms which prevents from a second addition. Accordingly, in our reactions, the choice of a non-polar aprotic solvent like chloroform is highly preferable since it does not promote proton transfer and is expected to favor protonated structures where the proton is sequestered within the macrocycle. Such a diminished nucleophilicity of the remaining secondary nitrogens resulting from protonation in non-polar solvents has already been invoked in the selective alkylation of other azamacrocycles with alkyl halides.<sup>16</sup>

The bis-macrocycles **3a-c** have been characterized by mass spectrometry and NMR spectroscopy.<sup>17</sup> In every cases, the electrospray mass spectra show the monoprotonated  $M+H]^+$  and the diprotonated  $M+2H]^2+$  ions with a relative ratio 40/60. The <sup>13</sup>C and <sup>1</sup>H NMR spectra are in agreement with the symmetric structure and show the expected signals for the monosubstituted cyclam ring as well as the additional signals due to the bridge (amide groups and methylene).

To conclude, the selective Michael addition described here affords an efficient one-step access to bis-tetraazacyclotetradecanes **3a-c** from unprotected cyclam. This procedure is hoped to be quite general and offers the opportunity to produce various bis-macrocyclic structures simply by changing the bis-acrylamide reactant (nature of the spacer between the two acrylamide groups). Moreover, the selectivity for monoaddition arising from protonation with one equivalent TosOH, depicted here in the case of cyclam **1**, is expected to be attainable with other azamacrocycles like cyclen possessing similar protonation constants. Current studies are focussing on the scope of this controled nucleophilic addition of unprotected azamacrocycles.

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13. **2a,b** are commercial products. **2c** has been prepared by acylation of 1,6-hexanediamine with acryloyl chloride in  $\text{CH}_2\text{Cl}_2$  in the presence of an excess of potassium carbonate.
14. **General procedure:** Bisalkylacrylamide **2** (1.0 mmol) and 2,4-di-*t*-Butylphenol (tip of spatula, radical inhibitor) are added to a solution of cyclam **1** (0.440 g, 2.2 mmol) and *p*-toluenesulfonic acid (0.418 g, 2.2 mmol) in 8.00 mL chloroform. The mixture is allowed to stir at room temperature for two to four days (TLC indicates the disappearance of **2**). After removal of the solvent under reduced pressure, acetonitrile (7.00 mL) is added and the mixture cooled overnight in the fridge in order to ensure complete precipitation of unreacted cyclam **1**. After filtration, the filtrate is concentrated and the crude product purified by column chromatography on silica gel using an elution gradient (eluent :  $\text{CHCl}_3 / \text{CH}_3\text{OH} / 32\% \text{NH}_4\text{OH}$  from 4/4/1 to 2/2/1 or 4/3/1).
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17. **Spectroscopic data:** **3a:** 90% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $\delta$  ppm): 8.21 (2H, s, broad, *NH*-CO), 4.63 (2H, m,  $\text{NHCH}_2\text{NH}$ ), 2.85-2.44 (42H, m,  $\text{CH}_2\text{N}$  and *NH*), 2.37 (4H, t,  $J = 7\text{Hz}$ ,  $\text{CH}_2\text{CONH}$ ), 1.75 (8H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz,  $\delta$  ppm) : 173.06 (CO), 54.41, 53.29, 50.91, 49.38, 49.29, 48.70, 48.37 and 47.72 ( $\text{CH}_2\text{N}$ ), 44.36 ( $\text{NHCH}_2\text{NH}$ ), 33.91 ( $\text{CH}_2\text{CONH}$ ), 28.37 and 26.00 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ). M.S. (Electrospray): 555 ( $\text{M}+\text{H}^+$ ; 65%), 278 ( $\text{M}+2\text{H}^{2+}$ ; 100%). **3b:** 82% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $\delta$  ppm): 7.91 (2H, s, broad, *NH*-CO), 3.35 (4H, s, broad,  $\text{CONHCH}_2\text{CH}_2\text{NHCO}$ ), 2.94 (6H, s, broad, *NH*), 2.81-2.43 (36H, m,  $\text{CH}_2\text{N}$ ), 2.39 (4H, t,  $J = 7\text{Hz}$ ,  $\text{CH}_2\text{CONH}$ ), 1.77 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 1.73 (4H, m,  $\text{CH}_2\text{CH}_2\text{CH}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 75.5 MHz,  $\delta$  ppm): 175.07 (CO), 54.59, 54.18, 51.62, 50.50, 49.70, 49.11, 48.32 and 47.82 ( $\text{CH}_2\text{N}$ ), 40.04 ( $\text{CONHCH}_2$ ), 33.42 ( $\text{CH}_2\text{CONH}$ ), 28.71 and 26.34 ( $\text{CH}_2\text{CH}_2\text{CH}_2$ ). M.S. (Electrospray): 569 ( $\text{M}+\text{H}^+$ ; 70%), 285 ( $\text{M}+2\text{H}^{2+}$ ; 100%). **3c:** 86% yield;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $\delta$  ppm): 7.64 (2H, t, *NHCO*), 3.67 (6H, s, broad, *NH*), 3.10 (4H, m,  $\text{CONHCH}_2\text{CH}_2$ ), 2.75-2.35 (36H, m,  $\text{CH}_2\text{N}$ ), 2.29 (4H, t,  $J = 7\text{Hz}$ ,  $\text{CH}_2\text{CONH}$ ), 1.69 (4H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 1.61 (4H, m,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 1.41 (4H, m,  $\text{CONHCH}_2\text{CH}_2\text{CH}_2$ ), 1.25 (4H, m,  $\text{CONHCH}_2\text{CH}_2\text{CH}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz,  $\delta$  ppm): 172.37 (CO), 54.47, 53.88, 50.84, 49.41, 49.20, 49.14, 47.97, 47.55 and 47.00 ( $\text{CH}_2\text{N}$ ), 38.72 ( $\text{CONHCH}_2$ ), 34.33 ( $\text{CH}_2\text{CONH}$ ), 28.18, 28.75, 25.62 and 25.78 ( $\text{CH}_2\text{CH}_2\text{CH}_2$  ring and bridge). M.S. (Electrospray): 625 ( $\text{M}+\text{H}^+$ ; 65%), 313 ( $\text{M}+2\text{H}^{2+}$ ; 100%).