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A Two Step Synthesis of the New "Octacyclam" and Some Other Octaazacycloalkanes via Reduction of Tetraamide Intermediates.

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Abstract : A convenient two step synthesis of new octaazamacrocycles via a 2+2 condensation of tetraamines and diethyloxalate followed by the reduction of the tetraamide intermediates is reported. This methodology can be applied to the preparation of other large polyazamacrocycles which might exhibit interesting complexing properties as anion receptors.

Large macrocyclic polyamines are of major interest in the field of coordination chemistry. As the size of the macrocyclic cavity increases, the ligand becomes more flexible and as a consequence polynuclear complexes of transition metal or heavy metal cations can be obtained. These polynuclear complexes are also useful tools in the study of metal-metal interactions and represent potential models for biological systems[1]. Moreover the large polyazacycloalkanes can be highly or even fully protonated in the neutral pH range to form the corresponding cyclic polyammonium cations which represent the most studied anion receptors. Indeed, these highly positively charged species exhibit a high affinity for biologically important inorganic or organic anions like phosphates or carboxylates. The stability of the supramolecular species thus formed is mainly due to Coulombian interactions and to the presence of a hydrogen bond network[2].

Although such ligands are attractive, their synthesis is not obvious and often involves a stepwise scheme. In most cases, the macrocycles have been synthesized according to the Richman and Atkins procedure or alternative routes[3,4]. This method allows the synthesis of the smaller tetraazacycloalkanes in good yields but is less convenient for the preparation of larger macrocycles since the yield of the final 1+1 cyclization step decreases as the length of the two reactants increases. These reactants can only be obtained after a fastidious sequence of reactions to increase the length of the chains. More recently, Paoletti et al. have developped a method to obtain some "giant-size" azamacrocycles[5]. The key step of their procedure lies in a final 2+2 cyclization which of course represents a real advantage in the synthesis of large macrocycles. In this case, the 2+2 condensation is favored by the presence of two piperazine rings which increase the rigidity of one of the reactants. Similar to previous methods, this one involves the use of a high molecular weight tosyl moiety as N-protective group but the regeneration of the secondary amines requires drastic conditions[6]. Another interesting 2+2 cyclization is the reaction of diethyloxalate with ethereal oxygen-containing diamines reported by Fukada et

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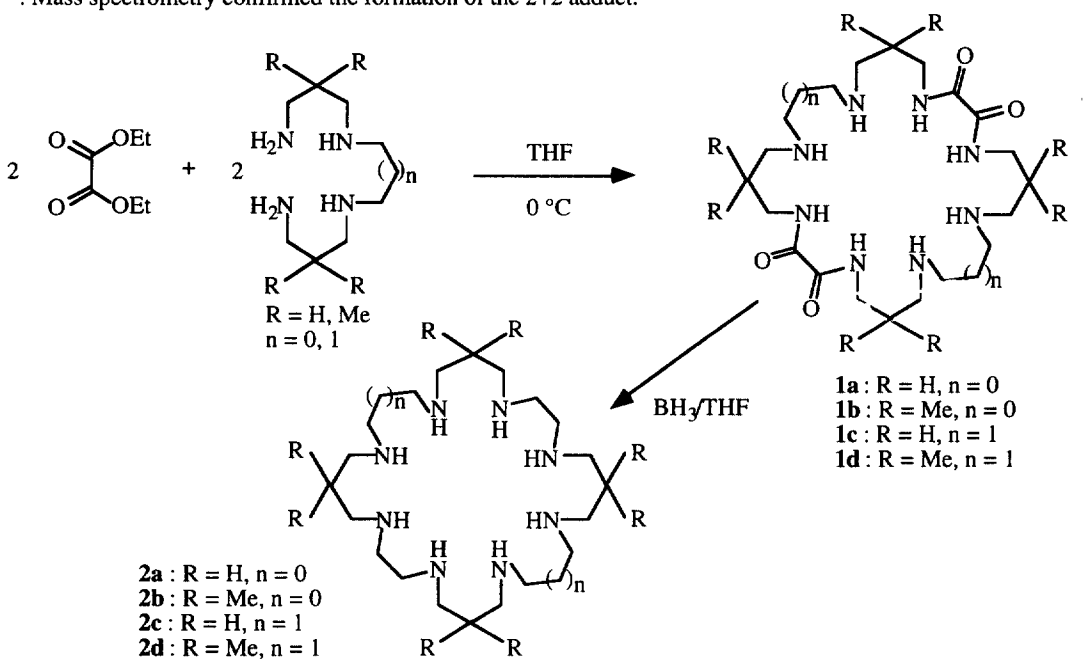
al[7]. Since the formation of cyclic diamides from the diester-diamine 1+1 condensation has been well studied, most of these reactions have been carried out starting from diethylmalonate or substituted diethylmalonate[6]. It is surprising to note that diethyloxalate has not been used as a building block in these diester cyclization reactions until Fukada's work. This derivative reacts by 2+2 cyclization rather than 1+1 cyclization. This result is not surprising considering that the reaction of diethyloxalate with two equivalents of 1,3-diaminopropane yields mostly the open chain N,N'-bis-(3-aminopropyl)-oxamide rather than the expected cyclic compound[8]. This selectivity is probably due to the rigidity of the diethyloxalate. The diethyl-2,6-pyridinedicarboxylate gives also preferentially the 2+2 cyclization and allows the formation of pyridine containing large azamacrocycles, but the reaction occurs in poor yield[9]. In previous work, we described the convenient synthesis of a C-tetramethylated cyclam from reduction of the 1+1 condensation product of diethyloxalate and a C-substituted tetraamine, even though the expected larger 2+2 cyclization product is the major compound[10].

In this paper, we report the two-step synthesis of the new 1,4,8,11,15,18,22,25-octaazacyclooctacosane ([28]aneN8) and 1,4,8,12,16,19,23,27-octaazacyclotriacontane ([30]aneN8) starting respectively from commercially available N,N'-bis(3-aminopropyl)ethylenediamine or N,N'-bis(3-aminopropyl)-1,3-propanediamine and diethyloxalate according to Scheme 1. By analogy with the hexacyclen, the macrocycle [28]aneN8 can be called "octacyclam". The corresponding octamethyl derivatives have been obtained according the same method. The four compounds have been fully characterized, as well as the tetraamide intermediates[11-18]. Mass spectrometry confirmed the formation of the 2+2 adduct.



Scheme 1

In a typical experiment, diethyloxalate in THF [(0.75 mol.l^{-1}) at 0 °C] is added dropwise to a solution of N,N'-bis(3-aminopropyl)ethylenediamine in THF [(0.75 mol.l^{-1}) at 0 °C]. Higher dilution increases reaction time and the proportion of 1+1 cyclization product. Increasing concentration favors the formation of polymers. Filtration of the white precipitate affords 1,4,8,11,15,18,22,25-octaazacyclooctacosane-2,3,16,17-tetraone (tetraoxooctacyclam) **1a** in 70 % yield. The reduction is performed by addition of a large excess of a 1M solution of borane in THF to a suspension of the tetraamide in THF at 0 °C. The mixture is allowed to reach room temperature and then refluxed for 1h. The reaction is quenched by addition of water and the solvents are evaporated. The residue is then refluxed in a 6M hydrochloric acid solution for 3h. After evaporation to dryness and addition of water, the solution is made strongly basic by addition of NaOH pellets and finally extracted with dichloromethane to yield the octacyclam **2a** as an oil in 50 % yield. The main difficulty of this reduction step is the extremely poor solubility of the cyclic tetraamides in organic solvents, especially the non methylated tetraoxooctacyclam **1a**. However, this reduction reaction can be carried out in reasonable yields. Increasing reaction times may lead to some degradation of the compound.

In conclusion, we wish to report a facile and versatile synthesis of two new octaazacycloalkanes and the corresponding C-octamethylated derivatives. The octacyclam exhibits a succession of ethylenic and trimethylenic moieties. This structural pattern might confer to this molecule an original acid-base behavior, inducing some particular coordination properties. The presence of eight methyl groups may also influence the basicity of the C-substituted derivatives. The determination of the pKa values of these large azamacrocycles and their complexation abilities are now under investigation. The main advantage of the reported method is the exceptional yield of the 2+2 cyclization step which is the crucial step in the synthesis of large macrocycles. Moreover, the procedure can be applied to the synthesis of a wide variety of large azamacrocyclic ligands. Finally, the poorly soluble tetraamide intermediates can also present a strong affinity towards specific guests.

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11. tetraoxomacrocycle **1a** : I.R. (KBr) $\nu_{C=O}$ = 1670 cm^{-1}. δ^1H (D_2O) : 1.53 (q, 8H), 2.71 (t, 8H), 2.94 (t, 8H), 3.01 (s, 8H). $\delta^{13}C$ (D_2O) : 27.5, 38.5, 45.5, 48.0, 163.3. Found : C. 52.58 ; H. 9,04 ; N. 24.64. $C_{20}H_{40}N_8O_4$ requires : C. 52.61 ; H. 8.83 ; N. 24.54. EIMS *m/z* = 457 $(M+H)^+$.
12. tetraoxomacrocycle **1b** : I.R. (KBr) $\nu_{C=O}$ = 1670 cm^{-1}. δ^1H ($CDCl_3$) : 0.88 (s, 24H), 1.48 (s, 4H), 2.48 (s, 8H), 2.73 (s, 8H), 3.15 (s, 8H), 9.11 (s, 4H). $\delta^{13}C$ ($CDCl_3$) : 24.6 ; 35.0 ; 50,0 ; 50,1 ; 60,6 ; 160.7. Found : C. 59.48 ; H. 10.19 ; N. 19.62. $C_{22}H_{44}N_8O_4$ requires : C. 59.13 ; H. 9.92 ; N. 19.70. FABMS *m/z* = 570 $(M+H)^+$.
13. tetraoxomacrocycle **1c** : I.R. (KBr) $\nu_{C=O}$ = 1670 cm^{-1}. δ^1H (D_2O) : 1.69 (q, 12H), 2.55 (t, 16H), 3.27 (t, 8H). $\delta^{13}C$ (D_2O) : 30.5 ; 40.1 ; 48.4 ; 49.1 ; 163.4. Found : C. 54.74 ; H. 9.03 ; N. 22.94. $C_{22}H_{44}N_8O_4$ requires : C. 54.51 ; H. 9.16 ; N. 23.13. EIMS *m/z* = 484 $(M)^+$.
14. tetraoxomacrocycle **1d** : I.R. (KBr) $\nu_{C=O}$ = 1670 cm^{-1}. δ^1H ($CDCl_3$) : 0.79 (s, 24H), 1.72 (s, 4H), 2.36 (s, 8H), 2.57 (q, 4H), 3.08 (s, 8H), 3,61 (t, 8H), 8.94 (s, 4H). $\delta^{13}C$ ($CDCl_3$) : 24.2 ; 34.6 ; 37,0 ; 49,5 ; 49,8 ; 60,3 ; 162.4. Found : C. 60.40 ; H. 9.78 ; N. 18.63. $C_{30}H_{60}N_8O_4$ requires : C. 60.37 ; H. 10.13 ; N. 18.77. EIMS *m/z* = 597 $(M+H)^+$.
15. macrocycle **2a** : δ^1H ($CDCl_3$) : 1.56 (q, 8H), 2.27 (s, 8H), 2.60 (s, 16H), 3.20 (t, 16H). $\delta^{13}C$ ($CDCl_3$) : 30.2 ; 48.3 ; 49,6. Found : C. 60.07 ; H. 11.80 ; N. 28.03. $C_{20}H_{48}N_8$ requires : C. 59.96 ; H. 12.08 ; N. 27.97. EIMS *m/z* = 401 $(M+H)^+$.
16. macrocycle **2b** : δ^1H ($CDCl_3$) : 0.98 (s, 24H), 1.95 (s, 8H), 2.52 (s, 16H), 2.69 (s, 16H). $\delta^{13}C$ ($CDCl_3$) : 24.4 ; 34.7 ; 49.5 ; 59.2. Found : C. 65.42 ; H. 12.30 ; N. 21.92. $C_{28}H_{64}N_8$ requires : C. 65.57 ; H. 12.58 ; N. 21.85. EIMS *m/z* = 513 $(M)^+$.
17. macrocycle **2c** : δ^1H ($CDCl_3$) : 1.54 (q, 12H), 2.58 (t, 8H), 2.64 (t, 8H), 2.67 (t, 8H), 3.24 (s, 8H). $\delta^{13}C$ ($CDCl_3$) : 28.9 ; 48.0 ; 48.4 ; 48.5, 48.6. Found : C. 61.32 ; H. 12.11 ; N. 26.01. $C_{22}H_{52}N_8$ requires : C. 61.62 ; H. 12.23 ; N. 26.15. EIMS *m/z* = 429 $(M+H)^+$.
18. macrocycle **2d** : δ^1H ($CDCl_3$) : 0.81 (s, 24H), 1.55 (q, 4H), 2.30 (s, 8H), 2.40 (s, 8H), 2.51 (s, 8H), 2.56 (s, 8H), 3,09 (t, 8H). $\delta^{13}C$ ($CDCl_3$) : 24.7 ; 30.2 ; 34.8 ; 49.4 ; 49.9 ; 59.4 ; 59.7. Found : C. 66.89 ; H. 12.40 ; N. 20.67. $C_{30}H_{68}N_8$ requires : C. 66.60 ; H. 12.68 ; N. 20.72. EIMS *m/z* = 541 $(M+H)^+$.