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Synthesis and characterization of ligands (1,4,8,11-tetraacryloyl) cyclam (L_1), (1,4,8,11-tétrabenzoyl) cyclam (L_2) and their Complexes of Pb(II)

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Abstract: *We describe the synthesis scheme of two tetraazamacrocycles N-tetrasubstituted. thus, (1,4,8,11-tétraacryloyl)cyclam (L_1) and (1,4,8,11-tétrabenzoyl)cyclam (L_2) and their lead (II) complex were synthesised. The carbonyls functions presents in these molecules are capable of reacting at the coordination of the metal. These compounds were characterized by IR spectroscopy, ^{1}H NMR, ^{13}C-NMR and mass spectrometry.*

Keywords: *Cyclam, Lead (II) complex, tetraazamacrocycle, N-functionnalization, complex of cyclam.*

I. Introduction

In these last years,The chemistry of cyclic polyamines and especially tetraazacycloalcanes whose two main representatives are 1,4,8,11-tetraazacyclotetradecane (cyclam) and the 1,4,7,10 tetraazacyclotetradecane (cyclene), has known considerable development [1]. These macrocycles form stable complexes with the transition elements and heavy metals. However, the methods of synthesis of these polyazacycloalkanes require generally many steps and the yields are often weak [2].The New methodologies for obtaining these polyazacycloalkanes partially or fully substituted are the subject of much research.In By varying the nature and position of substituent on a single macrocycle, we can to control her selectivity for an ion metal given, and modulate properties physicochemical of the complex resulting. Among these macrocycles, cyclam is very used Because of these complexing properties [3].Investigations into cyclam-derived ligands and their complexes have often been initiated by their use in medicine. For instance, it was suggested that cyclambased anti-HIV agents are more active *in vivo* in the form of metal ion complexes [1,2]Macrocyclic ligands are also commonly used as carriers of metal radioisotopes in targeted radiopharmaceuticals[3]For utilization in nuclear medicine, macrocyclic ligands are generally preferred to open-chain ligands due to the higher thermodynamic and mainly kinetic stabilities of their complexes.

II. Experimental

Benzoyl chloride is from Aldrich,acryloyl chloride and cyclam were prepared in the laboratory. The metal salts $Pb(NO_3)_2$ are generated by Janssen. The solvents are generated by Aldrich. The infrared spectra were recorded by using a spectrometer FTIR (4000 - 400 cm^{-1}). The RMN spectra were recorded in $CDCl_3$ solution, using a Bruker spectrometer ARX 400 MHz. Electrospray mass spectra were recorded in positive mode by using an API mass 1 spectrometer (Perkin-Elmer).

II.1. Synthesis of the ligand (1, 4, 8,11-tetraacryloyl)cyclam(L_1).

1.22 g (13.4mmol) of acryloyl chloride dissolved in 20 ml of dichloromethane was added dropwise to the mixture 0,6 g (3 mmol) of cyclam and 1.35 g (13.4 mmol) of triethylamine. The reaction mixture is stirred at a temperature of 80 ° C for 16 hours and then it is left at room temperature overnight. The excess acryloyl chloride was removed by filtration and the filtrate is evaporated under reduced pressure. Then the residue was washed with water and the organic phase is dried over sodium sulfate. The product thus recovered is evaporated and the addition of heptane causes cold precipitation of the expected product. The white solid was purified by chromatography on silica column, eluting with THF. The yield was 81%.

IR (KBr ; ν/cm^{-1}) :2916-2871(ν_{CH2}); 1700 ($\nu_{C=O}$) ; 1520 $(\nu_{C=C})_{ethylene}$; 1260 (ν_{C-N}). ^{1}HNMR ($CDCl_3$) δ_H(ppm) : 1,34 (H,CH_2) ; 2,63 (H, CH_2-N,α); 3,28 (H, CH_2-N,adjacent), 4,96 (H, $C=CH_2$, trans); 5,82 (H, $C=CH_2$, cis); 6,90 (H, CH=C). ^{13}CNMR($CDCl_3$) δ(ppm) : 21,5(C,CH_2) ; 47,62 (C, CH_2-N, α) ; 49,50(C,CH_2-N, adjacent); 126,57(C,$C=CH_2$,acryloyl); 131,80(C,CH=C,acryloyl); 162,70(C,C=O). ESI-MS: m/z = 417 $[M+H]^+$; m/z = 395$[M-O]^+$; m/z = 346$[M-(CH_2CHCO+C)]^+$; m/z = 321 $[M-(acryloyl+2CH_2)]^+$.

II.2. Synthesis of the ligand (1,4,8,11-tetrabenzoyl)cyclam (L_2).

The preparation was analogous to that of ligand (1,4,8,11-tetraacryloyl)cyclam (**L_1**) ,but benzoyl chloride (1.9g ; 13.4mmol) was used instead of acryloyl chloride. Brown solid, yield: 76%.
IR (KBr ; ν/cm^{-1}) : 3060 ($\nu_{=CHar}$) ; 2945-2860 (ν_{CH2}) ; 1720($\nu_{C=O}$) ; 1536 ($\nu_{C=C}$)$_{ar}$; 1205 (ν_{C-N}). ^{1}HNMR (CDCl$_3$) δ_H(ppm) : 1,89 (H, CH$_2$) ; 3,20(H, CH$_2$-N,α); 3,50(H,CH$_2$-N,adjacent), 7,63-8,03 (H,phenyl). ^{13}CNMR(CDCl$_3$) δ(ppm) : 20,95(C,CH$_2$) ; 45,71(C,CH$_2$-N,α); 48,96(C,CH$_2$-N,adjacent); 127,20-131,98(C,phenyl), 168,92 (C,C=O).

II.3. Synthesis of the complex [((1, 4, 8,11-tetraacryloyl)cyclam)Pb(NO_3)$_2$] (C_1)

To a solution of 0.28 g (0.86 mmol) of Pb(NO$_3$)$_2$ dissolved in 20 ml of mixture water/methanol (20/80) was added dropwise under stirring at a temperature of 60 °C, a solution of 0.3 g (0.72 mmol) of (1,4,8,11-tétraacryloyl) cyclam (**L_1**) dissolved in 15 ml of the same solvent. After12 hours at reflux, the lead Pb(NO$_3$)$_2$ in excess was removed by filtration. The resulting beige solid was washed with hexane and recrystallized in toluene. Yield:89%. IR (KBr ;ν/cm^{-1}) :2900-2858 (ν_{CH2}) ; 1695 ($\nu_{C=O}$)$_{free}$; 1685($\nu_{C=O}$)$_{connected}$; 1505 ($\nu_{C=C}$)$_{acryloyl}$; 1255(ν_{N-O}) ; 1245 (ν_{C-N}); 765($\nu_{N=O}$); 460(ν_{Pb-N}). ^{1}HNMR (CDCl$_3$) δ_H(ppm) : 1,47 (H, CH$_2$) ; 2,75(H, CH$_2$-N, α); 3,40(H, CH$_2$-N, adjacent); 5,08(H, CH$_2$=C, trans); 6,00(H, CH$_2$-N, cis); 6,95(H, CH=C, acryloyl). ^{13}CNMR (CDCl$_3$) δ(ppm) : 21,70 (C, CH$_2$) ;47,88(C, CH$_2$-N, α); 49,71(C, CH$_2$-N, adjacent); 126,64(C, C=CH$_2$, acryloyl); 131,90(C, CH=C, acryloyl); 162,73(C, C=O). ESI-MS: m/z = 746,5[M-H]$^+$; m/z = 623,5[M-2NO$_3$]$^+$; m/z = 591,1[M-(2NO$_3$+2CH$_2$)]$^+$; m/z = 521,1[M-(2NO$_3$+CH$_2$CH$_2$N+CH$_2$CHCO)]$^+$.

II.4. Synthesis of the complex [((1, 4, 8,11-tetrabenzoyl)cyclam)Pb(NO_3)$_2$] (C_2)

The lead Pb(NO$_3$)$_2$ (0.26 g ; 0.78 mmol) was suspended in the mixture water (20%)/methanol(80%) (20 ml) and (1,4,8,11-tetrabenzoyl)cyclam (**L_2**) (0.4g; 0.64mmol) dissolved in 15 ml of the same solvent was added dropwise under stirring at a temperature of 60 °C. After 12 hours at reflux, the lead Pb(NO$_3$)$_2$ in excess was removed by filtration. The resulting light brown solid was washed with hexane and recrystallized in toluene. Yield: 87%.IR (KBr;ν/cm^{-1}) : 3060 ($\nu_{=CHar}$) ; 2900-2820 (ν_{CH2}) ; 1700 ($\nu_{C=O}$) ; 1520 ($\nu_{C=C}$)$_{ar}$; 1300 (ν_{N-O}) ; 1175(ν_{C-N}); 760($\nu_{N=O}$); 470(ν_{Pb-N}). ^{1}HNMR (CDCl$_3$) δ_H(ppm) : 1,98 (H, CH$_2$) ; 3,46 (H, CH$_2$-N,α); 3,70 (H, CH$_2$-N, adjacent); 7,67-8,11 (H, phenyl). ^{13}CNMR (CDCl$_3$) δ(ppm) : 21,30(C, CH$_2$) ; 46,10(C, CH$_2$-N,α); 50,00(C,CH$_2$-N,adjacent); 128,20-132,95(C,phenyl); 169,97(C, C=O). ESI-MS: m/z = 880,5[M-NO$_3$]$^+$; m/z = 758,3 [M-(NO$_3$+C$_6$H$_5$)]$^+$; m/z = 729,3[M-(NO$_3$+C$_6$H$_5$CO+2H)]$^+$; m/z = 265,3[M-(NO$_3$+4benzoyl+cyclam)]$^+$.

III. Results and Discussion

The ligands (1,4,8,11-tetraacryloyl)cyclam (**L_1**) and (1,4,8,11-tetrabenzoyl)cyclam (**L_2**) were prepared according to the original method of synthesis of N-tetraalkylation described in the literature [4]. We condensed an equivalent of cyclam on four equivalents in excess of acryloyl chloride (**L_1**) and on four equivalents in excess of benzoyl chloride (**L_2**) differently. The reactions were carried out in mid dichloromethane (CH$_2$Cl$_2$) to a temperature of 80 ° C in the presence of triethylamine (Et$_3$N) according to the figure below (Fig.1)

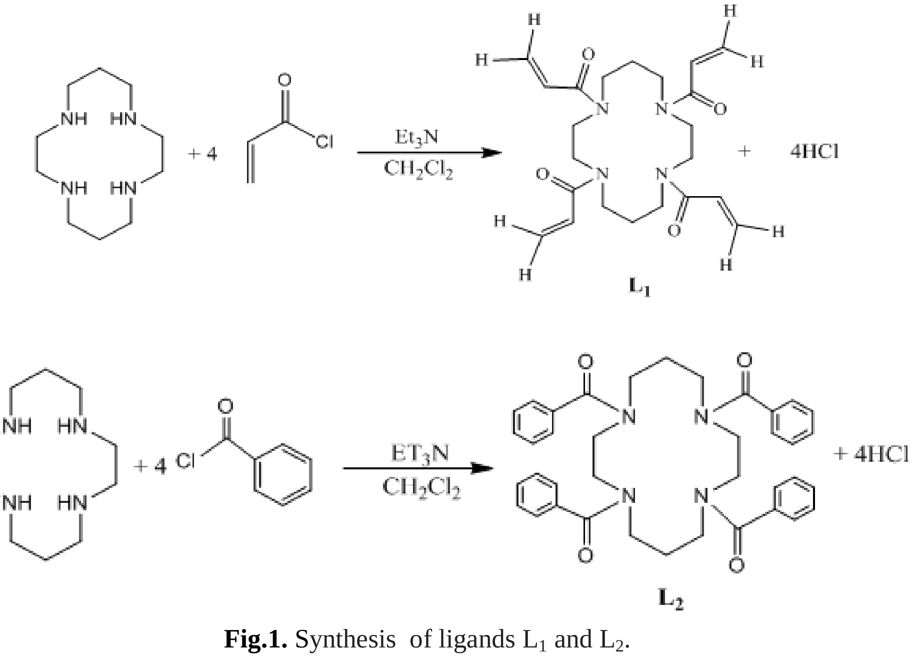

Fig.1. Synthesis of ligands L_1 and L_2.

To access the complexes [((1,4,8,11-tetraacryloyl)cyclam)Pb^{2+}] (**C_1**) and [((1,4,8,11-tetrabenzoyl) cyclam)Pb^{2+}] (**C_2**), we used the method of the condensation reaction described in the literature [4]. The ligand **L_1** or **L_2** dissolved in the water (20%)/methanol(80%) mixture, is simply added dropwise to the suspension of lead nitrate (II) in the same solvent. After twelve hours at reflux, successives complexes are isolated in good yield (Fig 2). Both complexes are stable in the open air. The ligands **L_1**, **L_2** and their complexes thus synthesized were characterized by IR spectroscopy, ^1H NMR, ^{13}C NMR and ESI MS spectrometry.

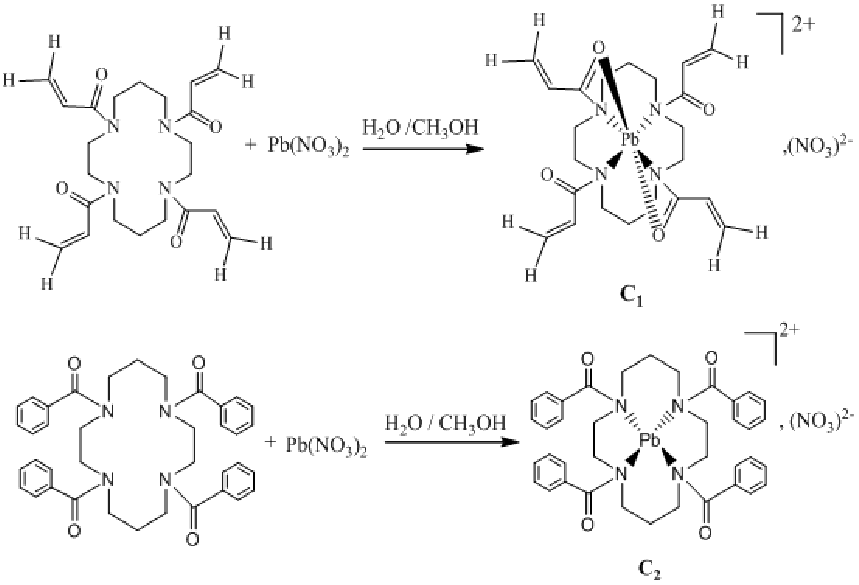

Fig.2. Complexing of ligands L_1 and L_2 by the $Pb(NO_3)_2$.

IR spectroscopy allows us to make a comparative study, following the disappearance and appearance of certain bands characteristic of functions present on the carbon chain of our molecules.On the two IR spectra of ligands **L_1** and **L_2** dispersed in KBr, the absence of the vibration band characteristic of secondary amine group ν(N-H) and its deformation in the plane expected at 3295 cm^{-1} and 1505 cm^{-1} respectively , show that the condensation has occurred [5]. On the one hand for the ligand **L_1**, the appearance of two new bands of a strong intensity at 1700 cm^{-1} and of medium intensity at 1520 cm^{-1} attributable respectively to carbonyl group stretching modes ν(C=O) and to ethylene group stretching modes ν(C=C) of the acryloyl chain and on the other hand for the ligand **L_2**, the appearance of a weak intensity band at 3060 cm^{-1}, of a strong intensity band at 1720 cm^{-1} and of a medium intensity band at 1536 cm^{-1} attributable respectively to the stretching modes ν(=CH)aromatic, ν(C=O) and ν(C=C)aromatic of the benzoyl confirm the incorporation of substituents acryloyl (**L_1**) and benzoyl (**L_2**) on the macrocyclecyclam. by comparison to the spectra of the corresponding free ligands, the infrared spectrum of complex [(1,4,8,11-tétraacryloylcyclam)Pb^{2+}] (**C_1**) in KBr is characterized by the presence of duplication of vibration band of carbonyl groups ν(C=O) free and ν(C=O) connected respectively at 1695 cm^{-1} and 1685 cm^{-1}.

This spectral signature shows that two of the four carbonyl functions are coordinated to the metal center[7] .The displacement of stretching modes bands ν(CH_2), ν(C=C) ethylene, ν(C-N) and ν(C-C) towards lower energies at (2900-2858) cm^{-1}, 1505 cm^{-1}, 1245 cm^{-1} and 1115 cm^{-1} suggests the involvement of nitrogen atoms in the coordination of the metal [6]. The complexation is confirmed by the presence of three new medium intensity bands at 1255 cm^{-1},765 cm^{-1} and 460 cm^{-1} corresponding to the stretching modes of links ν(N-O), ν(N=O) and ν(Pb-N) respectively [6,7].While on the IR spectrum of complex [(1,4,8,11-tétrabenzoylcyclam) Pb^{2+}] (**C_2**), the duplication of the band assigned to stretching modes of the carbonyl was not observed. These suggesting that the four carbonyl of complex **C_2** did not participate in the coordination of the metal. The bands allocated to stretching vibration ν(CH_2), ν(C=O), ν(C=C)aro, ν(C-N) and ν(C-C) are shifted towards lower energies. They have been observed at (2900-2820) cm^{-1}, 1700 cm^{-1}, 1520 cm^{-1}, 1175cm^{-1} and 1050 cm^{-1} respectively. The coordination is confirmed by the appearance of new bands at 1300 cm^{-1}; 760 cm^{-1} and 470 cm^{-1} assigned to the stretching modes of the link ν(N-O), ν(N=O) and ν(Pb-N) respectively. These observations indicate that the metal is bonded to the macrocycle by the four nitrogen atoms of the tertiary amines. The four carbonyl groups have been remained free. The ^1H NMR spectrum of the $CDCl_3$ solution of ligand **L_1** shows the presence of a quintet at 1.34 ppm, a triplet at 2.63 ppm and a singlet at 3.28 ppm corresponding to methylene protons (CH_2), to protons in α position of nitrogen (CH_2-N) and to adjacent protons of nitrogen (N-CH_2), respectively. The protons terminalsethylenicof the acryloyl chain in position trans and cis appear under form two doublets at 4.96 ppm and 5.82 ppm respectively. The ethylene protons appear under form a quadruplet at 6.90 ppm.While^{1}H NMR spectrum of the ligand **L$_2$**, puts in evidence the presence of a quintet at 1.89 ppm, a triplet at 3.20 ppm and a singlet at 3.50 ppm which attributed to methylene protons (CH_2), to protons in α position of nitrogen (CH_2-N) and to adjacent protons to nitrogen (N-CH_2) respectively. The phenyl protons of the chain benzamido appear as a triplet and a doublet between 7.63 to 8.03 ppm.

The ^{13}C-NMR spectrum of ligand **L$_1$** shows three characteristic peaks of the chain acryloyl at 126.57 ppm, 131.80 ppm and 162.70 ppm which were corresponding respectively to the two ethylenic carbons and to carbonyl group carbon (C=O) [6] . The peaks located at 21.5 ppm, 47.62 ppm and 49.50 ppm were assigned respectively to methylene carbons, to carbons in the alpha position of nitrogen (C-N) and to carbons adjacent to nitrogen (N-C) of cyclam.The ^{13}C-NMR spectrum of ligand **L$_2$** in $CDCl_3$solution is composed of nine signals in accordance with C2 symmetry of the molecule. The methylene carbons atoms; the carbons in α position of nitrogen (C-N) and the adjacent carbons to nitrogen (C-N) resonate at 20.95 ppm; 45.71 ppm and 48.96 ppm, respectively. The aromatic carbons of benzoyl resonate as a to five signals between 127.20 ppm and 131.98 ppm. Thecarbons of carbonyl groups (C=O) appear at 168.92 ppm [6,7].

All complexes (**C$_1$** and **C$_2$**) give very similar ^{1}H NMR and^{13}C NMR spectra to those of their corresponding ligands.Except that the signals of the protons and the carbons, characteristic of complexes **C$_1$** and **C$_2$**were shifted slightly toward higher energies. These displacements indicate that the complexing occurred.The values of chemical shifts of protons and carbons, of complex **C$_1$** and **C$_2$** and their allocations may be found in the experimental part.NMR results are consistent with those of infrared The compounds**L$_1$** ,**C$_1$**and **C$_2$** were characterized by ESI MS spectrometry. The mass spectrum of ligand **L$_1$** shows a peak at m /z = 417 corresponding at molecular ion $[M+H]^+$ with a relative abundance of 19%, and the ions m/z = 395 $[M-O]^+$, m/z = 346 $[M-(CH_2CHCO+C)]^+$ and m/z = 321 [M-(acryloyl+2CH_2)] corresponding to the fragments resulting from the dissociation of cyclam and pattern acryloyl. For its corresponding complex **C$_1$**, spectrum shows molecular ion deprotoned at m/z = 746,5 $[M-H]^+$ with a relative abundance of 20%. The different fragments are : m/z = 623,5 $[M-2NO_3]^+$, m/z = 591,1 $[M-(2NO_3+2CH_2)]^+$, m/z = 521,1 $[M- (2NO_3+CH_2CH_2N+CH_2CHCO)]^+$. While the molecular peak of complex **C$_2$** was not observed, but ions m/z = 880,5 $[M-NO_3]^+$, m/z = 758,3 $[M-(NO_3+C_6H_5)]^+$, m/z = 729,3 $[M-(NO_3+C_6H_5CO+2H)]^+$ and m /z =265,3 $[M-(NO_3+4\text{benzoyl}+\text{cyclam})]^+$ corresponding to the characteristic fragments of the loss of cyclam, of nitrate and the pattern benzoyl confirm the structure of the complex **C$_2$**. The experimental mass found, are in agreement with the theoretical mass.

The structures of complexes **C$_1$** and **C$_2$** (Fig.3) have been proposed based on the results spectroscopic analysis IR, ^{1}H NMR, ^{13}C-NMR and mass spectrometry.

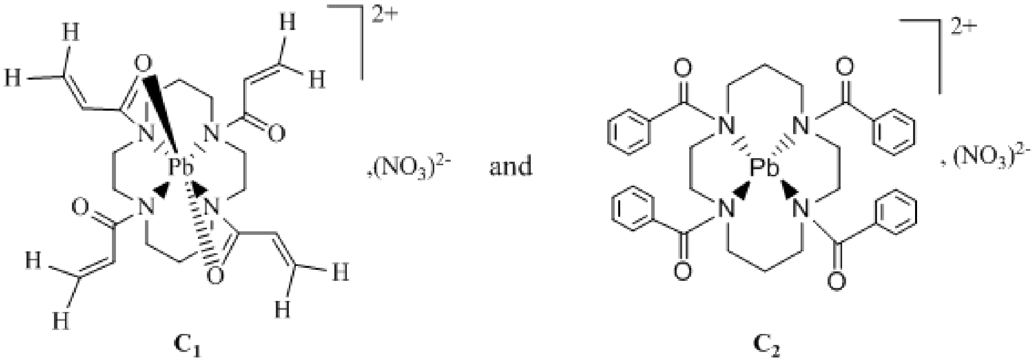

Fig.3. Suggested structures of complexes $C_1$and C_2.

IV. Conclusion

This work allowed us to confirm the formation of macrocyclic ligands N-tetra-substituted (1,4,8,11-tétraacryloyl)cyclam(**L$_1$**) and (1,4,8,11-tétrabenzoyl)cyclam (**L$_2$**) following the condensation of four equivalent in excess of acryloyl chloride or benzoyl chloride with an equivalent of cyclam. These ligands and their lead (II) complexes were obtained with good yields. The structures of these ligands and their complexes were confirmed by various conventional spectroscopic methods of analysis. Both complexes have an octahedral geometry. In both cases, the four nitrogen atoms of the cyclam participate in the coordination of the metal. In addition for the complex **C$_1$**, two of the four carbonyl groups also take part in the coordination of the metal. All these results show that the cyclam derivatives possess great flexibility in coordination. They are therefore good complexing agents for transition metals and heavy metals. More, the complexes derived from these ligands exhibit antiviral properties significant [8] and they can also be used as a contrast agent in MRI (Magnetic Resonance Imaging)[9,10].

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