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Protonated 14-membered 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetrazacyclotetradeca-7,14-diene Salts and Their Biological Activity

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***Abstract*—The 14-membered heterocyclic 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetrazacyclotetradeca-7,14-diene, [(Me6[14]N4diene)], salts with structural formula of [(Me6[14]N4diene)]Br2(H2O)2), [(Me6[14]N4diene)Cl2])(H2O)3, Me6[14]N4diene.(ClO4)2, Me6[14]N4diene.(PF6)2 and Me6[14]N4diene.(NO3)2 have been synthesized without the necessity of a template. The salts were characterized by FTIR, and NMR spectroscopic techniques. X-ray study showed that the macrocyclic cation consists of a pair of protonated amines and azomethine nitrogen atoms located diagonally and opposite to each other. Only the macrocylic bromide and perchlorate salts showed activity against gram-positive E. faecalis and gram-negative E. Coli.**

***Keywords*— Tetraaza; Curtis; Macrocylic; Metal Complexes; Biological Activity**

I. INTRODUCTION

The synthesis of 14-membered rings Curtis compounds were mostly based on the metal templation method [1], [2]. The removal of the central metal from the complex will then give the macrocylic ligand [3]. However, not all metals from the complexes can be easily removed. In the present work, a number of protonated 14-membered ring, 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetrazacyclotetradeca-7,14-diene*[(Me$_6$[14]N$_4$diene*] macrocyclics were obtained via one pot reaction without necessity of metal templation. Thus, allowing us to conduct the detailed studies on the synthesis of the macrocyclic compounds. This paper presents the structural investigation of the macrocylic salts with bromide, chloride, perchlorate and hexafluorophosphate counter anions and their biological activities.

II. METHODS

A. Chemicals and instrumentation

All solvents and chemicals were of analytical grade and were used without purification. Elemental analysis was carried out with Fison EA 1108 for hydrogen, carbon and nitrogen contain in the compound. Infrared spectra of the salts were recorded in the range 4000-200 cm^{-1} with the help of Perkin Elmer Spectrum GX as KBr pellets. NMR spectra were recorded in DMSO-d_6 using TMS as standard on JOEL FX-400 spectrometer. The single crystal X-ray study was conducted by using Bruker SMART Apex diffractometer.

B. Preparation of 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetrazacyclotetradeca-7,14-diene Salts

The Curtis salts *[(Me$_6$[14]N$_4$diene*) bromide was prepared according to the literature methods [4], [5] but with the addition of stoichiometric amounts of ammonium bromide (0.01mol) and ethylenediamine (0.01 mol) in 30 ml acetone. Some crystals were obtained from the solution after one day of evaporation. Similar experimental procedures were repeated for the preparation other salts with different ammonium salts (ammonium chloride, ammonium nitrate, ammonium perchlorate and ammonium hexafluorophosphate) (Figure 1).

C. Biological studies

Antibacterial activity test for all the *[(Me$_6$[14]N$_4$diene* salts against 10 types of bacteria were carried out by the well diffusion technique. The samples were dissolved in DMSO with the concentrations of 25 mg/ml. The results

were compared to commercially available streptomycin and chloramphenicol.

III. Results And Discussion

A. Synthesis of [($Me_6[14]N_4diene$] Salts

The reaction of ammonium bromide with ethylenediamine gave white solid crystal with molecular formula *[($Me_6[14]N_4diene$)]$Br_2(H_2O)_2$*). The yield was 65% with melting point of 113.4-125.3°C. The microelemental analysis data is in agreement with the formula of $C_{16}H_{40}N_4O_3Cl_2$. (expt C=38.9 H=7.5 N=11.6; cal C=40.2 H=7.9 N=11.1). The salt is soluble in water, methanol, ethanol, chloroform and dimethyl sulfoxide. The infrared spectrum showed the presence of the azomethine C=N and C-N stretching bands at 1667 and 1228cm^{-1}, respectively. The bands at 3468 cm^{-1} (sharp) and 3012 cm^{-1} (broad) are due to the primary amino and water OH stretchings, respectively. The high primary amino stretching than the normal value of 3260 cm^{-1} indicates the presence of protonated NH_2 group.

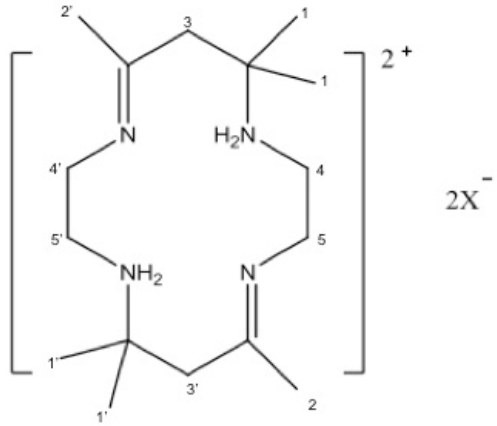

Fig 1. The structure of *[($Me_6[14]N_4diene$* salt

^{1}H NMR spectrum showed the presence of methyl proton at 2.06ppm and protonated amine at 4.89ppm. The methylene protons are at 1.49ppm. The ^{13}C NMR confirmed the formation of azomethine and C-N bond with the chemical shifts of 175.87ppm and 58.35ppm respectively. Ultra-violet visible spectrum shows a maximum absorption peak around 238nm (ε=22500) corresponding to $\pi \rightarrow \pi^*$ electronic transitions of azomethine chromofor.

The spectroscopic data was supported by X-ray investigation (Figure 2). The compound crystallized in triclinic crystal system with space group Pī, a=8.290(3), b=8.655(3), c=8.809(3) Å, α=72.797(6), β=75.373(6) γ=66.593(6)°, V= 547.4(3)Å^3 and Z= 2 [6]. The unit cell is different compared to its chloro and iodo analogs which are isostructural (Rohovec et al., 1999; Kennedy et al., 2011). The important feature for the salt is that each pair of azomethine and protonated N nitrogen atoms is diagonally opposite to each other. The asymmetric unit consists of one centrosymmetric ring, 2 bromine atoms and 2 water molecules. The structure is stabilized by O-H...Br and N-H...Br and intermolecular hydrogen bonds (Table 1).

The other [*($Me_6[14]N_4diene$*) salts are analogous except different in term of the counter anions and the solvated molecules.

TABLE I
INTRA AND INTER MOLECULAR HYDROGEN BONDS FOR $Me_6[14]N_4diene)Br_2])(H_2O)_2$

D--H..A	Type	D—H	H…A	D…A	D—H..A
O1W-H1WA…Br1^{II}	Inter	0.93(7)	2.49(6)	3.375(4)	159(5)
O1W-H1WB…Br1^{III}	Inter	0.72(4)	2.71(4)	3.411(4)	165(4)
N1-H1B…Br1^{i}	Inter	0.90	2.66	3.488(3)	153
N1-H1B…N4	Intra	0.90	2.09	2.753(4)	129

Symmetry Code: i) 1-x 1-y, -z ii) –x,1-y, 1-z

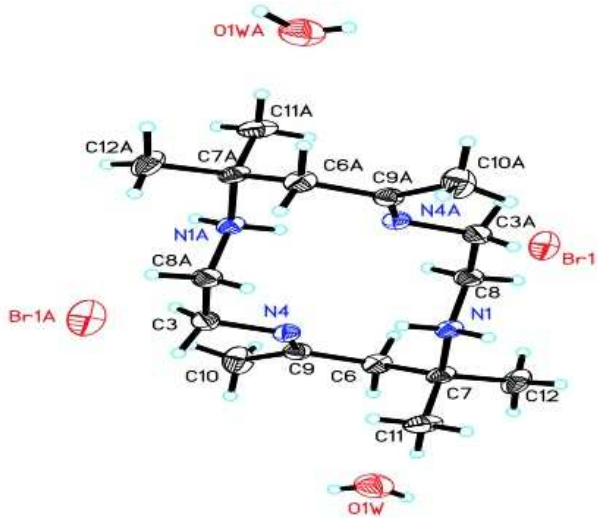

Fig 2. The molecular structure of *$Me_6[14]N_4diene)Br_2])(H_2O)_2$* drawn at 50% probability ellipsoid.

[($Me_6[14]N_4diene)Cl_2]$)$(H_2O)_3$: percentage yield = 66%; melting point = 98.8-99.1°C; elemental analysis, expt C=45.6 H=9.4 N=13.3; cal C=47.3 H=9.9 N=13.8; infrared analysis, C=N = 1667 cm^{-1}, C-N = 1228 cm^{-1}, N-H = 3468 cm^{-1}; ^{1}H NMR H(1,1') = 1.41ppm H(2,2') = 2.07ppm NH_2 = 5.12ppm; ^{13}C NMR C=N = 175.87ppm, C-N = 58.41ppm; UV λ_{max} = 235nm.

$Me_6[14]N_4diene.(NO_3)_2$: percentage yield = 68%; melting point = 103.1-104; elemental analysis, expt C=45.7 H=8.7 N=21.9; cal C=47.1 H=8.4 N=20.7; infrared analysis, C=N = 1667 cm^{-1}, C-N = 1223 cm^{-1}, N-H = 3435 cm^{-1}, ^{1}H NMR H(1,1') = 1.43ppm H(2,2') = 1.99ppm NH_2 = 5.15ppm, ^{13}C NMR C=N = 175.73ppm, C-N = 58.29ppm; UV λ_{max} = 229nm.

$Me_6[14]N_4diene.(ClO_4)_2$ percentage yield = 72%; melting point = 150.4-151.2; elemental analysis, expt C=40.5 H=7.3 N=11.8; cal C=39.5 H=7.1 N=11.8; infrared analysis, C=N = 1664 cm^{-1}, C-N = 1230 cm^{-1}, N-H = 3245 cm^{-1}, ^{1}H NMR H(1,1') = 1.27ppm H(2,2') = 1.87ppm, ^{13}C NMR C=N = 175.73ppm, C-N = 57.82ppm; UV λ_{max} = 237nm.

$Me_6[14]N_4diene.(PF_6)_2$: percentage yield = 70%; melting point = 156.8-159.8; elemental analysis, expt C=34.2 H=6.3 N=9.9; cal C=33.6 H=5.9 N=9.8; infrared analysis, C=N = 1667 cm^{-1}, C-N = 1228 cm^{-1}, N-H = 3469 cm^{-1}, ^{1}H NMR H(1,1') = 1.43ppm H(2,2') = 2.00ppm NH_2 = 4.85ppm, ^{13}C

NMR C=N = 176.12ppm, C-N = 58.17ppm; UV λ_{max} = 243nm.

B. Reaction Mechanism

A simple mechanism of the template reaction proposed by Curtis [4] involved acetone molecules with the metal-ethylenediamine complex. However, the present one pot reaction is an organic reaction without involving any metal. The presence of dimethyl and azomethine groups in the tetraaza microcycle indicate the role of acetone both keto and enol (tautomeric) forms in the condensation and cyclization steps.

C. Biological studies

Among the five chemically synthesized *[(Me_6[14]N_4diene] salts* evaluated against the ten bacteria only two compounds, *Me_6[14]N_4diene)Br_2])($H_2O)_2$* and *Me_6[14]N_4diene.($ClO_4)_2$* were effective against gram positive *E. faecalis (inhibition zone = 7.3 mm)* and gram negative *E. coli (inhibition zone =9.3 mm)*, respectively.

IV. CONCLUSIONS

The Curtis protonated macrocylic salt has been synthesized via one pot reaction using ammonium salts and ethylenediamine in acetone. Many of the salts showed low antibacterial activity against the tested bacteria. Further works on their complexes are on progress.

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