Asian Journal of Chemistry; Vol. 30, No. 7 (2018), 1431-1434

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2018.20984

Template Engineered Tetraazamacrocyclic Complexes and their Antibacterial Studies

MONIKA KAMBOJ[1,*], KIRAN JAIN[2] and D.P. SINGH[3]

[1]Department of Chemistry, Amity School of Applied Sciences, Amity University Uttar Pradesh, Lucknow Campus, Lucknow-226 028, India
[2]Department of Chemistry, M.L.N. College, Yamunanagar-135 001, India
[3]Department of Chemistry, National Institute of Technology, Kurukshetra-136 119, India

*Corresponding author: E-mail: monikakamboj@yahoo.com

Received: 4 January 2018; *Accepted*: 20 April 2018; *Published online*: 31 May 2018; AJC-18908

Template condensation reaction of ethylenediamine and acetonylacetone in the presence of metal ions(III) was implemented to synthesize 16 membered macrocyclic complexes as $[M(C_{16}H_{28}N_4)X]X_2$. The characterization of synthesized complexes was done by means of various physio-chemical techniques. Template synthesis, characterization, molecular modeling and *in vitro* antibacterial activities have been discussed.

Keywords: Antibacterial, Macrocyclic complexes, Template, Molecular modeling.

INTRODUCTION

Macrocyclic metal complexes are marvelous molecules due to their capability to bind different kinds of ligands. They play dominant role in bioinorganic chemistry for their many applications. The interest for these nitrogen containing macrocycles analogs is due to their analytical, industrial and medical applications [1]. Antiviral, anticarcinogenic [2] as well as antifertile [3] biological activities of macrocyclic complexes have gained the curiosity and has now been an emergent research area. Macrocyclic complexes also find useful place as MRI contrast agents [4,5].

Research on designing new Gd coordination complexes has amplified since the approval of $[Gd(DTPA)(H_2O)]_2$ [6]. These multiple applications of macrocyclic complexes have been the driving force for their rapid growth during the last two decades. Macrocyclic compounds are studied for various reasons: (i) they are relevant to the active centers of metalloenzymes; (ii) they are used as industrial catalysts; (iii) used as models for protein-metal binding sites in biological systems; (iv) as sequestering reagents for specific metal ions; (v) as models to study the magnetic exchange phenomena; (vi) as chemical sensors and batteries; (vii) as therapeutic reagents for the treatment of metal intoxication; and (viii) as medical imaging agents and in biomedical and fuel cell applications.

Diverse oxidation states are exhibited by transition metals and these can be organized with number of ligand. Hence, it has essential position within medicinal inorganic chemistry. Our group [7] had already reported *in vitro* antibacterial activities of metal(II) complexes resulting from acetonylacetone and ethylenediamine. The properties of these complexes prompted us to synthesize and characterize chromium(III) and iron(III) complexes derived from acetonylacetone and ethylenediamine.

EXPERIMENTAL

AR grade reagents were used for the synthesis of macrocyclic complexes. Metal(III) salts were used as supplied from S.D. Fine, Merck, Ranbaxy. The microanalyses of C, H and N were carried out at SAIF, CDRI, Lucknow, India. The IR spectra were recorded on FT-IR spectrophotometer at SAIF, CDRI Lucknow, India. The vibrating sample magnetometer (Model-PAR155) was used for measuring the magnetic susceptibility available at SAIF, IIT Roorkee, India. The metal contents in the complexes were estimated by standard method as reported in the literature [8]. Spectrophotometer (Cary 14) was used for recording electronic spectra in DMF. The digital conductivity meter (HPG System, G-3001) was used for measuring conductivity of the synthesized complexes. Melting points were determined in electrical melting point apparatus.

Synthesis of complexes: One-pot template method was applied for the synthesis of complexes. The process involves the refluxing of 10 mmol of ethylenediamine and 5 mmol of iron(III) or chromium(III) salt, respectively in methanol for 0.5 h. After 30 min, 20 mL of methanolic solution of acetonylacetone (10 mmol) was added to the above mixture. Subsequently, refluxing was continued for 8-10 h. The mixture was cool in desiccator at room temperature. The precipitates of complexes

were dark coloured, these were filtered, washed with solvent (such as methanol, acetone and diethyl ether) and dried in air. Yield: ~55-60 %. The solubility of these complexes was checked in DMF, DMSO and other common organic solvents. They were found to decompose above 270 ºC.

$$2C_2H_8N_2 + 2C_6H_{10}O_2 + MX_3 \xrightarrow[\sim 8\text{-}10\ h]{\text{Methanol}} [M(C_{16}H_{28}N_4)X]X_2 + 4H_2O$$

M = Cr(III) or Fe(III); X = Cl^-, NO_3^-, CH_3COO^-

Scheme-I: Synthesis of complexes derived from acetonyl-acetone and ethylenediamine with trivalent metal salts

Biological assay: Total four bacterial strains, *S. aureus* (MTCC 96), *B. subtilis* (MTCC 121), *E. coli* (MTCC 1652) and *P. aeruginosa* (MTCC 741) were screened for determination of minimum inhibitory concentration (MIC) of selected complexes. The procurement of these microbial cultures was done from microbial type culture collection (MTCC), IMTECH, Chandigarh, India. The Nutrient agar was used for sub-culturing bacteria. The culture conditions and antimicrobial activities were determined by reported method [9].

Molecular modelling: The ligand-M(III) complexes [M = Cr(III), Fe(III)]was optimized using molecular mechanic methods by Avogadro 1.2.0 program [10]. For each molecule numerous sets of energy minimization had to be carried out.

RESULTS AND DISCUSSION

The formula of macrocyclic complexes from analytical data (Table-1) are designated as: $[M(C_{16}H_{28}N_4)X]X_2$, where M = Cr(III) and Fe(III); X = Cl^-, NO_3^-, CH_3COO^-; 1:2 electrolytic nature of these complexes was established from their high valve of conductance (150-180 Ω^{-1} cm^2 mol^{-1}) [11]. Before and after decomposition, these complexes give positive tests for anions, specifying their presence inside and outside the sphere. An effort to obtain a single crystal, suitable for X-ray crystallography was in vain. So geometry for the complexes was inferred by analytical, spectroscopic and magnetic data.

IR studies: In the infrared spectrum of ethylenediamine, a medium intensity bands at about 3230 and 3260 cm^{-1} due to $\nu(NH_2)$, was found missing in the spectra of all the complexes. IR spectrum of acetonylacetone shows a strong intensity peak at 1700 cm^{-1} ascribed to >C=O group, was found missing in the spectra of all the complexes. The condensation of carbonyl groups and amino groups [12,13] and the assembly of macrocyclic Schiff's base [11] is further supported by presence of a new strong absorption band in the region 1615-1590 cm^{-1}. This may be attributed due to ν(C=N) [14,15]. The low value of ν(C=N) band, specify coordination of nitrogen to metal [16]. The bands present at 1350-1000 and 3130-2900 cm^{-1} may be assigned due to ν(C-N) and ν(C-H) vibrations, respectively.

Nitrate complexes: The absorption bands in the region 1430-1410, 1325-1280 and 1030-1010 cm^{-1}, indicated the unidentate mode of coordination of nitrate groups with metal ion (iron or chromium) [14] in all the nitrato complexes.

Acetate complexes: The absorption bands in the region 1650-1670 and 1258-1285 cm^{-1} is assigned to $\nu(COO^-)_{as}$ and $\nu(COO^-)_s$ stretching vibration of acetate ion. The coordination of the acetate ion with the central metal ion [14] is in unidentate manner as difference between ($\nu_{as} - \nu_s$) is greater than 144 cm^{-1}.

The far IR spectra show bands in the region 450-420 cm^{-1} corresponding to ν(M-N) vibrations in all the complexes [17-19] further gives an verification about the coordination of azometh-ine nitrogen [20]. The bands at 310-300 cm^{-1} may be allocated to ν(M-Cl) vibrations [17,20]. The bands at 210-250 cm^{-1} are allocated to ν(M-O) vibrations of nitrato group [21,22].

Magnetic measurements and electronic spectra

Chromium(III) complexes: Magnetic moment of Cr(III) complexes in the range of 3.96-4.25 B.M. relates to three unpaired electrons in the metal ion [23]. The absorption band in electronic spectra of chromium complexes recorded in DMSO at 9100-9250 cm^{-1}, 13200-13210 cm^{-1}, 17440-18240 cm^{-1}, 27350-27730 cm^{-1} and 34850 cm^{-1} may be assigned to transitions: $^4B_1 \rightarrow {}^4E_a$, $^4B_1 \rightarrow {}^4B_2$, $^4B_1 \rightarrow {}^4A_2$ and $^4B_1 \rightarrow {}^4E_b$, respectively [23].

Iron(III) complexes: The magnetic moment of Fe(III) complexes was found in the range of 5.79-5.83 B.M., corresponding to the five unpaired electrons [20]. The electronic absorption bands of iron complexes at 9810-9870, 15330-15570, 27500-27850 cm^{-1} are consigned as: $d_{xy} \rightarrow d_{xz}$, d_{yz} and $d_{xy} \rightarrow d_{z^2}$.

These spectral bands relates with the data of reported five coordinated square-pyramidal chromium(III) complexes and iron(III) complexes [23-25], whose structure are verified by X-ray measurements [24].

Molecular modelling: The optimized geometry of chromium complexes, $[Cr(C_{16}H_{28}N_4)Cl]^{2+}$ with auto-optimized energy of 1119.3 kJ/mol as shown in Fig 1. The four N-atoms in macrocyclic complex attain equatorial positions with Cr(III)-N distance being 1.93 Å. The chloride atom occupy axial position at distance of 2.30 Å from Cr(III) metal. The N-Cr-N and N-Cr-Cl angles are 96.71º and 75.26º, respectively (Fig. 1).

The auto optimized energy of $[Fe(C_{16}H_{28}N_4)Cl]^{2+}$ complex as shown in Fig. 2 is 1110.70 kJ/mol. The four N-atoms at equatorial position have Fe(III)-N distance of 1.95 Å. The chloride atom at axial position is at distance of 2.33 Å from Fe(III).

TABLE-1
ANALYTICAL DATA OF TRIVALENT CHROMIUM AND IRON METAL COMPLEXES DERIVED FROM ETHYLENEDIAMINE AND ACETONYLACETONE

Complexes	Colour	Elemental analysis (%): Found (calcd.)				m.,w. Found (calcd.)
		M	C	H	N	
$[Cr(C_{16}H_{28}N_4)Cl]Cl_2$	Black	11.81 (11.98)	44.20 (44.23)	6.12 (6.45)	12.40 (12.90)	– (434)
$[Cr(C_{16}H_{28}N_4)(NO_3)](NO_3)_2$	Dark brown	10.01 (10.11)	37.12 (37.35)	5.35 (5.44)	19.01 (19.06)	513.2 (514)
$[Cr(C_{16}H_{28}N_4)(OAc)](OAc)_2$	Brown	10.10 (10.29)	52.01 (52.30)	7.12 (7.30)	11.00 (11.08)	– (505)
$[Fe(C_{16}H_{28}N_4)Cl]Cl_2$	Light brown	12.27 (12.78)	43.57 (43.83)	6.11 (6.39)	12.41 (12.78)	436.3 (438)
$[Fe(C_{16}H_{28}N_4)(NO_3)](NO_3)_2$	Brown	10.28 (10.80)	37.01 (37.06)	5.11 (5.40)	18.26 (18.90)	– (518)
$[Fe(C_{16}H_{28}N_4)(OAc)](OAc)_2$	Brown	10.91 (11.00)	51.17 (51.80)	7.01 (7.30)	10.98 (11.00)	– (509)

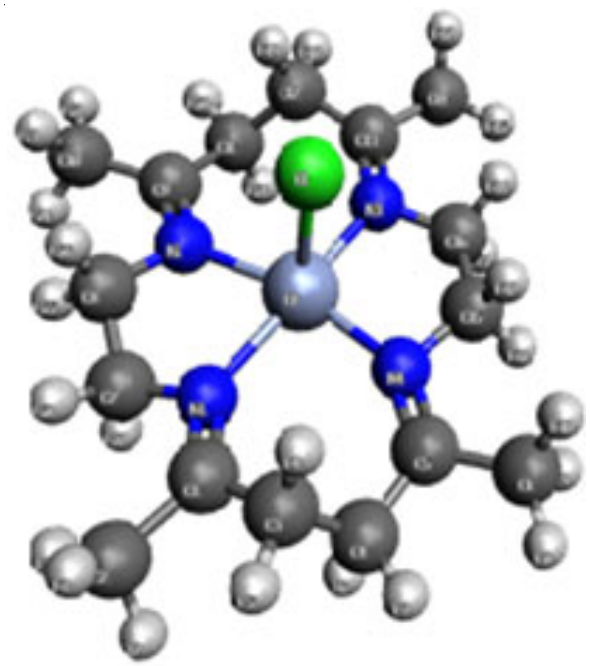


Fig. 1. A geometry optimized structure of complex $[Cr(C_{16}H_{28}N_4)Cl]^{2+}$

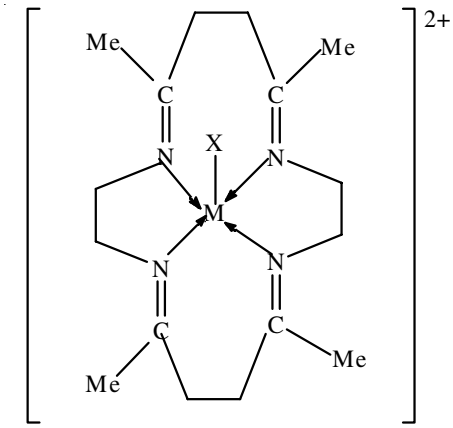
Fig. 2. A geometry optimized structure of complex $[Fe(C_{16}H_{28}N_4)Cl]^{2+}$

The N-Fe-N and N-Fe-Cl angles are 96.74º and 75.08º, respectively.

Antibacterial activity: The antibacterial activity of synthesized macrocyclic complexes has been evaluated by the agar well diffusion method [9] against Gram-positive and Gram-negative bacteria. Macrodilution tube method was adopted for determining the minimum inhibitory concentration (MIC) of the various complexes against various bacterial strains. Ciprofloxacin was used as standard antibiotic for equating the activities of these complexes against Gram-positive bacteria (*S. aureus* and *B. subtilis*) as well as Gram-negative bacteria (*E. coli* and *P. aeruginosa*). Complex **6** responded most effectively against *B. subtilis* with the maximum zone of inhibition of 21.6 mm and MIC of 32 µg/mL. Complexes **1**, **2**, **3**, **4** and **5** retort less significantly against some of the tested bacterial strains and showed the zone of inhibition ranging from 19.6 to 14.3 mm (Table-2). All the complexes respond less significantly against the bacterial strains *P. aeruginosa*.

Conclusion

In this work, six macrocyclic complexes were synthesized and characterized by various physio-chemical methods. Conductance value of 150-180 Ω^{-1} cm^2 mol^{-1} shows that they are 1:2 electrolytes. Before and after decomposition, these complexes give positive tests for anions, specifying their presence inside and outside the sphere. The infrared spectral data shows the coordination of azomethine nitrogen to metal. The magnetic moments value divulges that they are all paramagnetic. Based on spectral and other data, a square pyramidal geometry as shown in Fig. 3 may be proposed for all of these complexes. In biological studies, none of the synthesized macro-



M = Cr(III) or Fe(III); X = Cl^-, NO_3^-, CH_3COO^-

Fig. 3. Proposed structure of the metal complexes

TABLE-2
in vitro ANTIBACTERIAL ACTIVITIES AND MINIMUM INHIBITORY CONCENTRATION (MIC) OF SYNTHESIZED TRIVALENT TRANSITION METAL COMPLEXES DERIVED FROM ETHYLENEDIAMINE AND ACETONYLACETONE

Complexes	Diameter of growth of inhibition zone (mm)[x]				MIC (µg/mL)			
	a	b	c	d	a	b	c	d
$[Cr(C_{16}H_{28}N_4)Cl]Cl_2$	14.3	17.3	–	–	> 256	128	–	–
$[Cr(C_{16}H_{28}N_4)(NO_3)](NO_3)_2$	15.6	18.6	–	–	256	64	–	–
$[Cr(C_{16}H_{28}N_4)(OAc)](OAc)_2$	16.3	18.3	–	–	128	64	–	–
$[Fe(C_{16}H_{28}N_4)Cl]Cl_2$	17.0	19.6	15.6	–	128	64	128	–
$[Fe(C_{16}H_{28}N_4)(NO_3)](NO_3)_2$	15.3	16.3	–	–	256	128	–	–
$[Fe(C_{16}H_{28}N_4)(OAc)](OAc)_2$	17.0	21.6	16	–	128	32	128	–
Ciprofloxacin	27.6	26.3	25.0	25.3	05	05	05	05

[x]Values, including diameter of the well (8 mm), are means of three replicates; (–) No activity; a = *Staphylococcus aureus* (MTCC 96); b = *Bacillus subtilis*(MTCC 121); c = *Escherichia coli* (MTCC 1652); d = *Pseudomonas aeruginosa* (MTCC 741); Ciprofloxacin = Standard antibiotic

cyclic complexes were found to as effective as that of ciprofloxacin. It has been suggested that the polarity of the metal ion is reduced by chelation whereas its lipophilic nature rises mainly because of partial sharing of its positive charge with donor group within the whole chelate ring system [26,27] which in turn, favours its permeation through the lipoid layer of membrane thus causing the metal complex to cross the bacterial membrane more effectively thus increasing the activity of the complexes.

REFERENCES

1. B. Hariprasath, Deepthi, I.S. Babu, P. Venkatesh, S. Sharfudeen and V. Soumya, *J. Chem. Pharm. Res.*, **2**, 496 (2010).
2. S. Chandra and M. Pundir, *Spectrochim. Acta A*, **69**, 1 (2008); https://doi.org/10.1016/j.saa.2007.02.019.
3. S. Chandra, R. Gupta, N. Gupta and S.S. Bawa, *Transition Met. Chem.*, **31**, 147 (2006); https://doi.org/10.1007/s11243-005-6194-5.
4. K. Kumar and M.F. Tweedle, *Pure Appl. Chem.*, **65**, 515 (1993); https://doi.org/10.1351/pac199365030515.
   S.C. Jackels, B.R. Kroos, W.H. Hinson, N. Karstaedt and P.R. Moran, *Radiology*, **159**, 525 (1986); https://doi.org/10.1148/radiology.159.2.3961187.
5. A.D. Watson, S.M. Rockladge and C.B. Higgins, Magnetic Resonance Imaging of the Body, Raven Press, New York (1992).
6. J.R. Morrow and É. Toth, *Inorg. Chem.*, **56**, 6029 (2017); https://doi.org/10.1021/acs.inorgchem.7b01277.
7. D.P. Singh, R. Kumar, M. Kamboj and K. Jain, *Acta Chim. Slov.*, **56**, 780 (2009).
8. A.I. Vogel, A Text Book of Quantitative Chemical Analysis, Longman, London (1989).
9. I. Ahmad and A.Z. Beg, *J. Ethnopharmacol.*, **74**, 113 (2001); https://doi.org/10.1016/S0378-8741(00)00335-4.
10. P. Rathi, K. Sharma and D.P. Singh, *Spectrochim. Acta A, Mol. Biomol. Spectrosc.*, **130**, 72 (2014); https://doi.org/10.1016/j.saa.2014.03.046.
11. R. Kumar and R. Singh, *Turk. J. Chem.*, **30**, 77 (2006).
12. Q. Zeng, J. Sun, S. Gou, K. Zhou, J. Fang and H. Chen, *Transition Met. Chem.*, **23**, 371 (1998); https://doi.org/10.1023/A:1006994300484.
13. A.K. Singh, R. Singh and P. Saxena, *Transition Met. Chem.*, **29**, 867 (2004); https://doi.org/10.1007/s11243-004-1732-0.
14. L.K. Gupta and S. Chandra, *Transition Met. Chem.*, **31**, 368 (2006); https://doi.org/10.1007/s11243-005-0002-0.
15. A.K. Mohamed, K.S. Islam, S.S. Hasan and M. Shakir, *Transition Met. Chem.*, **24**, 198 (1999); https://doi.org/10.1023/A:1006903000739.
16. C. Lodeiro, R. Basitida, E. Bertolo, A. Macias and R. Rodriguez, *Transition Met. Chem.*, **28**, 388 (2003); https://doi.org/10.1023/A:1023672629805.
17. F.M.A.M. Aqra, *Transition Met. Chem.*, **24**, 337 (1999); https://doi.org/10.1023/A:1006962812246.
18. S. Chandra and R. Kumar, *Transition Met. Chem.*, **29**, 269 (2004); https://doi.org/10.1023/B:TMCH.0000020359.84853.72.
19. V.B. Rana, D.P. Singh, P. Singh and M.P. Teotia, *Transition Met. Chem.*, **7**, 174 (1982); https://doi.org/10.1007/BF01035836.
20. V.P. Krzyminiewska, H. Litkowska and W.R. Paryzek, *Monatsh. Chem.*, **130**, 243 (1999); https://doi.org/10.1007/PL00010204.
21. D.P. Singh, V. Malik, K. Kumar, C. Sharma and K.R. Aneja, *Spectrochim. Acta A*, **76**, 45 (2010); https://doi.org/10.1016/j.saa.2010.02.044.
22. Z.A. Siddiqi, S. Kumar, M. Khalid and M. Shahid, *Spectrochim. Acta A*, **72**, 970 (2009); https://doi.org/10.1016/j.saa.2008.12.019.
23. D.P. Singh, R. Kumar and J. Singh, *Eur. J. Med. Chem.*, **44**, 1731 (2009); https://doi.org/10.1016/j.ejmech.2008.03.007.
24. D.P. Singh, R. Kumar and J. Singh, *J. Enzyme Inhib. Med. Chem.*, **24**, 883 (2009); https://doi.org/10.1080/14756360802456397.
25. J.S. Wood, *Prog. Inorg. Chem.*, **16**, 227 (1972).
26. D.P. Singh, V. Malik, R. Kumar and J. Singh, *J. Enzyme Inhib. Med. Chem.*, **24**, 1201 (2009); https://doi.org/10.1080/14756360902779383.
27. D.P. Singh, M. Kamboj, K. Kumar, K. Jain and C. Sharma, *J. Coord. Chem.*, **64**, 502 (2011); https://doi.org/10.1080/00958972.2010.545398.