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SYNTHESIS, CHARACTERIZATION, ELECTROCHEMICAL AND ANTIBACTERIAL STUDIES OF MN_4-TYPE MACROCYCLIC COMPLEXES OF NI(II)

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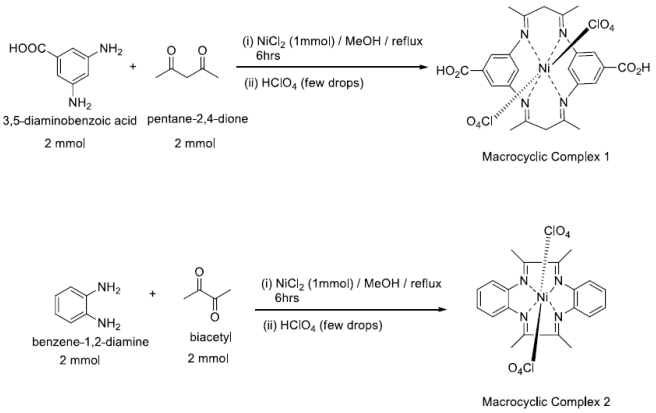
Herein, we designed and synthesized two novel MN_4-type macrocyclic complexes of Ni^{II} using a simple template-based strategy. The synthesized macrocyclic complexes were characterized by using several analytical techniques such as elemental analysis, FT-IR spectroscopy, UV-Vis spectroscopy, and mass spectrometry. The molar conductance was also measured to predict the electrolytic behavior of macrocyclic complexes. Furthermore, the complexes were subjected to electrochemical investigation utilizing cyclic voltammetric techniques. The results indicated a quasi-reversible peak for Ni^{II}/Ni^{I} redox couple with ΔE_p value is 0.195 V and $E_{1/2}$ value of –0.749 V *vs* Ag/AgCl electrode. The complexes stabilized the unusual oxidation state of the central metal ion. In addition, both complexes were tested for their antibacterial activities against pathogens like *E. coli, S. aureus, B. subtilis, C. albicans*, and *P. aeruginosa*, and both complexes were shown to have comparable antibacterial activity with the standard drug *Gentamycin*.



INTRODUCTION

Macrocyclic complexes in coordination chemistry play a crucial role in developing new materials for their potent applications in diverse sectors of chemistry and biochemistry.[1,2] The presence of variable donor sites, metal ion valencies, and geometries of the resultant complexes make the chemistry of macrocyclic compounds interesting.[3–5] Architectural design strategies for synthesizing macrocyclic ligands are based on the metal ion binding sites to tune the geometry of macrocyclic complexes being engineered finely. Macrocyclic ligands are potential ligands that show the most prominent binding in transition metal coordination chemistry because they give their metal complexes thermodynamic and kinetic stability.[6,7]

Synthetic N_4-macrocyclic compounds of saturated and unsaturated macrocyclic ligands with different transition metal ions were extensively investigated during the last few years.[8–10] Transition

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metal complexes also possess special features for biochemical processes based on their closed, planar tetraazamacrocyclic architectures.[12–15] The macrocyclic complexes are shown to have antibacterial capacities that depend upon the chelation of particular ligands that could frequently affect the biological activities of bio-metals.[16,17]

It has already been established that the accompanying factors that influence the properties of macrocyclic complexes are macrocyclic ring size, ligand charge, ligand moiety type, the extent of ligand unsaturation, etc. These properties can be tuned to develop efficient materials with suitable designs with significant stability, conductivity, and electron-rich electrochemistry is still under debate and attracted the scientific community working in the above fields. Considering the significance of macrocyclic systems, herein, we synthesized two MN_4-type macrocyclic complexes of Ni^{II} by using a simple template method) and which were characterized by using multiple analytical techniques. Furthermore, two newly synthesized complexes were investigated for electrochemical activity and antibacterial potency (against pathogens like *E. coli, S. aureus, B. subtilis, C. albicans*, and *P. aeruginosa*).

EXPERIMENTAL

1. Materials and methods

3,5-Diamino benzoic acid, $NiCl_2$, 1,3-diacetyl, o-phenylenediamine, $HClO_4$, and solvents like ethanol and methanol used in this study were of AR grade and procured from Merck (Mumbai, India) and used without no further purification. The instruments, Elemental analyzer (Vario EL-III Elemental Model), FT-IR Spectrometer (Nicolet NEXUS Aligent 1100, KBr pellets), Conductivity meter (TDS Meter 307 Systronics), UV–visible (Shimadzu spectrophotometer) were used for the characterization of macrocyclic complexes. Cyclic voltammetric studies were carried out on a CH-600 Electroanalyser setup in DMF with 0.1 M tetrabutylammonium perchlorate (TBAP) as a supporting electrolyte. Glassy carbon electrode, Ag/AgCl electrode, and Pt wire were used as the working electrode, reference electrode, and auxiliary electrode, respectively. Mass spectra were recorded on Eager Xperience and TOF MS ES +6018e[3], respectively.

2. Synthesis of macrocyclic complexes

To a 500 mL round bottom flask containing 100 mL of MeOH; 3,5 diamino benzoic acid (30.4 gm, 2 mol), 1,3-diacetyl (17.2 ml, 2 mol), and $NiCl_2$ (12.97 gm, 1 mol) were added and refluxed for six hours followed by addition of 4-5 drops of $HClO_4$ at the end of the completion of the reaction and the reaction mixture allowed to cool at room temperature. The light green precipitates obtained were purified in methanol. Similarly, the macrocyclic complex **2** was also synthesized by using o-phenylenediamine (21.6 gm, 2 mol), 1,3-diacetyl (11.6 ml, 2 mol) in place of 3,5 diamino benzoic acid (30.4 gm, 2 mol), diacetyl (17.2 ml, 2 mol) respectively as described above. A scheme representing the synthesis of two macrocyclic complexes is shown in Fig. 1. The characterization data of the two synthesized complexes is given below.

Complex **1:** Yield 75%, 0.05439 g, Color: Light green, mp 250–251°C; Molar conductance ($Ohm^{-1}\cdot cm^2\cdot mol^{-1}$), 174 (in DMSO) and 138 (in MeCN). *Anal. Calc.* for $C_{24}H_{24}N_4NiCl_2O_{12}$. Found, C % 41.77 (41.69), H% 3.51 (3.49), N % 8.12 (8.10), Cl % 10.28 (10.23), Ni % 8.51 (8.50), O % 27.82 (27.78). FT-IR (KBr, disc cm^{-1}), ν(COOH) 3340 bs; ν(C-H) 2950m; ν (ClO_4) 1092, 656, 620; ν (C=N) 1640m. UV-Vis (MeCN, λ_{max}), 375, 410 nm. MS: 690 $[M]^+$.

Complex **2:** Yield 88%, 0.04965 g, color: Blue m.p. > 275°C, Molar conductance ($Ohm^{-1}\cdot cm^2\cdot mol^{-1}$), 146 (in DMSO) and 124 (in MeCN). *Anal. Calc.* for $C_{20}H_{20}N_4NiCl_2O_8$. Found, C % 41.85 (41.81), H% 3.51 (3.50), N % 9.76 (9.72), Cl % 12.35 (12.31), Ni % 10.23 (10.20), O % 22.30 (22.28). FT-IR (KBr, disc cm^{-1}), ν (C-H) 2962m, ν(ClO_4) 1100, 660, 628, ν (C=N) 1632 (m). UV-Vis (MeCN, λ_{max}) = 367, 398 nm. MS = 573.71 $[M]^+$.

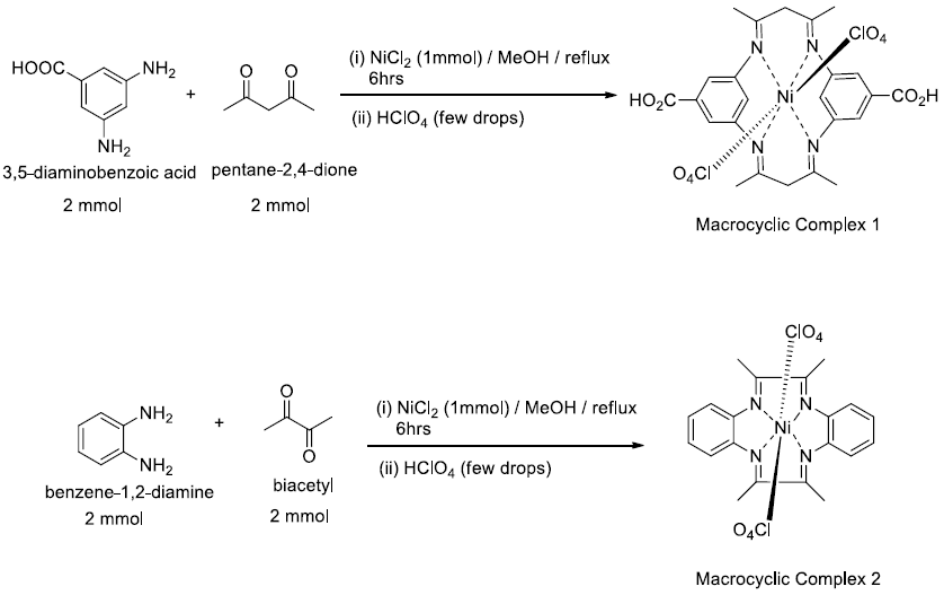


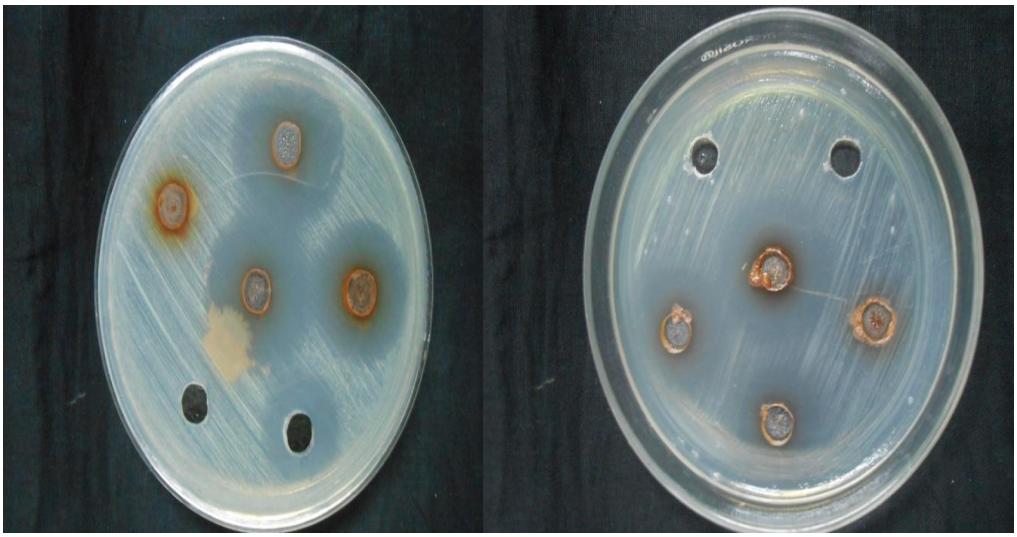
Fig. 1 – Scheme for the synthesis of macrocyclic complexes.

3. Electrochemical study

Cyclic voltammetry (CV) was employed to study the electrochemical behavior of two NiN4-macrocyclic complexes carried out using cyclic voltammetry in DMSO containing 0.1M TBAP as supporting electrolyte.

4. Antibacterial Study

The Agar-disc diffusion approach was used to assess the antibacterial activities of two complexes. The filter paper (Whatman no. 1) sterile disc of 5 mm diameter was impregnated with newly synthesized complexes (10 mg/ml of DMSO) and put in a nutrient agar plate at 37ºC for 12 hours in this technique. After 12 hours, the inhibition zones around the dried impregnated discs were determined. Antibacterial activity was categorized as highly active (>14 mm), moderately active (10–14 mm), mildly active (6–10 mm), and passive (< 5 mm). Gentamycin was utilized as a reference drug for comparison purposes. The photograph representing a zone inhibition for complexes **1** and **2** against *E. coli* is shown in Fig. 2.



(1) **(2)**

Fig. 2 – Antibacterial activity of the macrocyclic complexes (**1**) and (**2**) against *E. coli.*

RESULTS AND DISCUSSION

1. Characterization of complexes

The high molar conductance values (Table 1) for the two complexes supported the electrolytic (1:2) nature of metal complexes. The complexes are stable, and hygroscopic with higher melting points, insoluble in H_2O, and soluble in MeCN, DMF, and DMSO generating deep color in their solutions.

Table 1

Molar conductance data of the two macrocyclic complexes

Complex	Solvent	Molar Conductance ($\Omega^{-1}\cdot cm^2\cdot mol^{-1}$)	Type of electrolyte
1	MeCN	174	1:2
	DMSO	136	1:2
2	MeCN	146	1:2
	DMSO	124	1:2

IR spectral analysis obtained for two macrocyclic complexes indicated a large band near 1620–1660 cm^{-1} (C=N group) and the absence of bands near 1700 cm^{-1} (free > C=O group) and near 3450 cm^{-1} (free $–NH_2$ group) promoted the development of macrocyclic structures a set of complexes.[18,19] Complexes (**1**) and (**2**) revealed IR bands around 1100 cm^{-1}, and at 625 cm^{-1}, implying the existence of non-coordinated perchlorate.[20] The C-H stretching vibrations of aromatic rings and the CH_3 group can be assigned to the other characteristic bands for all complexes in the region ~1250 cm^{-1}, ~1100 cm^{-1}, ~620 cm^{-1}, and 2950 cm^{-1}, respectively. In addition to these bands, the complexes possess significant peaks between 656 and 625 cm^{-1} in their IR spectra which signifies the presence of two perchlorate groups in monodentate coordinate positions.

The IR spectra of two macrocyclic compounds exhibit easily identifiable bands at 1100 cm^{-1}, 625, and 656 cm^{-1} indicating the presence of two perchlorate bands. The obvious conclusion that can be drawn from these spectral and structural data is that the existence of a second perchlorate band between 600 and 700 cm^{-1} affirms the presence of a substantial interaction between the ClO_4 group and the metal cation, but does not enable us to differentiate between the various types of such interactions.[20] In addition, IR spectra show a band

in the region of 400–480 cm^{-1} can be assigned to M-N stretching.[21]

The absorption spectra of macrocyclic complexes were recorded in methanol containing 10^{-3} M solution of complexes, separately, at room temperature in the range of 200–800 nm. UV–vis spectrum of ligands in two macrocyclic complexes showed two strong absorption bands at 375 and 367 nm, respectively (Fig. 3). The first band, which occurs at higher energies and has a high amplitude, can be attributed to the Schiff imine base (C=N) chromophore. The second, weaker band, is due to the Ph groups attached to the carboxylic acid n to p* transition.[22] The UV spectrum of complexes **1** and **2** displays a shift to higher energy at 389 nm due to the azomethine nitrogen atoms being coordinated to the metal centers. The UV-Vis spectra of complex **2** also show a shoulder near 400 nm that indicates the presence of the charge transfer from the metallic center and the coordinating atoms of the ligand (i.e., metal-ligand charge transfer, MLCT).[23] The absorption bands of the two complexes were also observed at around 600 nm with significantly poor intensities ($\varepsilon = 0.288 \times 10^3$ mol^{-1} L cm^{-1}), which is attributed to the *d–d* transitions.

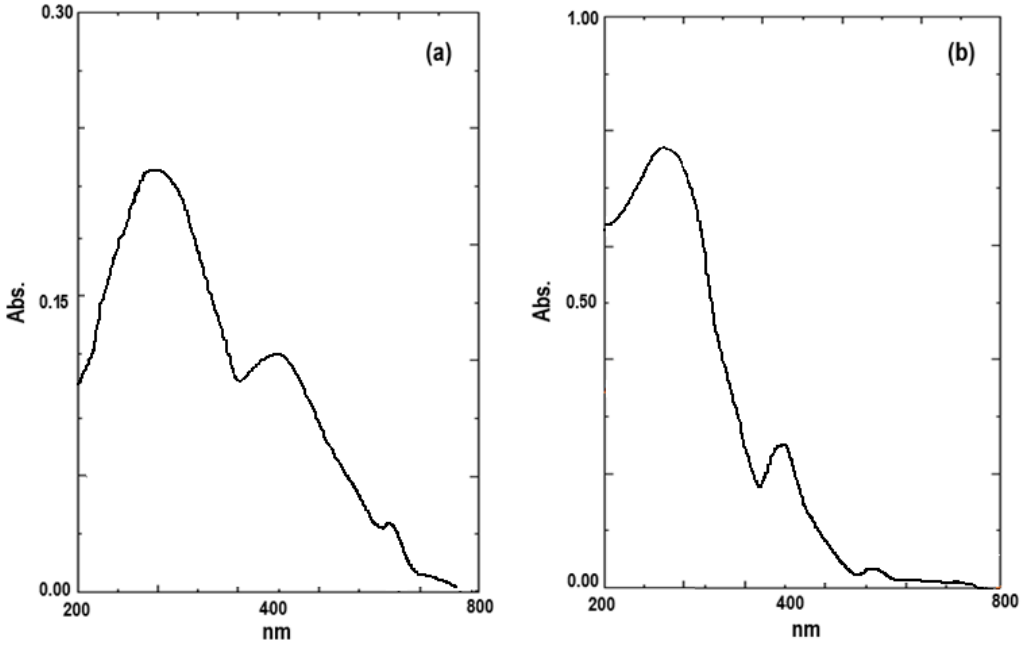


Fig. 3 – UV-vis spectra of Ni^{II} complexes **1** (a) and **2** (b).

The mass spectra of these tetraaza perchlorate coordinated macrocyclic complexes indicated molecular ion peaks (M+1) for $[C_{24}H_{24}N_4NiCl_2O_{12}]$ and $[C_{20}H_{20}N_4NiCl_2O_8]$ at m/z = 690 and 573 respectively. The complexes and the mass spectral data are in strong agreement to prove the structure of the reported complex.

2. Electrochemical studies

A representative cyclic voltammogram of nickel complexes is shown in Fig. 4. The results showed a quasi-reversible peak for a Ni^{II}/Ni^{I} redox couple having ΔE_p value is 0.195 V. The $E_{1/2}$ value for this redox couple is –0.749 V *vs* Ag/AgCl electrode.[24] In complex **1**, the nickel center has four coordinated nitrogen atoms. The coordinated nitrogen atoms stabilize the lower oxidation states, the Ni^{II} center is converted into Ni^{I}. Similar behavior was observed for complex **2** with little variation in corresponding peak positions.

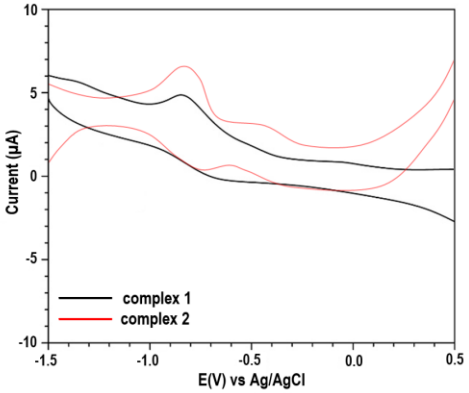


Fig. 4 – Cyclic voltammograms of complexes 1 and 2 recorded in 10^{-3} M solution of complex **1** in DMF in presence of 0.1 M TBAP as a supporting electrolyte, glassy-carbon as a working electrode, and Ag/AgCl as reference electrode; scan rate 0.1 V/s.

The macrocyclic framework enables each metal center with an essentially planar system and promotes synergistically unsaturated metal axial binding. It may change the redox activity of the macrocyclic system by effectively altering the redox potential or adjusting the reduction point. A collection of axial moieties could be achieved because charged axial ligands are found in incredibly insoluble content. In light of these considerations, neutral ligands such as N-donor heterocycles are used in the research study.

4. Antibacterial activity of macrocyclic complexes

The antibacterial activities of synthesized macrocyclic complexes of Ni^{II} (100 mg/mL) against the pathogens were investigated. The biological activities were compared with Gentamycin, a popular antibiotic and antifungal drug. About a baseline, the percentage inhibition of microbial growth was calculated as follows:

$$\text{Percentage of potency} = (C - T) \times 100/C$$

where, C = diameter of the bacterial growth in standard, T = diameter of the bacterial growth in the test.

A comparison of antibacterial activities of two $Ni^{II}N_4$ macrocyclic complexes against various pathogens is shown in Fig. 5. The macrocyclic complex (1) had the highest zone of inhibition against *E. coli* (20 mm), followed by *S. aureus* (19 mm), *B. subtilis* (18 mm) and *P. aeruginosa* (15 mm) & *C. albicans* (15 mm), while the macrocyclic complex (2) had the highest zone of inhibition against *B. subtilis* (18 mm) &*C. albicans* (18 mm) followed by *S. aureus* (16 mm), *P. aeruginosa* (16 mm) and *E. coli* (14 mm). The macrocyclic complexes **1** and **2** were found to be the most successful against the fungal pathogen *C. albicans*, followed by other macrocyclic complexes (1) (17 mm) (Fig. 5). It is suggested that antibacterial function either by killing the micro-organism, reducing the microbe's multiplicity, or blocking the binding sites of the micro-organism. Moreover, the antibacterial activity of macrocyclic frameworks is often dependent upon microbial species.[25]

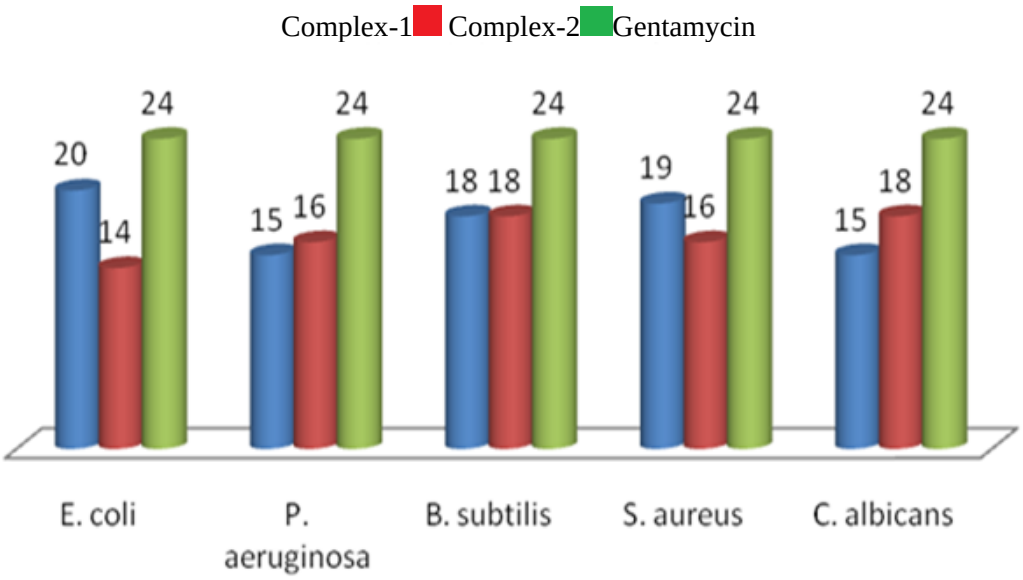


Fig. 5 – Graphical representation of the antibacterial activities of two $Ni^{II}N_4$ complexes (**1** & **2**) and their comparison against *Gentamycin* as a standard drug.

CONCLUSION

Herein, we describe the synthesis and characterization of two novel Ni-N4 macrocyclic complexes. The electrochemical studies revealed a comprehensive redox pathway that contributes to a better comprehension of biologically active metal complexes. Furthermore, these macrocycles have demonstrated a comparable level of antibacterial activity against several microorganisms. This study would be beneficial for the design of Schiff base-derived metal complexes that can serve as potential models in biological science, pharmaceuticals, energy conversion, and storage.

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