

Synthesis and Characterization of 3s,5s,7s-Adamantan-1-Amine Complexes with Metals of Biological Interest

Najma Sultana¹, Saeed Arayne M^{2*}, Amir Haider² and Hina Shahnaz³

¹Research Institute of Pharmaceutical Sciences, Faculty of Pharmacy, University of Karachi, Karachi, Pakistan

²Department of Chemistry, University of Karachi, Karachi, Pakistan

³Department of Environmental Science, Sind Madressatul Islam University, Karachi, Pakistan

Abstract

3s,5s,7s-adamantan-1-amine, tricyclo[3.3.1.1^{3,7}]decan-1-amine, 1-adamantanamine, 1-aminoadamantane, 1-aminotricyclo[3.3.1.1^{3,7}]decane, 1-adamantylamine or amantadine with a tricyclic amine with cage like structure is an antiviral and antiparkinsonian compound. It also is used to prevent and treat respiratory infections caused by influenza A virus. Eleven metal complexes of amantadine with metals of biological interest as Mg^{II}, Ca^I, Cr^{II}, Mn^{II}, Fe^I, Fe^{III}, Co^I, Ni^{II}, Cu^{II}, Zn^{II} and Cd^{II} have been synthesized and characterized by spectroscopic techniques IR, ¹H NMR, elemental analysis and atomic absorption spectroscopy. Prior to synthesis conductometric titrations were carried out to determine the mole ratios of drug metal interactions. In all complexes, amantadine acted as a monodentate ligand, two molecules of which are bound to the metal through the amino nitrogen showing a square planar geometry.

Keywords: Amantadine; Metal complexes; Conductance; FT-IR; ¹H-NMR

Introduction

Tricyclic amines have a great potential in the treatment and prevention of influenza A of which the most significant is amantadine, a synthetic alicyclic antiviral agent with an unusual cage like structure (Figure 1) [1]. Amantadine is an orally active antiparkinsonian and antiviral agent [2,3] discovered by workers at DuPont via an empiric screening program [1].

Amantadine hydrochloride possesses a unique, rigid, relatively unstrained ring system that is composed of three fused cyclohexane rings in the chair conformation [4]. Amantadine is considered to be the smallest repeating unit of the diamond lattice [5]. The symmetrical cage structure causes the infrared, nuclear magnetic resonance and mass spectra to be comparatively simple, as will be illustrated later.

Several metal complexes of amantadine are reported with iron [6], platinum [7], while other polyoxometalates containing Ce, W, Pr, Ni, V and Mn were reported by Liu and others [8]. Compounds of molybdenum and amantadine with the formulae, (C₁₀H₁₈N)₅PMo₁₂O₄₀Cl₂·5H₂O, (C₁₀H₁₈N)₆As₂Mo₁₈O₆₂·6CH₃CN·6H₂O [9], (C₁₀H₁₈N)₄Mo₈O_{26.6}(CH₃)₂SO [10] and trans-(AdNH)₂Mo(OSiMe)₃ [11] have also been reported. At physiological pH amantadine forms complex with sodium molybdate, as the amino group of the drug is free for its function as antiviral, this study

suggests that the co-administration of amantadine with molybdenum supplements should be avoided [8].

Physical properties as solubility in water, size and ionic nature which in turn are dependent on the pH of the medium [12-14] effect the absorption of a drug through gastrointestinal tract. As only the free and unchanged drug can function at the active site in the body, if molybdate reacts with amantadine or when the two are administered together, the solubility and absorption can be affected. Owing to the fact that molybdenum is neither present in the body nor is administered as drug. Alternatively, essential and trace elements can be studied for complexation with amantadine, as being the metals of biological interest. In this paper we report synthesis and characterization of eleven metal complexes of amantadine with Mg^{II}, Ca^{II}, Cr^{II}, Mn^{II}, Fe^{II}, Fe^{III}, Co^{II}, Ni^{II}, Cu^{II}, Zn^{II} and Cd^{II}, which were characterized by FT-IR, ¹H NMR, atomic absorption spectroscopy and elemental analysis.

Materials and Methods

Chemicals

Amantadine was purchased from Sigma-Aldrich USA. The essential and trace elements used were in the form of their hydrated chloride salts of magnesium, calcium, chromium, manganese, ferric, cobalt, nickel, copper, zinc and cadmium, all of analytical grade. Methanol (TEDIA, USA), hydrochloric acid, sodium hydroxide from Merck, Darmstadt, Germany. Deionized water was freshly prepared in the laboratory and all glasswares were washed with chromic acid and then thoroughly rinsed with deionized water.

Instruments

Electrical balance [Mettler Toledo AB54], pH meter [Mettler Toledo

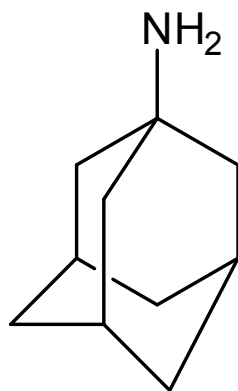


Figure 1: Amantadine.

*Corresponding author: Saeed Arayne M, Department of Chemistry, University of Karachi, Karachi-75270, Pakistan, Tel: +92-213-466-4402-03; E-mail: msarayne@gmail.com

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MP220], UV-Visible double beam spectrophotometer (Shimadzu 1601), 1 cm rectangular quartz cells, ground glass distillation assembly, (Quickfit), de-ionizer (Stedec CSW -300), water distillation unit (GFL type 2001/2, No. 10793600G), melting point apparatus (Gallenkamp), FT-IR spectrophotometer (Nicolet Avatar 330) and proton NMR (Bruker); CHN elemental analysis were carried on Carlo Erba 1106, HSF-254. The reactions were monitored on TLC plates coated with Silica gel HF-254 and compounds were observed under UV lamp (254 nm). Perkin-Elmer AAnalyst 700 atomic absorption spectrometer used for atomic absorption studies.

Conductometric titration of amantadine metal complexes

Prior to synthesis conductometric titrations were performed to study the stoichiometric ratio of amantadine metal interactions in aqueous medium using conductivity/TDS meter. In individual experiments metal solutions of 1 mM were prepared and titrated with 1 mM ligand solution at 25°C. Conductivity of reacting mixtures were recorded after each addition of metal solution aliquots.

Synthesis of amantadine metal complexes

Amantadine (2 mM) was dissolved in 0.1 N HCl and 1 mM of each of these element salts were individually dissolved in 10 mL of methanol. Both of these solutions were mixed together and refluxed for three hours; the solution was concentrated and filtered while hot and then kept undisturbed for crystal growth at room temperature. The growth of crystals had a different time of crystallization. Crystals of magnesium, calcium, and chromium and manganese complexes with amantadine appeared in 15 days while the iron complex took one month for crystallization. On the other hand, cobalt, nickel, copper, zinc and cadmium complexes took 25~30 days for their growth. These

metal complexes were recrystallized in absolute methanol, filtered, dried and physical characteristics were recorded.

Results and Discussion

Synthesis of complexes

A venture has been made to synthesize metal complexes of amantadine with various essential and trace elements in equimolar ratio in a mixture of hydrochloric acid and methanol. These complexes were then studied for their physicochemical parameters and characterized using techniques as IR, NMR and elemental analysis. Metals in all amantadine complexes were determined by using Pye-Unicam atomic absorption spectrometer (Table 1). Melting points were recorded on Gallenkamp melting point apparatus, while solubilities of all the complexes were checked and are present in Table 2.

IR Studies

All the synthesized complexes were studied spectroscopically in the IR region 4000 to 400 wavenumbers (cm^{-1}). The infrared spectrum of amantadine and their metal complexes were recorded as a potassium bromide disc method on a Nicolet Avatar 330 IR spectrophotometer. The main peak assignments are given in Table 3.

N-H stretch

The N-H stretching band of the amino group expected for amantadine is in the region 2961- 3087 [15,16] was observed for pure amantadine at 3038 cm^{-1} which shifts to 2900-3600 cm^{-1} .

For magnesium complex, N-H stretch band appeared at 3400 cm^{-1} as small band where as for calcium complex, a broad band was observed in the range of 3600-3100 cm^{-1} due to N-H stretching. In chromium and cadmium complexes, N-H stretch showed a short band at 3400 cm^{-1} , similarly in case of manganese, ferric chloride, cobalt, nickel, copper, zinc complexes a medium band was observed in the range of 3600-3100 cm^{-1} due to N-H stretching. While in ferrous ammonium citrate complex, N-H stretching showed a weak band in the region of 3400-3100 cm^{-1} .

The second incredibly significant peaks were asymmetric and symmetric stretching and their scissoring wagging and rocking which is the evidence of the attachment of metal with nitrogen of amine group. The CH_2 symmetric stretching was recorded at 2860 cm^{-1} , scissoring at 1449 cm^{-1} , rocking at 1263 cm^{-1} and wagging was at 1143 cm^{-1} . The comparison of the IR spectra of amantadine with metal complexes divulged that in case of all complexes the N-H stretching peak was shifted to 2914-3395 cm^{-1} in doublet and triplet weak bands.

CH_2 stretching (antisymmetric and symmetric)

Amantadine showed a very sharp band at 2900 cm^{-1} due to CH_2 antisymmetric and 2850 cm^{-1} due to CH_2 symmetric stretching whereas the reported peaks for antisymmetric is 2923 cm^{-1} and symmetric stretching at 2900 cm^{-1} [5]. For magnesium and calcium complex antisymmetric peaks appeared at 2900 cm^{-1} , 2950 cm^{-1} and symmetric very short band and sharp bands were observed at 2850 cm^{-1} for magnesium and calcium complexes. This band disappeared in chromium complex, whereas manganese, ferric chloride and ferric ammonium citrate nickel complexes showed suppressed bands of CH_2 stretching (antisymmetric and symmetric) at 2900 cm^{-1} . In cobalt complex very sharp symmetric band of CH_2 stretching was observed at 2850 cm^{-1} and in zinc and cadmium complexes very sharp asymmetric bands were observed at 2900 cm^{-1} and incredibly very short symmetric bands appeared between 2850-2860 cm^{-1} .

Metal	Concentration of standard (ppm)	Absorbance of standard	Absorbance of sample	Concentration of sample/50 mL	%	S.D
Mg	0.3	0.198	0.37	23800	23.8	0.000
Ca	4	0.191	5.3	30430	30.43	0.021
Cr	4	0.192	0.78	38780	38.78	0.012
Mn	2.5	0.19	1.86	39890	39.89	0.013
Fe	5	0.198	1.54	40100	40.10	0.025
Co	7	0.199	0.34	42340	42.34	0.020
Ni	7	0.198	5.35	42220	42.22	0.020
Cu	4	0.197	0.23	46120	46.12	0.012
Zn	1	0.204	1.81	44790	44.79	0.005
Cd	1.5	0.196	1.22	58230	58.23	0.004

Table 1: Atomic absorption analysis of amantadine metal complexes.

Sample	Melting point °C	Mole ratio	Solubility $\text{H}_2\text{O}:\text{HCl}$	Color
Amantadine	180		1:1	White
Amn+Mg	210	1:2	1:2	White
Amn+Ca	192	1:2	1:2	White
Amn+Cr	200	1:2	1:2	Green
Amn+Mn	228	1:2	1:2	White
Amn+ FeCl_3	112	1:2	1:2	Yellow
Amn+ FeSO_4	210	1:2	1:2	Light yellow
Amn+Co	218	1:2	1:2	Blue
Amn+Ni	212	1:2	1:2	Light green
Amn+Cu	210	1:1	1:2	Blue
Amn+Zn	202	1:1	1:2	Off white
Amn+Cd	232	1:1	1:2	White

Table 2: Physicochemical parameters of amantadine and its metal complexes.

Compounds	$\nu(\text{N-H})$ stretching	$\nu(\text{N-H})$ bending	$\nu(\text{N-H})$ oop bending	$\nu(\text{N-H})$ stretching	$\nu_{\text{asym}}(\text{CH}_2)$ stretch	$\nu_{\text{sym}}(\text{CH}_2)$ stretch	$\nu(\text{CH}_2)$ scissoring	$\nu(\text{CH}_2)$ rocking	$\nu(\text{CH}_2)$ wagging
Amantadine	2894	1608	811	1364	2860	-	1449	1263	1143
Amn+Mg	2920	1515	914	1080	2854	2711	1496	1313	1200
Amn+Ca	3300, 2914	1517	898	1090	2857	2708	1499	1366	1203
Amn+Cr	3123, 2923	1585	815	1090	2844	2658	1487	1329	1197
Amn+Mn	3212, 3073, 3046	1575	951	1092	2837	-	1479	1363	1203
Amn+FeCl ₃	3173, 3116, 3050	1595	961	1080	2850	-	1472	1366	1193
Amn+FeSO ₄	3176, 3119, 2954	1578	957	1077	2854	-	1476	1366	1197
Amn+CO	3365, 2906	1570	912	1094	2867	-	1480	1324	1206
Amn+Ni	3179, 2920-2904	1589	963	1080	2854	-	1472	1378	1203
Amn+Cu	3212, 3010-2910	1569	918	1090	2904	-	1476	1373	1207
Amn+Zn	3084, 2904	1574	964	1088	2850	-	1476	1311	1200
Amn+Cd	2914	1588	974	1097	2860	2728	1456	1366	1200

Table 3: Infrared assignments of amantadine metal complexes.

Drug & metal complex	(CH ₂) ₂	J Values (Hz)	(CH ₂) ₃	J Values (Hz)	(CH ₂) ₁₀	J Values (Hz)	NH
Amantadine	1.71, 1.42	2.13, 11.48	1.18, 1.56	2.79, 4.21	1.18, 1.78	7.85, 6.78	1.45, 1.48
Mg complex	1.59, 1.49	2.52, 11.57	1.23, 1.61	2.90, 4.35	1.23, 1.67	7.90, 6.30	-
Ca complex	1.68, 1.38	2.65, 11.64	1.20, 1.67	2.89, 4.41	1.45, 1.61	7.71, 6.27	-
Cr complex	1.65, 1.32	2.58, 11.76	1.21, 1.60	2.91, 4.56	1.43, 1.65	7.69, 6.22	-
Mn complex	1.64, 1.45	2.65, 11.63	1.01, 1.63	2.93, 4.77	1.32, 1.90	7.67, 6.31	-
Fe ⁺³ complex	1.68, 1.49	2.76, 11.60	1.29, 1.61	2.67, 4.29	1.29, 1.96	7.75, 6.36	-
Fe ⁺² complex	1.68, 1.37	2.31, 11.59	1.27, 1.70	2.7, 4.34	1.31, 1.82	7.93, 6.40	-
Co complex	1.62, 1.35	2.71, 11.62	1.21, 1.61	2.65, 4.43	1.38, 1.94	7.69, 6.29	-
Ni complex	1.60, 1.38	2.77, 11.48	1.23, 1.63	2.64, 4.67	1.23, 1.98	7.90, 6.30	-
Cu complex	1.78, 1.49	2.22, 11.68	1.09, 1.65	261, 4.33	1.29, 1.90	7.91, 6.22	-
Zn complex	1.62, 1.47	2.38, 11.71	1.09, 1.66	2.87, 4.38	1.44, 1.83	7.67, 6.24	-
Cd complex	1.55, 1.44	2.21, 11.56	1.22, 1.61	2.81, 4.41	1.27, 1.89	7.70, 6.29	-

Table 4: Chemical shifts (ppm) in ¹H NMR spectra of amantadine and its metal complexes.

N-H overtones, N-H deformation and CH₂ deformation

Amantadine showed N-H overtones at 2000 cm⁻¹, N-H deformation at 1608 cm⁻¹, 1535 cm⁻¹, 1364 cm⁻¹ and CH₂ deformation at 1449 cm⁻¹ while reported for N-H overtones at 2000 cm⁻¹, N-H deformation at 1608 cm⁻¹, 1364 cm⁻¹ and CH₂ deformation at 1452 cm⁻¹ [5] are observed. For magnesium complex, N-H deformation was observed at 1515 cm⁻¹, 1510 cm⁻¹, 1365 cm⁻¹ as suppressed bands and CH₂ deformation suppressed band at 1496 cm⁻¹. N-H overtones observed at 2000 cm⁻¹ for all amantadine complexes. For calcium complex, N-H deformation shifted to 1517-20 cm⁻¹, 1499 cm⁻¹ and 1366 cm⁻¹, N-H overtones at 2000 cm⁻¹ and CH₂ deformation suppressed at 1452 cm⁻¹ have been recorded. In all metal-amantadine complexes the N-H bending and C-N stretching were at a lower wavelength at 1515-1589 cm⁻¹ and 1097-1077 cm⁻¹, respectively.

CH₂ wag and fingerprint region

Amantadine showed CH₂ wag sharp band at 1320 cm⁻¹ and fingerprint region at 1300 cm⁻¹ and below while reported CH₂ wag at 1307 cm⁻¹ [5]. For magnesium complex, CH₂ wag at 1320 cm⁻¹ (suppressed and doublet band), for calcium and manganese, ferrous ammonium citrate, ferric chloride, nickel, copper, zinc and cadmium complexes complexes suppressed bands were observed 1307-1310 cm⁻¹.

Due to the coordination of the metal ion with amantadine the N-H, C-N bands shifted to higher frequencies and overlapped [15]. It may be inferred that metal ions were strongly coordinated with amantadine through direct association with primary amine group [16,17].

¹H NMR studies

By comparing main peaks of amantadine with its complexes (Table

4), it is observed that amine resonance was absent in the spectra of all metal complexes. The reported NH₂ (for C-1), β-CH₂ (for C-2, C-8, C-9), δ-CH₂ (for C-4, C-6, C-10), δ-CH (C-3, C-5, C-7) groups of actual drug, showed their presence at δ1.35, δ1.55, δ1.62, δ2.05 [5]. While the ¹NMR of the reference drug in D₂O at 600 MHz showed signal at 1.4 (d, 2H, J=12.27) assigned for C-1 inferred the presence of NH₂ group. A doublet at δ1.5 having coupling constant J=11.48 confirmed the presence of β-CH₂ groups for C-2, C-8, C-9 positions. A doublet appeared at δ1.78 assigned for δ-CH₂ groups at C-4, C-6, C-10 positions (J=7.85) and the presence of CH groups at C-3, C-5, C-7 showed singlet at s, H δ1.56.

The magnesium complex, in CD₃OD + CDCl₃ at 600 MHz, showed a doublet at δ1.49 having coupling constant J=2.52 confirmed the presence of β-CH₂ groups for C-2, C-8, C-9 positions. A doublet appeared at δ1.67 (J=7.9) assigned for δ-CH₂ groups at C-4, C-6, C-10 positions and the presence of γ-CH groups at C-3, C-5, C-7 showed singlet at δ1.61. Calcium complex confirmed the complex formation, and a doublet at δ1.68 having coupling constant J=11.64 confirmed the presence of β-CH₂ groups at C-2, C-8, C-9 positions. While γ-CH₂ groups at C-4, C-6, C-10 positions (J=2.65) showed doublet at δ1.61 and the presence of γ-CH groups at C-3, C-5, C-7 showed singlet at δ1.2. Chromium complex showed and confirmed the complex formation signal at δ1.65 confirmed the presence of β-CH₂ groups for C-2, C-8, C-9 positions. The γ-CH₂ groups at C-4, C-6, C-10 positions and γ-CH groups at C-3, C-5, C-7 showed singlet at δ1.6 and δ1.43. Manganese complex showed signals at δ1.65 having coupling constant J=2.65 confirmed the presence of β-CH₂ groups for C-2, C-8, C-9 positions. γ-CH₂ groups at C-4, C-6, C-10 positions and γ-CH groups at C-3, C-5, C-7 showed singlet at δ1.9 and 1.32.

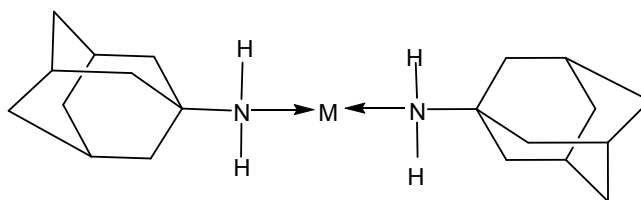


Figure 2: Proposed structure of amantadine metal complexes.

S.No	Compound	Chemical formula		C	H	N	C/S	Metal
1	Amantadine	C ₁₀ H ₁₇ N	Found	79.41	11.33	9.26		
			Calculated	79.75	11.9	8.79		
2	Amn + Mg	C ₁₀ H ₁₇ Cl ₂ Mg ₂ NO	Found	41.88	5.98	4.88		16.50
			Calculated	40.91	4.78	5.46	24.73	16.02
3	Amn + Ca	C ₁₀ H ₁₅ Cl ₂ Ca ₂ N	Found	40.0	5.03	4.66		26.69
			Calculated	40.45	5.1	3.79	23.61	26.59
4	Amn + Cr	C ₂₀ H ₃₂ Cl ₂ CrN ₂	Found	56.47	8.06	6.59	16.67	12.22
			Calculated	56.42	8.10	6.53	16.63	12.20
5	Amn + Mn	C ₂₀ H ₃₂ Cl ₂ MnN ₂	Found	56.08	8.00	6.54	16.55	12.83
			Calculated	56.05	8.01	6.58	16.50	12.88
6	Amn + Fechloride	C ₂₀ H ₃₂ ClFeN ₂	Found	55.96	7.98	6.53	16.52	13.01
			Calculated	55.91	7.93	6.58	16.57	13.09
7	Amn + Fe sulfate	C ₂₀ H ₃₂ FeN ₂ O ₄ S	Found	53.10	7.13	6.19		12.34
			Calculated	52.51	7.55	5.54	7.09	11.93
8	Amn + Co	C ₂₀ H ₃₂ ClCoN ₂	Found	55.56	7.93	6.48	16.40	13.63
			Calculated	55.59	7.99	6.42	16.47	13.68
9	Amn + Ni	C ₂₀ H ₃₂ ClNiN ₂	Found	55.59	7.93	6.48	16.41	13.58
			Calculated	55.61	7.99	6.50	16.47	13.60
10	Amn + Zn	C ₂₀ H ₃₂ ClZnN ₂	Found	54.75	7.81	6.38	16.16	14.90
			Calculated	54.70	7.88	6.42	16.20	14.96
11	Amn + Cd	C ₂₀ H ₃₂ CdClN ₂	Found	49.45	7.05	5.77	14.60	23.14
			Calculated	49.50	7.10	5.81	14.66	23.17

Table 5: CHN microanalysis of amantadine and its metal complexes.

Ferrous sulfate complex showed a doublet at δ 1.68 having coupling constant $J=11.59$ confirmed the presence of β -CH₂ groups for C-2, C-8, C-9 positions. δ -CH₂ groups at C-4, C-6, C-10 positions and γ -CH groups at C-3, C-5, C-7 showed singlet at δ 1.82 and δ 2.7. Similarly in ferric chloride complex doublet was observed at δ 1.68 ($J=11.6$) and at δ 1.49 indicated the NH₂ group for C-1, confirmed the complex formation, and β -CH₂ groups for C-2, C-8, C-9 positions.

The γ -CH₂ groups (C-4, C-6, C-10) and γ -CH groups (C-3, C-5, C-7) appeared at δ 1.96 (singlet) and at δ 1.29 (singlet). In the cobalt complex, the ¹NMR in CD₃OD at 600 MHz, confirmed the complex formation by showing doublet at δ 1.35 having coupling constant $J=2.71$ confirmed the presence of β -CH₂ groups for C-2, C-8, C-9 positions. At δ 1.8 (d, 6H, $J=1.84$, H-4, 6, 10) and singlet at δ 1.61 (C-3, C-5, C-7) showed the presence of δ -CH₂ groups and γ -CH groups. For nickel complex, a doublet at δ 1.6 having coupling constant $J=2.7$ confirmed the presence of β -CH₂ groups for C-2, C-8, C-9 positions. A singlet appeared at δ 1.98 assigned for δ -CH₂ groups (C-4, C-6, and C-10) and γ -CH groups (C-3, C-5, and C-7) showed singlet at δ 1.63 confirmed by signals δ 1.78 (d, 2H, $J=12.5$) for β -CH₂ groups at C-2, C-8, C-9 positions. While δ -CH₂ groups at C-4, C-6, C-10 positions and CH groups at C-3, C-5, C-7 showed singlet at δ 1.65 and at δ 1.9. In zinc complex, a doublet at δ 1.69 having coupling constant $J=11.71$ confirmed the presence of β -CH₂ groups for C-2, C-8, C-9 positions. A doublet appeared at δ 1.83 ($J=2.1$) for δ -CH₂ groups at C-4, C-6, C-10 positions and singlet for CH groups (C-3, C-5, C-7) at δ 1.66. Similarly in cadmium complex, the complex confirmed by the signals

of β -CH₂ groups (C-2, C-8, C-9), a doublet appeared at δ 1.89 ($J=7.7$) for δ -CH₂ groups for C-4, C-6, C-10 positions and for γ -CH groups (C-3, C-5, C-7) singlet at δ 1.27.

In case of all complexes the shifting of protons was observed at C2, C3 and C10 (Table 4). All the complexes showed resonance of methylene protons and other spectroscopic studies also account that there is an attachment of metal with the nitrogen of amine in amantadine molecule.

Structure of amantadine metal complexes

On the basis of above studies the amantadine nitrogen binds with metals and their proposed structures are shown as Figure 2. From the results obtained, it is proposed that amantadine forms complexes in the ratio of 2: 1 (drug: metal) [18]. The crystals of the complexes were very thin and we did not cope to obtain their X-ray crystallographs. The proposed formulae is established on the basis of spectroscopic and elemental analysis (Table 5) [6].

Conclusion

Complexes of metals of biological interest were synthesized with amantadine. The results from the elemental analysis, conductometric titration, AA spectroscopy, proton nuclear magnetic resonance and infrared studies reveals that in all complexes, amantadine acted as a monodentate ligand, two molecules of which were bound to the metal through the amino nitrogen showing a square planar geometry.

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