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

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Abstract

3s,5s,7s-adamantan-1-amine, tricyclo[3.3.1.13,7]decane-1-amine, 1-adamantanamine, 1-aminoadamantane, 1-amino-tricyclo[3.3.1.13,7]decane, 1-adamantylamine or amantadine with a tricyclic amine with cage like structure is an antiviral and antiparkinsonian compound. It is also used to prevent and treat respiratory infections caused by influenza A virus. Eleven metal complexes of amantadine with metals of biological interest as Mg²⁺, Ca²⁺, Cr³⁺, Mn²⁺, Fe²⁺, Fe³⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺ and Cd²⁺ have been synthesised 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 molar 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 empirical 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 amontadine with the formulae, (C₁₀H₁₈N)₅PMo₁₂O₄₀Cl₂.⁵H₂O, (C₁₀H₁₈N)₄Mo₈O₂₆.⁶(CH₃)₂SO₄ are characterized by FT-IR, ¹H NMR, elemental analysis and atomic absorption spectroscopy. Prior to synthesis conductometric titrations were carried out to determine the molar 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.

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 Mg²⁺, Ca²⁺, Cr³⁺, Mn²⁺, Fe²⁺, Fe³⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺ and Cd²⁺, 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]

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Instruments

Electrical balance [Mettler Toledo AB54], pH meter [Mettler Toledo]
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. 10791600G), 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 A Analyst 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 than 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.

| 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                  | 3.45                 | 42340                       | 42.34 | 0.020 |
| Ni      | 7                               | 0.198                  | 5.35                 | 42220                       | 42.22 | 0.020 |
| Zn      | 1.5                             | 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 H2O:HCl | Color   |
|---------|------------------|------------|--------------------|---------|
| Amantadine | 180             | 1.1        | White             |         |
| Amn+Mg   | 210              | 1.2        | White             |         |
| Amn+Ca   | 192              | 1.2        | White             |         |
| Amn+Cr   | 200              | 1.2        | Green             |         |
| Amn+Mn   | 228              | 1.2        | White             |         |
| Amn+FeCl3| 112              | 1.2        | Yellow            |         |
| Amn+FeSO4| 210              | 1.2        | Light yellow      |         |
| Amn+Co   | 218              | 1.2        | Blue              |         |
| Amn+Ni   | 212              | 1.2        | Light green       |         |
| Amn+Cu   | 210              | 1.1        | Blue              |         |
| Amn+Zn   | 202              | 1.1        | Off white         |         |
| Amn+Cd   | 232              | 1.1        | White             |         |

Table 2: Physicochemical parameters of amantadine and its metal complexes.
N–H overtones, N–H deformation and CH₄ deformation

Amantadine showed N–H overtones at 2000 cm⁻¹, N–H deformation at 1608 cm⁻¹, 1535 cm⁻¹,1364 cm⁻¹ and CH₄ 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 CH₄ deformation at 1452 cm⁻¹ [5] are observed. For magnesium complex, N–H deformation was observed at 1517 cm⁻¹, 1510 cm⁻¹, 1365 cm⁻¹ as suppressed bands and CH₄ 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 CH₄ 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].

1NMR 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–CH₃ (for C–4, C–6, C–10), δ–CH (C–3, C–5, C–7) groups of actual drug, showed their presence at 61.35, 61.55, 61.62, 62.05 [5]. While the ¹H NMR of the reference drug in D₂O at 600 MHz showed signal at 1.4 (d,2H, J=12.27) assigned for δ–CH₂ groups at C–4, C–6, C–10 positions [5]. 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.

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Table 3: Infrared assignments of amantadine metal complexes.

| Compounds | ν(N-H) stretching | ν(N-H) bending | ν(N-H) oop bending | ν asym(CH₃) stretch | ν sym(CH₃) stretch | υ(CH₃) scissoring | υ(CH₃) rocking | υ(CH₃) wagging |
|-----------|------------------|----------------|--------------------|---------------------|------------------|----------------|----------------|----------------|
| Amantadine | 1608 811 1364     | 2860           | -                  | 1449 1263 1143     | -                | -              | -              | -              |
| Amn+Mg    | 1517 900 1090    | 2857 2708      | 1499 1366 1203     | -                   | -                | -              | -              | -              |
| Amn+Cr    | 1517 900 1090    | 2850 2658      | 1487 1329 1197     | -                   | -                | -              | -              | -              |
| Amn+Ni    | 1517 900 1090    | 2850 2658      | 1487 1329 1197     | -                   | -                | -              | -              | -              |
| Amn+Zn    | 1517 900 1090    | 2850 2658      | 1487 1329 1197     | -                   | -                | -              | -              | -              |
| Amn+Cd    | 1517 900 1090    | 2850 2658      | 1487 1329 1197     | -                   | -                | -              | -              | -              |

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

| Drug & metal complex | (CH₃)₂ | J Values (Hz) | | (CH₃)₃ | J Values (Hz) | | (CH₃)₄ | J Values (Hz) | NH |
|---------------------|--------|--------------||--------|--------------||--------|--------------|----|
| Amantadine          | 1.71, 1.42 | 2.13, 11.48  | | 1.18, 1.56  | 2.78, 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  | 2.91, 4.56  | | 1.41, 1.61  | 7.71, 6.27  | -             |
| Cr complex          | 1.65, 1.32 | 2.58, 11.76  | | 1.21, 1.60  | 2.93, 4.77  | | 1.32, 1.90  | 7.67, 6.31  | -             |
| Mn complex          | 1.64, 1.45 | 2.65, 11.63  | | 1.01, 1.63  | 2.67, 4.29  | | 1.29, 1.96  | 7.75, 6.36  | -             |
| Fe complex          | 1.68, 1.49 | 2.76, 11.60  | | 1.29, 1.61  | 2.7, 4.34   | | 1.31, 1.82  | 7.93, 6.40  | -             |
| Fe complex          | 1.68, 1.37 | 2.31, 11.59  | | 1.27, 1.70  | 2.65, 4.43  | | 1.38, 1.94  | 7.69, 6.29  | -             |
| Co complex          | 1.62, 1.35 | 2.71, 11.62  | | 1.21, 1.61  | 2.64, 4.67  | | 1.23, 1.98  | 7.90, 6.30  | -             |
| Ni complex          | 1.60, 1.38 | 2.77, 11.48  | | 1.23, 1.63  | 2.61, 4.33  | | 1.29, 1.90  | 7.91, 6.22  | -             |
| Cu complex          | 1.78, 1.49 | 2.22, 11.68  | | 1.09, 1.65  | 2.87, 4.38  | | 1.44, 1.83  | 7.67, 6.24  | -             |
| Zn complex          | 1.62, 1.47 | 2.38, 11.71  | | 1.09, 1.66  | 2.81, 4.41  | | 1.27, 1.89  | 7.70, 6.29  | -             |
| Cd complex          | 1.55, 1.44 | 2.21, 11.56  | | 1.22, 1.61  | -             | | -             | -             | -             |
Ferrous sulfate complex showed a doublet at δ1.68 having coupling constant $J=11.59$ confirmed the presence of β–CH$_2$ groups for C–2, C–8, C–9 positions. δ–CH$_2$ groups at C–4, C–6, C–10 positions and γ–CH groups at C–3, C–5, C–7 showed singlet at δ1.82 and δ2.7. Similarly in ferric chloride complex doublet was observed at δ1.68 ($J=11.6$) and at δ1.49 indicated the NH$_2$ group for C–1, confirmed the complex formation, and β–CH$_2$ groups for C–2, C–8, C–9 positions. The γ–CH$_2$ groups (C–4, C–6, C–10) and γ– CH groups (C–3, C–5, C–7) appeared at δ1.96 (singlet) and at δ1.29 (singlet). In the cobalt complex, the 1NMR in CD$_3$OD at 600 MHz, confirmed the complex formation by showing doublet at δ1.35 having coupling constant $J=2.71$ confirmed the presence of β–CH$_2$ groups for C–2, C–8, C–9 positions. At δ1.8 (d, 6H, $J=1.84$, H–4, 6, 10) and singlet at δ1.67 (C–3, C–5, C–7) showed the presence of δ–CH$_2$ groups and γ– CH groups. For nickel complex, a doublet at δ1.6 having coupling constant $J=2.7$ confirmed the presence of β–CH$_2$ groups for C–2, C–8, C–9 positions. A singlet appeared at δ1.98 assigned for δ–CH$_2$ groups (C–4, C–6, and C–10) and γ–CH groups (C–3, C–5, and C–7) showed singlet at δ1.63 confirmed by signals δ1.78 (d, 2H, $J=12.5$) for β–CH$_2$ groups at C–2, C–8, C–9 positions. While δ–CH$_2$ groups at C–4, C–6, C–10 positions and CH groups at C–3, C–5, C–7 showed singlet at δ1.65 and at δ1.9. In zinc complex, a doublet at δ1.69 having coupling constant $J=11.71$ confirmed the presence of β–CH$_2$ groups for C–2, C–8, C–9 positions. A doublet appeared at δ1.83 ($J=2.1$) for δ–CH$_2$ groups at C–4, C–6, C–10 positions and singlet for CH groups (C–3, C–5, C–7) at δ1.66. Similarly in cadmium complex, the complex confirmed by the signals of β–CH$_2$ groups (C–2, C–8, C–9), a doublet appeared at δ1.89 ($J=7.7$) for δ–CH$_2$ groups for C–4, C–6, C–10 positions and for γ–CH groups (C–3, C–5, C–7) singlet at δ1.27.

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

| S.No | Compound | Chemical formula | C    | H    | N    | Cl/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$_2$MgN | 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$_2$CaN | 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$_{32}$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$_{32}$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 + Fe chloride | C$_{20}$H$_{32}$FeClN$_2$ | 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$_{32}$CoN$_2$ | 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$_{32}$NiN$_2$ | 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$_{32}$ZnN$_2$ | 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$_{32}$CdGin$_2$ | Found | 49.45 | 7.05 | 5.77 | 14.60 | 23.14 |
|      |          |                  | Calculated | 49.50 | 7.10 | 5.81 | 14.66 | 23.17 |

Figure 2: Proposed structure of amantadine metal complexes.

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

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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