New Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Zn(II), Cd(II), and Hg(II) Gibberellate Complexes: Synthesis, Structure, and Inhibitory Activity Against COVID-19 Protease

Moamen S. Refat[a,*], T. Altalhi[a], Safyah B. Bakare[b], Ghaferah H. Al-Hazmi[c], and Kehkashan Alam[d]

[a] Department of Chemistry, College of Science, Taif University, P.O. Box 11099, Taif, 21944 Saudi Arabia
[b] Faculty of Education, Shaqra University, Al Muzahimiyah, Shaqra, Riyadh Province, P.O. Box 205, 11972 Saudi Arabia
[c] Department of Chemistry, College of Science, Princess Nourah bint Abdulrahman University, Riyadh, 11671 Saudi Arabia
[d] Department of Chemistry, Faculty of Science, Aligarh Muslim University, Aligarh, 202002 India
*Corresponding author: moamen@tu.edu.sa

Received December 29, 2020; revised February 8, 2021; accepted May 6, 2021

Abstract—Transition metals such as Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Zn(II), Cd(II), and Hg(II) have been reacted with gibberellic acid (HGA) to give novel complexes, and those have been characterized by physical, spectral and analytical methods. The plant hormone gibberellate acts as a deprotonated bidentate ligand in the complexation reaction with central metal ions in the ratio 1:2 (Mn[II] : GA). The complexes [M(GA)2(H2O)2], where [M = Mn(II), Co(II), and Ni(II)] form octahedral structures, while [M(GA)2] complexes [M = Zn(II), Cd(II), and Hg(II)] display four-coordination geometry. The octahedral structures of Cr(III) and Fe(III) complexes are characterized by the general formula [M(GA)2(H2O)(Cl)]. Computational study carried out has determined possible interactions of the complexes with COVID-19 (6LU7).

Keywords: gibberellic acid; chelation; transition metals, COVID-19

DOI: 10.1134/S1070363221050194

INTRODUCTION

Gibberellic acid (HGA) is a tetra-terpenoid compound [1] that acts as a plant hormone stimulating plants growth and development. Understanding the appropriate mechanism of HGA transport and action upon plant growth, flower development, sexual expression, grain development, and seeds germination is the objective of extensive research [2, 3].

So far there are no publications on metals chelation with gibberellic acid, except our published paper devoted to the structural, morphological and biological properties of (NH4)2[PtL(H2O)2]Cl3·2H2O, [AuLCl2]·3H2O, [RuL(NH3)2Cl2]·6H2O, [VL(NH3)2Cl2]·2H2O, and [SeOL(H2O)Cl]·3H2O (where L: GA) complexes with the ions of Pt(II), Au(III), Ru(III), V(III), and Se(IV) [4]. In continuation of that research, we report here new transition metals Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Zn(II), Cd(II), and Hg(II) complexes with gibberellic acid. Influence of different ions nature upon chelation is discussed. Interactions of the complexes with COVID-19 protease (6LU7) by means of molecular docking are considered.

EXPERIMENTAL

Gibberellic acid and metal chlorides were received from Sigma–Aldrich Chemical Corporation, St. Louis, Mo, USA. Those were of analytical grade and used without further purification.

Melting points of all synthesized complexes were measured on a MPS10-120 melting point apparatus. Molar conductance of the complexes was measured in DMSO (1.0×10–3 mol/dm3) solutions at 30°C on a Jenway 4010 conductivity meter. Magnetic susceptibility measurements were performed on a SHERWOOD SCIENTIFIC magnetic susceptibility balance. IR spectra (KBr discs) were recorded on a Bruker FTIR spectrophotometer. UV-Vis spectra were recorded on a UV2 Unicam UV/Vis spectrophotometer. 1H NMR spectra were measured on a Bruker DRX-250 spectrometer (600 MHz) using DMSO-d6 as a solvent. ESR spectra were measured on a JES-FE2XG EPR spectrometer. Elemental analysis of the complexes was carried out on a PerkinElmer 2400 organic elemental analyzer. Percentage of the metal ions was determined by the gravimetric method.
The complexes of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Zn(II), Cd(II), and Hg(II) with gibberellic acid were prepared by the general procedure. The desired anhydrous metal chloride salt (1 mmol) was dissolved in 20 mL of distilled water, and the solution was slowly added to 20 mL of 2 mmol methanol (95%) solution of gibberellic acid upon magnetic stirring. The pH of the reaction mixture was maintained ca 7–8 by adding 10% alcoholic ammonia solution, and the mixture was refluxed for ca 2 h. The precipitate was filtered off while hot and washed with hot methanol, diethyl ether and dried over anhydrous CaCl$_2$ in a vacuum desiccator to give the corresponding solid complex.

**[Cr(GA)$_2$(H$_2$O)(Cl)]**. Dark blue, yield 66%, mp 245°C, $\Lambda_m = 12 \ \text{cm}^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$. IR spectrum, $\nu$, cm$^{-1}$: 1604 $v_{as}$(COO), 1331 $v_s$(COO). Found, %: C 57.21; H 5.49; M 6.46. C$_{38}$H$_{44}$ClCrO$_{13}$. Calculated, %: C 57.32; H 5.57; Cr 6.53. M 796.20.

**[Fe(GA)$_2$(H$_2$O)(Cl)]**. Reddish brown, yield 69%, mp 272°C, $\Lambda_m = 17 \ \text{cm}^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$. IR spectrum, $\nu$, cm$^{-1}$: 1590 $v_{as}$(COO), 1330 $v_s$(COO). Found, %: C 57.01; H 5.50; M 6.93. C$_{38}$H$_{44}$ClFeO$_{13}$. Calculated, %: C 57.05; H 5.54; Fe 6.98. M 800.05.

**[Mn(GA)$_2$(H$_2$O)$_2$]**. Light brown, yield 71%, mp 264°C, $\Lambda_m = 10 \ \text{cm}^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$. IR spectrum, $\nu$, cm$^{-1}$: 1565 $v_{as}$(COO), 1331 $v_s$(COO). Found, %: C 58.32; H 5.88; M 6.97. C$_{38}$H$_{46}$MnO$_{14}$. Calculated, %: C 58.39; H 5.93; Mn 7.03. M 781.71.

**[Co(GA)$_2$(H$_2$O)$_2$]**. Red, yield 68%, mp 257°C, $\Lambda_m = 11 \ \text{cm}^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$. IR spectrum, $\nu$, cm$^{-1}$: 1612 $v_{as}$(COO), 1379 $v_s$(COO). Found, %: C 58.04; H 5.87; M 7.44. C$_{38}$H$_{46}$CoO$_{14}$. Calculated, %: C 58.09; H 5.90; Co 7.50. M 785.71.

**[Ni(GA)$_2$(H$_2$O)$_2$]**. Green, yield 74%, mp 266°C, $\Lambda_m = 14 \ \text{cm}^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$. IR spectrum, $\nu$, cm$^{-1}$: 1612 $v_{as}$(COO), 1332 $v_s$(COO). Found, %: C 58.07; H 5.85; M 7.40. C$_{38}$H$_{46}$NiO$_{14}$. Calculated, %: C 58.11; H 5.90; Ni 7.47. M 785.47.

**[Zn(GA)$_2$]**. White, yield 64%, mp 283°C, $\Lambda_m = 9 \ \text{cm}^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$. IR spectrum, $\nu$, cm$^{-1}$: 1621 $v_{as}$(COO), 1333 $v_s$(COO). Found, %: C 60.21; H 5.56; M 8.46. C$_{38}$H$_{42}$ZnO$_{12}$. Calculated, %: C 60.36; H 5.60; Zn 8.65. M 756.12.

**[Cd(GA)$_2$]**. White, yield 66%, mp 289°C, $\Lambda_m = 13 \ \text{cm}^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$. IR spectrum, $\nu$, cm$^{-1}$: 1561 $v_{as}$(COO), 1330 $v_s$(COO). Found, %: C 56.77; H 5.20; M 13.78. C$_{38}$H$_{42}$CdO$_{12}$. Calculated, %: C 56.83; H 5.27; Cd 14.00. M 803.16.

**[Hg(GA)$_2$]**. White, yield 65%, mp 222°C, $\Lambda_m = 11 \ \Omega^{-1} \ \text{cm}^2 \ \text{mol}^{-1}$. IR spectrum, $\nu$, cm$^{-1}$: 1556 $v_{as}$(COO), 1329 $v_s$(COO). Found, %: C 51.19; H 4.72; M 22.43. C$_{38}$H$_{42}$HgO$_{12}$. Calculated, %: C 51.21; H 4.75; Hg 22.50. M 891.33.

**RESULTS AND DISCUSSION**

The synthesized Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Zn(II), Cd(II), and Hg(II) complexes were insoluble in common organic solvents such as methanol, ethanol, chloroform, or benzene, but soluble in DMSO and DMF. Molar conductance values of the complexes in DMSO were low (9–17 Ω$^{-1}$ cm$^2$ mol$^{-1}$) indicating those as non-electrolytes [5]. The physical and analytical data accumulated for the complexes were in good agreement with the proposed molecular formulae viz. [M(GA)$_2$(H$_2$O)$_2$] [where M = Mn(II), Co(II), and Ni(II)], [M(GA)$_2$] [where M = Zn(II), Cd(II), and Hg(II)] and [M(GA)$_2$(H$_2$O)(Cl)] [where M = Cr(III) and Fe(III)].

IR spectra of free gibberellic acid and its complexes are listed in Table 1. In case of the complexes, the stretching vibrations $\nu$(O–H) bands were recorded in the range of 3330–3396 cm$^{-1}$ due to deprotonation of the carboxylic group and its involvement in complexation with the central metal ions. The characteristic band of $\nu$(C=O) at 1750 cm$^{-1}$ of the free ligand was recorded at the same frequency as in IR spectra of the complexes. The band at 1660 cm$^{-1}$ assigned to the $\nu$(C=O) of free HGA was absent in the spectra of the synthesized complexes. There were recorded two new vibration bands in the ranges of 1621–1556 and 1379–1329 cm$^{-1}$ assigned to $v_{as}$(C=O) and $v_s$(C=O) of the carboxylate group. The calculated values of $[\Delta \nu$(COO)] (Table 2) that were in the range of 288–227 cm$^{-1}$ confirmed the bidentate coordination modes [5–7]. The new vibration bands in the range of 644–537 cm$^{-1}$ were assigned to $\nu$(M–O) [6].

**UV-Vis spectra** bands recorded for HGA in the range of 200–300 nm were assigned to $\pi\rightarrow\pi^*$ transitions. The broad band observed in the visible region of the complexes spectra was attributed to $d\rightarrow d$ transitions of the metal ions.

Electronic spectrum of Cr(III) complex exhibited the spin transitions at 393, 451 and 566 nm due to $^4A_{2g} \rightarrow ^4T_{1g}(P)(v_3)$, $^4A_{2g} \rightarrow ^4T_{1g}(F)(v_2)$, and $^4A_{2g} \rightarrow ^4T_{2g}(F)(v_1)$, respectively, and indicated an octahedral geometry of the complex, which was supported by $v_2$ to $v_1$ ratio of...
1.25 [7]. At room temperature magnetic moment of the complex was measured to be 3.61 B.M., close to the spin only value suggesting an octahedral geometry around chromium ion [8].

The spectrum of Mn(II) demonstrated the bands at 806 and 823 nm of the electronic transfers $^6A_{1g} \rightarrow ^4T_{2g}(G)$ and $^6A_{1g} \rightarrow ^4T_{1g}(G)$, respectively, and proposed the octahedral structure of Mn(II) ion [7]. The effective magnetic moment value of the complex was 5.92 B.M.

The spectrum of Fe(III) complex demonstrated the bands at 652 nm ($\nu_1$), 470 nm ($\nu_2$) and 447 nm ($\nu_3$) assigned to the transitions $^6A_{1g} \rightarrow ^4T_{1g}(D)$, $^6A_{1g} \rightarrow ^4T_{1g}$ and $^6A_{1g} \rightarrow ^4T_{2g}$, respectively. The magnetic moment value of 5.55 B.M. confirmed the high spin octahedral geometry of the complex [7].

The spectrum of Co(II) complex contained four bands at 308, 381, 680, and 820 nm attributed to C–T mixed with $^4T_{1g}(F) \rightarrow ^4T_{1g}(P)$, $^4T_{1g}(F) \rightarrow ^4A_{2g}$ and $^4T_{1g}(F) \rightarrow ^4T_{2g}(F)$ respectively assigned to octahedral Co(II) ion [9–12], which was confirmed by the effective magnetic moment value of 4.75 B.M. assigned to three unpaired electrons per Co(II) ion.

The spectrum of Ni(II) complex exhibited three electronic transition bands at 811, 611 and 386 nm assigned to $^3A_{2g} \rightarrow ^3T_{2g}(F)$ ($\nu_1$), $^3A_{2g}(F) \rightarrow ^3T_{1g}(F)$ ($\nu_2$) and $^3A_{2g}(F) \rightarrow ^3T_{2g}(P)$ ($\nu_3$) transitions, respectively.
attributed to octahedral geometry [7]. The $\mu_{\text{eff}}$ value of 3.20 B.M. corresponded to two unpaired electrons per Ni(II) ion with the ideal six-coordinated configuration.

The ratio of $\nu_2/\nu_1$ (1.32) supported the octahedral structure of the complex [7, 8].

The Zn(II), Cd(II), and Hg(II) complexes were determined to be diamagnetic demonstrating no d-d bands and their spectra demonstrated only charge transfer bands.

$^1$H NMR spectra. Gibberellic acid. $^1$H NMR spectrum, $\delta$, ppm: 1.07 s (3H, CH$_3$), 1.66 d (1H, $J = 6.6$ Hz, C$_{11}$H), 1.71–1.74 m (3H, C$_{4\beta}$H, C$_5$H, C$_6$H), 1.84 d (1H, $J = 6.6$ Hz, C$_{11}$H), 1.86 m (1H, C$_6$H), 1.91 m (1H, C$_4$H), 2.11 d (1H, $J = 16.2$ Hz, C$_8$H), 2.17 d (1H, $J = 16.2$ Hz, C$_9$H), 2.48 d (1H, $J = 10.6$ Hz, C$_{10a}$H), 3.02 d (1H, $J = 10.2$ Hz, C$_{10}$H), 3.55 d (1H, $J = 3.16$ Hz, C$_2$H), 3.87 s (1H, C$_7$OH), 4.85 s (1H, C$_2$OH), 5.10 d (1H, $J = 8.16$ Hz, C$_{\text{methylen}}$H), 5.56 d (1H, $J = 8.12$ Hz, C$_{\text{methylen}}$H), 5.78 m (1H, C$_3$H), 6.32 d (1H, $J = 9.36$ Hz, C$_4$H), 12.55 sb (1H, COOH).

The combination of microanalytical and spectroscopic characteristics of the gibberellic acid (Fig. 1) and its complexes (Fig. 2) indicated that the deprotonated acid acted as a bidentate chelate towards the studied metal ions giving the complexes [M(GA)$_2$(H$_2$O)$_2$] (where M = Mn(II), Co(II), and Ni(II)), [M(GA)$_2$] (where M = Zn(II), Cd(II), and Hg(II)), and [M(GA)$_2$(H$_2$O)(Cl)] (where M = Cr(III) and Fe(III)) (Fig. 2).

Molecular docking. In this study Auto Dock (ADT) programming was used for the docking procedure. Optimization of the ligand was performed prior to docking by Avogadro version 1.2. The structure of COVID-19 protease (6LU7) was downloaded from the Protein Data Bank (http://www.rcsb.org) [10]. In the AutoDock Tools, the 6LU7 was prepared for docking by adding polar hydrogen bonds and Kollman & Gasteiger charges. We characterized the grid size for the receptor, and Lamarckian Genetic Algorithm was appointed to do the molecular docking as portrayed in this study. The

$$\text{Cd(II) complex. } ^1\text{H NMR spectrum, } \delta, \text{ ppm: } 1.02 \text{ s (3H, CH}_3\text{), } 1.57 \text{ d (1H, } J = 6.6 \text{ Hz, C}_{11}\text{H), } 1.61-1.63 \text{ m (3H, C}_{\text{4}\beta}\text{H, C}_5\text{H, C}_6\text{H), } 1.76 \text{ d (1H, } J = 6.6 \text{ Hz, C}_{11}\text{H), } 1.83 \text{ m (1H, C}_8\text{H), } 2.03 \text{ m (1H, C}_9\text{H), } 2.11 \text{ d (1H, } J = 11.96 \text{ Hz, C}_{9}\text{H), } 2.38 \text{ d (1H, } J = 6.8 \text{ Hz, C}_9\text{H), } 2.46 \text{ d (1H, } J = 10.68 \text{ Hz, C}_{10a}\text{H), } 3.01 \text{ d (1H, } J = 10.6 \text{ Hz, C}_{10}\text{H), } 3.12 \text{ d (1H, } J = 13.64 \text{ Hz, C}_7\text{H), } 4.78 \text{ m (1H, C}_3\text{H), } 5.03 \text{ s (1H, C}_{\text{methylen}}\text{H), } 5.61 \text{ s (1H, C}_2\text{OH), } 5.71 \text{ d (1H, } J = 3.56 \text{ Hz, C}_{\text{methylen}}\text{H), } 5.73 \text{ d (1H, } J = 3.60 \text{ Hz, C}_{\text{methylen}}\text{H), } 6.26 \text{ d (1H, } J = 9.36 \text{ Hz, C}_9\text{H).}$$
output obtained was further analyzed and visualized utilizing the discovery studio program.

It was apparent that the complexes under study might have one-of-a-kind effects on COVID-19 protease. The active sites of 6LU7 were revealed from the PDB files using discovery studio (Table 3). The helical models of the compounds with 6LU7 are presented in Fig. 3, and the most conceivable docking present among 6LU7 and various compounds and interactions with different amino acids are represented in Fig. 4. The highest binding energy

| Complex | Binding free energy, kcal/mol | Total intermolecular energy, kcal/mol | Inhibition constant, μM | Interacting amino acids |
|---------|-------------------------------|--------------------------------------|-------------------------|-------------------------|
| Cd(II)  | −7.72                         | −9.37                                | 2.190                   | Glu166, Val3, Met49     |
| Hg(II)  | −7.27                         | −8.92                                | 4.690                   | Phe140, Leu141, Asn142, Glu166, Asn119 |
| Cr(III) | −6.77                         | −8.69                                | 10.850                  | Asn142, Val3, Glu166, Gln189 |
| Mn(II)  | −9.48                         | −11.67                               | 0.112                   | Ala193, Gly183, Thr190, Arg188, Gly179, Pro184 |
| Fe(III) | −5.89                         | −7.98                                | 47.960                  | Glu166, Val3, Leu4, Asn142, Leu141 |
| Co(II)  | −8.34                         | −10.54                               | 0.766                   | Val3, Met49, Leu141, Asn142, Asn119, Thr24 |
| Ni(II)  | −7.41                         | −9.80                                | 3.710                   | Met49, Gln189, Leu4, Val3, Ala2, |
| Zn(II)  | −7.76                         | −9.55                                | 2.050                   | Ala194, Asp197, Lys137, Leu286 |

Fig. 3. Helical models of giberelette complexes with (a) Co(II); (b) Cr(III); (c) Cd(II); (d) Mn(II); (e) Hg(II); (f) Fe(III); (g) Zn(II); and (h) Ni(II).
was determined for Mn(II) gibberellate complex (Table 3), which might act as a potential inhibitor of 6LU7.

**FUNDING**

Taif University Researches Supporting Project number (TURSP-2020/01), Taif University, Taif, Saudi Arabia.

**CONFLICT OF INTEREST**

No conflict of interest was declared by the authors.

**REFERENCES**

1. Gupta, R., and Chakrabarty, S.K., *Plant Signaling & Behavior*, 2013, vol. 8, no. 9, p. 1, article no. e25504. https://doi.org/10.4161/psb.25504

2. Katsumi, M., Foard, D.E., and Phinney, B.O., *Plant Cell Physiol.*, 1983, vol. 24, p. 379. https://doi.org/10.1093/oxfordjournals.pcp.a076527

3. Proebsting, W.M., Hedden, P., Lewis, M.J.,
4. El-Sayed, M.Y., Fetooh, H., Refat, M.S., Eldaroti, H.H., Adam, A.M.A., and Saad, H.A., *J. Mol. Liquids*, 2019, vol. 296, p. 111895. https://doi.org/10.1016/j.molliq.2019.111895

5. Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., Duan, Y., Yu, J., Wang, L., Yang, K., Liu, F., Jiang, R., Yang, X., You, T., Liu, X., Yang, X., Bai, F., Liu, H., Liu, X., Guddat, L.W., Xu, W., Xiao, G., Qin, C., Shi, Z., Jiang, H., Rao, Z., and Yang, H., *Nature*, 2020, vol. 582, p. 289. https://doi.org/10.1038/s41586-020-2223-y

6. Alam, K. and Khan, I.M., *Org. Electron.*, 2018, vol. 63, p. 7. https://doi.org/10.1016/j.orgel.2018.08.037

7. Deacon, G.B. and Phillips, R.J., *Coord. Chem. Rev.*, 1980, vol. 33, p. 227. https://doi.org/10.1016/S0010-8545(00)80455-5

8. Vogel’s, *Textbook of Quantitative Chemical Analysis*, Longman Scientific and Technical Publishers, New York: John Wiley & Sons, 1989.

9. Nakamoto, K., *Infrared Spectra of Inorganic and Coordination Compounds*, New York: Wiley, 1970.

10. Lever, A.B.P., *Inorganic Electronic Spectroscopy*, Amsterdam: Elsevier, 1997, 2nd ed.

11. Figgis, B.N., *Introduction to Ligand Field Theory*, New York: Wiley, 1978.

12. Yongxiang, M., Zhengzhi, Z., Yun, M., and Gang, Z., *Inorg. Chim. Acta*, 1989, vol. 165, p. 185. https://doi.org/10.1016/S0020-1693(00)83237-5