Coordination of isoniazid, an anti-tuberculosis (TB) drug with chromium, molybdenum, and tungsten metal carbonyls

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Isoniazid, an anti-tuberculosis (TB) drug has been coordinated with chromium, molybdenum, and tungsten metal carbonyls and three new zero-valent complexes fac-[M(CO)3(isoniazid)] (M = Cr, Mo, and W; 4, 5, and 6) (isoniazid = 4-H2NNHNOC5H4N) have been synthesized. Reaction of the complex precursors fac-[M(CO)3(CH3CN)] (M = Cr, Mo, and W; 1, 2, and 3) prepared ‘in situ’ with three equivalents of isoniazid in methanol at room temperature afforded high yields of isoniazid substituted metal carbonyl complexes 4, 5, and 6. The complexes have been characterized by elemental analyses, mass analysis, thermal analysis (TGA, EGA), FT-IR, UV/visible and 1H NMR spectroscopic techniques and powder X-ray diffraction (XRD). The FT-IR (KBr and methanol solution) spectra of the complexes 4, 5, and 6 exhibit two bands corresponding to v(C=O) of metal carbonyl groups and v(C=O) of coordinated isoniazid molecules. The bulky –CONHNH2 group of isoniazid molecules made more impact on the M–C bond strength of metal carbonyls and affects their fundamental modes of vibrations leading to the appearance of more number of v(C=O) bands. These steric effects are also reflected in the 1H NMR spectral features of the complexes when considering the complexes as a whole, wherein the four protons on the pyridine ring of the coordinated isoniazid molecules resonate at different chemical shifts. All the three complexes exhibit similar XRD pattern suggesting similar geometry.

Transition metal complexes with ligands of biological importance1 have received immense interest in bioinorganic chemistry. In recent years, there is considerable interest in the design and synthesis of new transition metal complexes with a variety of biologically important ligands2 for therapeutic and diagnostic applications3-5. One such characteristic development in organometallic chemistry is the emergence of ‘bioorganometallic chemistry’ which comprises the synthesis, characterization, reactions and applications of metal carbonyl complexes with ligands of biological importance6,7. These complexes offer the possibility of being used as labeling agents in carbonylmetallic immunoassay (CMIA)7.

The major aspect in carbonylmetallic immunoassay is the design and synthesis of labeling agents. This can be achieved by selecting suitable ligands of bioimportance including various drugs and their coordination with metal carbonyl complexes. Isoniazid is one of the well-known isonicotinic acid derivatives which is used as an anti-tuberculosis drug8,9 and also exhibit bacterial mutagenecity10. Its derivatives also inhibit copper (II)-containing serum amine oxidase11,12. As a part of our research to synthesize new metal carbonyl complexes with ligands of bioimportance13,14, we have been concentrating on the applicability of the complexes 1, 2, and 3 as the complex precursors. The complexes 1, 2, and 3 were found to be good complex precursor15 for the synthesis of new complexes not easily made by other synthetic routes. Only few complexes have been synthesized by utilizing these intermediate species16-22. In order to explore the synthetic utility of these complex precursors, to synthesize new metal carbonyl labeling agents and to study the coordination behaviour of isoniazid with metal carbonyls, we have synthesized and characterized the isoniazid coordinated metal carbonyl complexes 4, 5, and 6. The synthetic procedure adopted for the preparation of the complexes 4, 5, and 6 are shown in Scheme 1.

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Materials and Methods

All reactions were carried out in a Schlenk line under an atmosphere of purified dry argon. All chemicals and solvents were of reagent grade. The solvents were purified by standard methods and flushed with argon before use. Molybdenum hexacarbonyl (Merck), Chromium hexacarbonyl, tungsten hexacarbonyl, and CD$_2$COCD$_3$ (Sigma-Aldrich) were used without further purification. Isoniazid was recrystallised from methanol.

Elemental analyses (C, H, and N) were performed using a Heraeus CHN-O rapid elemental analyzer. FAB-MS was carried out on a VG 70-70H spectrometer. TGA was carried out on a Perkin-Elmer TGA 7 Thermogravimetric analyzer. EGA was carried out on a Balzers GAM 440 evaporated gas analyzer. FT-IR spectra were recorded on a Bruker IFS 66V FT-IR spectrometer and Perkin-Elmer 1760 FT-IR spectrometer as potassium bromide pellets or methanol solution. UV-Vis spectra were recorded in CH$_3$COCD$_3$ solution with tetramethylsilane as internal standard. Powder X-ray diffraction (XRD) patterns were obtained at room temperature using a Rigaku Miniflex X-ray diffractometer. The XRD pattern of the complexes were recorded using Fe-filtered Co-K$_\alpha$ ($\lambda = 1.7902$ Å) radiation. The 20 angle was scanned at a rate of 2°/min$^{-1}$.

Preparation of complexes fac-[$Cr(CO)_6$(isoniazid)$_3$] (4)

About 0.15 g of Cr(CO)$_6$ (0.6816 mmol) dissolved in 25.0 ml of CH$_3$CN was refluxed for 4 h to produce fac-[$Cr(CO)_6$(CH$_3$CN)$_3$] (1) 'in situ'. The solution of 1 was cooled to room temperature and treated with three equivalents of isoniazid (0.2804 g, 2.0449 mmol) in methanol (18.0 ml).

The initial bright yellow solution of 1 changes to deep orange, red and finally to reddish-brown. This solution was stirred at room temperature for 30 min, filtered and evaporated in vacuo to give the reddish-brown solid, fac-[$Cr(CO)_6$(isoniazid)$_3$] (4). Yield: 0.32 g (85.75%). [Found: C, 46.21; H, 3.87; N, 23.10. Calc. for C$_9$H$_2$N$_3$O$_6$Cr: C, 46.07; H, 3.87; N, 23.03%]. FT-IR (KBr disc, $\nu_{max}$/cm$^{-1}$): 2066w; 1930vs; 1899sh; 1827s; 1741vw ($\nu$(C=O)); 1665vs [v(C=O)]. FT-IR (MeOH, $\nu_{max}$/cm$^{-1}$): 2051s; 2041s; 1937s [v(C=O)]; 1685m; 1679m; 1663m [v(C=O)]. UV-Vis (MeOH, $\lambda_{max}$, nm (e)): 388 (4532); 266 (17636); 224 (16401); 215 (15026). $^1$H NMR (CD$_2$COCD$_3$, 297 K): $\delta$ 7.64 (1H, H$_b$, s, isoniazid at position-2); 7.75 (5H, H$_b$ & H$_t$, s, H$_b$ of isoniazid at positions-1, 2, and 3; H$_t$ of isoniazid at positions-1 and 3); 8.70 (6H, H$_b$ & H$_t$, s, isoniazid at positions-1, 2, and 3); 9.59 (1H, s, very weak, -NH of isoniazid at position-2); 9.96 (2H, s, -NH of isoniazid at positions-1 and 3).

fac-[$Mo(CO)_6$(isoniazid)$_3$] (5)

This brown-black solid complex was obtained following a similar procedure as described for complex 4 by reacting fac-[$Mo(CO)_6$(CH$_3$CN)$_3$] (2) with isoniazid. During the synthesis of complex 5, the initial pale yellow solution of 2 changes colour to orange, reddish-brown and finally to brown-black. Yield: 0.425 g (94.86%). [Found: C, 42.52; H, 3.63; N, 21.38. Calc. for C$_9$H$_2$N$_3$O$_6$Mo: C, 42.65; H, 3.58; N, 21.32%]. FT-IR (KBr disc, $\nu_{max}$/cm$^{-1}$): 2066w; 2012m; 1900vs; 1971sh; 1832w; 1747s [v(C=O)]; 1664vs [v(C=O)]. FT-IR (MeOH, $\nu_{max}$/cm$^{-1}$): 2069m; 2053s; 2035w; 2025w; 1934s [v(C=O)]; 1703s; 1684s; 1675s [v(C=O)]. UV-Vis (MeOH, $\lambda_{max}$/nm (e)): 402 (2306); 252 (24350); 232 (24661); 204 (37701). $^1$H NMR (CD$_2$COCD$_3$, 297 K): $\delta$ 7.69 (1H, H$_b$, s, isoniazid at position-2); 7.74 (4H, H$_b$ & H$_t$, m, H$_b$ of isoniazid at positions-2 and 3; H$_t$ of isoniazid at positions-1 and 3); 7.82 (1H, H$_b$, m, isoniazid at position-1); 8.66 (5H, H$_b$ & H$_t$, m, H$_b$ of isoniazid at positions-2 and 3; H$_t$ of isoniazid at positions-1, 2, and 3); 8.74 (1H, H$_b$, m, isoniazid at position-1).

fac-[$W(CO)_6$(isoniazid)$_3$] (6)

This reddish-brown solid complex was obtained following a similar procedure as described for complex 4 but, fac-[$W(CO)_6$(CH$_3$CN)$_3$] (3) was generated from W(CO)$_6$ after 48 h. During the synthesis of complex 6, the initial bright yellow solution of 3 changes to orange, red and finally to reddish-brown. Yield: 0.24 g (82.89%). [Found: C, 36.95; H, 3.16; N, 18.65. Calc. for C$_9$H$_2$N$_3$O$_6$W: C, 37.13; H, 3.12; N, 18.56%]. FT-IR (KBr disc, $\nu_{max}$/cm$^{-1}$): 2007m; 1884ws; 1819w; 1771s [v(C=O)]; 1664vs [v(C=O)]. FT-IR (MeOH, $\nu_{max}$/cm$^{-1}$): 2051s, broad; 2037s; 1934s; 1889sh; 1881m [v(C=O)]; 1692m; 1674s;
Results and Discussion

The isoniazid coordinated complexes 4, 5, and 6 are coloured solids and were synthesized in near quantitative yields. The complexes are quite stable in air. The stability of the complexes at ambient conditions decreases in the following order: Mo > W > Cr. The complexes are soluble in methanol, ethanol, acetone, acetonitrile, THF and insoluble in water, CHCl₃, CH₂Cl₂, benzene, and toluene.

The composition of the complexes was determined by elemental analysis. The resultant analytical data are in good agreement with the composition of the complexes as [M(CO)₃(isoniazid)]₃ (M = Cr, Mo, and W; 4, 5, and 6). The FAB-mass spectrum of the molybdenum complex 5 was recorded. The natural isotopic abundance for the metal has a wide range of mass numbers. Thus a series of peaks were observed for a particular fragment. A bunch of peaks at mass numbers (m/z) in the range 229-237 can be assigned to (Mo + isoniazid)⁺, 120-128 to [Mo + (CO)]⁺, 148-156 to [Mo + (CO)₂]⁺, 176-184 to [Mo + (CO)₃]⁺, 132-140 to [Mo + (CO)₂C]⁺, 104-112 to [Mo + C]⁺, 92-100 to Mo⁺, 257-265 to [Mo(isoniazid)(CO)]⁺, and 285-293 to [Mo(isoniazid)(CO)₂]⁺. The peak at mass number 185 can be assigned to the M+1 ion peak for the fragment [Mo + (CO)₃]⁺. Here M denotes the carbon atom of the coordinated carbonyl groups. Since the pyridine-based ligands are bound more weakly than CO with the metal, the isoniazid ligands are preferentially detached from the parent complex. Therefore, the peak corresponding to the parent molecular ion [Mo(CO)₃(isoniazid)]⁺ was not observed.

The pyridine-based ligands and their metal complex derivatives exhibit interesting thermal behaviour. Thermogravimetric analysis (TGA) of the complexes 4, 5, and 6 were studied under nitrogen atmosphere in the temperature region 50-800°C at a heating rate of 20°C min⁻¹. The TGA curves for the complexes 4, 5, and 6 are given in Fig. 1. In the complexes there are three major weight loss regions: (i) corresponding to the removal of coordinated CO groups in the region ~ 70-170°C; (ii) the decomposition of the coordinated isoniazid ligands from the metal complexes started at ~ 160°C to the complete detachment or decomposition up to ~ 400°C; and (iii) the decomposition of the corresponding metal carbonylate to metal oxide and/or metal oxide to metal at the latter high temperature region.

Thermogravimetric studies on these complexes indicate that three molecules of isoniazid are coordi-
nated to the metal in addition to three molecules of CO. This observation is in good accordance with the analytical data. The analytical, mass spectral and thermogravimetric data confirm the composition of the complexes as \([\text{M(CO)}_3\text{(isoniazid)}_3]\) (M = Cr, Mo, and W; 4, 5, and 6).

Evolved gas analysis (EGA) suggests that the coordination of both CO and isoniazid groups at the metal centre. The EGA profiles for the complexes 4, 5, and 6 are given in Fig. 2. In complex 4, most of the CO evolution appeared at two different temperatures 170 and 330°C. In complex 5, CO evolution occurred at two temperatures: a sharp peak at 170°C and a broad one at 230°C. The tungsten analogue 6 exhibits a less intense broad at 160°C and thereafter there is a gradual decrease in the CO evolution. In all the complexes there is a peak corresponding to the loss of NH\(_3\) (m/z 17). This NH\(_3\) peak comes from the fragmentation of the coordinated isoniazid groups. The other observed EGA peaks at mass numbers 18, 44, 51, 77, 78, 104, and 106 constitute the remaining fragmented species of isoniazid ligand. Careful analysis on the evolution of these species implies that, each complex follows a distinct pattern in the evolution of fragmented species. This is attributed to the difference in the bond strengths of the coordinated isoniazid ligands to metal atoms Cr, Mo, and W\(^{25,30}\) and thermal energy required for the breaking-away of the species from the coordinated isoniazid groups. This argument also holds good for the difference in thermal behaviour (TGA) exhibited by the complexes. EGA study suggests the coordination of both CO and isoniazid at the metal centre. It is a well-established fact that cleavage of CO moiety from organic compounds by thermal analysis is extremely difficult\(^{31}\). Hence, the possibility of CO evolution from isoniazid is much less compared to the coordinated CO groups.

**FT-IR spectral study**

In the FT-IR spectra (KBr) of the complexes 4, 5, and 6, there are at least two strong bands corresponding to v(C=O) at 1930 and 1827 cm\(^{-1}\) (complex 4) and 1900, 1774 cm\(^{-1}\) (complex 5) and 1884, 1771 cm\(^{-1}\) (complex 6) in addition to two or three weak bands. The observation of these strong bands suggests the presence of three CO groups arranged mutually cis to each other\(^{32,33}\) and facial geometry. All the complexes exhibit a strong band corresponding to v(C=O) due to the acid hydrazide group of isoniazid coordinated to the metal atom\(^{34}\). Moreover, the appearance of single v(C=O) band also suggests the coordination of three isoniazid ligands cis to each other. The combined analysis of both v(C=O) and v(C=O) bands confirms that the CO groups and isoniazid ligands are arranged in the facial geometry having C\(_3\)v symmetry.

In all the complexes two or three weak bands corresponding to v(C=O) were observed in addition to strong bands. This apparently shows that the three CO

![Fig. 2—EGA profiles of the complexes (a) fac-\([\text{Cr(CO)}_3\text{(isoniazid)}_3]\) (4); (b) fac-\([\text{Mo(CO)}_3\text{(isoniazid)}_3]\) (5) and (c) fac-\([\text{W(CO)}_3\text{(isoniazid)}_3]\) (6).]
groups experience interaction with the adjacently coordinated isoniazid in the crystal lattice. There are reports on complexes of group VI B metal carbonyls exhibit more number of carbonyl stretching bands in the facial geometry\textsuperscript{16,32,35,37}, contrary to the expected number of two bands for C\textsubscript{3v} symmetry. The reasons for such an observation may be due to the reduction in the Lewis acidity of the metals\textsuperscript{37} by the incorporation of strongly σ-donating ligands like isoniazid, which in turn decreases the metal-carbon bond strength of each coordinated carbonyl group in the complexes and weakening the M–C bond resulting in greater interaction of the CO groups with the metal and the coordinated isoniazid. In addition, the bulky isoniazid\textsuperscript{38} sterically hinder at the vicinity of M–CO groups affecting the fundamental vibrational modes of v(C=O). Isoniazid ligands also form intermolecular hydrogen bond\textsuperscript{38} with H, N, and O atoms of the complexes in the crystal lattices. Thus, these effects also make an impact on the v(C=O) mode and increases the number of v(C=O) bands. The intermolecular interaction between CO groups in the crystal lattice\textsuperscript{39} also contribute little to this observation.

The FT-IR spectra of the complexes in methanol solution exhibit bands corresponding to v(C=O) and v(C=O). The carbonyl stretching bands, v(C=O) appeared in the region 2050 cm\textsuperscript{-1} and 1900 cm\textsuperscript{-1}. This observation is in accordance with the assignment of facial geometry to the complexes. In methanol solution each isoniazid groups have their own interactions such as: intermolecular hydrogen bonding between the three isoniazid groups, hydrogen bonding with the solvent molecules, interaction with the adjacent metal carbonyl groups. These molecular interactions makes the v(C=O) mode of each isoniazid ligands to appear at separate wavenumber positions.

The \textsuperscript{1}H NMR spectra of the complexes 4, 5, and 6 were recorded in CD\textsubscript{3}COCD\textsubscript{3} at 297 K. The proton assignments on the ligand and position of the ligand assignments and the proposed structure of the complexes 4, 5, and 6 are shown in I. In all the complexes, there are at least two sets of multiplet signals one at around δ 8.0-9.0 ppm and another around 7.0-8.0 ppm. This corresponds to the presence of two different kinds of protons on the pyridine ring of the isoniazid ligands, one ortho to the coordinated nitrogen atom (H\textsubscript{a}H\textsubscript{a}') and another ortho to the acid hydrazone group, –CONHNH\textsubscript{2} (H\textsubscript{b}H\textsubscript{b}'). The calculated integral value of each multiplet is equal to six protons, i.e., H\textsubscript{a}H\textsubscript{a}' and H\textsubscript{b}H\textsubscript{b}' protons on three isoniazid ligands. There is further splitting within each multiplet suggesting that among the four protons on the pyridine ring of isoniazid, each proton resonate at different chemical shift positions (δ). i.e., within H\textsubscript{a}H\textsubscript{a}' protons, H\textsubscript{a} and H\textsubscript{a}' exhibit characteristic signals. In a similar manner H\textsubscript{b} and H\textsubscript{b}' protons exhibit characteristic signals. This suggests that three isoniazid ligands are cis to each other and three CO groups are also cis to each other. In all the complexes the isoniazid at position-2 experiences more interactions with other two isoniazid ligands at positions-1 and 3 and the steric interactions are reflected in the magnetically different environments of the H\textsubscript{a}H\textsubscript{a}' and H\textsubscript{b}H\textsubscript{b}' protons, and the resulting \textsuperscript{1}H NMR signals are observed at different δ values.

The \textsuperscript{1}H NMR spectrum of the molybdenum complex 5 shows that the H\textsubscript{a} proton at position-1 has interaction only with the adjacent CO group at C-5. Thus this proton exhibits a multiplet at δ 8.74 ppm. The calculated integral value of this signal is equal to one proton. The other five H\textsubscript{a} protons i.e., H\textsubscript{a} of isoniazid at positions-2 and 3 and H\textsubscript{a}' of isoniazid at position-2 experiences more interactions with other two isoniazid ligands at positions-1 and 3 and the steric interactions are reflected in the magnetically different environments of the H\textsubscript{a}H\textsubscript{a}' and H\textsubscript{b}H\textsubscript{b}' protons, and the resulting \textsuperscript{1}H NMR signals are observed at different δ values.

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{structure.png}
\caption{Proposed structure (c) for the complexes fac-[M(CO)\textsubscript{5}isoniazid\textsubscript{3}] (M = Cr, Mo, and W; 4, 5, and 6) with proton assignments on the ligand (a) and position of the ligand assignments (b).}
\end{figure}
sitions-1, 2, and 3 are present more or less in a similar environment and exhibit a multiplet at 8.66 ppm. The calculated integral value of this signal is equal to five protons. In a similar manner the H₆ proton of the isoniazid at position-1 exhibits a multiplet at 7.82 ppm. The calculated integral value of this signal is equal to one proton. All the other H₅ and H₆' protons (H₅ of isoniazid at positions-2 and 3; H₆' of isoniazid at positions-1 and 3) exhibits a multiplet at 7.74 ppm except the H₆' of isoniazid at position-2 which shows a separate singlet at 7.69 ppm. The calculated integral value of these later two signals is equal to five protons. The H₆' proton of isoniazid at position-2 is under more steric interaction exhibited by the adjacent isoniazid groups at positions-1 and 3. Moreover the H₆' proton also experiences more interaction due to the hydrogen bonding between the H, N, and O atoms of acid hydrazide group on each isoniazid ligand. As a result the signal is shifted to a lower δ value.

The corresponding tungsten complex 6 exhibits the following ¹H NMR pattern: the H₆ proton at position-1 appear as a less intense doublet at δ 8.79 ppm (J of H₆,H₇ 4.6 Hz) and the H₅ proton as less intense doublet at 7.87 ppm (J of H₅,H₆ 4.6 Hz). Other H₅ and H₆' protons (H₅ of isoniazid at positions-2 and 3; H₆' of isoniazid at positions-1, 2, and 3) exhibits a multiplet at 8.71 ppm and the H₅ and H₆' protons (H₅ of isoniazid at positions-2 and 3; H₆' of isoniazid at positions-1 and 3) exhibits a multiplet at 7.78 ppm. The H₆' proton of isoniazid at position-2 shows a singlet at 7.63 ppm.

Although the chromium analogue 4 has all different chemical environment in the protons on the pyridine ring of the isoniazid group, the chromium derivatives are more susceptible to solvent attack and has less M–N and M–C bond energy. This causes more interaction between the three isoniazid ligands and/or with the metal and metal carbonyl group. Therefore, all the H₅ and H₆ protons appear as a singlet at δ 8.70 ppm and all the H₆' and H₅' protons at 7.75 except the H₆' of isoniazid at position-2, exhibits a less intense singlet at 7.64 ppm. H₅ proton of isoniazid at position-1 and H₆' proton of isoniazid at position-3 are seems to be in a similar chemical environment. But at position-1, H₅ is in the opposite side of the bulky –CONHNH₂ group whereas in position-3, H₆' is on the same side of –CONHNH₂ group. Therefore, H₅ at position-1 experiences less interaction than that of H₆' at position-3 and all other H₅ and H₆' protons at other positions. Thus the H₅ proton at position-1 appear as a separate signal and resonate at a higher δ value. These arguments holds good for the occurrence of a separate downfield signal corresponding to H₅ proton at position-1 compared to H₅' proton at position-3 and other H₅ and H₆' protons at other positions. The detailed analysis on the ¹H NMR patterns of the protons at the pyridine ring of the isoniazid ligands, coordinated in the complexes 4, 5, and 6 shows that: there is a good similarity in the chemical shift positions of these complexes with that of the complexes of similar kind, containing coordinated pyridine-based ligands with different substituted groups at the pyridine ring.

The ¹H NMR signals corresponding to –NH proton of –CONHNH₂ moiety appeared as broad weak signals due to quadruple relaxation and other steric interactions experienced by these –CONHNH₂ moieties in the complexes. The signal corresponding to –NH resonance appeared at two places. From the integral of these two signals, it was observed that the signal at higher δ value corresponding to two –NH protons and the other signal corresponds to the remaining one –NH proton. The –NH proton of isoniazid groups at positions-1 and 3 constitute the signal at higher δ value and the –NH of the isoniazid at position-2 is responsible for the signal at lower δ value. The arguments given in the previous paragraphs holds good for these observations too.

The ¹H NMR signals corresponding to –NH proton appeared at δ 9.96 ppm and 9.59 ppm in both the chromium 4 and tungsten 6 complexes. In the molybdenum complex 5, the signals corresponding to –NH proton were not observed. Among the group VI B metal carbonyls, the molybdenum complexes has the tendency to exhibit more interaction between the isoniazid groups and/or with the metal carbonyl groups. In addition to this, quadruple relaxation also play a role in the diminishing of the signals. The observed chemical shift positions for –NH signals of the complexes are in good agreement with that of –NH resonance of 2- and 3- –CONHNH₂ substituted pyridine ligands. In all the complexes the signals corresponding to –NH₂ protons of –CONHNH₂ moiety of isoniazid ligands were not observed. Large molecular interactions between the coordinated isoniazid ligands and with the adjacent CO groups and quadruple relaxation causes the –NH₂ signals unobservable.

Several unsuccessful attempts were made to grow single crystals of complexes 4, 5, and 6 for X-ray
JESUDURAI et al.: ISONIAZID COMPLEXES OF Cr, Mo, AND W CARBONYLS

1615

Fig. 3—X-ray diffractogram of the complexes (a) fac-[Cr(CO)_3(isoniazid)_3] (4); (b) fac-[Mo(CO)_3(isoniazid)_3] (5); and (c) fac-[W(CO)_3(isoniazid)_3] (6).

studies. In order to get more information regarding the arrangement of atoms in the crystal lattice and hence the molecular arrangement around the metal centre, powder X-ray diffractogram of the complexes was recorded (Fig. 3). The XRD pattern of the three complexes are quite similar in the relative intensities of the peaks, 2θ values and d-values. These observations suggest that the molecular arrangement of the ligands around the metal atoms and geometry of the complexes are same.

During the synthesis of the complexes there is a gradual colour change from the complex precursors (1, 2, and 3) to the isoniazid coordinated complexes (4, 5, and 6). This observation indicates the stepwise removal of the three coordinated CH_3CN groups (1, 2, and 3) and the subsequent coordination of three isoniazid molecules, resulting in the generation of the title complexes 4, 5, and 6. All the intermediate species are highly air and moisture sensitive and during the reaction, the complex precursors changes its colour instantaneously upon addition of isoniazid in methanol. Therefore, we are unable to isolate the intermediate species and carry out kinetic studies. Based on these observations and other analytical and physical data such as elemental analyses, Mass, TGA, FT-IR, ^1^H NMR and powder XRD we assign the structure of the complexes as shown in I(c) (M = Cr, Mo, and W; 4, 5, and 6) with the position of the ligand assignments I(b).

Conclusion

The coordination of isoniazid, an anti-tuberculosis drug with group VI B metal carbonyls has been achieved. Three new isoniazid coordinated metal carbonyl complexes fac-[M(CO)_3(isoniazid)_3] (M = Cr, Mo, and W; 4, 5, and 6) have been synthesized and characterized. Elemental, Mass and Thermogravimetric analysis on the complexes confirms the composition of the complexes as [M(CO)_3(isoniazid)_3]. The observation of single stretching band corresponding to v(C=O) suggest the coordination of isoniazid at the metal centre and further suggests the coordination three molecules of isoniazid, present cis to each other in the facial geometry of the complexes. Large steric interactions exhibited by the three bulky isoniazid groups and the intermolecular hydrogen bonding between the H, N, and O atoms of the isoniazid groups and/or with the metal carbonyl groups affected the fundamental vibrational modes of v(C=O) of metal carbonyls. These effects were also reflected in the ^1^H NMR pattern of the complexes. Differentiation of the four protons on the pyrimidine ring of the isoniazid groups, coordinated in the metal carbonyl complexes was observed. The powder X-ray diffractogram of the complexes 4, 5, and 6 exhibits a similar pattern and suggests the presence of same arrangement of atoms in the crystal lattice and geometry in all the complexes.

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