MASS SPECTRA OF SOME TETRACHLOROMETALATE FLUOROQUINOLONES COMPLEXES

[1*]C. A. Akinremi, [2]J. A. Obaleye, [1]S. Adewuyi and [1]J.F. Adediji
[1]*Department of Chemistry, University of Agriculture, Abeokuta Ogun state, Nigeria.
[2]Department of Chemistry, University of Ilorin,Ilorin, Kwara state, Nigeria.
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*Corresponding author: cakinremi2002@yahoo.com

Abstract
The mass spectra of some previously reported tetrachlorometalate complexes of some fluoroquinolones are studied here. The infrared spectra suggest ionic complexes consisting of a tetrachlorometalate ion which is electrostatically attached to the ligand. The mass spectra of the ionic complexes showed similarity in fragmentations.

Keywords: ciprofloxacin, norfloxacin, ofloxacin, fluoroquinolone metal complexes, mass spectra.

Introduction

The crystal structures of some fluoroquinolone(FQ) complexes have shown that fluoroquinolone antibiotics can participate in the formation of complexes in a number of ways.[1-6] The complexes isolated from acidic media usually contain singly and /or doubly protonated fluoroquinolones(FQs) cations and chlorometalate or simple inorganic anions. These protonated fluoroquinolones are incapable of binding to the metal ion and only electrostatic interaction exists between the drug metal ions[1]. Examples of some protonated complexes of ciprofloxacin (cf) and norfloxacin (nf) are $(cfH_2)_2[ZnCl_4].2H_2O$[7],$(cfH_2)(cfH_3)[CuCl_4]Cl.H_2O$ [8], $(nfH_2).(nfH_3)[CuCl_4]Cl.H_2O$, $(nfH_2)(nfH_3)[ZnCl_4]Cl.H_2O$[9] and $(cfH_3)[FeCl_4]Cl.H_2O$ [10].

Mass spectroscopy is employed to measure relative molecular masses from which the molecular formulae is deduced and also to detect within the molecule the places at which it prefers to fragment.

In studies of some metal-fluoroquinolone complexes, by Zupancic and co-workers,[7,11] the fast atom bombardment[FAB.MS] was performed in the mass spec using m-nitrobenzyl alcohol (NBA) as matrix. In the mass spectrum of $[Co(cf)_2].H_2O$,[11] a strong mass peak appears at m/z 720 corresponding to $[Co(cf)(cfH_2]^+$ ions. Two other strong mass peaks were observed at m/z 332 and m/z 663 corresponding to $[cfH_2]^+$ and $[(cfH)(cfH_2)]^+$ions respectively. The mass peak for the molecular ions was not observed. For ionic compounds like $[(cfH_2)_2.[ZnCl_4].2H_2O$-I,[7] intense mass peaks at m/z 332 and 663 were observed corresponding to $[cfH_2]^+$ and $[(cfH)(cfH_2)]^+$ ions respectively. For compounds $(Zn(cf)_2].3H_2O$-II,[7] m/z 725, 727 and 729 was observed corresponding to $[Zn(cf)(cfH_2)^+]$ ion. This shows the presence of direct metal-ligand bonding in compound II. The FAB.MS was also used to measure the molecular mass of some copper-ofloxacin(Ofl) complexes [12]. The most intense peak was at m/z 784.2 corresponding to the molecular ion $[Cu(Ofl)_2]^+$, and that at 424.1 corresponds to $[Cu(Ofl)]^+$. Both the water molecules and the counter anions seem to be absent in the detected ionic fragments, so they may be only weakly bonded to the main fragments.

In this paper, fragmentation patterns of four tetrachlorometalate fluoroquinolones complexes with their mass spectra are reported in other to obtain a better understanding of their structure.

Materials and Methods

Materials

All reagents were received from commercial sources. Ciprofloxacin, Norfloxacin and ofloxacin were purchased from Sigma-Aldrich Chemie, Germany.

Instrumentation

The mass spectra data were obtained with a JEOL JMS-AX505HA mass spectrometer connected to a Hewlett-Packard HP 6890 series GC system (Normal ion [MF- Linear] system) by direct fast atomic bombardment (FAB) mode, at the Department of Chemistry, University of Idaho, Moscow, ID, USA. The matrix was 3-nitrobenzylalcohol for all the samples at an accelerating voltage of 3kv. Xenon gas was used in the FAB gun.

Table 1: Relevant I.R. frequencies (cm^{-1}) of tetrachlorometalate complexes of some fluoroquinolones (in KBr)

Tentative Assignment	$\upsilon(C=O)_c$	$\upsilon(C=O)_P$	$\upsilon_{as}(OCO)$	$\upsilon_s(OCO)$
Ofloxacin	1714.1(s,s)	1626.4(s,s)	-	-

[ofH$_3$][FeCl$_4$]Cl.H$_2$O	1705.6(s,s)	1619.1(s,s)	-	-
Norfloxacin	-	1616.7(s,s)	1581(s,m)	1393(s,m)
[nfH$_2$][nfH$_3$][CuCl$_4$]Cl.H$_2$O	1699.4(s,s)	1626.4(s,s)	-	-
[nfH$_3$][FeCl$_4$]Cl.H$_2$O	1699.4(bd,s)	1645.9(bd,s)	-	-
Ciprofloxacin	-	1626.6(s,m)	1597.2(s,s)	1373.5(s,s)
[cfH$_3$][FeCl$_4$]Cl.H$_2$O	1743.3(s,m)	1641.2(s,s)	-	-

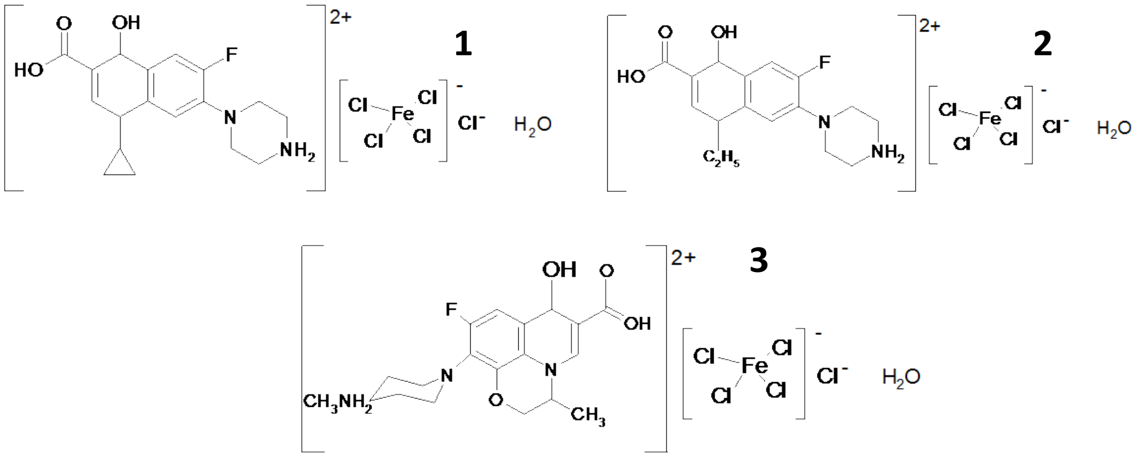


Figure 1: Ciprofloxacinium tetrachloroferrate(III) chloride Hydrate-(H$_3$cf)[FeCl$_4$]Cl.H$_2$O **2**.Norfloxacinium tetrachloroferrate(III) chloride Hydrate-(H$_3$(nf))[FeCl$_4$]Cl.H$_2$O **3.**.Ofloxacinium tetrachloroferrate(III) chloride Hydrate-(H$_3$(of))[FeCl$_4$]Cl.H$_2$O

Synthesis

The products were prepared as reported elsewhere [6,9,10]. 1.0 mmole each of the fluoroquinolone (ciprofloxacin, ofloxacin and norfloxacin) was dissolved in 10mL of 1M HCl solution. To this was added 20mL of 1.0mmole hydrated metal chloride salt ($CuCl_2.2H_2O$ $FeCl_3.6H_2O$) dissolved in 1.0M HCl. The solutions were stirred with a magnetic stirrer for 1 hr. The resulting solutions were concentrated and products collected by filtration. All the products were stored in well-labeled pre-weighed containers and dried over $CaCl_2$ in a desiccator. The products reported here are as follows; [oflH$_3$][FeCl$_4$]Cl.H$_2$O, [nfH$_3$][FeCl$_4$]Cl.H$_2$O, [nfH$_2$][nfH$_3$][CuCl$_4$]Cl.H$_2$O [9] and [cfH$_3$][FeCl$_4$]Cl.H$_2$O

Analysis

The nature of bonding of the ligands and the structure of the isolated metal complexes were elucidated on the basis of their physical and spectroscopic studies {conductivity measurements, elemental analysis, atomic absorption spectroscopy, ultraviolet-visible spectroscopy, infrared spectroscopy (Table 1) as has been reported elsewhere [6,10].

The most informative region in the IR spectra of fluoroquinolone and its metal complexes is usually 1800-1300cm^{-1} [1]. The IR spectrum of ofloxacin showed bands at 1714.1cm^{-1} assigned to $\upsilon(C{=}O)_c$ and at 1626.4cm^{-1} assigned to $\upsilon(C{=}O)_p$. This shows that the carboxyl group in the ligand is protonated, therefore the ligand exists in its nonionised neutral form. For the infrared spectra of ciprofloxacin and norfloxacin, no band exists for $\upsilon(C{=}O)_c$ at 1700 cm^{-1} while peaks appear for $\upsilon_{as}(OCO)$ and $\upsilon_s(OCO)$ at 1590 cm^{-1} and 1375 cm^{--1} for the resonance stabilized carboxylate anion, confirming its zwitterionic nature of the ligands. For the tetrachlorometalate complexes of ciprofloxacin and norfloxacin, strong bands assigned to $\upsilon(C{=}O)_c$ appeared around 1714-1699cm^{-1} indicating that the these ligands became protonated. The band for $\upsilon(C{=}O)_c$ present in ofloxacin was also found for [oflH$_3$][FeCl$_4$]Cl.H$_2$O. This showed that there is no direct metal coordination, since the carboxyl oxygen is not available to the metal ion as reported for ionic FQ complexes [1,7,8-10], suggesting that the compounds are ionic complexes consisting of a tetrachlorometalate ion which is electrostatically attached to the ligand. Based on these analyses, the structural formula was proposed as; [H$_3$(of)][FeCl$_4$]Cl.H$_2$O, [H$_3$(nf)][FeCl$_4$]Cl.H$_2$O, (H$_2$(nf)(H$_3$(nf)[CuCl$_4$]Cl.H$_2$O, (H$_3$cf)[FeCl$_4$]Cl.H$_2$O as shown in Figures 1-3. The crystal structure of compound $(nfH_2)(nfH_3)[CuCl_4]Cl.H_2O$ [9] and the biological properties of $(cfH_3)[FeCl_4]Cl.H_2O$ [10] has previously being reported.

Results and Discussion

Figures 4-7 show the expansions of mass spectra of the products. Tables 1-4 show the relevant m/z ratios and tentative assignments of mass spectra of four fluoroquinolone metal complexes. The four ionic complexes all showed peaks of their protonated ligands which is indicative of the ionic nature of the compounds. This may be why no molecular peak was observed, as the compounds are ionic and readily fragment in the ionization chamber at high energy they were subjected. This can be related to some previous studies on mass spectra of fluoroquinolone-metal complexes where only molecular compounds showed m/z of $[M(FQH)(FQH_2)^+]$ ions denoting the presence of metal-FQ coordination, while only strong mass peaks appeared for ionic compounds such as $[FQH_2^+]$ and $[(FQH)(FQH_2^+)]$ ions [7,11] showing only protonated ligands and no metal-FQ coordination The cleavage pattern of the compound $(H_3Cip)[FeCl_4]Cl.H_2O$ is as shown in scheme 1. The most intense peak at 306.8654 was observed as a result of loss of m/z 27 from m/z 333.9089. Loss of H_2O from m/z 306.8654 results in the formation of fragment ion m/z 288.8579.

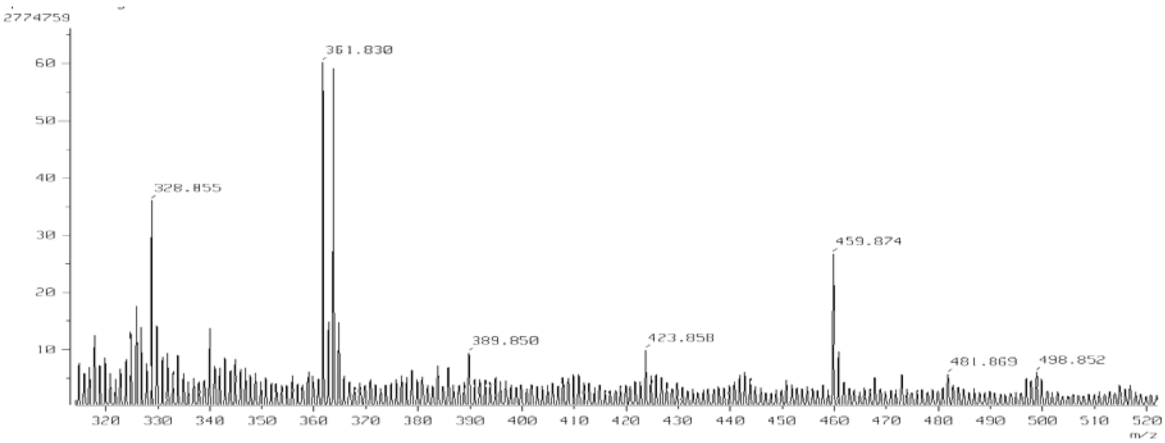
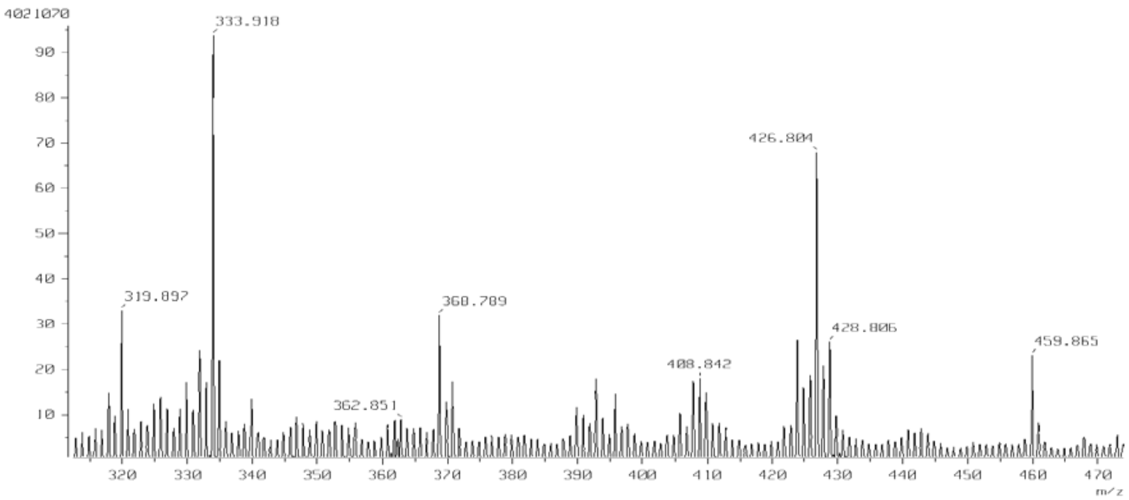
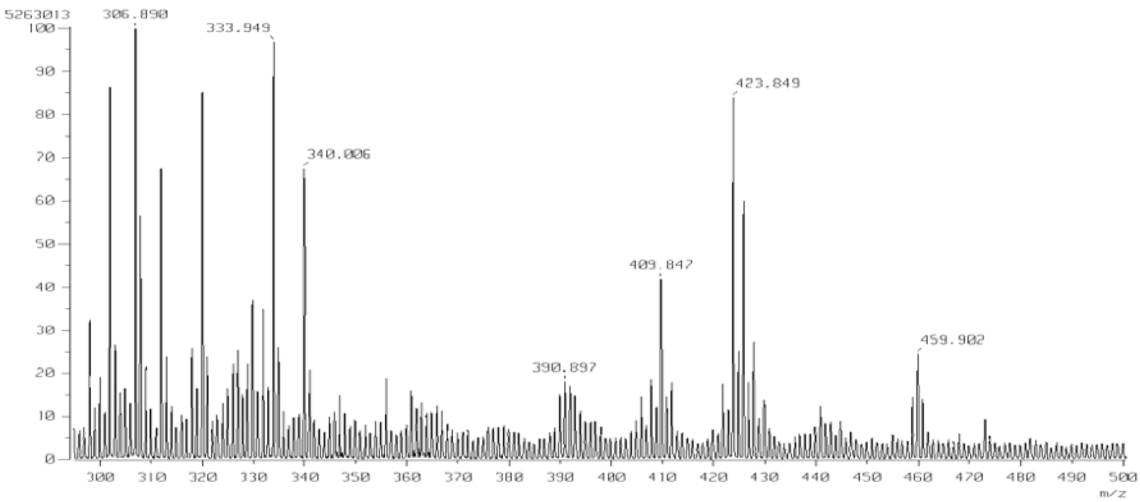


Figure 4: Expansions of Mass Spectra of $(H_3Cip)[FeCl_4]Cl.H_20$



Figures 5: Expansions of the Mass Spectra of $(H_2Nor)(H_3Nor)[CuCl_2]Cl.H_2O$



Figures 6: Expansions of Mass Spectra of $(H_3Nor)[FeCl_4]Cl.H_2O$

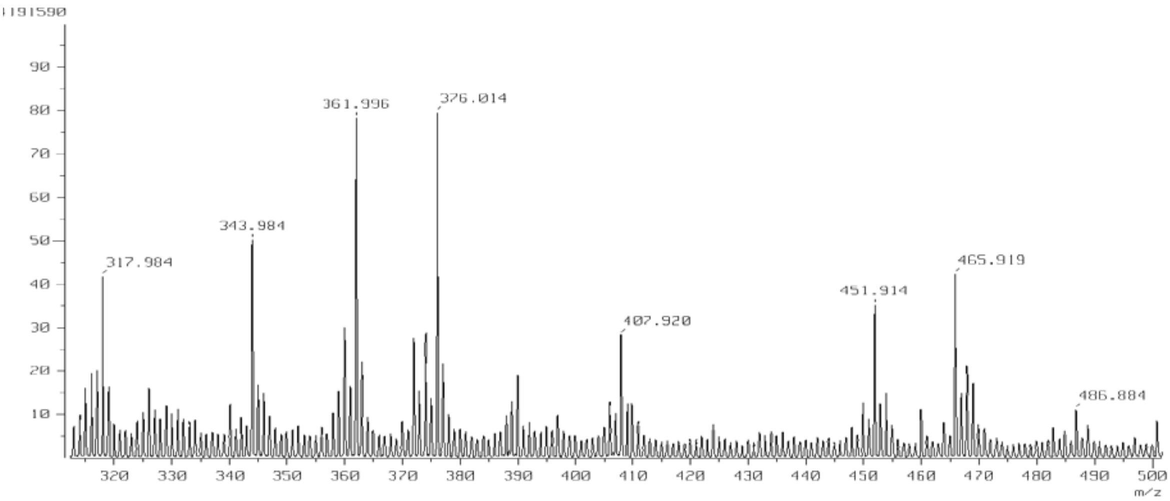


Figure 7: Expansions of Mass Spectra of $(H_3Ofl)[FeCl_4]Cl.H_2O$

Table 1: Relevant m/z ratio and tentative assignments of mass spectra of $(H_3Cip)[FeCl_4]Cl.H_2O$.

m/z ratio	Relative intensity	Tentative Assignment
333.9089	9.04	$(H_3Cip)^+$
332.8929	6.22	$(H_2Cip)^+$
331.8993	9.34	(HCip)
330.8934	8.70	(Cip)
306.8654	100	$(H_3Cip)^+$ - -CH=CH_2(-27)----L_3
288.8579	100	L_3-H_2O-(-18) ---- L_3^*
153.9250	100	$C_8H_{10}N_2F$------(L_3^*-135)
135.9534	100	$C_7H_5NO_2$------(m/z 135)

Table 2 Relevant m/z ratio and tentative assignments of mass spectra of $(H_2Nor)(H_3Nor)[CuCl_4]Cl.H_2O$.

m/z ratio	Relative intensity	Tentative Assignment
957.436	-	$(HNor)_3{}^{\cdot}$
624.5079	9.70	$(H_2Nor)(H_3Nor)$- OH (-17)
321.8465	6.76	$(H_3Nor)^+$
320.8710	11.24	$(H_2Nor)^+$
319.8970	33.04	$(HNor)^{\cdot}$
318.8682	9.61	(Nor)
306.8616	100	$(H_3Nor)^+$ -CH_3 (-15)----- L_3
288.8524	99.98	L_3-H_2O-(-18) ---- L_3^*
153.9235	100	$C_8H_{10}N_2F$------(L_3^*-135)
135.9509	100	$C_7H_5NO_2$------(m/z

135)

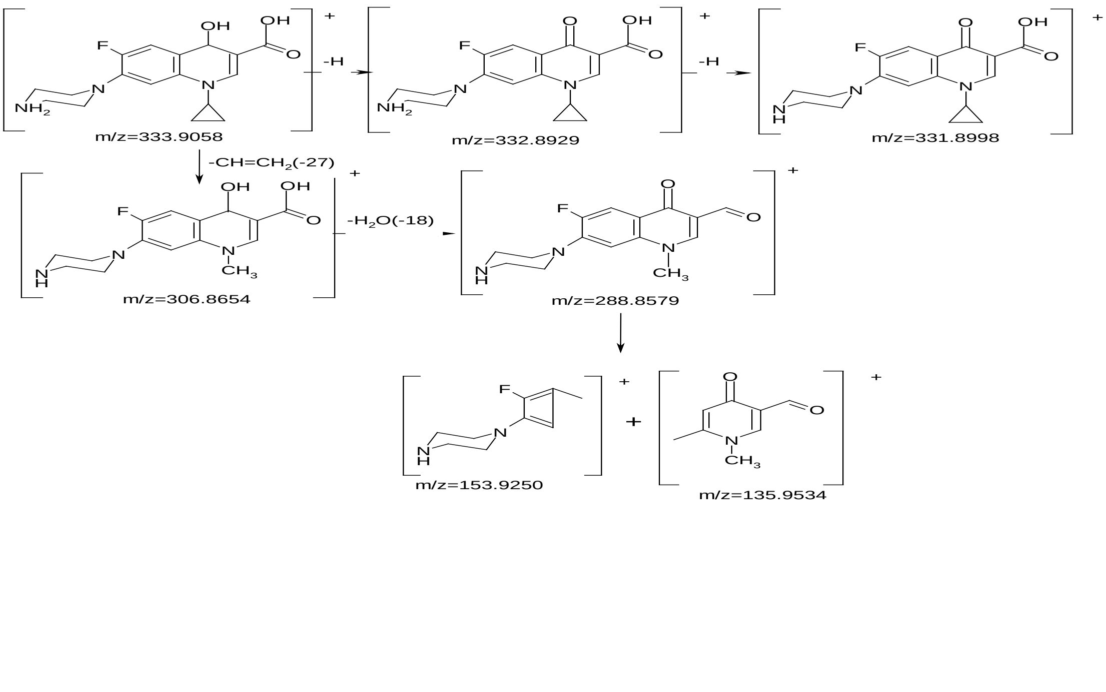
Table 3: Relevant m/z ratio and tentative assignments of mass spectra of $(H_3Nor)[FeCl_4]Cl.H_2O$.

m/z ratio	Relative intensity	Tentative Assignment
321.9165	6.76	$(H_3Nor)^+$
320.9254	11.24	$(H_2Nor)^+$
319.9357	33.04	(HNor)
318.8682	9.61	(Nor)
306.8907	100	$(H_3Nor)^+$ $-CH_3$ (-15)----- L_3
288.8782	99.98	L_3-H_2O-(-18) ---- L_3^*
153.9235	100	$C_8H_{10}N_2F$------(L_3^*-135)
135.9509	100	$C_7H_5NO_2$------(m/z 135)

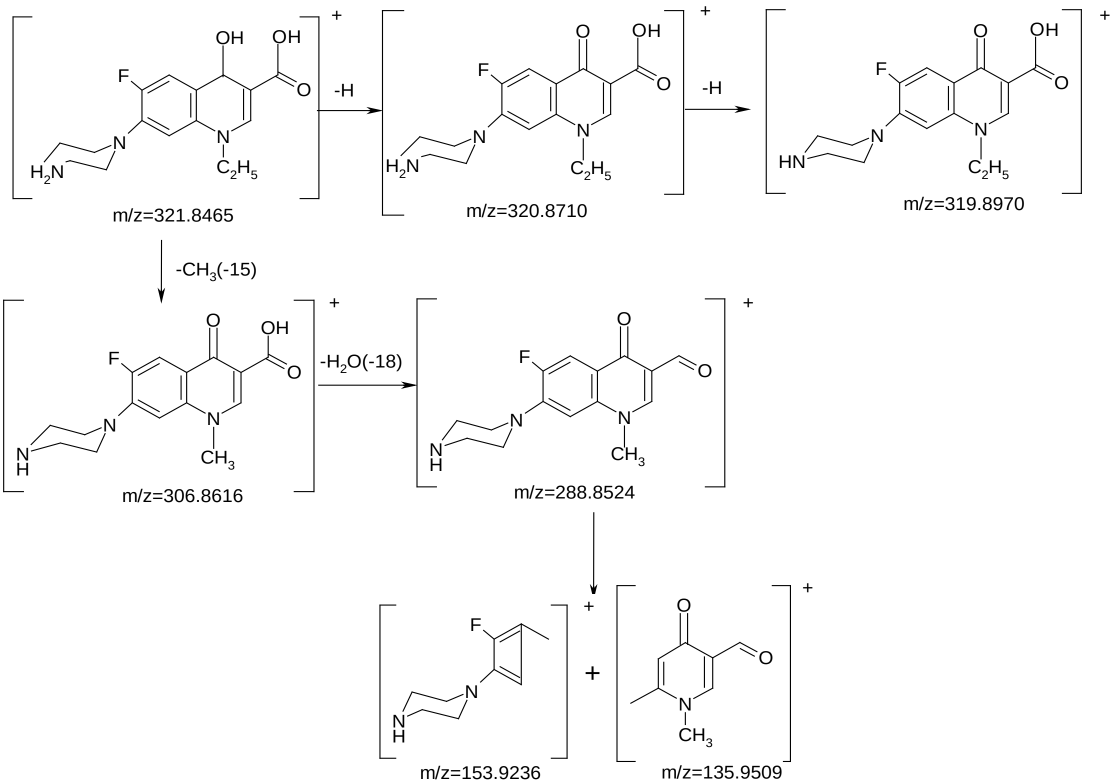
Table 4: Relevant m/z ratio and tentative assignments of mass spectra of $(H_3Ofl)[FeCl_4]Cl.H_2O$.

m/z ratio	Relative intensity	Tentative Assignment
776.9296	25.91	$(H_2Ofl)(HOfl)Cl.H_2O$
775.9283	36.67	$(HOfl)_2Cl.H_2O$
363.9467	9.42	$(H_3Ofl)^+$
362.9791	22.20	$(H_2Ofl)^+$
361.9791	78.24	(HOfl)
360.9635	16.47	(Ofl)
306.9395	99.97	$(H_3Ofl)^+$ -(-m/z57)----- L_3
288.9244	96.87	L_3-H_2O-(-18) ---- L_3^*
153.9658	99.99	$C_8H_{10}N_2F$------(L_3^*-135)
135.9880	99.99	$C_7H_5NO_2$------(m/z 135)

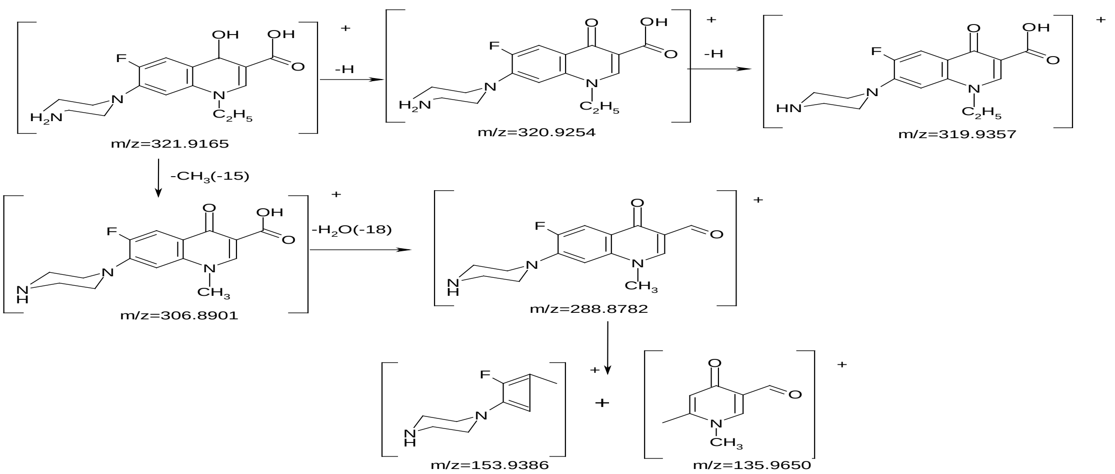
Intense peaks were observed at m/z 153.9250 and m/z 135.9534 as a result of fragmentation of m/z 288.8579. The fragmentation pattern of the compounds $(H_2Nor)(H_3Nor)[CuCl_4]Cl.H_2O$ and $(H_3Nor)[FeCl_4]Cl.H_2O$ are as shown in scheme 2 and 3. They both showed similar fragmentation pattern with a loss of methyl group (-m/z 15) from m/z 321 resulting in an intense peak at m/z 306. As exists in the fragmentation pattern of the compound $(H_3Cip)[FeCl_4]Cl.H_2O$, there was a loss of H_2O from m/z 306 resulting in the formation of fragment ion m/z 288. Intense peaks were also observed at m/z 153 and m/z 135 as a result of fragmentation of m/z 288. The cleavage pattern of the compound $(H_3Ofl)[FeCl_4]Cl.H_2O$ is as shown in scheme 4. An intense peak at 306.9395 was observed as a result of loss of m/z 57 from m/z 363.9467. Loss of H_2O from m/z 306.9395 results in the formation of fragment ion m/z 288.9244. Intense peaks were observed at m/z 153.9658 and m/z 135.9880 as a result of fragmentation of m/z 288.9244.



Scheme 1: Structures of possible fragments of $(H_3Cip)[FeCl_4]Cl.H_2O$



Scheme 2: Structures of possible fragments of $(H_2Nor)(H_3Nor)[CuCl_4]Cl.H_2O$



Scheme 3: Structures of possible fragments of $(H_3Nor)[FeCl_4]Cl.H_2O$

Conclusion

The infrared spectra of the ligands and the complexes indicate that the carboxylic group is not deprotonated, therefore the fluoroquinolone ligand is not directly coordinated to the metal. It is proposed that in this class of compounds, the ligand exist as a singly (+1) or doubly (+2) protonated cation as shown in schemes. The positive charge on the FQ ion is neutralized by the tetrachlorometalate anion and any extra chloride ion.

In general, the mass spectra of the four ionic fluoroquinolone complexes showed similar fragmentation pattern with fragment ions at m/z 306, 288, 153, 135. The FAB mass spectrum of some of the ionic tetrachlorometalate compounds of the FQs displayed m/z peaks for protonated ligands and common fragment ions. This indicates that there is no direct bond between the metal and ligand in this group of FQ compounds and confirms that only electrostatic interaction exists between the metal and drug as has been shown in similar studies of ionic quinolone compounds.

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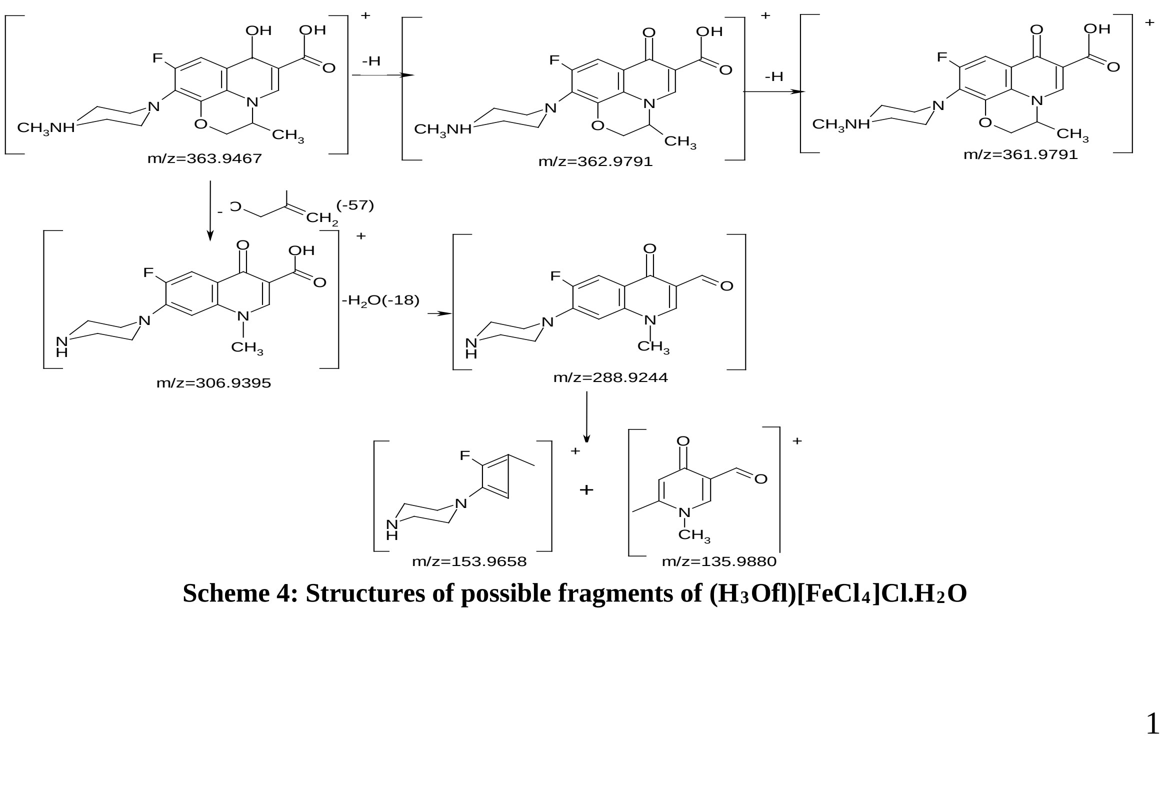

Scheme 4: Structures of possible fragments of $(H_3Ofl)[FeCl_4]Cl.H_2O$