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Thermal decomposition of some biologically active complexes of ruthenium (III) with quinolone derivatives

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Abstract A series of new complexes with mixed ligands of the type $RuL_2(DMSO)_mCl_3{\cdot}nH_2O$ ((**1**) L: norfloxacin (nf), $m = 1$, $n = 1$; (**2**) L: ciprofloxacin (cp), $m = 2$, $n = 2$; (**3**) L: ofloxacin (of), $m = 1$, $n = 1$; (**4**) L: enrofloxacin (enro), $m = 0.5$, $n = 4$; DMSO: dimethylsulfoxide) were synthesised and characterised by chemical analysis and IR data. In all complexes both fluoroquinolone derivative and DMSO act as unidentate. The thermal behaviour steps were investigated in synthetic air flow. The thermal transformations are complex processes according to TG and DTG curves including dehydration, quinolone derivative and DMSO degradation respectively. The final product of decomposition is ruthenium (IV) oxide.

Keywords Biological activity · Fluoroquinolone · Ruthenium complexes · Thermal behavior

Introduction

The chemistry of ruthenium–DMSO complexes has been widely developed because these species are versatile precursors in inorganic synthesis and some of them are antitumor agents [1–4]. The most attractive feature of these complexes is their anti-metastatic property, which is lacking in platinum-based drugs [5]. Further, the clinical use of platinum compounds was limited because the development of tumor resistance to the drugs and of their toxicity. Complexes of ruthenium with DMSO exhibit antitumor activity and are relatively nontoxic. A relatively new approach to the rational design of antitumor agents has been introduced based on some new quinolone molecules that display a novel action mode [6].

The selection of fluoroquinolones as ligands was generated by their improved antimicrobial activity [7] and the cytotoxic effects evidenced in the last years [8–10].

Based on those observations, new ruthenium (III) complexes with some antibacterials quinolone (norfloxacin, ofloxacin, ciprofloxacin, enrofloxacin) were synthetized and characterized. The complexes were formulated on the basis of analytical and spectral data as: $RuL_2(DMSO)_mCl_3{\cdot}nH_2O$ ((**1**) L: norfloxacin (nf), $m = 1$, $n = 1$; (**2**) L: ciprofloxacin (cp), $m = 2$, $n = 2$; (**3**) L: ofloxacin (of), $m = 1$, $n = 1$; (**4**) L: enrofloxacin (enro), $m = 0.5$, $n = 4$; DMSO: dimethylsulfoxide) The most probable structures of the compounds have been proposed.

The thermal analysis (TG, DTA) was performed in order to establish the thermal stability of these complexes during the pharmaceutical development studies. The thermal curves elucidated the composition and the number and nature of the solvent molecules also.

Experimental

All chemicals were purchased from Sigma–Aldrich, reagent grade and were used without further purification.

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Synthesis

A DMSO solution of ligand and $RuCl_3$ in a 2:1 molar ratio was heated under reflux for 6 h. The solution was turned into dark-brown. After cooling, a solution 2 M of NaCl has been added in order to obtain the solid product. The brown residue was filtered off and washed several times with distilled water and dried in air.

Chemical analyses and physical measurements

The chemical analyses were performed on a Perkin Elmer PE 2400 analyser (for C, H, N, S) and a AAS Carl Zeiss Jena AAS1 spectrometer (for Ru).

IR spectra were recorded in KBr pellets with a FT-IR VERTEX 70 (Bruker) spectrometer in the range 400–4000 cm^{-1}.

Complex $Ru(nf)_2Cl_3(DMSO)\cdot H_2O$ (**1**): Analysis, found: Ru, 10.56; C, 43.81; H, 4.25; N, 8.49; S, 3.81%; calculated for $RuC_{34}H_{44}Cl_3F_2N_4O_8S$: Ru, 10.72; C, 43.31; H, 4.67; N, 8.92; S 3.39%; IR (KBr pellet), cm^{-1}: $\nu(C{=}O)_c$, 1719 s; $\nu(C{=}O)_p$, 1616s; $\nu(S{=}O)$, 1022m.

Complex $Ru(cp)_2Cl_3(DMSO)_2\cdot 2H_2O$ (**2**): Analysis, found: Ru, 9.31; C, 42.58; H, 4.51; N, 7.34; S, 6.35%; calculated for $RuC_{38}H_{52}Cl_3F_2N_6O_{10}S_2$: Ru, 9.51; C, 42.93; H, 4.89; N, 7.90; S 6.03%; IR (KBr pellet), cm^{-1}: $\nu(C{=}O)_c$, 1723 s; $\nu(C{=}O)_p$, 1615s; $\nu(S{=}O)$, 1027s.

Complex $Ru(of)_2Cl_3(DMSO)\cdot H_2O$ (**3**): Analysis, found: Ru, 9.31; C, 44.97; H, 4.76; N, 8.63; S, 3.59%; calculated for $RuC_{38}H_{48}Cl_3F_2N_6O_{10}S$: Ru, 9.84; C, 44.44; H, 4.67; N, 8.19; S 3.12%; IR (KBr pellet), cm^{-1}: $\nu(C{=}O)_c$, 1721s; $\nu(C{=}O)_p$, 1617s; $\nu(S{=}O)$, 1025i.

Complex $Ru(enro)_2Cl_3(DMSO)_{0.5}\cdot H_2O$ (**4**): Analysis, found: Ru, 10.65; C, 47.88; H, 5.63; N, 8.94; S, 1.87%; calculated for $RuC_{39}H_{49}Cl_3F_2N_6O_{7.5}S_{0.5}$: Ru, 10.27; C, 47.60; H, 5.19; N, 8.54; S 1.62%; IR (KBr pellet), cm^{-1}: $\nu(C{=}O)_c$, 1722s; $\nu(C{=}O)_p$, 1615s; $\nu(S{=}O)$, 1026m.

The heating curves (TG, DTA and DTG) were recorded using a Labsys 1200 SETARAM instrument, with a sample weight of 6–15 mg over the temperature range of 20–900 °C, using a heating rate of 10 K/min. The measurements were carried out in synthetic air (flow rate 16.66 cm^3/min) by using alumina crucibles.

Results and discussion

Physico-chemical characterization of complexes

In this paper, we report the preparation and physico-chemical characterisation of some complexes with fluoroquinolone derivatives and DMSO (Fig. 1).

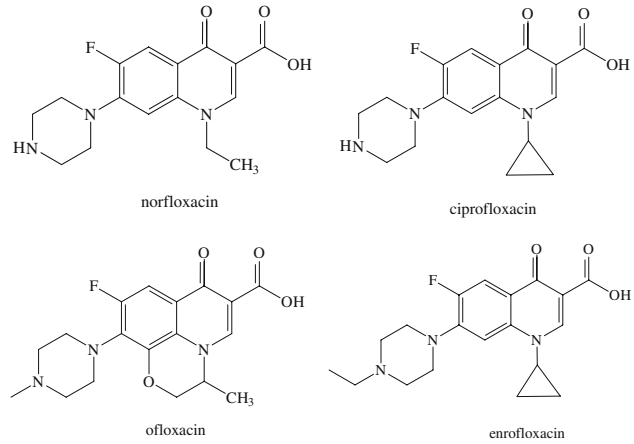

Fig. 1 The ligands formulas

The major goal of this paper was to evidence the thermal behaviour, in synthetic air flow, of these complexes that could behave as anticancer agents. The complexes have been formulated on the basis of chemical analysis and IR spectra as it follows:

$$Ru(nf)_2Cl_3(DMSO)\cdot H_2O \quad (\mathbf{1})$$
$$Ru(cp)_2Cl_3(DMSO)_2\cdot 2H_2O \quad (\mathbf{2})$$
$$Ru(of)_2Cl_3(DMSO)\cdot H_2O \quad (\mathbf{3})$$
$$Ru(enro)_2Cl_3(DMSO)_{0.5}\cdot H_2O \quad (\mathbf{4})$$

These compounds were obtained from the reaction of the $RuCl_3$ with quinolone derivative in DMSO.

In the IR spectra of complexes the characteristic patterns of quinolone and DMSO are shown, which indicate the unidentate coordination both for quinolone derivative and DMSO (Fig. 2a, b). These features are:

- the characteristic bands assigned to the both carboxylic and pyridonic carbonyl ($\nu(CO)_c$ and $\nu(CO_p)$ respectively can be identified in all complexes spectra [11]. The presence of these bands in complexes spectra shows that the carbonyl and carboxyl groups are not involved in coordination.
- the bands which appear in 2500–2800 cm^{-1} range in ligands spectra can be assigned to N^4(piperazyl)···H stretching vibrations. In the complexes spectra these bands disappears probably due to the N^4(piperazyl) binding at the metallic ion.
- the presence of DMSO molecule in complexes generates the appearance of a medium or strong band in 1020–1030 cm^{-1} range assigned to $\nu(S{=}O)$ stretching vibrations [12] characteristic to S-coordinated DMSO.

On the basis of the above data the proposed coordination for the complexes is given in Fig. 3.

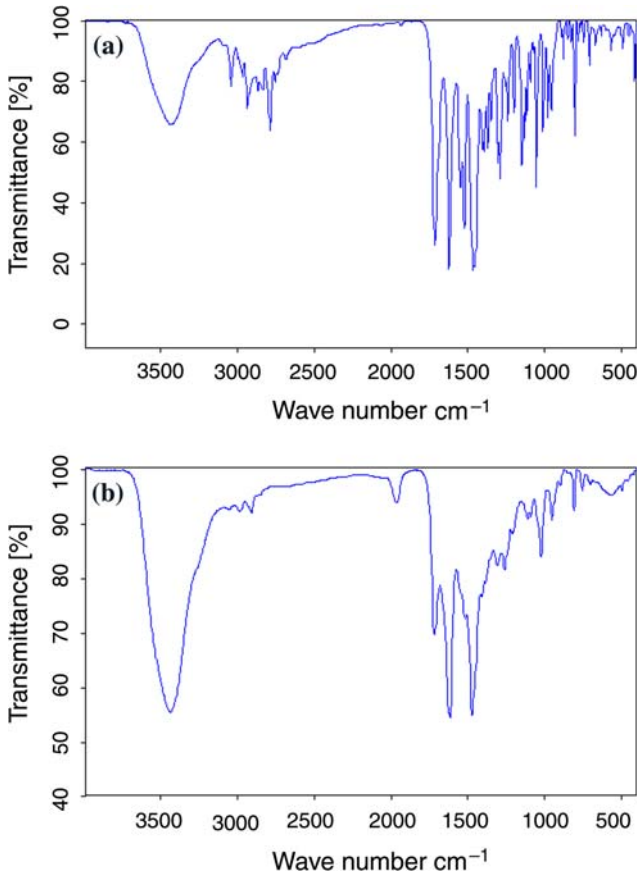

Fig. 2 IR spectra of norfloxacin (**a**) and corresponding ruthenium complex (**b**)

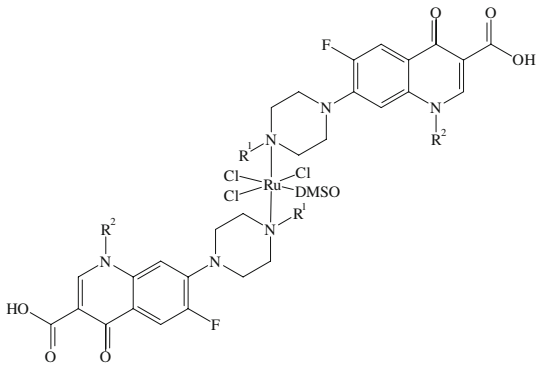

Fig. 3 The proposed formula of complexes

Thermal behavior of complexes

The main objective of this paper was to analyse the thermal behaviour of the complexes having in view the composition confirmation and the solvent molecule role assessment.

The results concerning the thermal degradation of the new complexes are presented as it follows.

Thermal decomposition of $Ru(nf)_2Cl_3(DMSO)\cdot H_2O$

The TG and DTA curves corresponding to the complex (**1**) heated in the 20–900 °C temperature range indicate that decomposition follows four steps (Fig. 4).

The first step of compound transformation consists in an endothermic elimination of both water and DMSO molecules (Table 1). The second step, exothermic, is not a single one being an overlapping of at least two processes as both TG and DTA curves indicate. This step corresponds to the partial norfloxacin oxidative degradation so the 1,4-diaza-1-cyclohexene fragments remain coordinated through N^4 (Fig. 5).

Next step, exothermic also, corresponds to organic part loss according to TG curve. The resulted intermediate, $RuCl_3$, turns in RuO_2 in the last step, process accompanied by an exothermic effect (found/calcd. overall mass loss: 85.83/85.86).

Thermal decomposition of $Ru(cp)_2Cl_3(DMSO)_2\cdot 2H_2O$

Complex (**2**) loses the water together with DMSO in the 55–160 °C range (Fig. 6). The second step, similar with that observed for (**1**) occurs with fluoroquinolone degradation. The thermal degradation of ciprofloxacin occurs in at least two successive processes as both TG and DTA indicate. In the third step the complex intermediate leads to $RuCl_3$ as a result of the diazole ring oxidative degradation. The remaining $RuCl_3$ generates RuO_2 but up to 1000 °C this transformation is not finished.

Thermal decomposition of $Ru(of)_2Cl_3(DMSO)\cdot H_2O$

The decomposition of complex (**3**) comprises also four steps and starts with water elimination, process that also occurs at high temperatures (Fig. 7). The anhydrous species releases

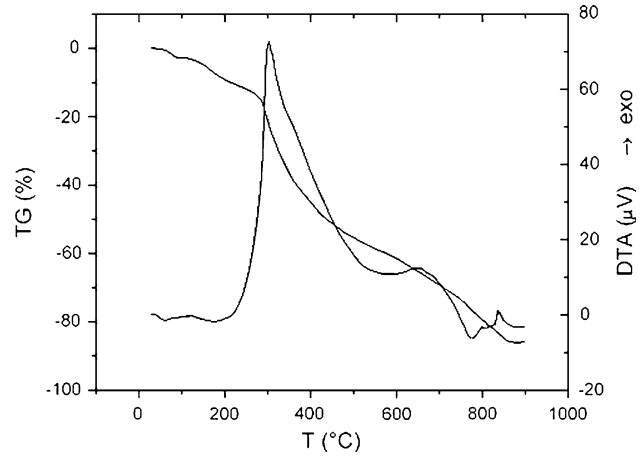

Fig. 4 TG and DTA curves of $Ru(nf)_2Cl_3(DMSO)\cdot H_2O$

Table 1 Thermal behaviour data (in synthetic air atmosphere) for complexes

Complex	Step	Thermal effect	Temperature range/°C	Δm_{exp}/%	Δm_{calc}/%
$Ru(nf)_2Cl_3(DMSO)\cdot H_2O$	1	Endothermic	60–227	10.14	10.20
	2	Exothermic	227–585	50.00	49.92
	3	Exothermic	585–790	17.81	17.85
	4	Exothermic	790–860	7.88	7.89
$Ru(cp)_2Cl_3(DMSO)_2\cdot 2H_2O$	1	Endothermic	55–340	18.08	18.10
	2	Exothermic	340–590	46.46	46.54
	3	Exothermic	590–740	15.88	15.84
	4	Exothermic	740–820	5.93	6.99
$Ru(enro)_2Cl_3(DMSO)0.5\cdot H_2O$	1	Endothermic	55–260	5.83	5.80
	2	Exothermic	260–550	50.33	50.28
	3	Exothermic	550–820	22.84	22.82
	4	Exothermic	820–900	7.26	7.56
$Ru(of)_2Cl_3(DMSO)\cdot H_2O$	1	Endothermic	75–250	9.33	9.36
	2	Exothermic	250–620	51.21	51.29
	3	Exothermic	620–840	19.05	19.13
	4	Exothermic	840–900	7.17	7.63

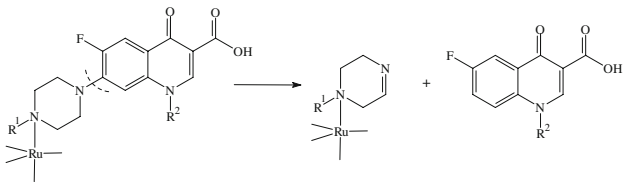

Fig. 5 The proposed second step complexes degradation

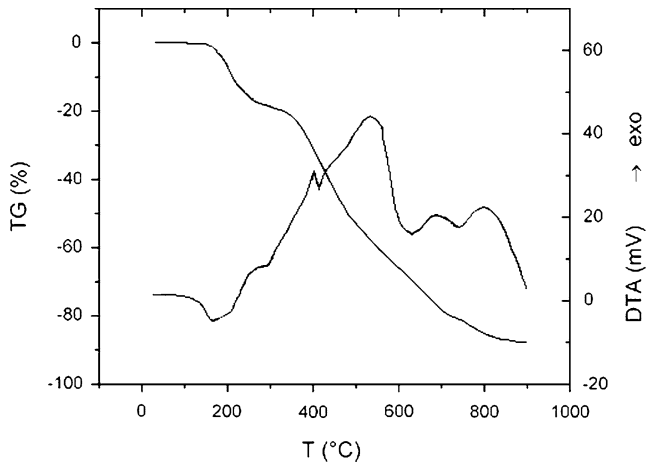

Fig. 6 TG and DTA curves of $Ru(cp)_2Cl_3(DMSO)\cdot H_2O$

then the DMSO group and the ofloxacin turns into heterocyclic diamine. This step comprises at least two processes as both TG and DTA indicate. The next step is also a complex one and consists in diamine elimination in two processes (according to TG and DTA). The final product is also RuO_2 (found/calcd. overall mass loss: 86.76/87.41).

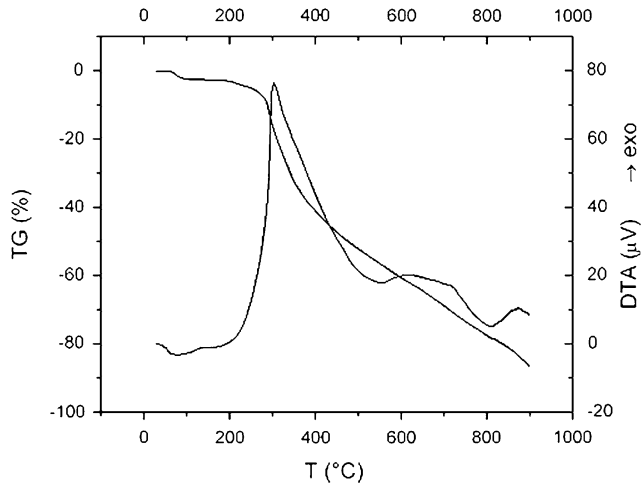

Fig. 7 TG and DTA curves of $Ru(enro)_2Cl_3(DMSO)\cdot H_2O$

Thermal decomposition of $Ru(enro)_2Cl_3(DMSO)_{0.5}\cdot H_2O$

According to the TG profile (Fig. 8) the decomposition of $Ru(enro)_2Cl_3(DMSO)_{0.5}\cdot H_2O$ (**4**) occurs in four, well-defined steps (found/calcd. overall mass loss: 86.26/86.46). After water loss in the 70–110 °C range, the DMSO elimination occurs in the second step. Next two steps, both complexes, consisting at least two processes as both TG and DTA indicate, correspond to enrofloxacin stepwise oxidative degradation. The chloride leads to RuO_2 in the final step according to the mass variation.

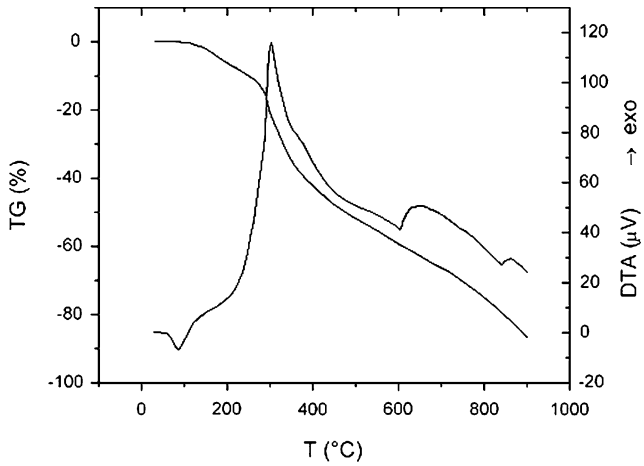

Fig. 8 TG and DTA curves of $Ru(of)_2Cl_3(DMSO)\cdot H_2O$

Conclusions

The new complexes of Ru(III) fluoroquinolone as ligands belong to a class of current interest coordination compounds having in view the cytostatic effect evidenced for similar species.

For all complexes fluoroquinolone derivative acts as unidentate according to IR data. The DMSO presence was evidenced also for all complexes.

Thermal analysis (TG, DTA) of these complexes elucidated the composition and also the number and nature of both water and DMSO molecules. It was also evidenced the existence of an intermediate step corresponding to the formation of a heterocyclic diamine for all compounds. The final product is ruthenium (IV) oxide.

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