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Comparison of the thermal stability of ciprofloxacin and its compounds

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Abstract

The thermal behaviour of ciprofloxacin, its hydrochloride and two copper (II) compounds of ciprofloxacin was studied by thermogravimetry (TG), differential scanning calorimetry (DSC), evolved gas analysis (EGA) and IR spectroscopy. In all the compounds studied, profound differences in the carboxylic ν(C=O) absorption were found after heating, which can be explained by the rearrangement of the hydrogen bonds.

Keywords: IR spectroscopy; Metal complexes; Quinolones; Thermal stability

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1. Introduction

Quinolones are well-known synthetic anti-bacterial agents that are active against many bacteria [1–4]. Ciprofloxacin (cf, 1-cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinoline-3-carboxylic acid) (Scheme 1) is a typical member of this family and is given to patients orally in the form of its hydrochloride salt [5].

The interactions of quinolones and metal ions have been studied by many authors [6–10]. We have reported the syntheses and characterization of numerous different quinolone compounds in our previous studies. It was found that copper(II) could be coordinated as a chelate to the carbonyl oxygen at position 4 and to the carboxylic oxygen [11]. A set of ionic compounds was also prepared. In these compounds, quinolone molecules are protonated, thus preventing the bonding of the metal to the quinolone. The positive charge of the quinolone molecules is compensated by halometallate anions [12, 13].

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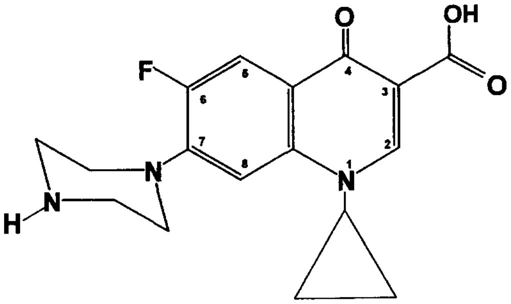

Scheme 1

We have decided to compare the thermal behaviour of free cf, its hydrochloride (cf.HCl.H_2O), the coordination compound $[Cu(cf)_2]Cl_2.6H_2O$ = **(I)**, and the ionic compound $[cfH_2]$ [cfH] $[CuCl_4]Cl$. H_2O = **(II)** (cfH_2 is a doubly protonated molecule of cf, cfH is a monoprotonated molecule of cf). IR spectroscopy was also used to elucidate the results.

2. Experimental

2.1. Methods

Analysis of carbon, hydrogen and nitrogen was carried out on a Perkin-Elmer 204 C microanalyser.

TG data were recorded in the temperature range from 25°C up to 800°C in a stream of dry air on a Mettler TA-3000 thermobalance. Platinum crucibles were used; sample weights were 10.0–25.0 mg. The heating rate was 10 K min^{-1}. All the samples were placed in an desiccator over sulphuric acid immediately after heating. Differential scanning calorimetry was carried out using a Perkin-Elmer DSC-7 calorimeter equipped with water cooling. The experimental conditions were: aluminium crucibles of 30 μl volume with four holes, dry nitrogen atmosphere with a 40 ml min^{-1} flow rate, and a heating rate of 10 K min^{-1}.

EGA (Evolved Gas Analysis) data (for sample **(I)** were obtained using a Netzsch STA 409 thermobalance and Leybold Inficon 200 mass spectrometer, interconnected by a capillary coupling system heated to 150°C. The sample weight was 161.5 mg, and heating rate 10 K min^{-1}. Data were recorded in the range from 25°C up to 400°C, a carrier gas flow rate (Ar) of 100 ml min^{-1} was used.

FT–IR spectra were recorded using KBr pellets or in Nujol and poly-(chlorotrifluoroethylene) oil mulls between CsI windows on a Perkin–Elmer 2000 FT-IR spectrometer or a Digilab FTS-80 Fourier spectrometer. Conditions: range 4000–400 (220) cm^{-1}, resolution 2–8 cm^{-1}, 10–60 scans.

2.2. Preparations

The samples of cf and cf.HCl.H_2O were kindly provided by Krka Pharmaceutical factory (laboratory samples), and copper(II) chloride (p.a., Riedel de Haën, Hannover) was used for the syntheses.

The metal compounds of quinolones were prepared as reported elsewhere [11, 12]. The orange compound **(II)** was synthesized in the system cf–$CuCl_2$ (HCl) for the first time, but all the analyses and its appearance confirmed that it is of the same type, i.e. ionic, as the copper(**II**)–norfloxacin (nf) compound with the formula [nfH_2] [nfH] [$CuCl_4$]Cl.H_2O [12] (calculated:%C, 44.16;%H, 4.44; %N, 9.09; found: %C, 43.92; %H, 4.23; %N, 9.04).

3. Results and discussion

The DSC data for all the compounds studied are collected in Table 1, and DSC curves of both copper(II) compounds (**I** and **II**) are given in Fig. 1. The TG curve of (**I**) has already been reported [11], and the TG curve of (**II**) is nearly the same as for [nfH_2] [nfH] [$CuCl_4$] Cl.H_2O [12].

The melting point of cf (277°C) is substantially higher than that of norfloxacin (nf) (219°C) [14]. The only difference between the two molecules is the substituent at N(1) (ethyl group in norfloxacin). There are no effects before melting in the DSC curve of cf that could be ascribed to solid–solid phase transitions. Such effects were, however, found in the case of nf [14].

The endothermic peak in the DSC curve of cf.HCl.H_2O at 167°C is probably the consequence of dehydration and the loss of moisture. The weight loss determined (6.62%) in the 25–174°C interval is higher than that calculated for one water molecule only (4.67%), but not high enough to correspond to the calculated loss for an HCl molecule (9.47%). The compound melts at 327°C, which is essentially higher than for cf and could prove the ionic character of the compound.

Table 1
DSC data of cf, cf. HCl.H_2O, (**I**) and (**II**)

	T_m/°C	ΔH/J g^{-1}
cf	277	188(4)
cf.HCl.H_2O	167	137(5)
	327	69(5)
(**I**)	111	292(5)
	238	125(5)
(**II**)	223	113(4)
	277	53(4)

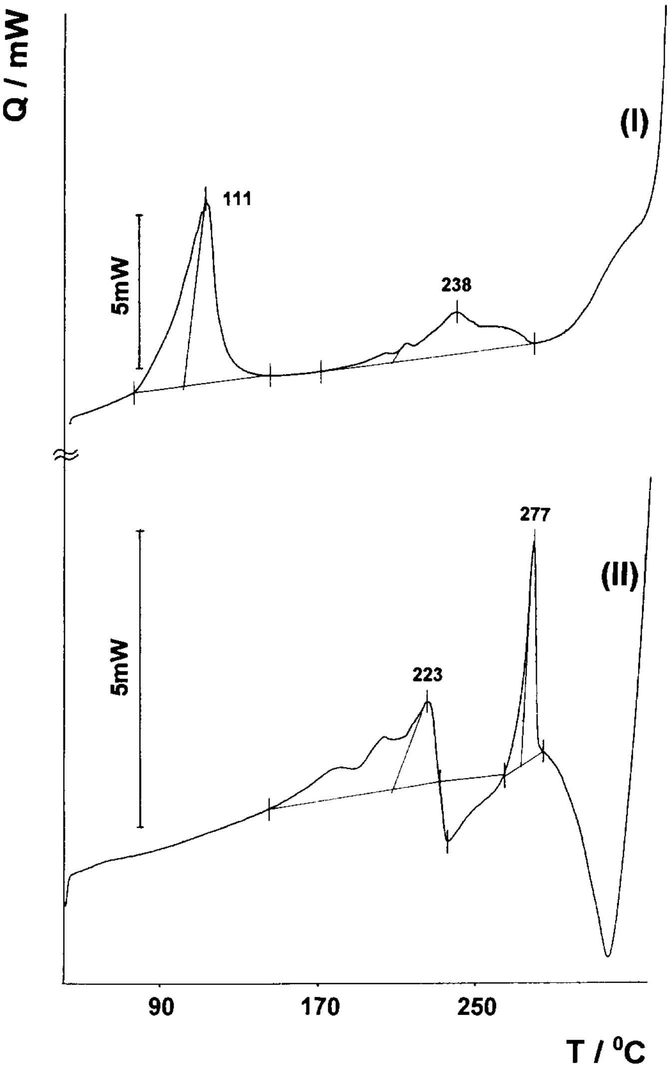

Fig. 1. DSC curves of (I) and (II).

The ionic compound (II) is first dehydrated. The determined weight loss in the 25–140°C region is 2.26%, which agrees with the loss of the water molecule and of some moisture. The subsequently determined weight loss of 9.43% in the 149–220°C region is difficult to explain. We tried to elucidate these results by EGA (Evolved Gas Analysis) of the ionic copper (II)–quinolone compound[15]. It was found that this compound is first dehydrated, and then (205–300°C) the pyrolysis begins with simultaneous evolution of water, hydrochloric acid and carbon dioxide. We assume similar behaviour in the case of (II) due to the similar nature of the two compounds.

The DSC curve of **(I)** is essentially different to that of **(II)**. This is not surprising if we recall the crystal structures of compound **(I)** and of the ionic compound $[nfH_2]$ $[nfH]$ $[CuCl_4]Cl.H_2O$ [11, 12]. The roles of the metal ions and the functional groups of the quinolones are in fact quite different. The EGA method confirmed that this compound is first dehydrated (peak temperature, 131°C) and that later decarboxylation occurs. The total decomposition of the sample starts at approximately 300°C (Fig. 2).

IR spectra of the original and the heated samples were compared in order to study the nature of the thermal processes. The temperatures were chosen from TG and (or) DSC curves, and the temperatures from before the total decomposition were mainly used. Our attention was centred on the positions of the bands of the $\nu(C{=}O)_C$ (C is carboxylic) and the $\nu(C{=}O)_P$ (P is pyridone) vibrations, which are listed in Table 2.

In nearly all the compounds, the observable absorptions in the spectral range 3500–2300 cm^{-1}, proving the presence of different hydrogen bonds are rearranged after heating. This is quite understandable because water molecules and chloride ions are involved in such interactions.

One of the most surprising facts is that in the spectrum of the original anhydrous cf sample the absorption of $\nu(C{=}O)_C$ does not appear at all. But we can find a band at 1725 cm^{-1} in the spectrum of the sample heated to 270°C (Fig. 3).

The sample of $cf.HCl.H_2O$ was heated to different temperatures. It was found that the $\nu(C{=}O)_C$ band was finally shifted from 1707 to 1733 cm^{-1} after heating. A similar trend, but to a smaller extent, was also established for **(II)**. The $\nu(C{=}O)_C$ peak found at 1701 cm^{-1} in the original sample was shifted to 1715 cm^{-1} in the sample heated to 225°C.

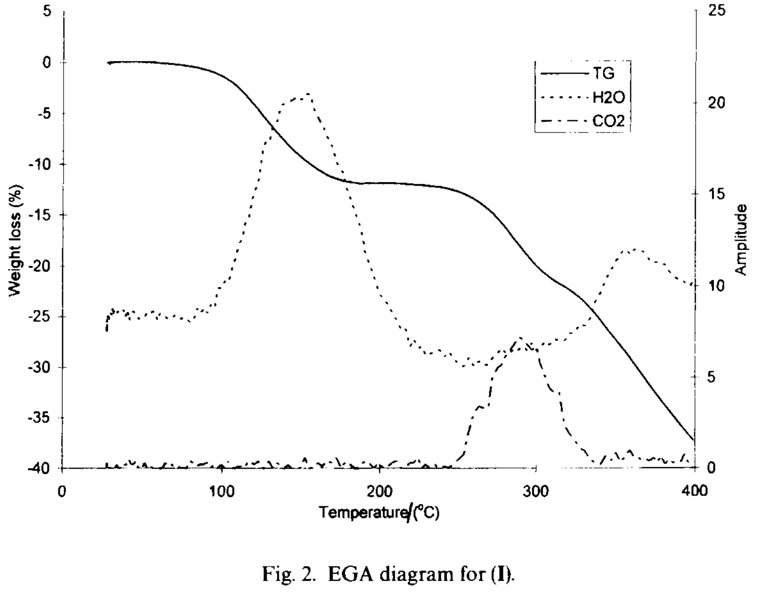

Fig. 2. EGA diagram for (I).

Table 2
Selected IR frequencies (cm^{-1}) of the original and heated samples.

	$\nu(C{=}O)_C$	$\nu(C{=}O)_P$
cf(original, white)	–	1618 s
cf(heated to 270°C, pale brown)	1725 m	1629 s
cf.HCl.H_2O (original, pale yellow)	1707 s	1625 s
cf.HCl.H_2O (heated to 110°C, pale yellow)	1709 s	1625 s
cf.HCl.H_2O (heated to 170°C, pale yellow)	1733 s	1628 s
cf.HCl.H_2O (heated to 300°C, brown)	1732 s	1628 s
$[Cu(cf)_2]Cl_2.6H_2O$ (original, green)	–	1628 s
$[Cu(cf)_2]Cl_2.6H_2O$ (heated to 160°C, green)	1723 vw	1631 s
$[Cu(cf)_2]Cl_2.6H_2O$ (heated to 190°C, green-brown)	1719 w	1629 s
$[Cu(cf)_2]Cl_2.6H_2O$ (heated to 300°C, brown)	1717 w	1617 s
$[Cu(cf)_2]Cl_2.6H_2O$ (heated to 400°C, black)	–	–
$[cfH_2]$ $[cfH]$ $[CuCl_4]Cl.H_2O$ (original orange)	1701 s	1626 s
$[cfH_2]$ $[cfH]$ $[CuCl_4]Cl.H_2O$ (heated to 225°C, brown)	1715 s	1628 s

s-strong, v-very, m-medium, w-weak

The IR spectrum of (**I**) demonstrates the different role of the carboxylic and ring carbonyl oxygens that are bonded to the copper ion. Above 1700 cm^{-1} there is no absorption which could be ascribed to $\nu(C{=}O)_C$ vibration. It has been reported for many metal–carboxylate complexes [16] that two bands in the spectrum should appear as the result of the bonded carboxyl group, but we were unable to assign them unequivocally. It is, however, interesting to note that a well-defined band at 1608 cm^{-1}, which is even stronger than the $\nu(C{=}O)_P$ absorption at 1628 cm^{-1}, appears in the spectrum. The heating of the sample changed the positions and the appearance of some peaks, which is probably the consequence of the changes in the coordination sphere of the metal. A weak band at 1723 cm^{-1} appears in the spectrum and the $\nu(C{=}O)_P$ band at 1631 cm^{-1} is well resolved. This band prevails over the absorption at around 1600 cm^{-1} which appears only as a shoulder. The observed changes were intensified with additional heating to 190°C. The position of the $\nu(C{=}O)_C$ band in the sample heated to 300°C was at 1717 cm^{-1}, and there are no $\nu(C{=}O)_C$ nor even $\nu(C{=}O)_P$ vibrations in the sample heated to 400°C, which confirms that this part of the molecule had decomposed.

Water molecules and chloride ions are involved in hydrogen bonding with different quinolone functional groups [17]. The bonds are thus weakened and the bands appear at lower wave numbers in the original samples. When water or hydrochloric acid molecules are removed from the structures by heating, some hydrogen bonds are broken or rearranged, and the result is a shift of the band frequency towards higher wave numbers.

We can see that this effect is less marked for the ring $\nu(C{=}O)_P$ vibrations whereas the carboxylic $\nu(C{=}O)_C$ vibration is more sensitive to these changes.

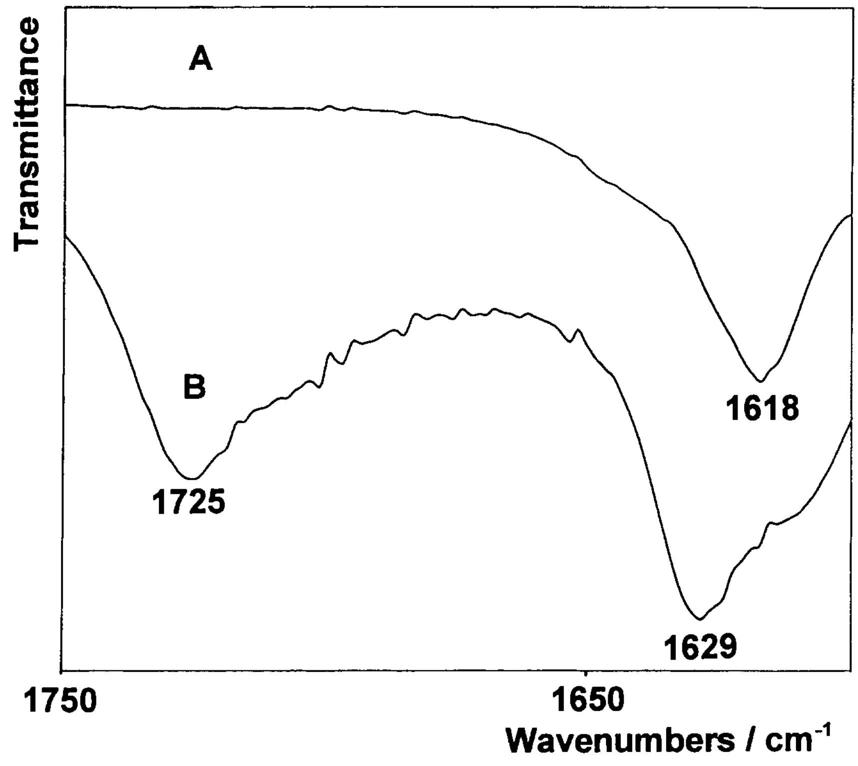

Fig. 3. A part of the ciprofloxacin IR spectrum before (A) and after heating to 270°C (B).

Our results are in fair agreement with the study of the thermal decomposition of cinoxacin complexes [18, 19].

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