MAGNESIUM, CALCIUM AND BARIUM PERCHLORATE COMPLEXES OF CIPROFLOXACIN AND NORFLOXACIN

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Abstract

The interaction of magnesium, calcium and barium perchlorate with ciprofloxacin (CIP) and norfloxacin (NOR) has been investigated. Elemental analysis, FTIR, electrical conductivity and thermal analysis have been used to characterize the isolated complexes. The results support the formation of complexes of the formula $[M(NOR)_2](ClO_4)_2.xH_2O$ and $[M(CIP)_2](ClO_4)_2.xH_2O$ (M = Mg^{+2}, Ca^{+2} and Ba^{+2}). The FTIR spectra of the isolated complexes suggest that CIP and NOR act as bidentate ligands through the ring carbonyl oxygen atom and one of the oxygen atoms of the carboxylic group.

Introduction

Ciprofloxacin (CIP) and Norfloxacin (NOR) are quinolone antibacterial agents used in the treatment of a wide range of infections. All of the quinolone antibiotics share 4-oxo-3-carboxylic acid groups (Figure 1) which are essential for their bactericidal activity.[1,2] Quinolone antibiotics are complexing agents for a variety of metal ions including alkaline earth metal ions. Although reports indicate that the coordination of quinolones to metal ions such as Mg^{2+} and Ca^{2+} appear to be important for the activity of the quinolone antibiotics,[3-7] it has a detrimental effect on their absorption.[8-13] Early studies by Nakano demonstrated the ability of the quinolone naldixic acid to complex a variety of metal ions.[14] The crystal structures of quinolone complexes[15-30] indicate that quinolone antibiotics can participate in the formation of complexes in a number of ways. Complexes isolated from acidic media usually contain singly and/or doubly protonated quinolones that are incapable of bonding to the metal ion and in these cases only electrostatic interaction was observed between the drug and the metal ions.[15-18,29] In other cases,[19-23, 28, 30] it was found that neutral quinolones in the zwitterionic state are capable of forming simple complexes. In these complexes the quinolone acts as a bidentate ligand through the ring carbonyl group at position 4 and through one of the oxygen atoms of the carboxylato group at position 3. Quinolones can also act as bridging ligands and thus capable of forming polynuclear complexes.[28,30]
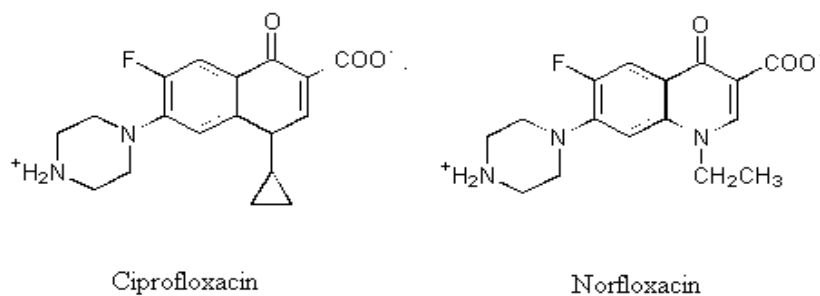
Figure1: The zwitterionic structure of ciprofloxacin (CIP) and norfloxacin (NOR).

Several complexes of quinolone antibiotics with alkaline earth metal have been isolated and characterized by x-ray diffraction. Turel *et. al.* reported[29] the synthesis and the characterization of a CIP adduct of $MgSO_4$. The crystal structure indicated that the adduct contains a doubly protonated ciprofloxacin ion that is incapable of binding to the metal ion. Chen *et. al.* reported[30] the synthesis of two dimeric complexes of norfloxacin with $MgCl_2$ and $CaCl_2$. The crystal structures of these complexes showed that the carbonyl oxygen and one of the oxygen atoms of the carboxylate group of the NOR ligand are directly bonded to the metal ions.[30] To our knowledge, the complexes prepared by Chen[30] are the only examples that reveal the ability of quinolones to coordinate directly to alkaline earth metal ions.

The interaction of quinolones with alkaline earth metal ions and the biologically active complexes formed from this interaction are particularly important.[31,32] In this work, the isolation and characterization of the complexes formed from the interaction of CIP and NOR with magnesium, calcium and barium perchlorate in methanol is reported. FTIR spectroscopy, electrical conductivity and thermal analysis have been used to elucidate the structure and the properties of the complexes formed from this interaction.

Results and discussion

Table 1 summarizes the carbon, hydrogen and nitrogen elemental analysis of the isolated complexes. The results obtained indicate that all of the isolated complexes are formed from the reaction of the metal salt with drug in 1:2 molar ratio. All of the complexes reported herein are white air stable solids at room temperature. The thermogravimetric analysis (TGA) and differential scanning calorimetery (DSC) indicate that all of the water content of these solids is lost at a temperature below 130 °C. No separate weight loss that can be attributed to the loss of coordinated water was observed probably because of the weak interaction of the water molecules and the metal ions in these complexes. The TGA and the DSC data indicate that all of the complexes isolated are unstable and decomposes in two steps at temperatures above 270 °C which is characteristic of the quinolone complexes.[35] Examination of solubility of these complexes shows that they are insoluble in benzene, chloroform and dichloromethane and other nonpolar solvents, slightly soluble in water, methanol and ethanol and soluble in DMF and DMSO. The electrical conductivity of the isolated complexes indicates that all of the complexes are 1:2 electrolytes. The IR spectra shown in Figure 2 for the complexes of NOR with calcium, magnesium and barium perchlorate show three strong bands at 1143, 1115 and 1086 cm^{-1}. These three bands are absent in the spectrum of the free NOR and occur in the region were the ν_3 band of the ClO_4^- ion is expected.[36] The appearance of these three bands and the known weak coordinating properties of the perchlorate anion confirm that the counter anion in these complexes is the perchlorate ion. The conductivity data and the preparation of the complexes from neutral methanol solutions rules out the possibility of the formation of hydroxo-, mixed hydroxo-drug-complexes or complexes that contain singly or doubly protonated quinolones as counter cation. The complexes of CIP with these salts showed similar spectral and conductometric behavior. The IR spectra of the complexes of NOR and CIP with alkali metal perchlorate show a strong broad absorption near 3400 cm^{-1} and three medium-intensity broad bands at 2840, 2484 and 2030 cm^{-1}. These bands can be assigned to the vibrations of the quaternized nitrogen of the piperazinyl group which indicate that the zwitterionic form of NOR and CIP is involved in the coordination to the metal ions investigated.[37]

Table 1: Elemental analysis and the proposed formulas of the complexes isolated.

Compound	C		H		N	
	Calc.	Found	Calc.	Found	Calc.	Found
$Mg(CIP)_2(ClO_4).6H_2O$	41.85	41.45	4.75	4.78	8.61	8.55
$Mg(NOR)_2(ClO_4)_2.4H_2O$	41.15	41.13	4.75	4.81	9.00	8.93
$Ca(CIP)_2(ClO_4).4H_2O$	41.94	41.62	4.55	4.30	8.63	8.54
$Ca(NOR)_2(ClO_4)_2.4H_2O$	38.99	39.05	4.91	4.48	8.54	8.47
$Ba(CIP)_2(ClO_4).2H_2O$	39.46	39.86	3.89	3.93	8.12	8.19
$Ba(NOR)_2(ClO_4)_2.5H_2O$	36.09	35.97	4.35	4.02	7.89	7.81

We made several attempts to prepare a series of complexes similar to those shown in Table 1 but contain the drug and the metal salt in 1:1 molar ratio by changing the salt to drug ratio reacted. In all of these attempts, the elemental analysis of the precipitate collected either failed to give the correct stoichiometry or indicated the formation of 1:2 complexes.

Structure of the Isolated Complexes

Figure 2 shows the FTIR spectra of NOR and its complexes with $Mg(ClO_4)_2$, $Ca(ClO_4)_2$ and $Ba(ClO_4)_2$. The strong bands observed at 1730 and 1616 cm^{-1} in the spectrum of the free NOR have been assigned before to the stretching vibration of the carboxylic (vCOOH) and the carbonyl groups (vCO), respectively.[15,16,38, 39] The measured spectrum for the free CIP is similar to that reported by Turel *et. al.*[40] The vCO of ciprofloxacin was observed 1623 cm^{-1}.[40] The main feature of the spectrum of CIP is the absence of the vCOOH vibration, a behavior that is consistent with zwitterionic nature of ciprofloxacin established by x-ray diffraction.[40] Turel *et. al.*[40] assigned two
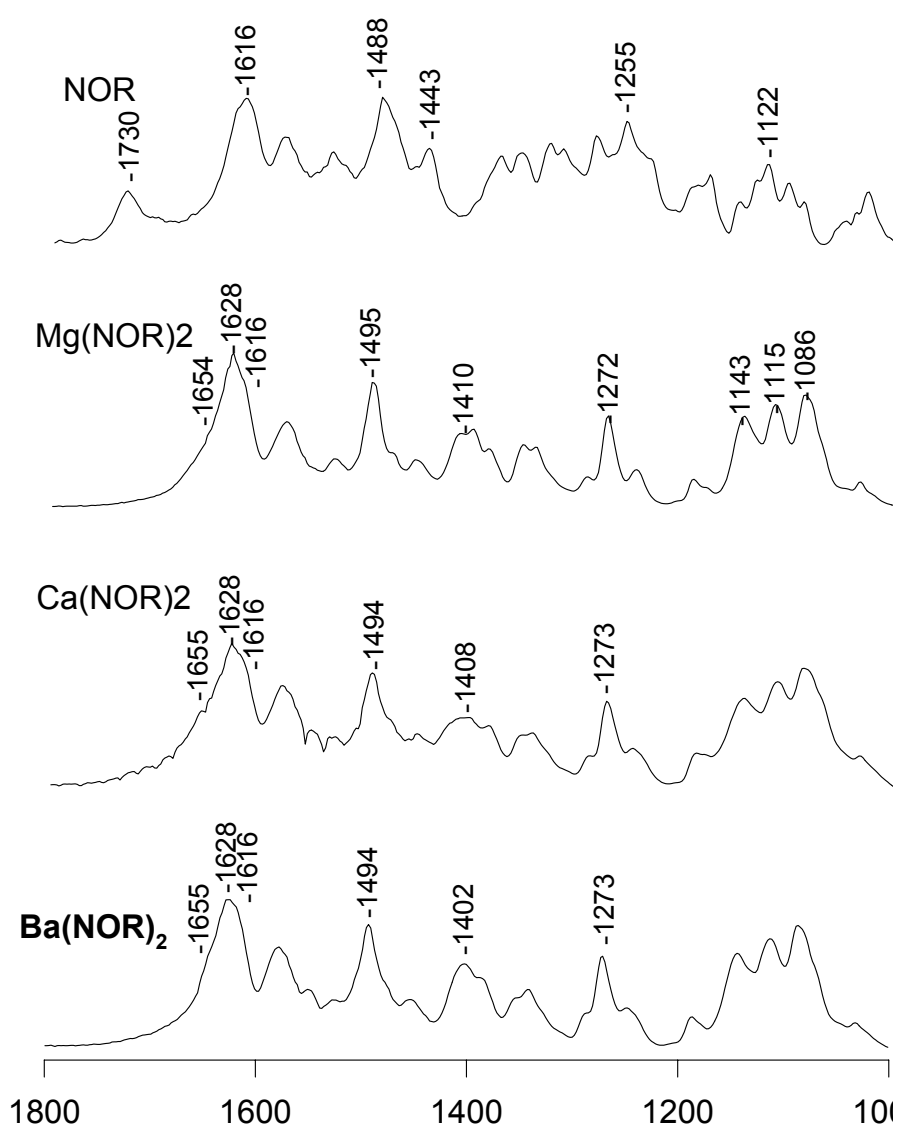
Figure 2: The FTIR spectra of norfloxacin and its complexes with Mg^{2+}, Ca^{2+} and Ba^{2+} perchlorate.

bands at 1585 cm^{-1} and 1380 cm^{-1} in the spectrum of CIP for the asymmetric and the symmetric stretching of the deprotonated carboxylato group, respectively.[40]

The IR spectra of NOR with Mg^{2+}, Ca^{2+} and Ba^{2+} perchlorate shown in Figure 2 display all the features of neutral zwitterionic quinolone complexes. Although the IR spectrum of CIP is different from that of NOR, the spectra of their complexes are remarkably similar. The $\nu COOH$ band observed at 1730 cm^{-3} for NOR disappears, a behavior that is indicative of the involvement of the carboxyl group in the interaction with metal ion. The spectral region between 1650 cm^{-1} and 1350 cm^{-1} is very congested which complicate the assignment of the stretching modes of the ligated carboxylato group. The intense band at 1628 cm^{-1} in the spectra of $Mg(NOR)_2^{2+}$, $Ca(NOR)_2^{2+}$ and $Ba(NOR)_2^{2+}$ appears to be composed of at least three peaks at 1618 cm^{-1}, 1628 cm^{-1} and 1652 cm^{-1}. The peak at 1628 cm^{-1} is absent in the spectrum of the free NOR and can be reasonably assigned to the asymmetric stretching vibration of the ligated COO$^-$ group. The spectra of $Mg(NOR)_2^{2+}$, $Ca(NOR)_2^{2+}$ and $Ba(NOR)_2^{2+}$ also show another medium intensity bands at 1412 cm^{-1}, 1401 cm^{-1} and 1401 cm^{-1}, respectively. These bands are absent in spectrum of NOR and most likely due to the symmetric vibration of the ligated COO$^-$ group. The band at 1380 cm^{-1} in the spectrum of CIP that was assigned to the symmetric stretch of COO$^-$ by Turel *et. al.*[40] disappears from the spectra of the complexes which confirms their assignment. However, the peak observed at 1580 cm^{-1} in the IR spectrum of CIP and assigned to the asymmetric stretch of COO$^-$ group of CIP persists in the spectra of the complexes. Also the observation of a peak with similar intensity at 1585 cm^{-1} in the spectrum of NOR which contains a protonated carboxyl group indicate that assignment of this band to the asymmetric stretch of COO$^-$ group is doubtful.[40]

It is established that the carboxylato group can act as unidentate, bidentate or as bridging ligand and distinction between these binding states can be made from the frequency separation ($\Delta\nu = [\nu_a(COO)-\nu_s(COO)]$) between the symmetric and the asymmetric stretching of this group.[36,41] By examining the symmetric and the asymmetric stretching vibrations of large number of caboxylato complexes with known crystal structure, Deacon and Phillips[41] established the criteria that can be used to distinguish between the three binding states of the carboxylate complexes. These criteria are: (i) unidentate carboxylato complexes exhibit $\Delta\nu$ values which are much larger than those of the ionic salts ($\Delta\nu >200$ cm^{-1}), (ii) bidentate or chelating carboxylato

complexes, exhibit $\Delta\nu$ significantly smaller than ionic values ($\Delta\nu$ <100 cm^{-1}), and finally, (iii) bridging complexes show $\Delta\nu$ comparable to the ionic values ($\Delta\nu \approx$150 cm^{-1}).
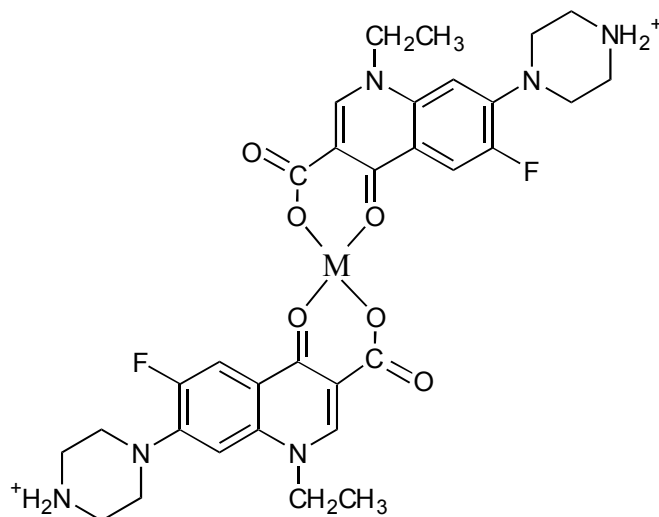

Figure 3: The proposed structure of the complexes isolated.

The observed $\Delta\nu$ for the Mg(NOR)$_2$$^{2+}$, Ca(NOR)$_2$$^{2+}$ and Ba(NOR)$_2$$^{2+}$ are 216 cm^{-1}, 227 cm^{-1} and 227 cm^{-1}, respectively which suggest a unidentate interaction of the carboxylate group.

The νCO in the spectrum of NOR appears at 1617 cm^{-1}. In the spectra of Mg(NOR)$_2$$^{2+}$, Ca(NOR)$_2$$^{2+}$ and Ba(NOR)$_2$$^{2+}$, the νCO is slightly effected by the interaction with the metal ion and appear as a shoulder near 1616 cm^{-1}. Similar behavior has been observed in several quinolone-metal ion complexes.[38,39] Therefore, NOR and CIP in the isolated complexes appear to act as a bidentate ligand through the oxygen atom of the carbonyl group and one of the oxygen atoms of the carboxylic group.

The FTIR data shown in Figure 2 cannot rule out the possibility of formation of polymeric complexes. However, the C, H and N elemental analysis of the complexes reported in this work are different form the values reported for the dimeric complex isolated by Chen *et. al.*[30] which indicate that these complexes are, most probably,

monomeric. The spectral evidences presented and the known coordinating properties of CIP and NOR suggest that the most likely structure of the isolated complexes is as shown in Figure 3.

Conclusions

The above results show that quinolone antibiotics are strong complexing agents for alkaline earth metal ions and the complexes formed involves direct coordination of the metal ion to the quinolone. The coordination of quinolones to metal ions increases their solubility in water and other polar solvents.

Experimental

Measurement: The FTIR spectra of the complexes were recorded in KBr disks using Nicolet Impact 410 Fourier transform infrared spectrophotometer. The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were measured using Shimadzu DSC-50 instrument. Electrical conductivity was measured using WTW LF 318 conductivity meter. Carbon, hydrogen and nitrogen were analysed at the Laboratoire d'Analyse Elementaire, Montreal, Quebec, Canada. The percentage of carbon, hydrogen and nitrogen used in the determination of the formulas of the complexes were the average of two measurements.

Materials: Ciprofloxacin and Norfloxacin used in this study were obtained from a local drug company. $Mg(ClO_4)_2.6H_2O$ (99%), $Ca(ClO_4)_2.4H_2O$ (99%) and $Ba(ClO_4)_2.3H_2O$ (98%) were from Aldrich Chemical Company and were used without further purification. HPLC grade methanol was used as a solvent.

Synthesis: All of the complexes were prepared by using the same procedure. In a typical experiment, 0.6 mmol ($\approx$ 0.2 g) of CIP or NOR suspended in 30 mL of methanol was mixed with another solution containing 0.3 mmol of the salt in methanol. The reaction mixture was stirred for 24 hours at room temperature. After that, the volume of the reaction mixture was reduced and the white precipitated complex was filtered off and washed with methanol and dichloromethane. The isolated complexes were desiccated over calcium chloride under reduced pressure for several days. The isolation of a single complex was checked using thin layer chromatography.

Acknowledgements

References and Notes

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Povzetek

Raziskane so bile interakcije magnezijevega, kalcijevega in barijevega perklorata s ciprofloksacinom (CIP) in norfloksacinom (NOR). Izolirani kompleksi so bili analizirani s pomočjo elementne analize, FTIR, električne prevodnosti in termične analize. Rezultati nakazujejo tvorbo kompleksov s formulo $[M(NOR)_2](ClO_4)_2 \cdot xH_2O$ in $[M(CIP)_2](ClO_4)_2xH_2O$ (M = Mg^{+2}, Ca^{+2} in Ba^{+2}). FTIR spekter izoliranih kompleksov kaže da CIP in NOR delujeta kot bidentatna liganda z obročnim karbonilnim kisikovim atomom in enim od kisikovih atomov v karboksilatni skupini.