

Complexes of Fe(III) ions with mefenamic acid

Halina Bojarowicz^{a,*}, Zenon Kokot^{a,*}, Andrzej Surdykowski^b

^aDepartment of Pharmaceutical Analysis, Medical Center of Postgraduate Education, 3 Debowa St., 85-626 Bydgoszcz, Poland

^bFaculty of Chemistry, N. Copernicus University, 7 Gagarina St., 87-100 Torun, Poland

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Abstract

Mononuclear and binuclear complexes of mefenamic acid with Fe(III) ions of formulae $\text{Na}[\text{Fe}(\text{C}_{15}\text{H}_{14}\text{O}_2\text{N})_4]$ and $\text{Fe}_2\text{Cl}(\text{C}_{15}\text{N}_{14}\text{O}_2\text{N})_5$ were obtained in the solid phase. Characterization of the complexes was performed by elemental analysis and visible, IR, ^1H and ^{13}C NMR spectroscopy and possible structures are proposed.

Keywords: Mefenamic acid; Fe(III) complex; IR spectroscopy; NMR spectroscopy; Elemental analysis

1. Introduction

Mefenamic acid (MA) {2-[(2,3-dimethylphenyl) amino]benzoic acid} is a non-steroidal drug with anti-inflammatory, analgesic and antipyretic activity [1]. The molecular structure of MA (presence of carboxylate and amino groups) suggests the possibility of complex formation with metal ions. Such species often possess more potent pharmacological activity and lower toxicity than the free drug.

Based on the reactivity of MA and other non-steroidal anti-inflammatory drugs in 2-deoxyribose solutions with Fe(III) ions, it was shown that these drugs can prevent Fe^{3+} complexation with other biologically important compounds [2].

In contradiction to the above findings, other

in vivo studies showed, that there were no differences between the metabolism of ^{59}Fe in monkey red cells from animals administered 100–200 $\mu\text{g kg}^{-1}$ of drug daily for 13 weeks and the control group [3]. These data suggest that the complexes between MA and Fe(III) ions, which may form in vivo, are not stable.

Because MA is used in therapy in relatively high doses and iron is a metal that plays an important role in biological processes, the interaction between mefenamic acid and Fe(III) should be clearly understood. In previous studies [4,5] it was shown, that MA forms with Fe(III) ions (in methanol–aqueous solutions) coloured complexes of various compositions, depending on the molar ratio of the reagents. In the presence of a ligand excess, mononuclear complexes with M:L ratios 1:1, 1:2, 1:3 and 1:4 were formed, but in the presence of an excess of Fe(III) ions, a binuclear brown–red complex was formed [4].

* Corresponding authors.

Table 1
Elemental analysis of complexes

Formula	Molecular weight	Content of the element determined (calculated)		
		C (%)	H (%)	N (%)
Na[Fe(C ₁₅ H ₁₄ O ₂ N) ₄]	1039.96	69.3, 69.06 (69.30)	5.32, 5.5 (5.43)	5.55, 5.46 (5.39)
Fe ₂ Cl(C ₁₅ H ₁₄ O ₂ N) ₅	1348.55	67.12, 67.2 (66.79)	5.17, 5.31 (5.23)	5.34, 5.39 (5.19)

In the present study, elemental analysis and visible, IR, ¹H and ¹³C NMR spectroscopy were used to elucidate the possible structure of MA–Fe(III) complexes obtained in the solid state.

2. Experimental

Mefenamic acid was obtained from Pharmaceutical Works "Polfa" (Pabianice, Poland). Stock solution (0.01 mol dm⁻³) was prepared by dissolution of a weighed sample in methanol. The solutions retained their stability for 50 days; no studies were conducted over longer periods.

A stock solution of 0.3 mol dm⁻³ Fe(ClO₄)₃ in 0.5 mol dm⁻³ HClO₄ was prepared by mixing (in stoichiometric quantities) BaCO₃ and Fe₂(SO₄)₃, both dissolved in HClO₄ (0.5 mol dm⁻³), and the precipitated BaSO₄ was filtered. Iron and barium ions were determined by gravimetric and complexometric methods.

All other chemicals were of reagent-grade quality.

Elemental analyses were carried out using a Perkin-Elmer CHN 2400 Elemental Analyser.

IR spectra were obtained in the solid state using KBr pellets and were recorded from 4000 to 300 cm⁻¹ on a Specord M-80 instrument (Carl Zeiss, Jena, Germany).

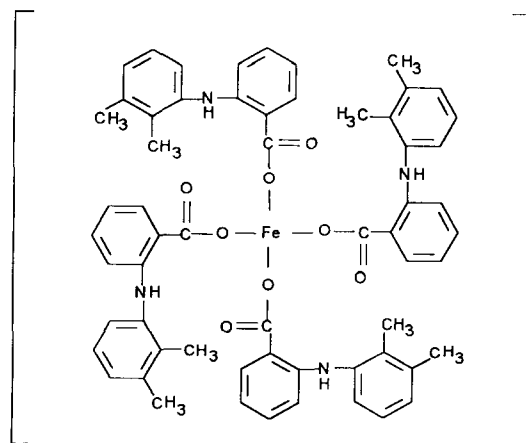
NMR spectra were recorded on a Varian Gemini 200 BB instrument operating at 199.97 MHz for ¹H NMR and 50.289 MHz for ¹³C NMR. Chemical shifts are quoted in ppm downfield from tetramethylsilane. All spectra

were determined in dilute CDCl₃ solutions at a probe temperature of 27°C.

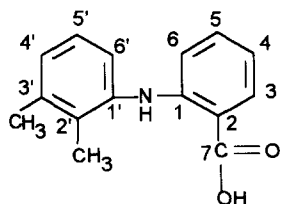
Magnetic susceptibility measurements of a powdered sample were carried out at room temperature by the Faraday method with Hg[Co(NCS)₄] as a calibrant.

A complex of formula Na[Fe(C₁₅H₁₄O₂N)₄] was obtained by the reaction of Fe(ClO₄)₃ with mefenamic acid, in the presence of an excess of the ligand, in methanol–water (90:10, v/v) at pH 2.80 and constant ionic strength *I* = 0.1 (maintained by using NaClO₄), according to the procedure described previously[5].

The binuclear complex was obtained by the reaction of FeCl₃ and mefenamic acid, with an excess of Fe(III) ions, in methanol–water (80:20, v/v) at pH 2.70, as described previously [4].



(1). Mononuclear complex of Fe(III) ion with mefenamic acid ([FeL₄]⁻).



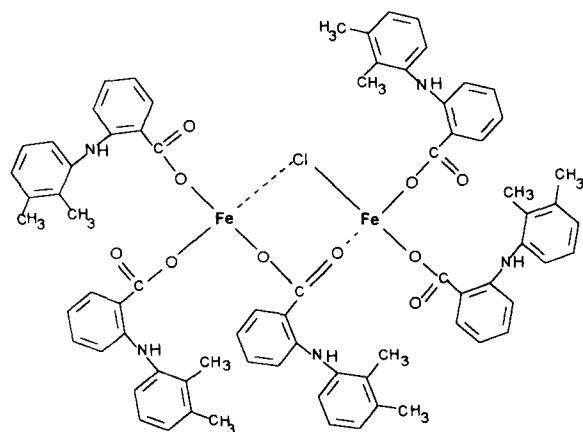
(2). Mefenamic acid.

3. Results and discussion

Depending on the MA:Fe(III) stoichiometric ratio, mefenamic acid forms various coordination compounds with iron(III) ions in methanol–aqueous solutions. Spectrophotometric investigations showed that in the system MA–Fe(III) in the presence of a ligand excess, mononuclear complexes of the types FeL , FeL_2 , FeL_3 and FeL_4 were formed [5]. The molar absorption coefficient ($\epsilon = 1570$), calculated for solutions of the mononuclear complex (FeL_4) at 550 nm, is significantly higher than that normally expected for a d–d transition and may be attributed to the charge-transfer transition [6].

Spectrophotometric investigations of the reaction of MA with FeCl_3 showed that in the presence of an excess of the metal, a binuclear complex was formed with the formula Fe_2L_5 [4]. The molar absorption coefficient ($\epsilon = 1140$), calculated at 495 nm, was characteristic of a charge-transfer transition (similarly as for the mononuclear complexes).

The results of elemental analysis are shown in Table 1. As can be seen, there is a good agreement

(3). Binuclear complex of Fe(III) ions with mefenamic acid (Fe_2L_5).

between the experimental carbon, hydrogen and nitrogen contents and those calculated from the proposed formulae.

In the case of the complexes with Fe(III): mefenamic acid ratios of 1:1 and 1:2, chelate bonds formation via the nitrogen atom of the amino group and the oxygen atom was proposed [7]. Chelate-type coordination was also suggested for the ML_3 complex [8]. However, the existence of the chelate rings is not consistent with the weak electro–donor properties of the amino group of MA [4]. Also, methyl groups *ortho* to the nitrogen atom may cause steric hindrance to such chelate coordination.

The IR spectrum of the FeL_4 complex shows the N–H stretching vibration band at 3360 cm^{-1} (3310 cm^{-1} in MA). The shift of the N–H bond stretching vibrations to higher wavenumbers (in the case of the FeL_4 complex) indicates the absence of metal–nitrogen bonding. Thus, based on our earlier investigations [5], we can assume that the FeL_4 complex consists of four molecules of deprotonated mefenamic acid interacting with iron through the oxygen of the carboxylate group, as shown in formula 1. Probably a tetrahedral arrangement is formed, as was found for other Fe(III) complexes [9,10].

The differences between the wavenumbers of asymmetric and symmetric stretching for the carbonyl group were calculated. In the case of the complex $\Delta\nu = 1618 - 1400\text{ cm}^{-1} = 218\text{ cm}^{-1}$, but for the ionic form $\Delta\nu = 1610 - 1370\text{ cm}^{-1} = 240\text{ cm}^{-1}$. The smaller $\Delta\nu$ value calculated for the complex suggests the existence of bridge-type or chelate-type bonding between the metal and ligand [11]. According to the shift criterion [12], in the case of chelate-type bonding, the asymmetric stretching (ν_a) of the carbonyl group of the complex is at lower and symmetrical stretching (ν_s) is at higher wavenumbers than in the free anion. When bridge-type bonding exists in the complex, both ν_a and ν_s are at higher wavenumbers than in the ionic form. In our case, we obtained $\nu_a(\text{ionic form}) = 1610\text{ cm}^{-1}$, $\nu_a(\text{complex}) = 1618\text{ cm}^{-1}$ and $\nu_s(\text{ionic form}) = 1370\text{ cm}^{-1}$, $\nu_s(\text{complex}) = 1400\text{ cm}^{-1}$. In contradiction to the structure proposed above, this may indicate that in the complex in the solid state there is also bridge-type bonding between

the metal and MA.

Binuclear complexes of iron(III) with anthranilic acid and some other bidentate ligands with the formula Fe_2L_5 were studied by Vasisht and Narula [13]. They indicated that in $\text{Fe}_2\text{Cl}(\text{o-NH}_2\text{C}_6\text{H}_4\text{CO}_2)_5$ the amino group is uncoordinated, but anthranilic acid molecules were coordinated through the carboxylate oxygen.

The IR spectrum of $\text{Fe}_2\text{Cl}(\text{C}_{15}\text{H}_{14}\text{O}_2\text{N})_5$ shows sharp, strong $\nu(\text{N-H})$ bands at 3485 and 3380 cm^{-1} . This clearly indicates that the amino group in the MA molecule is uncoordinated and does not participate in the formation of the chelate bond. Another unusual feature is a strong band at 1650 cm^{-1} assigned to $\nu(\text{C=O})$, which may be ascribed to a monodentate carboxylate group. In addition, strong bands at 1575 and 1395 cm^{-1} are observed, which are due to the asymmetric and symmetric vibrations of the carboxylate group. Their separation ($\Delta\nu(\text{CO}_2)=180 \text{ cm}^{-1}$) indicates bridge-type bonding [14]. This reveals that the carboxylate groups of MA present in the Fe_2L_5 complex are not equivalent, but rather that both monodentate- and bridging-type bonds occur.

The ^1H and ^{13}C NMR spectra of $\text{Fe}_2\text{Cl}(\text{C}_{15}\text{H}_{14}\text{O}_2\text{N})_5$ show the presence of paramagnetic Fe(III) ions and also indicate strong antiferromagnetic coupling between them. The above statement is in a good correlation with the magnetic moment of the compound ($3.26 \text{ BM mol}^{-1} \text{ Fe}^{3+}$) calculated at room temperature. For some ^1H NMR resonances, relaxation times T_1 were measured: $\delta = 2.03 \text{ ppm}$, $T_1 = 17.7 \text{ ms}$; $\delta = 5.76 \text{ ppm}$, 15.4 ms ; $\delta = 6.46 \text{ ppm}$, 60.4 ms ; $\delta = 7.05 \text{ ppm}$, 25.8 ms . Resonances at 2.03 ppm can be assigned to both methyl groups, but other resonances are not observed or cannot be precisely assigned to the individual hydrogens of the two aromatic rings. One can only correlate longer relaxation times with a larger distance from the paramagnetic centre.

More information about the structure of the complex was obtained from the ^{13}C NMR spectra. Some resonances are broad, but most of them were split. Based on NMR studies of mefenamic acid (**2**) [15], there are possibilities of localization of some of the chemical shifts observed.

In the ^{13}C NMR spectra one can observe (1) splitting of resonances from the carboxylate group

(at ca. 170.5 ppm) and from C-1 (at 150.3 and 152.9 ppm); (2) a broad signal of C-2 (ca. 112.5 ppm); and (3) sharp signals and a small split for C-6' (at 124.9 and 125.1 ppm); similar behaviour is observed for resonances assigned to the methyl groups.

These data indicate various coordination modes of the ligand. Broadening and splitting of the ^{13}C resonances assigned to the carboxylate group and to the ring connected to this group indicate that the iron ions in the Fe_2L_5 complex are coordinated through the unequivalent carboxylate groups.

Based on our spectroscopic and magnetic investigations, we can propose a structure of the binuclear complex of Fe(III) with mefenamic acid in which the central ions are in the pseudo-tetrahedral symmetry as shown (**3**). However, it does not rule out the possibilities of other modes of binding.

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