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THE INTERACTION OF PIROXICAM WITH SOME METAL IONS IN AQUEOUS SOLUTION

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ABSTRACT

The interaction of various metal ions, such as Co(II), Cu(II), La(III), Ce(III), Y(III) and Al(III), with piroxicam in aqueous solution has been studied by spectroscopic methods. The interaction of the metal ions with HMBDC (4-hydroxy-2-methyl-1,2λ-benzothiazine-1,1-dioxide-3-methyl-carboxylate) has also been studied for comparison. It was found that Al(III) and Y(III) ions interact significantly with both piroxicam and HMBDC to form 1:1 complexes in aqueous solution. The stability constants of the complexes have been determined at $\mu \rightarrow 0$. The thermodynamic parameters for the complex formations have also been calculated from the Gibbs–Helmholtz plot. On the basis of the spectroscopic and thermodynamic evidence, the binding sites of piroxicam and HMBDC to the metal ions are suggested.

INTRODUCTION

Some *N*-heterocyclic carboxamides of the 4-hydroxy-2*H*-1,2-benzothiazine-1,1-dioxide system have anti-inflammatory properties [1,2]. Among them piroxicam (4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-1,2-benzothiazine-3-carboxamide) has been used as an effective anti-inflammatory drug [3]. However, it is known that piroxicam causes subsidiary ill effects in some patients, specifically cutaneous photosensitivity [4–6]. Recently, it has been reported that the metabolic product of piroxicam in the biological system shows highly photosensitizing properties [7].

In order to investigate the possible role of the metal ions in this photosensitizing effect of piroxicam in biological systems, we have studied the interaction of some metal ions with piroxicam in aqueous solution using

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spectroscopic methods. The interaction of the metal ions with a piroxicam-related compound, HMBDC (4-hydroxy-2-methyl-1,2λ-benzothiazine-1,1-dioxide-3-methyl-carboxylate) has also been studied.

EXPERIMENTAL

The piroxicam was obtained from Yu Han Corperation in Korea. The compound was recrystallized three times from methanol solution before use. It is a bright white crystal having a melting point of 198–200 °C. The HMBDC was synthesized by modifying the method described in the literature [8] and recrystallized three times before use. The melting point of HMBDC has been found to be 166–168 °C.

Stock solutions of the metal ions, except Y(III), were prepared by dissolving appropriate amounts of the corresponding metal chlorides in water. The stock solution of Y(III) ion was prepared by dissolving the appropriate amount of Y_2O_3 in concentrated HCl solution and diluting it with water. The stock solutions of the metal ions were standardized by the EDTA back titration method with Eriochrome Black T indicator. The water used as the solvent was distilled in the presence of $KMnO_4$.

A Beckman UV-5260 spectrophotometer and a SLM 4800 Aminco spectrofluorometer were used to measure the absorption and fluorescence spectra, respectively. In the fluorescence spectra measurements, a narrow excitation slit (4 nm) was used to minimize the photolysis of the compounds.

A spectrophotometric method described by Klotz and Ming [9] was adopted to determine the stability constants of the complexes formed by the interactions of the metal ions with piroxicam or HMBDC. If C_L and C_M represent the total concentrations in moles/litre of the ligand and metal ion, respectively, the stability constant (K_1) of the complex can be written as

$$K_1 = \frac{\alpha C_L}{(C_M - \alpha C_L)(1-\alpha)C_L} = \frac{\alpha}{(C_M - \alpha C_L)(1-\alpha)} \tag{1}$$

where α is the mole fraction of the ligand bound to the metal ion. α can be obtained spectrophotometrically using the following equation

$$\alpha = \frac{A_t - A_M - \epsilon_1 Cd}{(\epsilon_2 - \epsilon_1)Cd} \tag{2}$$

where A_t is total absorbance of the solution, A_M is the absorbance of the metal ion in the solution, C is the molar concentration of the absorbing species and d is the thickness of the cell. ϵ_1 and ϵ_2 are the molecular extinction coefficients of the ligand and the metal complex, respectively. The absorbance of the metal ion at the wavelength (340 nm) studied is practically nil. ϵ_1 can be obtained from the absorbance of a ligand solution at a known concentration. The absorbance of the solution at the fixed ligand

concentration was plotted against the reciprocal of the total metal ion concentration. ϵ_2 can be evaluated from the absorbance determined by extrapolation of the plot.

All the measurements were made at three different temperatures to calculate the thermodynamic parameters of the complexations. The concentrations of the species were corrected in the calculation of the stability constants for the ionic strength of $\mu \rightarrow 0$ using the Davies equation [10].

RESULTS AND DISCUSSION

Absorption and emission spectra

The absorption spectrum of piroxicam and the effects of the metal ions on the absorption spectrum in aqueous solution are shown in Fig. 1. The spectrum of piroxicam shows a maximum absorption band at 356 nm. The concentration of piroxicam was 2.5×10^{-5} M. There are no significant changes in the intensity and position of the maximum absorption band of the spectrum with the addition of La(III), Ce(III) or Mg(II) ions into the piroxicam solution. This means that there is no detectable interaction of these ions with the piroxicam. However, the maximum absorption band at 356 nm disappears with the addition of Co(II) or Cu(II) ions into the piroxicam solution. Piroxicam may be catalytically hydrolysed by Co(II) and

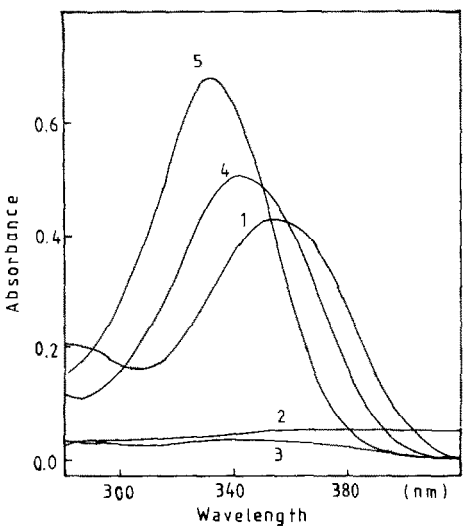


Fig. 1. Absorption spectra of piroxicam in various salt solutions: $C_{pir} = 2.50 \times 10^{-5}$ M; 1. $C_M = 0.00$ or 1.00×10^{-3} M for M = Mg(II), Ce(III) and La(III); 2. $C_M = 1.00 \times 10^{-3}$ M for M = Cu(II); 3. $C_M = 1.00 \times 10^{-3}$ M for M = Co(II); 4. $C_M = 1.00 \times 10^{-3}$ M for M = Al(III); and 5. $C_M = 2.00 \times 10^{-3}$ M for M = Y(III).

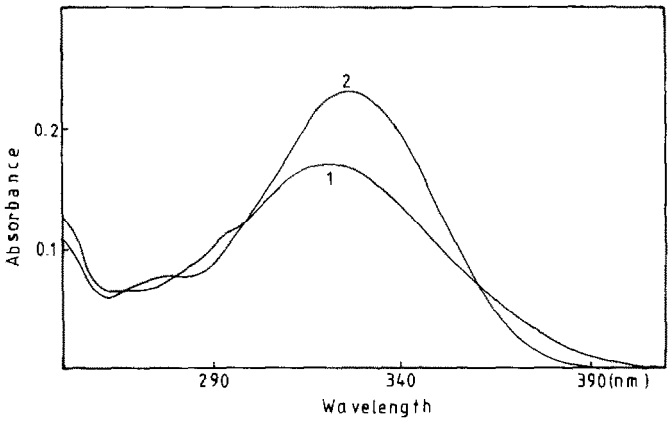
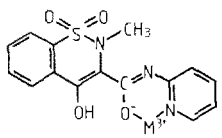


Fig. 2. Absorption spectra of HMBDC: 1. $C_{HMBDC} = 2.50 \times 10^{-5}$ M; 2. $C_{HMBDC} = 2.50 \times 10^{-5}$ M, $C_M = 9.00 \times 10^{-4}$ M for M = Al(III).

Cu(II) ions. We are continuing to study these interesting phenomena. The concentration of each metal ion in the solution was 1.0×10^{-3} M.

The addition of Al(III) or Y(III) ions into the piroxicam solution causes an increase in the intensity and a blue shift of the maximum absorption band of the spectrum, indicating the significant interaction of these ions with piroxicam. The concentrations of Al(III) and Y(III) ions in the solution were 1.0×10^{-3} M and 2.0×10^{-3} M, respectively. In the complexation of piroxicam with Al(III) and Y(III) ions, the binding sites of the piroxicam may be the carbonyl oxygen atom of the carboxamide group and the nitrogen atom of the pyridyl group



Donating the π-electron density of the pyridyl ring to the metal ion tends to lower the energy of the π-orbitals of piroxicam. Thus, the maximum wavelength of the $\pi \rightarrow \pi^*$ transition band would be blue shifted.

HMBDC also interacts with Al(III) ion in aqueous solution. As shown in Fig. 2, the absorption spectrum of HMBDC is significantly changed with the addition of Al(III) ion. In contrast with the case of piroxicam, the maximum absorption band of HMBDC is red shifted, as expected. The possible donor sites of HMBDC to the metal ion are the carbonyl oxygen atom of the methyl ester group and the hydroxy oxygen atom of the benzothiazine ring. This tends to confirm that piroxicam interacts with the metal ions through the nitrogen atom of the pyridyl ring but not through the hydroxy oxygen atom of the benzothiazine ring. HMBDC has a carboxylate ester as a side chain of the benzothiazine, while piroxicam has a carboxamide group.

There is no significant fluorescence emission in aqueous solutions of either piroxicam or HMBDC. Even the addition of metal ions Al(III) or Y(III) to the aqueous solution of HMBDC does not cause the emission of fluorescence. However, in the case of the piroxicam solution, solutions including Al(III) or Y(III) ions emit fluorescence at $\lambda_{max} = 464$ nm for Al(III) ion, and $\lambda_{max} = 461$ nm for the Y(III) ion. This indicates that the metal ions interact with piroxicam but not with HMBDC in the excited state. This also suggests that the binding sites of piroxicam are different from those of HMBDC. Again, the metal ions Y(III) and Al(III) form six-membered chelates with the oxygen donor atom of the carboxamide group and the nitrogen atom of the pyridyl ring of piroxicam in the excited state. The cyclic structure made by the metal ion enhances the quantum yield. The fluorescence emission spectra were measured at 340 nm excitation and an O.D. of 0.3.

Thermodynamic parameters

The dependence of the absorption band of piroxicam on the concentration of Al(III) ion is shown in Fig. 3. A typical set of spectrophotometric data used in the calculation of the 1:1 complex formation constant of Y(III)–piroxicam is given in Table 1.

The temperature dependence of the stability constant is not very large. The enthalpy change (ΔH_1) and entropy change (ΔS_1) of the complex formation were obtained from the linear least-squares analysis of the Gibbs–Helmholtz plot. Figure 4 is the Gibbs–Helmholtz plot of the Y(III)–piroxicam system. The thermodynamic parameters calculated are given in Table 2. The relative errors estimated are less than 20% for ΔH_1 and less than 10% for ΔS_1.

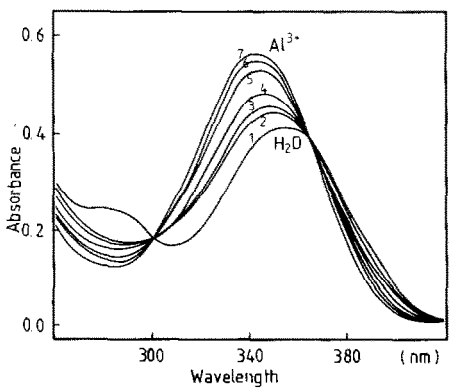


Fig. 3. Dependence of the absorption spectrum of piroxicam on the concentration of Al(III) ion in aqueous solution: $C_{pir} = 3.00 \times 10^{-5}$ M, $C_{Al^{3+}} =$ (1) 0.00 M, (2) 3.00×10^{-5} M, (3) 4.00×10^{-5} M, (4) 6.00×10^{-5} M, (5) 1.00×10^{-4} M, (6) 4.00×10^{-4} M, and (7) 5.00×10^{-4} M.

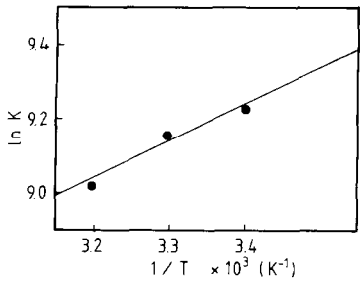


Fig. 4. Gibbs–Helmholtz plot of the Y(III)–piroxicam system.

These thermodynamic parameters provide further evidence that the metal ions interact with the piroxicam through the nitrogen atom of the pyridyl ring. It should be noted that the metal complex formation of piroxicam is exothermic while that of HMBDC is endothermic. It is obvious that the driving force for the metal complex formation of HMBDC is the large positive entropy effect.

TABLE 1

Typical set of spectroscopic data for the Y(III)–piroxicam system at 20 °C and $\mu \rightarrow 0$

$C_{Y^{3+}} \times 10^4$ (M)	Absorbance at 340 nm	α
0.800	0.390	0.318
1.20	0.400	0.347
1.60	0.416	0.394
2.00	0.449	0.491
6.00	0.525	0.715
10.0	0.575	0.862
18.0	0.585	0.891
24.0	0.587	0.897
32.0	0.609	0.962
36.0	0.601	0.938
40.0	0.622	1.00

$C_{pir} = 2.50 \times 10^{-5}$ M, $\epsilon_1 = 1.13 \times 10^4$ M^{-1} cm^{-1} for piroxicam, $\epsilon_2 = 2.49 \times 10^4$ M^{-1} cm^{-1} for Y(III)–piroxicam.

TABLE 2

Thermodynamic parameters for the complex formations of piroxicam and HMBDC with metal ions in aqueous solution at 20 °C and $\mu \rightarrow 0$

Complexes	log K_1	ΔH_1 (kJ mol^{-1})	ΔS_1 (kJ K^{-1} mol^{-1})
Al(III)–piroxicam	4.4 ± 0.2	-3.7	72.3
Y(III)–piroxicam	4.0 ± 0.2	-8.6	47.6
Al(III)–HMBDC	4.2 ± 0.1	12.7	124

The oxygen donor site in aqueous solution would be the better organizer of the solvent molecule than the nitrogen donor site. Thus, the disruption of the organized solvent structure around the oxygen donor site would cause the large positive entropy in the interaction of the metal ion with HMBDC. It would also require more energy to dissolve the oxygen donor site than the nitrogen donor site. This accounts for the exothermicity of the piroxicam system and the endothermicity of the HMBDC system.

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