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THERMOANALYTICAL BEHAVIOUR OF THE CAPTOPRIL–COBALT(II) COMPLEX

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ABSTRACT

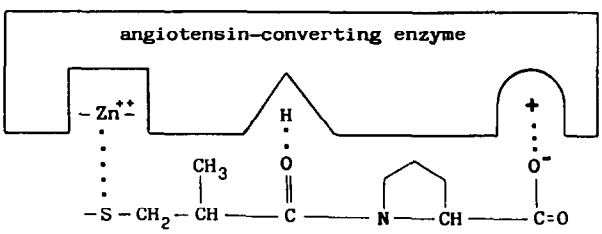
Captopril (H_2L) reacts with cobalt(II) in aqueous solution at a neutral pH forming a deep red complex. The reaction rate depends on the temperature, pH, metal ion and ligand concentrations. A solid compound precipitates by acidification of the solution. The chemical, potentiometric, and spectroscopic analyses of the solid complex give the simplest formula, $Co(HL)_2 \cdot H_2O$, and suggest that the sequence of the bonds is S–Co–S, with the carboxylic group of the ligand remaining uncoordinated.

The thermal behaviour of the captopril and its cobalt complex was studied by thermogravimetry, differential thermal analysis and differental scanning calorimetry in dynamic nitrogen and oxygen atmospheres.

INTRODUCTION

Captopril, 1-[2(S)-3-mercapto-2-methyl-1-oxopropyl]-L-proline, is a potential drug for the treatment of high blood pressure that can result from overproduction of angiotensin II.

Captopril inhibits the enzyme which catalyzes the conversion of inactive angiotensin I to angiotensin II. The mechanism of the action has not been proved, but probably occurs through interaction with the enzyme, a zinc-containing metalloprotein, at its active site [1].



Captopril

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We are currently performing a systematic investigation into the reactions of captopril with some transition metal ions to verify experimental conditions, mechanism and complexation reactions which may also provide a better understanding of the biological activity of this molecule. The present paper reports some results on the captopril–cobalt(II) complex.

EXPERIMENTAL

Apparatus

The thermal measurements were carried out using a Perkin–Elmer TSG-2 thermal analyser, DTA 1700, and a DSC-7 differential scanning calorimeter, connected to a model 3600 Data Station equipped with a software package, running on the data station itself. TG, DTA and DSC runs were made in a stream of nitrogen or oxygen (flow rate about 50 ml min^{-1}). The heating rate was 10 °C min^{-1}, with samples of 2–3 mg.

The mass spectra were obtained on a Kratos MS 80 mass spectrometer coupled with a DG 30 data system, operating in electron-impact mode. Samples were introduced via the direct insertion probe. The temperature source was at 250 °C, the temperature probe 230–280 °C and the electron energy 70 eV.

IR and visible spectra were recorded using Perkin–Elmer 125 grating IR and Perkin–Elmer 320 UV–VIS spectrophotometers.

An Orion EA 940 pH-meter with an Orion 91.04 combined glass electrode were used for the pH measurements.

Reagents

The captopril was a gift from Squibb, Anagni (Italy), and was not less than 99% purity. The cobalt(II) was in the form of perchlorate hexahydrate ("Alfa"). All other chemicals were analytically pure.

Preparation of the solid compound

To avoid degradation of the captopril by air oxidation under mildly acid or alkaline conditions, all the reactions in aqueous solution were performed in a pure nitrogen atmosphere.

In aqueous solution at neutral pH, captopril ($C_L = 5 \times 10^{-3}$ mol l^{-1}) reacts with cobalt(II) ($C_M = 5 \times 10^{-5}$ mol l^{-1}) giving a red complex species ($\lambda_{max} = 515$ nm, $\epsilon = 2.8 \times 10^4$ l mol^{-1} cm^{-1}). At room temperature, the reaction is complete after about 5 days, at 37 °C after about 2 days, and if the solution is heated in a boiling water bath, after 1 h. The reaction rate

depends on the metal and/or ligand concentrations and on the pH of the solution. The reaction does not occur if the concentrations are $< 1 \times 10^{-3}$ mol l^{-1} or if pH < 6. The complexation reaction is not reversible and acidification of the solution yields a red colloidal precipitate.

The solid complex was prepared by the slow addition of a solution of cobalt(II) (1.5 g as perchlorate hexahydrate in about 50 ml of water) to a solution of captopril (4.5 g in about 200 ml of water, with addition of NaOH solution to pH 7). The mixture was heated in a boiling water bath for 1 h, then cooled at room temperature. The precipitate was filtered off, washed with water, and purified by dissolving in dilute NaOH solution, and precipitating again with perchloric acid. Finally, it was washed with distilled water and dried in a vacuum over silica gel. The complex is a red powder, slightly soluble in water and ethanol, insoluble in diethylether or chloroform. The chemical analysis was in agreement with the simplest formula $Co(HL)_2 \cdot H_2O$ (F.W. 509.49).

RESULTS AND DISCUSSION

Captopril

The literature reports some data on the crystal structure of captopril [2], its physico-chemical and analytical characteristics [3], the conformational and acid–base equilibria [4] and the oxidative or hydrolytic effects in aqueous solution [5]. No data are available on the thermal behaviour of this molecule.

The thermogravimetric analysis (TG) in a dynamic O_2 atmosphere (Fig. 1, curve a) shows that captopril is stable up to 155 °C and then decomposes in at least three steps. The first inflection occurs at 27% mass loss (155–240 °C) corresponding to the methyl and carboxylic groups. The process is accompanied by a small exothermic peak in the DTA curve measured in O_2 (Fig. 2, curve a) resulting from the superimposition of the methyl oxidative decomposition and the decarboxylation of the molecule, which occurs with absorption of thermal energy as shown by the endothermic peak in the DTA curve recorded in N_2 (Fig. 2, curve b). The second step leads to an unknown intermediate at about 320 °C. Probably, evolution of the pyrrolinium group occurs (an endothermic peak in the DTA curve recorded in N_2) as well as the partial pyrolysis of the molecule, which produces an endothermic peak in DTA in O_2. The loss in mass proceeds at a slow rate up to about 480 °C, where the rate increases and rapid pyrolysis takes place, as shown by a large exothermic peak in DTA in O_2 and several small endothermic peaks in DTA in N_2. No residue is observed at 550 °C. TG in an N_2 atmosphere (Fig. 1, curve b) shows that decomposition occurs in unresolved steps between 185 and 670 °C, confirming the decomposition trend of the molecule. The initial

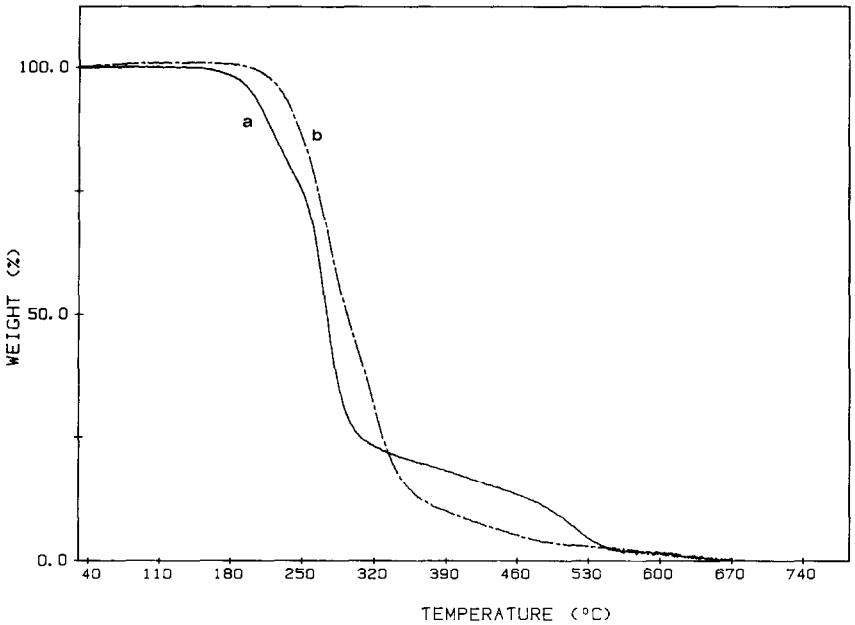

Fig. 1. TG curves for captopril in oxygen (a) and nitrogen (b) atmospheres.

decomposition temperature is delayed by the absence of the methyl pyrolysis and the first inflection at about 300 °C corresponds to the evolution of the carboxylic and pyrrolinium groups (mass loss 52%).

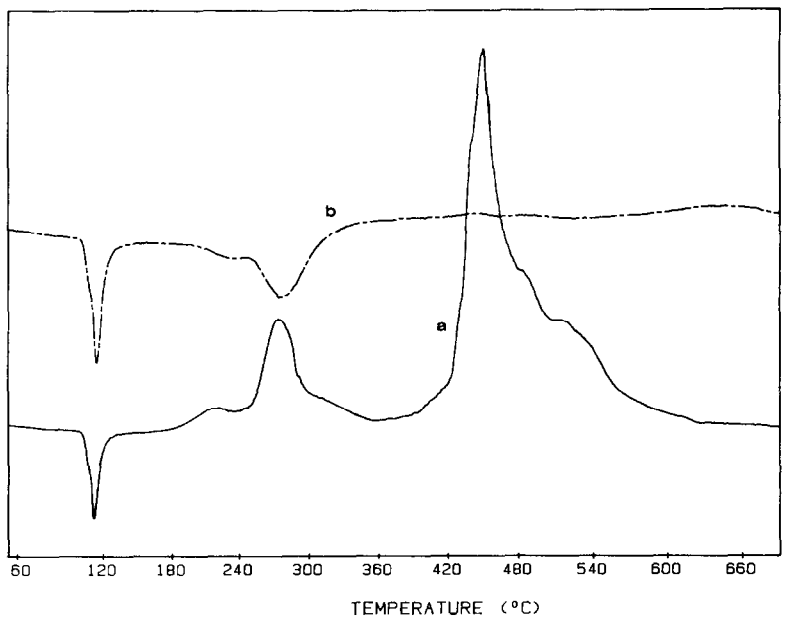

Fig. 2. DTA curves for captopril in oxygen (a) and in nitrogen (b) atmospheres.

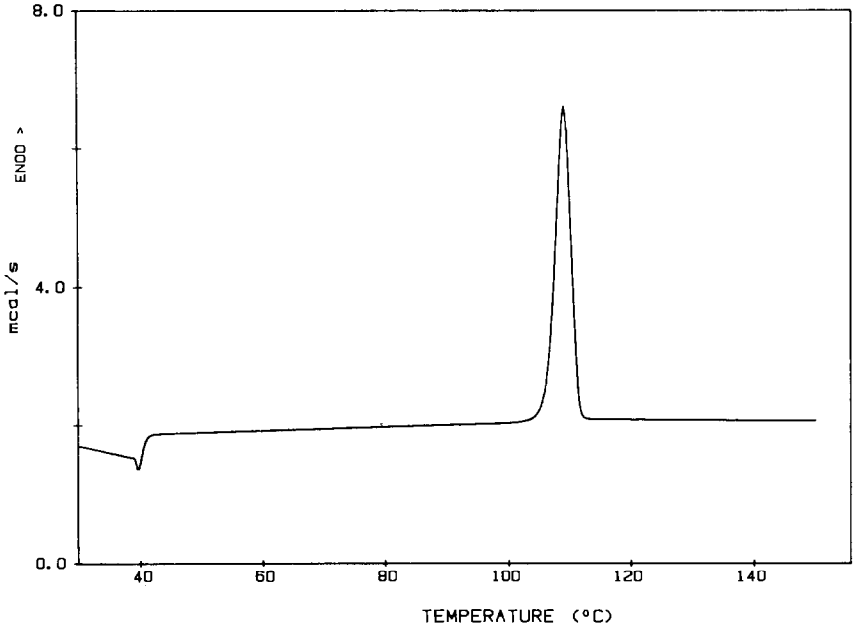

Fig. 3. DSC curve for captopril in a nitrogen atmosphere.

The DTA curves in both O_2 and N_2 atmospheres exhibit an intense and sharp endothermic effect at about 107 °C, which corresponds to the fusion of the captopril.

A quantitative analysis of the process was performed by DSC (Fig. 3), the melting point (107.7 °C), the melting heat (26.3 kJ mol^{-1}) and the purity (> 99.7%) of the captopril being calculated.

Cobalt(II)–captopril complex

Potentiometric, spectroscopic and thermal analyses were performed on the solid compound in order to better characterise its structure.

Potentiometric titration with NaOH solution confirms the presence of two moles of acid hydrogen per mole of complex: both titrated completely at about pH 9 ($pK_{a_1} = 6.5$, $pK_{a_2} = 7.7$).

In the IR spectrum (KBr disc), the absence of the ν_{S-H} band at 2567 cm^{-1} and the presence of the protonated carboxylic group at about 1730 cm^{-1} ($\nu_{C=O}$) [6], proves that only the mercapto group of the ligand is involved in the cobalt complexation. This was confirmed by the absence of the mercapto-proton triplet at 155 ppm in the NMR spectrum.

TG in dynamic O_2 (Fig. 4, curve a) shows a weight loss in the range 40–100 °C, in accordance with the evolution of a water molecule (calc. 3.53%, found 3.5%).

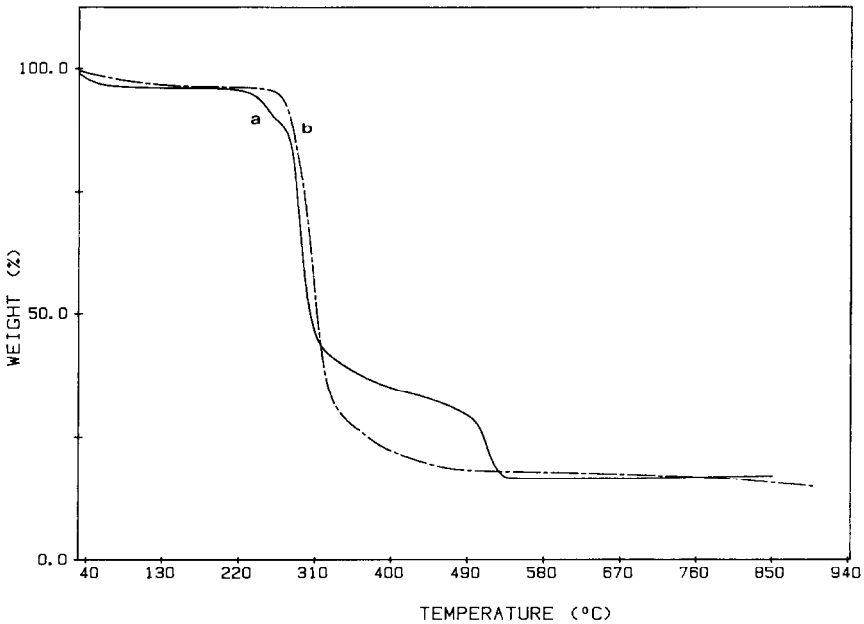

Fig. 4. TG curves for the captopril–cobalt(II) complex in oxygen (a) and in nitrogen (b) atmospheres.

The anhydrous complex is stable up to about 210 °C and then decomposes in at least three steps. In the first step, corresponding to the loss of the two methyl groups (calc. 5.88%, found 5.9%) at 265 °C, a second process is superimposed, corresponding to the partial decomposition of the ligand (48% mass loss at 325 °C). The intermediate shows a continuous slow mass loss until about 485 °C, where the decomposition rate increases giving a residue of Co_2O_3 (calc. 16.28%, found 16.5%) at 535 °C.

In dynamic N_2 atmosphere (Fig. 4, curve b), the anhydrous complex exhibits a higher thermal stability than in O_2: it begins to decompose at about 240 °C showing a mass loss of around 75% at 500 °C in unresolved steps. The residue, mainly CoS_x, loses mass at a very slow rate and does not reach a constant weight, not even at 900 °C. The decomposition delay in nitrogen is explained by the inhibition of the oxidative decomposition of the methyl groups. In fact, in the DTA curve in O_2 atmosphere (Fig. 5, curve a), the decomposition of the complex begins with an exothermic peak at around 210 °C and the reaction rapidly becomes endothermic when the carboxylic groups are eliminated.

DTA in N_2 atmosphere (Fig. 5, curve b) shows only one endothermic peak at about 240 °C. The second decomposition process occurs, as in the ligand molecule, with an exothermic peak in O_2 atmosphere, which becomes endothermic in N_2 (evolution of the pyrrolinium group), while the oxidative decomposition of the intermediate produces large exothermic peaks in oxygen and some very small endothermic peaks in nitrogen.

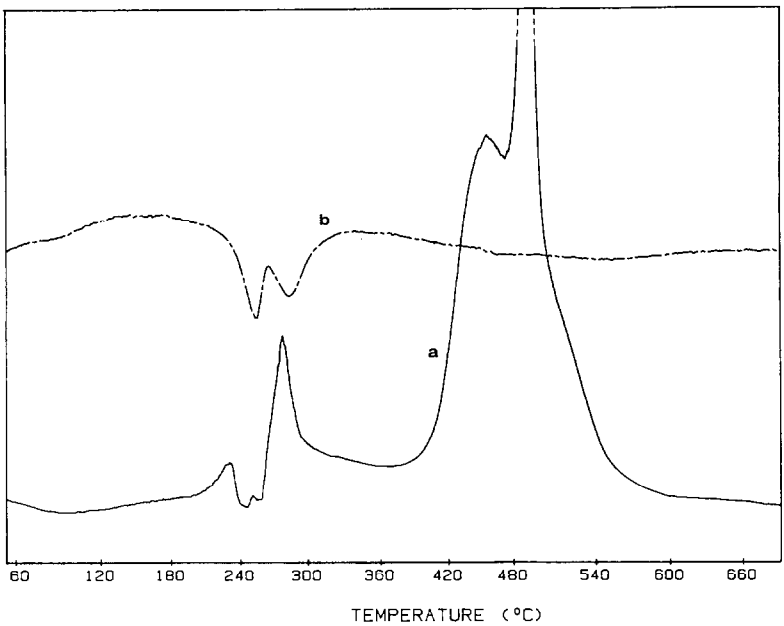

Fig. 5. DTA curves for the captopril–cobalt(II) complex in oxygen (a) and in nitrogen (b) atmospheres.

The mass spectrum of the complex confirms the proposed mechanism of decomposition. It starts with decarboxylation leaving a fragment with $m/e = 446$. The next important step is the cleavage of the $S-CH_2$ bond with formation of a fragment with $m/e = 139$, which breaks down into the pyrrolinium ion ($m/e = 70$) and dimethylketene ($m/e = 69$).

CONCLUSIONS

In aqueous solution, captopril reacts with cobalt(II) giving a deep red complex. The reaction, very slow at room temperature, does not take place in acidic medium (pH < 6). When the complex is formed under correct conditions, it seems to be irreversible, and the subsequent acidification of the solution causes precipitation of a complex, with a metal to ligand molar ratio of 1 : 2, without any regression of the equilibrium. These results suggest that the *cis* form of captopril, more stable at neutral pH [4], probably reacts with cobalt(II).

The potentiometric and spectroscopic analyses show that cobalt(II) is bound to the mercapto group, while the carboxylic group of the ligand is uncoordinated. The ketonic oxygen probably also interacts with the metal ion, forming two stable six-membered rings.

The thermal and calorimetric studies show that the complex is more stable than the ligand. The first decomposition temperature, the thermoanalytical behaviour, and the final residue are influenced by the gas atmosphere in the furnace and agree with the proposed structure of the complex.

AKNOWLEDGMENT

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