

COMPLEXES OF THE ACE-INHIBITOR CAPTOPRIL

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Abstract

The interaction of transition metals with captopril has been studied and discussed. The paper summarizes the results obtained for the characterization of the complexation processes and determination of the structure and properties of the complexes formed.

Rezumat

În prezenta lucrare s-a studiat și s-a discutat interacțiunea metalelor tranziționale cu captoprilul. Lucrarea însumează rezultatele obținute pentru caracterizarea reacțiilor de complexare a captoprilului și determinarea structurilor, respectiv proprietăților compușilor formați.

Keywords: captopril, transition metals, complexes

Introduction

Captopril (CPL) (Fig 1), 1-(3-mercapto-2-D-methyl-1-oxopropyl)-L-proline (S,S), is used therapeutically as an antihypertensive agent. It acts as a potent and specific inhibitor of angiotensin-converting enzyme. It is used in the management of hypertension, in heart failure, following myocardial infraction and in diabetic nephropathy.

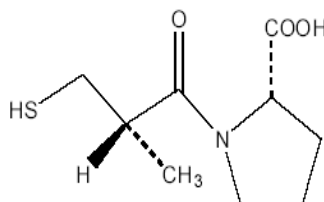


Figure 1

Structure of captopril

As a representative of the ACE-inhibitor class of antihypertensive, captopril (CPL), was studied for several reasons: first, it seems to be one of the most widely used drug of the group and, secondly, because it contains several donor groups, namely COOH, C=O, SH and proline nitrogen [3].

In the mid-1980's several papers were published, claiming that

probably the effect of captopril can be connected also to its relation to copper and zinc, and to changes in their homeostasis. It seemed possible, that in this way the antihypertensive action of the drug could be explained, together with some of its side effects [1,2].

The interest in this field was the reason that in the late 1980's the first publications appeared on the interaction between CPL and copper/zinc [7]. In these studies, however, the system copper(II)–CPL was investigated always in the presence of other ligands, capable of keeping copper in +2 oxidation state so as to prevent its reduction. The ideas regarding the new possible functions of captopril have spread later in several directions, in order to explain different aspects of the physiological effect of the drug [4].

Metal ions are important for the course of the vital functions of the living organisms where they occur under the form of complex or chelate combinations, as well as for the methods of analysis and control of the medical substances by forming complexes.

The stability of these complex combinations depends on: the nature of the metal ion generating the complex, the nature of the ligand, the relative affinity of the donor atoms for the acceptor atoms and ions and the affinity for electrons of the central metal atom and with the basic character of the ligand. The participation of some given functional groups within a metal bond depends on its level of competition with the existing neighbouring functional groups, as well as on the competition of the protons and of the metal ions with the potential donor atoms.

Materials and methods

All materials were of reagent grade and were used without further purification. Captopril was obtained from Labormed Trading SRL, and the other substances used for synthesis were purchased from either Reactivul Bucuresti or Merck Germany.

The interaction between metal ions and N and O peptidic atoms takes place during the formation of some chelate cycles.

The N and O atoms are also donors and the cycles that are formed are stable.

a. Composition of $[\text{Me}(\text{CPL})_n\text{X}_m]$, where Me = Mn, Cd, Ni, Zn, Co and $\text{X} = [\text{HgI}_4]^{2-}$. 0.68g HgCl_2 were dissolved, by heating, in 20mL distilled water; potassium iodide was added in the solution till the complete solubilisation of the initially formed precipitate of mercury iodide (II). The obtained solution, containing the complex anion $[\text{HgI}_4]^{2-}$ is treated, under continuous stirring, with 60 mL solution containing in grams the amount of salt of the metals needed to complexate 1g of captopril. The obtained

precipitates of different colours are filtered through a Büchner funnel, washed 3 times with warm water and alcohol and then dried in an exicator on a filter paper. The formation of these complexes, noted as Me-Captopril, can be observed from the elemental analysis results. From a physicochemical point of view, they can be characterized by molecular weight, colour and melting point (mp) (Table I).

Table I.
Physicochemical features of the Me - captopril complexes

	Molecular formula and weight	Colour	Melting point (°C)	C% Found/ Calculated	H% Found/ Calculated	N% Found/ Calculated	S% Found/ Calculated
1.	[Cd(CPL) ₂][HgI ₄] M=1255.18	White	210	17.09/ 17.21	2.56/ 2.39	1.88/ 2.23	5.58/ 5.10
2.	[Zn(CPL) ₂][HgI ₄] M=1244.18	White	165	16.94/ 17.80	3.02/ 2.48	1.86/ 2.31	5.54/ 5.29
3.	[Ni(CPL) ₂][HgI ₄] M=1199.48	Greenish yellow	170	18.07/ 18.02	3.02/ 2.50	1.95/ 2.33	6.08/ 5.33
4.	[Co(CPL) ₂][HgI ₄] M=1199.68	Light pink	180	17.84/ 18.01	2.86/ 2.51	1.93/ 2.31	6.14/ 5.43
5.	[Mn(CPL) ₂][HgI ₄] M=1195.68	White-crystals	182	18.04/ 18.06	2.64/ 2.50	1.94/ 2.34	5.85/ 5.35

The captopril forms complexes with transition metals such as Zn, Cd, Ni, Co, Mn in the presence of the [HgI₄]²⁻ anion of tetraiodomercuriat type.

The formation of these complexes and their structure are observed in the elementary analysis data as well as in the IR spectra of the metal complexes with modified values of the wavelength due to the presence of the Me- captopril bonds.[9]

b. Composition of the captopril complex of copper(II), Cu₂^{II}CPL₂(H₂O)₂ [5]

In aqueous solution at a molar ratio of Cu:CPL=1:2 and ambient temperature, copper(II) is reduced to copper(I) which forms with an excess of captopril a yellow diamagnetic complex Cu^ICPL, quite stable kinetically as a solid substance, when isolated and dried immediately after its formation and precipitation. In air, but only in the presence of H₂O, copper(I) in the complex is easily oxidized by O₂ to copper(II), and the corresponding green copper(II) complex of captopril Cu₂^{II}CPL₂(H₂O)₂ is formed, which is kinetically and thermodynamically stable. The details of this study together with the reaction mechanism scheme are given elsewhere [6].

The composition of the complex was found by elemental analysis and t.g./d.s.c. (thermal gravimetric/derivate scanning calorimetry) study revealed the presence of endothermic effects at 366 and 477 K. The first is due to the presence of water, strongly bonded in the complex. The t.g.

analysis performed at 471 K, and the elemental analysis data, indicated a Cu:L:H₂O of 1:1:1. The second d.s.c. peak is connected with destructive processes within the complex [5].

Results and discussion

Studying the IR spectra of the complexes of captopril with transition metals, we observed that the band corresponding to the -C=O group within the carboxyl from 1748 cm⁻¹ decreases at the spectra of the complexes compared to the IR spectrum of captopril. A wider band appears at 1600 cm⁻¹ due to the overlapping of the bands corresponding to the -C=O group within the amide group. In addition, due to the -C=O group within the carboxyl (COO-) we have observed the appearance of a 1450 cm⁻¹ band.

For the Zn-captopril complex, the band corresponding to the -C=O group within the carboxyl (-COO⁻) decreases. Finally, we assume that for some metals the reactions were not performed completely or it is possible that complexation reactions take place between metals and some degradation products of captopril that may be formed in the working environment of these complexes.

The spectral properties of captopril complex of copper(II), Cu₂^{II}CPL₂(H₂O)₂

The coordination mode and structure were studied by spectral infrared (I.R.), E.P.R. (electron paramagnetic resonance) spectroscopy and by magnetochemical measurements. The I.R. spectral data indicated the participation of COOH, C=O and SH groups in coordination, together with H₂O, which is also included in the inner coordination sphere of copper. The presence of water is indicated by a band at 3400 cm⁻¹, not present in the free ligand spectrum, that disappears after heating the complex at 471K. The coordination of copper(II) through the carboxylate group of captopril follows the disappearance of ν(COOH) at 1755 cm⁻¹ in the free ligand spectrum and the presence of ν_s(COO) and ν_{as}(COO) at 1412 and 1635 cm⁻¹ respectively in the spectrum of the complex.

It is supported also by the absence of the bands for the dimeric form of the free ligand at 3000 and 2650 cm⁻¹. The last two frequencies are related to intermolecular hydrogen bonds between two molecules of the ligand including the COOH and C=O functions [5,6]. The participation of the thiol group in coordination is evident from the disappearance of ν(S-H) at 2580 cm⁻¹ and of δ(S-H) at 910 cm⁻¹, from the observed shift of ν(C-S) at 980 cm⁻¹ in the ligand to 925 cm⁻¹ in the complex and from the new band at 350 cm⁻¹, due to ν(M-S) [6]. The role of the amide oxygen in the coordination was suggested by the shift of the amide I band in the spectrum of the complex to lower frequencies [8] and its broadening in comparison with the free ligand.

The magnetochemical measurements at ambient temperature gave a value of $\mu = 0.84$ B.M. (Bohr magneton), that strongly supports the assumption of the binuclear character for the complex. This fact was confirmed also by the e.p.r. spectrum and its temperature influence. At ambient temperature (295 K) the powder sample of the green complex exhibits signals at 260, 4840 and 6180 G (Gauss), together with the characteristic signal for a monomeric copper(II) species at approximately 3300 G. The temperature influence on the intensity of the e.p.r. signals permitted the evaluation of the exchange coupling constant, following the Heisenberg–Dirac–Van Vleck equation as $2J = -312 \text{ cm}^{-1}$, where J represents total electron angular momentum quantum number.

The green complex, $\text{Cu}_2^{\text{II}}\text{CPL}_2(\text{H}_2\text{O})_2$, was obtained in a microcrystalline form, unsuitable for a single-crystal X-ray diffraction.

Conclusions

The results summarized in this paper show that captopril, which is used for regulating arterial blood pressure, forms complexes with transition metals. The mononuclear complexes are formed in aqueous solutions in the physiological pH-range (neutral or slightly alkaline media).

The complexes were investigated with respect to their main physicochemical properties - spectral, magnetochemical (magnetic susceptibility, magnetic moment, E.P.R. spectra) and thermochemistry (thermal gravimetric/derivate scanning calorimetry).

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