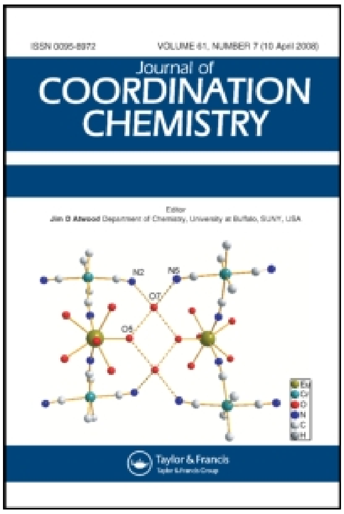

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OXOVANADIUM(IV) COMPLEXES OF CAPTOPRIL

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OXOVANADIUM(IV) COMPLEXES OF CAPTOPRIL

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The interaction between the VO^{2+} cation and captopril was investigated in solution and in the solid state. Spectral measurements in solution (IR and electronic spectra) showed that at pH = 6.5 the interaction occurs through the COO^- and C=O groups. In the solid state a dimeric vanadyl(IV) complex, bridged by a pair of carboxylate groups of two ligand molecules, is formed. These results are supported by elemental analysis as well as by magnetochemical and TG/DTA measurements.

Keywords: oxovanadium(IV); captopril; solution studies; solid complex; structure; thermal behavior

INTRODUCTION

Captopril (1-[2(S)-3-mercapto-3-methylpropionyl]-L-proline; Figure 1) is a well known antihypertensive drug which acts as a potent inhibitor of the hydrolase of angiotensin I. [1]

As part of a series of model studies related to vanadium metabolism, including its interactions with pharmacologically active ligands [2-8] we have now investigated the behavior of the VO^{2+}/captopril system at two different pH-values (4.0 and 6.5).

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EXPERIMENTAL

Materials

Reagent grade $VOCl_2$, 50% solution (Carlo Erba) and captopril (Sigma) were used in all the experiments as supplied.

Methods

Electronic spectra were measured with a Hewlett-Packard 8453 diode-array spectrophotometer. Quartz cells (1 cm width) were used. Diffuse reflectance spectra were recorded on a Shimadzu UV-300 spectrophotometer, using MgO as an internal standard. IR spectra were recorded with a Perkin Elmer 580 B spectrophotometer using KBr pellets. Solution measurements were performed on thin films between AgCl plates, in the ranges where H_2O does not absorb. Raman spectra were measured with a Spex-Ramalog double monochromator spectrometer, using the 514.5 nm line of an argon ion laser for excitation. The rotating disk technique was used, because the solid complex was burned by the laser light.

Room temperature magnetic susceptibilities were determined with a Cahn-2000 instrument, calibrated with $Hg[Co(SCN)_4]$ in the usual way. The magnetic field strength was 6 KGauss. Thermogravimetric (TG) and differential thermal analysis (DTA) were performed on a Shimadzu thermoanalytical system (models TG50 and DTA50). Alumina was used as a DTA standard.

Analytical determinations of vanadium were performed spectrophotometrically, as tungstophosphovanadic acid. [9] C,H,N and S contents were

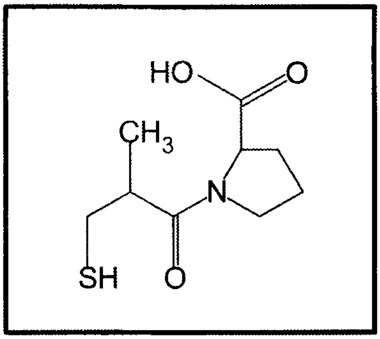

FIGURE 1 Schematic structure of captopril (HCapt).

determined by standard elemental analysis techniques. Sodium was determined by flame photometry.

Preparations

a) Synthesis of the solid complex:

2 mmol of captopril were dissolved in 10 mL of methanol; 1 mmol of $VOCl_2$ solution was added; the pH of the resulting solution was raised with 1M NaOH up to pH 4.0. After cooling a light-blue microcrystalline precipitate was obtained. It was filtered on a G4 fritted-glass funnel, washed several times with small portions of methanol and dried over $CaCl_2$. Anal Calcd. for $Na_2[VO(C_9H_{14}NO_3S)(OH)_2]_2$: C, 31.73; H, 4.70; N, 4.11; S, 9.40; Na, 6.76; V, 14.99. Found: C, 31.98; H, 5.07; N, 3.92; S, 9.20; Na, 6.34; V, 16.00. Yield was over 80%.

b) Preparation of the violet complex in solution:

4 mmol of captopril were dissolved in 20 mL of 50% HCl and 1 mmol of $VOCl_2$ was added. The pH of the solution was adjusted by addition of $NaHCO_3$ until a value of 6.5 was reached; excess $NaHCO_3$ was filtered off and a violet solution was obtained. The same results were obtained using 2/1 or 1/1 ligand to metal ratios, but these solutions immediately decomposed, even working in a nitrogen-atmosphere. Due to the precipitation of the pure ligand in all cases, attempts to precipitate a solid complex with different solvents failed. $NaHCO_3$ was selected to reach this pH-value because hydrolysis of VO^{2+} occurs immediately when NaOH is used, even at high ligand to metal ratios (up to 100:1) and working under nitrogen.

c) Preparation of the sodium salt of captopril:

This salt was prepared for comparative purposes. It can be precipitated after mixing aqueous solutions of the drug with NaOH in a 1/1 molar ratio and addition of an excess of methanol. It is washed with methanol and dried over $CaCl_2$.

RESULTS AND DISCUSSION

Solid Complex

The diffuse reflectance spectrum of the solid shows bands at 790 and 630 nm, which are shifted to the red with respect to $[VO(H_2O)_5]SO_4$ (770 and 625 nm).

This shift suggests coordination of the VO^{2+} cation through carboxylate groups. [5] The UV/visible spectrum, measured with the reaction mixture in methanol at pH 4, before cooling, shows bands at 802 nm ($\epsilon = 24\ M^{-1}{\cdot}cm^{-1}$) and 622 nm ($\epsilon = 15\ M^{-1}\ cm^{-1}$) (Figure 2), indicating the same interaction in both the solid and liquid phase.

The IR spectrum of the solid complex was recorded to 200 cm^{-1} and compared with those of the pure ligand and its sodium salt. The assignment of the most characteristic and important bands is shown in Table I.

In the free ligand, the 3000-2400 cm^{-1} region shows a broad and strong band, probably due to formation of a dimeric structure by carboxylate interactions. Inside this broad band there appeared a sharp band at 2566 cm^{-1} that was assigned to ν(SH). [10] This broad band is absent in the spectra of both the sodium salt of captopril and the vanadyl(IV) complex suggesting the absence of this intermolecular interaction. The ν(SH) band is now observed at 2561 or 2559 cm^{-1}, respectively, with a lower intensity. As shown in Table I the ν(SH) and δ(SH) bands appear in the three substances, indicating the lack of interaction of this group with the metal center.

The strong 1750 cm^{-1} band of captopril assigned to the C=O stretching of the COOH group, is absent in the sodium salt and in the VO^{2+} complex. In the

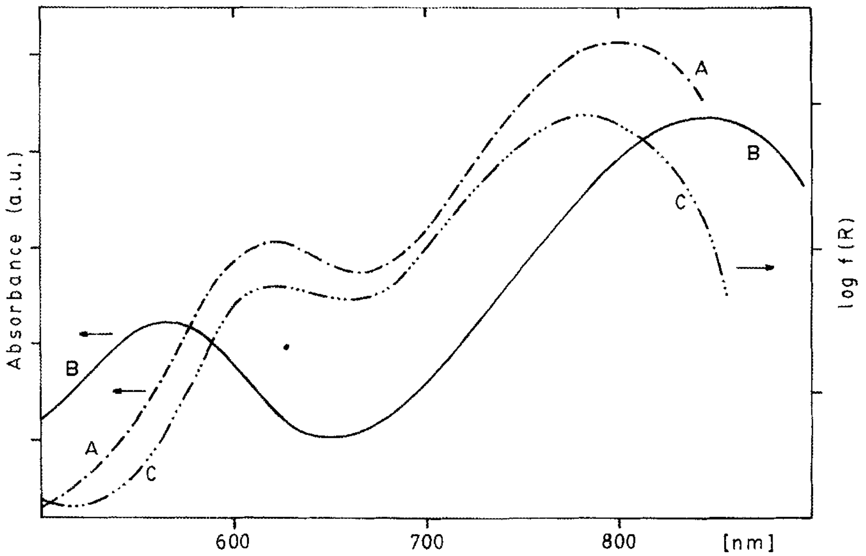

FIGURE 2 Electronic spectra of **A**: VO^{2+}/captopril methanolic solution at pH 4 (L:M = 0.1M:0.05M); **B**: VO^{2+}/captopril aqueous solution at pH 6.5 (L:M = 0.3M:0.75M); **C**: solid complex precipitated at pH 4 (diffuse reflectance spectrum).

TABLE I Vibrational data for some of the characteristic bands of captopril (HCapt), its sodium salt (NaCapt) and the VO^{2+} complex precipitated at pH 4 (VO/Capt)

Assignment	*HCapt(IR)*	*NaCapt(IR)*	*VO/Capt(IR)*	*VO/Capt(Raman)*
ν(SH)	2566 s	2561 w	2559 w	2570 w
ν(COOH)	1750 s			
ν_{as}(COO$^-$)		1622 s	1563 s	1565 w
ν_s(COO$^-$)		1400 m	1420 s	1418 sh
amide I	1610sh/1592s	1598 s	1617s/1588s	1616w/1594w
ν(CN)	1334 m	1330 m	1330 m	1328 w
ν(V=O)			990 s	997 vs
δ(SH)	901 m	917 w	920 w	916 w

vs: very strong; s: strong; m: medium; w: weak; sh: shoulder

sodium salt, two new bands appeared at 1622 cm^{-1} (ν_{as}(COO$^-$)) and 1400 cm^{-1} (ν_s(COO$^-$)), showing the formation of an anionic carboxylate. [11] The shift of these bands to 1563 and 1420 cm^{-1}, respectively, after complex formation is indicative of bridging carboxylate groups, joining two metal centers. [11-13]

The possibility of an interaction of the amide I group of the ligand with the VO^{2+} cation is excluded, because no change was observed in this band in the three compounds.

The typical V=O stretching motion appears at 990 cm^{-1}. The position of this band also suggests coordination of VO^{2+} through oxygenated ligands. [5, 14]

To complement the vibrational spectroscopic information, Raman data for the most characteristic vibrations of the vanadyl(IV) complex are also included in Table I. The shifts of this band in relation to those of the other two compounds were similar to those observed in the IR spectra.

The presence of bridging carboxylate groups is demonstrated by the vibrational spectrum of the complex so we measured the magnetic susceptibility to verify the presence of magnetic interactions between the two coupled metallic centers. The value of 1.76 BM, obtained at 293 K, clearly shows the absence of interactions. This behavior can be explained as a relatively large separation of the metal centers. As the magnetic orbitals of the VO^{2+} cations are of the xy type, [13] and these orbitals are not directed towards the bridging ligands, the only possibility for a magnetic coupling is a σ overlap between these orbitals [12, 13] requiring the presence of very close metal centers.

The results of all the applied methods allow the structure schematized in Figure 3 to be postulated for the complex. This stoichiometry is also supported by investigation of the thermal behavior of the compound. The TG/DTA traces are shown in Figure 4. Up to 325°C, a weight loss of 32% is observed and this pyrolytic process is accompanied by the strongly exothermic DTA peak at 263°C. In the second step, which extends up to 510°C, a further weight loss of *ca.* 33% is observed, in combination with another, well defined exothermic DTA signal at 435°C. IR analysis of the solid residue, shows the presence of $NaVO_3$. Therefore, the following general decomposition scheme can be formulated:

$$Na_2[VO(Capt)(OH)_2]_2 \Rightarrow 2NaVO_3 + CO_2 + H_2O + \text{other products}$$

for which a theoretical mass loss of 64.20% is calculated, which is in excellent agreement with the experimentally observed value (65%).

The pure ligand is decomposed in one main step between 180 and 300°C, accompanied by two DTA signals (105°C, sharp endo; 285°C, weak, broad exo). After 300°C, a slow mass release is observed, which continues up to the highest attained measurement temperature (500°C) and is accompanied by three weak exothermic DTA-signals (330, 405 and 445°C).

Violet Complex in Solution

The electronic spectrum of a freshly prepared aqueous solution with a 4:1 ligand to metal ratio, shown in Figure 2, has bands at 840 nm ($\epsilon = 13\ M^{-1}\ cm^{-1}$) and 565 nm ($\epsilon = 7\ M^{-1}\ cm^{-1}$). These band positions suggest the interaction of the

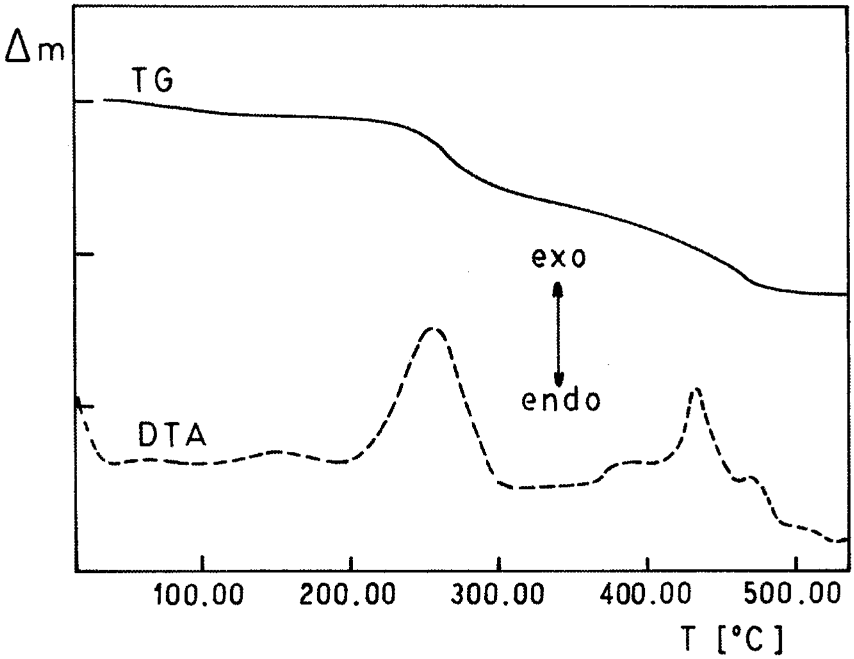

FIGURE 3 Schematic structure proposed for the anion of the solid complex precipitated at pH 4.

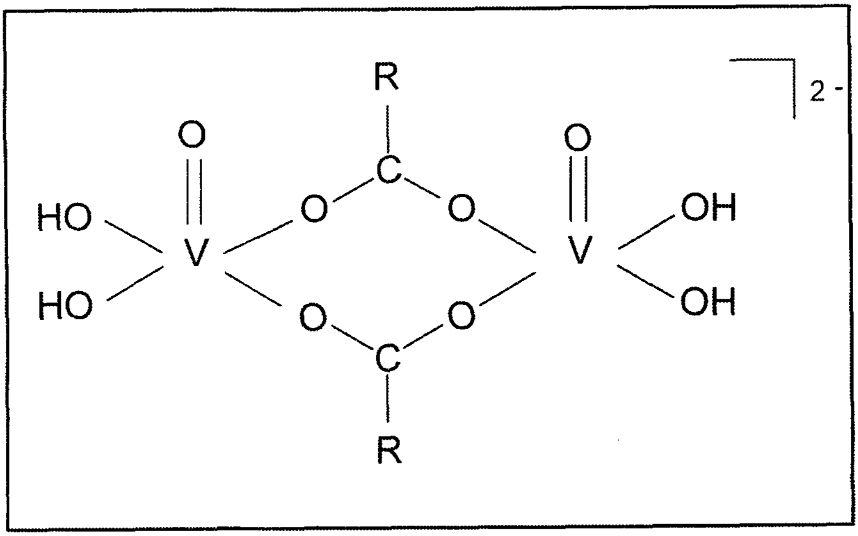

FIGURE 4 TG and DTA traces for the thermal decomposition of the complex precipitated at pH 4. (O_2-flow: 60 ml/min; heating rate: 10°C/min).

VO^{2+} cation with oxygen donors, similarly to those found in related systems. [15] Coordination through the -SH group is excluded, because in this case the absorptions would occur at higher energies. [2]

IR spectroscopic measurements in solution confirm this statement, because the ν(SH) band could be clearly identified at 2560 cm^{-1}. On the other hand, in the 1600-1300 cm^{-1} region, the free ligand measured at pH 6.5 shows bands at 1395 cm^{-1} ($\nu_s(COO^-)$), 1370 cm^{-1} (δ(CH)) and 1330 cm^{-1} (ν(CN)). A new band located at 1502 cm^{-1} is observed in the solution of the complex, which suggests participation of the amide carbonyl in bonding, as its displacement after coordination is similar to that found in a previously investigated Zn(II)/captopril complex. [16] The other bands remain in their original positions.

In the 1300-900 cm^{-1} region, the free ligand presents some bands which change appreciably in form and intensity after complexation, especially those absorptions located at 1155 and 1124 cm^{-1}, probably from skeletal modes. [16] Interestingly, the typical ν(VO) stretching band could not be observed, because of the broadness of the main band in this region, located between 1400 and 900 cm^{-1}. These results, together with those obtained from the electronic spectrum, allow speculation on the possible participation of both the carboxylate group and the carbonyl (amide I) moiety in bonding.

Further work is in progress to determine the physiological action of these VO^{2+}/captopril complexes.

CONCLUSIONS

The accumulated experimental evidence about the oxovanadium(IV)/captopril interactions allow the following conclusions:

1. At pH 4.0 a solid microcrystalline complex could be prepared. Although the characterization of this species is not definitive, the data allow the bridged structure depicted in Figure 3 or, perhaps, a system with higher nuclearity, maintaining the same VO^{2+}/captopril/OH^- ratios. Magnetic measurements show the lack of coupling between the metal centers.
2. Another complex species, generated at pH 6.5, could not be isolated as a solid. Solution measurements indicate participation of the carboxylate and the carbonyl (amide I) groups in bonding.
3. In both cases no participation of the -SH group in bonding could be observed, in contrast to what is observed in the case of the Zn(II) [16] and Cu(II) [17] complexes of captopril.

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