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Interaction of the VO^{2+} Cation with Suprofen

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SUMMARY. The interaction of the oxovanadium (IV) cation with the anti inflammatory drug *Suprofen* has been investigated by means of electronic absorption spectroscopy in solution. The drug binds to the oxocation through its carboxylate group generating a 2:1 ligand-to-metal complex. Some comparisons with related compounds are made.

RESUMEN. "Interacción del Catión VO^{2+} con Suprofen". La interacción del catión oxovanadio (IV) con la droga antiinflamatoria *Suprofen* fue investigada por espectroscopía electrónica de absorción en solución. La droga se liga al oxocatión a través de su grupo carboxilato, generando un complejo de estequiometría ligando-metal 2:1. Se realizan comparaciones con algunos compuestos relacionados.

INTRODUCTION

As a part of a research project devoted to the study of the interaction of anti inflammatory drugs with some relevant biometals [1,2], we have initiated some investigations with Suprofen. Recently, we could thoroughly characterized [3] a previously reported dimeric Cu (II) complex [4], and isolate a solid mononuclear Co (II) complex [5] containing this ligand.

Considerable interest in *Suprofen* (α-methyl-4-(2-thienyl-carbonyl)phenylacetic acid, Fig. 1a, abbreviation HSup) was shown since it was found to exhibit analgesic, antipyretic and anti inflammatory activity [6], properties which are common among a number of non-steroidal arylalkanoic acid derivatives [7]. The antiinflammatory activity of this drug can be described as SOD mimetic [3,4], because it is apparently related to its ability to catalyze disproportionation of the superoxide radical anion (SOD), one crucial metabolic species contributing to tissue damage in inflammatory joint diseases.

KEY WORDS: VO^{2+}, Suprofen, Ibuprofen, Electronic Spectra.
PALABRAS CLAVE: VO^{2+}, Suprofen, Ibuprofen, Espectros Electrónicos.

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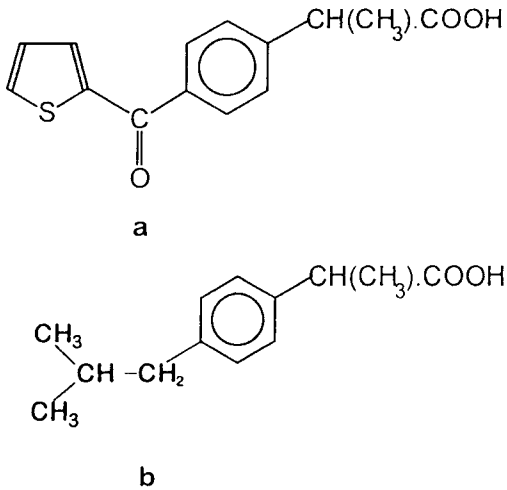

Figure 1. Schematic structure of the two drugs assayed as ligands: a. *Suprofen*; b. *Ibuprofen* .

As VO^{2+} is probably the most relevant vanadium cationic species present in biological fluids and cellular systems [8-10], we have investigated its mode of interaction with this drug. For comparative purposes, the interaction of the same cation with *Ibuprofen* (2-(4-isobutylphenyl) propionic acid, Fig. 1b, abbreviation HIbu), another drug with similar characteristics, was also analyzed and some comparisons with other similar VO^{2+} complexes were made.

EXPERIMENTAL

Suprofen and *Ibuprofen* from Sigma, $VOSO_4.5H_2O$ from Merck, and $VOCl_2$ from Carlo Erba (50% solution) were used as supplied.

The electronic spectra were measured in freshly prepared methanolic solutions, working under anaerobic conditions, in order to prevent oxidation phenomena.

As discussed below, in the case of *Suprofen,* it is not possible to work in aqueous solution. Therefore, the spectroscopic measurements were performed in a methanolic solution of sodium suprofenate, prepared as follows: 0.500 g (1.921 mmol) of *Suprofen* were dissolved in *ca.* 5 ml of methanol; to this solution 3.0 ml of a methanolic 0.641 M sodium methanolate solution (freshly prepared by reaction of methanol with metallic sodium) were slowly added. The resulting pale yellow solution, of pH = 5, was used for the studies with the VO^{2+} cation.

Different attempts to isolate a VO^{2+}/ *Suprofen* complex in the solid state failed.

The electronic absorption spectra were measured with a Shimadzu UV-300 spectrophotometer, using 10 mm quartz cells.

RESULTS AND DISCUSSION

For the preparation of metallic *Suprofen* complexes, the drug is usually dissolved in 0.1 M NaOH, to generate the soluble sodium suprofenate, which is then mixed with an aqueous solution of the desired metal cation [3-5]. This general procedure fails in the case of the VO^{2+} cation because the pH value of the aqueous solution which is necessary to deprotonate the drug supersedes the upper pH stability limit for the $[VO(H_2O)_5]^{2+}$ species, and precipitation of hydrolyzed vanadium (IV) oxide occurs. Therefore, we have worked in methanolic media, as described in the experimental part.

The electronic spectra of a VO^{2+}/suprofenate solution confirms the complexation of the cation. In order to determine the stoichiometry of the complex a spectrophotometric titration [11] was performed monitoring absorbance changes as a function of the metal-to-ligand ratio at a constant wavelength (860 nm). One of such titrations is shown in Fig. 2. The results clearly point to the generation of a 2:1 suprofenate: VO^{2+} complex of the type $[VO(Sup)_2]$.

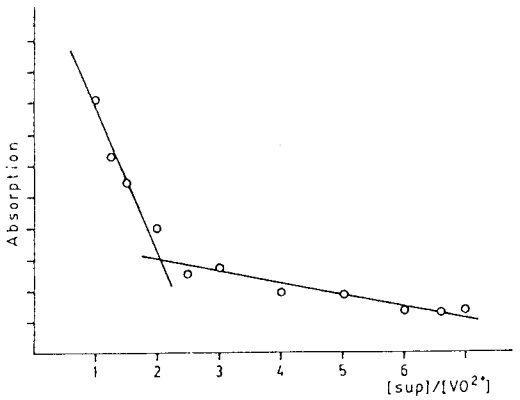

Figure 2. Spectrophotometric titration of VO^{2+} with *Suprofen* (0.05 M) at pH = 5.0 and at λ = 860 nm.

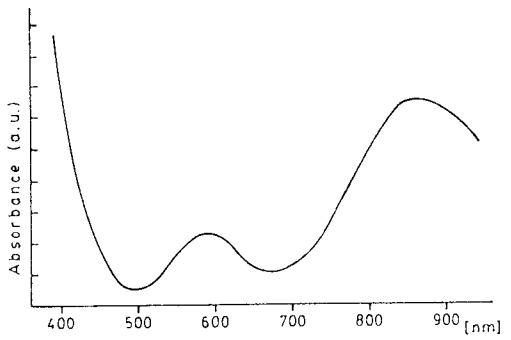

Figure 3. Electronic absorption spectrum of $[VO(Sup)_2]$ in methanolic solution at pH = 5.0.

A typical electronic absorption spectrum of this species is shown in Fig 3. The two typical absorption bands are located at 860 nm (ε = 32.0 $L.mol^{-1}.cm^{-1}$) and 590 nm (ε = 10.5 $L.mol^{-1}.cm^{-1}$). These bands are assigned to the $b_2 \rightarrow e$ and $b_2 \rightarrow b_1$ transitions in the well known MO schema of Ballhausen and Gray [12,13]. A methanolic solution of $VOSO_4$ presents these bands at 790 and *ca.* 625 (shoulder) nm. The comparison shows that the lower energy band suffers a read-shift, whereas the other presents a blue-shift after complexation. As this second band gives directly the 10 Dq value of the complex [12,13], the commented shift shows that suprofenate generates a somewhat stronger crystal field than methanol.

These results may be compared with that previously obtained in our laboratory for $[VO(mal)_2]^{2-}$ and $[VO(bzmal)_2]^{2-}$ (mal = malonate; bzmal = benzylmalonate), in which the ligands interact with the VO^{2+} cation through its two carboxylate moieties [14]. In both cases, the two typical transitions are found at 798 and 588 nm [15,16].

Other literature data concerning electronic spectra of VO^{2+} carboxylate complexes (*i.e.* oxalate [13], acetate and haloacetate [17], different tartrate species [18] and other simple carboxylic acids [19,20]) show clearly that the $b_2 \rightarrow e$ transition covers a wide energy range (between 750 and 970 nm) whereas the $b_2 \rightarrow b_1$ transition lies in a more restricted range (540-606 nm; *cf.* also reference [19]) which appears as characteristic for this ligand type.

The commented results clearly demonstrate that in the $[VO(Sup)_2]$ complex, the ligand to metal interaction involves the carboxylate group of the two suprofenate moieties, which in this case must evidently act as a bidentate ligand.

To complement this study, we have also investigated the behavior of *Ibuprofen* as a ligand for VO^{2+}. In this case, 0.200 g of this ligand (1 mmol) were dissolved in 10 ml of methanol. To this solution 0.1 mmol of a $VOCl_2$ solution was added and the pH raised stepwise by dropwise addition of a concentrated NaOH solution. Metal to ligand interaction starts at a pH-value around 3.5 and can followed up to *ca.* pH = 6.5, without hydrolysis of the oxocation. The electronic spectrum of the complex species present absorption maxima at 845 nm (ε = 25 $L.mol^{-1}.cm^{-1}$) and 595 nm (ε = 14.5 $L.mol^{-1}.cm^{-1}$).

As can be seen, this spectral pattern is very similar to that measured in the *Suprofen* complex (Fig. 3), also suggesting in this case the generation of a [VO $(Ibu)_2$] species in which the ligand interacts with the metal center through its carboxylate group.

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