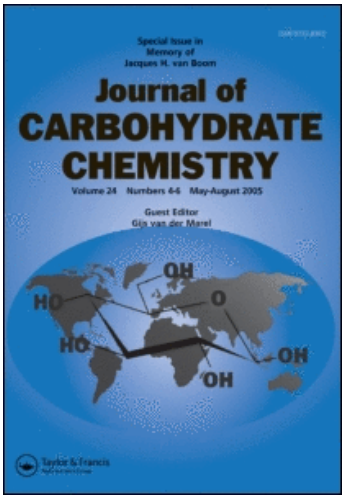

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REVIEW

OXOVANADIUM(IV) COMPLEXES OF CARBOHYDRATES

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1. INTRODUCTION

Although the generation of coordination compounds between metallic cations and carbohydrates is a field of increasing interest,[1–4] the chemistry of metal-sugar interactions still remains unexplored in many respects. Sugars interact with essential and toxic elements by acting either as reductants or chelators. Depending on the characteristics of the cation, as well as on the pH value of the solution, the complexing ability of sugars may involve deprotonated hydroxyl groups. Additionally, in most cases, extra substituents are needed to anchor the metal ion at low pH favoring the subsequent hydroxyl coordination in neutral or basic media.

The interaction of sugars with different vanadium species is of considerable interest in vanadium biochemistry and especially in relation to its metabolism in the higher forms of life[5,6] and to its biological detoxification.[6,7] On the other hand, the fact that sugar residues are also present in numerous important biomolecules generates additional interest in attaining wider insight into the interaction of simple sugars with vanadium species.

It is also well known that carbohydrates are efficient one-electron reducing agents of vanadates (V)[8–13] generating oxovanadium (IV), VO^{2+}, probably the biologically most relevant vanadium species. Vanadates themselves are able to generate cyclic esters with many sugars and sugar containing biomolecules.[14–18] As some aspects of this chemistry have been recently reviewed,[17,19,20] these systems shall not be further considered and this review is essentially focused on complexes of the oxovanadium (IV) cation.

Despite the aforementioned interest in vanadium/carbohydrate interactions, in the most exhaustive review on metal coordination to carbohydrates published to date (1993),[3] less than ten references on systems of this type are given. However, considering that many investigations have been performed in recent years, it is timely to provide a general overview on the synthesis, properties, and physicochemical characterization of VO^{2+} carbohydrate complexes.

A number of studies on these systems has been performed only in solution, using different spectroscopic techniques but, in some cases, solid complexes of different compositions and stoichiometries could be also isolated and characterized.

2. MONOSACCHARIDE COMPLEXES

2.1. General Behavior in Solution

The interaction of oxovanadium (IV) with different simple sugars has been investigated in neutral and basic aqueous solutions by Branca *et al.*,[21] using EPR and electronic absorption spectroscopy. This study provided a clear insight into the main characteristics of these interactions. The following carbohydrates were used in these studies: D-fructose, D-ribose, D-mannose, D-galactose, D-xylose, D-glucose, D-lyxose, L-sorbose, L-arabinose, 2-deoxy-D-galactose, 2-deoxy-D-glucose, 2-deoxy-D-ribose, methyl β-D-arabinopyranoside, methyl β-D-xylopyranoside, methyl β-D-galactopyranoside, phenyl β-D-galactopyranoside, methyl α-D-glucopyranoside, and methyl α-D-mannopyranoside.

These ligands can be categorized into two classes. The first one is comprised of sugars where all adjacent hydroxyl groups are in *trans* positions relative to each other and these ligands are ineffective for metal chelation. The second class is comprised of sugars having at least two adjacent hydroxyl groups *cis* to one other.

On the basis of EPR results it has been shown that this second group of ligands interact with the VO^{2+} cation generating mononuclear oxovanadium (IV)-sugar complexes. Strictly speaking, two complexes (**I** and **II**) may be distinguished in these cases. Complex **I** is the predominant species in solution with the VO^{2+}: sugar ratio of 1:1, whereas at 1:2 molar ratio, species **II** can be detected. The latter

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complex is formed in the pH range 9–10, reaching a concentration maximum at pH 12, and is subsequently partially transformed into complex **I**. As ligand excess strongly favors the formation of complex **II**, a species with 1:2 metal-to-ligand stoichiometry is suggested.

On the basis of electronic absorption spectra the formation of a third complex, not observed using EPR spectroscopy, is observed in the pH range 7–9. This species is probably a dimeric dihydroxo-bridged complex which, being strongly magnetically coupled, does not exhibit EPR signals. In more basic solutions this complex is transformed into **I**, in which the VO^{2+} cation is probably coordinated to one doubly deprotonated sugar moiety and two hydroxyl groups. At higher pH values, another sugar molecule displaces these hydroxyl groups generating complex **II**, with the stoichiometry $VO(sugar)_2$.

Analysis of these results conclusively demonstrated that simple sugars may be effective chelating agents for oxovanadium (IV). The complexation is favored in basic media and only occurs with sugars possessing couples of adjacent *cis* hydroxyl groups. The ability of *cis* OH^- couples to chelate the cation has been related to the structural rearrangements (essentially, the decrease of the O—C—C—O torsion angle in the formed five-membered chelate rings) needed to allow the coordination by the sugar molecule.

2.2. Complexes of D-Ribose

The interaction of VO^{2+} with D-ribose is of particular interest due to the presence of this sugar moiety in nucleotides. This sugar is present in all purine and pyrimidine nucleosides, but not in thymidine in which it is replaced by 2′-deoxyribose.[22,23]

All the information accumulated thus far related to the interaction of the oxovanadium (IV) cation with ribonucleotides is in accord with assigning the phosphate chain and the *cis* couple of C(2′), C(3′) deprotonated hydroxyls of ribose as the effective VO^{2+} binding sites.[6, 23–31] In di- and tri-phosphate nucleosides the former set is active in acidic media and the latter in alkaline solutions; both of them may be jointly involved in the intermediate pH range.

Most of the experimental evidence also suggests that monophosphate nucleosides behave in a different manner,[23,30,31] a behavior probably related to the less effective donor capacity of the monophosphate moiety, compared with the di- or tri-phosphate units.[31] Accordingly, at low pH values, monophosphate nucleosides form weak complexes involving the phosphate group. These complexes are rather unstable to hydrolysis conditions and generate solid precipitates at pH values between 3 and 5, which redissolve as the pH increases. Finally, at pH values above 10, the VO^{2+} cation is chelated again by ribose moieties.[23,30,31] In the case of AMP, the 1:2 metal-to-ligand stoichiometry of the complex generated at pH 11.0 was confirmed by spectrophotometric titration experiments. Similar experiments performed with D-ribose alone gave identical results.[30] Recent EPR studies also support the formation of the previously mentioned 1:2 complex species.[31]

It has been demonstrated that coordination of the VO^{2+} cation with nucleosides itself is also possible at high pH values. As expected, the interaction only occurs with ribonucleosides and again implies the participation of two pairs of deprotonated hydroxyls of the ribose moieties.[23, 32]

As 2-deoxyribose does not have the necessary adjacent *cis*-hydroxyl groups to interact with a metallic center, the behavior of 2-deoxythymidine phosphates is different. These nucleotides usually interact with VO^{2+} in a way similar to the ribonucleotides in acidic pH ranges, but in alkaline solution they are unable to bind the cation and hydrolysis is observed.[26] In fact, it appears that no interaction of 2-deoxyribose with any metal cation has ever been observed.[33]

Solid VO^{2+}complexes of D-ribose, with different stoichiometries, have also been reported. A green solid of composition $Na_4[VO(D\text{-}Rib)_2]\cdot H_2O$ was prepared by reacting the di-sodium salt of D-ribose (prepared *in situ* by reaction of the saccharide with sodium metal in methanol) with bis(acetylacetonato)oxovanadium(IV), $VO(acac)_2$, in methanol.[34] The complex was characterized by electron absorption, IR and EPR spectroscopic techniques. The results of these studies, together with the magnetic measurements, confirmed the formation of a mononuclear oxovanadium (IV) species. The hyperfine splitting parameters of the EPR spectra indicate the presence of a VO^{2+} unit in a $VO(O)_4$ environment suggesting an axially compressed d^1_{xy} configuration.

Another species, of stoichiometry $Na_3[VO(D\text{-}Rib)_2(OH)]\cdot 4H_2O$, was obtained by mixing $VOCl_2$ and D-ribose aqueous solutions, and adjusting the pH of the solution to 12 with sodium hydroxide. Precipitation of the complex was accomplished by successive addition of methanol and ethanol and decantation of the supernatant layers up to the generation of a green powder. The analysis of the electronic, IR and Raman spectra of this complex clearly confirmed the interaction of VO^{2+} with pairs of deprotonated *cis*-diol groups of D-ribose.[35]

A second mixed ligand complex, of stoichiometry $Na_2[VO(D\text{-}Rib)_2(OH)Cl]\cdot CH_3OH$, was recently reported by Bandwar and Rao.[36] It was obtained by reaction of the disodium salt of D-ribose with $VOCl_2$ in methanolic solutions. On the basis of the spectroscopic analyses, and, as shown in Figure 1, the rather unusual coordination number 7 was postulated for the cation in this complex.

2.3. Other Monosaccharide Complexes

A number of solid VO^{2+} complexes with other monosaccharides have been prepared and characterized in recent years. Different synthetic strategies have been employed. C.P.Rao and coworkers typically reacted $VO(acac)_2$ or oxovanadium (IV) chloride in methanolic solutions with a sodium salt of the saccharide (generated by reaction of the saccharide with metallic sodium in methanol).[34,36,37] A homoleptic VO^{2+} complex with D-glucose, of stoichiometry $[VO(D\text{-}Glc)_2]$, could be obtained by this procedure, but using $VOSO_4.2H_2O$ as the vanadium source. Characterization of the complex by different spectroscopic methods suggests the formation of a five-membered chelate with participation of the oxygen atoms of the C(1)—OH and the deprotonated C(2) hydroxyl group.[38] In the other complexes

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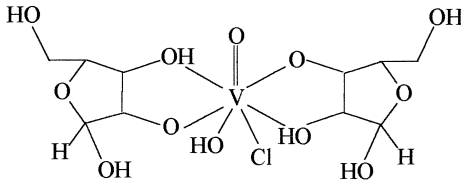

Figure 1. Structure proposed for the $[VO(D\text{-}Rib)_2(OH)Cl]^{2-}$ complex.

obtained by this procedure, using $VO(acac)_2$ as the starting material, doubly deprotonated saccharide moieties act as ligands. On the other hand, different coordination spheres are generated starting with $VOCl_2$. In these cases, the chloride ion together with one OH^- anion may participate in bonding, as suggested in the case of the D-ribose complex described in the preceding section (cf. Figure 1).

In our own group a different preparative route has been usually employed. In this case 2 mmol of a saccharide was dissolved in a small amount of water and the pH of the solution adjusted to 12 by addition of sodium hydroxide. One mmol of $VOCl_2$ was added to these alkaline solutions, maintaining the pH value. The solid complexes were obtained by successive additions of absolute ethanol and discarding the supernatant until a powdered solid was formed.[39,40] Using this method, each sugar moiety present in the coordination sphere acts as a dianionic chelator and, due to the higher working pH value, the sugars are additionally deprotonated, generating anionic complexes with higher charges than those obtained with Rao's procedure.

A very peculiar behavior is observed for the $Na_6[(VO)_2(D\text{-}Fru)_5]\cdot 4H_2O$ complex which, apparently, is a dimer formed by two $VO(D\text{-}Fru)_2$ moieties linked by a fructose bridge.[39]

The compositions of all the VO^{2+}/monosaccharide complexes reported so far are summarized in Table 1. All these complexes are formed as green powders, which are usually hygroscopic and have very high water solubility.

Table 1. Composition of the Known Oxovanadium (IV) Monosaccharide Complexes

Complex	Ref.	Complex	Ref.
$[VO(D\text{-}Glc)_2]$	38	$Na_4[VO(L\text{-}Sor)_2]\cdot 3H_2O$	34
$Na_2[VO(D\text{-}Glc)_2]\cdot CH_3OH$	37	$Na_4[VO(D\text{-}Gal)_2]\cdot 5H_2O$	40
$Na_3[VO(D\text{-}Glc)_2(OH)]\cdot 5H_2O$	39	$Na_2[VO(D\text{-}Gal)_2(OH)Cl]\cdot 0.5H_2O$	36
$Na_2[VO(D\text{-}Glc)_2(OH)Cl]\cdot H_2O$	36	$Na_2[VO(D\text{-}Gal)_2]\cdot CH_3OH$	37
$Na_2[VO(D\text{-}Fru)_2]$	37	$Na_2[VO(D\text{-}Gal)_2(H_2O)]$	34
$Na_6[(VO)_2(D\text{-}Fru)_5]\cdot 4H_2O$	39	$Na_4[VO(D\text{-}Man)_2]\cdot 8H_2O$	40
$Na_2[VO(D\text{-}Fru)_2(OH)Cl]\cdot 5H_2O$	36	$Na_3[VO(D\text{-}Man)_2(OCH_3)]\cdot 4CH_3OH$	37
$Na_2[VO(D\text{-}Xyl)_2]\cdot CH_3OH$	34	$Na_5[VO(D\text{-}Lyx)_2(OH)]\cdot 6H_2O$	40
$Na_4[VO(D\text{-}Xyl)_2]\cdot 5H_2O$	40	$Na_4[VO(D\text{-}Lyx)_2]\cdot 2H_2O$	34
$Na_2[VO(D\text{-}Xyl)_2(HO)Cl]\cdot CH_3OH\cdot 1.5H_2O$	36	$Na_2[VO(Ino)_2]$	34
$Na_4[VO(D\text{-}Ara)_2]\cdot CH_3OH\cdot 3H_2O$	34	$Na_4[VO(D\text{-}Rib)_2]\cdot H_2O$	34
$Na_4[VO(D\text{-}Ara)_2]\cdot 5H_2O$	40	$Na_3[VO(D\text{-}Rib)_2(OH)]\cdot 4H_2O$	35
$Na_4[VO(L\text{-}Ara)_2]\cdot 5H_2O$	40	$Na_2[VO(D\text{-}Rib)_2(OH)Cl]\cdot CH_3OH$	36

The electronic absorption spectra are almost identical with the reflectance spectra obtained from the respective solids, suggesting the presence of similar species in solution and in the solid state.

2.4. General Physicochemical Properties of Monosaccharide Complexes

Oxovanadium (IV) complexes coordinated by pairs of doubly deprotonated sugar moieties usually display a very characteristic electronic absorption spectrum. As an example, that generated by the interaction of VO^{2+} with D-ribose, is shown in Figure 2. The three band spectral pattern has been generally assigned to the expected d-d transitions in the frame of the Ballhausen and Gray schema[34,37,39–41] (i.e. $b_2 \rightarrow a_1$; $b_2 \rightarrow b_1$ and $b_2 \rightarrow e$, going from higher to lower energies).[42] Notwithstanding, a different assignment may also be possible,[41] and we currently are investigating this aspect.

Circular dichroism studies with some of the complexes confirmed that the ligands are bidentate and chelating,[34] whereas ^{1}H NMR spectra were not useful for characterization purposes, as they showed the expected line broadening due to the presence of a paramagnetic metal center.[34,37]

The IR spectra of all the complexes present were broad and scarcely defined bands, with the loss of the fine structure usually found with the isolated saccharides. The characteristic stretching vibration of the V═O group is found, in all cases, at relatively low energies, between 920 and 960 cm^{-1} (cf. ref.[34,37,39–41]). These rather low values have been explained on the basis of possible hydrogen-bond interactions between free hydroxyl groups of the ligand molecules and the oxo-group of the complex.[34,37] It is very difficult to identify with certainty the position of the metal-to-ligand vibrations.

EPR spectra recorded for most of these complexes either in aqueous solutions or in the solid state showed the characteristic eight-line pattern (I = 7/2) of the oxovanadium (IV) cation[21,34,37] and their *g* and **A** values are in agreement with the presence of $VO(O_4)$ coordination spheres.

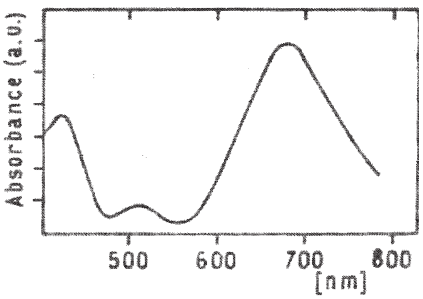

Figure 2. Electronic absorption spectrum of a VO^{2+}/D-ribose solution (1:2 relation) at pH 12.

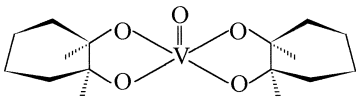

Figure 3. Schematic representation of the VO^{2+}/sugar interaction in simple 1:2 complexes.

The complexes are highly stable towards oxidation or degradation, as confirmed by the fact that samples dissolved in water or dimethylsulfoxide and stored for about eight weeks, exhibited no changes in their EPR patterns.[34,37]

Investigations of the electrochemical behaviour of a great number of the mentioned monosaccharide complexes have been performed in aqueous solution, at different pH values, by means of cyclic voltamperommetry using a hanging mercury drop or a Pt working electrode and a Ag/AgCl reference electrode.[34,37] An irreversible reduction peak related to the V(IV) → V(III) transformation was detected in all cases. Working at a scan speed of 100 mV/s, the reduction potentials were found to lie in the range between −1.15 to −1.70 V.

Unfortunately, up to now it has been impossible to obtain single crystals of any of the described monosaccharide complexes adequate for an X-ray crystallographic structural analysis.[34,39,40] Notwithstanding, all the thus far accumulated spectroscopic data for the simplest 2:1 sugar: VO^{2+} complexes strongly support the formation of bis-chelated species of the type shown in Figure 3. The anionic charge of these species would be equal to 2 if only the pairs of coordinated hydroxyls are deprotonated, and become higher in the case of additional deprotonation of OH-groups on the sugar moieties.

If additional ligands, such as an OH^- group or a H_2O molecule, were incorporated into the coordination sphere of the cation, they would be located in a *trans* position in relation to the oxo group. The simultaneous incorporation of two additional anionic ligands generates a structure of the type proposed in Figure 1.

3. DISACCHARIDE COMPLEXES

Only four oxovanadium (IV) complexes with disaccharides as ligands have been reported. These are the complexes of sucrose,[39] turanose,[39] and maltose,[37,40] with the following stoichiometries:

$Na_3[VO(D\text{-}Suc)_2OH]\cdot H_2O$
$Na_3[VO(D\text{-}Tur)_2OH]\cdot 3H_2O$
$Na_5[VO(D\text{-}Mal)_2OH]\cdot 10H_2O$
$Na_3[VO(D\text{-}Mal)_2]\cdot CH_3OH$

The first three were prepared by reaction of aqueous solutions of $VOCl_2$ and the corresponding disaccharide in a 1:2 ratio and subsequent precipitation with absolute ethanol.[39,40] The last was obtained from $VO(acac)_2$ and the disodium salt of maltose, in methanolic solution.[37] Magnetic susceptibility measurements confirm the presence of an isolated VO^{2+} center in all of them.

Also these complexes are hygroscopic and highly soluble in water. The sucrose complex is rather unstable in solution.

The electronic spectra of the first three complexes show the typical three band pattern characteristic of VO^{2+}/saccharide complexes,[39,40] whereas the fourth species only presents two bands.[37] Analysis of the IR spectra of the complexes showed that the cation coordinated with the fructose unit in both the sucrose and the turanose complexes.[39] In the case of the maltose complexes, no definite interaction schema could be derived from the very complicated spectra.[37,40] The characteristic υ(VO) stretching frequencies are found at 931, 924, 925 and 930 cm^{-1}, respectively for the sucrose, turanose, and the two maltose complexes.

$Na_5[VO(D\text{-}Mal)_2OH]\cdot 10H_2O$ shows a very interesting and complex thermal behaviour. The ten water molecules are given off in four successive steps between 20 and 181°C, involving 2 + 2 + 4 +2 molecules.

4. COMPLEXES OF CARBOHYDRATE DERIVATIVES AND OF POLY-SACCHARIDES

A number of oxovanadium (IV) complexes with some carboxylate derivatives of carbohydrates (uronic acids and lactobionic acid) and sugar phosphate esters, as well as with polysaccharides, has been also investigated in solution and in the solid state. This is also a field of increasing interest and much work rest to be done regarding this type of ligands.

4.1. Complexes with Carbohydrate Acids and Esters

D-galacturonic acid (Figure 4a) reduces vanadates (V) to oxovanadium (IV) in acid solution, with generation of formic acid.[43] The interaction of VO^{2+} with D-galacturonic acid has been investigated in solution by means of spectroscopic and potentiometric methods.[44–46]

Coordination is initiated at pH = 3 by the carboxylate group (pK = 3.28)[45] to yield a $VO(galact)_2$ complex. With increasing pH-values, one or two sugar hydroxyl groups, those at C(4) and C(3) atoms, are deprotonated and involved in coordination. Mononuclear complexes of the types $[VO(D\text{-}galact)_2]^{2-}$ and $[VO(D\text{-}galact)_2]^{4-}$, containing the di-negative and tri-negative anions, respectively, are

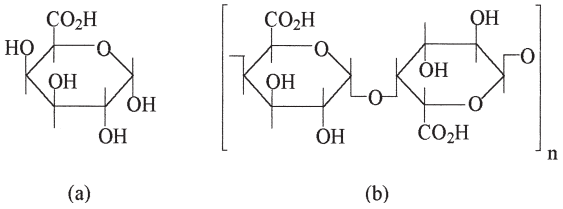

Figure 4. D-galacturonic acid (**a**) and polygalacturonic acid (**b**).

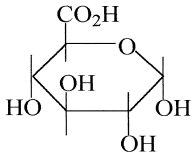

Figure 5. D-glucuronic acid.

formed. The first of these complexes involves coordination through the carboxylate and the deprotonated C(4) hydroxyl and the second one is *bis* chelated by the two deprotonated OH groups.[44,45] The last species again presents an electronic spectral pattern which closely resembles that shown in Figure 2.[45]

In contrast, and at high pH values, the EPR and ENDOR spectra of concentrated solutions of oxovanadium (IV) and D-galacturonic acid shows the formation of a dinuclear species.[46] A metal-metal distance of about 5 Å, and bonding through the carboxylate group and the deprotonated C(4), C(3) and C(2) hydroxyls is assumed. This implies the adoption of an open-chain structure stabilized by the dimer complex formation. This result is very interesting due to the fact that the abundance of the open-chain form in sugars is usually very low in comparison to the two closed anomeric α and β forms. In the present case, the formation of a very stable dimeric complex is evidently the driving force for the sugar rearrangement. The open-chain form behaves as an analogue of tartaric acid, yielding a dimeric species of comparable stability.[46,47]

D-glucuronic acid (Figure 5) also interacts with oxovanadium (IV), but the different configuration of the C(4) hydroxyl group, compared to D-galacturonic acid, generates a different behaviour. As discussed above, in the case of D-galacturonic acid, the first chelate complex is formed by simultaneous coordination of the carboxylate and the deprotonated C(4) hydroxyl.

Although the carboxylate group of glucuronic acid has a comparable pK-value (3.07),[45] the coordination to the C(4) hydroxyl is sterically less favourable and an increase of pH is needed to generate a second deprotonated hydroxyl group in order to produce a $[VO(D\text{-glucur})_2]^{4-}$ species with two pairs of deprotonated sugar hydroxyls coordinated to the metal center. This behaviour implies that in this case the di-negative anion is not formed. However, on the other hand, spectroscopic results suggest the formation of a polymeric species at pH $>$ 5 which, apparently, is different from the dimeric species found in the case of D-galacturonic acid.

A green microcrystalline solid of composition $Na_4[VO(D\text{-galact})_2]\cdot 8H_2O$ could be prepared by reaction of aqueous solutions of $VOCl_2$ and D-glucuronic acid in a 1:2 ratio, at pH 12, and subsequent precipitation by successive additions of ethanol and methanol.[48] The electronic reflectance spectrum of the solid shows again the typical three-band pattern with maxima at 740, 500 and 425 nm. The characteristic ν(VO) IR-band is found at 941 cm^{-1} and the detailed analysis of this spectrum suggests the involvement of the deprotonated hydroxyl groups of C(1) and C(2) in bonding.[48]

The interaction of VO^{2+} with D-glucuronic acid has been also investigated by differential IR spectroscopy in solution and some details of the bonding at different pH values could be deduced from these measurements.[49] Interestingly, at pH 5, in which the previous studies showed the formation of a polymeric species, participation of the carboxylate group in bonding was confirmed and two independent υ(VO) bands, at 991 and 980 cm^{-1} were found, suggesting the presence of two structurally nonequivalent VO^{2+} cations.[49]

Lactobionic acid (Figure 6), an oxidation product of lactose, is another carbohydrate acid which can generate stable metal chelates. Its interaction with oxovanadium (IV) has been investigated by Kozlowski et al. by means of potentiometric and spectroscopic techniques.[50,51] It was shown that five complex species are formed starting at very low pH values (<3).

The coordination behaviour of lactobionic acid resembles that of D-galacturonic acid. The first formed species $[VO(lactbion)_2]$ involves chelation through the deprotonated carboxylate ($pK = 3.53$)[50] and the vicinal OH-group. The stepwise deprotonation and metal coordination of one and two vicinal hydroxyl groups yields $[VO(lactbion)_2]^-$ and $[VO(lactbion)_2]^{2-}$, involving (COO^-, OH; COO^-, O^-) and ($2COO^-$, $2\ O^-$) binding, respectively. The formation of $[VO(lactbion)_2]^{3-}$, and $[VO(lactbion)_2]^{4-}$, above $pH = 8$ suggests that the metal can induce the deprotonation of two adjacent hydroxyls in each ligand molecule. In the last complex, coordination occurs through a pair of deprotonated OH^- groups of each ligand. Circular dichroism spectroscopy rules out hydroxo binding, even at very high pH values, substantiating that only lactobionic acid is bound to the cation showing that its coordination to four deprotonated hydroxyl oxygen atoms is very effective and overcomes the tendency towards hydrolysis.[50,51] The stability constants for the lactobionic acid complexes are two to four orders of magnitude higher than those of D-galacturonic acid. This fact has been attributed to the more flexible structure of the linear fragment of lactobionic acid in contrast to the rigid cyclic structure of D-galacturonic acid. This higher flexibility allows the formation of less hindered chelate rings and, consequently, more stable complexes.[50]

The investigation of the chelating ability of phosphate esters of carbohydrates has also generated interest in recent years. D-ribose-5-phosphate (D-Rib-5P) is a ligand of special interest in relation to VO^{2+}/nucleotide interactions[6,30] and a number of simple complexes containing this phosphate ester have been recently char-

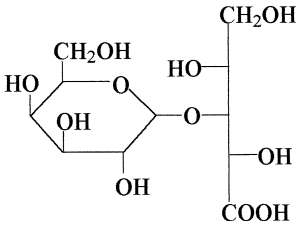

Figure 6. Lactobionic acid.

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acterized.[35] By mixing aqueous solutions of D-ribose-5-phosphate and $VOCl_2$ in a 2:1 molar ratio (final pH-value 6), a light blue powder of composition $Na_2[VO(D\text{-}Rib\text{-}5P)(OH)(H_2O)_2]\cdot 2H_2O$ precipitates immediately. If this complex is redissolved by dropwise addition of 1M HCl up to pH 3, and subsequent addition of a small volume of ethanol, another blue species of stoichiometry $[VO(D\text{-}Rib\text{-}5P)(H_2O)_3]Cl$, can be isolated. The vibrational spectroscopic investigation shows phosphate coordination in both cases and suggests that this group acts as a bidentate ligand in the first case and as monodentate in the second one. However, it is not clear if the Cl^- anion participates in bonding in the second case.[35] The electronic spectra of these two complexes shows bands at 840−830 and 640−630 nm, which are typical for phosphate coordination, whereas the characteristic υ(VO) stretching vibration is located at around 990 cm^{-1}.

A different complex, of stoichiometry $Na_6[VO(D\text{-}Rib\text{-}5P)_2]\cdot 6H_2O$, can be isolated at pH 12. In this case, coordination of the oxocation takes place through two pairs of deprotonated OH-groups of the sugar moiety and, as expected, the electronic spectrum is totally similar to that of the D-ribose complex, $Na_3[VO(D\text{-}Rib)_2(OH)]\cdot 4H_2O$, described in Sect.2.2.[35]

The interaction of the VO^{2+} cation with D-glucose-1-phosphate (D-Glc-1P) has also been recently investigated in our laboratory.[52] 2:1 mixtures of this ligand with $VOCl_2$ in aqueous solutions generate two different complexes by adjustment of the pH of these solutions to different values. At pH 4 a species of composition $Na[VO(D\text{-}Glc\text{-}1P)_2\ (H_2O)Cl]\cdot 4H_2O$ can be isolated, whereas at pH 6 a second complex of stoichiometry $Na_3[VO(D\text{-}Glc\text{-}1P)_2\ (OH)]\cdot 6H_2O$ is obtained. Infrared spectra of these complexes clearly show interaction of the oxocation with the phosphate groups of D-Glc-1P, suggesting monodentate coordination in the first case and bidentate coordination in the second one. The characteristic υ(VO) stretching vibration is found at 982 and 976 cm^{-1} respectively.

The thermal behaviour of these complexes is very interesting. The degradation of $Na[VO(D\text{-}Glc\text{-}1P)_2(H_2O)Cl]\cdot 4H_2O$ at temperatures up to 1000°C generates a complex residue whose main component seems to be $NaVOPO_4$.[52–54] The thermolysis of the other complex produces a mixture of Na_3PO_4 and β–VPO_5.[55]

It should be noted that interaction with OH-groups could not be observed, even at high pH-values. This interaction is evidently hindered because of the lack of a pair of *cis*-hydroxyl groups in the D-Glc-1P molecule.[52]

4.2. Complexes with Polysaccharides

These types of systems have been scarcely investigated. Information is so far available only for two of them: polygalacturonic acid and chondroitin sulfate A.

The interaction of polygalacturonic acid (Figure 4b) with VO^{2+} and other divalent transition metal cations has been investigated by spectroscopic methods.[44,56] The results suggest that the polymer interacts with the metal center only through two carboxylate groups, which act as monodentate ligands. The coordination sphere is completed with water molecules.[56]

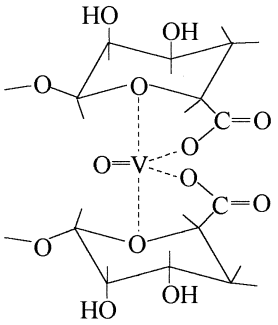

Figure 7. Proposed interaction between VO^{2+} and chondroitin sulfate A, compatible with the spectroscopic results.

Chondroitin sulfate A (CSA) is a well-known mucopolysaccharide present in connective tissues and other mineralized systems, containing alternate units of D-glucuronic acid and *N*-acetyl-D-galactosamine. The sulfate group is located on the *N*-acetylgalactosamine residues. The array of regularly repeating carboxyl and sulfate groups generates a high negative charge on the polymer. The interaction of this polysaccharide with VO^{2+} was investigated in solution by electron absorption and IR spectroscopy.[57] Spectrophotometric titrations performed at pH 5.0 suggest the formation of a $VO(CSA)_2$ complex. This could be confirmed by vibrational spectroscopic analysis, which additionally shows that the bonding of the oxocation occurs through the carboxylate group and the glycosidic oxygen of the D-glucuronate moieties as depicted in Figure 7.[57]

In order to extend the results of this study and to confirm some details of the VO^{2+}/CSA interactions, we have also investigated the behaviour of the oxocation towards the components of the mucopolysaccharide, D-glucuronic acid and *N*-acetyl-D-galactosamine. The results with D-glucuronic were described in the previous section, those obtained with the other one are briefly mentioned here. Spectroscopic measurements were performed at different metal-to-ligand ratios and pH-values. In all cases at pH 4.0, the reaction mixtures begin to precipitate without complex formation. At pH 12.0 the precipitates redissolve and the solutions show the typical electronic spectra of the oxocation coordinated to two deprotonated OH-groups of the sugar unit. A 1:2 metal-to-ligand stoichiometry was determined by spectrophotometric titration.[49] D-galactosamine shows a totally similar behaviour.[49]

5. COMPLEXES OF L-ASCORBIC ACID

L-ascorbic acid (Figure 8) is closely related to the carbohydrate chemistry discussed in this review[58] and is also a very important species in relation to vanadium biochemistry and detoxification.[5–7]

The stoichiometry and kinetics of the vanadium (V) reduction by L-ascorbic acid have been determined.[59] Its reducing ability has been found higher than those

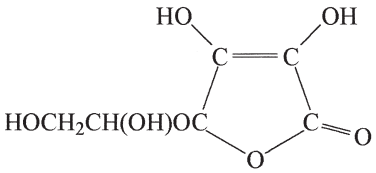

Figure 8. Structure of ascorbic acid (H_2Asc).

of most of the common hexoses and pentoses.[13] The VO^{2+} cation generated in this process interacts not only with an excess of L-ascorbic acid[13] but, apparently, also with dehydroascorbic acid.[60–62] The redox behaviour of the acid is complicated by the participation of simultaneous proton transfer reactions.[63, 64]

Two different solid complexes of VO^{2+} with L-ascorbic acid were obtained, using a general synthetic procedure developed by Jabs and Gaube for the synthesis of metal ascorbates.[65] Working at pH 3, a species of composition $[VO(HAsc)(OH)(H_2O)_2]\cdot H_2O$ was isolated whereas at pH 7 another complex of composition $Na_2[VO(HAsc)_2(OH)_2]$ was obtained.[66] In these complexes, the acid acts as a monodentate ligand, through its deprotonated 3-hydroxo group, generating complexes of very low stability, in agreement with the absence of chelate binding. The infrared and electronic spectra of these complexes have been investigated in detail.[66]

Other complexes, with the stoichiometries $[VO(Asc)_2]$, $Na_2[VO(Asc)_2]$ and $[VO(Asc)(H_2O)_2]$ have been also mentioned in the literature.[12,13] Some other species, containing ascorbate and OH^- ligands, could be recently isolated in our laboratory after interaction of an excess of L-ascorbic acid with a metavanadate solution.[67]

On the other hand, oxovanadium (IV) can also interact with the oxidation products of L-ascorbic acid. As known,[58,66] dehydroascorbic acid, generated as the primary oxidation product, is also very unstable and undergoes a rapid series of transformations. It degrades first to 2,3-diketogulonic acid, which can further be degraded to a mixture of L-threonic and oxalic acids. Although all these species could interact with the VO^{2+} cation, a thorough investigation of this ligand system showed that the primary complex generated by interaction of the oxocation with dehydroascorbic acid is very unstable towards oxidation. It hydrolyzes irreversibly with opening of the lactone ring generating 2,3-diketogulonic acid, producing a 2:1 ligand to metal complex, in which the enolized form of the mentioned acid acts as a bidentate chelator.[66] A solid sodium salt of this complex species, of composition $Na_2[VO(C_6H_6O_7)_2]\cdot 3H_2O$, was isolated and characterized.[66]

6. BIOLOGICAL ACTIVITY OF VO^{2+} CARBOHYDRATE COMPLEXES

It is well known that vanadium compounds present different biological and pharmacological effects.[8, 9, 68–70] In particular, their insulin-mimetic activity[8, 69, 71–74] and the potential antitumoral activity[9,68,69] of some of its compounds have

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generated great attention and interest in recent years. The biological activity of some of the reviewed complexes has been also investigated in this context. A brief summary of some representative studies is presented in this section.

It has been demonstrated that a mixture of vanadium (V), ascorbic acid and H_2O_2, in the presence of phosphate, generates ·OH radicals. In addition, the oxovanadium (IV) produced in this reduction process can in turn generate alkyl and alkoxyl free radicals from cumene-OOH (a model lipid hydroperoxide).[75] As free radicals derived from lipid hydroperoxides cause damage to cellular systems, it becomes evident that these types of radicals together with the reactive species originated during the ascorbate reduction of vanadium (V) to vanadium (IV), may be significantly involved in the vanadium (V) induced cellular injuries.[75]

Other studies performed directly with some of the reviewed oxovanadium (IV) complexes of ascorbic acid and monosaccharides show that these compounds cause substantial single strand breaks in DNA and produce lipid peroxidation.[12] The DNA cleaving ability is especially important in the case of the $[VO(asc)_2]$ and $[VO(asc)(H_2O)_2]$ ascorbato complexes. These complexes showed also the highest activity of lipid peroxidation.[12] Monosaccharide complexes did not show appreciable cleavage of DNA in the absence of H_2O_2.[12]

Potent DNA cleaving, in the presence of H_2O_2, was also observed in the case of the group of complexes of composition $Na_2[VO(sacch)_2(OH)Cl]$.[36] It was suggested that the mechanism involve the generation of ·OH radicals from H_2O_2 by a Fenton-type reaction.

Some of the known monosaccharide complexes of oxovanadium (IV) also present an interesting protective activity against the degradation of RNA because they inhibited RNase activity.[34] In contrast, they have no effect on DNase. This behavior suggests that these complexes closely mimic the substrate portion of the RNase-catalysed RNA hydrolysis acting as transition-state analogues to RNase.[34] On the other hand, the isolation of RNA from most animal cells is performed by the inhibition of RNase using a mixture of $VOSO_4$ and ribonucleosides.[76]

The isolation of *vanadobin*, a low molecular weight compound containing oxovanadium (IV) and a reducing sugar as the vanadium-binding substance in one species of tunicate, the ascidia *Sydneiensis Samea*, constitute an interesting example of a natural system involving VO^{2+} and a carbohydrate.[77,78]

Finally, it is worth remembering that ascorbic acid appears as the most efficient detoxification agent for vanadium in humans.[7, 69, 79] It is probably the least toxic of all the drugs investigated for this purpose and can be orally administered in large doses. Its mode of action may be related to its efficient reducing power against vanadium (V), the more toxic oxidation state of the element.

7. CONCLUSIONS AND PERSPECTIVES

A large series of studies on the interaction of the VO^{2+} cation with different types of saccharides and closely related molecules have been performed in recent

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years bringing new insights into these systems which have important biological significance and impact.

There are still a number of very interesting problems and aspects that remain open to future research. Efforts should be particularly directed to the structural characterization of oxovanadium (IV) saccharide complexes. If it is not possible to attain single crystals adequate for crystallographic studies, at least EXAFS studies, as those recently performed for iron-saccharide complexes,[80] should be attempted. Moreover, the synthesis and detailed characterization of new complexes, with disaccharides and saccharide derivatives, constitute another point of interest for wider development of the field. Studies on the interaction of the VO^{2+} cation with simple and complex (hyaluronan-type[81]) polysaccharides should be expanded, as these systems are of particular biological importance.

Speciation studies and stability constant determinations of the different VO^{2+}/saccharide systems is also a field that should be explored more deeply. Apparently, only two systems of this type have thus far been investigated in this respect.[45,50]

The investigation of effects of vanadium/saccharide complexes on cells in culture should be also extended, as this methodology is a valuable way to advance in the knowledge of its biological effects (for a recent review cf. ref.[82]). Finally, possible pharmacological effects of these complexes should be explored in more detail, especially regarding their insulin-mimetic and antitumoral activities.

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9. REFERENCES

1. Burger, K.; Nagy, L. Metal Complexes of Carbohydrates and Sugar-type Ligands. In *Biocoordination Chemistry: Coordination Equilibria in Biologically Active Systems*; Burger, K., Ed.; Ellis Horwood: New Jersey, 1990; 236–270.
2. Yano, S. Coordination Compounds Containing Sugars and their Derivatives. Coord. Chem. Rev. **1988**, *92*, 113–156.
3. Whitfield, D.M.; Stojkovski, S.; Sarkar, B. Metal Coordination to Carbohydrates. Structures and Function. Coord. Chem. Rev. **1993**, *122*, 171–225.
4. Yano, S.; Otsuka, M. Sugar-Metal Ion Interactions. In *Metal Ions in Biological Systems*; Sigel, A; Sigel, H. Eds.; Marcel Dekker: New York, 1995; 27–60.

5. Baran, E.J. Model Studies Related to Vanadium Metabolism. Bol. Soc. Chil. Quím. **1997**, *42*, 247–256.
6. Baran, E.J. Oxovanadium (IV) and Oxovanadium (V) Complexes Relevant to Biological Systems. J. Inorg. Biochem. **2000**, *80*, 1–10.
7. Baran, E.J. Vanadium Detoxification. In *Vanadium in the Environment, Part 2: Health Effects*; Nriagu, J.O. Ed.; J.Wiley: New York, 1998; 317–345.
8. Thompson, K.H.; McNeill, J.H.; Orvig, C. Vanadium-Containing Insulin Biomimetic Drugs. In *Metallopharmaceuticals II*; Clarke, M.J.; Sadler, P.J. Eds.; Springer: Berlin, 1999; 139–158.
9. Köpf-Maier, P.; Köpf, H. Organometallic Titanium, Vanadium, Niobium, Molybdenum and Rhenium Complexes: Early Transition Metal Antitumor Drugs. In *Metal Compounds in Cancer Therapy*; Fricker, S.P. Ed.; Chapman & Hall: London, 1994, 109–146.
10. Virtanen, P.O.I.; Oikarinen, E.; Yli-Pyky, A. Kinetics of the Oxidation of D-Galactose with Vanadium (V). Finn. Chem. Lett. **1989**, *16*, 53–59.
11. Bandwar, R.P.; Rao, C.P. Relative Reducing Abilities in Vitro of Some Hydroxy-Containing Compounds, Including Monosaccharides, Towards Vanadium (V) and Molybdenum (VI). Carbohydr. Res. **1995**, *277*, 197–207.
12. Sreedhara, A.; Susa, N.; Patwardhan, A.; Rao, C.P. One Electron Reduction of Vanadate (V) to Oxovanadium (IV) by Low-Molecular-Weight Biocomponents Like Saccharides and Ascorbic Acid. Biochem. Biophys. Res. Commun. **1996**, *224*, 115–120.
13. Sreedhara, A.; Susa, N.; Rao, C.P. Vanadate and Chromate Reduction by Saccharides and L-Ascorbic Acid: Effect of Isolated V (IV) and Cr (III) Products on DNA Nicking, Lipid Peroxidation, Cytotoxicity and on Enzymatic and Non-Enzymatic Antioxidants. Inorg. Chim. Acta **1997**, *263*, 189–194.
14. Tracey, A.S; Gresser, M.J. Vanadium (V) Oxyanions. Interaction of Vanadate with Cyclic Diols and Monosaccharides. Inorg. Chem. **1988**, *27*, 2695–2702.
15. Geraldes, C.F.G.C.; Castro, M.M.C.A. Interaction of Vanadate with Monosaccharides and Nucleosides: A Multinuclear NMR Study. J. Inorg. Biochem. **1989**, *35*, 79–93.
16. Rehder, D. The Bioinorganic Chemistry of Vanadium. Angew. Chem. Int. Ed. Engl. **1991**, *30*, 148–167.
17. Crans, D.C. Interaction of Vanadates with Biogenic Ligands. In *Metal Ions in Biological Systems*; Sigel, H.; Sigel, A. Eds.; Marcel Dekker: New York, 1995; Vol. 31, 147–209.
18. Rajak, K.K.; Baruah, B.; Rath, S.P.; Chakravorty, A. Sugar Binding to VO^{3+}. Synthesis and Structure of a New Mannopyranoside Vanadate. Inorg. Chem. **2000**, *39*, 1598–1601.
19. Crans, D.C. Aqueous Chemistry of Labile Oxovanadates: Relevance to Biological Studies. Commun. Inorg. Chem. **1994**, *16*, 1–33.
20. Crans, D.C. Enzyme Interactions with Labile Oxovanadates and Other Polyoxometalates. Commun. Inorg. Chem. **1994**, *16*, 35–76.
21. Branca, M.; Micera, G.; Dessi, A.; Sanna, D. Oxovanadium (IV) Complex Formation by Simple Sugars in Aqueous Solution. J. Inorg. Biochem. **1992**, *45*, 169–177.
22. Baran, E.J. Química Bioinorgánica. McGraw Hill-Interamericana de España S.A.: Madrid, 1995; 15–17.
23. Baran, E.J. Vanadyl (IV) Complexes of Nucleotides. In *Metal Ions in Biological Systems*; Sigel, H.; Sigel, A. Eds.; Marcel Dekker: New York, 1995; Vol.31, 129–146.

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24. Sakurai, H.; Goda, T.; Shimomura, M.; Yoshimura, T. ATP (Adenosine Triphosphate)-Vanadyl Complex. Biochem. Biophys, Res. Commun. **1982**, *104*, 1421–1426.
25. Sakurai, H.; Goda, T.; Shimomura, M.^{31} P- and ^{13}C-NMR Study of the ATP (Adenosine Triphosphate)-Vanadyl Complex. Biochem. Biophys. Res. Commun. **1982**, *108*, 474–478.
26. Urretavizcaya, G.; Baran, E.J. Wechselwirkung des Vanadyl (IV)-Kations mit Nucleotiden in wässriger Lösung. Z. Naturforsch. **1987**, *42b*, 1537–1542.
27. Etcheverry, S.B.; Ferrer, E.G.; Baran, E.J. Neue Beweise über die Wechselwirkung des Vanadyl(IV)-Kations mit Nucleotiden:^{31} P-NMR- und IR-Messungen in Lösung. Z. Naturforsch. **1989**, *44b*, 1355–1358.
28. Cini, R.; Giorgi, G.; Laschi, F.; Sabat, M.; Sabatini, A.; Vacca, J. Potentiometric and Electron Spin Resonance Investigation of the Interactions Between Adenosine-5′-Triphosphate (atp) and Triphosphate Ligands with Vanadyl Ion. Synthesis and Characterization of Solid-Vanadyl-atp Compounds from Acidic Aqueous Solution. J. Chem. Soc. Dalton Trans. **1989**, 575–580.
29. Williams, P.A.M.; Baran, E.J. A Spectrophotometric Study of the Interaction of VO^{2+} with Adenine in Nucleotides. J. Inorg. Biochem. **1992**, *48*, 15–19.
30. Williams, P.A.M.; Baran, E.J. A Spectrophotometric Study of the Interaction of VO^{2+} with Monophosphate Nucleotides. J. Inorg. Biochem. **1993**, *50*, 101–106.
31. Micera, G.; Dessi, A.; Sanna, D. Binding of Oxovanadium (IV) to Guanosine 5′-Monophosphate. Inorg. Chem. **1996**, *35*, 6349–6352.
32. Williams, P.A.M.; Etcheverry, S.B.; Baran, E.J. Interaction of the Vanadyl (IV) Cation with Nucleosides. An. Asoc. Quím. Argent. **1994**, *82*, 13–17.
33. R.B.Martin, R.B.; Mariam, Y.H. Interactions Between Metal Ions and Nucleic Bases, Nucleosides, and Nucleotides in Solution. In *Metal Ions in Biological Systems*; Sigel, H.; Sigel, A. Eds.; Marcel Dekker: New York, 1979; Vol. 8, 57–124.
34. Sreedhara, A.; Rao, C.P.; Rao, B.J. Transition Metal Saccharide Chemistry and Biology: Synthesis, Characterization, Electrochemistry and EPR Studies of Oxovanadium (IV) Complexes of Saccharides and their Derivatives and *in Vitro* Interaction of Some of These with Ribonuclease and Deoxyribonuclease. Carbohydr. Res. **1996**, *289*, 39–53.
35. Williams, P.A.M.; Etcheverry, S.B.; Baran, E.J. Synthesis and Characterization of Solid Vanadyl (IV) Complexes of D-Ribose and D-Ribose-5-Phosphate. J. Inorg. Biochem. **1997**, *65*, 133–136.
36. Bandwar, R.P.; Rao, C.P. Transition Metal Saccharide Chemistry and Biology: Vanadyl-Monosaccharide Complexes and their *in Vitro* Effect on pUC-18 DNA. J. Inorg. Biochem. **1997**, *68*, 1–6.
37. Sreedhara, A.; Raghavan, M.S.S.; Rao, C.P. Transition-Metal Saccharide Interactions: Synthesis and Characterization of Vanadyl Saccharides. Carbohydr. Res. **1994**, *264*, 227–235.
38. C.P.Rao, C.P.; Kaiwar, S.P. Homoleptic Glucose Complexes of VO^{2+} and Cr^{3+}. Inorg. Chim. Acta **1991,** *186*, L11–12.
39. Etcheverry, S.B.; Williams, P.A.M.; Baran, E.J. Synthesis and Characterization of Oxovanadium (IV) Complexes with Saccharides. Carbohydr. Res. **1997**, *302*, 131–138.
40. Williams, P.A.M.; Etcheverry, S.B.; Baran, E.J. Characterization of New Oxovanadium (IV) Complexes of Saccharides. Carbohydr. Res. **2000**, *329*, 41–47.
41. Baran, E.J. Spectroscopic Studies of Oxovanadium Coordination Compounds. J. Coord. Chem., in the press.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

42. Ballhausen, C.J.; Gray, H.B. The Electronic Structure of the Vanadyl Ion. Inorg. Chem. **1962**, *1*, 111–122.
43. Micera, G.; Deiana, S.; Dessi, A.; Pusino, A.; Gessa, C. Oxidation of D-Galacturonic Acid by Vanadium(V). Inorg. Chim. Acta **1986**, *120*, 49–51.
44. Branca, M.; Micera, G.; Dessi, A.; Kozlowski, H. Proton Electron Nuclear Double Resonance Study of Oxovanadium (IV) Complexes of D-Galacturonic and Polygalacturonic Acids. J. Chem. Soc. Dalton Trans. **1989**, 1283–1287.
45. Micera, G.; Dessi, A.; Kozlowski, H.; Radomska, B.; Urbanska, J.; Decock, P.; Dubois, B.; Olivier, I. Oxovanadium (IV) and Copper (II) Coordination by D-Galacturonic and D-Glucuronic Acids. Carbohydr. Res. **1989**, *188*, 25–34.
46. Branca, M.; Micera, G.; Sanna, D.; Dessi, A.; Kozlowski, H. Stabilization of the Open-chain Structure of D-Galacturonic Acid in a Dimeric Complex with Oxovanadium (IV). J. Chem. Soc. Dalton Trans. **1990**, 1997–1999.
47. Pettit, L.D.; Swash, J.L.M. Complexes of D-, L-, DL- and meso-Tartaric Acid with Hydrogen and Oxovanadium (IV) Cations. J. Chem. Soc. Dalton Trans. **1978**, 286–290.
48. Etcheverry, S.B.; Williams, P.A.M.; E.J.Baran, E.J. Synthesis and Characterization of a Solid Vanadyl (IV) Complex of D-Glucuronic Acid. J. Inorg. Biochem. **1996**, *63*, 285–289.
49. Etcheverry, S.B.; Williams, P.A.M.; Baran, E.J. A Spectroscopic Study of the Interaction of the VO^{2+} Cation with the Two Components of Chondroitin Sulfate. Biol. Trace Elem. Res. **1996**, *51*, 169–176.
50. Kozlowski, H.; Bouhsina, S.; Decock, P.; Micera, G.; Swiatek, J. Vanadyl (IV) Complexes of Lactobionic Acid: Potentiometric and Spectroscopic Studies. J. Coord. Chem. **1991**, *24*, 319–323.
51. Micera, G.; Sanna, D. Spectroscopic Methods for the Characterization of Vanadium Complexes. In *Vanadium in the Environment, Part 1: Chemistry and Biochemistry*; Nriagu, J.O. Ed.; J.Wiley: New York, 1998; 131–166.
52. Gagliardi, L.; Williams, P.A.M. Preparation and Characterization of Glucose-1-Phosphate An. Asoc. Quím. Argent. **1999**, *87*, 165–172.
53. Lii, K.H.; Li, C.H.; Chen, T.M.; Wang, S.L. Synthesis and Structural Characterization of Sodium Vanadyl (IV) Orthophosphate $NaVOPO_4$. Z. Kristallogr. **1991**, *197*, 67–73.
54. Baran, E.J; Vassallo, M.B; Lii, K.H. Vibrational Spectra of β-$LiVOPO_4$ and $NaVOPO_4$. J. Raman Spectrosc. **1994**, *25*, 199–202.
55. E.Bordes, E.; Courtine, P. Some Selectivity Criteria in Mild Oxidation Catalysis. Vanadium-Phosphorus-Oxygen Phases in Butene Oxidation to Maleic Anhydride. J. Catal. **1979**, *57*, 236–252.
56. Deiana, S.; Erre, L.; Micera, G.; Piu,P.; Gessa, C. Coordination of Transition-Metal Ions by Polygalacturonic Acid: a Spectroscopic Study. Inorg. Chim. Acta **1980**, *46*, 249–253.
57. Etcheverry, S.B.; Williams, P.A.M.; Baran, E.J. The Interaction of the Vanadyl (IV) Cation with Chondroitin Sulfate A. Biol. Trace Elem. Res. **1994**, *42*, 43–52.
58. Davies, M.B.; Austin, J.; Partridge, D.A. *Vitamin C: Its Chemistry and Biochemistry*; Royal Society of Chemistry: London, 1991.
59. Kustin, K.; Toppen, D.L. Reduction of Vanadium (V) by L-Ascorbic Acid. Inorg. Chem. **1973**, *12*, 1404–1407.
60. Kriss, E.E.; Yatsimirskii, K.B.; Kurbatova, G.T.; Grigoréva, S.S. Reduction of Vanadate by Ascorbic Acid Studied by an EPR Method. Russ. J. Inorg. Chem. **1975**, *20*, 55–59.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

61. Kriss, E.E.; Kurbatova, G.T.; Yatsimirskii, K.B. An Electron Spin Resonance Study of the Kinetics of the Reduction of Polyvanadate by Ascorbic Acid. Russ. J. Inorg. Chem. **1975**, *20*, 59–61.
62. Baran, E.J.; Ferrer, E.G.; Williams, P.A.M. Interaction of the Vanadyl (IV) Cation with Ascorbic Acid and Related Systems. J. Inorg.Biochem. **1995**, *59*, 600.
63. Davies, M.B. Reactions of L-Ascorbic Acid with Transition Metal Complexes. Polyhedron **1992**, *11*, 285–321.
64. Creutz, C. The Complexities of Ascorbate as a Reducing Agent. Inorg. Chem. **1981**, *20*, 4449–4452.
65. Jabs, W.; Gaube, W. Zur Darstellung von Ascorbatkompklexen einiger 3d-Elemente. Z. Anorg. Allg. Chem. **1984**, *514*, 179–184.
66. Ferrer, E.G.; Williams, P.A.M.; Baran, E.J. Interaction of the Vanadyl (IV) Cation with L-Ascorbic Acid and Related Systems Z. Naturforsch. **1998**, *53b*, 256–262.
67. Ferrer, E.G.; Baran, E.J. Reduction of Vanadium (V) with Ascorbic Acid and Isolation of the Generated Oxovanadium (IV) Species. Biol. Trace Elem. Res. **2001**, in the press.
68. Djordjevic, C. Antitumor Activity of Vanadium Compounds. In *Metal Ions in Biological Systems*; Sigel, H.; Sigel, A. Eds.; Marcel Dekker: New York, 1995; Vol. 31, 595–616.
69. Baran, E.J. La Nueva Farmacología Inorgánica. XVII. Compuestos de Vanadio. Acta Farm. Bonaerense **1997**, *16*, 43–52.
70. Morinville, A.; Maysinger, D.; Shaver, A. From Vanadis to Atropos: Vanadium Compounds as Pharmacological Tools in Cell Death Signalling. Trends Pharmacol. Sci. **1998**, *19*, 452–460.
71. Thompson, K.H. Vanadium and Diabetes. BioFactors **1999**, *10*, 43–51.
72. Badmaev, V.; Prakash, S.; Majeed, M. Vanadium: A Review of its Potential Role in the Fight Against Diabetes. J. Alternat. Complement. Med. **1999**, *5*, 273–291.
73. Thompson, K.H.; McNeill, J.H.; Orvig, C. Vanadium Compounds as Insulin Mimics. Chem. Rev. **1999**, *99*, 2561–2571.
74. Orvig, G.; Thompson, K.H.; Cam, M.C.; McNeil, J.H. Vanadium Compounds as Possible Insulin Modifiers. In *Uses in Inorganic Chemistry in Medicine*; Farrell, N.P. Ed.; Royal Society of Chemistry: Cambridge, 1999: 93–108.
75. Ding, M.; Gannet, P.M.; Rojanasakul, Y.; Liu, K.; Shi, X. One-Electron Reduction of Vanadate by Ascorbate and Related Free Radical generation at Physiological pH. J. Inorg. Biochem. **1994**, *55*, 101–112.
76. S.L.Berger, S.L.; Birkenmeier, C.S. Inhibition of Intractable Nucleases with Ribonucleoside-Vanadyl-Complexes: Isolation of Messenger Ribonucleic Acid from Resting Lymphocytes. Biochemistry **1979**, *18*, 5143–5149.
77. Michibata, M.; Miyamoto, T.; Sakurai, H. Purification of Vanadium Binding Substance from the Blood Cells with Special Reference to Identification of Vanadocytes. Biochem. Biophys. Res. Commun. **1986**, *141*, 251–257.
78. Michibata, M.; Hirata, J.; Terada, T.; Sakurai, H. Autonomous Fluorescence of Ascidian Blood Cells with Special Reference to Identification of Vanadocytes. Experientia **1988**, *44*, 906–907.
79. Jones, M.M.; Basinger, M.A. Chelate Antidotes for Sodium Vanadate and Vanadyl Sulfate Intoxication in Mice. J. Toxicol. Environ. Health **1983**, *12*, 749–756.
80. Rao, C.P.; Geetha, K.; Raghavan, M.S.S.; Sreedhara, A.; Tokunaga, K.; Yamaguchi, T.; Jadhav, V.; Ganesh, K.N.; Krishnamoorthy, T.; Ramaiah, K.V.A.; Bhattacharyya, R.K. Transition Metal Saccharide Chemistry and Biology: Synthesis, Characteriza-

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tion, Solution Stability and Putative Bio-relevent Studies of Iron-Saccharide Complexes. Inorg. Chim. Acta **2000**, *297*, 373–382.
81. Lapcik, jr.L.; Lapcik, L.; De Smedt, S.; Demeester, J.; Chabrecek, P. Hyaluronan: Preparation, Structure, Properties, and Applications. Chem. Rev. **1998**, *98*, 2663–2684.
82. Etcheverry, S.B.; Cortizo, A.M. Bioactivity of Vanadium Compounds on Cells in Culture. In *Vanadium in the Environment, Part 1: Chemistry and Biochemistry*; Nriagu, J.O. Ed.; J.Wiley: New York, 1998; 359–394.

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