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Review

The coordination chemistry of Vitamin C: An overview

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Contents

Abstract

An overview is presented of aspects of the coordination chemistry of Vitamin C (L-ascorbic acid) and up-to-date information about the structures and properties of a selection of ascorbate complexes covering the literature from the first synthetic reports which emerged about two decades ago. After a brief introduction concerning the ligand characteristics of ascorbic acid, the review includes pure complexes with transition metals with special attention to the recently described polynuclear complexes, complexes with rare earth metals and mixed ligand complexes. Finally, a section is devoted to the biomedical importance of the complexes. The highlights in these topical areas are briefly discussed.

Keywords: Vitamin C; Ascorbic acid; Ascorbate complexes; Coordination compounds; Bioinorganic chemistry

Abbreviations: A, ascorbate dianion $(C_6H_6O_6)^{2-}$; baea, bis(aminoethyl)amine; bipy, bipyridine; Bu, butyl; $CDCl_3$, deutorated chloroform; CD_3OD, deutorated methanol; Cp, cyclopentadiene; CP/MAS, cross-polarization/magic angle spinning; 3D, three dimensional; 2D, two dimensional; dach, diaminocyclohexane; DHA, dehydroascorbic acid; DEPT, distortionless enhancement by polarization transfer; DMF, dimethylformamide; DMSO, dimethylsulfoxide; D_2O, deutorated water; en, ethylenediamine; Et, ethyl; HA, ascorbate monoanion $(C_6H_7O_6)^-$; H_2A, ascorbic acid $(C_6H_8O_6)$; HETCOR, heteronuclear correlation; H_2Or, orotate monoanion; Me, methyl; MeOH, methanol; NaHA, sodium ascorbate; *n*-Bu, *n*-butyl; *n*-Pr, *n*-propyl; ox^{2-}, oxalate; ph, phenyl; phen, 1,10-phenanthroline; salen, *N*,*N*′-bis(salicylidene)ethylenediamine; STM, scanning tunneling microscopy; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; trimen, *N*,*N*,*N*′-trimethylethylenediamine

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1. Introduction

Vitamin C was first isolated in 1928 by the Hungarian biochemist and Nobel Prize winner Szent-Györgyi [1]. In the nearly 80 years since its discovery, Vitamin C has become "the most famous but yet least understood of the vitamins". The most vital role of Vitamin C is no doubt that of the primary, water-soluble antioxidant in the human body.

Vitamin C is the L-enantiomer of ascorbic acid (meaning "without scurvy", the disease caused by a Vitamin C deficiency). The defining part of the substance is the ascorbate monoion, which possesses both acid and base properties. The term "Vitamin C" is not only used to refer to "L-ascorbic acid" but also for its first oxidation product "dehydroascorbic acid". The monoclinic crystal structure of the acid itself was established in the 1960s by X-ray and neutron diffraction analyses [2–4] and is approximated by the 2D structure given in Fig. 1. A 3D STM image on gold coated mica substrate given in Fig. 2 correlates well with crystallography. The image corresponds to the HOMO orbital of the L-ascorbic acid molecule for both of its keto- and enol-tautomeric forms and also for the anionic form [5].

In spite of the simplicity of this sugar molecule, its biochemistry is poorly understood due to a very complicated redox chemistry which makes the molecule both an interesting and intriguing reducing agent in inorganic systems. The interaction of Vitamin C with metal ions goes back almost 50 years to the early work of Udenfried et al. [6] about the oxidation of Vitamin C by dioxygen. Many solution studies have since been carried out on reactions between ascorbic acid and metal ions. The important work of Martell in this field established the catalytic role of metals in the oxidation of Vitamin C ([7] and the references therein) and was followed by several other studies involving equilibria between ascorbate and metal ions [8,9]. Relatively fewer studies have been reported regarding the isolation and characterization of solid complexes of ascorbic acid. The first synthetic reports emerged in the 1980s [10–12] however the coordination chemistry of Vitamin C has not progressed in a steep rise due to the problems associated with (i) the chemical instability of ascorbic acid [13–15], (ii) the low stability constants [7] and (iii) the reluctance of the complexes toward crystallization.

The reactions of L-ascorbic acid with transition metal complexes were reviewed by Davies in 1992 [16]. The present article is mainly confined to the advances in the coordination chemistry of Vitamin C, with particular attention to the synthesis and structural description of isolated complexes, notably during the period 1990–2005, including also the earlier literature related to the subject.

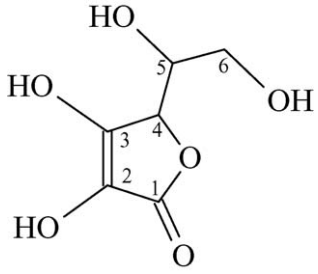


Fig. 1. L-Ascorbic acid.

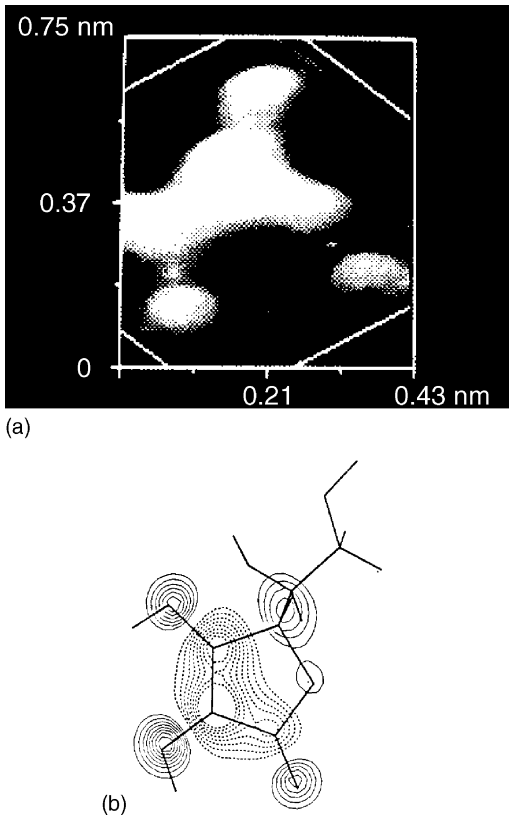


Fig. 2. (a) 3D STM image and (b) contour plot of the charge density of the HOMO orbital of ascorbic acid [5].

2. Ligand characteristics of Vitamin C

Structurally, ascorbic acid (H_2A) is a sugar acid, a γ-lactone and an ene-diol. As a weak dibasic acid ($pKa_1 = 4.25$ and $pKa_2 = 11.79$), the monoanion (HA) forms at pH 4–5 with deprotonation of O(3)–H and the dianion (A) forms at pH 11–12 with deprotonation of the O(2)–H [17]. The mono-anionic form is more stable due to the delocalization of the negative charge between the oxygen atoms at the 1- and 3-positions [18]. At physiological pH, the resonance stabilized HA undergoes two separate one-electron transfer steps to dehydroascorbic acid (DHA) via ascorbate free radical [19,20]. DHA (Fig. 3), is reduced back to H_2A by various cellular reductants. It retains the nutritional and physiological activity of H_2A but with different biological roles in cell-culture systems [21].

Although H_2A has several donor atoms capable of metal complex formation, the interaction of HA with metals mainly occurs monodentately through the O(3) atom [22–26] or by chelation via O(3) and O(2) [10,27], as shown in Fig. 4, depending on the nature of the metal cation and the pH of the solution. O,O′-chelation should be the normal kind of coordination for A as concluded by NMR studies [28–30]. In the solid state, several other bonding modes have been proposed including the participation of the carbonyl oxygen and side chain OH groups [31–36].

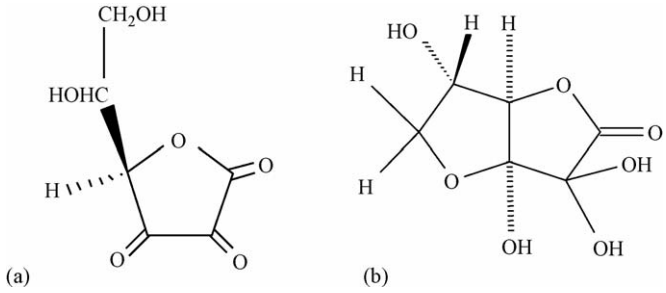


Fig. 3. The structure of dehydroascorbic acid: (a) standard representation and (b) predominant form in aqueous solution.

Unexpected coordination via carbon atoms (C,O-chelation) have been crystallographically [37,38] and computationally [39] verified for platinum mixed ascorbates. These various coordination modes will be discussed in some detail in the following sections.

The stabilities of the complexes are generally less than might have been expected. The formation constants of the 1:1 complexes are in the range of 10 to $10^{3.6}$ [7]. The values are quite small possibly because of the low negative charge on the ligand anion. The data on complexes with fully deprotonated ligand (A) is ambiguous, excluding a potentiometric study by Benetis et al. [28], and limited due to the fact that in alkaline solutions the effect of the metal ions catalyzing the oxidation of H_2A and the rate of autooxidation increase many fold. Jabs and Gaube determined the ligand field parameters of the HA ligand and suggested that ascorbate should take an intermediate position in the spectroscopic series around H_2O and ox^{2-} and just before the fluoride ligand in the nephelauxetic series [24]. Later, Cieslak-Golonka et al. calculated crystal field parameters of some chromium ascorbate complexes for octahedral and tetragonal symmetries from diffuse reflectance spectra [34]. They found that the Dq values are in the region 1600–1800 cm^{-1} and larger in solution, typical of oxygen ligands.

Experimental work with H_2A demands substantial care referring to the unstable nature of the acid. Deoxygenation of the medium is important to prevent the irreversible oxidation to DHA. DHA is more reactive, unstable and a much less effective ligand than ascorbate itself [21,40]. Ferrer et al. [25] demonstrated that the primary complexes generated by the interaction of DHA with metal ions are not stable and irreversibly hydrolyze to diketogulonic acid complexes of the related metal. Use of deionized water is another necessity for experimental studies in aqueous phase since many metal ions and complexes in their high valence state catalyze this oxidation process. H_2A has both one-electron and two-electron reducing ability and is oxidized by metal ions via both inner- and outer-sphere redox mechanisms [7,16,41]. pH is also an important factor in the decomposition of H_2A. When H_2A is heated in aqueous acidic solutions, evolution of CO_2 occurs by anaerobic degradation [42]. In alkaline solutions, oxalic acid and trihydroxybutyric acids are formed as further oxidation products of DHA [43]. Further, non-oxidizing metals catalyze oxalate formation in a pH-independent manner. The observations of Ünaleroglu et al. [44] and later of Arendse et al. [45], Orioli et al. [46] and Baruah et al. [47] demonstrate the possible role of trace metals on endogeneous oxalate production as a consequence of ascorbic acid metabolism.

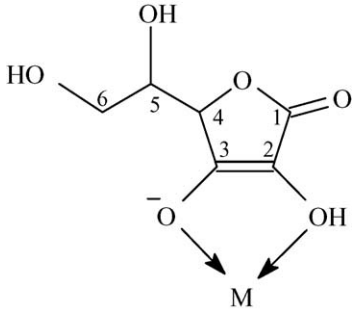


Fig. 4. Chelate-type coordination of ascorbate monoanion.

3. Complexes with transition metals

3.1. General

Nearly all the work on transition metal pure ascorbate complexes has been performed with the first-row metals and on powdered samples. Since no single crystal data are available, the structural assignments have been generally deduced from UV/vis, NMR, IR and magnetic measurements.

Due to the unstable nature of the molecule and hydrolytic instabilities of the complexes there have not been many reports on the isolation of solid complexes of ascorbic acid. The proposed structures of the pure ascorbate complexes have generally been the subject of controversy in the absence of X-ray crystal data. Another reason for the reluctance of the complexes to crystallization might be the extensive hydrogen bonding with the protic solvent molecules in which the preparations are generally carried out. The first systematic synthesis and isolation of binary ascorbate complexes with redox-inert transition metals were reported by Jabs and Gaube [11]. Complexes of the type $M(HA)_n{\cdot}xH_2O$ ($M = TiO^{2+}$, $n = 2$, $x = 2$; $M = Cr^{3+}$, $n = 3$, $x = 6$; $M = Mn^{2+}$, Co^{2+}, Ni^{2+}, Zn^{2+}, $n = 2$, $x = 4$) were obtained through the reaction:

$$MSO_{4(aq)} + Ba(OH)_{2(aq)} + 2H_2A \rightarrow M(HA)_n{\cdot}xH_2O_{(aq)} + BaSO_{4(s)} + 2H_2O \quad (1)$$

and precipitating the complex by an organic solvent like methanol or acetone. The complexes were characterized by their hydrolytic and conductivity properties, magnetic moments, electronic and infrared spectra and considered to be octahedrally coordinated with the ene-diolate group of HA where the anionic oxygen is the donor atom [24]. Four years later, they reported a bidentate complex of A with Ti(IV) but obtained limited spectral data for $K_2Ti(A)_3$ due to the low solubility of the compound in all common organic solvents [30].

The interaction of Zn(II), Cd(II) and Mn(II) with H_2A has been investigated in the solution and solid phases. The solid salts of the type $M(HA)_2{\cdot}2H_2O$ were isolated by reacting the hot solution of H_2A with a hydrated metal carbonate or acetate [32]. Spectroscopic evidence showed that in aqueous solution, the bonding of the Zn(II) and Mn(II) ions is through the O(3) and

O(2)–H groups (chelation) while the Cd(II) ion bonding is via the O(8) atom only. In the solid state, the bonding of these metal ions would be through two acid anions via O(3), O(2) of the first and O(1), O(3) of the second anion, as well as to two H_2O molecules, resulting in a six-coordinated metal ion. A point of special interest in Tajmir's work, is the application of ^{13}C NMR spectroscopy as a tool to indicate the bonding mode of the HA ligand (monodentate or bidentate) by observing the changes in the chemical shifts of the C(2) and C(3) atoms. The assignments of the ^{13}C NMR chemical shifts of H_2A and its metal ion salts have been reported in the literature [48–50]. Upon acid ionization, drastic changes are observed for the chemical shifts of C(3) (~20 ppm downfield), C(2) (downfield or upfield), C(1) (downfield) and C(4) (downfield). The positions of C(5) and C(6) are not affected significantly. The observed change for C(3) is due to the related variations in bond lengths and delocalization of the electron distribution throughout the ene-diol and carbonyl groups as a result of ionization of the acid at this position. Consequently, the C(2) carbon shows a considerable upfield shift if the bonding to the metal is through the C(3) atom only, as for alkaline and alkaline earth salts [31]. On the other hand, a downfield shift of C(2) is indicative of chelation through the O(2) and O(3) atoms (Table 1).

3.2. Vanadium

Ascorbic acid is an effective vanadium detoxification agent and reduces V(V) species by a one-electron mechanism. The stoichiometry and kinetics of this reduction process were studied by Kustin and Toppen [51] and later by Ding et al. [52] at physiological pH. The VO^{2+} cation generated in this process can interact with excess H_2A. Upon mixing solutions of V(V) and H_2A, Kustin and Toppen observed a transient species which absorbs at 425 nm. Vanadate reduction by saccharides and ascorbic acid has been also investigated by Rao and co-workers [53]. H_2A was found to have a greater reducing ability than many hexoses and pentoses and complexes of the types $[VO(HA)_2]$, $Na_2[VO(A)_2]$ and $[VO(HA)_2(H_2O)_2]$ were isolated [54].

Monodentate, low stability vanadyl ascorbate complexes prepared from the reaction of various vanadyl salts with HA have also been mentioned in the literature. The interaction of VO^{2+} with H_2A was first reported by Evtushenko et al. to yield a solid vanadyl ascorbate complex [23]. Two different monodentate solid complexes, $[VO(HA)(OH)(H_2O)_2]\cdot H_2O$ and $Na_2[VO(HA)_2(OH)_2]$, were obtained by Ferrer et al. under different pH conditions [25], by following the synthetic procedure described by Jabs and Gaube [11]. The authors then reported a vanadyl complex of ascorbic acid, $K_{1.5}Na_{0.5}[VO(HA)(OH)_3]$, together with a diketogulonic acid (which is one of the oxidation products of H_2A) complex, starting with sodium metavanadate as the VO^{2+} precursor [55]. They proposed a structure where the HA ligand is bonded by its deprotonated O(3) atom and three OH groups complete a square pyramidal geometry with the oxo group on the apex of the pyramid. This later report clearly demonstrates the activity of the oxovanadium(IV) cation in further complexing with the oxidation products of H_2A. It appears that VO^{2+} complexes with DHA which then hydrolyzes via lactone ring opening to generate the diketogulonic acid complex, $Na_2[VO(C_6H_6O_7)_2]$.

3.3. Chromium

Chromium ascorbate complexes are of considerable interest in biocoordination chemistry since ascorbate is known as one of the major metabolic reductants for Cr(VI) [56]. In vitro reduction of Cr(VI) by ascorbic acid occurs via an inner-sphere reaction to produce Cr(III) and DHA as final products passing through the genotoxic Cr(V/IV) intermediates [56,57] (2):

$$3HA^- + 2Cr(VI) \rightarrow 3DHA + 2Cr(III) + 3H^+ \quad (2)$$

Due to the complexity of the redox chemistry of Cr(VI) species, the isolation and characterization of the final products are difficult. A family of complexes prepared by reduction of several Cr(VI) species by ascorbate, with the general formula shown below, have been reported by Cieslak-Golonka et al. [34,58–60]:

$$K_{(n+2m+z-3)}[Cr^{III}(HA)_n(A)_m(OH)_z]\cdot yH_2O$$
$$(n = 0\text{–}3, m = 0\text{–}2, z = 0\text{–}3, y = 0\text{–}7)$$

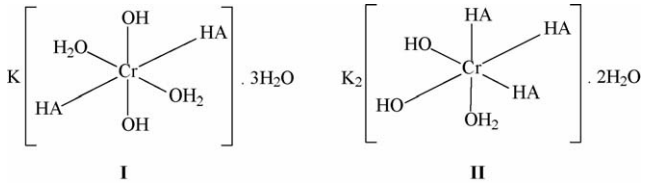
Although the hydrolysis of the metal ascorbate complexes might be expected to form the dianionic ligand (A) in alkaline solutions according to Eq. (3), where z = oxidation state of the metal-*n*-*m*, the first coordination sphere involves the monoanionic ligand at neutral pH for most transition metals [24]. Therefore it is not easy to assign the type of the ligand from the analytical results alone:

$$[M(HA)_n(H_2O)_m]^x + H_2O \Leftrightarrow [M(HA)_{n-1}(A)(H_2O)_m]^{x-1} + H_3O^+ \quad (3)$$

Recently, two anionic ascorbate complexes, $K[Cr(HA)_2(OH)_2(H_2O)_2]\cdot 3H_2O$ (**I**) and $K_2[Cr(HA)_3(OH)_2(H_2O)]\cdot 2H_2O$ (**II**), prepared via chromate reduction in THF, have been reported by Zümreoglu-Karan et al. [26]. The procedure described appears to be effective in avoiding the formation of the undesired products and allows the characterization of the final Cr(III) products that do not suffer from the rapid and complex redox chemistry in aqueous solutions. A minor amount of water was added since no significant reaction occurred in pure THF. Structural information obtained by UV/vis spectra, magnetic measurements, ^{13}C NMR spectroscopy demonstrated the monodentate coordination of HA ligands to Cr(III) while vacant sites are occupied by hydroxo and aqua ligands.

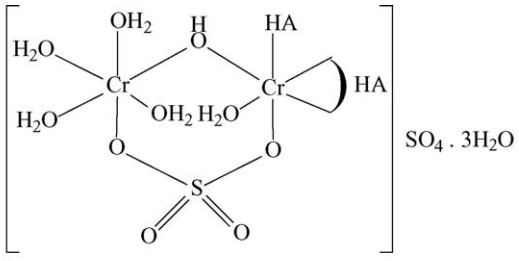
Table 1
Selected ^{1}H and ^{13}C NMR data of ascorbate complexes (δ in ppm, d doublet, m multiplet, q quartet, s singlet, t triplet)

Compound (solvent)	H4	H5	H6,H6′	Ref.	C1	C2	C3	C4	C5	C6	Ref.
L-Ascorbic acid (pH 2, D_2O)	4.97	4.09	3.76	[44]	174.0	111.8	156.4	77.1	69.9	63.1	[49]
L-Ascorbic acid (pH 7, D_2O)	4.50	4.02	3.74	[44]	178.0	114.1	176.2	79.2	70.6	63.6	[49]
NaHA (D_2O)	4.44(d)	3.98(m)	3.74(m)	[45]	178.09	113.85	176.34	79.28	70.46	63.46	[31]
$(Cp)_2Ti(HA)_2$ (CD_3OD)	4.79(d)	3.90(m)	3.70(m)	[23]	–	–	–	–	–	–	
$(Me)_2Sn(A)\cdot H_2O$ (CD_3OD)	4.63(d)	3.85(m)	3.70(m)	[23]	–	–	–	–	–	–	
$(Me)_2Sn(A)$ (D_2O)	–	–	–		176.6	119.9	167.0	78.9	70.7	63.6	[77]
$(Me)_2Sn(A)$ (CP/MAS)	–	–	–		171.4	124.0	167.1	80.1	77.9	70.0	[77]
					170.4	123.1	165.9				
							164.7				
$(Et)_2Sn(A)\cdot H_2O$ (CD_3OD)	4.62(d)	3.87(m)	3.70(m)	[23]	–	–	–	–	–	–	
$(Bu)_2Sn(A)$ (CD_3OD, $CDCl_3$)	4.78(d)	3.92(td)	3.68(d)	[32]	172.90	119.50	156.30	77.20	70.70	63.60	[36]
$(Bu)_2Sn(A)$ (CP/MAS)	–	–	–		171.5	125.5	163.6	77.1	69.4	63.5	[77]
$(Bu)_3Sn(HA)$ (CD_3OD, $CDCl_3$)	4.06(s)	3.77(m)	3.65(m)	[32]	169.00	119.00	153.00	74.30	71.44	64.50	[36]
$(Me)_2Tl(HA)\cdot 1/2C_3H_8O$ (D_2O)	–	–	–		178.5	114.5	176.1	79.5	70.7	63.7	[77]
$(Me)_2Tl(HA)\cdot 1/2C_3H_8O$ (CP/MAS)	–	–	–		177.5	113.3	174.9	78.2	71.7	64.3	[77]
$Cr(HA)_3\cdot 3H_2O$ (D_2O)	–	–	–		177.37	121.33	160.22	80.23	72.81	66.00	[67]
$K[Cr(HA)_2(OH)_2(H_2O)_2]\cdot 3H_2O$ (D_2O)	–	–	–		177.88	113.59	175.97	78.87	70.07	63.07	[26]
$K_2[Cr(HA)_3(OH)_2(H_2O)]\cdot 2H_2O$ (D_2O)	–	–	–		176.98	114.34	172.28	78.52	68.69	62.99	[26]
$[Cr_2(\mu\text{-}OH)(\mu\text{-}SO_4)(HA)(H_2O)_6]SO_4\cdot 2H_2O$ (D_2O)	–	–	–		176.34	120.24	158.63	79.23	71.89	65.13	[65]
$[Cr_4(\mu\text{-}OH)_2(\mu\text{-}SO_4)(HA)_4(H_2O)_8]SO_4\cdot 2H_2O$ (D_2O)	–	–	–		181.79	126.33	163.96	84.73	73.79	70.74	[65]
$[Cr_2(\mu\text{-}OH)_2(H_2O)(HA)_3(OH)]\cdot 4H_2O$ (D_2O)	–	–	–		174.33	117.63	158.86	77.00	69.48	62.63	[67]
$[Cr_3(\mu\text{-}O)_3(H_2O)_6(HA)_3]\cdot 4H_2O$ (D_2O)	–	–	–		175.74	118.58	163.03	78.32	70.69	63.83	[67]
$[Co(NH_3)_5(HA)]^{2+}$ (D_2O)	–	–	–		178.83	113.63	177.56	79.94	70.66	63.56	[80]
$[Co(NH_3)_4(HA)]^{2+}$ (D_2O)	–	–	–		181.80	112.31	176.38	83.31	70.61	63.60	[80]
$\{Cu(A)\}_n$ (d_6-DMSO)	5.54	4.24(m)	3.83(q),4.17(q)	[31]	–	–	–	–	–	–	
$Zn(HA)_2\cdot 2H_2O$ (D_2O)	–	–			177.8	122.45	174.37	78.77	70.60	63.24	[32]
$Zn(HA)_2\cdot 4H_2O$ (D_2O)	4.48	3.97(m)	3.67-3.790(m)	[66]	176.03	120.10	173.71	76.88	68.19	61.02	[73]
						112.97	173.42	76.14			
[Pt(en)(C^2,O^5–A)] (D_2O)	–	–	–		197.8	71.3	178.4	81.9	84.8	64.4	[83]
[Pt(R,R-dach)(C^2,O^5–A)] (d_6-DMSO)	4.01(d)	3.90(t)	3.18(d)		198.5	69.3	175.6	80.6	85.8	64.8	[83]
[Pt(R,R-dach)(C^2,O^5–A)] (d_7-DMF)	–	–	–		198.7	67.8	174.6	78.2	84.2	62.5	[83]
[Pt(R,R-dach)(C^2–HA)(O^3–HA)] (D_2O)	–	–	–	C^2-HA	201.1	69.1	181.4	80.8	69.8	61.9	[83]
	–	–	–	O^3-HA	176.5	114.2	169.5	78.4	69.8	62.7	[83]
[Pt(R,R-dach)(C^2-HA)Cl] (D_7-DMF)	–	–	–		201.3	65.8	178.8	83.8	73.1	63.4	[83]

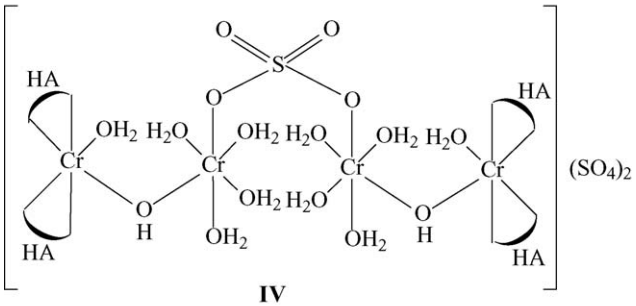


I II

Research on polynuclear chromium ascorbate complexes is a stimulating area due to the bioimportance of the complexes as alternatives for chromium based nutritional supplements (e.g. chromium picolinates) and as synthetic models for the biologically active form of Cr(III). In their pioneering work, Schwarz and Mertz demonstrated the role of Cr(III) in glucose metabolism and suggested the term "Glucose Tolerance Factor" (GTF), for the complexes stimulating insulin action [61]. The Cr(III) relationship to the naturally occurring Cr-bonding oligopeptide has been thoroughly investigated by Vincent [62] [62 and the references therein], following the isolation of the low molecular weight chromium bonding substance from mammals [63,64]. Vincent recommended the term "chromodulin" for this metalloprotein. Spectroscopic studies on chromodulin have indicated a multinuclear assembly of Cr(III) ions [64] and therefore synthetic efforts to prepare polynuclear Cr(III) complexes as functional biomimetics have since received interest. Rao and co-workers reported polynuclear chromium ascorbate complexes by reducing chromate with H_2A [54]. They have comprehensively described transition metal saccharide complexes but the structures of their ascorbate complexes, particularly of the claimed anionic, binuclear chromium ascorbate complex ($K_3[Cr_2(\mu\text{-}OH)(A)_4]\cdot H_2O$), are less clear. In 2002, two polynuclear complexes, a dimer ($[Cr_2(\mu\text{-}OH)(\mu\text{-}SO_4)(HA)(H_2O)_6]SO_4\cdot 2H_2O$) and a tetramer ($[Cr_4(\mu\text{-}OH)_2(\mu\text{-}SO_4)(HA)_4(H_2O)_8](SO_4)_2\cdot 2H_2O$) involving sulfate and hydroxo bridges and ligating ascorbate were isolated from aqueous solutions [65]. The complexes reported were prepared under identical experimental conditions but for different aging periods. Structural formulae were proposed on the basis of microanalytical and thermal analysis results, IR, ^{13}C NMR and mass spectral data and magnetic measurements. The complexes are cationic with sulfate ions acting as counterions as well as bridging ligands. A μ-hydroxo-μ-sulfato bridged structure involving an ascorbate ligand is assigned for the dimer (**III**), in accord with the results of the applied analytical methods. In view of the multitude of possible structures, chain and bicyclic structures (**IV**, **V**) have been proposed for the tetramer. The complexes may be regarded as models for collagen-bonding chromium species [66] and in this sense ascorbic acid appears to be a potential masking agent in the tanning process.



III



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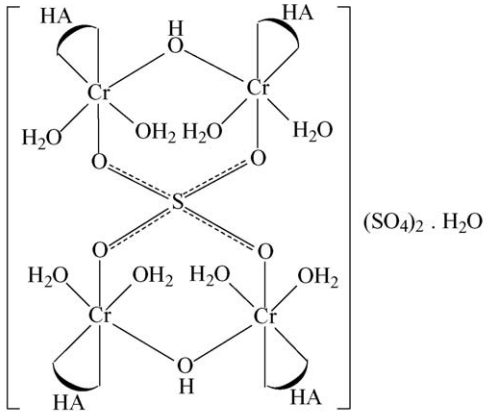
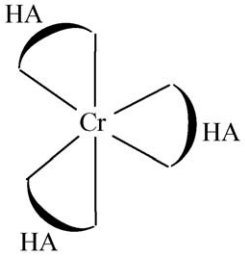


V

More recently, two novel polynuclear chromium ascorbate complexes have been prepared by Zümreoglu-Karan et al. and physicochemically analyzed in a comparative manner with their mononuclear analogue, $Cr(HA)_3\cdot 3H_2O$, [67]. The water soluble, green products were generated via complexation of HA with Cr(III) in aqueous solutions by applying the experimental procedure described by Jabs and Gaube in 1984 [11]. The chemical composition, mass spectral and thermal data fitted with formulations of $Cr_2(\mu\text{-}OH)_2(H_2O)(HA)_3(OH)\cdot 4H_2O$ and $Cr_3(\mu\text{-}O)_3(H_2O)_6(HA)_3\cdot 4H_2O$. ^{13}C NMR data indicated chelate-type coordinations of the HA ligand (δ(C-2) = 121.33 ppm) for the

mononuclear complex (**VI**), but failed to provide satisfactory information for the polynuclear complexes since no drastic changes in the chemical shifts were noticed. However the observed bulk magnetic behavior of the complexes indicated polynuclear structures whose existence were supported by indirect but substantial evidence. In the mononuclear complex, the d^3 electronic configuration gives rise to spin-only magnetic moments but in polynuclear complexes antiferromagnetic coupling between the Cr(III) centers results in lower values. Conforming with the temperature dependent magnetic susceptibility data and the mass spectral interpretation, structures **VII** and **VIII** have been proposed where the complexes are octahedrally coordinated by chelating ascorbate groups and the vacant coordination sites are occupied by H_2O and OH/O ligands supplied by *olation/oxolation* processes. In the absence of X-ray crystal data, further experimental and even computational work are necessary for the justification of the proposed structures.



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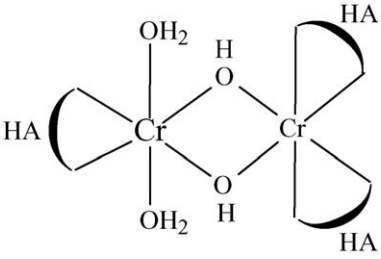

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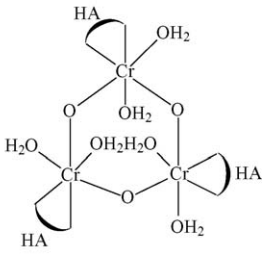
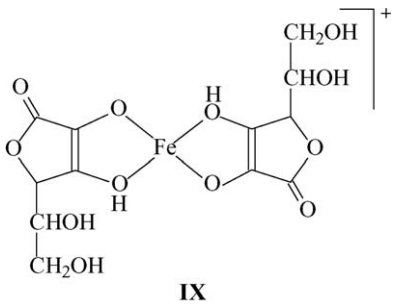


VIII

3.4. Iron

It is known that H_2A significantly enhances the iron uptake in the intestine [68]. The oxidation of H_2A by ferric ion in aqueous solution proceeds through an inner-sphere mechanism involving a Fe-chelate complex which then intermediately converts into DHA in a number of steps [7]. Martinez et al. isolated a solid deep blue iron(III) complex of the ascorbate system [10]. They concluded from chemical studies and from the Mössbauer spectrum that iron is present as Fe(III) and suggested the chelate structure (**IX**) based on the NMR data. Jabs et al. isolated a yellowish-white, polymeric Fe(II)-ascorbate from MeOH solution as a pyrophoric powder [69]. The magnetic and Mössbauer data ($\mu_{exp}/\mu_B = 4.87$ at room temperature and $\delta = 1.26\,mm\,s^{-1}$ and $\Delta E_Q = 2.90\,mm\,s^{-1}$ at 100 K) indicated that iron center is a high spin Fe(II), with the $^5T_{2g}$ ($S = 2$) ground state term, in a distorted octahedral environment. An octahedral coordination of iron atoms in $\{Fe(A)_x\}$ can only be realized in a polymeric structure, in which the ascorbate dianions use all their oxygen atoms as donor atoms, except the ether oxygen of the lactone ring. Two mixed valence Fe(II,III)-ascorbate complexes with bridging hydroxo groups have been reported by Rao and co-workers [70]. The formulations given as $Na_3Fe_2C_{24}H_{26}O_{25}\cdot 2H_2O$ and $Na_3Fe_3C_{36}H_{41}O_{38}\cdot 3H_2O$ in the report, can possibly be revised as $Na_3[Fe^{II}Fe^{III}(A)_3(HA)(\mu\text{-}OH)(H_2O)_2]$ and $Na_3[Fe^{II}(Fe^{III})_2(A)_3(HA)_3(\mu\text{-}OH)_2(H_2O)_3]$, respectively, on the basis of elemental analysis and low temperature Mössbauer data. The complexes have been analyzed by a variety of physical methods and the presence of high spin iron centers with pseudo-octahedral environments has been established by EXAFS and XANES studies. However the authors refrained from speculating on the inner-sphere bonding of the ligands present.

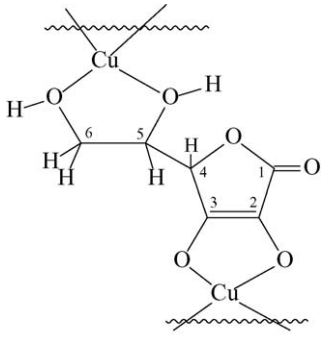


IX

3.5. Copper

In the 1990s, Messerschmidt et al. crystallized the enzyme ascorbate oxidase and showed by crystallography that the enzyme contains a trinuclear cluster of Cu(II) ions and a mononuclear Cu(II) [71]. It is of interest therefore to investigate reactions of copper(II) and ascorbic acid to provide valuable information for biological systems. It is well-known that ascorbic acid is quite easily oxidized by Cu(II) and Fe(III) [7]. In 1997, Yamamoto et al. [72] reported the formation of a stable ascorbate bridged binuclear complex in deoxygenated aqueous solutions in the presence of a bipy ligand chelating at the opposite site of the ascorbate but they could not succeed in the isolation. Years after, the stabilizing effect of a chelating amine ligand was reestablished. Ünaleroglu et al. isolated and characterized a stable Cu(II)-ascorbate complex (**X**) from the reaction of Cu(II)-methoxide and H_2A, in dry dichloromethane and in the presence of TMEDA [35]. The green complex thus prepared is paramagnetic and the measured susceptibility leaves no doubt about the dipositive oxidation state of copper. The complex is stable under anaerobic conditions but rapidly deteriorates upon contact with water while showing exceptional stability in DMSO. ^1H NMR spectrum reveals the nonequality of C(6)–H and C(6)–H′ protons as a result of the hindered rotation around the C(5)–C(6) bond. The coordination of anionic oxygen atoms from one ascorbate unit and the side chain oxygen atoms from another give rise to

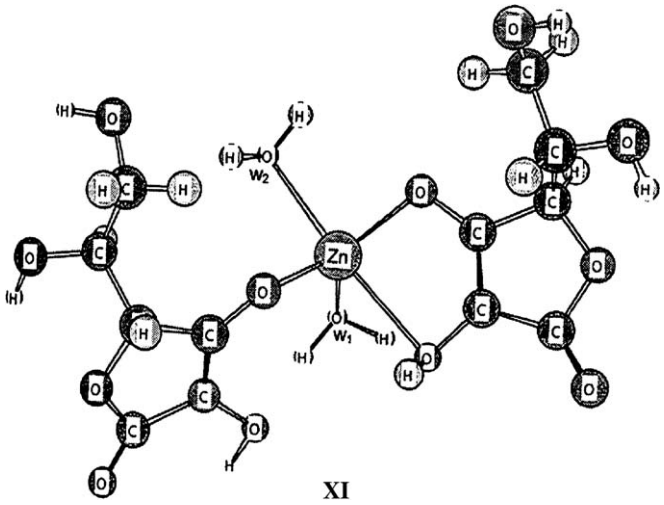
four-fold coordination of Cu(II). This structural unit propagates throughout the polymer.



X

3.6. Zinc

The interaction of Vitamin C with zinc is also important since zinc is an essential trace element required for the activity of more than 200 metalloenzymes. Among the early works, Evtushenko et al. had reported a zinc ascorbate complex where bonding is through the C(3)–O^- only [23]. The complex reported by Jabs and Gaube, $Zn(HA)_2{\cdot}4H_2O$, was considered as an octahedral complex with monodentate ascorbate ligands but chelate-type coordination was not excluded [11,12,24]. The complex later reported by Tajmir-Riahi, $Zn(HA)_2{\cdot}2H_2O$, was suggested to be a chelate through the C(3)–O^- and C(2)–O atoms of the first ascorbate, C(3)–O^- and C(1)=O of the second, based on the IR and ^{13}C NMR studies [32]. This speculative structure of zinc ascorbate was reexamined in 2002 by a combined experimental and computational study for $Zn(HA)_2{\cdot}4H_2O$ [73]. Semi-empirical PM3 calculations and ^{13}C NMR data agreed on a five-fold coordination around Zn(II) where one ascorbate binds monodentately, the other bidentately and two water molecules occupy the remaining sites of a distorted square pyramid (**XI**).



XI

4. Complexes with rare earth metals

Ascorbate complexes of the lanthanides from cerium(III) to lutecium(III) and yttrium and lanthanum were first reported in 1988 [74]. The compounds were obtained as hygroscopic, volumineous, hydrated complexes with ratios of Ln:HA = 1:3 and 1:2 (Ce and Tm). IR spectra and thermal stability were investigated and bidentate bonding of ascorbate was suggested. Later, a lanthanum complex with the formula $La(HA)_3{\cdot}4H_2O$ was isolated by Tajmir-Riahi and characterized by ^{13}C NMR and FTIR spectroscopies [33]. Chelation through the O(2) and O(3) atoms was suggested in the solution phase on the basis of the downfield shift of C(3) chemical shift. IR spectrum of the complex provided additional information about the solid state structure. The free acid carbonyl stretching shifted to lower frequencies and split into two components indicating that aggregation of the complexes occur via C(1)=O bridges. In another study, the interaction of europium(III) and samarium(III) with H_2A was investigated by solution studies and mixed ligand complexes with 1.10-phenanthroline were isolated [75]. The stabilities of the complexes, $[Eu(A)]^+$ and $[Sm(A)]^+$, were determined as $\log \beta_1 = 8.15$ and $\log \beta_2 = 7.30$, respectively. The addition of phen ligand aids in the stabilization of the complex by favorable charge transfer to the central metal.

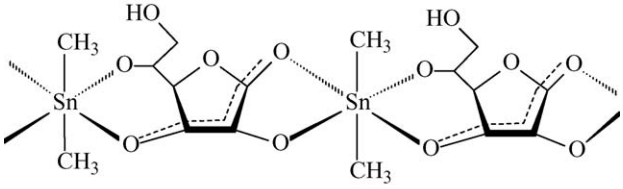
5. Mixed ligand complexes

The catalytic activity of the metal ions on the oxidation of H_2A can possibly be suppressed by mixed ligand formation. To the author's knowledge, the first report about mixed ascorbate complexes was published in 1984 [76]. The stabilities of ternary 1:1:1 metal/amine/H_2A systems (where M = Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and amine = en, baea, dpt, phen) were examined and complex formation with π-bonding ligands like phen was found to give higher $\log K$ values.

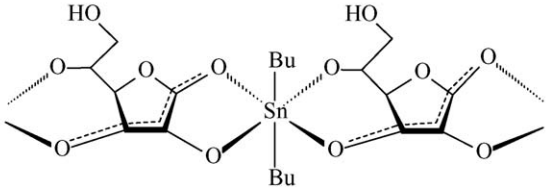
5.1. Titanium and tin

The first mixed ligand ascorbate complexes isolated are the organometallic $Cp_2Ti(HA)_2$, $Me_2Sn(A){\cdot}H_2O$ and $Et_2Sn(A){\cdot}H_2O$ [27]. On the basis of the IR and NMR evidence, it was suggested that the HA ligand coordinates as a monoanion to Ti but dianion to Sn. Casas et al. reported the preparation of $Me_2Sn(A)$, $Me_2Tl(HA)$ and $Bu_2Sn(A)$ by reacting H_2A with the corresponding metal compounds ($Me_2TlOOCCH_3$, Me_2SnO and Bu_2TlCl_2) in MeOH [77]. The new compounds were studied by both multinuclear solution NMR (^1H, ^{13}C, ^{205}Tl and ^{119}Sn) and CP/MAS ^{13}C NMR spectroscopies (Table 1). The thallium compound was found to behave like NaHA while for the tin derivatives, the metal appeared to interact with the A anion through the O(1), O(2) and O(3) atoms of the lactone ring. The authors suggested an octahedral environment around tin in $Me_2Sn(A)$ (**XII**) based on the J values [$^2J(^1H–^{119}Sn) = 88.9$ Hz; $^1J(^{13}C–^{119}Sn) = 757.7$ Hz] with possible involvement of side chain oxygen atoms in coordination. Very recently, organotin(IV) ascorbates of the general formulae $R_3Sn(HA)$ (where R = Me, *n*-Pr, *n*-Bu and Ph) and $R_2Sn(A)$ (where R = *n*-Bu and Ph) have been synthesized in the form of yellow powders by the reaction of R_2SnCl_{4-n} ($n = 2$ or 3) with NaHA in MeOH [36]. The researchers interpreted the spectro-

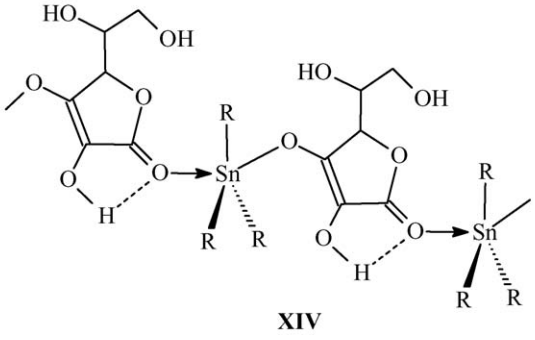
scopic information available, particularly the ^{119}Sn Mössbauer data, and proposed ascorbate-bridged polymeric structures for the dialkyl- (Q.S = 2.83 mm s^{-1}, IS = 1.17 mm s^{-1}) and trialkyl-tin (Q.S = 2.83 mm s^{-1}, IS = 1.17 mm s^{-1}) ascorbates. For $Bu_2Sn(A)$, a linear polymeric structure where O(1), O(2), O(3) and O(5) participates in a *trans* coordination around octahedral tin was proposed (**XIII**). For the $Bu_3Sn(HA)$ compound, a distorted trigonal bipyramidal geometry was proposed in which A is mono-anionic and bidentate, coordinating through O(1) and O(3) (**XIV**). The other di- and tri-alkyltin(IV) ascorbates were suggested to possess similar structures however the authors did not comment on the distinct ^{13}C NMR chemical shifts of the ascorbate carbons.



XII



XIII



XIV

5.2. Chromium

Cieslak-Golonka et al. prepared complexes by reducing Cr(VI) with a mixture of two cellular reductants and reported anionic hydrated Cr(III) ascorbate complexes mixed with cysteine and glutathione ligands from the point that ascorbic acid and glutathione have a synergistic effect in the process of Cr(VI) reduction [58–60]. All complexes exhibited a tetragonal deformation around Cr(III). Recently, a complex bearing two vitamins, C and B13 (orotic acid), on the same Cr(III) center was isolated which can best be formulated as $[Cr(HA)_2(H_2Or)(H_2O)_2]$ [78]. The results of experimental and computational studies suggested monodentate coordination of the two HA ligands and bidentate coordination of the orotate ligand.

5.3. Iron

A series of mixed ligand iron complexes with non-ionized ascorbic acid and with formulations of $K_2[Fe(CNO)_4(H_2A)]$, $Na_2[Fe(N_3)_4(H_2A)]$ and $Na_2[Fe(CNS)_4(H_2A)]$ have been synthesized by the reduction of the metal salt and ligands in water–ethanol medium [79]. The compounds were found to be monomeric and 1:2 electrolytes. Room temperature magnetic susceptibility measurements indicated spin-paired complexes with two electrons. Electronic spectra in DMF suggested penta-coordination and the reporter presumed a distorted square pyramidal configuration where H_2A acts as a neutral ligand coordinating through its lactone O-atom.

5.4. Cobalt

Solid complexes of the type $[Co(NH_3)_5(HA)]Cl_2{\cdot}H_2O$ and $[Co(NH_3)_4(HA)]Cl_2{\cdot}H_2O$ have been isolated [80]. Evidence for the monodentate coordination in the pentaammin complex and bidentate coordination in the tetraammin complex came from the ^{13}C NMR chemical shifts. The spectrum of the pentaammine complex showed marked similarities with the sodium ascorbate salt (Table 1), indicating the coordination of the Co(III) ion through the ionized O(3) atom. On the other hand, the spectrum of the tetraammine cation exhibited considerable downfield shifts for C(1) (∼5 ppm) and C(4) (∼3 ppm) indicative of chelate formation via O(1) and O(4).

In another study with Co(III), the rate of complexation with $[Co(salen)(H_2O)_2]^+$ was studied and kinetic parameters for the formation of monodentate and chelate complexes, $[Co(salen)(OH)(HA)]^-$ and $[Co(salen)(A)]^-$, and for the subsequent slow internal reduction of Co(III) by the coordinated ascorbate moieities were reported [81].

5.5. Platinum

Since the discovery of the antitumor activity of *cis*-platin by Rosenberg et al. [82], more than 2000 *cis*-platin analogues have been prepared. Hollis et al. [37] synthesized the Vitamin C analogues, the [*cis*-Pt(diamine)(A)] and [*cis*-$Pt(RNH_2)_2(HA)_2$] where diamine = $(NH_3)_2$, en or dach. These complexes represent the first transition metal ascorbates to yield to complete structural characterization. The ascorbate ligand in these compounds is bound to Pt in a unique fashion. Crystallographic studies showed that the ascorbate ligand is coordinated to the metal through the C(2) atom and a deprotonated hydroxyl group, O(5), in the *cis*-dach analogue (Fig. 5), while the bis(ascorbate) complex contains one C(2)-bound and one O(3)-bound HA moieties as indicated by the ^{195}Pt NMR spectrum [83]. These compounds were prepared from the reaction of H_2A with a variety of diaminediaquaplatinum(II) complexes and a variety of products were identified by using multinuclear (^{1}H, ^{13}C and ^{195}Pt) NMR and HPLC techniques. The reaction (4) initially produces kinetically favored, oxygen bound (via O(2) and O(3)) intermediates but carbon bonding at C(2) is thermodynamically favored. In addition to crystallographic data, Holllis et al. provided reliable NMR data for a series of Pt-ascorbate complexes by applying

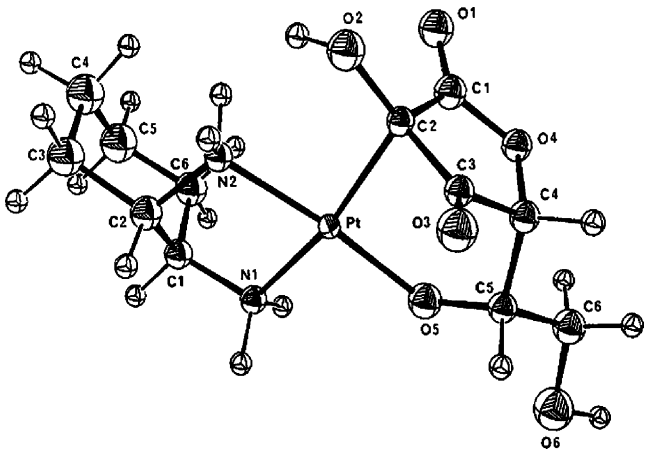


Fig. 5. The structure of [Pt(*cis*-dach)(A)] chelate [37].

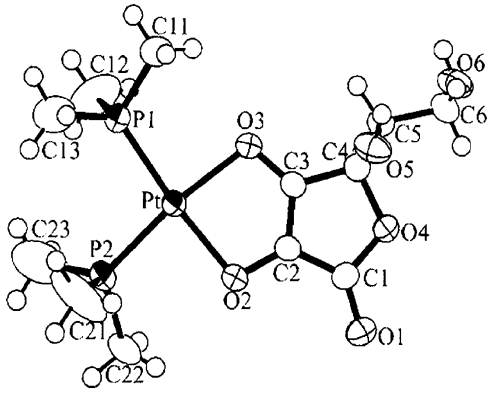
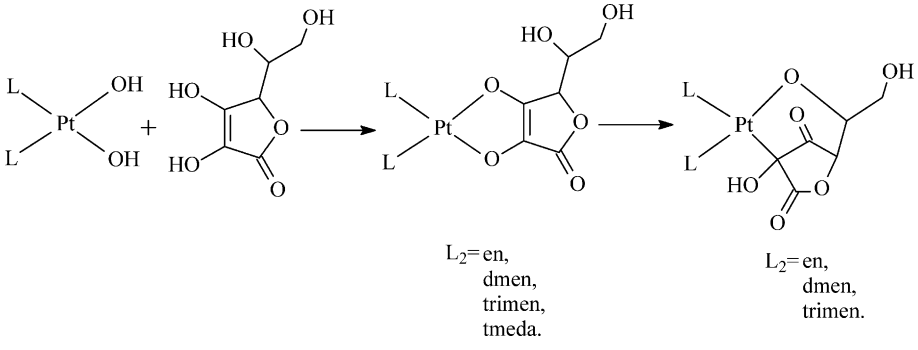


Fig. 6. The structure of [Pt(PMe$_3$)$_2$(A)] chelate [38].

HETCOR and DEPT methods (Table 1):



(4)

In 1996, the first crystalline O(2),O(3)-chelated complex, [Pt(PMe$_3$)$_2$(A)] (Fig. 6), was reported by Yuge and Miyamoto from the reaction of *cis*-[Pt(OH)$_2$(PMe)$_2$] and H$_2$A [38]. They later confirmed the stabilizing effect of ethylenediamine derivatives on C(2),O(5)-chelation and noted that the bulkiness of the diamine ligand brings about a steric hindrance on Pt–C bond formation [84]. More interestingly, they reported the first linkage isomers of transition metal ascorbates, by isolating the [Pt(trimen)(A–C(2),O(5)] and [Pt(trimen)(A–O(2),O(3)], from the same mother solution (Fig. 7).

6. Biomedical importance of Vitamin C complexes

The discovery and medical application of Vitamin C go back to the 16th and 17th centuries in preventing the disease "scurvy" among the sailors. We are now familiar with many uses of Vitamin C in agricultural, pharmaceutical, food and industrial areas [85]. It is needed for many physiological functions in human body. Perhaps the most important functions of the vitamin are in enhancing the response of the body's immune system, pulmonary function and iron absorption [86]. Many health benefits have been attributed to ascorbic acid in preventing or curing states from the common cold [87,88] and wound healing [89] to chronic and infectious diseases. Daily intakes in large doses are claimed to lower the risks of coronary heart disease [90], atherosclerosis [91], hypertension [92], cataract [93] and AIDS [94]. Extensive animal, clinical and epidemiological studies have been carried out on the role of ascorbic acid in the prevention of different types of cancer. The results were found to be inconclusive except gastric cancer [95]. Lately, some of these beneficial effects of Vitamin C have been the subject of debate [96], however the research in this area still continue.

Apart from L-ascorbic acid itself, the applications of its metal complexes in biology and medicine have been the subject of many investigations. The interest in uses of metal ascorbates mainly continues in the following directions:

1. curing symptoms related with Vitamin C and metal ion deficiencies,
2. development of therapeutic agents with potential antitumor, antibacterial, antioxidant, antihypoxic, catalytic and similar activities,
3. serving as synthetic models for metal containing biological systems.

There are many studies exploring the potential medical [36,97–99] and catalytic [100] applications of metal ascorbates, most of which are in patent formulations. *Cis*-diamineplatinum(II) ascorbate complexes have shown promise as antitumor agents [37,97,98]. These platinum complexes may be regarded as second generation compounds based on *cis*-platin [82], which is probably the best known example of a small, metal containing drug. The complex [Pt(phen)$_2$]A, was shown to exert an inhibiting cytotoxic effect on target tumor cells [75]. Phenanthroline based rare earth ascorbates have been regarded as low toxicity candidates for antitumor drugs. Organometal-

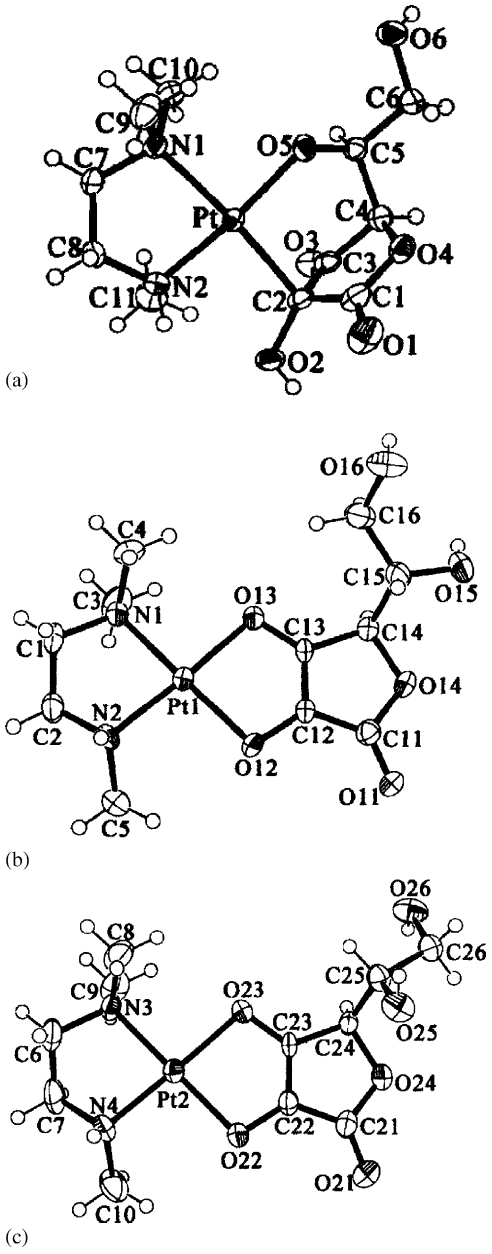


Fig. 7. Linkage isomers of [Pt(trimen)(A)]. (a) [Pt(trimen)(A–C(2),O(5)], (b and c) denotes to two crystallographically independent molecules of [Pt(trimen)(A–O(2),O(3)] [84].

lic tin(IV) ascorbates were first suggested as antitumor agents by Cardin and Roy [27] and a recent study of Nath et al. [36] has revealed their mild anti-inflammatory and mild hypotensive activities. Diorganotin(IV) derivatives have been found to show better activity than the triorganotin(IV) derivatives due to the formation of a hydroxo-mixed ascorbate complex upon hydrolysis at physiological pH values and thus enabling coordination with cellular constituents through the labile OH group.

DNA cleavage properties of several vanadyl ascorbates [54], $K_3[Cr_2(\mu\text{-}OH)(A)_4]$ [54], $Na_3[Fe_2(\mu\text{-}OH)(A)_4(H_2O)_2]$ [70], $[Cr_2(\mu\text{-}OH)(\mu\text{-}SO_4)(HA)(H_2O)_6]SO_4$ [101] have been demonstrated by in vitro experiments. These DNA cleavage properties of the complexes would be desirable in a cancer drug provided it can be targeted at cancerous cells.

Besides these potential applications, metal ascorbates may be considered as biomimetic models for enzymatic processes. In this sense, iron ascorbate [69] and copper ascorbate [35] can be suggested for NO reductase and ascorbate oxidase, respectively. Vanadium diascorbates represent endogeneous quabain-like factors in human urine [102]. Polynuclear chromium ascorbate complexes [65,67] can be regarded as models for the insulin stimulating forms of chromium and for collagen-bonding species in the tanning process.

7. Conclusions

Despite the potential versatility of Vitamin C as a ligand, only few complexes have been fully characterized by spectroscopic and single crystal X-ray diffraction studies. The single crystal X-ray studies of amine-mixed platinum ascorbates are unique in the sense that ascorbate is C,O-bound. No single crystals of other compounds were isolated which means that no complete structure determination has been carried out for most ascorbate complexes. Different types of coordination modes; O-bound, O,O′-chelation were suggested mainly based on spectroscopic experiments.

Among the biomedical applications of these complexes, their potential as antitumor agents has been highlighted. The complexes cited and the case studies presented in this review represent a number of examples on the forefront of the mysterious coordination chemistry of Vitamin C. There is much to discover.

Acknowledgements

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