Polyhedron Vol. 11, No. 3, pp. 285–321, 1992
Printed in Great Britain

0277–5387/92 $5.00+.00
Pergamon Press plc

POLYHEDRON REPORT NUMBER 41

REACTIONS OF L-ASCORBIC ACID WITH TRANSITION METAL COMPLEXES

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INTRODUCTION

L-Ascorbic acid is found naturally in a wide variety of plants and animals.[1] It is essential to man, though its biochemical role is not completely understood. It is not produced by the human body and the only source is from diet. Vitamin C is the term frequently used to refer to L-ascorbic acid in a nutritional context and it also encompasses the oxidation product, dehydroascorbic acid. The role of Vitamin C in the cure and prevention of scurvy is extremely well studied and documented.[2,3]

The structure of L-ascorbic acid in the solid state has been determined by X-ray crystallography[4] to be that shown in Fig. 1. A most notable feature of this structure is the ene-diol arrangement. This structure produces acid–base behaviour such that the 3-hydroxyl is ionized first.[5]

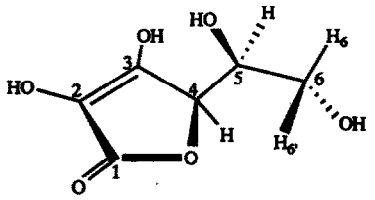


Fig. 1. Structure of L-ascorbic acid.

A fundamental feature of the chemistry of L-ascorbic acid is its redox behaviour. In an excellent résumé of the complex redox behaviour of L-ascorbic acid, Creutz[6] pointed out that the oxidation and reduction reactions of L-ascorbic acid and its redox companions are complicated by the intervention of simultaneous proton transfer reactions. The structures of the various redox products are shown in Fig. 2. A further factor in this area is the formation of a comparatively stable radical, HA^-, which is itself a strong acid with a pK_a of -0.45.[7]

Of particular interest in the context of transition metal chemistry is the fact that L-ascorbic acid will form chelate complexes with transition metal ions. In most cases the structures of these species have been deduced from spectroscopic studies of one sort or another and it is generally believed that such complexes are formed to produce a five-membered ring with the ene-diol part of the molecule.[8] Fairly recently, however, a crystal structure of an ascorbate complex of platinum(II) has revealed a metal–carbon bond[9] (*vide infra*).

The oxidation of ascorbic acid by dioxygen is of fundamental importance, since much of the loss of Vitamin C from food and drink will be due to such a process. This, too, turns out to be a complex process, involving as it does many of the reactions mentioned above including, frequently, the intervention of transition metal ions as catalysts and the formation of transition metal complexes of ascorbic acid as intermediates.

This review is intended to cover aspects of the reactions of ascorbic acid and related compounds involving transition metals, particularly those which have appeared in the literature over the last 10–15 years. It is always hard to know where to draw the line in a review such as this and therefore the choice of references may appear arbitrary in some cases, nevertheless, it has been the author's intention to cover the major work during that time and to include earlier work where that is of particular importance to the development of the subject.

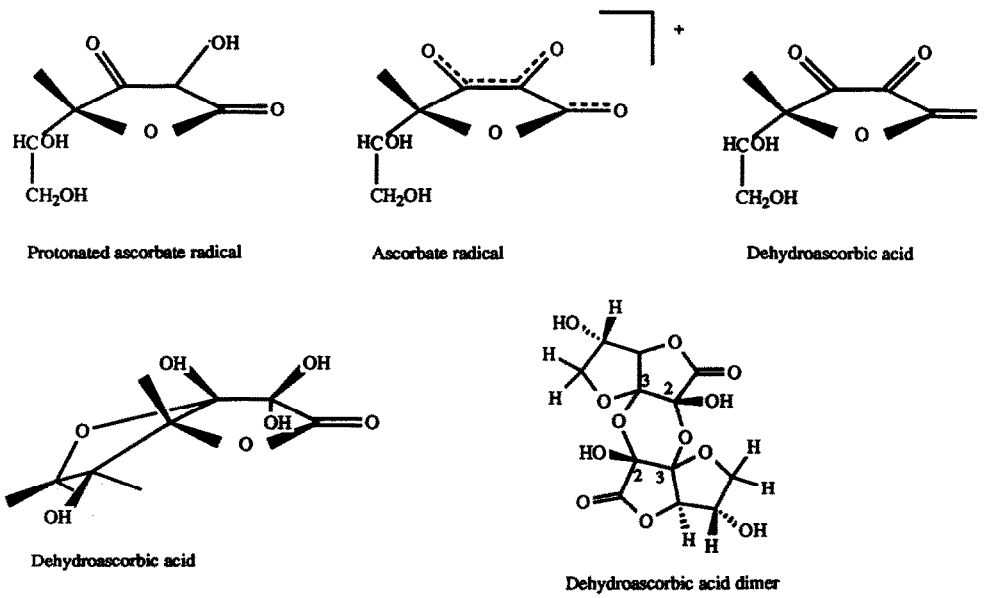


Fig. 2. Various compounds associated with ascorbic acid.

COMPLEXES FORMED BY L-ASCORBIC ACID

This section will consider the formation of complexes with transition metal ions where it is clear that a relatively stable detectable species is formed and not where a complex is a transient intermediate in an ascorbic acid reaction involving metal ions. There have not been many reports of the isolation of solid complexes of ascorbic acid. Jabs, Gaube and other workers have described the isolation of some crystalline complexes of a variety of transition metal ions (TiO^{2+}, Cr^{3+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}).[10–13] These were generally prepared by the reaction of the metal ion sulphate with ascorbic acid in the presence of barium hydroxide and with the very careful exclusion of dioxygen. These workers have described an investigation of the IR and NMR spectra of titanyl ascorbate complexes. In a more recent study, Jabs and co-workers[14] have isolated complexes of L-(+)-ascorbic acid and 5,6-O-isopropylidene-L-ascorbic acid with titanium(IV). The complexes were prepared in ethanol or tetrahydrofuran as solvent. Both ligands formed complexes of the form, $K_2Ti(A)_3$, while 5,6,-O-isopropylidene-L-ascorbic acid also formed the complex $(\eta^5\text{-}C_5H_5)_2Ti(A)$. A pH study of the aqueous solutions of many of these complexes has resulted in a model of the description of the protolytic behaviour. Martinez and Uribe[15] isolated a solid deep blue iron(III) complex of the ascorbate system, which they conclude has the formula $[(HA)_2Fe]^-$. The absorption spectrum of the complex is similar to that of the transient blue intermediate observed by Lawrence and Ellis[16] in a study of the oxidation of ascorbic acid by iron(III) ions. This is also a feature of other studies of this and related systems, as will be discussed in some detail later. Martinez and Uribe concluded from chemical studies and from the Mössbauer spectrum that iron is present as iron(III). They also suggest from the NMR spectra that the ascorbic acid is chelated to the iron through the oxygen atoms on the 2 and 3 carbons, so that the structure suggested is that shown in Fig. 3.

There appears to be only one transition metal complex of ascorbic acid where an unambiguous structure determination has been carried out. Hollis *et al.*[9] isolated a series of complexes of ascorbic acid of the type *cis*-[Pt(RNH$_2$)$_2$-(ascorbate)]. They were able to isolate the ascorbate complex in which the other ligand was *cis*-1,2-diaminocyclohexane (*cis*-dach) and determined the structure using X-ray crystallography. As expected the ascorbate acts as a bidentate ligand, but the surprising feature of the bonding was that it was not through the *cis*-oxygen atoms, but through the 2-C and the oxygen attached to 5-C. The structure is shown in Fig. 4.

NMR studies of the series of related complexes showed that Pt—C bonding was to be found in them all. Clearly, these findings make the speculation about the structures of other ascorbate complexes that much more interesting. These workers also prepared a bis(ascorbate) complex, which, on the basis of NMR data is suggested to contain one ascorbate which is oxygen-bonded and one which is carbon-bonded to platinum. Isomers of these *cis*-dach compounds are also described. Some of these complexes have shown good anti-tumour behaviour *in vivo*.

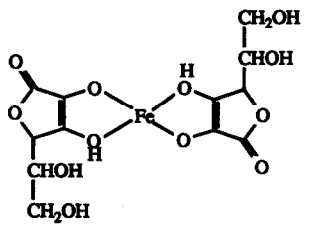


Fig. 3. Suggested structure for the iron(III)-ascorbic acid complex.

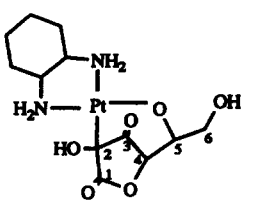


Fig. 4. The *cis*-dach-platinum(II) complex of ascorbic acid.

In a more recent study, Basch and co-workers[17] discussed the possible electronic structure of the related complex *cis*-diammine(ascorbato)platinum(II). They used valence-electron self-consistent field calculations using the molecule *cis*-$Pt(NH_3)_2(CH_2OH)(OCH_3)$ as a model in the calculation of ligand binding energies. It is concluded that the platinum–carbon bond to the ascorbate moiety is strong and exhibits a large *trans* influence. The calculated value is over 800 kJ mol^{-1}, more than 160 kJ mol^{-1} greater than the Pt—O bond energy. The reduction in the dissociation energy of the Pt—N bond *trans* to the Pt—C bond is so large that the former is labilized and the authors speculate that it is the remaining species which will coordinate with DNA and that this has a bearing on the possible uses of such complexes in cancer chemotherapy.

There has been much speculation about the structures of other complexes involving ascorbic acid or ascorbate anions. None of the speculations anticipated the structure determined for the platinum complex by Hollis *et al.* but it is conceivable that this type of bonding might be unique to platinum complexes.

Kriss has suggested from an investigation of literature data and his own measurements[18] that complexes formed with a variety of dipositive cations, Ca^{2+}, VO^{2+}, and from Mn^{2+} to Zn^{2+} and also Cd^{2+}, are in fact monodentate after consideration of a variety of possible bidentate structures. However, a ^{13}C NMR study by Nordenskioeld *et al.*[19] using spin-lattice relaxation times reached the conclusion that for the metal ions Co^{2+}, Fe^{2+} and Mn^{2+} at pH 8.5, the ascorbate–metal ion complexes are formed by chelation with O(2) and O(3) of the ascorbate ion.

Similar techniques have been applied to the system of Ni^{2+} ions in the presence of ascorbic acid.[20] From equilibrium measurements, it was concluded that at high pH (8.5) the only metal species was $[NiO]^0$. It is reasoned that the complex has pseudo-octahedral symmetry from the electronic spectrum, while ^{13}C relaxation data showed that the ascorbate is chelated to the metal through oxygens 2 and 3. The proposed structure of the complex is shown in Fig. 5.

A very interesting recent development has been the preparation of the amorphous, blue complex (ascorbato)pentaammineruthenium(III) as the trifluoromethanesulphonate salt from the reaction of ascorbic acid in alkaline solution with $[(NH_3)_5RuCl]Cl_2$, followed by precipitation using sodium tetrafluoromethane sulphonate.[21] A similar complex was made from the related tetramethylreductic acid, Fig. 6, and 3-O-methylascorbate, Fig. 7.

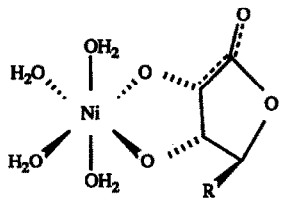


Fig. 5. Structure of the nickel(II) complex of L-ascorbic acid.

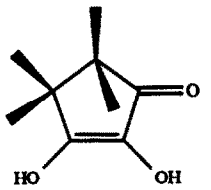


Fig. 6. Tetramethylreductic acid.

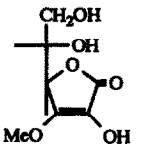


Fig. 7. 3-O-methylascorbic acid.

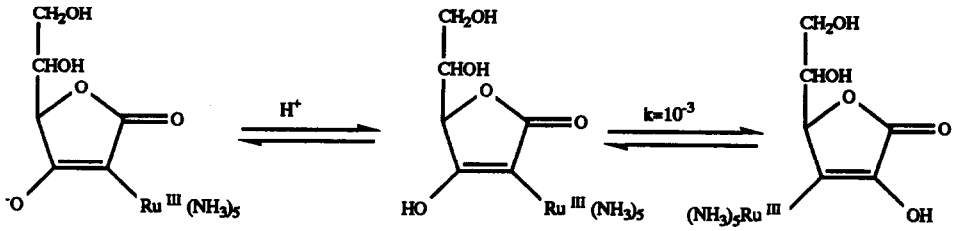


Fig. 8. Ascorbic acid-ruthenium(III) complex equilibria.

The complexes were studied in detail using ESR spectroscopy, cyclic voltammetry and NMR spectroscopy. In addition the kinetics of the reaction of the ascorbate complex with dioxygen were studied and this will be discussed later. In fact, Clarke and co-workers were able to detect two ascorbato complexes, depending on the pH at which the original reaction was carried out. Interpretation of the NMR spectra of the tetramethylreductic acid complex suggested that for the ascorbato complex, equilibria of the type shown in Fig. 8 operate.

Cyclic voltammetry showed a reversible oxidation with $E^0 = 0.237$ V for $[(HA)(NH_3)_5Ru]^+$ for a one-electron oxidation.

Ascorbate complexes of the lanthanides from cerium(III) to lutecium(III) and yttrium and lanthanum have been prepared.[22] IR spectra and thermal stability were investigated.

EQUILIBRIA INVOLVING ASCORBIC ACID AND METAL IONS

Although there have been few structural studies of ascorbate complexes with metal ions, there have been many studies of equilibria occurring between ascorbate and metal ions. Most of these have involved spectroscopic measurements, though potentiometric and kinetic studies have also generated equilibrium constants.

Martell[23] has reviewed the formation of metal ion complexes with ascorbic acid and ascorbate anions and has drawn attention to the fact that the stabilities are in general less than might have been expected. In fact, the complexes formed are relatively weak and even the complex between Al^{3+} and HA^- has a stability constant of only 10.[3,6]

The combination of problems associated with rapid redox reactions, hydrolysis and precipitation of metal ions has meant that there have been very few studies of complex formation with ascorbate at high pH, that is, under conditions where the deprotonated chelate complex would be produced.

Some authors have postulated the formation of complexes between the fully protonated ascorbic acid molecule and metal ions[24] as intermediates in redox reactions. It seems unlikely that such complexes have anything but a transient existence. For example, titration of the green copper(II) complex produced at about pH 3 with perchloric acid rapidly produces an almost colourless solution below about pH 1.3, which has the characteristic spectrum of the aquacopper(II) ion.[25]

Mixed complexes are also formed. Thus, the diaquabis(bipyridyl)copper(II) ion reacts rapidly with ascorbic acid to produce a green complex[26] which has not yet been obtained in the solid form.

OXIDATION OF ASCORBIC ACID BY METAL IONS

The redox reactions (Table 1) of L-ascorbic acid are of fundamental importance. The great complexity of such reactions has been outlined above and has been thoroughly examined by Creutz.[6] The vast majority of the reductions of metal ions by ascorbic acid have been carried out in the pH range 2–8. Creutz has pointed out that under these conditions, ascorbic acid itself may exist as H_2A or HA^-. A one-electron oxidation will produce either $HA^{\cdot}$ or $A^{\cdot -}$ and a two-electron oxidation will produce dehydroascorbic acid.

Note that $HA^{\cdot}$ is a strong acid ($pK_a -0.45$[7]) and thus in most of the studies carried out on metal ion oxidations described below by ascorbic acid, $HA^{\cdot}$ will lose a proton to give $A^{\cdot -}$.

The majority of studies of oxidation of ascorbic acid by metal ions have proposed the formation of ascorbate free radical, which has been shown to have the structure shown in Fig. 2, in the rate determining step. In all cases the overall product is assumed to be dehydroascorbic acid. The nature

Table 1. Rate constants for outer sphere reactions of complex ions with ascorbic acid species

Transition metal complex	$M^{n+}+H_2A$ k_1 ($M^{-1}s^{-1}$)	$M^{n+}+HA^-$ k_2 ($M^{-1}s^{-1}$)	$M^{n+}+A^{2-}$ k_3 ($M^{-1}s^{-1}$)	Temperature (°C)	Ionic strength (M)	Reference
Group 6 complexes						
$[(H_2O)_5CrOCr(H_2O)_5]^{4+}$	6	7.2×10^{-5}		25	1.0	134
$[Mo(CN)_8]^{3-}$		1.58×10^{4}		15	0.12	33
$[W(CN)_8]^{3-}$		1.53×10^{2}		15	0.06	33
Group 7 complexes						
$[Mn(aq)]^{3+}$	6.0×10^{3}			20	3.0	35
$[Mn(OH)(aq)]^{2+}$	5.3×10^{4}			20	3.0	35
Group 8 complexes						
$[Fe(sphen)_3]$	7.6×10^{5}	3.2×10^{9}		20	1.0	81
$[Fe(bphen)_3]$	4.6×10^{5}	2.8×10^{9}		20	1.0	81
$[Fe(nphen)_3]$	3.8×10^{6}	4.0×10^{9}		20	1.0	48
$[Fe(cphen)_3]$	2.0×10^{5}	7.5×10^{9}		20	1.0	48
$[Fe(phen)_3]$	3.0×10^{4}	1.5×10^{9}		20	1.0	48
$[Fe(mphen)_3]$	$< 1.0\times10^{4}$	7.9×10^{5}		20	1.0	48
$[Fe(dmphen)_3]$		4.1×10^{8}		20	1.0	48
$[Fe(bpy)_3]$		5.4×10^{8}				
$[Fe(phen)_2(CN)_2]^{+}$		8.3×10^{6}		20	1.0	81
$[Fe(bpy)_2(CN)_2]^{+}$		4.0×10^{6}		20	1.0	81
$[Fe(phen)_2(CN)_4]^{-}$		4.8×10^{4}		20	1.0	81
$[Fe(CN)_6]^{3-}$		8.6×10^{2}			1.0	44
$[Fe(CN)_5(thiourea)]$	11.1×10^{-2}	66.0	8.78×10^{7}	25	1.0	46
Ferrocenium ion		1.7×10^{3}		25	0.1	135
Reconst. $Mb(H_2O)$						
MP		2.6×10^{-2}	9.5×10	25	0.30	51
DP		7.9×10^{-3}	3.5×10	25	0.30	51
PP(native)		1.2×10^{-2}	6.9×10	25	0.30	51
PP(reconst.)		1.2×10^{-2}	5.6×10	25	0.30	51
DADP		3.1×10^{-1}	1.5×10^{-3}	25	0.30	51
DPDP		3.3×10^{-1}	2.5×10^{-3}	25	0.30	51
DFDP		1.2	5.9×10^{-3}	25	0.30	51
PPDME		3.0×10^{-1}	1.4×10^{4}	25	0.30	51
BrCN mod PP		3.4	2.1×10^{4}	25	0.30	51
Met Mb(Im)	1.1×10^{-2}	5.8×10^{2}		25	0.30	52
Met Mb(MeIm)	4.1×10^{-2}	4.1×10^{2}		25	0.30	52
$[Fe(pic)_2(OH)]$		6.38×10^{3}				136
$Ru(bpy)_3^{3+}$	2.96×10^{6}	1.24×10^{9}		25	1.0	107
$Ru(dmbpy)_3^{3+}$	1.66×10^{5}	4.35×10^{8}		25	1.0	107
$Ru(NH_3)_5py^{3+}$			6.0×10^{8}	25	0.1	137
$Ru(CN)_6^{3-}$	6.6×10^{4}	4.4×10^{6}				108
$(NH_3)_5RuORu(NH_3)_4ORu(NH_3)_5$		3.61×10^{6}				
$Ru(NH_3)_5py^{3+}$		3.53×10^{2}		25	0.10	56
$Ru(NH_3)_5pz^{3+}$		3.70×10^{4}		25	0.10	56
$Ru(NH_3)_5pzCH_3^{4+}$		1.88×10^{8}		25	0.10	56
$Ru(NH_3)_5isn^{3+}$		4.44×10^{3}		25	0.10	56
$Ru_2(NH_3)_{10}pz^{5+}$		4.88×10^{3}		25	0.10	56
$Ru_2(NH_3)_{10}pz^{5+}$		3.48×10^{7}		25	0.10	56
$Os(bpy)_3^{3+}$	4.22×10^{3}	4.21×10^{7}		25	1.0	107
$Os(dmbpy)_3$	$\leqslant 6$	1.18×10^{6}		25	1.0	107
Group 9 complexes						
$CoW_{12}O_{40}^{5-}$	77.4	2.4×10^{5}		25	1.0	66
$Co(bpy)_3^{3+}$		0.13	2.1×10^{6}	25	0.10	138
$Co(aq)^{3+}$	2.8×10^{2}			25	1.0	60

Table 1—*continued*

Transition metal complex	$M^{n+}+H_2A$ k_1 ($M^{-1}s^{-1}$)	$M^{n+}+HA^-$ k_2 ($M^{-1}s^{-1}$)	$M^{n+}+A^{2-}$ k_3 ($M^{-1}s^{-1}$)	Temperature (°C)	Ionic strength (M)	Reference
$Co(OH)^{2+}$	7.3×10^5			25	1.0	60
$Co(phen)_3$		0.40	5.8×10^6	25	0.10	62
$Coen(phen)_2$			1.0×10^6	25	0.10	62
$Co(Me_6[14]4,11\text{-dieneN}_4)(H_2O)$		3.4		25	0.1	65
$Co(Me_6[14]4,11\text{-dieneN}_4)(OH)$		1.1×10^2		25	0.1	65
$Co(Me_6[14]\text{tetraeneN}_4)(H_2O)$		4.2×10		25	0.1	65
$Co(Me_4[14]\text{tetraeneN}_4)(OH)$		1.3×10^3		25	0.1	65
$Co(\text{ms-Me}_6[14]\text{aneN}_4)(H_2O)$		4.2×10		25	0.1	65
$Co(\text{ms-Me}_6[14]\text{aneN}_4)(OH)$		5.5×10		25	0.1	65
$Co([14]\text{aneN}_4)(OH)$		2.9×10		25	0.1	65
$[Co(NH_3)_5Cl]^{2+}$	7.3×10^{-5}	1.8×10^{-3}	355	25	0.20	64
$[Co(C_2O_4)_3]^{3-}$	1.2×10^{-4}	4.1×10^{-3}	20	25	1.0	61, 63
$[Co(NH_3)_6]^{3+}$		2.7				139
$[IrCl_6]^{2-}$	4×10^2	2.8×10^7		20	1.0	81, 47
$[Ir(H_2O)Cl_5]^-$	5×10^3	2.6×10^8		20	1.0	81, 47
$[Ir(H_2O)_2Cl_4]$	1.05×10^5	2.0×10^9		20	1.0	81, 47
$[IrBr_6]^{2-}$	$<2\times10^2$	5.9×10^7		20	1.0	81, 47
Group 10 complexes						
Ni^{IV}	3.02×10^5 (protonated oxidant) 1.36×10^4 (deprotonated oxidant)			25	0.1	70
Ni^{III}(cyclam)	250			25	1.0	76
Ni^{III}(tet-a)	2.85×10^3			22	1.0	76
Ni^{III}(tet-c)	2.52×10^3			25	1.0	76
$Ni(9\text{-aneN}_3)_2^{3+}$	0	5.2×10^6		25	1.0	78
$Pt^{IV}(NH_2Pr^i)_2Cl_2(OH)_2$	0.103			25		82
Group 11 complexes						
$Cu(TAAB)^{2+}$		7.1		25	0.10	92

of the products is generally deduced from the stoichiometry of the reaction and the visible absorbance of the reduced metal ion. Only occasionally have direct analytical techniques been used to demonstrate the nature of the oxidation of ascorbic acid by metallic ions.

Group 5 complexes

It is perhaps worth discussing at this point some older work on the reaction of the ascorbic acid system with vanadium(V), since this system like that with iron(III) and unlike most others studied seems to show inner sphere electron-transfer behaviour. A brown colour rapidly appears and then disappears when ascorbic acid is reacted with vanadium(V).[27] Kusten and Toppen were able to demonstrate that this brown intermediate has an UV–vis spectrum with an absorption maximum at 425 nm. The kinetics showed a first order dependence on ascorbic acid, but the rate law at constant ascorbic acid concentration was that shown in eq. (1).

$$k_{obs} = \frac{kK[V^V]}{(1+K[V^V])}. \quad (1)$$

The mechanism proposed to account for this rate law is therefore that of an inner sphere redox reaction of the form shown in Scheme 1.

$$V^{V} + H_2A \rightleftharpoons [V^{V}H_2A] \quad \text{Ascorbic acid complex}$$
$$[V^{V}H_1A] \longrightarrow V^{IV} + \text{radical} \quad \text{Rate determining}$$
$$\text{Radical} + V^{V} \longrightarrow V^{IV} + A \quad \text{Fast}$$

Scheme 1.

The reactions were all carried out at high hydrogen ion concentrations (0.20–1.00 M) where H_2A is the predominant ascorbic acid species.

Group 6 complexes

As expected, 3 moles of ascorbic acid react with 2 moles of chromate(IV) ion[28] and the kinetics of the reaction indicate that it involves a pre-equilibrium deprotonation.

$$H_2CrO_4 \rightleftharpoons H^+ + HCrO_4^-,$$

with the possibility of other equilibria, including the formation of dichromate at higher acid concentrations and ascorbate anions at lower hydrogen ion concentrations as well as the possible formation of $[HCrO_3]^-$.

The nature of chromium(V) as an intermediate in the reduction of chromium(VI) by ascorbate has been investigated using EPR spectroscopy by Goodgame and Joy.[29] The system was studied in the pH range 7.0–8.5 and under these conditions a comparatively long-lived chromium(V) species was produced. The EPR spectrum of an equimolar mixture of chromium(VI) and ascorbate at pH 7.0 gave a band at $g = 1.979$ typical of chromium(V), which decreased with a half-life of about 15 min. At pH 7.5, however, there was a sharp doublet in the EPR spectrum centred at $g = 2.005$, which was attributed to the ascorbate radical. Use of TRIS as a buffering agent influenced the EPR signal, suggesting that it formed complexes with chromium(V).

Reduction of chromium(VI) species usually results in the formation of chromium(III), so that chromium(V) and chromium(IV) will feature to a greater or lesser extent in the course of the reduction. Ghosh *et al.*[30] have studied the reduction of chromium(V) as the complex shown in Fig. 9, i.e. bis-(2-ethyl-2-hydroxybutyrato)oxochromate(V) and the stoichiometry of the reaction indicates the process:

$$H_2A + Cr^{V}O \longrightarrow A + Cr^{III} + H_2O.$$

The chromium(III) product is the bis-chelated complex $(H_2O)_2Cr^{III}L_2^+$ with evidence for a further bis-chelated species in which another water is replaced by a carboxylate from the buffering acid (2-ethyl-2-hydroxybutyric acid). The reaction profile for the process measured at 600 nm is shown in Fig. 10.

This behaviour is explained by the sequence of reactions shown in Scheme 2.

$$Cr^{V} + H_2A \longrightarrow Cr^{IV} + HA^{\cdot} + H^+$$
$$Cr^{V} + HA^{\cdot} \longrightarrow Cr^{IV} + A + H^+$$
$$Cr^{IV} + H_2A \longrightarrow Cr^{III} + HA^{\cdot} + H^+$$
$$Cr^{IV} + HA^{\cdot} \longrightarrow Cr^{III} + A + H^+$$

Scheme 2.

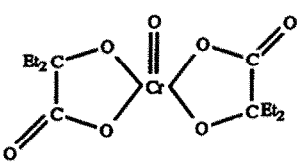


Fig. 9. Bis(2-ethyl-2-hydroxybutyrato)oxochromate(V).

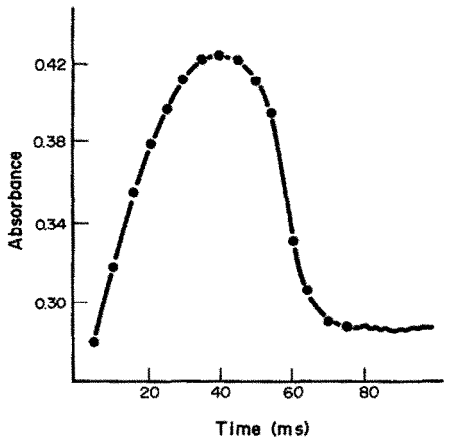


Fig. 10. Kinetic profile for reaction of chromium(V) chelate with ascorbic acid.

The reaction is autocatalytic in that only the first two are important in the early stages, while the third reaction becomes more important and increases the available HA˙ which reacts more rapidly with chromium(V) than chromium(IV). The solution of the differential equations for this sequence of reactions allowed calculation of the points indicated by the filled circles in Fig. 10. The authors deduce that at least three out of the above reaction steps are inner sphere processes, though the autocatalysis requires HA˙ to be uncomplexed "after it is formed but before it is destroyed".

Ghosh and Gould have also studied iron-catalysed[31] and copper(II)- and vanadium(IV)-catalysed[32] reduction of peroxide-bound chromium(IV) and this will be discussed later.

The oxidizing agents $[Mo(CN)_8]^{3-}$ and $[W(CN)_8]^{3-}$ have been widely studied in a variety of redox reactions for many years. El-Zaru and Hodali[33] recently investigated the reduction of these species by ascorbic acid. These were presumably outer sphere and the reaction of $[Mo(CN)_8]^{3-}$ was found to be very much faster than that of $[W(CN)_8]^{3-}$.

Group 7 complexes

The reaction of the manganese species[34,35] $[Mn^{3+}aq]$ at various hydrogen ion concentrations also involves the reaction of $[Mn(OH)aq]^{2+}$ and also a contribution from the reaction of H_2A with both of these species. It is concluded, however, that the acid dependent pathway is largely represented by the reaction:

$$[Mn(OH)aq]^{2+} + H_2A \longrightarrow [Mnaq]^{2+} + \text{radical}.$$

Ascorbic acid reacts with the pertechnate ion in strong acid solution to form a red coloured compound.[36] These workers studied the kinetics of formation of this species. Rather surprisingly the reaction was found to be second order in hydrogen ion concentration and as well as the protonated species TcO_4H being invoked, the ion H_3A^+ is also proposed as an intermediate in the process. The actual nature of the red product is unknown, but it is speculated that it is a complex of Tc^V and dehydroascorbic acid.

Group 8 complexes

Martell[22] has summarized his work on the oxidation of ascorbic acid by iron(III). Since that time, there has been much interest in the reactions of iron(III) and its complexes with ascorbic acid and some questions concerning this reaction remain unanswered, though there has been considerable progress. The mechanism originally proposed for the reaction of the iron(III) aqua ion with ascorbic acid was an inner sphere process which involves the formation of an iron(III) chelate complex in which an electron is transferred from the ascorbate to the iron(III) to produce the iron(III)–radical complex. This then converted into dehydroascorbic acid in a number of steps. The key part of this mechanism is, of course, the formation of the intermediate complex. Lawrence and Ellis[16] have

examined the reaction in the wavelength range 450–650 nm and detected a fast initial increase in absorbance, followed by a slower decrease, which they have interpreted as being due to the rapid formation of an unstable complex, which slowly decays to the products. They were able to produce a spectrum of this transient complex, to which they assigned the formula $[FeHA]^{2+}$. It has a broad absorption with a wavelength maximum of 560 nm and this compares well with that of the much more recently prepared blue complex of iron(III) and ascorbic acid which was obtained from mixtures of iron(III) chloride and ascorbic acid at fairly high pH.[15] Lawrence and Ellis assigned a formation constant of about 0.6 and the molar absorbance at the maximum wavelength was about 11 mol^{-1} cm^{-1}, which appears to be rather less than that obtained subsequently for the blue complex which has been isolated.[15] They were also able to estimate the rate of formation of the transient complex and on the basis of their data were able to propose a mechanism which involved the formation of a monodentate complex similar to those proposed by Martell[22] (see Scheme 3).

$$Fe^{2+} + H_2A \rightleftharpoons Fe^{*}HA^{2+}$$

Monodentate

$$Fe^{*}HA^{2+} \rightleftharpoons FeHA^{2+}$$

Chelated

$$FeHA^{2+} \rightleftharpoons Fe^{2+} \text{———} HA^{\cdot} \quad \text{Electron transfer}$$

$$Fe \text{———} HA^{\cdot} \rightleftharpoons Fe^{2+} + H^{+} + A^{+\cdot}$$

$$A^{-\cdot} + Fe^{3+} \rightleftharpoons Fe^{2+} + A$$

Scheme 3.

Martell[22] also proposed an inner sphere mechanism for the oxidation of ascorbic acid by iron(III) modified by complexation with various chelating agents. The major effect of chelation was to slow the reaction down and as expected, the more stable the complex formed with the chelating ligand, the slower the reaction. It might be expected that this is evidence for a first step involving chelate loss, but Martell has pointed out that the decrease in rate does not correlate with rates predicted by a mechanism involving an equilibrium in which the free metal ion is produced. A mixed ligand chelate complex has therefore been proposed involving the ascorbate anion.

More recently evidence for the formation of transient complexes in this system has been reported. Thus, Keypour *et al.*[37] reported two short-lived species at pH 2, when they studied the reaction of iron(III) chloride with ascorbic acid. They assigned one of these to the species $[FeHA]^{2+}$, while the other was assumed to be an iron(II) complex of the ascorbate radical. Martinez and co-workers have extensively studied the iron(III) ascorbate system over a number of years.[15,38,39] They isolated a dark blue solid from a mixture of iron(III) chloride and ascorbate at high pH, but they also observed a transient species in the investigation of the system at pH 5. Martinez *et al.*[40] have also observed a red short-lived species in the reaction of tris(oxalato)ferrate(III) with ascorbic acid. It seems likely that this is a mixed oxalate/ascorbate complex. More recently, Ghosh and Gould have also observed the formation of a blue intermediate in this reaction.

We have seen that Creutz[6] has demonstrated the complex nature of the ascorbic acid redox system. Xu and Jordan[41] have discussed how the reaction with iron(III) is made more difficult to interpret because over a range of pH values and in the presence of potential ligands, a wide variety of iron(III) complexes may be involved, including the formation of hydroxo complexes and oligomerization at higher pH values.[42] Further, it has been pointed out by these workers that such is the case in the study by Ghosh and Gould[41] where acetato complexes are present as well as hydroxo iron(III) species at pH 4.4. Hynes and Kelly[43] have further invoked the decomposition of $[FeCl]^{+}$ as a complication in the reaction of iron(III) chloride with ascorbic acid.

This was the situation prevailing when Xu and Jordan[41] carried out a careful study and detailed interpretation of the reaction of aqueous iron(III) with ascorbic acid. Unlike other investigations, this was carried out under conditions such that there was an excess of iron(III) ($2–7 \times 10^{-3}$ M) over ascorbic acid (2×10^{-4} M), while following the absorbance change at 560 nm. Under these conditions, it was found that the reaction occurred in two stages, which were manifested as a rapid increase in absorbance ($t_{1/2}$ = 10–20 ms) and a slower decrease ($t_{1/2}$ = 200 ms). The first rapid stage of this reaction is attributed to a substitution reaction between $[Fe(H_2O)_6]^{3+}$ and ascorbic acid. The rate of the first reaction is much faster than expected for such a substitution at this substrate. The most likely model which gives a reasonable fit to the experimental data, suggested by Xu and Jordan, is shown in Scheme 4.

$$H_2A \overset{K_a}{\rightleftharpoons} HA^- + H^+$$

$$[Fe(H_2O)]^{3+} \overset{K_m}{\rightleftharpoons} [Fe(OH)]^{2+} + H^+$$

$$[Fe(H_2O)]^{3+} + HA^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [FeHA]^{2+}$$

$$[Fe(OH)]^{2+} + H_2A \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} [Fe(HA)]^{2+}$$

$$[Fe(H_2O)]^{3+} + H_2A \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} [Fe(H_2A)]^{3+}$$

$$[Fe(H_2A)]^{3+} \overset{K'_a}{\rightleftharpoons} [Fe(HA)]^{2+} + H^+$$

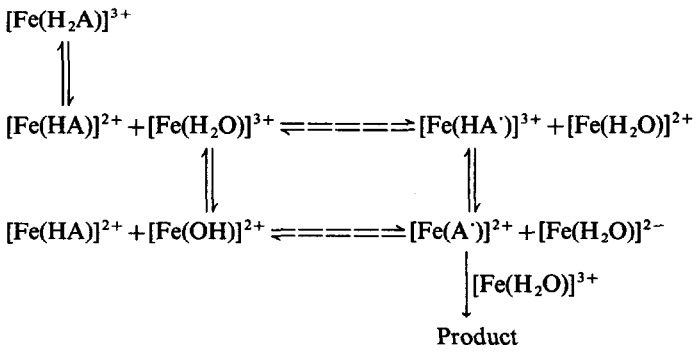
Scheme 4.

This scheme gives the rather complicated rate law shown in eq. (2).

$$k_{obs} = ((k_1K_a + k_3K_m)[H^+] + k_4[H^+]^2)\frac{[Fe^{III}]_T}{(K_m + [H^+])(K_a + [H^+])} + \frac{K'_a}{\frac{[Fe(HA)]^{2+}[H^+]^2}{[Fe(H_2O)^{3+}][H_2A]}(K'_a + [H^+])}. \quad (2)$$

The question of the unusually high rate of substitution of the ascorbate at $[Fe(H_2O)_6]^{3+}$ is addressed by the authors who suggest that it is due "to the unusually large bite distance between the oxygen atoms in ascorbic acid, which allows the ascorbic acid to approach more easily over an octahedral edge with two oxygens simultaneously moving towards the centre of separate octahedral faces, where they have the most favourable interaction with iron(III) in a precursor complex".

The slower reaction is believed by Xu and Jordan to be a redox reaction, which proceeds via the pathway illustrated in Scheme 5.



Scheme 5.

This scheme is supported by the experimental data, including the fact that the observed rate constant decreases with increasing added iron(II). These workers have drawn attention to an interesting outcome of their analysis, that the ratio of the rate constants for the reactions of $[Fe(HA)]^{2+}$ with $[Fe(H_2O)]^{3+}$ and $[Fe(OH)]^{2+}$, respectively, is 2.7×10^{-2} and hence, $[Fe(OH)]^{2+}$ is more reactive than is $[Fe(H_2O)]^{3+}$ despite the fact that the latter is a better oxidizing agent than the former.

The reaction between hexacyanoferrate(III) ion and ascorbic acid is considerably slower than that for the hexaaquairon(III) ion.[44] However, there is the same linear dependence on ascorbic acid concentration, an inverse dependence on hydrogen ion concentration and excellent pseudo-first order kinetics when ascorbic acid was present in large excess over the hexacyanoferrate(III) ion. No doubt many undergraduate students would be able to testify that the dependence of the rate on ionic strength is in good agreement with the Debye–Hückel limiting law for activity coefficients,

since the reaction has featured in an excellent experiment for the undergraduate laboratory.[45] The rate increases with increasing ionic strength as expected for the interaction between two negative species, such as $[Fe(CN)_6]^{3-}$ and HA^-. Whether the reaction involves an inner or outer sphere electron transfer remains a moot point. The methods used for following the kinetics were such that they could say nothing about the early seconds of the reaction, but the plots did not show any observable departure from first order kinetics. Once more the rate determining step proposed is that of the formation of the ascorbate radical,

$$[Fe(CN)_6]^- + HA^- \longrightarrow HA^{\cdot} + [Fe(CN)_6]^{4-},$$

followed by the rapid reduction of another mole of hexacyanoferrate(III) by the ascorbate radical.

Macartney and Macauley[46] have studied the reaction of the thioureapentacyanoferrate(III) ion with ascorbic acid over a sufficient pH range to ensure that the rates attributable to all three ascorbic acid species came into play and the mechanism is shown to involve the formation of the free radicals from H_2A, HA^- and A^{2-}.

The Marcus theory has been applied to this system and is included later in this review as part of the unification of a large amount of data from a wide variety of systems.

Most of the iron(III) systems which we have dealt with above have been clearly inner sphere. However, there seems to be no doubt about the outer sphere nature of the reduction of 2,2′-bipyridine and 1,10-phenanthroline derivatives of iron(III), which have been thoroughly studied by Pelizetti and co-workers[47,48] and also somewhat more recently by Kimura and co-workers.[49] The latter group differ in their data on the reduction of the tris(1,10-phenanthroline)iron(III) complex, in that they observed a term in the rate law which is independent of hydrogen ion concentration. These workers suggested that the difference arises because of the different ionic strength conditions used by the two groups—the acid independent path is more easily observed at low ionic strengths. The effect of ionic strength on the first order rate constant is that expected for the reaction of two oppositely charged species.

Pelizetti and co-workers[48] have also studied a range of iron(III) complexes of derivatives of 1,10-phenanthroline. The complexes studied were:

tris(5-nitro-1,10-phenanthroline)iron(III),
tris(5-chloro-1,10-phenanthroline)iron(III),
tris(5-methyl-1,10-phenanthroline)iron(III), and
tris(5,6-dimethyl-1,10-phenanthroline)iron(III).

This gives an excellent series to investigate subtle changes in kinetic behaviour with systematic change of ligand. There was good agreement among these complexes that all except the 5-nitro complex gave essentially the same rate law. This complex, however, did not show the same dependence of observed rate constant on hydrogen ion concentration and it is suggested that this reaction involves a different rate determining process, possibly with precursor complex formation at the achievement of the diffusion controlled limit. A small apparent dependence upon hydrogen ion concentration is in fact attributed to a medium effect involving possibly Na^+. An outer sphere mechanism is confirmed in all cases, except the 5-nitro complex, by the fact that a plot of $\log k_2$ against E^0 gives a straight line and the proposed mechanism is given in Scheme 6.

$$H_2A \rightleftharpoons HA^- + H^+$$

$$Fe^{III}L_3 + HA^- \rightleftharpoons Fe^{II}L_3 + HA^{\cdot}$$

$$Fe^{III}L_3 + HA^{\cdot} \longrightarrow Fe^{II}L_3 + A + H^+$$

Scheme 6.

This gives an inverse hydrogen ion concentration dependence and is first order in complex concentration and ascorbic acid concentration if:

$$k_3[Fe^{III}L_3] \ggg k_{-2}[Fe^{II}L_3].$$

Studies of metalloporphyrin complexes provide valuable information which may produce a model for many biological systems involving such molecules. Tondreau and Wilkins[50] have

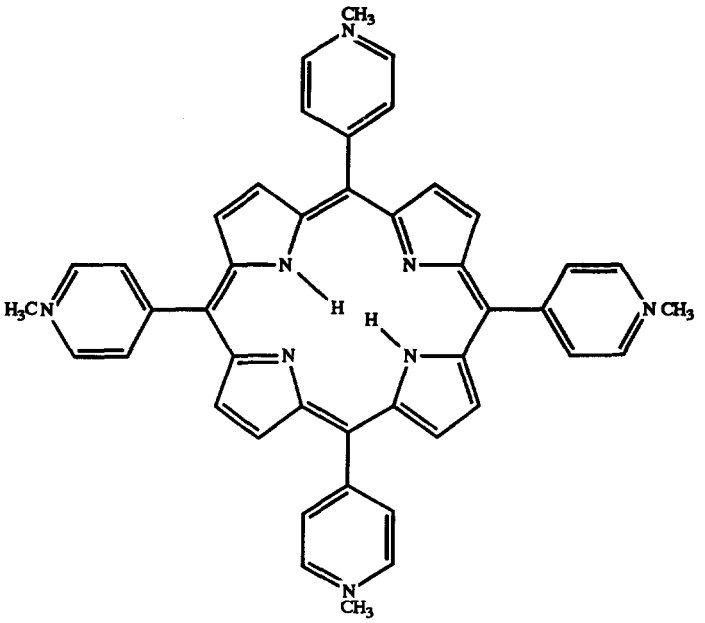


Fig. 11. Tetrakis(N-methylpyridinium-4-yl)porphine.

studied monomeric and dimeric iron(III) complexes of tetrakis(N-methylpyridinium-4-yl)porphine (TMpyP) (Fig. 11).

The iron(III) complex may exist as a monomer, $[Fe(TMPyP)(OH)]^{2+}$, or as the dimer $[(TMPyP)Fe—O—Fe(TMPyP)]^{8+}$. The reactions of both species with L-ascorbate at pH 7.0 and 8.0 were studied and reactions with both species are biphasic. The fast step in this process is rather intriguingly assigned to the formation of an adduct:

$$Fe(TMPyP)(OH)]^{4+} + 2HA^- \overset{K}{\rightleftharpoons} [Fe(TMPyP)(HA)_2]^{3+} + OH^-,$$

where $K = 2.4 \times 10^7\ M^{-2}$ at pH 8.0.

The final product of the reaction of both the dimer and the monomer with L-ascorbate is $[Fe(TMPyP)(H_2O)_2]^{4+}$. The second (slow) step is first order in the iron complex and independent of concentration of ascorbate ion. The authors feel unable to distinguish between the possibilities that this slow reaction is simply an intermolecular transfer of an electron from the ascorbate to iron(III) or that the adduct is a dead-end complex.

Tsukahara and co-workers[51] have studied the kinetics of the reduction by the ascorbate of BrCN-modified metmyoglobin and metmyoglobin reconstituted with 2,4-disubstituted deuterohaemin and with protohaemin dimethyl ester. Modification of the distal histidylimidazole with BrCN produced a form in which the distal histidyl residue could not hydrogen bond to coordinated water and the sixth coordination position on the iron was vacant. This form and modification of the haem propionates to their methyl esters resulted in an increase in rate of reduction by ascorbate compared with that of the natural form and the authors conclude that this suggests that change of iron from six-coordination to five-coordination is important.

For reduction by ascorbate[51] of the metMb(H_2O) reconstituted with 2,4-disubstituted deuterohaemins (—CHO, $—COC_2H_5$, $—COCH_3$ and —H), there is a linear correlation between the logarithm of the second order rate constants (k_1 for reduction by HA^- and k_2 for reduction by A^{2-}) and the pK_3 of the acid dissociation constants of the porphyrin monocation such that:

$$\log k_1 = -0.88pK_3 + 2.46$$

and

$$\log k_2 = -0.92pK_3 + 6.34.$$

This is interpreted as suggesting that electronic factors are predominant in these reactions.

In earlier work Tsukahara and Yamamoto[52] studied the reaction of ascorbic acid with sperm whale skeletal muscle myoglobin with a variety of additives. Imidazole and 1-methylimidazole accelerated the reaction and azide and cyanide had an inhibiting effect. The reaction is interpreted in terms of HA^- and A^{2-} with metMb(H_2O), with metMb(Im), with metMb(CN) and with metMb(N_3). In the last two cases, the reaction was too slow to be measured. Expansion of the haem pocket induced by coordination with imidazole is suggested as a reason for the increased reaction rate in the presence of imidazole.

The effect of ionic strength on the rate of ascorbate reduction of sperm whale and horse heart metmyoglobins has been studied by Tsukahara[53] in the pH range 7.29–8.29, giving rate constants for the reaction of both HA^- and A^{2-}. Horse heart metMy(H_2O) reacted faster than that of the sperm whale. A linear correlation between the logarithm of the second order rate constants and the square root of the ionic strength is interpreted in terms of an outer sphere mechanism.

Ruthenium complexes. The reduction of "ruthenium brown" to "ruthenium red" by the ascorbic acid system has been studied.[54] The reaction oxidation process is:

$$\underset{\text{Ruthenium brown}}{[(NH_3)_5RuORu(NH_3)_4ORu(NH_3)_5]^{7+}} + e \rightleftharpoons \underset{\text{Ruthenium red}}{[(NH_3)_5RuORu(NH_3)_4ORu(NH_3)_5]^{6+}}.$$

The pattern here is essentially similar to that observed for less complex species and the reaction mechanism resulting in the production of $HA^{-\cdot}$ is proposed, presumably via an outer sphere mechanism.

The kinetics of the reaction of ascorbic acid by the ruthenium(III) ion itself and the complexes dichlorotetraaquaruthenium(III), iminodiacetatoruthenium(III) and ethylenediaminetetraacetatoruthenate(III) have been studied by Taqui Khan and Shukla.[55] The reaction is found to be inner sphere and the mechanism proposed involves the formation of mixed ligand–metal-chelate–ascorbate complexes (1 : 1 : 1) and metal–ascorbate (1 : 1) complexes in the pre-equilibrium steps. The mechanism of the reaction which is suggested is shown in Scheme 7.

$$H_2A \rightleftharpoons HA^- + H^+$$

$$[Ru^{III}] + HA^- \overset{K_1}{\rightleftharpoons} [Ru^{III}(HA)] + 2H_2O$$

$$[Ru^{III}(HA)] \xrightarrow{k_1} [Ru^{II}] + HA^{\cdot}$$

$$[Ru^{III}] + HA^{\cdot} \xrightarrow{\text{Fast}} [Ru^{II}] + A + H^+$$

Scheme 7.

Where Ru^{II} and Ru^{III} represent the various complex ions of ruthenium(II) and ruthenium(III), respectively, with the appropriate charges. The observed second order rate constant k_2 is then:

$$k_2 = \frac{k_2 K_1 K_a}{[H^+]}. \tag{3}$$

The variation of rate with ionic strength is consistent with the charge of the reacting species.

The substitution-inert complexes $[Ru_n(NH_3)_{5n}L]^{m+}$ (where $n = 1$, L = 5 pyrazine, pyridine, isonicotinamide, $m = +3$; $n = 1$, L = methylpyrazinium, $m = +4$; $n = 2$, L = pyrazine, $m = +5$ and $+6$) have been studied.[56] The reactions are all outer sphere and the species $[Ru_2(NH_3)_{10}(pyrazine)]^{6+}$ is shown to produce $[Ru_2(NH_3)_{10}(pyrazine)]^{5+}$ as the primary reaction product. The mechanism for all complexes involves a one-electron rate determining step and rapid reaction between the starting material and the ascorbate anion, giving the rate law:

$$k_{obs} = \frac{2k_5 K_a [H_2A]}{(K_a + [H^+])}, \tag{4}$$

where k_5 is the rate of the slow reaction:

$$Ru^{III} + HA^+ \longrightarrow Ru^{II} + HA^{\cdot}.$$

The data are interpreted in terms of the Marcus relationship as modified by Sutin[57] and a value of

10^6 M^{-1} s^{-1} is obtained for the rate constant for the HA^-/HA couple. There was no evidence for a redox reaction involving H_2A.

Taqui Khan *et al.*[58] have investigated the photochemical oxidation of ascorbic acid using platinum loaded TiO_2 in an aqueous solution of tris(bipyridyl)ruthenium(II). The ascorbic acid is present as a sacrificial agent and under the conditions used 130 dm^3 h^{-1} of hydrogen were obtained.

The intervention of an ascorbatoruthenium(III) complex is proposed by Taqui Khan and co-workers[59] in the mechanism for the epoxidation of cyclohexane by dioxygen catalysed by dichlorotetraaquaruthenium(III) in the presence of ascorbic acid.

Group 9 complexes

Redox reaction of kinetically inert cobalt(III) complexes have historically presented important opportunities for the study of both outer sphere and inner sphere reductions of metal ion complexes. In many cases there is little opportunity of forming a bridge and the complexation reaction with ascorbic acid or ascorbate is likely to be slower than the redox reaction. This is well illustrated by the reduction of the hexaaquacobalt(III) ion by ascorbic acid.[60] This was studied at comparatively high hydrogen ion concentration, so that H_2A was the only reductant, while the conditions allowed for the possibility of the reaction of $[Co(OH)(aq)]^{2+}$ as well as $[Co(aq)]^{3+}$. The kinetics of the reaction were readily interpreted in terms of the series of reactions shown in Scheme 8.

$$[Co(aq)]^{3+} \overset{K_h}{\rightleftharpoons} [Co(OH)(aq)]^{2+}$$

$$[Co(aq)]^{3+} + H_2A \xrightarrow{k_0} Co^{II} + H_2A^+$$

$$[Co(OH)aq]^{2+} + H_2A \xrightarrow{k_1} Co^{II} + H_2A^{\cdot}$$

$$[Co(aq)]^{3+} + H_2A^{\cdot} \xrightarrow{\text{fast}} Co^{II} + A$$

$$[Co(OH)(aq)]^{2+} + H_2A^{\cdot} \xrightarrow{\text{fast}} Co^{II} + A$$

Scheme 8.

Even at the fairly high hydrogen ion concentration used in this work, the reaction is fast and has to be followed using stopped flow techniques. There is no evidence for the formation of an intermediate complex and the reaction is assumed to proceed by an outer sphere mechanism.

The reaction of ascorbic acid in acid solution with tris(oxalato)cobaltate(III) ion is much slower.[61] Kimura and co-workers have shown that it too is an outer sphere reaction and has features in common with the reduction of $[Co(phen)_3]^{3+}$ and $[Co(bpy)_3]^{3+}$,[62] where phen = 1,10-phenanthroline and bpy = 2,2′-bipyridine. It is suggested that the high values for H_2A^+/H_2A and HA/HA^- couples determined in this work arise from the change from a low spin cobalt(III) complex to a high spin cobalt(II) complex in the product. There has recently been a study of this reaction in basic solution up to pH 10.0.[63] This allowed the opportunity of measuring the rate of reaction of the complex with A^{2-}, which is present in significant quantities at these higher pH values. It is therefore possible in this system to compare the rate constants for reaction with all three ascorbic acid species in Scheme 9.

$$H_2A + [Co(C_2O_4)_3]^{3-} \longrightarrow A^- + [Co(C_2O_4)_3]^{4-} + 2H^+$$

$$HA^- + [Co(C_2O_4)_3]^{3-} \longrightarrow A^- + [Co(C_2O_4)_3]^{4-} + H^+$$

$$A^{2-} + [Co(C_2O_4)_3]^{3-} \longrightarrow A^- + [Co(C_2O_4)_3]^{4-}$$

Scheme 9.

The very significant increase in rate shown here is accompanied by a large drop in activation enthalpy and no variation in the activation entropy, so that the increase in rate is attributed to the activation enthalpy barrier for the electron-transfer process.

It is hard to see how $[Co(phen)_3]^{3+}$ and $[Co(bpy)_3]^{3+}$ could react with the ascorbic acid system

other than by an outer sphere process and this proves to be the case.[62] When one of the phen ligands is replaced by ethylenediamine, giving $[Coen(phen)_2]^{3+}$, the complex is only reduced by A^{2-} while $[Co(en)_2(phen)]^{3+}$ and $[Co(en)_3]^{3+}$ are not reduced at all by the ascorbic acid system. The authors ascribe this lack of reactivity to the differences in the redox potentials of these complexes.

The reaction of chloropentaamminecobalt(III) ion with L-ascorbic acid in aqueous solution has been studied in the pH range 0.8–2.0.[64] An outer sphere mechanism is proposed with the ascorbic acid radical as the first product which then rapidly reduces a further mole of complex. The product of the reaction is cited as $[Co(NH_3)_5Cl]^+$, but presumably this labile species quickly decomposes to produce $[Co(H_2O)_6]^{2+}$.

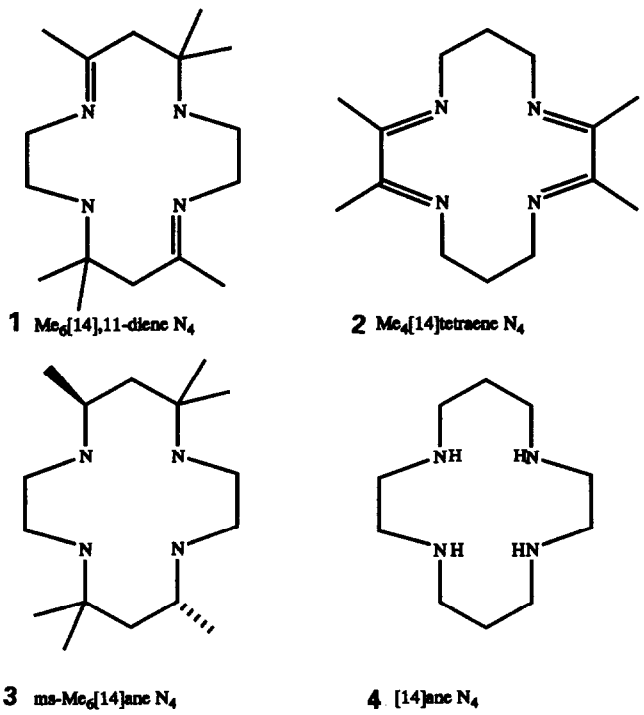
Tsukahara *et al.*[65] have studied the reactions of ascorbic acid with cobalt(III) complexes of four macrocyclic ligands. These are shown in Fig. 12. The complexes were all of the type $[CoL(H_2O)_2]^{3+}$, where L is one of the macrocyclic ligands. For complexes of ligands **1**, **2** and **3**, the usual behaviour: first order in complex, first order in ascorbic acid and inverse variation of k_{obs} with hydrogen ion concentration was observed. The mechanisms of the reactions were interpreted in terms of all possible equilibria involving H_2A, HA^- and A^{2-} and the deprotonated and doubly deprotonated complex. However, it is conceded that under the conditions used the complex underwent loss of only one proton and A^{2-} and is not a factor in the rate law.

The cobalt(III) complex of **4**, however, reacts with ascorbic acid in a two-stage process, though the product at the end of the second stage is $[Co^{II}([14]aneM_4)(H_2O)_2]^{2+}$ ion at pH 3. The biphasic behaviour was attributed to the intervention of oxygen, present in traces even in the nitrogen atmosphere used in the experiments, according to the reaction:

$$[Co([14]aneN_4)(H_2O)_2]^{2+} + O_2 \longrightarrow [(H_2O)Co([14]aneN_4)_2O_2]^{4+}.$$

All the reactions of these complexes with ascorbic acid were considered to be outer sphere, as expected from the known slow exchange rate of H_2O in these complexes.

The complex ion 12-tungstocobaltoate(III) $[Co^{III}O_4W_{12}O_{36}]^{6-}$ is unusual because both oxidation states of cobalt occupy a tetrahedral site. One of the consequences of this is that there is reversible reduction of the Co^{III}/Co^{II} couple and the complexes are substitutionally inert, leading to the probability of outer sphere mechanisms. The reaction with ascorbic acid has been studied.[66] As usual, the reaction was very pH dependent, even at the high hydrogen ion concentrations used in



1 $Me_6[14],11\text{-diene } N_4$ **2** $Me_4[14]\text{tetraene } N_4$

3 $ms\text{-}Me_6[14]\text{ane } N_4$ **4** $[14]\text{ane } N_4$

Fig. 12.

this study (0.04–1.00 M). The mechanism is consistent with the rate law which is given in Scheme 10.

$$H_2A \rightleftharpoons HA^- + H^+ \quad (K_a)$$

$$[Co^{III}] + H_2A \xrightarrow{k_1} [Co^{II}] + H^+ + HA^{\cdot}$$

$$[Co^{III}] + HA^- \xrightarrow{k_2} [Co^{II}] + HA^{\cdot}$$

$$[Co^{III}] + HA^{\cdot} \xrightarrow{\text{fast}} [Co^{II}] + A + H^+$$

Scheme 10.

The rate law is given in eq. (5).

$$\frac{d[Co^{III}]}{dt} = \frac{2\{k_1 + k_2K_a/[H^+]\}[Co^{III}][H_2A]_T}{(1 + K_a/[H^+])} \quad (5)$$

Application of the Marcus relationship to this system gave a value of 1.31 V for the H_2A/HA^- couple.

Perhaps the best known cobalt(III) complex is Vitamin B_{12}. Like most cobalt(III) complexes red Vitamin B_{12} may be reduced to the orange cobalt(II) form fairly easily. There were fears at one time that large doses of Vitamin C (so-called megadoses) could result in the destruction of Vitamin B_{12} and thus cause deficiency diseases.[67] Although it now seems likely that this fear was illfounded, there has been interest in the reaction of Vitamin B_{12} with L-ascorbic acid. Nazhat *et al.*[68] studied the reaction of L-ascorbic acid with Vitamin B_{12} to investigate the conditions under which the destruction of the latter occurred. Vitamin B_{12a} is the aqua complex of Vitamin B_{12} and it has been found that it is rapidly reduced to the cobalt(II) (B_{12r}) form by L-ascorbic acid.[69] This reaction is essentially quantitative and the B_{12r} may be readily re-oxidized by an excess of dioxygen to B_{12a} and hydrogen peroxide is produced by the oxidation of ascorbate. Again in an excess of oxygen this process is essentially quantitative. However, at low concentrations of dioxygen the B_{12r} reacts with the hydrogen peroxide. This reaction is irreversible and thus results in the destruction of the Vitamin B_{12} and it seems that there is damage to the corrin structure of the vitamin.

Group 10 complexes

There have been a number of studies of the kinetics and mechanisms of reactions of nickel(IV) complexes with ascorbic acid. Like the platinum(IV) complexes discussed below, these are of interest because the nickel(IV) is a two-electron oxidizing agent.

Lappin and co-workers[70] have used nickel(IV) complexes of the hexadentate ligand shown in Fig. 13.

The complex formed with nickel(IV) is substitutionally inert and can be optically resolved. The usual first order dependence on complex concentration and ascorbic acid concentration was observed, but the pH range studied was rather more extensive than many of the reactions discussed previously, viz. between pH 1 and 6. In fact, the plot of pH against second order rate constant had a minimum in the region of pH 4. Below pH 2.5, the usual inverse dependence of the second order rate constant on hydrogen ion concentration prevailed, indicating that in this region deprotonation of H_2A was the important factor affecting variation in rate.

ESR spectral measurements of the solution of nickel(IV) complex containing ascorbic acid gave

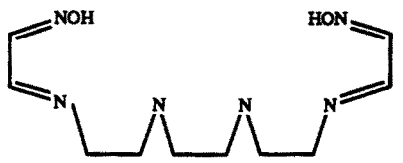
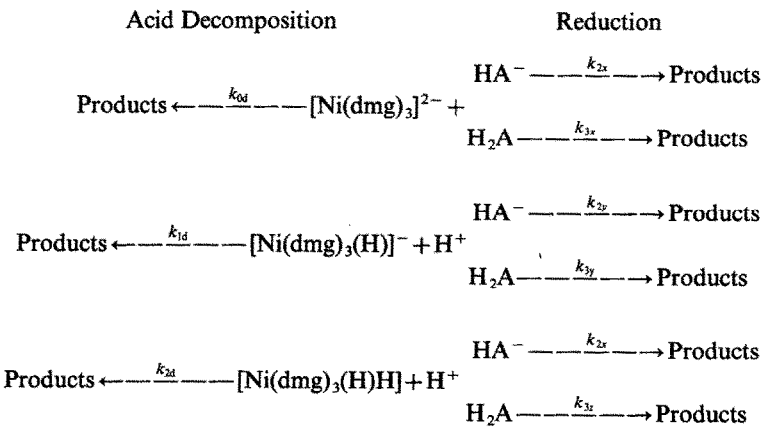


Fig. 13.

no evidence for the presence of ascorbate free radicals, but with values of $g = 2.155$ and $g_{11} = 2.033$ there is a suggestion that a nickel(III) moiety is a transient species formed during the reaction. This implies that the redox reaction involves two consecutive electron transfer processes rather than the simultaneous transfer of two electrons. The "bell shaped" curve of pH against observed rate constant is characteristic of a reaction rate which is dependent on two protonation equilibria. The first of these is, of course, the H_2A/HA^- equilibrium. The second protonation would have pK_a of about 3.7. The authors originally concluded that an equilibrium involving a nickel(IV) complex was involved.[70] However, in a subsequent publication[71] on the reduction of $[Ni^{IV}L]^{2+}$ by $[Co(phen)_3]^{2+}$, the authors offer a reinterpretation of the original data. They now conclude that the spectra recorded during the reaction and shown in the previous paper[70] are in fact characteristic of a nickel(III) complex. The pH dependence indicating a proton equilibrium with a pK_a of 3.7 is then attributable to the protonation of this nickel(III) complex. This leaves the overall interpretation of the remainder of the kinetics essentially the same.

Despite the presence of chiral centres on ascorbic acid, the redox reaction with this nickel(IV) complex showed no evidence of chiral discrimination of the type observed when nickel(IV) complexes react with some other reducing agents.

The paucity of information about the reactions of ascorbic acid with two-electron reducing agents was part of the driving force for the study of the reaction between ascorbic acid and the tris(dimethylglyoximato)nickelate(IV) anion.[72] This is one of the few studies where dehydroascorbic acid was positively identified using Roe's method[73] as the product of the oxidation of ascorbic acid was quantitatively determined for the stoichiometry of the reaction. Although this method does not give entirely satisfactory quantitative data,[74] nevertheless, even rough data and positive identification of dehydroascorbic acid as a product is valuable. The reaction of this complex is complicated by proton-assisted decomposition of the nickel(IV) complex which also involves intramolecular redox reactions. This gives rise to a very complex dependence of the rate on pH, though above pH 7 the redox reaction becomes predominant. The sequence of events over the whole pH range is that described in Scheme 11.



Scheme 11.

This, of course, gives an extremely complex set of rate equations. However, many of the constants in these equations have been evaluated by utilizing data from a previous study[75] of the acid hydrolysis of the nickel(IV) complex. Since there was no sign of a limiting rate with initial ascorbic acid concentration, there was no detectable intermediate and because of the substitution-inert nature of the complex, it is concluded that the reaction involves an outer sphere electron-transfer effect. Furthermore, ESR spectra of the paramagnetic nickel(III) intermediate suggest that electron transfer occurs in two steps, each involving a single electron.

In the light of the nickel(III) intermediates proposed in the above studies, it is interesting that McAuley *et al.*[76] have looked at the oxidation of ascorbic acid by three nickel(III) complexes of the macrocycles:

cyclam,
meso-(5,12)-7,7,14,14,Me_6-14-ane-1,4,8,11-N_4(teta), and
(5,14)-7,7,12,12,Me_6-14-ane-1,4,8,11-N_4(tet-c).

The reactions were first order with respect to complex and ascorbic acid concentrations and inversely dependent on hydrogen ion concentration. The proposed mechanism includes the possibility of what is called a "proton ambiguity" when reaction with HA^- is concerted, since there are two possibilities:

$$[Ni^{III}L]^{3+} + H_2A \longrightarrow [Ni^{II}L]^{2+} + HA^{\cdot} + H^+$$

$$[Ni^{III}L(OH)]^{2+} + H_2A \longrightarrow [Ni^{II}L]^{2+} + HA^{\cdot},$$

and the rate equation includes both of these reactions. The sulphate ion (which is known to form complexes with nickel(III)[77]) produced a marked decrease in rate with increasing sulphate ion concentration giving a linear dependence of k_{obs}^{-1} vs $[SO_4^{2-}]_T$ at constant ascorbic acid concentration.

McAuley *et al.* have studied the reduction of bis(1,4,7-triazacyclononane)nickel(III).[78] The data are consistent with reaction of the complex with both H_2A and HA^- and the product is the complex $Ni(9\text{-ane})_2^{2+}$. The Marcus relationship was applied to the system.

Recently, Latos-Grazynski and co-workers[79] noted that the nickel(II) complex of 5,10,15,20-tetraphenyl-21-thiaporphyrin was reduced by L-ascorbic acid to the corresponding nickel(I) complex.

The rate law for the oxidation of ascorbic acid by the hexachloroplatinate(IV) ion[80] does not appear to involve a term which is independent of hydrogen ion concentration. This contrasts with the hexachloroiridate(IV) complex.[81] This reaction again involves a two-electron oxidizing agent. The proposed first and rate determining step is the formation of the ascorbate radical and $[PtCl_5]^{2-}$, followed by rapid reaction between these to give the products (A and $[PtCl_4]^{2-}$).

Evans and Green[82] have studied the reaction of ascorbic acid with one of the second generation platinum-containing anti-cancer drugs, *cis,cis,trans*-$[Pt^{IV}(NH_2PR^i)Cl_2(H_2O)_2]$, CHIP. It is thought possible that the effectiveness of this drug is enhanced by the reduction of ascorbic acid *in vivo*. The study showed that ascorbic acid reduced the CHIP, to the Pt^{II} species *cis*-$[Pt(NH_2Pr^i)Cl_2]$. The kinetic measurements were interpreted in terms of an equilibrium of the type shown in Fig. 14.

The work by Pelizzetti and co-workers on the oxidation of ascorbic acid by $[IrCl_6]^{2-}$ and $[IrBr_6]^{2-}$[81] has been confirmed, complemented and extended by Drury and De Korte.[83] These workers obtained an identical rate law to that of Pelizzetti and co-workers and deduced that the mechanism proposed by these workers is correct. The effect of ionic strength on k_3 (rate constant attributed to reaction with HA^-) has been studied. The rate of reaction with H_2A with the oxidants (k_2) is assumed to be independent of ionic strength (due to the absence of charge on H_2A) and was measured and found to give parallel straight lines for plots of $\log k_3$ against $I^{1/2}/(1+I^{1/2})$ for lithium perchlorate/perchloric acid and sodium perchlorate/perchloric acid. The gradients of these lines (1.9 and 1.85, respectively) confirm that this is a reaction between a -1 and -2 charged species. The difference results in different values of $\log k_3$ at infinite dilution viz. 6.49 for this work and 6.58 in Pelizzetti and co-workers' paper.[81] The ionic strength plots were not straight lines for the corresponding reaction of $[IrBr_6]^{2-}$. An extended version of the Debye–Hückel expression incorporating the effective sizes of the hydrated ions is applied and the authors conclude that sodium perchlorate or lithium perchlorate may be used for ionic strength adjustment at low concentrations of supporting electrolytes. However, at high concentrations it is believed that lithium perchlorate is "vastly superior" to sodium perchlorate, the specific medium effects on the Marcus calculations are assessed and a revised value of 1.31 V is suggested for the H_2A^+/H_2A couple. Closer agreement is obtained for the $HA^{\cdot}/HA^-$ couple, but the comments of Creutz should be noted in this context.

Group 11 *complexes*

In the nineteenth century the effectiveness of citrus fruit juice in the treatment and cure of scurvy was questioned even though because of its use scurvy had long been eliminated from the British

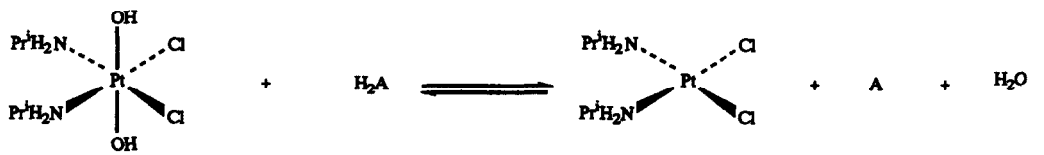


Fig. 14. Equilibrium of CHIP with ascorbic acid.

Navy. The reason, it was found later, was because fruit juice concentrated in copper vessels soon lost virtually all its antiscorbutic properties.[84] This was due to the catalytic effect of copper(II) ions in promoting the oxidation and eventual destruction of Vitamin C in the fruit juices. Thus, the reactions of copper(II) ions with the ascorbic acid system have a special significance. It is also interesting that enzymes such as ascorbate oxidase are copper containing enzymes.[85] There has been much work carried out on this system and until very recently the various studies have produced a confusing picture. Thus, earlier work[86] showed that the reduction of copper(II) ions by ascorbate in acetate buffer showed a second order dependence on copper(II) concentration, first order dependence on ascorbic acid concentration and a complex dependence on pH, which was related to the difference in reactivity of H_2A, HA^-, aquacopper(II) ions and acetatocopper(II) species.

More recently, Martinez *et al.* studied the reaction of copper(II) with ascorbic acid in chloride medium.[87] This reaction involves both chloro complexes of copper(II) and copper(I) and is fundamentally different from the reaction in a weakly complexing medium like perchlorate ions.[88]

The question of catalysis for the oxidation of ascorbic acid by a variety of oxidants, but particularly dioxygen has been the subject of a large number of studies and has been a topic of some controversy. A new feature of these investigations has been the nature of the reaction between copper(II) ions and ascorbic acid in the absence of these oxidizing agents. The problem has been recently thoroughly and, in many ways, decisively addressed by Xu and Jordan.[89] A major difference between their study and most of the other related studies is that they used a concentration of copper(II) in the measurements of reaction rates which was very much larger than the ascorbate concentration. This was in order to avoid various complications such as the formation of higher ascorbate complexes of copper(II). Under these conditions, the experimental data were found to be satisfactorily represented by a rate expression such as that shown in eq. (6).

$$k_{obs} = (a + b[Cl^-])\frac{[Cu^{2+}]}{(K_a + [H^+])}. \tag{6}$$

The reaction scheme proposed by these workers is that shown in Scheme 12.

$$H_2A \overset{K_a}{\rightleftharpoons} HA^- + H^+$$

$$Cu^{2+} + HA^- \overset{K_f}{\rightleftharpoons} [Cu(HA)]^+$$

$$Cu^{2+} + HA^- \xrightarrow{k_1} Cu^+ + HA^{\cdot}$$

$$[Cu(HA)]^+ \xrightarrow{k_2} Cu^+ + HA^-$$

$$HA^{\cdot} \rightleftharpoons A^{-\cdot} + H^+$$

$$Cu^{2+} + A^{-\cdot} \xrightarrow{fast} Cu^+ + A$$

Scheme 12.

The rate law which they have derived for this scheme is that shown in eq. (7).

$$k_{obs} = \frac{(k_1K_a + k_2K_fK_a)}{(K_a + [H^+] + K_fK_a[Cu^{2+}])}[Cu^{2+}]. \tag{7}$$

When the conditions are such that $[H^+] \gg K_fK_a[Cu^{2+}]$, the above expression reduces to that shown in eq. (8)

$$k_{obs} = \frac{(k_1K_a + k_2K_fK_a)}{(k_a + [H^+])}[Cu^{2+}]. \tag{8}$$

This is of the same form as the experimentally determined rate law with $b = (k_1K_a + k_2K_fK_a)$ and $[Cl] = 0$.

By predicting a value of 4.4 $M^{-1}\ s^{-1}$ for the outer sphere reaction, Xu and Jordan showed clearly that the copper(II)-ascorbate reaction does not proceed by an outer sphere mechanism.

There is now much evidence that the chloride ion exerts considerable influence over the kinetics of reactions involving copper(II) and ascorbic acid. Xu and Jordan have interpreted this influence on the direct anaerobic reaction of copper(II) and ascorbic acid by chloride ions in terms of the set of reactions shown in Scheme 13.

$$H_2A \rightleftharpoons HA^- + H^+$$

$$Cu^{2+} + Cl^- \rightleftharpoons [CuCl]^+$$

$$[CuCl]^+ + HA^- \rightleftharpoons [CuCl(HA)]$$

$$[CuCl(HA)] \longrightarrow CuCl + HA^{\cdot}$$

$$[CuCl]^+ + HA^- \longrightarrow CuCl + HA^{\cdot}$$

$$HA^{\cdot} \rightleftharpoons A^{\cdot -} + H^+ \text{ Fast}$$

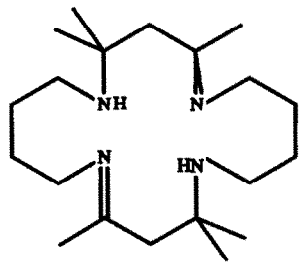
$$Cu^{2+} + A^{\cdot -} \longrightarrow Cu^+ + A \text{ Fast}$$

Scheme 13.

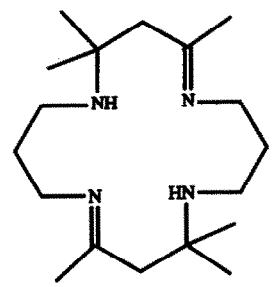
Macrocyclic copper(II) complexes have been used in the study of electron transfer from ascorbic acid to copper(II) since they have the advantage of being stable under the conditions of the reaction.[90] Complexes of the ligands shown in Fig. 15 were studied. Rate constants and other kinetic data are not given in this paper, but it is found that reaction of **III** was first order with respect to copper, reaction of **II** was second order with respect to copper and **I** did not react at all. This is interpreted as showing that the electron is transferred through a $p\pi$–$d\pi$ interaction but not through the σ bond. The macrocyclic ligand tetrabenzo[b,f,j,n][1,5,9,13]tetraazacyclohexadecene, (TAAB) (Fig. 16) forms stable copper(II) and copper(I) complexes.[91] The kinetics of the reduction of the copper(II) complex by ascorbic acid[92] gives the rate law shown in eq. (9).

$$k_{obs} = \frac{k[H_2A]}{[H^+]}. \tag{9}$$

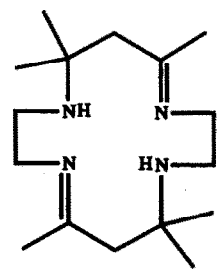
This is interpreted as arising from an outer sphere electron transfer by ascorbic acid to form the



I Trans[18]diene



II Trans[16]diene



III Trans[14]diene

Fig. 15.

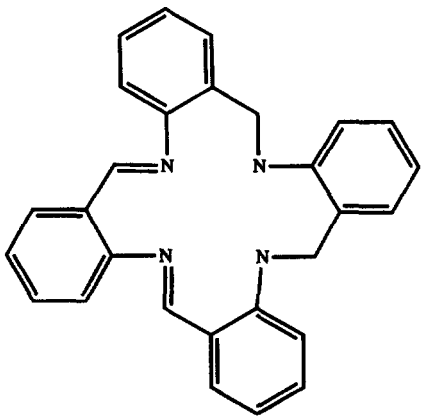


Fig. 16. Tetrabenzo[b,f,j,n][1,5,9,13]tetraazacyclohexadecine.

ascorbate radical in the normal way and the data have been interpreted using the Marcus theory.

The use of macromolecular copper(II) complexes in the oxidation of ascorbic acid has been extended to polymeric species by the reaction of copper(II)-poly-4-vinylpyridine complexes.[93] The reaction was studied anaerobically by measurement of the half-life of the reaction. It has been shown[94] that in these complexes, Cu^{2+} ions are able to bind up to 45% of non-quaternized pyridine residues to form tetrapyridine complexes. The relative molecular mass of the polymers used was $(6 \text{ to } 8) \times 10^4$, which may then contain up to 80 Cu^{2+} ions in the tetrapyridine form. At pH 3.5 the half life ($t_{1/2}$) in terms of concentration of ascorbic acid is given by eq. (10).

$$t_{1/2} = a + \frac{b}{[H^+]}. \tag{10}$$

This is interpreted in terms of an inner sphere mechanism involving the formation of an ascorbic acid/copper(II)/PVP complex(c). The authors also suggest that such a mechanism would result in the production of dehydroascorbic acid radicals $A^{-\cdot}$. These were detected using flow experiments. The suggested mechanism is shown in Scheme 14:

$$H_2A \rightleftharpoons HA^- + H^+$$

$$Cu^{II}(PVP) + HA^- \rightleftharpoons C$$

$$C \xrightarrow{k_1} Cu^{I}PVP + H^+ + D^{-\cdot}$$

$$D^{-\cdot} + Cu^{II}PVP \longrightarrow D + Cu^{I}PVP \text{ dehydroascorbic acid}$$

Scheme 14.

and the resulting rate expression is given as eq. (11).

$$t_{1/2} = \frac{1}{2k_1} + \frac{[H^+]}{2k_1 K_a K_c [H_2A]_o} \cdot \ln 2. \tag{11}$$

The intervention of copper(III) in reactions of copper enzymes has been suggested.[95] It is of interest, therefore, to investigate reactions of copper(III) complexes with ascorbic acid. Many complexes of copper(III) are insoluble in water or are unstable.[96] However, for the copper(III) complex shown in Fig. 17 the stoichiometry of the reaction varied according to the relative concentrations of ascorbic acid and copper(III) complexes as shown below:

$$[H_2A] \ll [Cu^{III}]\ 2Cu^{III} + H_2A \longrightarrow 2Cu^{II} + A + 2H^+$$

$$[H_2A] \gg [Cu^{III}]\ Cu^{III} + H_2A \longrightarrow Cu^{I} + A + 2H^+.$$

The kinetics were studied over a wide pH range and the rate showed the typical bell-shaped curve

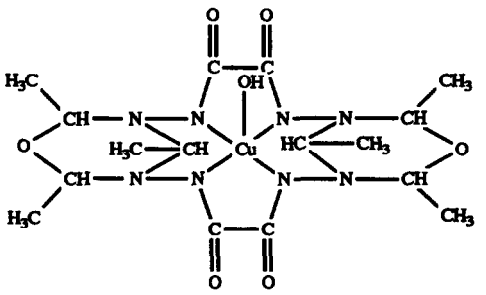


Fig. 17. Copper(III) complex.

commonly found in reactions involving two equilibria involving protons. The proposed mechanism for this reaction is shown in Scheme 15.

$$H_2A \rightleftharpoons HA^- + H^+$$

$$Cu^{III}aq \rightleftharpoons Cu^{III}OH + H^+$$

$$Cu^{III}aq + H_2A \xrightarrow{k_1} Cu^{II} + \text{radical}$$

$$Cu^{III}OH + H_2A \xrightarrow{k_2} Cu^{II} + \text{radical}$$

$$Cu^{III}aq + HA^- \xrightarrow{k_3} Cu^{II} + \text{radical}$$

$$Cu^{III}OH + HA^- \xrightarrow{k_4} Cu^{II} + \text{radical}$$

$$[Cu^{III}aq]_1 + \text{radical} \longrightarrow Cu^{II} + A$$

Scheme 15.

It is notable that the copper(II) product does not react with oxygen to re-form the copper(III) complex. The copper(II) complex of the above ligand, prepared independently, does however react with oxygen to form the copper(III) complex.

Silver(I) may be titrated directly with ascorbic acid using variamine blue as an indicator[97] and the kinetics of the reaction have been studied by Mushran and co-workers.[98] They conclude that this reaction has a rate determining step reaction between HA^- and Ag^+. However, there is no evidence for or against an outer or inner sphere mechanism. The reaction shows an inverse dependence on $[H^+]$, though one would have liked more data to support this rather than log/log plots.

The reduction of gold(III) by ascorbic acid has been studied over a range of chloride concentrations.[99] The rate was dependent on the inverse square of the chloride concentration.

Lanthanides and actinides

Ascorbic acid has frequently been used as a redox titrant.[100] The mechanisms of reactions of ascorbic acid with typical titration oxidizing agents is therefore of considerable interest. Ascorbic acid has been found to react comparatively slowly with cerium(IV) and the kinetics of the reaction have been studied.[101] Cerium(IV) reactions have the additional interest that like other lanthanide elements, cerium forms complex species in aqueous solution with oxoanions such as sulphate ions. The sulphate and hydrogensulphate ions show considerable inhibition of the reaction due to the formation of complex species such as $[Ce(SO_4)_3]^{2-}$. The kinetics are interpreted in terms of an inner sphere reaction in which there is a rapidly achieved pre-equilibrium involving the formation of cerium(IV)-ascorbic acid complex and the rate determining step is the decomposition of this complex to form Ce^{3+} and HA˙.

The oxidation of ascorbic acid by neptunium(VI) in acid aqueous solution has been studied.[102] Over the range of acid concentrations 0.05–1.00 M, no hydrogen ion dependent path could be discerned.

Miscellaneous reactions

An inner sphere mechanism has been proposed for the reaction of mercury(II) acetate by ascorbic acid in acetic acid solution.[103]

More complex reactions which involve ascorbic acid, almost incidentally as part of a redox "cocktail", include its use in the photolytic release of hydrogen from water.[104] A recent variation of the well-known bromate–iodide clock reaction[105] has been studied from a mechanistic standpoint with molybdenum and vanadium as catalysts. A different mechanism was espoused for Mo^{VI} and W^{VI}. For Mo^{VI}, the rate law was:

$$\text{Rate} = k_2[BrO_3^-][I^-][H^+]^2 + k_2'[BrO_3^-][I^-][H^+]^2[Mo^{VI}], \tag{12}$$

where $k_2 = 44\ dm^9\ mol^{-3}\ s^{-1}$ and $k_2' = 4.3 \times 10^6\ dm^{12}\ mol^{-3}\ s^{-1}$. This is due to catalysis by Mo^{VI} of the component bromate and iodate of the clock reaction.

For V^V the rate law was:

$$\text{Rate} = k_1'[BrO_3^-][V^V] + k_2[BrO_3^-][I^-][H^+]^2, \tag{13}$$

where $k_1' = 9.6\ dm^3\ mol^{-1}\ s^{-1}$ and $k_2 = 42.6\ dm^9\ mol^{-3}\ s^{-1}$. In this the direct reaction between bromate and ascorbic acid is catalysed.

APPLICATION OF THE MARCUS RELATIONSHIP TO OUTER SPHERE REACTIONS OF ASCORBIC ACID

The outer sphere oxidation of ascorbic acid has been treated theoretically many times using the Marcus relationship.[106] The most frequently used approach has been to use the relationship to estimate the standard electrode potential of the half reaction:

$$HA^- \rightleftharpoons HA^{\cdot} + e.$$

Values between 0.9 and 1.1 V have often been obtained.[81] These are rather different from the value of 0.70 V obtained by other techniques.[6] More recently a valuable contribution to the debate has been provided by Macartney and Sutin,[107] who examined the kinetics of oxidation of ascorbic acid by tris(2,2′-bipyridine) complexes of osmium(III), ruthenium(III) and nickel(III). Rate constants and activation enthalpies and entropies were determined for the reaction with H_2A, HA^- and A^{2-}. The results were treated using a modified version of the Marcus relationship[57] in which:

$$k_{12} = (k_{11}k_{12}K_{12}f_{12})^{1/2}W_{12}. \tag{14}$$

In this equation k_{12} is the rate constant for the cross reaction, k_{11} and k_{22} are the rate constants for the component exchange reactions and K_{12} is the equilibrium constant for the cross reaction. f_{12} is defined by the equation:

$$\ln f_{12} = \frac{\{\ln K_{12} + (w_{12} - w_{21})/RT\}^2}{4\ln\dfrac{k_{11}k_{22}}{A_{11}A_{22}} + \dfrac{w_{11}+w_{22}}{RT}}. \tag{15}$$

W_{12} is then defined by:

$$W_{12} = \exp\{-(w_{12} + w_{21} - w_{11} - w_{22})/RT\}.$$

w_{ij} can then be calculated from:

$$w_{ij} = \frac{z_i z_j e^2}{D_a \sigma_{ij}(1 + \beta\sigma_{ij}\sqrt{\mu})} \tag{16}$$

and A_{ij} from:

$$A_{ij} = \left\{\frac{4\pi N\sigma^2 \nu_n \delta r}{1000}\right\}_{ii}. \tag{17}$$

w_{ij} is the work required to bring the ions i and j, having charges z_i and z_j to a separation distance of σ_{ij} and Macartney and Sutin take this as the sum of the radii of i and j.

$$\beta = \left(\frac{8\pi Ne^2}{1000 D_a kT}\right)^{1/2} \tag{18}$$

and ν_n is the nuclear frequency that destroys the activated complex. δr is the thickness of the reaction layer.

Macartney and Sutin have plotted $\log(k_{12}/k_{11}k_{22}W_{12})$ vs $\log(K_{12}f_{12})$ for complexes reacting with HA^- and have obtained a reasonable straight line. Such a plot is shown in Fig. 18. A value of 0.71 V was used for the redox potential for the $HA^-/HA^{\cdot}$ couple.

A similar calculation was carried out for 28 reactions in which data were available for the oxidation of H_2A, using 1.23 V for the $H_2A/H_2A^{\cdot+}$ couple and these are shown in Fig. 19.

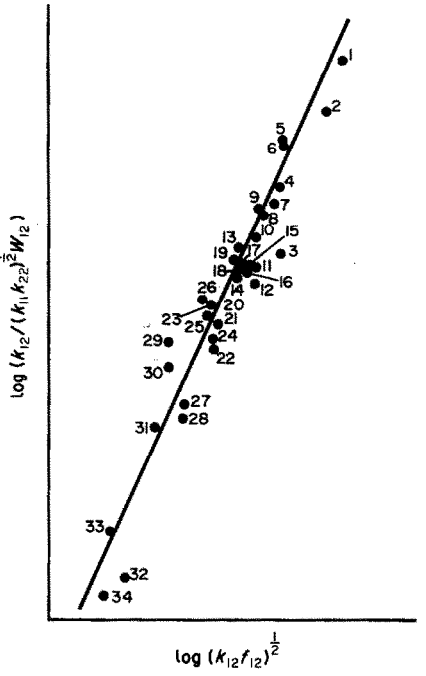


Fig. 18. Plot of $\log(k_{12}/k_{11}k_{22})^{1/2}W_{12}$ against $\log(k_{12}f_{12})^{1/2}$ for oxidation of HA^-.

KEY

No.	Complex	Ref.	No.	Complex	Ref.	No.	Complex	Ref.
1.	$[Ni(bipy)_3]^{3+}$	107	13.	$[Fe(mphen)_3]^{3+}$	48	25.	$[*Ru(5,6\text{-}dmphen)_3]^{2+}$	141
2.	$[Ni(dmbpy)_3]^{3+}$	107	14.	$[Fe(bpy)_3]^{3+}$	81	26.	$[*Ru(phen)_3]^{2+}$	141
3.	$[Ru(bpy)_3]^{3+}$	107	15.	$[CoW_{12}O_4]^{5-}$	66	27.	$[*Ru(dmbpy)_3]^{2+}$	141
4.	$[Fe(nphen)_3]^{3+}$	48	16.	$[*Ru(bphen)_3]^{2+}$	141	28.	$[Os(dmbpy)_3]^{3+}$	107
5.	$[Ni(tet\text{-}a)]^{3+}$	76	17.	$[*Ru(cphen)_3]^{2+}$	14	29.	$[*Ru(3,5,6,8\text{-}tmphen)_3]^{2+}$	141
6.	$[Ni(tet\text{-}c)]^{3+}$	76	18.	$[Fe(dmphen)_3]^{3+}$	48	30.	$[*Ru(3,4,7,8\text{-}tmphen)_3]^{2+}$	141
7.	$[Fe(sphen)_3]^{3+}$	81	19.	$[IrCl_6]^{2-}$	81	31.	$[Ru(NH_3)_4bpy]^{3+}$	140
8.	$[Fe(bphen)_3]^{3+}$	81	20.	$[Ni(cyclam)]^{3+}$	76	32.	$[Co(phen)_3]^{3+}$	62
9.	$[Fe(cphen)_3]^{3+}$	48	21.	$[Fe(dmbpy)_3]^{3+}$	81	33.	$[Fe(CN)_5tu]^{2-}$	46
10.	$[Fe(phen)_3]^{3+}$	48	22.	$[*Ru(bpy)_3]^{2+}$	141	34.	$[Co(bpy)_3]^{3+}$	62
11.	$[Fe(phen)_3]^{3+}$	49	23.	$[*Ru(mphen)_3]^{2+}$	141			
12.	$[Ru(dmbpy)_3]^{3+}$	107	24.	$[Os(bpy)_3]^{3+}$	107			

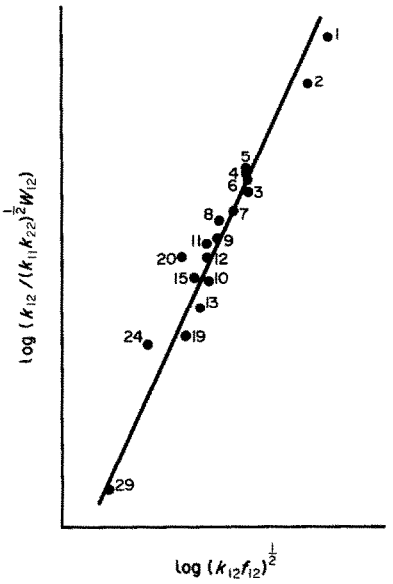


Fig. 19. Plot of $\log(k_{12}/k_{11}k_{22})^{1/2}W_{12}$ against $\log(k_{12}f_{12})^{1/2}$ for oxidation of H_2A.

KEY: Complexes 1–28, as for Figure 18.

Fewer data are available for the oxidation of A^{2-}, but using a value of 0.015 V fair agreement was obtained for eight oxidants, shown in Fig. 20. The application of the modified Marcus relationship to this very wide variety of reactions involving oxidation of ascorbic acid by many oxidants provides a very good correlation of these disparate outer sphere reactions.

More recently, Hoddenbagh and Macartney[108] have studied the reduction of the hexacyanoruthenate(III) ion in acid solution by a variety of reducing agents, one of which was ascorbic acid. They used a similar method of correlation using the modified Marcus relationship, plotting

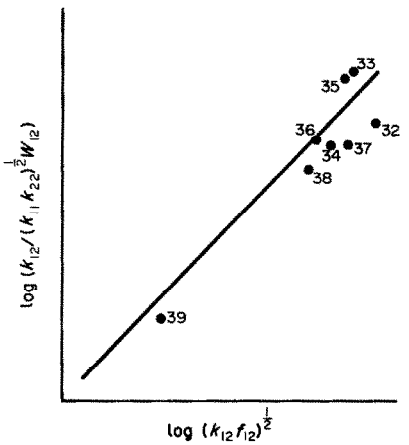


Fig. 20. Plot of $\log(k_{12}/k_{11}k_{22})^{1/2}W_{12}$ against $\log(k_{12}f_{12})^{1/2}$ for oxidation of A^{2-}.

KEY

No.	Complex	Ref.	No.	Complex	Ref.
32.	$[Co(phen)_3]^{3+}$	62	36.	$[Co(tpy)_2]^{3+}$	140
33.	$[Fe(CN)_5tu]^{2-}$	46	37.	$[Ru(dipic)_2]^{-}$	140
34.	$[Cu(bpy)_3]^{3+}$	62	38.	Cytochrome c	142
35.	$[Ru(NH_3)_5py]^{3+}$	140	39.	Catechol anion radical	143

$\ln (k_{12}/k_{22})^{1/2} \cdot W_{12}$ vs $\ln (K_{12}f_{12})^{1/2}$ and again obtained very good agreement for 12 different reducing agents.

REACTIONS OF L-ASCORBIC ACID CATALYSED BY TRANSITION METAL IONS

Much work has been carried out on the catalysis of the so-called "auto-oxidation" of ascorbic acid, particularly by copper(II). This process is in fact the oxidation of ascorbic acid by dissolved oxygen, usually in aqueous solution. Such reactions are of particular significance because copper(II) has a role in reactions involving a number of enzymes such as ascorbate oxidase. The earlier work has been reviewed previously[1,109] and we will only consider the more recent work on this subject. It is also found that copper(II) catalyses a number of redox reactions involving metallic complexes such as those of cobalt(III)[61] and these will also be considered in this section.

Catalysis of oxidation by dioxygen by copper(II)

(1) *Copper*(II) *catalysis in the absence of potential ligands.* This is meant to refer to catalysis by copper(II) in aqueous solution in which the ions present do not react significantly with copper(II) such as perchlorate and nitrate ions. The early work on this by Taqui Khan and Martell has been summarized elsewhere.[1,109] A major feature of this work and subsequent papers by other workers has been the question of the order of the reaction with respect to dissolved oxygen. It looks as if the order of the reaction varies from 0.5 to 1.0, depending on the initial concentration of dioxygen. Several of the more recent studies have proposed mechanisms for the reaction based on an order of 0.5 with respect to dioxygen.[110,111] There is much evidence from a variety of sources[112] that copper(II) in ascorbic acid solutions is present as a complex with ascorbate ion. Indeed, at relatively high concentrations such solutions are green and have a broad absorbance at about 410 nm.[113] This absorbance is believed to be predominantly due to the presence of the monomeric complex $[CuHA]^+$. Jameson and Blackburn[111] have provided evidence for the presence of a dimeric species of the type $[Cu_2(HA)_2]^{2+}$ and have invoked this as a significant factor in the mechanism of the reaction with dioxygen. Their most recent work on this system[114] has resulted in a proposal of the mechanism shown in Scheme 16.

Initiation:

$$[Cu_2(HA)_2]^{2+} \xrightarrow{k_1} [Cu^I(HA)] + Cu^I + A + H^+$$

$$Cu^I + HA^- \xrightarrow{K_M} [Cu^I(HA)]$$

Propagation:

$$[Cu^I(HA)] + O_2 \xrightarrow{k_2} [Cu^I(HA)O_2]$$

$$[Cu^I(HA)O_2] \xrightarrow{k_3} Cu^I + HO_2^- + A'$$

Termination:

$$[Cu^I(HA)O_2] + [Cu^I(HA)] \xrightarrow{k_4} [Cu_2(HA)_2]^{2+} + O_2^{2-}$$

$$O_2^{2+} + 2H^+ \longrightarrow H_2O_2$$

Scheme 16.

Application of the steady state treatment to this mechanism gives eq. (19) for the rate of disappearance of dioxygen;

$$-\frac{d[O_2]}{dt} = \frac{2k_1k_2k_3}{k_4} \cdot K_M \cdot K_{DH}^{1/2}[Cu^{2+}][HA^-][O_2]^{1/2} \qquad (19)$$

where K_{DH} refers to the equilibrium:

$$2[Cu(HA)]^+ \overset{K_{DH}}{\rightleftharpoons} [Cu_2(HA)_2]^{2+}.$$

This rate law is in agreement with the observed kinetics. It is interesting to compare this treatment with that for the same system by Shtamm and co-workers.[115] They obtained the same rate equation as Jameson and Blackburn in a study which included an investigation of the effect of ligands which formed very weak complexes with copper(II) and fairly strong complexes with copper(I). The mechanism proposed by them is also a chain mechanism with the formation and reaction of copper(I) as an essential feature. This is shown in Scheme 17.

Initiation:

$$2Cu^{2+} + HA^- \longrightarrow 2Cu^+ + A + H^+$$

Propagation:

$$H^+ + Cu^+ + O_2 \longrightarrow Cu^{2+} + HO_2$$

$$HO_2 + HA^- \longrightarrow A^{\cdot -} + H_2O_2$$

$$A^{\cdot -} + Cu^{2+} \longrightarrow Cu^+ + A$$

Termination:

$$Cu^+ + HO_2 \longrightarrow Cu^{2+} + HO_2^-$$

Scheme 17.

The essential difference between the two mechanisms is that Jameson and Blackburn's mechanism involves the formation of a copper(II) dimeric complex incorporating ascorbate and copper(I) complexes of ascorbate and ascorbic acid and oxygen instead of the formation of HO_2 radicals and Cu^+ in the propagation stage. Shtamm and co-workers established the intermediacy of copper(I) by introducing one of two complexing agents into the system and measuring the dioxygen uptake. Acetonitrile was introduced. This forms moderately strong complexes with copper(I) and weak complexes with copper(II). The other ligand was allyl alcohol. This does not form complexes with copper(II), but forms stable complexes with copper(I). The effect of these additions was that the acetonitrile caused initial acceleration in rate due to the increased formation of copper(I) followed by a diminution in rate with increasing concentration as the more stable copper(I) complexes are formed. Allyl alcohol on the other hand produced no acceleration but showed a continuous diminution in rate as the stable copper(I) allyl alcohol complex is formed and is less reactive towards dioxygen.

(2) *Complexes of copper*(II). In biological systems the catalytic ability of copper ions is harnessed and enhanced by providing a suitable matrix in the form of a protein molecule to which the copper is bonded.[85] There has been some interest, therefore, in the effect of complexing of copper ions on their catalytic activity towards the oxidation of ascorbic acid, sometimes with a view to constructing possible models for copper enzymes.

Systems in which the catalytic ability of the copper ions is enhanced are of course of particular interest. We have already seen that copper(II) in the presence of acetonitrile at low concentration shows enhanced catalytic activity,[115] and on the other hand, addition of allyl alcohol diminishes catalysis by copper(II) ions.

Several groups of workers[116] have investigated the effects of halide ions on the rates of reactions catalysed by copper(II) and particular interest has centred on the chloride ion. Jameson and Blackburn[117] have carried out a particularly thorough study of the effects of chloride ion on the rate of oxidation of ascorbic acid by dioxygen. It became very clear early on in the work of Ogata and Kosugi[118] that chloride and to a lesser extent bromide ions had an accelerating effect on the auto-oxidation of ascorbic acid. They also found that as the concentration of halide ions was increased there was a point at which the rate reached a maximum. It was suggested that the effect arose from the formation of mixed halide/ascorbate complexes of copper(II). Jameson and Blackburn have carried out a more detailed study of the same system in chloride media,[114] including

an investigation of the species in solution using pH titrations. The more recent of these two papers describes studies of the variation of the rate with copper concentration and chloride ion concentration, each at various pH values. The rate law determined for this system is shown in eq. (20)

$$k_{obs} = \frac{a+b[Cl^-]}{c+d[Cl^-]+e[Cl^-]^2} \tag{20}$$

and this is interpreted as being due to pre-equilibria involving the formation of $[CuCl]^+$, $[Cu_2ACl_4]^{2-}$, $[Cu(H_2A)]^{2+}$, $[Cu(HA)]^+$ and the acid–base equilibria of ascorbic acid. The rate equation gives a maximum as noted experimentally at low chloride ion concentrations. Values of the constants in this equation were evaluated using a fitting procedure and values of various equilibrium constants were calculated. These workers suggest that the process is a chain reaction with $[Cu_2ACl_2]$ as the reactant species. The initiation of the chain reaction is considered to be that shown below:

$$[Cu_2ACl_2] \longrightarrow Cu^+ + [Cu^ICl_2]^- + A.$$

The propagation and termination steps are then similar to that discussed above for the reaction in the absence of chloride. The authors point out that the acceleration at low chloride concentrations is due to the higher efficiency of the initiation process in the presence of chloride.

Fabre and Lapinte[1,116] also studied the effect of chloride ion on copper catalysis along with the effects of many other ions and molecules. They concluded that the catalytic effect of copper(II) is more enhanced by those ligands which stabilize copper(I) and ligands which stabilize copper(II) inhibit the reaction rate.

Shtamm *et al.*[115] have discussed the role of chloride ions in the light of the earlier work of Jameson and Blackburn[111] and conclude that the acceleration followed by inhibition produced by chloride ions was due to a process analogous to that observed for the addition of acetonitrile (see above). These conclusions may not be at variance with the generation of copper(I) ions by $[Cu_2ACl_2]$ in the initiation stage of the mechanism described by Jameson and Blackburn.[117] It may not, however, be necessary to invoke a complex involving ascorbate at this stage.

Studies of the effects of other ligands have not approached the chloride studies either in detail or thoroughness. The effects of other halide ions such as bromide ions are known[116] but no rate equations have been produced to allow deduction of a mechanism. This is unfortunate because the equilibrium behaviour of both copper(II)[118] and copper(I) in bromide media is well known and should throw light on the nature and mechanisms of copper catalysed oxidation of ascorbate by dioxygen.

Histidylhistidine has been shown to have an accelerating effect on the copper(II) catalysed oxidation of ascorbic acid.[119] Takamura *et al.* have examined the nature of the complexes of histidylhistidine with copper(II) and studied the effect on the rate of oxidation of ascorbic acid of these and other amino acid and peptide complexes. Only histidylhistidine and polyhistidine enhanced the catalytic action of copper(II) at pH 3.8. As the pH is increased, the accelerating effect of the histidylhistidine decreases, so that at pH 5.3 and above the ligand inhibits the catalytic activity of the copper(II). This is interpreted as being due to the ultimate formation of tetradentate histidylhistidine complexes at higher pH values. The accelerating effect appears to be due to enhancement of the coordinating ability of the copper(II), since the mechanism proposed involves the formation of ascorbate–copper(II) complex–oxygen species. The understanding of the mechanism operating in this system would benefit from further kinetic study. Takamura *et al.* did not present kinetic data in terms of a rate law and a knowledge of the dependence of the rate on dioxygen concentration and copper(II) concentration could aid the deduction of a mechanism which adequately describes the behaviour of this system.

It has been known for many years that the complex of copper(II) with poly-4-vinylpyridine is an efficient catalyst for the oxidation of ascorbic acid by dioxygen.[120] This is an interesting system, since the polymeric nature of the ligand system allows some control over the nature of the environment around the copper(II). Skurlatov and co-workers[93] have studied the kinetics of the reaction of ascorbic acid with oxygen in the presence of this catalyst. The kinetics of the reaction of the reduced form (Cu^Ipvp) with dioxygen were also studied. The proposed mechanism involves the formation of a pvp–copper–dioxygen complex and is cyclic, as shown in Fig. 21.

The formation of a copper(I) moiety and its subsequent reaction with dioxygen are an essential

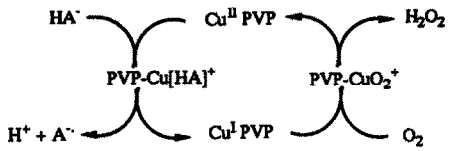


Fig. 21. Formation of the PVP-oxygen complex.

feature of this reaction. The relative contribution of the two reactions depends upon the pH, in that at pH 3.5, the rate of [Cu^{I}pvp] with dioxygen is rate-limiting, but at pH 4.5, reaction of [Cu^{II}pvp] with HA^- is rate-limiting.

Catalysis of oxidation of dioxygen by other transition metal ions

Other transition metal ions do not appear to be as efficient as copper(II) in the catalysis of the oxidation of ascorbic acid by dioxygen. The pioneering work on the catalytic effects of iron(III) and iron(III)-chelate complexes by Taqui Khan and Martell has been reviewed.[1] These workers have studied the catalytic behaviour of vanadyl[121] and uranyl ions.[122] These reactions all involve the possibility of facile oxidation. However, Federova *et al.*[123] have shown that the reaction of ascorbic acid with dioxygen in aqueous pyridine is catalysed by Co^{2+}, Ni^{2+}, Mn^{2+} and Zn^{2+}. Co^{2+} and Ni^{2+} ions were found to be more effective catalysts than Mn^{2+} and Zn^{2+} by a factor of *ca* 10. The rate law was the same for all the metals and is given in eq. (21).

$$\text{Rate} = \frac{\{k_1 + k_2[\text{py}]\}[HA^-][M^{2+}][O_2]}{[H^+](1 + K_a[H^+])} \tag{21}$$

The authors suggest that the mechanism of the reaction is a radical process, but not a chain reaction. The role of the metal ions in the process is not a redox function but to increase the rate of radical formation. It is interesting that other cations with non-variable valency, but which also form complexes with ascorbic acid show no catalytic activity, e.g. Mg^{2+}, Ca^{2+} and Cd^{2+}.[124] The oxidation of ascorbic acid by dioxygen in methanol is also catalysed by N,N′-ethylenebis(salicylideneaminato) cobalt(II), Co(salen).[125] It is suggested that this is a model for oxygen carriers in biological systems. In methanol, Co(salen) exists as the complex $[Co(salen)_2O_2]$ in the presence of dioxygen and it is suggested that in methanol, it is this complex with which the ascorbic acid reacts. The proposed mechanism which involves the formation of a monomeric dioxygen complex and which is in agreement with the observed kinetics is given in Scheme 18.

$$[\text{Co(salen)}] + O_2 \underset{K_2}{\overset{K_1}{\rightleftharpoons}} [\text{Co(salen)}O_2]$$

$$[\text{Co(salen)}O_2] + H_2A \rightleftharpoons [H_2A\text{Co(salen)}O_2]$$

$$[H_2A\text{Co(salen)}O_2] \xrightarrow{k} [\text{Co(salen)}] + H_2A^{\cdot+} + O_2^{-\cdot}$$

Scheme 18.

Again this interesting system would benefit from a more detailed study.

The early work of Martell and Taqui Khan on the catalysis by iron(III) and its complexes of the oxidation of ascorbic acid by dioxygen[1] has been more recently extended and complemented by studies of similar systems involving ruthenium(III). The kinetics of the catalysis by ruthenium(III), ruthenium(III)-EDTA and ruthenium(III)-IMDA were studied[126] in the pH range 1.50–2.75. In all three cases the kinetics were first order in both the ruthenium(III) species and the ascorbic acid. As is frequently the case there was an inverse dependence on hydrogen ion concentration. As far as dioxygen concentration was concerned, the order was half for catalysis by ruthenium(III) and zero when the chelate complexes were catalysts. Ruthenium trichloride was the ruthenium(III) species used and in the pH range of this study it was assumed that $[RuCl_2(H_2O)_4]^+$ was the active catalytic agent. The half order dependence on dioxygen is explained by the mechanism in Scheme 19.

$$H_2A \rightleftharpoons HA^- + H^+$$

$$[RuCl_2(H_2O)_4]^+ + HA^- \rightleftharpoons [RuCl_2(H_2O)_2(HA)] + 2H_2O$$

$$2[RuCl_2(H_2O)_2(HA)] + O_2 \rightleftharpoons [RuCl_2(H_2O)(HA)]_2O_2 + 2H_2O$$

$$[RuCl_2(H_2O)(HA)]_2O_2 + 2H_2O \xrightarrow[\text{slow}]{H^+} 2[RuCl_2(H_2O)_4]^+ + 2A + 2H_2O$$

Scheme 19.

The structure proposed for $[RuCl_2(H_2O)(HA)]_2O_2$ is shown in Fig. 22.

The zero order dependence on dioxygen when the metal chelate species catalyse the reaction is explained by a rather different mechanism (see Scheme 20).

$$H_2A \rightleftharpoons HA^- + H^+$$

$$[Ru^{III}L(H_2O)]^{(n-3)-} + HA^- \rightleftharpoons [Ru^{III}L(HA)]^{(n-2)-} + H_2O$$

$$[Ru^{III}L(HA)]^{(n-2)-} \xrightarrow[\text{RDS}]{\text{slow}} [Ru^{II}L]^{(n-2)-} + HA^{\cdot}$$

$$[Ru^{III}L(H_2O)]^{(n-3)-} + HA^{\cdot} \xrightarrow{\text{fast}} [Ru^{II}L(H_2O)]^{(n-2)-}A + H^+$$

$$2[Ru^{II}L(H_2O)]^{(n-2)-} + O_2 \xrightarrow[H^+]{\text{fast}} 2[Ru^{III}L(H_2O)]^{(n-3)-} + H_2O_2$$

Scheme 20.

The order of catalytic activity decreases in the order of the increase of the stability constants of the ascorbate complexes of the metal ion species.

The effect of temperature on these reactions has also been studied[127] and thermodynamic parameters for the formation of the above μ-peroxoruthenium ascorbate complex and the formation of mixed ligand complexes with ascorbic acid have been determined.

The Udenfriend system[128] has been known for many years as the use of Fe^{III}-EDTA-ascorbic acid in the presence of dioxygen which oxidizes a large number of saturated and unsaturated organic substrates. Taqui Khan and Shukla[129] have shown that the hydroxylation of toluene to cresols by dioxygen may be catalysed by a Ru^{III}-EDTA-ascorbic acid analogue of the Udenfriend system. The reaction was studied in a 50% mixture of 1,4-dioxane and water in the pH range 1.50–2.50. Unlike the oxidation of ascorbic acid by molecular oxygen catalysed by Ru^{III}-EDTA discussed above in which there was a zero order dependence on dioxygen, in this system in the presence of toluene there was a first order dependence on dioxygen. The mechanism proposed by Taqui Khan and Shukla is shown in Fig. 23.

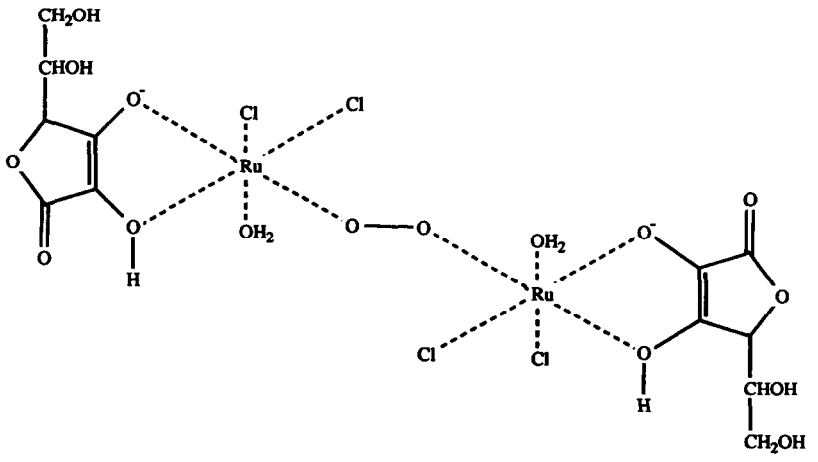


Fig. 22. Proposed structure of $[RuCl_2(H_2O)(HA)]_2O_2$.

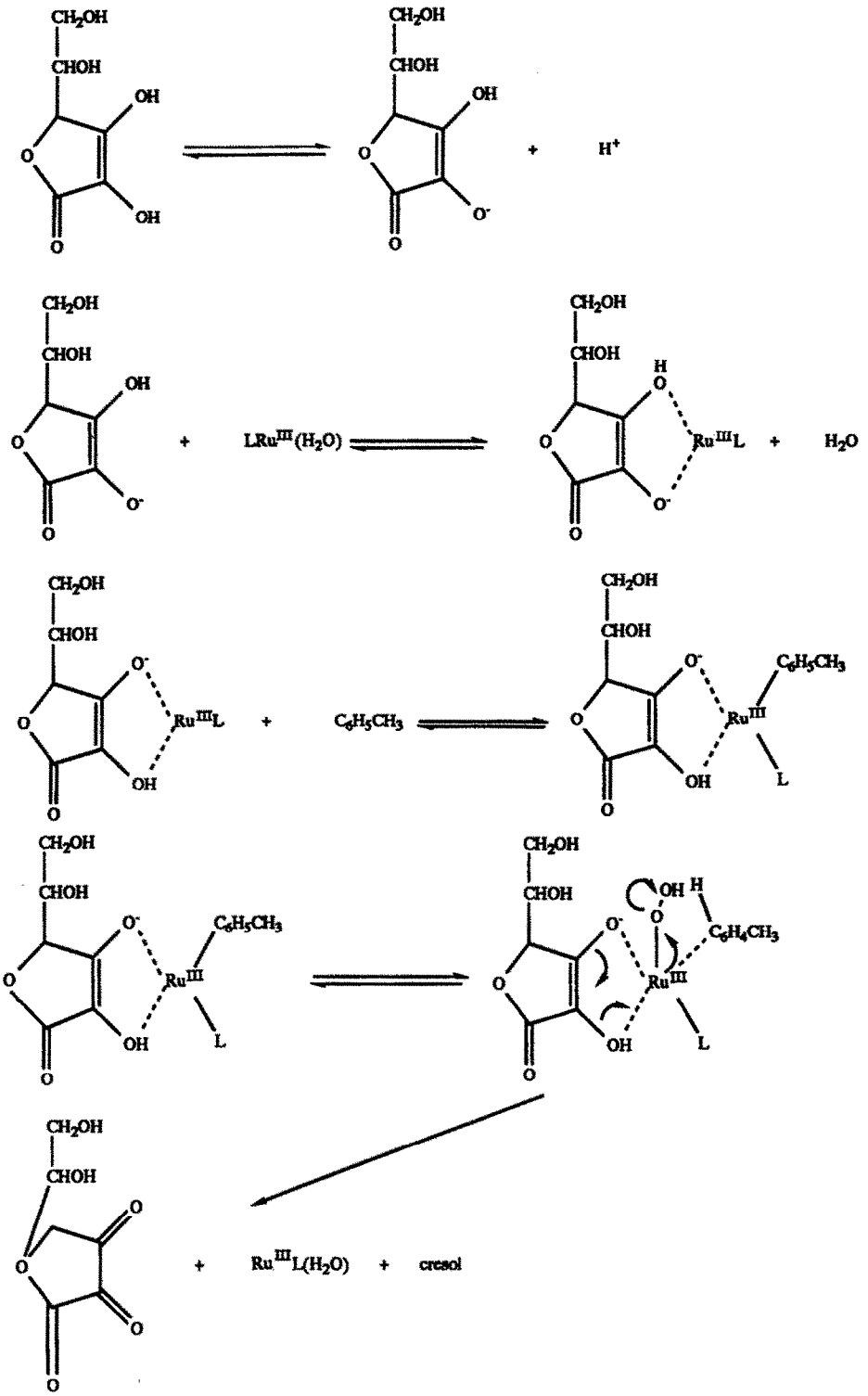


Fig. 23. Proposed mechanism for ruthenium analogue of the Udenfriend system.

Catalysis of oxidation of ascorbic acid by other oxidizing agents

Peroxodisulphate is readily reduced by ascorbic acid[130] and the reaction is efficiently catalysed by copper(II) ions.[131] The suggested mechanism involves a chain reaction with a redox cycle of copper(I) and copper(II) with the production of sulphate radicals (see Scheme 21).

$$X + Cu^{2+} \rightleftharpoons Cu^{+} + X^{\cdot +}$$

$$(X = H_2A + HA^{-})$$

$$S_2O_8^{2-} + Cu^{+} \longrightarrow Cu^{2+} + SO_4^{\cdot -} + SO_4^{2-}$$

$$Cu^{+} + SO_4^{\cdot -} \longrightarrow Cu^{2+} + SO_4^{2-}$$

$$Cu^{+} + X^{\cdot +} \longrightarrow Cu^{+} + A + H^{+}$$

$$X^{\cdot +} + SO_4^{\cdot -} \longrightarrow SO_4^{2+} + A + H^{+}$$

Scheme 21.

The catalysis of the reaction between ascorbic acid and peroxodiphosphate in acetate buffers has also been the subject of a recent study.[144] In this work, the authors conclude that for this reaction there is essentially no uncatalysed path and that if any reaction occurs it is due to the presence of traces of copper(II) or other metal ions in the reagents or the solvent used. They concluded that the rate law for the reaction is shown in eq. (22).

$$\text{Rate} = \frac{[H_2A]_T[Cu^{II}](k_1[H^+] + k_2K_a^{\,1} + k_3K_a^{\,2}/[H^+])}{(K_a^{\,1} + [H^+])}; \tag{22}$$

where:

$$Cu^{II} + H_2A \longrightarrow \text{products} \qquad k_1$$

$$Cu^{II} + HA^{-} \longrightarrow \text{products} \qquad k_2$$

$$Cu^{II} + A^{2-} \longrightarrow \text{products} \qquad k_3.$$

$K_a^{\,1}$ and $K_a^{\,2}$ are the acid dissociation constants of ascorbic acid and $k_1 = 27$, $k_2 = 1.2 \times 10^3$ and $k_3 = 1.1 \times 10^{10}$.

Ascorbic acid has been shown to reduce aquacobalt(III) ions[60] and some other cobalt(III) complexes such as tris(oxalato)cobaltate(III) ions.[63] Kimura *et al.* noted that the reduction of the oxalato complex was catalysed by copper(II) ions. It was subsequently found[132] that the reduction of a number of other cobalt(III) complexes by ascorbic acid is also catalysed by copper(II). The catalysis of the reaction of ascorbic acid with tris(oxalato)cobaltate(III) by copper(II) was studied by Davies.[23] The kinetics of the reaction proved to be approximately first order in the complex. The dependence of the rate on ascorbic acid reached a limiting value and there was a linear dependence on copper(II) concentration. In common with many copper(II) catalysed reactions of ascorbic acid there was a linear relationship with the reciprocal of the observed pseudo first order rate constant and hydrogen ion concentration. The mechanism proposed involved pre-equilibria in which complexes of copper(II) and ascorbic acid and ascorbate ions were formed. Subsequent experiments, however, suggest that the formation of a copper(II) ascorbic acid complex is unlikely. The mechanism also involved the inner sphere electron transfer from ascorbic acid to cobalt(III) via a complex formed between the tris(oxalato)cobaltate(III) and the copper(II)-ascorbate moiety.

The ruthenium(III)-EDTA complex discussed in the previous section has also been found to catalyse the oxidation of ascorbic acid by hydrogen peroxide.[133] This is rather similar to the catalysis of the dioxygen reaction in that this, too, has kinetics which are independent of the concentration of hydrogen peroxide. Once more the rate determining step is considered to be the formation of the $[Ru^{II}L]^{2-}$ ion.

The reaction of $Cr^{IV}(dien)(O_2)_2$ with ascorbic acid (where dien = diethylenetriamine) is slow, but is catalysed by copper(II), vanadium(IV) and vanadium(V).[32] The stoichiometry of 5:2 for $H_2A:Cr^{IV}$ indicates that both chromium(IV) and peroxo ligands are reduced in the reaction. The

kinetics of the reactions show that a limiting rate is produced with increasing ascorbic acid concentration. The mechanism proposed for the copper ion catalysed reaction is shown in Scheme 22.

$$H_2A \rightleftharpoons H^+ + HA^- \qquad K_a = 9.8\times10^{-5}\,M$$

$$Cu^{2+}(aq) + HA^- \rightleftharpoons [Cu^{II}(HA)]^+ \qquad K_L = 3\times10^{2}\,M^{-1}$$

$$[Cu^{II}(HA)]^+ + H_2O \rightleftharpoons [Cu^{II}(HA)(OH)] + H^+ \qquad K'_a = 4\times10^{-5}\,M$$

$$[Cu^{II}(HA)(OH)] + [Cr^{IV}(O_2)] \longrightarrow Cu^{II} + A^{-\cdot} + [Cr^{III}(O_2)_2]^- + H_2O \qquad k = 8\times10^{2}\,M^{-1}s^{-1}$$

$$A^{-\cdot} + Cr^{IV}(O_2)_2 \longrightarrow A + [Cr^{III}(O_2)_2]^- \qquad \text{Fast}$$

$$[Cr^{III}(O_2)_2]^- + 4H_2A + 8H^+ \longrightarrow 2Cr^{III} + 8H_2O + 4A \qquad \text{Fast}$$

Scheme 22.

The rate law corresponding to this is then that given in eq. (23).

$$\text{Rate} = \frac{k[Cr^{IV}][Cu]_T[H_2A]_T K_a K_1 K'_a}{(K'_a + [H^+])(K_L K_a [H_2A]_T) + [H^+](H^+ + K_a)}. \tag{23}$$

As can be seen from the above scheme, the catalytically active species is $[Cu^{II}(HA)(OH)]$. Catalysis by the two vanadium species occurs by a similar process (see Scheme 23).

$$2VO_2^+ + H_2A + 2H^+ \longrightarrow 2VO^{2+} + A + 2H_2O \qquad k = 1.0\times10^{2}\,M^{-1}s^{-1}$$

$$VO^{2+} + HA^- \rightleftharpoons [VO(HA)]^+ \qquad K_L = 4\times10^{2}\,M^{-1}$$

$$VO^{2+} + OAc^- \rightleftharpoons [VO(OAc)]^+ \qquad K_{Ac} = 9\,M^{-1}$$

$$[VO(HA)]^+ + Cr^{IV}(O_2)_2 \longrightarrow VO^{2+} + A^{-\cdot} + [Cr^{III}(O_2)_2]^- + H^+ \qquad k = 9.8\times10^{2}\,M^{-1}s^{-1}$$

Scheme 23.

Acetate provides inhibition of rate. The rapid reactions which follow the above are similar to those of the copper catalysis described earlier.

It is suggested that the appearance of acetate and ascorbate in the coordination sphere of the product is due to a transient Cr^{III}---O species which is rapidly converted to a labile Cr^{IV}---OH species.

Ghosh and Gould have also studied the catalysis by iron(III) and iron(II) of the reduction of $[Cr^{IV}(dien)(O_2)_2]$ by ascorbic acid. As for Cu and VO^+, the stoichiometry of the reaction of the $H_2A : Cr^{IV}$ is 5 : 2 and both Cr^{IV} and O_2^{2-} are reduced. Again, the products contain ascorbate bound to chromium(III) and at high concentrations of acetate ions, acetate is also bound to chromium(III) in the products. The reaction is catalysed by iron(III) and iron(II) whether or not EDTA is present, though it is slower in the presence of EDTA. The reaction of iron(III) with ascorbate in this system is observed to be biphasic, with the interesting result that the rate of formation of the ascorbate-iron(III) complex is less than that of the electron transfer process which results in the destruction of the complex. It is also interesting that the complex formed in the catalytic system is not the same as that formed in the iron(III)-ascorbate system. It is suggested that in this catalytic system, a monoligated complex is the catalytically active species. The steps involved in the reaction are proposed to be those in Scheme 24.

$$Fe^{II} + [Cr^{IV}(O_2)_2] \longrightarrow Fe^{III} + [Cr^{III}(O_2)_2]^- \qquad k = 4\times10^{3}\,M^{-1}s^{-1}$$

$$Fe^{III} + HA^- \rightleftharpoons [Fe^{III}(HA)]^{2+} \qquad K = 5\times10^{3}\,M^{-1}$$

$$[Fe(HA)]^{2+} + [Cr^{IV}(O_2)_2] \longrightarrow Fe^{III} + HA^{\cdot} + [Cr^{III}(O_2)_2]^- \qquad k = 1.5\times10^{3}\,M^{-1}s^{-1}$$

$$HA^{\cdot} + [Cr^{IV}(O_2)_2] \longrightarrow A + [Cr(O_2)_2]^- + H^+ \qquad \text{Fast}$$

$$[Cr^{III}(O_2)_2]^- + 2H_2A + 4H^+ \longrightarrow Cr^{III} + 4H_2O + 2A \qquad \text{Fast}$$

Scheme 24.

The first step contributes only to the early seconds of the reaction. In the presence of EDTA, the reaction is zero order in the chromium(IV) complex. The rate law is given in eq. (24).

$$-\frac{d[Cr^{IV}]}{dt} = \frac{kK[H_2A][Fe]}{(1+K[H_2A])}. \tag{24}$$

The sequence of reactions shown in Scheme 25 is believed to be operating.

$$Fe^{III}EDTA + HA^- \rightleftharpoons Fe^{III}(EDTA)(HA^-) \qquad K = 88\,M^{-1}$$
$$Fe^{III}(EDTA)(HA^-) \longrightarrow Fe^{II}(EDTA) + HA^{\cdot} \qquad k = 43\,s^{-1}$$
$$HA^{\cdot} + Cr^{IV}(O_2)_2 \longrightarrow Cr^{III}(O_2)_2 + A + H^+ \qquad \text{Fast}$$
$$Fe^{III}(EDTA) + Cr^{IV}(O_2)_2 \longrightarrow Cr^{III}(O_2)_2 + Fe^{III}(EDTA) \qquad \text{Fast}$$

Scheme 25.

Acknowledgements—The author would like to thank Mrs Margaret Haw for her extensive help with the manuscript preparation and Mr Peter Hague for technical assistance.

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