Comparative study of oxidation by chromium(v) and chromium(vi) †

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The kinetics and mechanism of the oxidation of 2-deoxy-D-glucose (dGlc) by Cr^{VI} which yields 2-deoxy-D-gluconic acid and Cr^{III} as final products when a ten-fold or higher excess of sugar over Cr^{VI} is used, have been studied. The redox reactions occur through $Cr^{VI} \longrightarrow Cr^{IV} \longrightarrow Cr^{III}$ and $Cr^{VI} \longrightarrow Cr^{V} \longrightarrow Cr^{III}$ paths. The experimental data were fitted with a multilinear regression program. The complete rate law for the chromium(vi) oxidation reaction is expressed by $-d[Cr^{VI}]/dt = \{c[H^+] + (d + e[H^+] + f[H^+]^2) [dGlc]\}[Cr^{VI}]$, where $c = (5 \pm 1) \times 10^{-4} \, dm^3 \, mol^{-1} \, s^{-1}$, $d = (3 \pm 2) \times 10^{-4} \, dm^3 \, mol^{-1} \, s^{-1}$, $e = (115 \pm 13) \times 10^{-4} \, dm^6 \, mol^{-2} \, s^{-1}$ and $f = (402 \pm 17) \times 10^{-4} \, dm^9 \, mol^{-3} \, s^{-1}$, at 50 °C. Chromium(v) is formed in a rapid step by reaction of the radical dGlc and Cr^{VI} and Cr^{V} reacts with dGlc faster than does Cr^{VI}. The chromium(v) oxidation of dGlc follows the rate law $-dCr^{V}/dt = (k_1 + k_2[H^+])[dGlc][Cr^{V}]$, where $k_1 = 2.52 \times 10^{-4} \, dm^3 \, mol^{-1} \, s^{-1}$ and $k_2 = 54.0 \, dm^6 \, mol^{-2} \, s^{-1}$, at 25 °C. The EPR spectra show that three 1:1 Cr^{V}:dGlc intermediate complexes $(g_1 = 1.9781, g_2 = 1.9752, g_3 = 1.9758)$ are formed in rapid pre-equilibria before the redox steps.

Hexavalent chromium, in many different compounds, is a well established carcinogen and mutagen.[2-5] There is, therefore, appreciable interest in determining the mode of action of chromium species derived from initial chromium(vi) compounds taken into the body.[6] Until now, the major co-ordination sites involved in chromium binding in natural systems have been found to be hydroxyl and thiol donors, which form stable esters with chromate and stabilize chromium(v) intermediates after further interaction with biological reductants.[7-11] For this reason, some sugars, or their derivatives, may play an important role in the chemistry of Cr^{VI}, especially in the environment.[12] Besides, the observation of chromium(v) intermediates in the selective oxidation of organic substrates by Cr^{VI} and the implication of Cr^{V} in the mechanism of Cr-induced cancers has generated a considerable amount of interest in its chemistry[13-16] and biochemistry.[17,18] We are studying the possible fate of Cr^{VI} and Cr^{V} in biological systems by examining reactions of Cr^{VI} with low-molecular-weight biological and model reductants, as a means of more fully understanding the processes involved in the genotoxicity of chromium.

In previous work we have found that the number and arrangement of hydroxyl groups in polyhydroxylic molecules affect the oxidation rate of Cr^{V}.[19-24] In any case the first reaction step involves the formation of a chromium(vi) ester which is followed by the slow redox steps with C(1)OH and C(2)OH being the preferred co-ordination sites in the electron-transfer precursor. For aldoses,[19] 2-acetamidoaldoses[23] and 2-amino-aldoses[24] the formation of this precursor has been interpreted as a rapid pre-equilibrium, with the kinetics showing typical saturation curves for aldoses and 2-aminoaldoses. On the other hand, 2-deoxy-D-glucose (dGlc) with no hydroxyl group at C(2)

forms with Cr^{VI} a precursor ester which behaves as a steady state.[1] In this paper we propose a more complete mechanism to explain the kinetic behaviour of Cr^{VI} in this particular system and show that, in the steps corresponding to the chromium(v) oxidation of dGlc, three chromium(v) intermediates are formed in rapid pre-equilibria before the slow redox steps take place. The evidence presented here indicates the stabilization of these intermediates at pH 5–7.

Experimental

Materials

2-Deoxy-D-glucose (Sigma grade), potassium dichromate (BDH), sodium perchlorate (Fluka grade) and perchloric acid (G.R., E. Merck) were used without further purification. Aqueous solutions were prepared in doubly distilled water.

Spectrophotometric measurements

Kinetic measurements were made at 350 nm by monitoring the absorbance changes on a Guilford Response II spectrophotometer with fully thermostatted cell compartments. The observed pseudo-first-order rate constants (k_{obs}) were determined from the linear part of plots of $\ln(A_{350})$ vs. time. The formation of Cr^{III} was monitored at 570 nm (and/or 410 nm). At the end of the reaction the two d–d bands ascribed to Cr^{III} were observed at $\lambda_{max} = 408$ ($\varepsilon = 22.6$) and 572 nm ($\varepsilon = 17.1 \, dm^3 \, mol^{-1} \, cm^{-1}$). The band at 408 nm changed with time and shifted towards shorter wavelengths (391 nm) showing higher intensities ($\varepsilon = 29.3 \, dm^3 \, mol^{-1} \, cm^{-1}$), as a consequence of the complexation of Cr^{III} by the oxidation product: 2-deoxy-D-gluconic acid (dGlca).[21] Under the same conditions, solutions of chromium(iii) or Cr^{III}–dGlc (1:2) showed bands at 409 ($\varepsilon = 19.7$) and 576 nm ($\varepsilon = 15.0 \, dm^3 \, mol^{-1} \, cm^{-1}$). The identification of dGlca as the only reaction product under any of the conditions used here has been made as previously described.[1]

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† Chromic oxidation of 2-deoxy-D-glucose. Part 2.[1]
Non-SI unit employed: G $= 10^{-4}$ T.

Free radical detection

A solution of potassium dichromate (1.0 cm^3, 1.0 mol dm^{-3}) in 0.5 mol dm^{-3} HClO$_4$ was added to a mixture of dGlc (1.0 cm^3, 0.6 mol dm^{-3}) in 1 mol dm^{-3} HClO$_4$ and acrylonitrile (1.0 cm^3) at 50 °C. After 30 min a white precipitate appeared. Control experiments (without dGlc or oxidant present) did not show the formation of a precipitate.

EPR measurements

The EPR spectra were obtained on a Bruker ESP 300 E spectrometer. The microwave frequency was generated with a Bruker 04 ER (9–10 GHz) and measured with a Racal-Dana frequency meter. The magnetic field was measured with a Bruker NMR-probe gaussmeter. A Bruker liquid-nitrogen cryostat was used for measurements between 80 K and room temperature.

Results and Discussion

Chromium(VI) oxidation of dGlc

Values of the pseudo-first-order rate constants (k_{obs}) for several aldose and perchloric acid concentrations are summarized in Table 1. Plots of k_{obs} vs. [dGlc], in the proton concentration range studied, are shown in Fig. 1. From these plots the following observations may be made.

The dependence of the rate constant k_{obs} on [dGlc] is linear, with a positive intercept [equation (1)]. The intercepts depend

$$k_{obs} = a + b[\text{dGlc}] \qquad (1)$$

on [H$^+$] and this dependence, defined as k_{obs}([dGlc] = 0) = f([H$^+$]), is also linear [equation (2)]. The slopes $b =$

$$a = c[\text{H}^+] \qquad (2)$$

dk_{obs}/d[dGlc] vary with [H$^+$] (Fig. 2) according to the quadratic expression (3). Substituting for a and b in equation (1), the complete rate law (4) is obtained.

$$b = d + e[\text{H}^+] + f[\text{H}^+]^2 \qquad (3)$$

$$v = -\text{d}[\text{Cr}^{VI}]/\text{d}t = k_{obs}[\text{Cr}^{VI}] = \{c[\text{H}^+] + (d + e[\text{H}^+] + f[\text{H}^+]^2)[\text{dGlc}]\}[\text{Cr}^{VI}] \qquad (4)$$

We have studied this system previously[1] with a much more restricted approach. For instance, we neglected the term independent of the organic substrate, a criterion adopted as a consequence of the negative values found in certain cases for the y-axis intercept. So, we supposed that the term had to be null. A more detailed examination of the data shows that this is not the case and that the mechanism is more complicated than that supposed previously. In order to minimize errors we thought that if we worked with the whole set of data simultaneously we could obtain the value of the term independent of the substrate. To do this, on the basis of a multilinear regression program,[25] a program was developed to fit a function of several variables. In practice, this program permits us to adjust parameters common to several experiments made under different conditions (e.g. acidity or temperature).

In a first approach to obtain values of c–f k_{obs} was fitted against [dGlc] (or [H$^+$]) at fixed [H$^+$] (or [dGlc]). Parameters obtained in this way were used as starting values for adjustment of k_{obs} using the multilinear regression program. Thus, this method of calculation enabled us to obtain c–f as global rate constants from the whole experimental data set. The values $c = (5 \pm 1) \times 10^{-4}$ dm^3 mol^{-1} s^{-1}, $d = (3 \pm 2) \times 10^{-4}$ dm^3 mol^{-1} s^{-1}, $e = (115 \pm 13) \times 10^{-4}$ dm^6 mol^{-2} s^{-1} and $f = (402 \pm 17) \times 10^{-4}$ dm^9 mol^{-3} s^{-1} were used to find k_{calc} in Table 1 which is in excellent agreement with the experimental k_{obs} over the whole range of concentrations used.
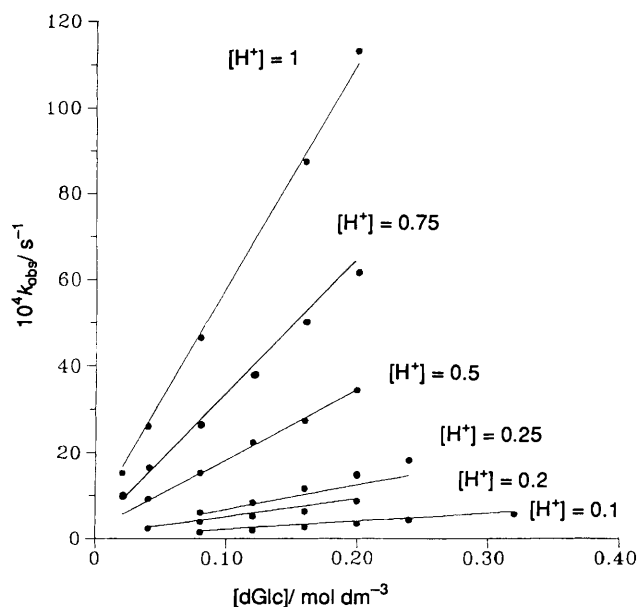

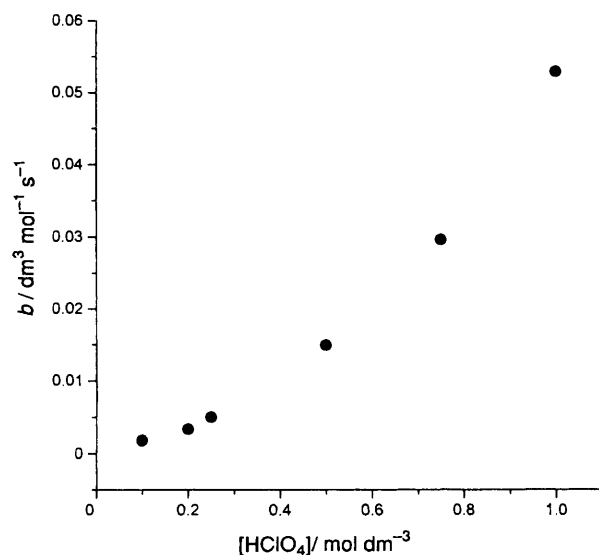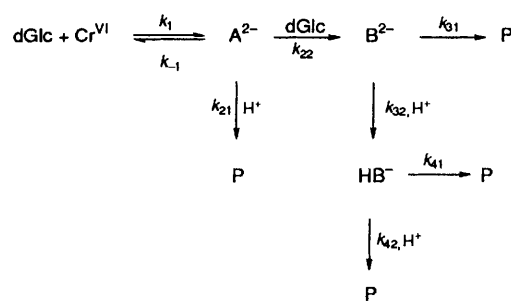Fig. 1 Effect of [dGlc] on k_{obs} at 50 °C and $I = 1$ mol dm^{-3}

Fig. 2 Effect of [HClO$_4$] on the slope b at 50 °C and $I = 1$ mol dm^{-3}

According to all the experimental data, the oxidation of dGlc by Cr^{VI} should occur through four parallel slow steps leading to the redox products. A mechanism taking account of this and explaining the extremely slow reaction at higher pH is proposed in Scheme 1. In the pH range studied, Cr^{VI} exists mainly as Cr$_2$O$_7$$^{2-}$.[26] Thus, the first step of the proposed mechanism may be interpreted as the formation of a monochelate with dGlc acting as a monodentate ligand bound to Cr^{VI} at the anomeric hydroxyl group to yield the anionic species A^{2-}. This

Scheme 1 A^{2-} = [(dGlcH$_{-1}$)O$_2$(H$_2$O)(OH)CrOCrO$_3$]$^{2-}$, B^{2-} = [(dGlcH$_{-1}$)$_2$O$_2$(H$_2$O)CrOCrO$_3$]$^{2-}$, P = Cr^{IV} + dGlca

intermediate may decompose directly to the products through an acid-catalysed step or gives B^{2-} $\{[Cr_2O_7H_2(dGlc)_2]^{2-}\}$ in the presence of a second dGlc molecule. This second intermediate B^{2-} yields the redox products directly or after being mono- or di-protonated.

If A^{2-} behaves as a steady state, the rate law corresponding to this mechanism may be expressed as in equation (5). If

$$-d[Cr^{VI}]/dt = k_{obs}[Cr^{VI}] = \{(k_{21}[H^+] + k_{31}k_{22}[dGlc] +$$
$$k_{41}k_{32}k_{22}[dGlc][H^+] + k_{42}k_{32}k_{22}[H^+]^2[dGlc]k_1[dGlc] \times$$
$$[Cr^{VI}]\}/\{k_{-1} + k_{21}[H^+] + k_{22}[dGlc]\} \quad (5)$$

$k_{22}[dGlc] \gg k_{-1} + k_{21}[H^+]$, equation (5) can be simplified to the experimentally observed form (6). Relative values of the

$$v = \{(k_1k_{21}/k_{22})[H^+] + k_1k_{31}[dGlc] +$$
$$k_1k_{32}k_{41}[H^+][dGlc] + k_1k_{32}k_{42}[H^+]^2[dGlc]\}[Cr^{VI}] \quad (6)$$

products of the kinetic parameters demonstrate that the acid-catalysed paths yielding the redox products through B^{2-} are 40 and 130 times faster than the only non acid-catalysed step, which explains the very slow reaction at neutral pH. Another important point in this mechanism is that intermediates A^{2-} or B^{2-} should correspond to species where dGlc binds Cr^{VI} weakly, in accordance with no spectrophotometric indication of ester formation. This is explained if dGlc binds Cr^{VI} at the anomeric hydroxyl group only to form the chromium(VI) intermediate precursor of the redox steps.

After the slow steps, reactions (7)–(9) may take place.

$$dGlc + Cr^{IV} \longrightarrow dGlc^{\bullet} + Cr^{III} \quad (7)$$

$$dGlc^{\bullet} + Cr^{VI} \longrightarrow dGlca + Cr^{V} \quad (8)$$

$$dGlc + Cr^{V} \longrightarrow dGlca + Cr^{III} \quad (9)$$

Chromium(IV) formed in the slow steps yields the final Cr^{III} and the radical dGlc$^{\bullet}$ in subsequent fast step. Thus, Cr^{V} formed by rapid reaction of the radical and Cr^{VI} can further oxidize dGlc as will now be discussed. The radical formation is supported by the observed polymerization after addition of acrylonitrile.

Chromium(v) oxidation of dGlc

The reaction of $K_2Cr_2O_7$ (0.075 mol dm^{-3}) with dGlc ($\geqslant 0.75$ mol dm^{-3}) in $HClO_4$ and 25 °C resulted in the formation of a relatively long-lived chromium(v) species (Fig. 3). As the ratio of dGlc : Cr^{VI} increased, the relative intensity of the two chromium(v) signals, at $g_1 = 1.9781$ and $g_{2(av)} = 1.9754$ at every pH employed, was approximately constant. At a ratio of 10 : 1 the total amount of Cr^{V} observed reached a maximum concentration at $t < 3$ min at any pH and slowly decayed with time. At pH < 1.6 no significant Cr^{V} was detected 24 h after the start of the reaction, when a 10 : 1 ratio was used. On the other hand, in the range pH 3–7, Cr^{V} remained in the solution after

several days. At low temperature (100 K) the chromium(v) spectral lines broadened (50 G) and collapsed to one signal with axial geometry $g_\| = 1.9930$ and $g_\perp = 2.0042$ [Fig. 4(a)]. The ultimate fate of the chromium in these reactions is a chromium(III) species. Fig. 4(b) shows the typical broad EPR signal ($g = 1.9826$) observed at later times at 100 K in these reactions.

Our EPR spectroscopic studies on the oxidation of dGlc by Cr^{VI} indicate that at least two chromium(v) complexes ($g_1 = 1.9781$ and $g_2 = 1.9754$) form and decay with the same rate constants. At higher pH, but at any [dGlc] : [Cr^{VI}]$_0$ ratio, the single chromium(v) EPR signal at $g_{2(av)} = 1.9754$ is replaced by two partially overlapping peaks at $g_2 = 1.9758$ and $g_3 = 1.9752$ (the signals were deconvoluted numerically by fitting of spectra by Lorentzian derivatives). Fig. 3 shows the spectra of the species formed in the reaction mixtures at different pH together with the simulated spectra (the second signal being simulated with different component ratios). The time course of the peak-to-peak height of the first derivative of the signals as a function of time for an initial ratio dGlc : Cr$^V = 10 : 1$
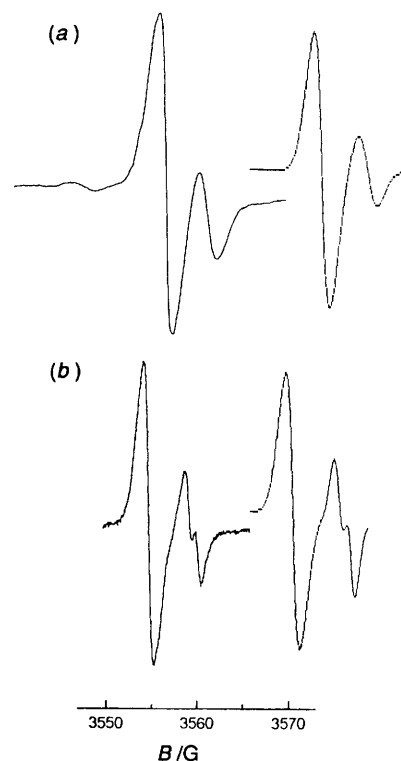

Fig. 3 Typical X-band EPR signal of a mixture of dGlc and Cr^{VI} (10 : 1 mole ratio) in HClO$_4$ at (a) pH 4, 12 min after mixing, (b) pH 7, 4 min after mixing, and the corresponding simulated spectra (linewidth = 1.2 G); 25 °C, gain = 8 × 10^5, modulation amplitude = 1.6 G, centre field = 3555 G, frequency = 9.85 GHz

Table 1 Calculated and observed pseudo-first-order rate constants ($10^4\ k/\text{s}^{-1}$)

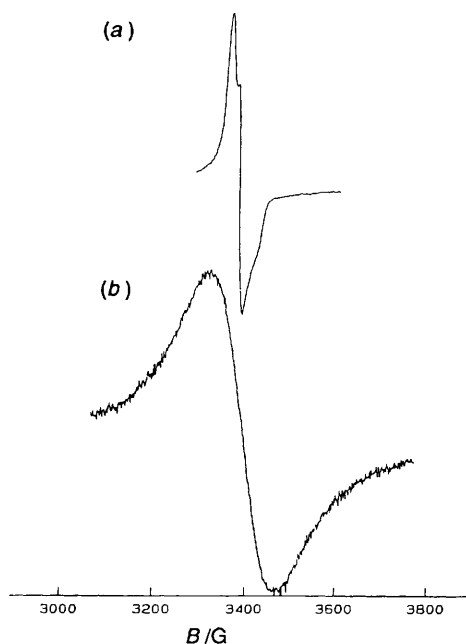| [dGlc]/mol dm^{-3} | [HClO$_4$]/mol dm^{-3} | | | | | | | | | | | | |
| | 0.10 | | 0.20 | | 0.25 | | 0.50 | | 0.75 | | 1.00 | |
	k_{calc}	k_{obs}	k_{calc}	k_{obs}	k_{calc}	k_{obs}	k_{calc}	k_{obs}	k_{calc}	k_{obs}	k_{calc}	k_{obs}
0.02	—	—	—	—	—	—	5.59	6.33	9.87	10.5	15.2	15.3
0.04	—	—	2.62	2.43	—	—	8.80	9.25	16.2	16.9	25.6	26.1
0.08	1.93	1.45	4.29	3.88	5.71	6.03	15.2	15.3	28.8	27.0	46.4	46.5
0.12	2.66	1.92	5.96	5.18	7.98	8.37	21.7	22.4	41.4	38.3	—	—
0.16	3.39	2.65	7.63	6.36	10.2	11.7	28.1	27.4	54.0	50.9	87.9	87.5
0.20	4.12	3.45	9.30	8.76	12.5	15.0	34.5	34.4	66.6	62.3	109	113
0.24	4.85	4.35	—	—	14.8	18.2	—	—	—	—	—	—
0.32	6.31	5.63	—	—	—	—	—	—	—	—	—	—

Fig 4. (*a*) X-band EPR signal of a frozen solution (100 K) of a mixture of dGlc and Cr^{VI} at pH 7. Gain = 5×10^4, modulation amplitude = 5.05 G, centre field = 3400 G, frequency = 9.43 GHz. (*b*) Room-temperature final X-band EPR spectrum. Gain = 2×10^4, modulation amplitude = 6.4 G, centre field = 3400 G, frequency = 9.42 GHz

at different pH shows that the two (three) signals decay at comparable rates; therefore, these chromium(v) intermediates are in rapid equilibrium compared to the time-scale of their subsequent reduction to Cr^{III}. Even though all the signals decay at the same rate at each pH, this rate increases with decreasing pH, indicating that proton catalysis is also present in the oxidation of the sugar by Cr^{V}. Since the only oxidation product is 2-deoxy-D-gluconic acid, the intramolecular electron transfer must take place within a complex where the ligand is co-ordinated *via* the anomeric hydroxyl group.

We quantified the rate of disappearance of Cr^{V} from the peak-to-peak heights (and/or areas) of the EPR signals as a function of time. Values of the pseudo-first-order rate constant (k^{V}) for disappearance of Cr^{V} at four different pH values are given in Table 2. Experiments performed at constant $[H^+]$ and $[Cr^{VI}]_0$, showed a first-order dependence on [dGlc], $k^{V}/[dGlc] = k = f([H^+])$. Thus, the proton dependence could be estimated from plots of $k^{V}/[dGlc]$ *vs.* $[H^+]$. This approach gave a kinetic dependence of the type $f([H^+]) = k^{V}/[dGlc] = k_1 + k_2[H^+] = 2.52 \times 10^{-4} + 54.0[H^+]$, and the total kinetic law for the oxidation of dGlc by Cr^{V} may be expressed as $-d[Cr^{V}]/dt = k^{V}[Cr^{V}] = (2.52 \times 10^{-4} + 54.0[H^+])[dGlc]-[Cr^{V}]$. This means that the chromium(v) intermediates in rapid equilibrium decay to the products directly or through an acid-catalysed step. Since the latter is much faster than the non-catalysed step at high $[H^+]$, the oxidation occurs mainly through the acid-catalysed path, which explains why we could not observe the chromium(v) signal in the proton concentration range used in the kinetic study to determine the chromium(vi) kinetic law. Another important fact is that the relative intensities of the two main signals are independent of pH and, when the third signal appears, the relative areas of the signals at $g_1 = 1.9781$ and $g_{2(av)} = 1.9754$ remain the same: 2.6 (g_1/g_2 ratio). Thus, the equilibrium involving protons should constitute the minor complex and its deprotonated form.

What are the structures of these chromium(v) species? The chromium(v) EPR signal has been shown to be sensitive to co-ordination.[27] The $g_{iso} = 1.9781$ value in this work is typical of five-co-ordinate oxochromate(v) complexes and is significantly larger than the values observed for six-co-ordinated oxo-chromate(v) complexes.[28] Five-co-ordination has also been

Table 2 Observed rate constants for the reduction of Cr^{V} by dGlc

pH	$10^4 k^{V}$ (s⁻¹)
3.0	408
4.0	42.4
5.2	3.59
6.7	2.78

The same values were obtained by using an equation taking into account either both the growth and decay or only the decay of Cr^{V}. $T = 25\ °C$; $[Cr^{VI}]_0 = 0.075$, [dGlc] = 0.75 mol dm⁻³.
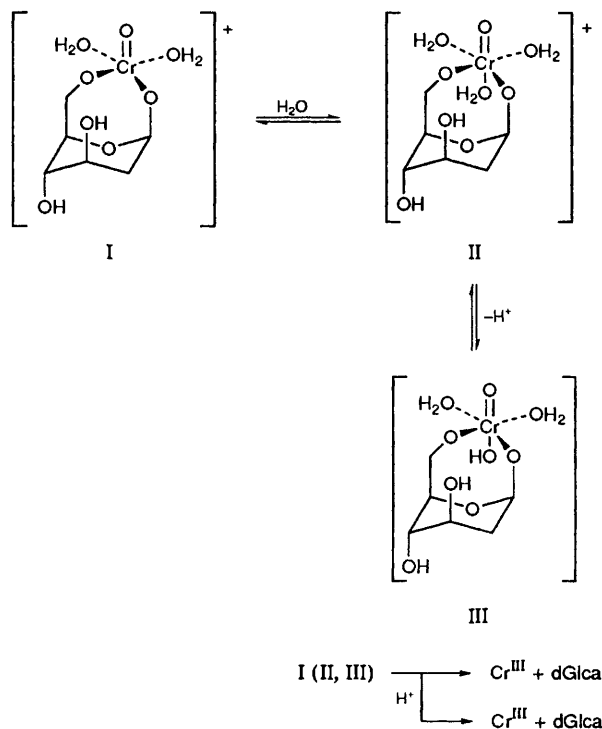
Scheme 2

confirmed in the crystal structure of an isolated complex.[29] For the six-co-ordinate oxochromate species it has been proposed that the sixth position is occupied by a molecule of the solvent yielding $[CrOL_2(OH_2)]$ where L is a bidentate alkoxide ligand, and the proportion of the aqua complex with respect to $[CrOL_2]$ seems to increase with increasing ability of the solvent (solv) to act as a ligand.[30] The g value for these six-co-ordinate oxochromate(v) complexes varies between 1.9702 and 1.9714. A signal found at $g = 1.9755$ has been assigned to $[CrO(L)(solv)_3]$.[27] Thus, in the present work, the three complexes involved in the rapid equilibrium preceding the redox steps, could be of the form $[CrO(dGlcH_{-2})(H_2O)_2]^+$ **I** ($g_1 = 1.9781$), $[CrO(dGlcH_{-2})(H_2O)_3]^+$ **II** ($g_2 = 1.9752$) and its deprotonated form $[CrO(dGlcH_{-2})(H_2O)_2(OH)]$ **III** ($g_3 = 1.9758$), with dGlc acting as bidentate ligand. In aqueous media it had been observed that a change from H_2O to OH^- as the sixth ligand only shifts the g_{iso} value by about 0.0006 unit,[27] as observed in the present case.

The lack of a resolved superhyperfine pattern from the protons prevented a more detailed analysis of the spectra. This fact has been attributed to rapid Berry twists present in five-co-ordinate chromium(v) complexes which render all the protons equivalent on the EPR time-scale.[31] Spectra in frozen solutions do not resolve the coupling [Fig. 4(*a*)] because it is obliterated by the broad signals observed in the glass at liquid-nitrogen temperatures.

Thus, considering all the above observations, a mechanism for the oxidation of dGlc by Cr^{V} can be written as in Scheme 2.

We propose that Cr^V formed in the fast step (8) reacts with dGlc to yield three intermediate chromium(v) complexes. In all of them the Cr^V:dGlc ratio is 1:1 as deduced from the first-order kinetic law for both Cr^V and dGlc. We propose that in all three species dGlc binds Cr^V at the C(1)OH and C(6)OH hydroxyl groups, but co-ordination through C(3)OH and C(1)OH may not be disregarded. The important point here is that at least two alkoxy groups are implied in the binding in accordance with the observed g_{iso} values. Since the only reaction product is dGlca the electron transfer should occur within the complex(es) with dGlc bound to Cr^V at the anomeric hydroxyl group. This suggests the β anomer of dGlc is the reactive species because it favours the dGlc–Cr^V binary complex with dGlc acting as a bidentate ligand, while the α anomer should bind Cr^V at C(1)OH only. Complexes **II** and **III** afford the minor EPR signal and they are proposed to be species in which a water molecule occupies the sixth position of **I** in equilibrium with its deprotonated form, the last being better observed at higher pH.

All the kinetic observations confirm the mechanism in Scheme 2. At any pH, we could observe the decay of Cr^V only, *i.e.* Cr^V is formed faster than it decays. This implies that the rate-determining step must involve reduction of Cr^{VI} to Cr^{IV} and that Cr^V has to form in a subsequent rapid step, as supposed from the chromium(vi) decay data.

Another interesting fact which supports our previous discussion is that, under the same experimental conditions, aldoses form more 'stable' chromium(v) complexes than does dGlc.[19] This relative 'stability' of the chromium(v) complexes is related to the presence of the C(2)OH in the aldoses which favours the formation of a five-membered ring species. We have observed that the C(6)OH affects the $k_{ox}/K_{complexation}$ ratio in the chromium(vi) oxidation, and differences in the EPR lines of chromium(v) complexes formed with L-rhamnose and D-mannose were attributed to the participation of C(6)OH in the mannose–chromium(v) complex. This supports our hypothesis that C(6)OH, instead of C(3)OH, binds to the chromium.

Acknowledgements

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