

Kinetics of oxidation of some monosaccharides by pyridinium chlorochromate (PCC)[†]

Raj K Dhar[‡]

Indian Institute of Technology, Hauz Khas, New Delhi 110 016

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The oxidation kinetics of glucose, considered as a model compound for reducing sugars, with pyridinium chlorochromate in perchloric acid medium has revealed a linear correlation between the observed rate constant k_{obs} and $[\text{glucose}]$, $[\text{H}^+]$. A comparison of D-glucose oxidation with its various C-1 and C-2 substituted derivatives shows that inductive, steric and shielding effects may all be important which explains the reactivity as 2-deoxy-D-glucose > D-glucose > 1- α -methyl- α -D-glucopyranoside > 2-amino-2-deoxy-D-glucose hydrochloride. A comparison between α and β -anomers of some monosaccharides reveals that β -anomer is oxidised faster than α -anomers. Further, activation energy and thermodynamic parameters have been evaluated for D-glucose oxidation and mechanism consistent with experimental observation is attempted.

In carbohydrate chemistry, D-glucose plays an important role because it is the unit of which starch, cellulose and glycogen are made up. In view of this, studies on oxidation of D-glucose and other monosaccharides have been given a great deal of attention¹⁻¹². Surprisingly, there has been no systematic oxidation studies carried out to examine the effect of substituents on C-1 and C-2 position of D-glucose. Hence, the present study is undertaken. For this oxidation study, PCC as the Cr oxidant was chosen in view of its ease of preparation¹¹, high stability¹² and because of the fact that it is a mild and selective oxidant for a wide range of substrates^{12,13}. Attempt has also been made to compare the oxidation rates of α and β -anomers of some sugars which further substantiates the mechanism of oxidation.

Materials and Methods

Perchloric acid (Merck GR) was used for preparing solutions of different acid concentrations. Deuterium oxide (BARC, India) was of 99.5% purity. All sugars used for kinetic studies were of highest purity grade, procured either from Sigma Chemicals or E. Merck. These were used without further purification after drying *in vacuo* for at least 4 hr and the solutions of these sugars were made always fresh in deionized water, by direct weighing.

Pyridinium chlorochromate (PCC)

Chromium trioxide (100 g, 0.7 mol) was rapidly added with stirring to 6 N hydrochloric acid (184 ml, 1.7 mol). After 5 min the homogeneous solution was cooled to 0°C and pyridine (79.1 g, 1 mol) was carefully added over 15 min. Recooling to 0°C gave a yellow-orange solid which was collected on a sintered glass filter and dried *in vacuo* for 2-3 hr (yield 150.5 g, 78%). UV-visible spectrum of PCC showed λ_{max} at 350 nm in pure water and in acidic medium.

Kinetic measurement

All kinetic measurements were carried out at 350 nm, in a thermostated cell compartment of Pye-Unicam SP-500 or SP-700 spectrophotometer instrument. The rate constants k_0 , k_2 and activation energy (E_a) were obtained using standard programmes of regression analysis by ICL 2960 computer.

Tests for intermediate radicals were carried out through initiation of polymerisation of purified acrylonitrile in a nitrogen atmosphere under typical kinetic conditions for all sugars. No polymerisation was observed.

Product analysis of D-glucose was carried out under typical kinetic conditions. The products were identified by paper chromatography in comparison with the oxidation products of D-glucose by bromine and nitric acid separately¹⁴. A solvent system of 1-butanol-acetic acid-water (4:1:5) was used and detection was carried out with the alkaline silver nitrate. Paper chromatography of the syrup obtained from the oxidation of D-glucose with PCC indicated the presence of gluconic acid. This is in

[†] Dedicated to Prof. Herbert C. Brown on his 80th birthday

[‡] Present address: Chemistry Department, Louisiana State University (LSU) Baton Rouge, La 70808 USA.

Table 1—Values of observed rate constants, $k_0 \times 10^3 \text{ s}^{-1}$, for the oxidation of D-glucose by pyridinium chlorochromate (PCC)
 $I = 1 \text{ mol dm}^{-3}$, $[\text{PCC}] = 1.4 \times 10^{-3} \text{ mol dm}^{-3}$

Temp. (°C)	[D-glucose] $\times 10^2$ mol dm^{-3}	[HClO ₄], mol dm^{-3}			
		0.25	0.50	0.75	1.00
23	2	1.00	3.35	5.05	7.31
	4	2.36	6.08	10.00	19.60
	6	3.80	7.46	13.33	32.80
	8	4.60	9.93	19.10	34.50
	10	5.73	14.50	23.80	46.30
	20	13.60	27.50	40.80	92.50
33.5	2	2.34	6.11	14.80	24.60
	4	5.50	12.50	30.56	48.60
	6	7.26	18.80	43.00	76.00
	8	8.70	26.10	58.31	106.0
	10	9.43	32.10	62.70	117.0
	20	18.20	62.10	126.0	227.0
43.5	2	4.78	10.61	32.60	40.50
	4	9.89	21.20	61.60	82.30
	6	11.90	45.80	108.0	132.0
	8	14.40	48.10	137.0	194.0
	10	17.10	59.90	154.0	247.0
	20	31.50	147.0	266.0	516.0
53.5	2	5.70	—	64.48	86.30
	4	12.70	75.10	98.63	147.0
	6	20.83	88.50	123.2	209.0
	8	25.20	101.5	160.0	290.6
	10	39.90	122.0	247.0	366.4
	20	58.10	250.0	462.0	644.8

Table 2—Bimolecular rate constants $k_2 \times 10^3 (\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1})$ for the oxidation of D-glucose by PCC
 [Ionic strength = 1 mol dm^{-3}]

Temp. (K)	[HClO ₄], mol dm^{-3}			
	0.25	0.50	0.75	1.00
296.15	0.69	1.35	1.98	4.71
306.65	0.83	3.10	6.03	11.15
316.65	1.41	7.53	12.73	26.78
326.65	2.93	10.88	22.96	31.30

agreement with the observation that the aldonic acid invariably remains in equilibrium with corresponding γ and δ -lactones in acidic medium^{14,15}. D-glucose oxidation also indicated the presence of formic acid and arabinose. Formic acid was tested by initially treating the oxidized product with Zn/HCl followed by addition of chromotropic acid which gave positive test for formaldehyde, thus, confirming the presence of formic acid¹⁶. Arabinose was confirmed

Table 3—Values of the activation parameters for the oxidation of D-glucose by PCC at 1 mol dm^{-3} ionic strength

[HClO ₄] (mol dm^{-3})	E_a (kJ mol^{-1})	$\Delta H^\ddagger$ (kJ mol^{-1})	$\Delta S^\ddagger$ (e.u.)	$\Delta G^\ddagger$ (kJ mol^{-1})
0.25	38.14	35.42	-42.74	93.84
0.50	57.26	54.54	-26.14	90.28
0.75	65.07	62.35	-18.96	88.24
1.00	52.90	50.18	-27.24	87.41

rates of oxidation were found to increase with increase in $[\text{H}^+]$, the slopes of the plots of overall bimolecular rate constants, $\log k_2$ versus $\log [\text{H}^+]$ at four by hydrazone formation and co-TLC of the hydrazone¹⁷ with an authentic sample of arabinose.

Results and Discussion

An inspection of the observed rate constants (k_0) shows that the k_0 values rise markedly with increase in [D-glucose] (Table 1). The plots of k_0 against [D-glucose] were linear passing through the origin thereby confirming first order dependence in [D-glucose]. The bimolecular rate constants have been calculated from the slopes of these lines and are given in Table 2 at four different temperatures. The rates of oxidation were found to increase with increase in $[\text{H}^+]$, the slopes of the plots of overall bimolecular rate constants, $\log k_2$ versus $\log [\text{H}^+]$ at four different temperatures were approximately 1, showing thereby first order dependence in [acid]. The order in oxidant is one as revealed by the linearity of $\log (a/a-x)$ versus time plot passing through the origin. These observations lead to the rate law (1):

$$-\frac{d[\text{PCC}]}{dt} = k[\text{D-glucose}][\text{PCC}][\text{H}^+] \quad \dots (1)$$

The oxidation of D-glucose has been carried out at four different temperatures, viz. 296, 306, 316 and 326 K. The activation parameters were calculated from the linear plots of $\log k_2$ versus T^{-1} . Activation energies and the related thermodynamic parameters are listed in Table 3. The values of activation energy for D-glucose oxidation lie between 38.14 and 52.90 kJ mol^{-1} . Constancy of $\Delta G^\ddagger$ ($90 \pm 3 \text{ kJ mol}^{-1}$) suggests that there is a mutual compensation effect of $\Delta H^\ddagger$ and $\Delta S^\ddagger$. A comparison of previous studies¹⁰ on oxidation of D-glucose demonstrates that pyridinium chlorochromate (PCC) is faster oxidizing agent than PCC with lower activation energy.

The rates of oxidation of D-glucose were determined both in water and in deuterium oxide. The rate $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$ was found to be 3. Comparison of

Table 4—Comparison of oxidation rates of α - and β -anomers
 $[PCC] = 1.30 \times 10^{-3} \text{ mol dm}^{-3}$, $[H] = 4 \text{ mol dm}^{-3}$, $T = 22^\circ\text{C}$,
 $I = 5.6 \text{ mol dm}^{-3}$

Anomers	$k_2 \text{ (dm}^3 \text{ mol s}^{-1}\text{)}$
α -D-Glucopyranoside	1.565
β -D-Glucopyranoside	1.738
1- <i>o</i> -Methyl- α -D-glucopyranoside	0.507
1- <i>o</i> -Methyl- β -D-glucopyranoside	0.699

acid base equilibrium in water and in deuterium oxide indicates that for any proton catalyzed reaction one should expect a solvent isotopic effect¹⁸ k_{D_2O}/k_{H_2O} about to 2.5. The observed high value of 3 in the present study may not be due to participation of second proton in the oxidation as no deviation has been observed in the first order dependence in $[H^+]$. Two acid-catalyzed processes may be assumed, one being the acid-catalyzed mutarotation and the other protonation of the anomer or the protonation of the PFC species. It is likely that protonation of PFC species is the dominant factor. This is reflected in the energy of activation (Table 3) and increase in rate constant with increase in ionic strength (Values of $10^3 k_0$ are 0.046, 0.191, 0.510, 0.806 and 2.93 s^{-1} at ionic strengths of 1.0, 2.0, 2.5, 3.0 and 4.0 mol dm^{-3} respectively under the conditions D-glucose = 0.02 mol dm^{-3} , $[PCC] = 1.6 \times 10^{-3} \text{ mol dm}^{-3}$ and $\text{temp} = 28^\circ\text{C}$).

PCC effects the oxidation of D-glucose to mostly gluconic acid besides formic acid and arabinose as the products of oxidation. Oxidation of these products under the kinetic conditions is insignificant, since, all the kinetics were carried out under pseudo-first order conditions.

In aqueous acidic solutions, D(+)-glucose predominantly exists in equilibrium between pyranose forms with free aldehyde form as the intermediate, beside furanoid forms¹⁹, which are too low in concentrations to make any impact towards competing for oxidation with above intermediates. The pyranoid form being more stable constitutes more than 99% of the total [D-glucose]. Further, attempt to compare the oxidation rates of individual anomers (α and β) under the present kinetic condition were not successful suggesting that rate of mutarotation is many times greater than the rate of oxidation under normal kinetic conditions. Hence, the rate of oxidation of these epimers was measured at higher $[H^+]$ and at higher ionic strength. Under these conditions, the oxidation rates are considerably fast. The conditions under which kinetic measurements were carried out, only 30% completion of the reaction for

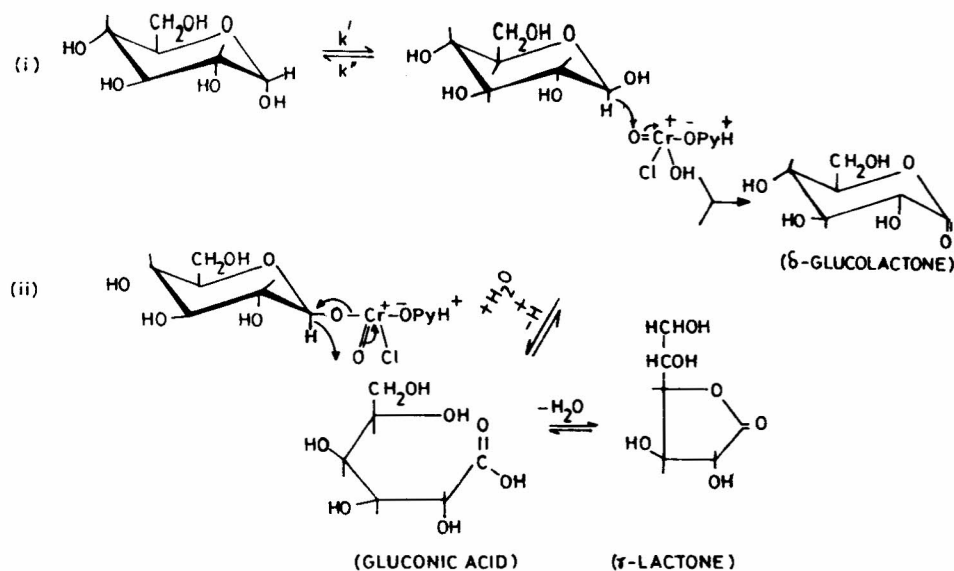
these pure epimers was noticed in less than 100 seconds from the start of the reaction. It is presumed that even in this short time of kinetic measurement, these epimers must have mutarotated to a certain degree. Nevertheless, comparison of oxidation rates of individual anomers at higher ionic strength (Table 4) revealed that β -anomer² is oxidised faster, though comparison for mutual oxidation rates is small ($\beta/\alpha = 1.11$ for α and β -D-glucopyranoside and $\beta/\alpha = 1.37$ for 1-*o*-methyl- α - and β -D-glucopyranoside), yet it gives justification for β -anomer being oxidised faster in preference to α -anomer. The slightly higher rates of β -D-anomer could be explained on the basis of $\Delta 2$ effect of Reeves²⁰, where on axial hydroxyl group on C-2 bisects the oxygen valences of C-1, such an arrangement results in the maximum repulsion of the oxygen atom, thus facilitating the approach of PCC.

The reaction is presumed to follow a direct hydride ion transfer of the axial-anomeric H of the β -pyranose. The hydride ion transfer can occur in two ways: (1) direct hydride ion transfer, (2) via ester formation. Both these paths lead to the formation of gluconic acid (Scheme 1). In acidic solution, gluconic acid invariably remains in equilibrium between γ - and δ -lactones. This hydride ion transfer is similar to the oxidation of alcohols by PCC²¹.

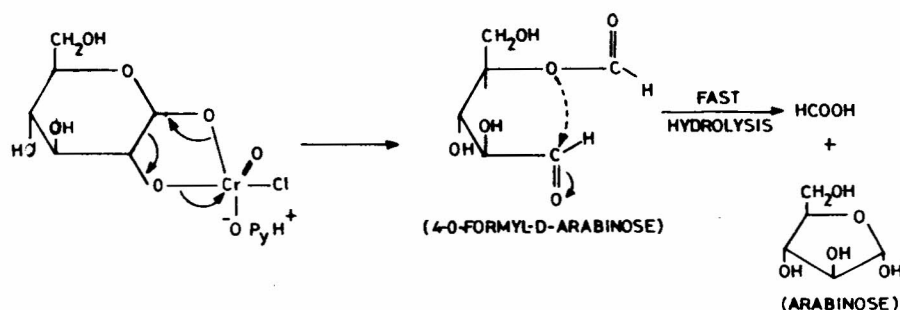
The formation of arabinose and formic acid leads to a mechanism (Scheme 2) which shows involvement of C-1 and C-2 hydroxyl groups. However, there was no intermediate complex formation seen either kinetically or spectrophotometrically in the present investigations. But the product identification suggests that there may be an intermediate complex formation involving C-1 and C-2 hydroxyl groups similar to the oxidation of cyclohexanediol²². The intermediate complex breaks leading to the formation of 4-*o*-formyl-D-arabinose which, however, in protic solvent cannot be stable and, therefore, immediately hydrolyses to formic acid and arabinose. 4-*o*-Formyl-D-arabinose can be identified by NMR in aprotic solvent as the oxidised product²³.

Oxidation of D-glucose by PCC (Schemes 1 and 2) is presumed to go via ionic mechanism since the reaction mixture failed to induce polymerisation of acrylonitrile. The positive salt effect suggests the involvement of cation-cation and cation-dipole interactions. It is believed that this reaction involves ion-dipole type interaction, dipole being the sugar and ion being the protonated PCC, since unprotonated aldose is more nucleophilic than protonated aldose²³.

Further, a comparison of D-glucose oxidation with those of various C-1 and C-2 substituted D-glucose derivatives has been carried out. The plots of k_0



Scheme 1



Scheme 2

Table 5—Comparison of oxidation rates of D-glucose with various C₁ or C₂-substituted derivatives of D-glucose
 [PCC] = 1.40×10^{-3} mol dm⁻³, $I = 1$ mol dm⁻³, [HClO₄] = 1 mol dm⁻³, temp = 26°C

[Sugars] (mol dm ⁻³)	$k_0 \times 10^4$ (s ⁻¹)				$k_2 \times 10^2$ (dm ³ mol ⁻¹ s ⁻¹)	Relative rate
	0.01	0.02	0.03	0.04		
D-Glucose	0.726	1.361	2.240	2.850	0.725 ± 0.025	1.00
2-Deoxy-D-glucose	0.903	1.920	2.820	3.64	0.911 ± 0.022	1.25
1- <i>o</i> -Methyl- α -D-glucopyranoside	0.261	0.626	0.971	1.320	0.352 ± 0.002	0.48
2-Amino-2-deoxy-D-glucose HCl	0.142	0.301	0.401	0.502	0.118 ± 0.007	0.16

against the concentration of various substituted D-glucose derivatives were linear passing through the origin (Fig. 1), thus confirming first order dependence in these [sugars]. A mutual comparison of oxidation rates of these sugars demonstrated: 2-deoxy-D-glucose > D-glucose > 1-*o*-methyl- α -D-glucopyranoside > 2-amino-2-deoxy-D-glucose hydrochloride (Table 5). It could be that, inductive, steric, and shielding effects are all important and difficult to separate from each other. It is not clear whether effect is electronic or steric since substituents modify con-

formational stability. 2-Amino-2-deoxy-D-glucose hydrochloride is oxidised very slowly because of the shielding effect of the ammonium group in acidic solution and the effect of ammonium group is related to the distance from the oxygen atom. However, the same trend has been observed also in case of acid catalysed hydrolysis of glycosides²⁴. The enhanced rate of oxidation of 2-deoxy-D-glucose may be due to two effects: (1) the removal of OH group at C-2 which would enhance the rate of interaction of PCC with the C-1 H transfer (as hydride ion) and (2)

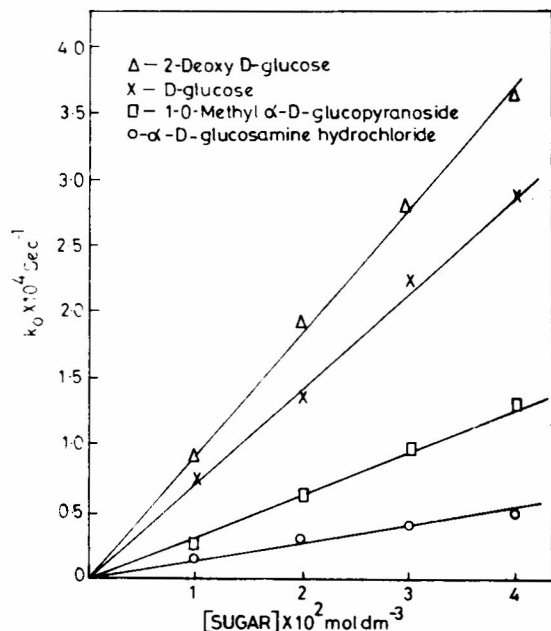


Fig. 1—Plots of k_{obs} versus [sugar] at 26°C

probably the absence of OH group would remove the restriction on rotation and thereby leading to a conformational stability with the PCC interaction.

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