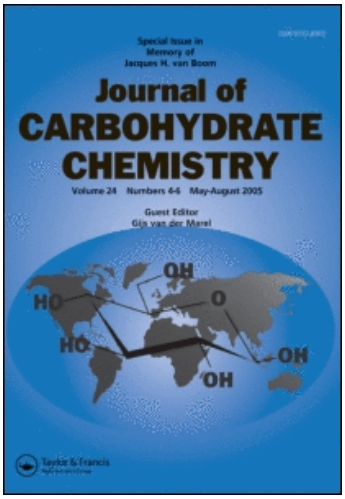

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KINETICS AND MECHANISM OF THE OXIDATION OF URONIC ACIDS BY SODIUM *N*-CHLOROBENZENESULPHONAMIDE IN ALKALINE MEDIUM

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ABSTRACT

The kinetics of oxidation of D-glucuronic acid and D-galacturonic acid (UA) by sodium *N*-chlorobenzenesulphonamide or chloramine-B (CAB) in alkaline medium at 35 °C has been investigated and the rate law, rate = k [CAB][UA][HO^-] was observed. The product, benzenesulphonamide had no influence. Increase of ionic strength increased the rate and when the dielectric constant of the medium was decreased, the rate was decreased. The rate increased in D_2O medium and the inverse solvent isotope effect $k(D_2O)/k(H_2O)$ was 2.00. Proton inventory was studied for the reactions in H_2O-D_2O mixtures. Activation parameters have been determined from the Arrhenius plots. The mechanism assumes the formation of an enediol anion followed by its oxidation by the positive halogen in a rate limiting step.

INTRODUCTION

The chemistry of *N*-halogeno compounds has received considerable attention because of their application in reactions where selective and/or limited oxidations of compounds are required. Compounds in which the *N*-halogen bond is attached to an aromatic moiety, generally known as organic *N*-haloamines, are stable and are suitable

as mild oxidants for a variety of reductants. The prominent member of this group is chloramine-T(p-$CH_3C_6H_4SO_2NClNa\ 3H_2O$ or CAT) which contains chlorine in the +1 state and is a byproduct in the manufacture of saccharin. The benzene analogue chloramine-B ($C_6H_5SO_2NClNa\ 1.5H_2O$ or CAB) is easy to prepare and has been employed in the oxidation of diverse substrates.

A review of literature shows that although some monosaccharides have been oxidised, there is limited information on the oxidation[1,2] of uronic acids (UA) by positive halogen compounds from a kinetic point of view. It is reported that D-glucuronic acid is not oxidized by sodium hypoiodite[2] but undergoes degradative oxidation with periodate.[1] The uronic acid can be oxidised by bromine to the respective aldaric acid.[3] As part of our broad programme on the mechanistic studies of sugars[4] with organic haloamines, we report the kinetics of oxidation of D-glucuronic acid and D-galacturonic acid by CAB at 35 °C in the present communication. Oxidation was erratic in acid medium, but was found to be smooth in the presence of NaOH at the C-1 carbon without affecting the C-6 carboxyl group, leading to the formation of D-glucaric and D-galactaric acids.

RESULTS AND DISCUSSION

The kinetics of oxidation of sugars by CAB was investigated at several initial concentrations of the reactants. With pseudo first order conditions under which $[Sugar]_o >> [CAB]_o$ and constant $[HO^-]$, plots of log [CAB] vs time were linear for each $[CAB]_o$. ($r > 0.9994$, $s \leq 0.01$) values of k_{obs} obtained from these plots were constant for the different initial concentrations of CAB employed, thus indicating a first order dependence of rate on $[CAB]_o$ (Table 1). This was further confirmed from the unit slopes obtained from the linear plots of log $[-dc/dt]_o$ vs.log $[CAB]_o$ using the initial velocity method. A slight decrease, however in k_{obs} values was noted at higher $[CAB]_o$ which could possibly be attributed to a side reaction[5] forming $NaClO_3$. Values of k_{obs} increased with increase in uronic acid concentration $[UA]_o$ (Table 1) and plots of log k_{obs} vs log $[UA]_o$ were linear with unit slope ($r > 0.9969$, $s \leq 0.03$). Also, the second order rate constants $k_2 = k_{obs}/[UA]_o$ were constant confirming the first order dependence on $[UA]_o$. Further, a plot of k_{obs} vs. $[UA]_o$ gives a straight line passing through the origin ($r > 0.9993$, $s \leq 0.01$) indicating that the intermediates formed are of transient existence (Figure 1).

Table 1. Effect of varying $[CAB]_o$ and $[UA]_o$ on the rate of oxidation of uronic acids at 35 °C

$[HO^-]_{eff} = 10.0 \times 10^{-2}$ M ; I = 0.4 M

$[CAB]_o \times 10^3$ M	$[UA]_o \times 10^2$ M	$k_{obs} \times 10^4$ (sec^{-1})	
		D-Glu acid	D-Gal acid
0.9	1.0	5.85	6.28
1.0	1.0	5.76	6.14
1.5	1.0	5.66	6.14
2.0	1.0	5.70	6.16
2.5	1.0	5.80	6.06
3.0	1.0	5.76	5.98
3.5	1.0	5.40	5.90
4.0	1.0	5.25	5.86
1.0	0.5	2.99	3.06
1.0	2.0	11.79	12.38
1.0	3.0	17.60	18.89
1.0	4.0	23.10	25.45
1.0	5.0	28.30	31.90
1.0	6.0	36.50	38.20

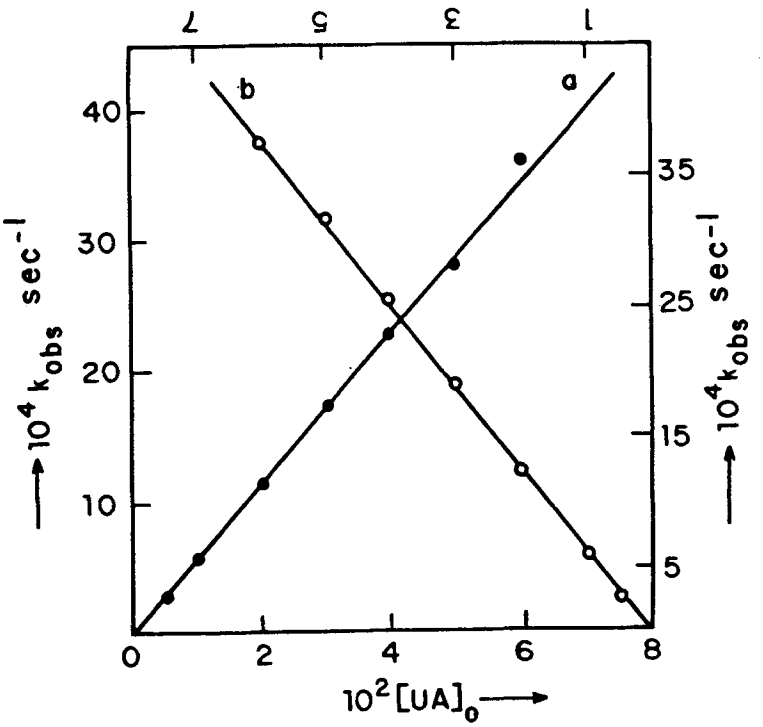


Figure 1. Plot of k_{obs} vs. $[UA]_o$; $[CAB]_o = 1.0 \times 10^{-3}$M, $[HO^-]_{eff} = 10.0 \times 10^{-2}$M, I = 0.4M, temp = 35 °C, a = D-Glucuronic acid; b = D-Galacturonic acid.

Table 2. Effect of varying $[HO^-]_o$ on the reaction rate at 35 °C

$[CAB]_o = 1.0\times10^{-3}M$; $[UA]_o = 1.0\times10^{-2}$ M; I=0.4M.

$[HO^-]_{eff} \times 10^2$ M	$10^4 k_{obs}$ (sec^{-1})	
	D-Glu acid	D-Gal acid
4.0	2.25	2.77
6.0	3.50	4.15
8.0	5.40	5.78
10.0	5.76	6.14
15.0	9.45	10.86
20.0	12.79	14.76
25.0	16.50	18.06
30.0	18.50	22.50

a. $[HO^-]_{eff}$ indicates that its neutralization by the uronic acid has been taken into account.

The rate of reaction also increased with increase in alkali concentration (Table 2) and plots of log k_{obs} vs.log $[HO^-]$ were linear with unit slope, ($r>0.9930$, $s\leq0.04$) thus indicating a first order dependence on $[HO^-]$. Further, a plot of k_{obs} vs. $[HO^-]$ passes through the origin ruling out an alkali independent path for the reaction.

Addition of the reaction products, benzenesulphonamide and chloride ion, the latter in the form of NaCl did not affect the rate. It may thus be inferred that the sulphonamide is not involved in a pre-equilibrium step with the oxidant.

The ionic strength (I) of the medium was varied by adding a concentrated solution of $NaClO_4$. The rate increased with increase in ionic strength. A conventional Debye-Hückel plot of log k_{obs} vs. $(I)^{1/2}$ resulted in a straight line ($r>0.9958$, $s\leq0.03$) with slopes of 0.7 and 0.8 for D-glucuronic acid and D-galacturonic acid, respectively (Figure 2).

The solvent composition of the reaction medium was varied by the addition of methanol (0-40%). The rate decreased with increase in methanol content. Plots of log k_{obs} vs.1/D where D is the dielectric constant of the medium were linear ($r>0.9985$, $s\leq0.02$) with a negative slope (Figure 3).

The reaction was studied at different temperatures (303-318K). From the Arrhenius plots of log k_{obs} vs.1/T which were linear ($r>0.9980$, $s\leq0.04$) the activation

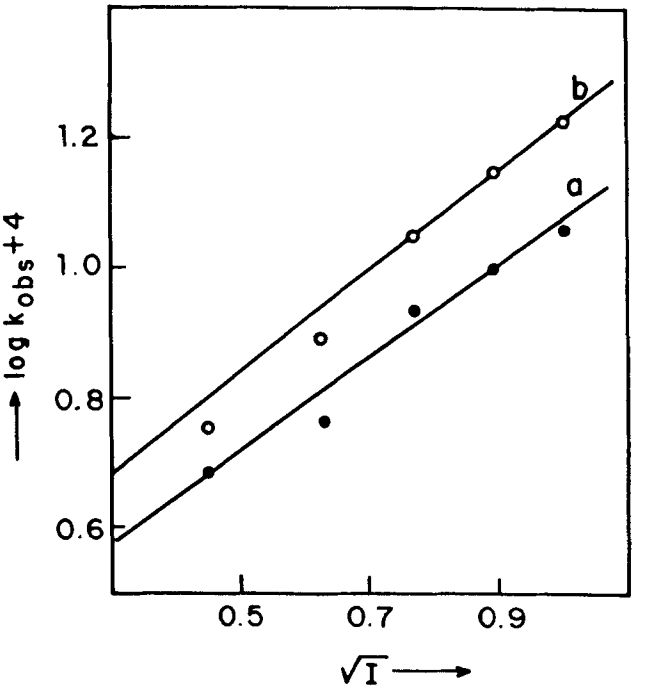


Figure 2. Plot of log k_{obs} vs $I^{1/2}$; $[CAB]_0$ = 1.0×10^{-3}M, $[UA]_0$ = 1.0×10^{-2}M, $[HO^-]_{eff}$ = 10.0×10^{-2}M, temp = 35 °C; a = D-Glucuronic acid; b = D-Galacturonic acid.

energy E_a was calculated from the slope. Values of the other kinetic parameters, $\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$ and log$A$ were computed[4] from the measured E_a values (Table 3).

Rate studies in D_2O medium showed that the reaction is faster in heavy water. The normal solvent isotope effect $k(H_2O)/k(D_2O)$ is 0.5 for both glucuronic and galacturonic acids (Table 4). The reaction was studied in H_2O - D_2O mixtures containing varying deuterium atom fractions 'n' (Table 4) and proton inventory plots relating the rate constant knobs with 'n' are given in Figure 4.

Olefinic monomers such as acrylonitrile and freshly prepared 10% acrylamide solution under nitrogen atmosphere were added to the reaction mixture to initiate polymerization if free radicals are present. The lack of polymerization indicated the absence of free radicals in the reaction mixture. Proper control experiments were also conducted.

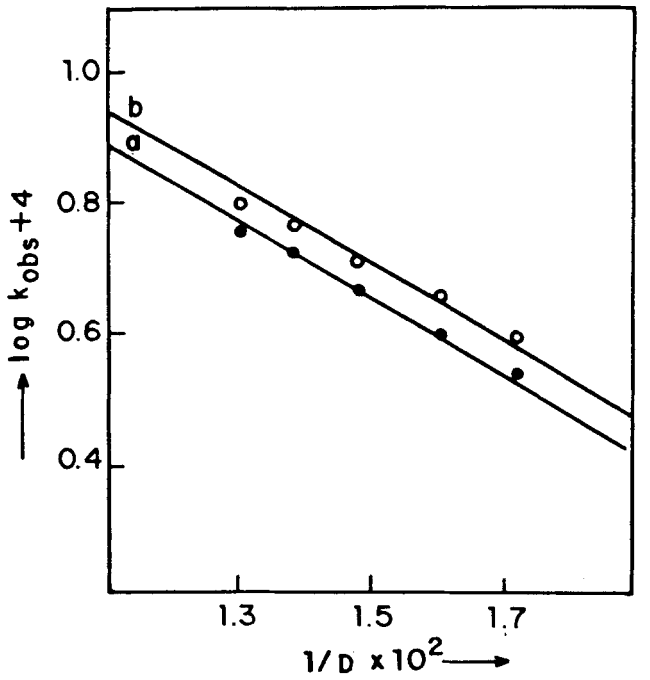


Figure 3. Plot of log k_{obs} vs 1/D; $[CAB]_o$ = 1.0×10^{-3}M, $[UA]_o$ = 1.0×10^{-2}M, $[HO^-]_{eff}$ = 10.0×10^{-2}M, I = 0.4M, temp = 35 °C; a = D-Glucuronic acid; b = D-Galacturonic acid.

Table 3. Kinetic and Thermodynamic Parameters for the Oxidation of uronic acids with CAB at 35 °C.

	E_a kJmol^{-1}	$\Delta H^{\neq}$ kJmol^{-1}	$\Delta S^{\neq}$ JK^{-1}mol^{-1}	$\Delta G^{\neq}$ kJmol^{-1}	Log$A$
D-Glu acid	111.5	108.8	45.7	94.7	18.6
D-Gal acid	95.8	93.2	- 3.8	94.4	16.0

The sodium salts of *N*-aryl-*N*-halosulphonamides behave like strong electrolytes in aqueous solution and Bishop and Jennings,[6] Morris and coworkers,[7] Hardy and Johnston[8] and Higuchi et al[9,10] have explained the several types of equilibria present in acid and alkaline solutions of these compounds. Thus chloramine - B (RNClNa where

Table 4. Proton inventory studies for oxidation of uronic acids by CAB in H_2O-D_2O mixtures at 35 °C.

$[CAB]_o = 1.0\times10^{-3}$M; $[UA]_o = 1.0\times10^{-2}$M; $[HO^-]_{eff} = 10.0\times10^{-2}$M; I = 0.4M

Atom fraction of D (n)	$10^4\ k^n_{obs}$ (sec^{-1})	
	D-Glu acid	D-Gal acid
0.00	5.76	6.14
0.25	6.50	6.95
0.50	8.20	8.50
0.75	9.80	10.20
0.94	11.50	12.20

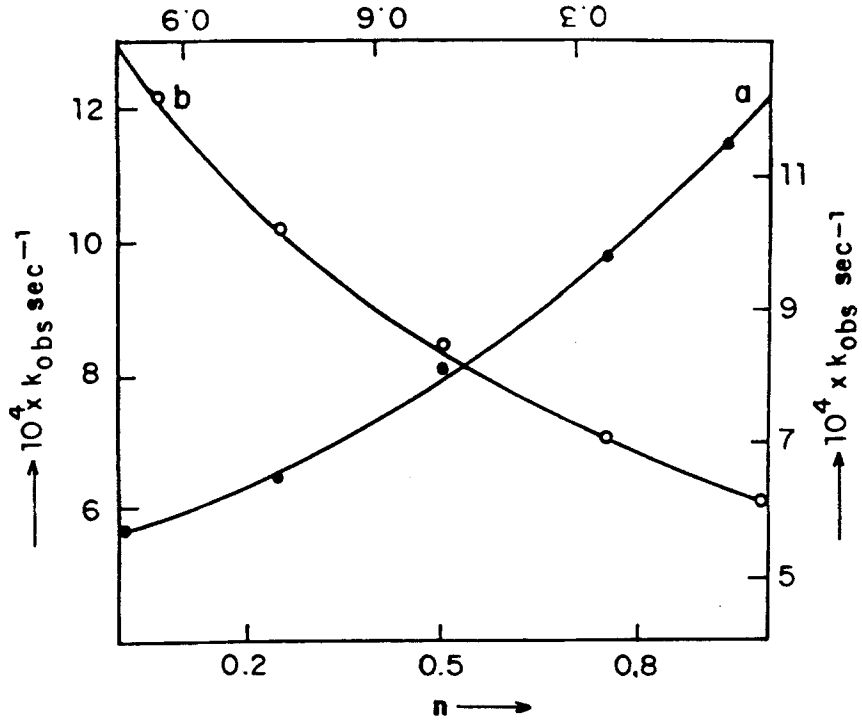


Figure 4. Proton inventory plots for the oxidation of D-Glucuronic acid (a) and D-Galacturonic acid (b) by CAB in H_2O-D_2O mixtures at 308K. Experimental conditions are as in Table 4.

$R=C_6H_5SO_2-$) ionizes in aqueous solution and furnishes different oxidant species. The anion is protonated in acid solutions and forms the free acid RNClH. The free acid has not been isolated but evidence for its presence in solution has been adduced through potentiometric[7] and conductometric titrations,[11] with aqueous CAB solutions. Further RNClH can undergo hydrolysis/disproportionation giving rise to dichloramine-B ($RNCl_2$) and HClO.

Thus in acid solutions, the probable oxidising species are RNClH, the dichloramine $RNCl_2$ and HClO.

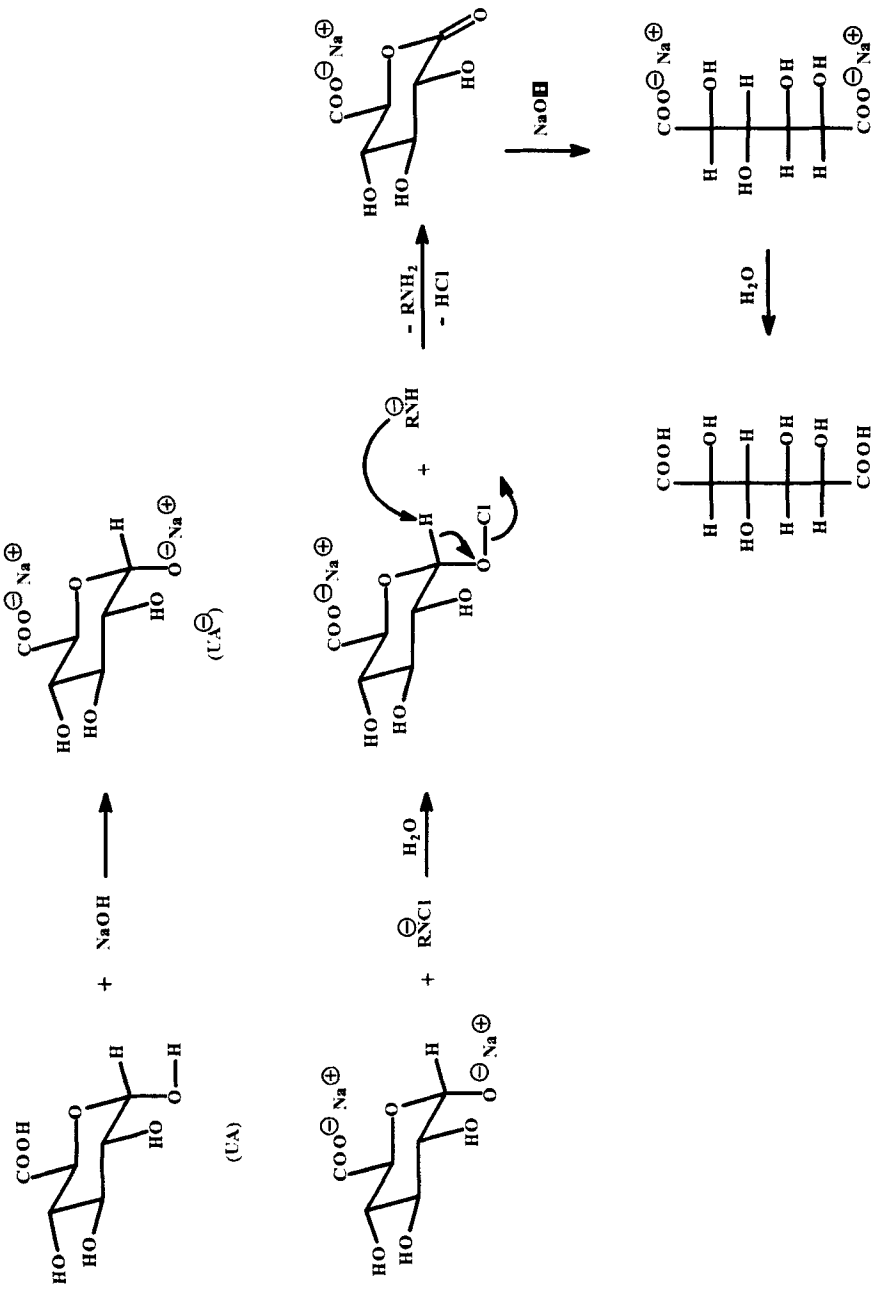
In alkaline solutions the anion $RNCl^-$ assumes importance although it can form RNClH and ClO^- ion through hydrolysis.

Since kinetic investigations of D-glucuronic acid and D-galacturonic acid have been made in alkaline medium, $RNCl^-$ and HO^- ions and RNClH are the likely oxidising species. But formation of RNClH envisages a retardation of rate by HO^- ion and also by the added reaction product benzenesulphonamide (RNH_2). Since no such kinetic effect was noticed, it is probable that the anion $RNCl^-$ itself acts as the oxidant.

The experimental rate law is, rate $= k$ [CAB][UA][HO^-] where UA represents the sugar molecule. In alkaline medium it is likely that the sugar undergoes the familiar Lobry de Bruyn-Alberda van Ekenstein transformation and the enediol anion (UA^-) formed reacts with the oxidant in a rate limiting step.

A possible mode of oxidation of the uronic acids as illustrated by D-glucuronic to D-glucaric acid, is shown in Scheme 1. The sugar reacts in the pyranose form to give the anion, which is subsequently attack the positive halogen of the $RNCl^-$. Elimination of benzenesulphonamide anion followed by HCl results in a lactone which on hydrolysis forms the aldaric acid. The kinetic picture of the attack on UA by HO^- and $RNCl^-$ ions and their oxidation to aldaric acids have been made explicit by detailed mechanistic steps in Scheme 1 and this leads to the required rate law, rate$=k'$ [CAB][UA][HO^-] where $k'=k_1k_2/k_{-1}$ [H_2O].

(i) The proposed mechanism is supported by the increase in rate in D_2O medium. Since DO^- is a stronger base than HO^- by a factor of 2, we expect a doubling of rate in heavy water medium.[12] The value of the inverse solvent isotope effect, $k(D_2O)/k(H_2O)$ is found to be 2.0 for both substrates, thus justifying our expectations



Scheme 1

and also substantiating a pre-equilibrium hydroxyl ion transfer.[12] Proton inventory plots (Figure 4, Table 4) could throw some light on the nature of the transition state.[13,14,15] A qualitative examination of the proton inventory plots by comparing their curvature with standard curves available in literature, shows that there is a single transition state and one HO^- ion is involved in its formation.[15]

(ii) A primary salt effect is observed as the rate increases with increase in ionic strength of medium and this is indicative of involvement of two negative ions in the reaction sequence.[16] The plot of log k_{obs} vs.$(I)^{1/2}$ is linear with a slope of 0.7-0.8 (Figure 2). The expected slope of unity has not been realised,[16] possibly due to the fact that the ionic strength is well above the formal Debye-Huckel range and there is Bjerrum ion pair formation. It is also probable that there is charge delocalization in the sugar or oxidant molecule participating in the rate limiting step (Scheme 1).

(iii) The rate decreased with decrease in the dielectric constant (D) of the medium. A plot of log k_{obs} vs.1/D was linear with a negative slope (Figure 3), which enables us to compute[17] the value of d_{AB}, the size of the activated complex of the reaction. From the slope of Fig. 3, d_{AB} is found to be 4.26 and 5.28 Å respectively for D-glucuronic acid and D-galacturonic acid. The values are found to be reasonable in comparison with those of other reactions of similar nature.[17]

(iv) The rate determining step (Scheme 1) involves an interaction between similarly charged ions which would require a very high activation energy. The values obtained are quite high being around 100 kJ mol^{-1}. The positive $\Delta S^{\neq}$ shows that there is more disorder in the transition state while the constancy of $\Delta G^{\neq}$ values indicates that a similar mechanism is operative in the oxidation of the two uronic acids.

CONCLUSION

Kinetic investigations with the two uronic acids, D-glucuronic acid and D-galacturonic acid reveal that there is not much difference in their oxidation behaviour with CAB in alkaline medium. The rate constants are almost identical (second order rate constant $k_2 = 5.95 \pm 0.19$ dm^3 mol^{-1} sec^{-1}) and oxidation follows an identical rate law. It may be concluded that structural differences at C-4 carbon have no influence on the macroscopic rate constants and other kinetic parameters.

EXPERIMENTAL

Materials and methods. Chloramine-B was prepared[18] by passing chlorine through a solution of benzenesulphonamide in 4.0M NaOH for 1 h at 343K. The product was collected, dried and recrystallized from water (mp 170 °C with decomposition). Its purity was checked by iodometry for its active chlorine content and also by its ^1H and ^{13}C NMR spectra. An aqueous solution of the compound was prepared, standardized and preserved in brown bottles to prevent its photochemical deterioration. D-Glucuronic acid (Sigma) and D-galacturonic acid monohydrate (Sigma) were used without further purification. Fresh aqueous solutions of sugars were prepared whenever required. All other reagents were of analytical grade. Concentrated $NaClO_4$ solution was used throughout to maintain a constant high ionic strength of the medium. Solvent isotope studies were made with D_2O (99.4%) supplied by the Bhabha Atomic Research Centre, Trombay, India. Triply distilled water was used in the preparation of aqueous solutions.

Stoichiometry. The mixture containing uronic acid and alkali with an excess of CAB was kept for 24 h at 35 °C. Iodometric determination of the unconsumed CAB indicated that one mol of oxidant was needed per mol of sugar to give the corresponding dicarboxylic acid. The stoichiometry of the reaction can be represented by equation (1):

$$C_6H_{10}O_7 + RNClNa + H_2O \longrightarrow C_6H_{10}O_8 + RNH_2 + Na^+ + Cl^- \quad \ldots\ldots \quad (1)$$

(Here R stands for $C_6H_5SO_2^-$).

The reaction product, benzenesulphonamide was detected by TLC using light petroleum-chloroform-1-butanol (2:2:1 v/v/v) as the solvent and iodine for detection (R_f = 0.88).

After removal of benzenesulphonamide with ether, the residual solution was then concentrated and analysed by paper chromatography (1-butanol-acetic acid-water, 4:1:5 v/v) and detected with *p*-anisidine hydrochloride (R_f = 0.19 for D-glucaric acid and 0.16 for D-galactaric acid).

Kinetic measurement. Requisite amounts of alkali, sugar and $NaClO_4$ solutions and water (for constant total volume) were thermostated at 35 °C in a pyrex boiling

tube coated black on the outside. The alkali concentration was adjusted to allow for the neutralization of carboxyl group at C-6 carbon. A known volume of CAB solution also thermostated at the same temperature was then rapidly added to initiate the reaction. The rate of oxidation was followed by withdrawing aliquots of the reaction mixture at different intervals of time and estimating the unconsumed CAB iodometrically. The reaction was monitored for two half lives. The pseudo first order constants k_{obs} calculated from the linear plots of log [CAB] vs time were reproducible within $\pm 3\%$.

Regression analysis of experimental data to obtain regression coefficient 'r' and 's', standard deviation of points from the regression line was performed with an EC-72 statistical calculator.

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