Kinetics and Mechanism of the Oxidation of Primary Alcohols by *N*-Bromoacetamide in Alkaline Solution

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The kinetics of the oxidation of seven primary alcohols by *N*-bromoacetamide has been studied in alkaline solution. The main product of the oxidation is the corresponding aldehyde. The reaction is first order with respect to the oxidant and alcohol. The oxidation of [1,1-$^2H_2$]ethanol indicates an absence of a primary kinetic isotope effect. The rate decreases with the increase in the concentration of hydroxide ion. Addition of acetamide decreases the reaction rate. The rates were determined at five different temperatures and the activation parameters were evaluated. The activation enthalpies and entropies of the oxidation of seven alcohols are linearly related. Hypobromite ion has been postulated as the reactive oxidizing species. A mechanism involving rate-determining nucleophilic attack of hypobromite ion on the alcohol molecule has been proposed.

Although many reports about the mechanism of the oxidations by *N*-halogenoamides such as *N*-bromosuccinimide [1] and *N*-bromoacetamide [2] (NBA) in acid solution are available, there seems to be none about alkaline solution. It is known, however, that the mechanisms of several redox reactions change with the changes in the reaction conditions *e.g.* reactions of chloramine T [3] and permanganate ion.[4] We therefore report the kinetics of the oxidation of several primary alcohols by NBA in aqueous alkaline solution and discuss the mechanistic conclusions. For the purpose of comparison, the oxidation of some of the alcohols by hypobromite ion was also studied.

Experimental

Materials.—All alcohols were commercial products. Their purification and the preparation of NBA have been described previously.[2] [1,1-$^2H_2$]Ethanol was prepared by Kaplan's method.[5] Its isotopic purity (n.m.r.) was 92 ± 5%. While the effect of varying the concentration of sodium hydroxide on the reaction rate was studied, the ionic strength was kept constant at 0.20M by using sodium perchlorate. Hypobromous acid was freshly prepared by the action of bromine on yellow mercury(II) oxide.[6] It was then neutralized by sodium hydroxide.

Product Analysis.—In a typical experiment ethanol (4.60 g, 0.1 mol), NBA (2.79 g, 0.02 mol), and sodium hydroxide (0.40 g, 0.01 mol) were made up to 100 ml in water. The mixture was kept for *ca.* 20 h in the dark to ensure completion of the reaction. It was then treated overnight with an excess (200 ml) of a saturated solution of 2,4-dinitrophenylhydrazine in 2M-HCl. The precipitated 2,4-dinitrophenylhydrazone (DNP) was filtered off, dried, weighed, recrystallized from ethanol, and weighed again. The product was identical (m.p. and mixed m.p.) with an authentic sample of the DNP of acetaldehyde. Similar experiments with other alcohols yielded the DNP of the corresponding aldehydes in 66—78% yields after recrystallization.

Stoicheiometry.—Ethanol (0.46 g, 0.01 mol), NBA (6.95 g, 0.05 mol), and sodium hydroxide (2.0 g, 0.05 mol) were made up to 100 ml in water. When the reaction was complete, the residual NBA was determined iodometrically. Several determinations with various alcohols indicated a 1 : 1 stoicheiometry.

Kinetic Measurements.—The reactions were carried out under pseudo-first-order conditions by keeping an excess of the alcohol over the oxidant. All reactions were carried out in the blackened flasks to avoid any photochemical reactions and were followed iodometrically for over 60% of the reaction. Rate constants were computed from the linear ($r > 0.98$) plots of log [Oxidant] against time. Duplicate kinetic runs showed that the rates were reproducible to within ±3%. The rates of oxidation by sodium hypobromite were also determined iodometrically.

Results

The oxidation of alcohols by NBA in alkaline solution results in the formation of the corresponding aldehydes. Analysis of products and determination of stoicheiometry indicate the overall reaction (1).

$$RCH_2OH + MeCONHBr + OH^- \longrightarrow RCHO + MeCONH_2 + Br^- + H_2O \quad (1)$$

Rate Laws.—The rates and other experimental data were obtained for all the alcohols investigated. As the results are similar only those for ethanol are reproduced. The reaction is found to be first order with respect to the oxidant. Individual kinetic runs were strictly first order with respect to the oxidant. Further the first-order rate coefficient did not vary with the initial concentration of NBA (Table 1). The order with respect to the alcohol is also one (Table 2). Under the condition of constant ionic strength the rate decreases with an increase in the concentration of hydroxide ion (Table 3). The oxidation of [1,1-$^2H_2$]ethanol indicated an absence of a primary kinetic isotope effect (Table 4). Addition of acetamide reduces the rate of oxidation of ethanol (Table 5). The oxidation of seven primary alcohols were studied at different temperatures (Table 6) and the activation parameters were evaluated (Table 7). The average errors in the values of ΔH^*, ΔS^*, and ΔG^* (at 298 K) are ±3 kJ mol^{-1}, ±5 J mol^{-1} K^{-1}, and ±5 kJ mol^{-1} respectively.

Oxidation by Sodium Hypobromite.—The oxidation of methanol, ethanol, butan-1-ol, and 2-chloroethanol by hypobromite ion was also studied. The reactions are first order with respect to the oxidant and the substrate. The rate decreases with an increase in the concentration of alkali (Table 8). The rates were determined at different temperatures and the activation parameters were calculated (Table 9).

Table 1. Dependence of the reaction rate on oxidant. [EtOH] 1.8M, [OH⁻] 0.10M, *T* 298 K

10^3[NBA]/M	2.0	5.0	7.5	10.0	12.5
10^6k_1/s^{-1}	5.92	5.78	5.78	5.55	5.62

Table 2. Dependence of the reaction rate on substrate. [NBA] 0.005M, [OH⁻] 0.10M, *T* 298 K

[EtOH]/M	0.36	0.72	1.08	1.80	2.52	3.60
10^6k_1/s^{-1}	1.17	2.30	4.72	5.78	8.20	12.0

Table 3. Dependence of the reaction rate on hydroxide ion. [NBA] 0.005M, [EtOH] 3.6M, *I* 0.20M, *T* 298 K

[OH⁻]/M	0.02	0.04	0.08	0.10	0.12	0.16
10^6k_1/s^{-1}	8.75	8.00	6.65	5.78	5.07	4.72

Table 4. Kinetic isotope effect in the oxidation of ethanol and [1,1-$^2H_2$]ethanol. [NBA] 0.005M, [OH⁻] 0.10M, *T* 298 K

[EtOH]/ M	Type	10^6k_1/ s^{-1}	
0.36	$\alpha\alpha$-$^1H_2$	1.17	
0.72	$\alpha\alpha$-$^1H_2$	2.30	10^6k_H 3.22 ± 0.03 l^{-1} mol^{-1} s^{-1}
1.80	$\alpha\alpha$-$^1H_2$	5.78	
0.35	$\alpha\alpha$-$^2H_2$	1.12	
0.70	$\alpha\alpha$-$^2H_2$	2.25	10^6k_D 3.20 ± 0.01 l^{-1} mol^{-1} s^{-1}
1.50	$\alpha\alpha$-$^2H_2$	4.80	
	k_H/k_D 1.01		

Table 5. Effect of acetamide on the reaction rate. [NBA] 0.005M, [EtOH] 3.6M, [OH⁻] 0.10M, *T* 298 K

10^3[Acetamide]/M	0.0	2.0	4.0
10^6k_1/s^{-1}	12.0	11.2	10.6
10^3[Acetamide]/M	6.0	8.0	10.0
10^6k_1/s^{-1}	9.83	9.17	8.36

Table 6. Rate constants for the oxidation of primary alcohols, RCH_2OH, by NBA in the presence of 0.10M-sodium hydroxide

	10^7k/l mol^{-1} s^{-1}				
R	298 K	303 K	308 K	313 K	318 K
H	490	708	1 020	1 420	1 910
Me	32.2	60.0	103	165	270
Et	27.7	54.7	92.0	150	247
Pr^n	25.6	52.7	89.0	148	245
Pr^i	1.55	3.17	6.30	12.2	23.0
$MeOCH_2$	895	1 360	1 750	2 330	2 980
$ClCH_2$	1 340	1 950	2 440	3 250	4 000

Table 7. Activation parameters for the oxidation of primary alcohols, RCH_2OH, by NBA in alkaline solution

R	ΔH*/kJ mol^{-1}	$-\Delta S$*/ J mol^{-1} K^{-1}	ΔG*/kJ mol^{-1}
H	56.2	150	101
Me	87.0	69	108
Et	88.9	64	108
Pr^n	92.1	54	108
Pr^i	108	23	115
$ClCH_2$	47.3	171	98.3
$MeOCH_2$	50.8	163	99.4

Table 8. Dependence of the rate of oxidation by hypobromite ion on alkali. [OBr⁻] 0.005M, [EtOH] 3.6M, *I* 0.20M, *T* 298 K

[OH⁻]/M	0.02	0.04	0.06	0.10	0.14	0.20
10^6 k_1/s^{-1}	9.32	8.85	8.05	6.62	5.20	4.25

Table 9. Rate constants and activation parameters for the oxidation of primary alcohols, RCH_2OH, by hypobromite ion in the presence of 0.10M-sodium hydroxide

	10^7k/l mol^{-1} s^{-1}					
R	298 K	303 K	308 K	ΔH*/ kJ mol^{-1}	$-\Delta S$*/ J mol^{-1} K^{-1}	ΔG*/ kJ mol^{-1}
H	646	910	1 300	55.8	149	100
Me	37.1	63.4	105	80.8	87	107
Pr^n	26.3	46.8	80	86.5	72	108
$ClCH_2$	1 530	2 040	2 650	44.2	181	98

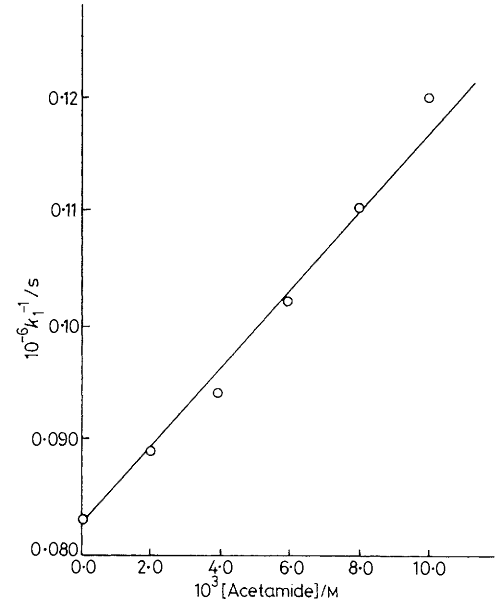

Figure 1. Plot of inverse of the observed rate constant against the concentration of acetamide (for reaction conditions see Table 5)

Discussion

The activation enthalpies and entropies of the oxidation of the seven alcohols are linearly related (*r* 0.9988). The correlation was tested and found genuine by applying Exner's criterion.[7] The isokinetic temperature computed from this plot is 396 K. Current views do not attach much physical significance to isokinetic temperatures.[8] The linear correlation, however, implies that all the alcohols are oxidised by the same mechanism and the changes in the rate are governed by changes in both enthalpy and entropy of activation.

The retarding effect of added acetamide suggests that the pre-equilibrium step involves a process (2) in which acetamide is one of the products. If this equilibrium is involved in the oxidation process then the rate should be an inverse function of acetamide concentration. A plot of inverse of observed rate constant against [acetamide] is linear (Figure 1, *r* 0.9952).

$$MeCONHBr + H_2O \rightleftharpoons MeCONH_2 + HOBr \quad (2)$$

Even at the lowest concentration of alkali used, hypobromous acid will exist exclusively as hypobromite ion (3). Another

$$\mathrm{HOBr} + \mathrm{OH}^- \longrightarrow \mathrm{H_2O} + \mathrm{OBr}^- \qquad (3)$$

possible reaction, disproportionation of NBA to *NN*-dibromoacetamide (4), can be ruled out in view of the strict first-order dependence of the reaction rate on NBA. Thus the most likely oxidizing species is hypobromite ion. The postulation of

$$2\mathrm{MeCONHBr} \rightleftharpoons \mathrm{MeCONH_2} + \mathrm{MeCONBr_2} \qquad (4)$$

hypobromite ion as the reactive species is supported by the results of the oxidation of some of the alcohols by sodium hypobromite. The effect of [OH⁻] on the rate of oxidation of ethanol by hypobromite ion is parallel to that observed in the oxidation by NBA. Similarly the rates of oxidation and the activation parameters in both cases are of same order. Moreover, an isokinetic relationship exists between log[Rate] of the oxidations of the alcohols by NBA and hypobromite ion (*r* 0.9990).

The absence of a primary kinetic isotope effect confirms that the C–H bond is not cleaved in the rate-determining step. The decrease in the rate of oxidation with increasing concentration of hydroxide ion led us to suggest that the rate-determining step is a reversible nucleophilic attack of a hypobromite ion on the alcohol molecule resulting in the formation of a hypobromite ester [reaction (5)]. Hypohalite esters are known to decompose readily [9] to carbonyl products [reaction (6)].

$$\mathrm{RCH_2OH} + \mathrm{OBr}^- \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathrm{RCH_2OBr} + \mathrm{OH}^- \qquad (5)$$

$$\mathrm{R{-}\overset{H}{\underset{H}{C}}{-}O{-}Br} \xrightarrow[k']{\text{fast}} \mathrm{RCHO} + \mathrm{H}^+ + \mathrm{Br}^- \qquad (6)$$

$$\mathrm{H}^+ + \mathrm{OH}^- \xrightarrow[\text{fast}]{\text{very}} \mathrm{H_2O} \qquad (7)$$

A rigorous treatment of the rate equations describing the reaction sequence in equations (5) and (6) is difficult. However, by applying the steady-state approximation for the concentration of hypobromite ester, we can derive rate equations (8) or (9) for the above mechanism.[10] From this, it may be seen that the

$$\mathrm{Rate} = \frac{k'k_f\,[\mathrm{RCH_2OH}]\,[\mathrm{OBr}^-]}{k' + k_r\,[\mathrm{OH}^-]} \qquad (8)$$

$$1/\mathrm{Rate} = \frac{1}{k' + k_r[\mathrm{OH}^-]} + \frac{k_r[\mathrm{OH}^-]}{k'k_f[\mathrm{RCH_2OH}][\mathrm{OBr}^-]} \qquad (9)$$

inverse of the rate of reaction will vary linearly with [OH⁻]. Figure 2 shows that such linearity is observed in oxidations by both NBA and hypobromite ion (*r* 0.9901 and 0.9949, respectively). The slope and intercept have values of 0.75 and 0.97 respectively for NBA oxidation while the corresponding values for the oxidation by hypobromite ions are 0.74 and 0.84. The similar behaviour observed in the two reactions further confirms that the oxidations by NBA and hypobromite ion follow the same mechanistic pathway. The agreement between derived and observed rate laws supports the proposed mechanism.

A rate-determining bimolecular nucleophilic substitution is also supported by the effect of structure on the reactivity of the alcohols. As in other bimolecular nucleophilic substitutions, branching at the α- or β-carbon decreases the rate of reaction,[11] and the introduction of electron-withdrawing groups like chloro and methoxy increases the rate sharply.[12] The structure–reactivity relationship obtained here is opposite to that observed in the oxidation of alcohols by NBA in acid solution.[2] In that case introduction of electron-withdrawing groups decreased the reaction rate while alkyl-substituted alcohols reacted faster than methanol.[2]

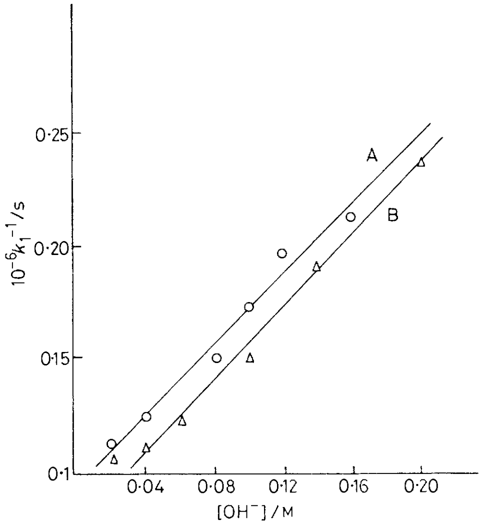

Figure 2. Effect of hydroxide ions on the rate of oxidation of ethanol. A, by NBA; B, by hypobromite (for reaction conditions see Tables 3 and 8)

The negative entropy of activation also supports the above mechanism. When two reacting molecules combine to form a single activated complex, the restrictions on their motion obviously increase, as they can no longer move independently. This results in a large negative entropy of activation.

An alternate route for the formation of hypobromite ester involving an attack of the alkoxide ion on hypobromous acid [reaction (10)] can be ruled out on two grounds. First the formation of an alkoxide ion is catalysed by alkali and the inverse dependence on [OH⁻] observed here is not compatible with

$$\mathrm{RCH_2O}^- + \mathrm{HOBr} \rightleftharpoons \mathrm{RCH_2OBr} + \mathrm{OH}^- \qquad (10)$$

$$\mathrm{RCH_2OH} + \mathrm{OH}^- \rightleftharpoons \mathrm{RCH_2O}^- + \mathrm{H_2O} \qquad (11)$$

reaction (11). Secondly hypobromous acid does not exist free in alkaline solution.

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