

Kinetics and mechanism of oxidation of alcohols

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Abstract This paper describes the kinetics and mechanism of oxidation of several monohydric alcohols to the corresponding aldehydes and ketones by bis(quinuclidine)bromine(I) bromide in the presence of pyridinium trifluoroacetate. All evidence from the thermodynamic parameters, deuterium kinetic isotope effect, and Hammett reaction constants supports a two-step mechanism and suggests that the transfer of hydride ion from the substrate to the oxidant is the rate-determining step.

Keywords Carbonyl compounds · Isotope effects · Structure–reactivity relationship · Rate constants

Introduction

The oxidation of alcohols to the corresponding aldehydes and ketones is still one of the most important transformations in organic synthesis [1]. There are numerous methods available in the literature [2]. Hypervalent iodine reagents are of increasing interest as oxidants in organic reactions owing to their mild, selective, and environmentally friendly oxidizing properties [3]. I_2O_5 was reported as a mild and efficient reagent for oxidation of alcohols in water [4]. A facile approach for oxidation of alcohols to carbonyl compounds using iron(III) nitrate as a benign reagent was recommended [5]. *N*-Halo compounds are known to be versatile oxidizing agents, e.g., bromoamine-B [6], *N*-chlorocarbamate [7], pyridinium fluorochromate (PFC) [8], pyridinium chlorochromate (PCC) [9], *N*-bromoacetamide [10], *N*-bromosuccinimide [11], and *N*-chlorosuccinimide [12].

Bis(quinuclidine)bromine(I) bromide (BQB), a two-coordinate halogen(I) species containing a central hypervalent bromine, has been reported as an efficient oxidizing reagent for alcohols [13], but the mechanistic pathway has never been deeply investigated. We therefore aimed to study the kinetics of the oxidation of primary and secondary alcohols with the oxidant BQB in the presence of pyridinium trifluoroacetate.

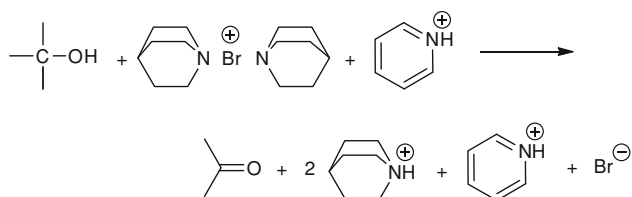
One approach to elucidate the oxidation mechanism is through the use of structure–reactivity profiles coupled with isotope effect measurements. Therefore, the rates of oxidation of *meta*- and *para*-substituted benzyl alcohol have been determined in order to investigate the electronic effects of substituents on the reaction. In addition, the effect of temperature on the rate and primary kinetic isotope effect (PKIE) measurements were undertaken to add more insight into the reaction mechanism speculated by Blair and co-workers [13].

Results and discussion

Stoichiometry and product analysis

The stoichiometry of the overall oxidation of secondary alcohols to the corresponding ketones using BQB was confirmed by material balance studies carried out by Blair et al. using GC technique. Additionally, analyses of the oxidation of cyclohexanol and 4-*tert*-butylcyclohexanol showed that the respective ketones formed in 95.7 and 100 % yield, respectively [13]. Interestingly, the results obtained from the current work in some ways resemble the aforementioned data. Thus oxidation of 2-propanol and benzyl alcohol afforded acetone and benzaldehyde in 96 and 94 % yield, respectively, being determined via their

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**Scheme 1**

2,4-dinitrophenylhydrazine (DNPH) adducts. All the results are in accordance with the overall reaction in Scheme 1.

General kinetics description

The pseudo-first-order rate constant k_{ps} (Table 1) increases with the increase in [alcohol] in the range 0.1–0.5 mol dm⁻³, and plot of log [alcohol] against k_{ps} is linear with slope ~ 1 , indicating the first-order dependence in [alcohol]. The rate is first order in BQB concentration between 1×10^{-3} and 5×10^{-3} mol dm⁻³, as shown by the nearly constant k_{ps} in each run. The rate increased linearly with an increase in pyridinium ion (PyH⁺) concentration, indicating the first-order dependence in [PyH⁺]. It is more likely that in the presence of PyH⁺, the oxidant may be decomposed (Scheme 2) and the quinuclidinium bromide ion (QBr⁺) may function as an effective oxidant species similar to PFC oxidation [8].

Rate law

The measured pseudo-first-order rate constants (k_{ps}) according to Eq. (1) were converted to third-order rate constants (k_3) using the derived Eq. (3):

$$k_{ps} = \text{rate}/[\text{BQB}] \quad (1)$$

$$k_3 = \text{rate}/[\text{BQB}][\text{Alcohol}][\text{PyH}^+] \quad (2)$$

$$k_3 = k_{ps}/[\text{Alcohol}][\text{PyH}^+] \quad (3)$$

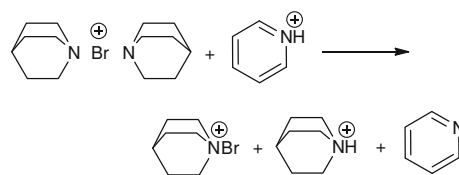
Effect of temperature–activation parameters

Table 2 lists the third-order rate constants of some alcohols at different temperatures. The activation parameters evaluated from the linear Eyring plots of $\ln(k_3/T)$ versus $1/T$ with a correlation coefficient (r) better than 0.997 in the temperature range 303–323 K are given in Table 3 and Fig. 1.

The activation enthalpies and entropies are linearly related and the isokinetic temperature is 258 °C. The existence of a linear relationship between ΔH^\ddagger and ΔS^\ddagger indicates that a similar mechanism is operating in the series. Even though the high isokinetic temperature

Table 1 Effect of varying concentration on the rate of reaction of 2-propanol with BQB in the presence of pyridinium trifluoroacetate (PyH⁺) in chloroform at 323 K

[2-Propanol]/ mol dm ⁻³	[BQB]/ mol dm ⁻³	[PyH ⁺]/ mol dm ⁻³	$k_{ps}/$ s ⁻¹ × 10 ⁴
0.5	0.005	0.01	10.62
0.3	0.005	0.01	8.64
0.25	0.005	0.01	6.62
0.18	0.005	0.01	3.84
0.10	0.005	0.01	2.21
0.25	0.005	0.05	5.31
0.25	0.004	0.05	5.41
0.25	0.003	0.05	5.45
0.25	0.002	0.05	5.38
0.25	0.001	0.05	5.40
0.25	0.005	0.06	5.76
0.25	0.005	0.07	7.07
0.25	0.005	0.08	7.50
0.25	0.005	0.10	9.12

**Scheme 2****Table 2** Temperature dependence of third-order rate constant of oxidation of some alcohols

Alcohol	$k_3/\text{mol}^{-2} \text{dm}^6 \text{s}^{-1} \times 10^2$				
	303 K	308 K	313 K	318 K	323 K
2-Propanol	1.176	1.692	2.240	3.334	4.248
Benzyl alcohol	0.442	0.676	0.966	1.326	2.000
4-Ethylbenzyl alcohol	1.348	1.946	2.904	3.874	5.379
4-Methoxybenzyl alcohol	6.620	9.056	12.10	15.78	20.41
1-Phenylethanol	2.346	3.416	4.70	6.48	8.608

[Alcohol] = 0.25 mol dm⁻³, [BQB] = 5.0×10^{-3} mol dm⁻³, and [PyH⁺] = 5.0×10^{-2} mol dm⁻³

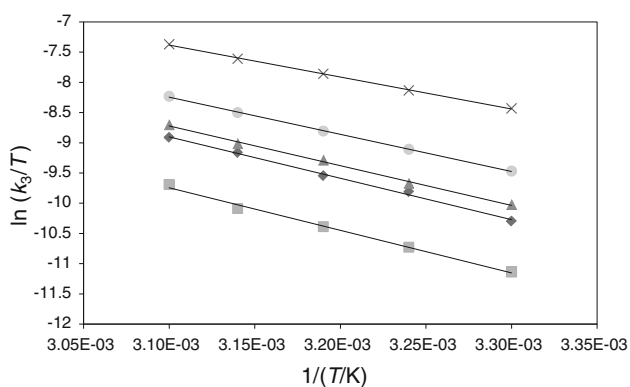
suggests that the reaction is an enthalpy-controlled one, the analysis of activation parameters reveals the lowest entropy of activation for the slowest reaction and vice versa indicating that both parameters are important in controlling the rate of the reaction.

The closest analogy to our reaction is the oxidation of 2-propanol by polypyridyl ruthenium(III) and ruthenium(IV) complexes in the solvents water and acetonitrile. The reported values for the enthalpy of activation and the

Table 3 Activation parameters for the reaction of some alcohols with BQB in the presence of PyH⁺

Alcohol	$\Delta H^\ddagger /$ kJ mol ⁻¹	$-\Delta S^\ddagger /$ J K ⁻¹ mol ⁻¹	$\Delta G^\ddagger /$ kJ mol ⁻¹
2-Propanol	52.2	110.3	86.8
Benzyl alcohol	58.5	97.5	89
4-Ethylbenzyl alcohol	54.7	100.4	86.1
4-Methoxybenzyl alcohol	43.9	122.7	82.3
1-Phenylethanol	51.1	107.5	84.7

[Alcohol] = 0.25 mol dm⁻³, [BQB] = 5.0 × 10⁻³ mol dm⁻³, and [PyH⁺] = 5.0 × 10⁻² mol dm⁻³

**Fig. 1** Eyring plots for oxidation of some alcohols with BQB in the presence of PyH⁺: diamonds 2-propanol, squares benzyl alcohol, triangles 4-ethylbenzyl alcohol, crosses 4-methoxybenzyl alcohol, circles 1-phenylethanol

entropy of activation were varied, depending on the ruthenium oxidation state and the solvent being used ($\Delta H^\ddagger = 33 \pm 4$ to 38 ± 4 kJ mol⁻¹ and $-\Delta S^\ddagger = 50 \pm 25$ to 176 ± 20 J K⁻¹ mol⁻¹) [14].

Considerable differences between these values and the energy parameters obtained from the work presented here are apparent ($\Delta H^\ddagger = 52.2$ kJ mol⁻¹ and $\Delta S^\ddagger = -110.3$ J K⁻¹ mol⁻¹). This discrepancy may be attributed to the extent of α -C–H bond-breaking in the transition state of each reaction. However, this is not unexpected because different oxidizing agents and solvents were used in the indicated reactions.

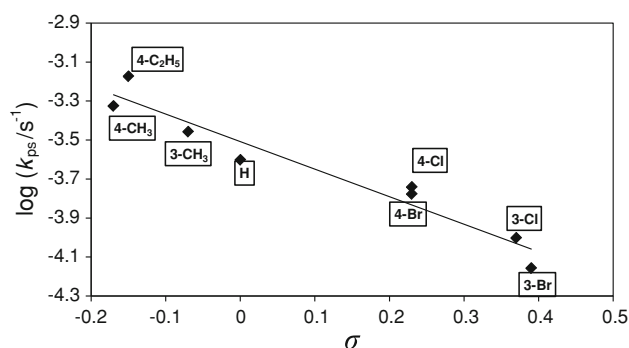
Effect of substituent on the aromatic ring

The rates of oxidation of a series of substituted benzyl alcohols including electron-releasing and electron-withdrawing groups were measured. Pseudo-first-order rate constants (k_{ps}) are collated in Table 4.

Table 4 Pseudo-first-order rate constants of oxidation of alcohols at 323 K

Alcohol	$k_{ps}/s^{-1} \times 10^4$	Div/%	Relative rates
X–C ₆ H ₄ CH ₂ OH			
X = H	2.50	2.3	1.0
4-CH ₃	4.73	2.0	1.9
3-CH ₃	3.49	2.3	1.4
4-C ₂ H ₅	6.72	2.5	2.7
4-CH ₃ O	25.5	1.9	10.0
4-Cl	1.81	2.1	0.7
3-Cl	0.922	3.0	0.4
4-Br	1.67	2.6	0.67
3-Br	0.695	2.2	0.9
2-Propanol	5.31	2.5	2.1
1-Phenylethanol	10.8	1.7	4.3

[Alcohol] = 0.25 mol dm⁻³, [BQB] = 5.0 × 10⁻³ mol dm⁻³, and [PyH⁺] = 5.0 × 10⁻² mol dm⁻³

**Fig. 2** Hammett plot of log k_{ps} versus σ for the oxidation of *m*- and *p*-substituted benzyl alcohols at 323 K

The plot of k_{ps} versus the σ and σ^+ values of the substituents under investigation leads to a sensitivity factor in the Hammett equation $\rho = -1.69$ ($r = 0.933$) and $\rho^+ = -1.27$ ($r = 0.990$) (Figs. 2, 3). This implies that the reactions are accelerated by electron-donating groups and decelerated by electron-withdrawing substituents. The rate decreases in the order p -OCH₃ > p -C₂H₅ > p -CH₃ > m -CH₃ > p -Cl > p -Br > m -Cl > m -Br

The reaction with the *p*-methoxy substituent proceeds by about 10 times faster than the parent benzyl alcohol and about 36 times faster than *m*-bromobenzyl alcohol.

Kinetic isotope effects

The oxidation of 2-propanol-2-d and 2-propan(ol-d) by BQB was investigated to ascertain the importance of the α -C–H and/or O–H bond cleavage in the rate-determining step. The observed rate constants for oxidation of 2-propanol, 2-propanol-2-d, and 2-propan(ol-d) at concentrations

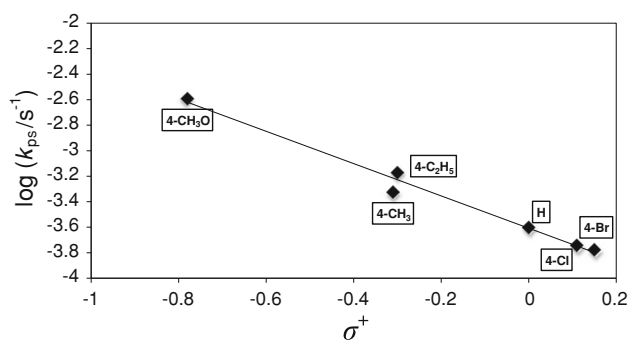


Fig. 3 Hammett plot of $\log k_{ps}$ versus σ^+ for the oxidation of *p*-substituted benzyl alcohols at 323 K

0.25 mol dm⁻³ alcohol, 5.0 × 10⁻³ mol dm⁻³ BQB, and 0.05 mol dm⁻³ PyH⁺ at 308 K are (k_{ps}/s^{-1}) 2.115 × 10⁻⁴, 0.429 × 10⁻⁴, and 1.28 × 10⁻⁴, respectively. The indicated rate constant of each compound is the mean of five kinetic runs with deviation of ±2 % from the mean. Thus the value $k_H/k_D = 4.9$ indicates the breakage of the α -C-H bond in the slow rate-determining step. The k_{OH}/k_{OD} value of 1.6 could represent a large secondary isotope effect or extremely small primary effect, and the rupture of the O-H bond in a rate-determining step can be ruled out.

Quite similar isotope effects have been found for the oxidation of (CH₃)₂CDOH and (CH₃)₂CHOD in water by ruthenium(IV) complexes ($R_H/R_D = 5.2 \pm 0.8$ and 1.1 ± 0.1 , respectively), and in a similar way the importance of the cleavage of the α -C-H bond in the slow rate-determining step was proposed [14]. Moreover, the isotope kinetic values for the oxidation of α -methylbenzyl alcohols by dimethyldioxirane are comparable to our results [15].

Mechanism

On the basis of the kinetic data, a probable mechanism for the oxidation of the alcohols under study by BQB has been proposed (Scheme 3). It has been suggested that the BQB ion acts as an effective oxidizing species and the reaction is presumed to follow a direct hydride shift in a slow rate-determining step. This is much the same as the oxidation of

alcohols by PCC [16]. The proposed mechanism in this work has been supported by Hammett reaction constants; the modest negative ρ values obtained imply that electron-releasing substituents facilitate the oxidation and suggest the removal of hydride ion to be in the rate-limiting step.

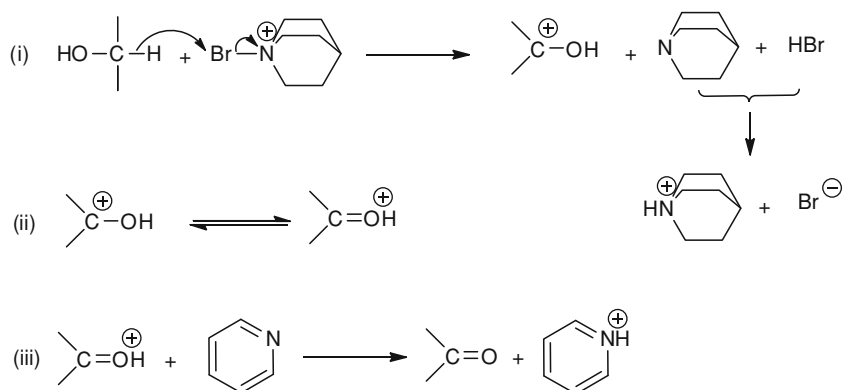
The values of reaction constants ρ and ρ^+ obtained in this work, although not highly negative, are in agreement with the suggested resonance structures of the developed electron-deficient carbonyl carbon (step (ii) in Scheme 3), and comparable to those obtained for the oxidation of benzyl alcohols by chromic acid ($\rho = -1.16$) [17] and nitrous acid ($\rho = -1.07$) [18]. The better correlation with σ^+ indicates the development of the positive charge in the transition state on a carbon atom adjacent to the benzene nucleus which can be delocalized into the nucleus itself.

This mechanism has also been supported by the deuterium isotope effect. The presence of substantial PKIE ($k_H/k_D = 4.9$) shows that the reaction involves the cleavage of the α -C-H bond in the slowest step of the reaction, a feature which is quite similar to what was observed in the oxidation of these substrates by PFC [8], chromic acid [17], and 2,2-bipyridylchromic acid [19]. The small value for k_{OH}/k_{OD} (1.6) excludes the cleavage of the O-H bond in a rate-determining step.

Intrinsically, this is in complete agreement with the work done by Thompson and Meyer in which a two-electron hydride transfer from the α -carbon atom to Ru^{IV}=O and one-electron H-atom oxidation for Ru(III) hydroxy complexes and once again from the α -carbon group were suggested in the oxidation of 2-propanol by polypyridyl ruthenium complexes [14].

In conclusion, all the evidence presented above points to the fact that the oxidation of monohydric alcohols by BQB in the presence of pyridinium trifluoroacetate is consistent with a mechanism involving more than one step and confirms that the cleavage of the α -C-H bond of the alcohol is the slow rate-determining step followed by deprotonation of the protonated carbonyl compound by pyridine in a fast step (Scheme 3, step (iii)) in the proposed mechanism.

Scheme 3



Materials and methods

General methods

A Bausch and Lomb 2000 spectronic UV spectrophotometer was used for kinetic measurements. Proton NMR spectra were obtained on a Varian T-60 spectrometer at 60 MHz using CDCl_3 as the solvent.

Materials

Alcohols of reagent grade were obtained from various sources. The solid alcohols were purified by recrystallization from suitable solvents to constant melting point and liquid alcohols by distillation either at atmospheric pressure or in vacuo. 2-Propanol-2-d (98 %) and 2-propan(ol-d) (98 %) were purchased from Cambridge Isotope Laboratories and Aldrich Chemical Company, respectively. Chloroform was washed with water, dried (CaCl_2), refluxed with CaSO_4 , then distilled and stored in the dark. BQB was prepared by the literature method from quinuclidine [13]. The crude product was crystallized from CH_2Cl_2 to give 97 % yield of nonhygroscopic, homogeneous material identified by its ^1H NMR spectrum.

Product analysis

The product analysis was carried out under kinetic conditions, i.e., with excess substrate over the oxidant. The products of oxidation were the corresponding aldehydes and ketones and were identified by their DNPH derivatives. Typical experiments were represented by the oxidation of 2-propanol and benzyl alcohol as follows.

Oxidation of 2-propanol

Bis(quinuclidine)bromine(I) bromide (0.381 g, 1.0 mmol), 1.925 g pyridinium trifluoroacetate (10 mmol), and 3 g isopropyl alcohol (50 mmol) were dissolved in 10 cm^3 chloroform. The reaction mixture was stirred for 6 h at 35 °C, then cooled to room temperature. It was then treated with an excess of freshly prepared solution of DNPH and stored in the refrigerator for 24 h. The precipitated 2,4-dinitrophenylhydrazone was filtered and recrystallized from ethanol. The product was identical (m.p. and mixed m.p.) to an authentic sample of acetone hydrazone. The weight of the derivative was 0.228 g (96 % yield of acetone based on the oxidant BQB).

Oxidation of benzyl alcohol

A mixture of 0.453 g BQB (1.1 mmol), 2.12 g pyridinium trifluoroacetate (11 mmol), and 5.94 g benzyl alcohol

(55 mmol) in 10 cm^3 chloroform was stirred for 8 h at 40 °C. After addition of DNPH to the cooled solution, the hydrazone adduct formed immediately and the reaction mixture was allowed to stand 12 h to ensure complete precipitation. We obtained 0.296 g of the hydrazone (94 % yield of benzaldehyde).

Kinetic measurements

All the kinetic measurements were carried out under pseudo-first-order conditions keeping an excess of alcohol over BQB. Taking 2-propanol as the representative alcohol, solutions in chloroform were made up to contain 0.1–0.5 mol dm^{-3} of 2-propanol, $1.0\text{--}5.0 \times 10^{-3}$ mol dm^{-3} of BQB, and 0.01–0.1 mol dm^{-3} of pyridinium trifluoroacetate.

Solutions were thermostated separately to the required temperature in a water bath and mixed together at zero time, placed in the spectrophotometer using 1-cm-path-length silica cells, and the reaction was followed by recording the decrease in the oxidant BQB absorbance at 400 nm, where alcohols and products have negligible absorbance. The temperature was maintained constant at ± 0.01 °C by means of a Julabo FLO water thermostat, the water being circulated through the cell holder. The reactions were followed for about three half-lives in the case of slow reactions and for more than four half-lives for the faster ones. The kinetic runs were performed at least in duplicates and indicate a reproducibility of 2–3 %. Pseudo-first-order rate constant, activation parameters, and Hammett reaction constants were determined using a least-squares procedure, and standard deviation was in the range 1–3 %.

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