Kinetics and mechanism of the oxidation of some *a*-hydroxy acids by hexamethylenetetramine-bromine

DIMPLE GARG and SEEMA KOTHARI*

Department of Chemistry, J N V University, Jodhpur 342 005, India
e-mail: seema@goraexports.com; skothari23@rediffmail.com

Abstract. The oxidation of lactic acid, mandelic acid and ten monosubstituted mandelic acids by hexamethylenetetramine-bromine (HABR) in glacial acetic acid, leads to the formation of the corresponding oxoacid. The reaction is first order with respect to each of the hydroxy acids and HABR. It is proposed that HABR itself is the reactive oxidizing species. The oxidation of *a*-deuteriomandelic acid exhibits the presence of a substantial kinetic isotope effect ($k_H/k_D = 5.91$ at 298 K). The rates of oxidation of the substituted mandelic acids show excellent correlation with Brown's s^+ values. The reaction constants are negative. The oxidation exhibits an extensive cross conjugation between the electron-donating substituent and the reaction centre in the transition state. A mechanism involving transfer of a hydride ion from the acid to the oxidant is postulated.

Keywords. Kinetics; oxidation; *a*-hydroxy acids; hexamethyleneteramine-bromine.

1. Introduction

Hexamethylenetetramine-bromine (HABR) was first reported as a synthetic reagent for the oxidation of alcohols to carbonyl compounds in 1994.[1] HABR is a non-hygroscopic solid, easily handled and storable. It is not affected by ordinary exposure to light, air or water and has no offensive odour of bromine. Hence, it is a safe and convenient source of active bromine in comparison to bromine which is a highly toxic oxidizer. We have undertaken a study of the kinetics and mechanism of oxidations by HABR and some reports have emanated from our laboratory on the mechanistic aspects of oxidations by HABR.[2–5] A perusal of literature showed that the kinetics and mechanism of the oxidation of hydroxy acids by HABR has not been investigated so far. Hydroxy acids may be oxidized either as alcohols yielding corresponding oxoacids[6] or may undergo decarboxylation to yield an aldehyde.[7] In the present work, the kinetics of oxidation by HABR, in glacial acetic acid, of lactic acid (LA), mandelic acid (MA) and ten substituted mandelic acids have been described. Attempts have been made to correlate rate and structure in this reaction. Mechanistic aspects are discussed.

2. Experimental

2.1 *Materials*

HABR was prepared by the reported method[1] and its purity checked by an iodometric method and melting point determination. Contrary to the earlier report,[1] we found that the active bromine content of this complex is 2 mol per mole of the reagent. LA, MA and nitromandelic acids used were commercial products of the highest purity available and were used as such. Halogeno-, alkyl- and *p*-methoxymandelic acids were prepared from the corresponding benzaldehydes by cyanohydrine formation followed by acid hydrolysis.[8] Solutions were standardized by alkalimetry. *a*-Deuteriomandelic acid (DMA) was prepared by the method of Kemp and Waters,[9] and its isotopic purity, as ascertained by its NMR spectrum was $94 \pm 5\%$. Glacial acetic acid was purified by refluxing it with CrO_3 and acetic anhydride for 6 h and then distilled.[10]

2.2 *Product analysis*

The formation of oxoacids as the product of the oxidation was confirmed by its characteristic positive spot test, given by a completely reduced reaction mixture.[11] The quantitative estimation of oxoacids were carried out under kinetic conditions. In a typical experiment,

*For correspondence

mandelic acid (0·1 mol) and HABR (0·01 mol) were dissolved in 100 ml glacial acetic acid. The reaction mixture was allowed to stand in the dark for ≈ 6 h to ensure completion of the reaction. Most of the solvent was removed by distillation under reduced pressure. The solution was then treated with excess (250 ml) of a saturated solution of 2,4-dinitrophenylhydrazine in 2 mol dm^{-3} HCl and kept overnight in a refrigerator. The precipitated 2,4-dinitrophenylhydrazone (DNP) was filtered off, dried, weighed, recrystallized from ethanol, and weighed again. The yields of DNP before and after recrystallization was 2·22 g (91%) and 2·03 g (83%) respectively. The identity of product was established by comparing the m.p. of the DNP derivative with the literature value.[12] The DNP was found identical (m.p. = 192°C and mixed m.p. = 194°C) with the DNP of phenylglyoxylic acid (m.p. = 196–7°C).[12] In similar experiments, with other hydroxy acids, the yield of the corresponding oxoacids was in the range of 77–87%, after recrystallization.

2.3 *Stoichiometry*

To determine the stoichiometry, HABR (0·05 mol) and MA (0·01 mol) were made up to 100 ml in glacial acetic acid. The reaction was allowed to stand for ≈ 10 h to ensure the completion of the reaction. The residual HABR was determined iodometrically. Several determinations, with different concentrations of MA, showed that the stoichiometry is 2 : 1 i.e. two moles of hydroxy acids are oxidized per mole of HABR.

2.4 *Spectral studies*

UV-Vis spectra of HABR, hexamethylenetetramine (HXA) and bromine were obtained, on a HP diode-array rapid scanning spectrophotometer (Model 8452A) with a scanning speed of 600 nm s^{-1}. The solvent was glacial acetic acid and temperature was ≈ 298 K.

2.5 *Kinetic measurements*

The reactions were studied under pseudo first-order conditions by maintaining an excess (× 20 or greater) of the hydroxy acid over HABR, solvent glacial acetic acid. The reactions were carried out at constant temperature (± 0·1 K) and were followed iodometrically by monitoring the decrease in [HABR] for up to more than 80% of the reaction. Pseudo first-

order rate constants, k_{obs}, were evaluated from linear plots ($c^2 > 0.995$) of log [HABR] against time. Duplicate kinetic runs showed that the rates were reproducible to within ± 4%. The second order rate constant, k_2, was calculated by the following relation: $k_2 = k_{obs}/$ [hydroxy acid]. We have used coefficient of determination (c^2), standard deviation (sd) and Exner's[13] parameter ψ, as the measures of goodness of fit in correlation analysis.

3. Results

Rates and other experimental data were obtained for all the hydroxy acids. Since the results are similar, only representative data are reproduced here.

Oxidation of the hydroxy acids by HABR results in the formation of the corresponding oxoacids as individual compounds. Analyses of product and stoichiometric determinations indicate the following overall reaction.

$$2RCH(OH)COOH + (CH_2)_6N_4Br_4 \rightarrow$$
$$RCOCOOH + (CH_2)_6N_4 + 4HBr \quad (1)$$
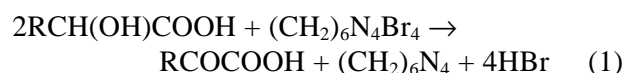
3.1 *Rate laws*

The reactions are first order with respect to HABR as evidenced by a linear plot of log [HABR] time. The pseudo first-order rate constants do not depend on the initial concentration of HABR (table 1). This further confirms first-order dependence of rate on oxidant concentration. Reaction rates increase linearly with increase in the concentrations of the hydroxy acid (table 1). A plot of log k_{obs} vs log [hydoxy acid] is linear ($c^2 > 0.999$) with a slope = 0.97 ± 0.02, indicating that the order with respect to hydroxy acid is also one.

3.2 *Induced polymerization of acrylonitrile*

Oxidation of hydroxy acids, under nitrogen atmosphere, failed to induce polymerization of acrylonitrile. Further, addition of acrylonitrile had no effect on the rate (table 1).

3.3 *Effect of temperature*

Rates of oxidation of hydroxy acids were determined at different temperatures between 298 and 328 K and the activation parameters were calculated (table 2).

Table 1. Rate constants for the oxidation of mandelic acid by HABR at 318 K.

[MA] (mol dm^{-3})	10^3 [HABR] (mol dm^{-3})	10^4 k_{obs} (s^{-1})
0·2	1·0	1·20
0·4	1·0	2·30
0·6	1·0	3·15
1·0	1·0	5·40
2·0	1·0	11·2
3·0	1·0	16·0
5·0	1·0	27·5
3·0	1·0	15·8[a]
1·0	0·4	5·37
1·0	0·8	5·45
1·0	2·0	5·31
1·0	3·0	5·51
1·0	4·0	5·40
1·0	1·0	5·48[b]
1·0	1·0	5·37[c]

[a]Contained 0·005 mol dm^{-3} acrylonitrile; [b]Contained 0.02 mol dm^{-3} HXA; [c]Contained 0.02 mol dm^{-3} sodium bromide

3.4 *Kinetic isotope effect*

To ascertain the importance of the cleavage of the **a**-C–H bond in the rate-determining step, the oxidation of DMA was studied. The results showed (table 2) that the reaction exhibited a substantial kinetic isotope effect (k_H/k_D = 5·91 at 298 K).

3.5 *Effect of hexamethylenetetramine*

An addition of hexamethylenetetramine (HXA) showed no effect on the rate of oxidation (table 1).

3.6 *Effect of bromide ion*

The rate of oxidation of the hydroxy acids was not affected by the addition of sodium bromide (table 1).

3.6 *Spectral studies*

Study of the UV-Vis spectra of HABR (0·001 mol dm^{-3}) and an equivalent amount of bromine (0·002 mol dm^{-3}) in glacial acetic acid at ≈ 298 K, showed that there is some difference in the nature of the spectra of HABR and bromine. There is a broad peak for HABR in the range of 300–310 nm and a peak at 278 nm for bromine. Their optical densities showed large variations (figure 1). Hexamethylenetetramine (HXA) had no appreciable absorption in this range. Further, the spe-

ctrum of HABR did not show any change in experimental time period (≈ 2 h). When a solution of HABR in glacial acetic acid was evaporated to dryness under reduced pressure, HABR was recovered unchanged. This confirmed that HABR retained its integrity in acetic acid.

4. Discussion

The linear correlation between log k_2 of twelve hydroxy acids at 298 and 328 K (c^2 = 0·9994; slope = 0·857 ± 0·002) shows that an isokinetic relationship exists in the oxidation of hydroxy acids by HABR.[14] The value of the isokinetic temperature is 834 ± 28 K. Isokinetic relationship is a necessary condition for the validity of linear free energy relationships. It also implies that all the hydroxy acids so correlated are oxidized by similar mechanisms.[14]

In the present reaction, HABR itself is suggested as the reactive oxidising species from the spectral evidence and the isolation of unchanged HABR when a solution of HABR in glacial acetic acid is evaporated to dryness. Similar reactive oxidising species are suggested in the oxidation of organic sulphides by HABR.[3] The nil effect of added HXA or bromide ion on the rate of oxidation is reminiscent of the results obtained earlier[3] and indicates that the following equilibrium (2) does *not* exist in the solution.

$$(CH_2)_6N_4Br_4 \rightleftharpoons 2Br_2 + (CH_2)_6N_4. \qquad (2)$$
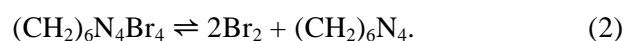
Nothing much is known about the structure of HABR. For the sake of convenience, we have shown one of the two reactive portions as $>$N**L** Br**L** Br.[5] For the nature of the bonding, it can be suggested that there is an interaction between the non-bonded pair of electrons on nitrogen and bromine represented by dotted lines.

It is good to mention here that the use of HABR in an acid medium has advantages over the use of bromine because the kinetics of oxidation by bromine in acid medium (pH ≤ 5) is complex.[15] In this system the probable oxidizing species may be Br_2, HOBR or Br_3^-. However, such complications do not arise with HABR as it retains its integrity in acetic acid.

4.1 *Correlation analysis of reactivity*

Rate constants of the oxidation of MA and ten mono-substituted mandelic acids were correlated in terms

Table 2. Rate constants and activation parameters of the oxidation of substituted mandelic acids by HABR[a].

Substitutent	$10^4 k_2 (dm^3 mol^{-1} s^{-1})$ at temp. (K)				ΔH^* (kJ mol^{-1})	ΔS^* (J mol^{-1} K^{-1})	ΔG^* (kJ mol^{-1})
	298	308	318	328			
H	1·30	2·71	5·40	11·0	55·1 ± 0·6	−135 ± 2	95·2 ± 0·5
p-F	1·92	3·90	7·65	16·1	52·9 ± 1·1	−136 ± 4	93·3 ± 0·9
p-Cl	0·71	1·49	3·05	6·49	55·3 ± 0·9	−136 ± 3	95·8 ± 0·7
p-Br	0·605	1·31	2·72	5·65	55·9 ± 0·5	−135 ± 2	96·1 ± 0·4
p-Me	6·57	12·0	21·8	43·7	46·8 ± 1·5	−147 ± 5	90·4 ± 1·2
p-Pr^i	5·68	10·9	20·4	39·8	48·3 ± 0·9	−143 ± 3	90·7 ± 0·7
p-OMe	74·5	120	195	352	37·9 ± 1·5	−157 ± 5	84·6 ± 1·2
m-Cl	0·164	0·383	0·838	1·91	61·5 ± 0·8	−127 ± 3	99·3 ± 0·6
m-NO$_2$	0·037	0·095	0·222	0·521	66·6 ± 0·3	−122 ± 1	103 ± 0·3
p-NO$_2$	0·021	0·055	0·140	0·322	69·3 ± 0·4	−118 ± 1	104 ± 0·3
m-Br	0·155	0·360	0·788	1·74	60·7 ± 0·5	−130 ± 2	99·4 ± 0·4
LA	0·43	0·92	1·92	3·70	55·9 ± 0·2	−141 ± 1	97·9 ± 0·2
DMA	0·22	0·47	0·96	2·00	57·1 ± 0·6	−143 ± 2	99·6 ± 0·5
k_H/k_D	5·91	5·76	5·62	5·50			

[a][oxidant] = 0·001 mol dm^{-3}; [hydroxy acid] = 0·5 to 5·0 mol dm^{-3} depending on the reactivity of the hydroxy acid
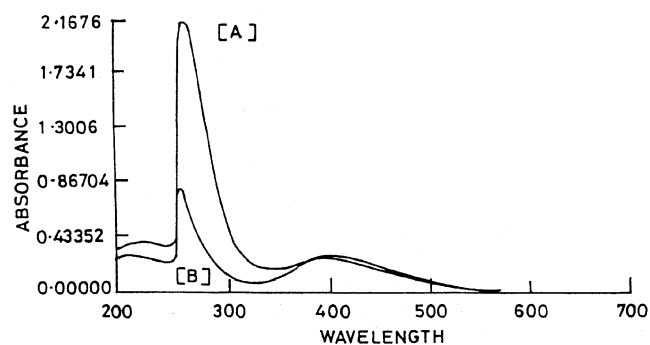
Figure 1. UV-Vis spectra of (**A**) 0·001 mol dm^{-3} HABR and (**B**) 0·002 mol dm^{-3} bromine; Temperature – 298 K; Solvent – Glacial acetic acid.

Table 3. Temperature dependence of the reaction constant for the oxidation of substituted mandelic acids by HABR[a].

Temp. (K)	$\mathbf{r}^+$	r^2	sd	$\mathbf{y}$	h^b
298	−2·27±0·01	0·9999	0·007	0·010	−3·89
308	−2·13±0·01	0·9999	0·010	0·023	−3·57
318	−2·02±0·01	0·9998	0·014	0·015	−3·27
328	−1·95±0·01	0·9998	0·013	0·015	−2·96

[a]No. of data points = 11; [b]*h* = intercept

of the Hammett equation[16] but the attempts failed to yield significant correlation (3) with Hammett's $\mathbf{s}$ values. The main deviating points correspond to para-substituents capable of electron donation by resonance viz. methoxy, methyl, isopropyl, fluoro etc. Their rates are higher than those required by their Hammett's $\mathbf{s}$ values.

$$\log k_2 = -2·92 \pm 0.25 \ \mathbf{s} - 3·53, \qquad (3)$$

$c^2 = 0·9403$; sd = 0·27; $n = 11$; $\mathbf{y} = 0·26$; temperature = 298 K.

Here, *n* is the number of data points.

The rate constants were, therefore, correlated in terms of Brown's[17] $\mathbf{s}^+$ values (4). An excellent correlation (figure 2) with large reaction constants were obtained (table 3):

$$\log k_3 = \mathbf{r}^+ \mathbf{s}^+ + \log k_0. \qquad (4)$$

Here, k_0 is rate constant for MA.

4.2 *Mechanism*

A hydrogen abstraction mechanism leading to the formation of free radicals may be discounted in view of the failure to induce polymerization of acrylonitrile[18] and the large values of the reaction constants. In most hydrogen abstraction reactions, the reaction constants have small magnitude.[16]

The observed substantial kinetic isotope effect ($k_H/k_D = 5·91$ at 298 K) suggests that the $\mathbf{a}$-C–H bond is cleaved in the rate-determining step. Corre-

lation analysis of the substituent effect indicates the presence of a highly electron-deficient reaction centre in the rate-determining step. The fact that an excellent correlation is obtained with Brown's s^+ values suggests that there is resonance interaction, in the transition state, between a developing positive centre at the reaction site and the substituent. Thus, the transition state approaches a carbocationic in character. Therefore, the transfer of a hydride-ion from the acid to the oxidant is indicated (scheme 1). The proposed mechanism is, however, supported by the observed negative entropy of activation for the conversion of the reactant molecules into the activated complex. As the process involves large charge separation in the transition state resulting in an increase in the total number of charges, the two ends become highly solvated. This results in an immobilization of a large number of solvent molecules, reflected in loss of entropy. Two moles of the hydroxy acids are oxidized per mole of the oxidant.
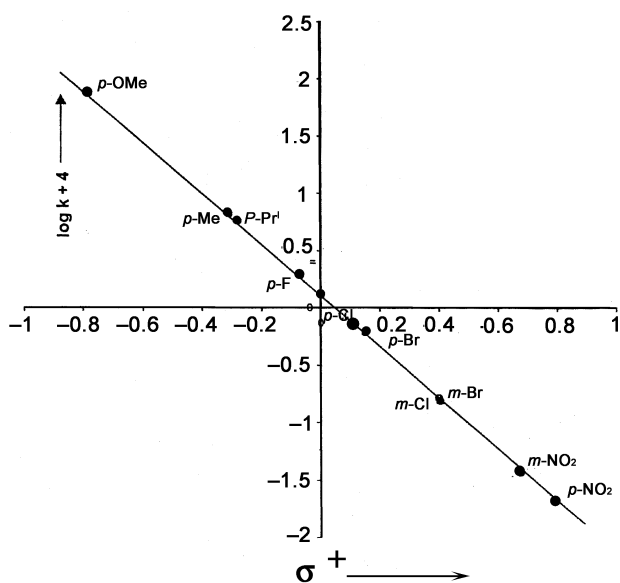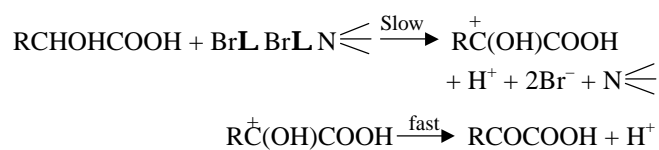

Figure 2. Brown's plot for the oxidation of MA by HABR at 298 K.

$$RCHOHCOOH + BrL\!BrL\,N\!\!\overset{Slow}{\underset{}{\rightleftharpoons}}\!\!\overset{+}{R}C(OH)COOH$$
$$+ H^+ + 2Br^- + N\!\!\overset{}{\underset{}{\leftleftarrows}}$$
$$\overset{+}{R}C(OH)COOH \overset{fast}{\longrightarrow} RCOCOOH + H^+$$

Scheme 1.

It is of interest to compare the results of oxidation of *a*-hydroxy acids by other oxidants containing halogen. The rates of oxidation of *a*-hydroxy acids by benzyl trimethylammonium tribromide (BTMAB)[19] are reported to involve the formation of an intermediate complex in the pre-equilibrium stage, which then collapses to an acylhypobromite derivative in the rate-determining step, leading to the formation of the corresponding carbonyl compound in the fast step. However, the reactions of the oxidation of MA by both sodium N-bromobenzenesulphonamide (BAB)[20] and N-bromoacetamide (NBA)[21] are of first order with respect to both the acid and the oxidant. The oxidation of MA by NBA is reported to involve the formation of hypobromite ester in the slow step prior to the formation of the corresponding carbonyl compound. However, the oxidation of MA by BAB undergoes oxidative decarboxylation to produce the carbonyl compound. In the oxidation by PHPB[22] and BTMACI,[23] the reactions involve hydride-ion transfer from the acid to the oxidant to give a carbocationic species in the rate-determining step which leads to the formation of the corresponding oxyacid as the final product. This is essentially similar to the mechanism suggested in the present reaction. The oxidations of MA by two halochromates, viz. pyridinium chlorochromate (PCC)[24] and pyridinium bromochromate (PBC),[25] are reported to involve an ester intermediate formation in the pre-equilibrium stage, which undergoes decomposition in the subsequent slow step via a cyclic, concerted and symmetrical transition state to give the corresponding oxoacid. However, the results of the correlation analysis show that the oxidation by PBC exhibits excellent correlation in terms of Brown's s^+ values, whereas PCC oxidation correlate well with Hammett's s values. To account for the results of the correlation analysis, an alternate mechanism involving direct hydride-ion transfer to the oxidant is also proposed. It seems that the mechanism of the oxidation of *a*-hydroxy acids depends on the nature of the oxidant.

Further, it is observed that oxidations of *a*-hydroxy acids by HABR follow similar reaction path to that of alcohols,[5] involving hydride-ion transfer from the substrate to the oxidant in the rate-determining step. Rate laws are similar and both the oxidations exhibit substantial kinetic isotope effect of about the same order. Cleavage of the *a*-C–H bond is suggested in the rate-determining step of both the reactions. Oxidations of *a*-hydroxy acids show excellent correlation with Brown's s^+ values, though the oxidation rates

of alcohols correlate well with Charton's triparametric LDR equation.[26] Regression coefficients in both the reactions are negative indicating an electron-deficient reaction centre in the transition state of the reaction.

Acknowledgement

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