Indian Journal of Chemistry
Vol. 37B, May 1998, pp. 443 - 447

Oxidation of α-hydroxyacids by *N*-bromophthalimide—Dependence of mechanism on *p*H of the medium

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Received 25 July 1996; accepted (revised) 12 May 1997

The oxidation of α-hydroxyacids, namely mandelic acid, lactic acid, malic acid, benzilic acid and atrolatic acid and *N*-bromophthalimide to give the corresponding carbonyl compounds, has been carried out. It was of interest to determine whether the alcoholic OH or the carboxylic OH is involved in the oxidative decarboxylation of α-hydroxy acids which have bifunctional groups. A study of the dependence of rate on the *p*H of the medium was expected to differentiate between these two routes. Further, the α-hydroxyacids may react as simple alcohols and undergo oxidation involving a C–H bond cleavage to give keto acids which may subsequently undergo decarboxylation. A comparative study of mandelic acid and mandelic acid-α_d indicates the absence of primary kinetic isotope effect, ruling out the above possibility. It is likely that acyl hypobromite is a precursor for oxidation at higher *p*H and the involvement of alkyl hypobromite cannot be ruled out at lower *p*H. The NBP and NBS oxidations of α-hydroxyacids are found to be well correlated.

There are several reports available in the literature on the oxidation of α-hydroxyacids by reagents such as N-bromosuccinimide[1], N-bromoacetamide[2], trichloroisocyanuric acid[3], N-bromobenzene sulphonamide[4], N-chlorobenzene sulphonamide[5], 1-chlorobenzo triazole[6], N-bromosaccharin[7], and bromate[8]. However, there is no reported study using N-bromophthalimide (NBP) as an oxidising agent. NBP has some definite advantages over other N-halogeno oxidants[9,10]. It is extremely stable in the solid state when kept out of light and moisture. Its standard solutions have excellent keeping qualities. In its reaction with α-hydroxyacids it is of interest to determine whether the alcoholic or the carboxylic-OH is involved in the oxidative decarboxylation.

Materials and Methods

N-Bromophthalimide (NBP) (Aldrich sample) was used as such. This had 99% purity as shown by iodometric estimation of its solutions. The melting point of the sample was found to be 482K. Solutions of NBP were prepared as and when necessary and kept covered with blue cloth in order to avoid decomposition under the influence of light.

Mandelic acid (MA), lactic acid (LA), malic acid (MLA) and atrolactic acid (AA) of extra pure variety were again purified by distillation or recrystallisation. Benzilic acid (BA) was prepared from benzil[11]. Acetic acid (Glaxo ExcelaR) was purified by the method of Orton and Bradfield[12,13]. Deuteromandelic acid was prepared by the method of Kemp and Waters[14]. Sodium acetate (Glaxo ExcelaR) was used. All substrates were dissolved in acetic acid-water mixtures and sodium acetate was added in calculated amounts to the solution before making up to the required volume. The solutions were preserved in the dark. Kinetics of the reaction were followed by adding the oxidant to the substrate under thermostated conditions and estimating the unreacted oxidant iodometrically by withdrawing aliquots of the reaction mixture at regular intervals of time. All reactions were carried

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out under pseudo first order conditions using tenfold excess of [substrate] over [NBP].

The primary oxidation product of mandelic acid was benzaldehyde and that of benzilic acid was benzophenone as characterised by the melting points of their 2,4-dinitrophenylhydrazones.

Stoichiometry. Known concentrations of aqueous acetic acid solutions of the substrate and oxidant were thermostated. Varying quantities of each of these solutions were mixed in such a way that the oxidant was always in excess. The unreacted oxidant was then estimated after 24 and 48 hours to confirm the completion of the reaction. From the amount of oxidant consumed, assuming complete reaction of the reductant, stoichiometry was calculated. One mole of the oxidant was consumed by one mole of the substrate.

Results and Discussion

The reaction is of first order in [NBP] as indicated by the linearity of a plot of log [NBP] versus time for each of the substrates studied. This is further confirmed by the fact that the first order rate constant is invariant with different initial concentrations of NBP (Table I). The effect of varying the concentrations of α-hydroxyacids on rate shows that the reaction order is unity with respect to the substrate also (Table I). Further, a plot of log k_1 versus log [substrate] is linear with a slope of unity and the plot of k_1 versus [substrate] is linear and the line passes through the origin. The rate law for the reaction at constant concentration of NaOAc is found to be:

$$-\frac{d[\text{NBP}]}{dt} = k_{obs}[\text{NBP}][\text{RR'COHCO}_2\text{H}] \quad \ldots (1)$$

Addition of acrylonitrile to the reaction mixture does not induce polymerisation. Therefore, the reaction does not involve the formation of free radicals. For all the α-hydroxyacids under study, the rate increases as *p*H increases in the range 3 to 6 (Table II, Figure 1).

At *p*H 5, which is higher than the pK_a of all the acids, the substrates are all completely dissociated and the reaction can take place between the anion of the acid and NBP. The carboxylate ion reacts with NBP to give an acyl hypobromite inter-

Table I—Effect of varying [oxidant] and [substrate] on reaction rate

{[NaOAc]=0.2 mol dm^{-3}; Solvent=50% aq. HOAc (v/v)}

[NBP] $\times10^3$ mol dm^{-3}	[MA] $\times10^2$ mol dm^{-3}	Temp. 303K $k_1\times10^5$ s^{-1}	[MLA] $\times10^2$ mol dm^{-3}	Temp. 323K $k_1\times10^5$ s^{-1}	[AA] $\times10^2$ mol dm^{-3}	Temp. 303K $k_1\times10^5$ s^{-1}	[LA] $\times10^2$ mol dm^{-3}	Temp. 323K $k_1\times10^5$ s^{-1}	[BA] $\times10^2$ mol dm^{-3}	Temp. 303K $k_1\times10^5$ s^{-1}
2.0	3.0	14.0	3.0	16.9	2.0	46.3	3.0	8.00	2.0	52.8
2.5	2.5	13.9	3.0	17.3	2.0	44.2	3.0	7.95	2.0	55.0
3.0	3.0	13.9	3.0	17.0	2.0	48.2	3.0	8.05	2.0	54.0
3.5	–	–	–	–	2.0	42.8	–	–	–	–
4.0	3.0	14.1	3.0	17.4	–	–	3.0	8.00	2.0	52.0
2.0	2.0	9.32	2.0	11.5	2.5	57.9	2.0	5.03	3.0	80.3
2.0	4.0	17.6	4.0	20.9	3.0	70.1	4.0	9.01	4.0	95.0
2.0	5.0	25.2	5.0	29.3	3.5	85.0	5.0	13.5	4.5	114.1
2.0	6.0	28.1	6.0	35.6	4.0	92.1	6.0	14.5	5.0	142.1
2.0	8.0	37.0	–	–	–	–	–	–	–	–

Table II—Effect of varying *p*H on reaction rate

{[NBP]=2.0×10^{-3} mol dm^{-3}; Solvent=50% aq. HOAc (v/v); [Substrate]= 2.0×10^{-2} mol dm^{-3}}

*p*H	[MA] $k_1\times10^5$ s^{-1} at 303K	[LA] $k_1\times10^5$ s^{-1} at 323K	[MLA] $k_1\times10^5$ s^{-1} at 323K	[BA] $k_1\times10^5$ s^{-1} at 303K	[AA] $k_1\times10^5$ s^{-1} at 303K
3.20	9.20	5.06	1.25	53.8	48.3
4.03	23.0	5.74	1.98	63.1	59.2
4.64	31.3	–	–	–	–
5.03	42.1	6.52	2.72	74.1	70.2
5.55	52.0	6.91	3.21	89.9	87.2
5.90	64.1	7.30	3.62	–	–

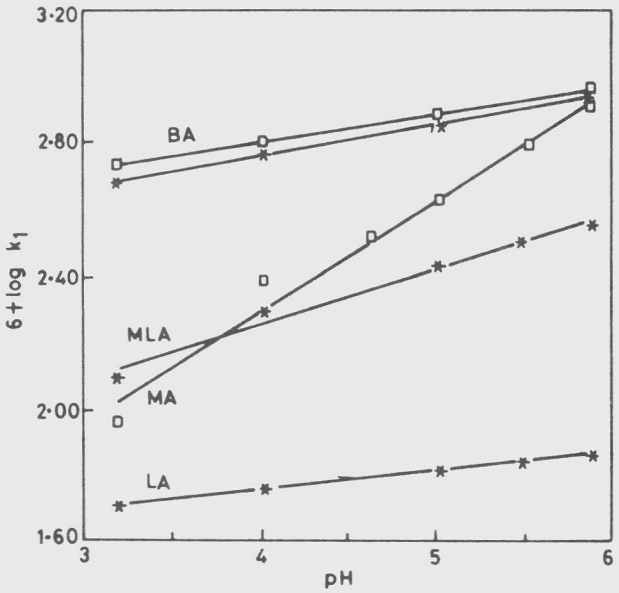
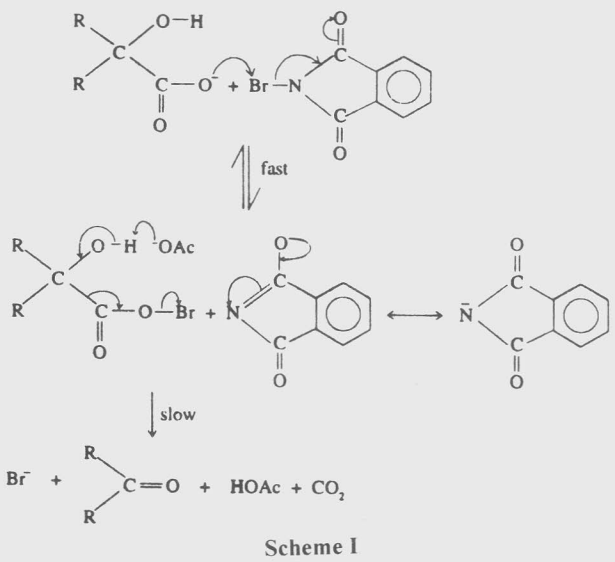


Figure 1—Effect of varying *p*H on reaction rate {[NBP]=2.0×10^{-3} mol dm^{-3}; Solvent=50% aq. HOAc (v/v); [Substrate]=2.0×10^{-2} mol dm^{-3}}



Scheme I

mediate, as has been suggested for bromine oxidation of oxalic acid[15]. This intermediate decomposes to give the carbonyl compound. Such a path way has been suggested in the oxidation of α-hydroxyacids by chloramine T[16] and N-bromosuccinimide (NBS)[1]. In the present case OAc^- could function as a base and it has been found that an increase in concentration of sodium acetate increases the rate. Scheme I could account for the kinetic observations.

Pink and Stewart[17] have proposed a similar mechanism for the oxidation of mandelic acid by bromine.

One argument against the formation of acyl hypobromite from α-hydroxy acid is the difficulty in envisaging a nucleophilic attack by the oxidising species on –COOH in acidic medium. In such an event, that is with an un-ionised carboxylic acid group which can exist below *p*H 5, an alkyl hypobromite may appear to be a reasonable intermediate for the oxidative decarboxylation.

Levitt and Malinouski[18] have shown that hypohalite esters decompose readily to carbonyl compounds.

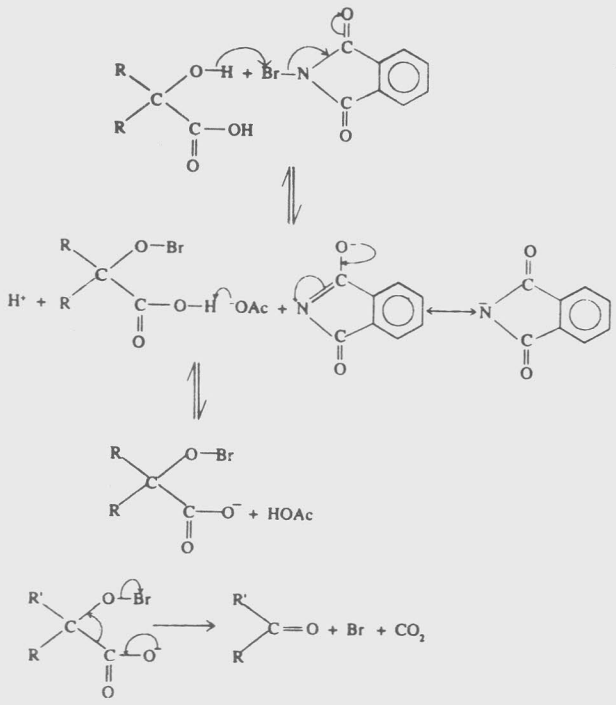
The replacement of hydroxyl by hypobromite is favourable to decarboxylation as the bromine atom is a better leaving group than hydrogen[19] (cf. Scheme V). This mechanism is similar to that proposed for the oxidation of α-hydroxyacids by aqueous bromine in acid medium in the presence of Ag^+ ions[20].

The results may also be interpreted in terms of a concerted reaction between the undissociated carboxylic acid, hyprobromous acid and base. But such a concerted mechanism is unlikely, because in the present study, an insensitivity to solvent isotope effect is observed (Table III).

The *p*H profile for the oxidation of α-hydroxyacids by NBP is found to be linear in the *p*H range 3 to 6. A similar *p*H rate profile is reported by Auckett and Barker[19] for the oxidation of *p*-chloromandelic acid by hypobromous acid. According to them the carboxylate ion is commonly more reactive in decarboxylation than the undissociated acid and as *p*H increases beyond the pK_a of these acids, they exist increasingly in the ionised form.

Oxidation of α-hydroxyacids can proceed through a hydride ion transfer mechanism. This has been suggested for the chlorine oxidation of the substrates[21]. However, the absence of any primary kinetic isotope effect in the oxidation of mandelic acid (Table III, k_H/k_D=1.05) and the facility with which benzilic acid and atrolactic acid (with the absence of secondary hydrogen) undergo oxidative decarboxylation, in the present study, proves that the hydride ion transfer mechanism is untenable under the conditions employed.

The reaction rate is retarded by the addition of phthalimide which is one of the products of the



Scheme II

Table III—Isotope effect on the oxidation of mandelic acid {[substrate]=2.0×10^{-2} mol dm^{-3}; [NBP]=2.0×10^{-3} mol dm^{-3}; Temp.: 303K

Substrate	Solvent	$k_1\times s^{-1}$
$C_6H_5CHOHCOOH$	CD_3COOH/D_2O (50:50)	4.42×10^{-5}
$C_6H_5CDOHCOOH$	CD_3COOH/D_2O (50:50)	4.20×10^{-5}
$C_6H_5CHOHCOOH$	CH_3COOH/H_2O (50:50)	4.12×10^{-5}

k_H/k_D=1.05

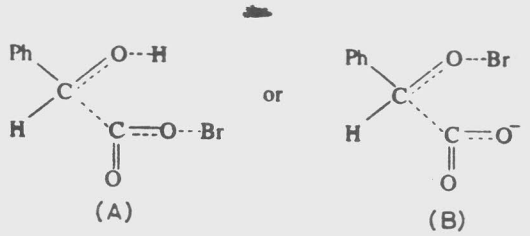
reaction. This points to the existence of a pre-equilibrium step as shown below:

(i) NBP+HOAc⇌BrOSAc+phthalimide ... (2)

(ii) NBP+H_2O⇌HOBr+phthalimide ... (3)

The positive bromine from NBP can be transferred to the α-hydroxyacid through the intermediate formation of acetyl hyprobromite or hypobromous acid.

The rate of oxidative decarboxylation is found to follow the order: lactic acid<malic acid<mandelic acid<atrolactic acid<benzilic acid. This can be explained on the basis of a transition state **A** or **B**, which involves a partial bond formation of the carboxyl group.



The aryl group stabilises the transition state more than the alkyl group. Therefore, the reactivity of the hydroxyacids parallels the stability of formation of the carbonyl group, CH_3CHO< PhCHO<$PhCOCH_3$<$(Ph)_2CO$. The mechanism follows through a product-like transition state, as shown.

The oxidation of α-hydroxyacids has been studied at 303K, 313K & 323K and the data are presented in Table IV. Arrhenius parameters evaluated from linear plots of log k_2 versus $1/T$ are presented in Table V. A near constancy of free energy of activation values suggests that all the hydroxyacids undergo oxidation involving the same mechanism.

The oxidation of α-hydroxyacid by NBP seems to parallel that of NBS. A plot of log k_{NBS} versus log k_{NBP} is linear with a slope of 0.9. Corresponding rate constants at various *p*H values for both the reagents are presented in Table VI.

It may be concluded that, above *p*H 5, one can envisage a mechanism with an acyl hypobromite

Table IV—Effect of varying temperature on reaction rate {[substrate]= 2.0×10^{-2} mol dm^{-3}; [NaOAc]=0.2 mol dm^{-3}; [NBP]=2.0×10^{-3} mol dm^{-3}; Solvent: 50% aq. HOAc (v/v)}

Substrate		Temperature (K)		
		303	313	323
MA	$k_1\times10^4\ s^{-1}$	0.932	2.02	4.21
LA	$k_1\times10^5\ s^{-1}$	1.46	2.86	5.01
MLA	$k_1\times10^5\ s^{-1}$	1.85	4.13	11.5
BA	$k_1\times10^4\ s^{-1}$	5.28	12.4	22.9
AA	$k_1\times10^4\ s^{-1}$	4.63	9.92	18.4

Table V—Arrhenius parameters

Substrate	E_a kJ mol^{-1}	$\Delta H^{\ddagger}$ kJ mol^{-1}	$-\Delta S^{\ddagger}$ JK^{-1} mol^{-1}	$\Delta G^{\ddagger}$ kJ mol^{-1}
MA	61.3	58.7	87.6	85.3
LA	53.2	50.6	129	89.9
MLA	72.0	69.5	65.3	89.3
BA	51.6	49.0	103	80.4
AA	54.9	52.5	123	89.8

Table VI—

{[MA]2.0×10^{-2} mol dm^{-3}; Solvent: 50% aq. HOAc (v/v); [oxidant]=2.0×10^{-3} mol dm^{-3}; Temp.: 303K}

Oxidant		*p*H				
		3.17	4.04	4.64	5.05	55.0
NBS	$k_1\times10^4$ s^{-1}	0.42	1.68	2.75	3.71	4.46
NBP	$k_1\times10^4$ s^{-1}	0.92	2.30	3.13	4.20	5.20

intermediate (Scheme I) for the reaction because an ionised carboxyl group is capable of taking up positive bromine more readily than alcoholic hydroxyl. But below *p*H 5, in presence of un-ionised carboxyl group, the involvement of an alkyl hypobromite intermediate cannot possibly be ruled out (Scheme II).

Acknowledgement

One of the authors (SR) is grateful to UGC, New Delhi for financial assistance under FIP programme and to Women's Christian College for the use of facilities in the Chemistry Laboratory and to Dr S Sundaram, Department of Chemistry, Ramakrishna Mission Vivekananda College, Chennai for his valuable help.

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