Bull. Chem. Soc. Jpn., 63, 2404—2407 (1990) [Vol. 63, No. 8

Methoxybromination of Cinnamic Acid by *N*-Bromosuccinimide

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(Received September 26, 1989)

With cinnamic acid in aqueous methanol *N*-bromosuccinimide yields 2-bromo-3-methoxy-3-phenylpropionic acid. It is a second-order reaction independent of [H$^+$] at moderately high [H$^+$]. At low [H$^+$] the rate increases with decrease in [H$^+$]. The reaction is inhibited by succinimide. The reaction rate decreases with increase in methanol content of the medium. Mechanistic pathways of the reaction are discussed and a rate equation is derived.

N-Bromosuccinimide (NBS) bromination[1-3] and oxidation[4,5] of saturated organic compounds in protic solvents have received considerable attention. There seems to be no detailed study on the reactions of NBS with unsaturated compounds in protic solvents. We have studied the reactions of NBS with β,γ-unsaturated alcohols.[6-8] Here we report methoxybromination of cinnamic acid — a simple and convenient method of synthesising bromomethoxy acid — and its kinetics and mechanism. Crotonic acid with NBS in aqueous acetic acid has yielded dibromo acid.[9]

Results and Discussion

The reaction of NBS with cinnamic acid in aqueous methanol in presence of perchloric acid yields 2-bromo-3-methoxy-3-phenylpropionic acid. The stoichiometry of the reaction is 1 : 1. Hence the reaction is represented as

$$(CH_2CO)_2NBr + C_6H_5CH{=}CHCOOH + CH_3OH \rightarrow$$
$$C_6H_5CH(OCH_3)CHBrCOOH + (CH_2CO)_2NH$$

Methoxybromination is a second-order reaction—first order each with respect to NBS and cinnamic acid (acid). Under second-order conditions plots of $\ln([NBS]_0[Acid]/[Acid]_0[NBS])$ against time when $[NBS]_0 \neq [Acid]_0$, and $[NBS]_{consumed}/[NBS]$ against time when $[NBS]_0=[Acid]_0$ are linear. A typical second-order plot is shown in Fig. 1 ($10^3[NBS]_0=1.5$ mol dm^{-3}, $10^3[Acid]_0=2.0$ mol dm^{-3}, $10^2[H^+]=1.62$ mol dm^{-3}, solvent 50% (v/v) aqueous methanol, temp 35 °C, correlation coefficient, $r=0.9996$ and standard deviation, $s=0.0100$). The second-order rate constant determined at different [Reactants]$_0$ remains constant (Table 1). At fixed [Reactants]$_0$ and ionic strength, μ (maintained with sodium perchlorate) the rate of the reaction is independent of [H$^+$] at moderately high [H$^+$] but at low [H$^+$] it increases with decrease in [H$^+$] as shown in Table 1. Even at low [H$^+$] the reaction follows second-order rate law. Figure 2 shows a linear second-order plot at low [H$^+$]. ($10^3[NBS]_0=10^3[Acid]_0=2.0$ mol dm^{-3}, $10^3[H^+]=1.15$ mol dm^{-3}, $10^2\mu=8.0$ mol dm^{-3}, solvent 50% (v/v) aqueous methanol, temp 35 °C, $r=0.9983$ and $s=0.1186$).[10]

Ionic strength of the medium has no influence on the reaction rate (Table 1). The reaction is inhibited by succinimide. Initial addition of succinimide to the reaction mixture suppresses the reaction rate substantially. Under the conditions $10^3[Reactants]_0=2.0$ mol dm^{-3} and $10^2[H^+]=1.62$ mol dm^{-3} the second-

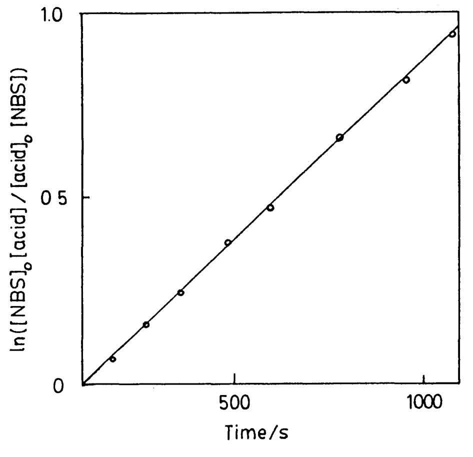


Fig. 1. Second-order rate plot for NBS-cinnamic acid reaction at moderately high [H$^+$].

Table 1. Second-Order Rate Constants for Methoxybromination of Cinnamic Acid by NBS in 50% Aqueous Methanol at 35 °C

$10^3[NBS]_0$ mol dm^{-3}	$10^3[Acid]_0$ mol dm^{-3}	$10^2[H^+]$ mol dm^{-3}	k dm^3 mol^{-1} s^{-1}
0.50	2.00	1.62	1.74±0.09
1.00	2.00	1.62	1.76±0.08
1.50	2.00	1.62	1.91±0.06
1.75	2.00	1.62	2.02±0.10
2.00	2.00	1.62	1.96±0.07
2.00	2.50	1.62	1.79±0.13
2.00	3.00	1.62	1.90±0.19
2.00	3.50	1.62	1.95±0.13
2.00	4.00	1.62	1.86±0.26
2.00	2.00	0.115	3.43±0.20[a]
2.00	2.00	0.437	2.51±0.07[a]
2.00	2.00	0.603	2.26±0.12[a]
2.00	2.00	1.62	1.81±0.24[a]
2.00	2.00	3.39	1.88±0.07[a]
2.00	2.00	4.47	1.72±0.08[a]
2.00	2.00	6.17	1.83±0.02[a]
2.00	2.00	1.62	2.09±0.16[b]

a) μ=0.08 mol dm^{-3}. b) μ=0.14 mol dm^{-3}.

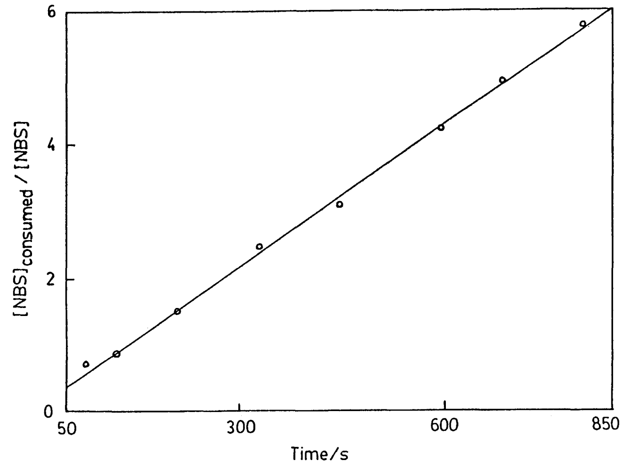


Fig. 2. Second-order rate plot for NBS-cinnamic acid reaction at low [H^+].

order rate constant decreases from 0.570±0.014 to 0.124±0.005 $dm^3\,mol^{-1}\,s^{-1}$ when 10^2[Succinimide]$_0$ is increased from 1.0 to 4.0 $mol\,dm^{-3}$ in 50% (v/v) aqueous methanol at 35 °C. However, in the absence of initially added succinimide at moderately high as well as low [H^+] the reaction uninhibited by the product formed follows a clean second-order rate law (Figs. 1 and 2). Non-linear plots of [Acid]$_0$ ln [Acid]—[NBS]$_0$ ln [NBS] against time (Fig. 3, conditions as in Fig. 1) and ([Reactants]$_0$/[Reactants])+ ln ([Reactants]/[Reactants]$_0$) against time (Fig. 4, conditions as in Fig. 2) at moderately high and low [H^+] respectively confirm the absence of first-order inhibition by succinimide when formed in low concentration, i.e., at fixed [H^+] the rate law

$$-d[NBS]/dt = k[NBS][Acid]/[Succinimide]$$

does not hold. Here, the concentration of consumed NBS is taken as the concentration of succinimide.

The dielectric effect is positive. The rate of the reaction increases from 0.445±0.015 to 5.11±0.14 $dm^3\,mol^{-1}\,s^{-1}$ when methanol content in the medium is decreased from 70 to 30% (v/v) at 35 °C. The activation parameters of the reaction at [H^+]=0.0162 $mol\,dm^{-3}$ in the absence of initially added succinimide in 50% (v/v) aqueous methanol have been calculated from the rate measurements at 15, 25, and 35 °C through Eyring plot.

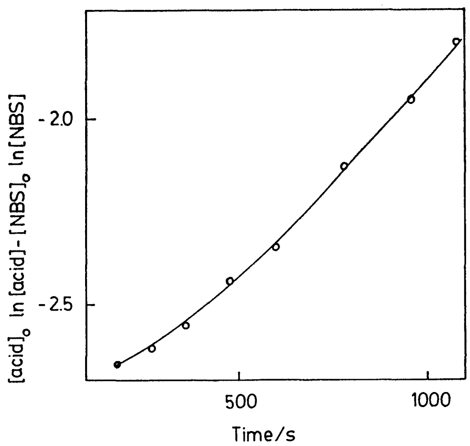


Fig. 3. Reactants —second-order, succinimide (formed)— inverse first-order rate plot at moderately high [H^+].

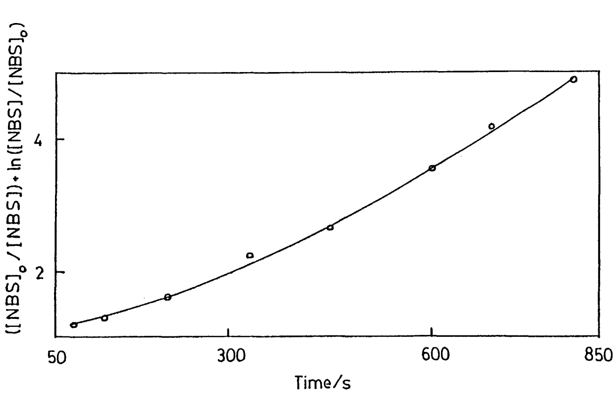


Fig. 4. Reactants —second-order, succinimide (formed)— inverse first-order rate plot at low [H^+].

$$\Delta H^{\#} = 17.8\ kJ\,mol^{-1}$$

$$\Delta S^{\#} = -182\ J\,K^{-1}\,mol^{-1}$$

$$\Delta G^{\#} = 73.8\ kJ\,mol^{-1}\ (at\ 35\ ^\circ C)$$

The possible reactive species of NBS in acidic medium are NBS itself, protonated NBS ($NBSH^+$), HOBr, and solvated bromonium ion.[6–8] With the oxidising species cinnamic acid may react in its molecular form or through its anion. The reaction has been studied at [H^+] range 0.00115 to 0.0617 $mol\,dm^{-3}$. Under this concentration range protonation of cinnamic acid is less likely. The reaction is not catalysed by H^+ and hence $NBSH^+$ and protonated cinnamic acid (if at all protonated) are ruled out as the reactive species. The reaction of $NBSH^+$ with cinnamate ion should be independent of [H^+]. But $NBSH^+$-cinnamate ion reaction pathway is unlikely as the reaction fails to exhibit neutral salt effect. The rate of formation of solvated bromonium ion from molecular NBS under identical conditions is about one-tenth of the rate of the title reaction.[7] Hence Br^+ is unlikely to be the reactive species. Protonation of NBS should facilitate the release of Br^+. But formation of Br^+ through $NBSH^+$ is not considered as the pH titration curve of NBS-$HClO_4$ shows no appreciable protonation. HOBr is formed by the hydrolysis of molecular NBS.[7,8] Methoxybromination of cinnamic acid even at low [H^+] follows second-order rate law (Fig. 2). If HOBr were to be the reactive species its interaction with the substrate should be rate determining. In that case in the absence of initially added succinimide inhibition by succinimide formed is to be observed. As it is not so (Figs. 2 and 4) HOBr is less likely to be the reactive species. On the basis of the rate dependence on [H^+]— rate is independent of [H^+]

at moderately high $[\mathrm{H}^+]$ but increases with decrease in $[\mathrm{H}^+]$ at low $[\mathrm{H}^+]$— the reaction is proposed to proceed via two competitive paths, one independent of $[\mathrm{H}^+]$ and the other inhibited by H^+. Molecular NBS is suggested as the reactive species and is proposed to react with cinnamic acid (Scheme 1) and cinnamate ion as well (Scheme 2). For the suggested mechanistic routes the over all rate law is derived as

$$\frac{-\mathrm{d[NBS]}}{\mathrm{d}t}= \left[\frac{k_1k_2}{k_{-1}[\text{Succinimide}]+k_2}+\frac{K_\mathrm{a}k_3}{[\mathrm{H}^+]}\right][\text{NBS}][\text{Acid}] \tag{1}$$

In the absence of initially added succinimide and at moderately high $[\mathrm{H}^+]$, with the approximations $k_{-1}[\text{Succinimide}] < k_2$ and $K_\mathrm{a}k_3/[\mathrm{H}^+] \ll k_1$, the composite rate equation (Eq. 1) reduces to the simple second-order rate law (Eq. 2)

$$-\mathrm{d[NBS]}/\mathrm{d}t = k_1[\text{NBS}][\text{Acid}] \tag{2}$$

which has been experimentally observed, the experimental second-order rate constant, $k=k_1$. Thus in moderately high acid medium ($[\mathrm{H}^+] > 0.016\ \mathrm{mol\,dm^{-3}}$) and in the absence of initially added succinimide the reaction is mainly through one path, i,e., rate-determining formation of $\mathrm{Ph\overset{+}{C}HCHBrCOOH}$ by the transfer of positive bromine to the substrate (Scheme 1). The cyclic intermediate visualized may decompose instantaneously leading to $\mathrm{Ph\overset{+}{C}HCHBrCOOH}$ making the intermediate non-existent.

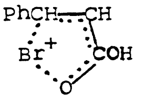
$$\mathrm{(CH_2CO)_2NBr + PhCH{=}CHCOOH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C + (CH_2CO)_2N^-}$$

$$\mathrm{C \xrightarrow{k_1} Ph\overset{+}{C}HCHBrCOOH}$$

$$\mathrm{Ph\overset{+}{C}HCHBrCOOH + CH_3OH \longrightarrow PhCH(OCH_3)CHBrCOOH + H^+} \quad \text{fast}$$

$$\mathrm{(CH_2CO)_2N^- + H^+ \longrightarrow (CH_2CO)_2NH} \quad \text{fast}$$

where C≡



Scheme 1.

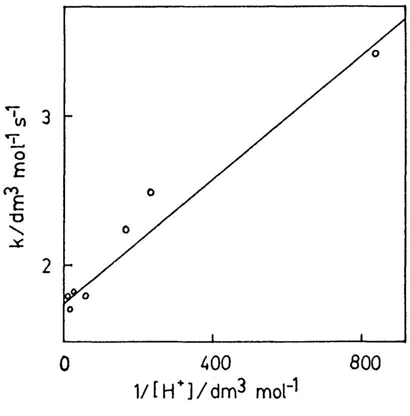


Fig. 5. Dependence of k on $1/[\mathrm{H}^+]$.

In the absence of initially added succinimide, with the approximation $k_{-1}[\text{Succinimide}] < k_2$, the over all rate equation (Eq. 1) simplifies to rate law (3).

$$-\mathrm{d[NBS]}/\mathrm{d}t = (k_1 + K_\mathrm{a}k_3/[\mathrm{H}^+])[\text{NBS}][\text{Acid}] \tag{3}$$

The second-order rate constant, $k=k_1+K_\mathrm{a}k_3/[\mathrm{H}^+]$. Linear plot of k versus $1/[\mathrm{H}^+]$ with a positive intercept (Fig. 5, r=0.9674, s=0.1679) confirms rate law (3). At low $[\mathrm{H}^+]$ ($[\mathrm{H}^+] < 0.006\ \mathrm{mol\,dm^{-3}}$) besides the rate-limiting transfer of Br^+ from molecular NBS to cinnamic acid (Scheme 1) NBS-cinnamate ion reaction pathway (Scheme 2) is operative significantly.

At moderately high $[\mathrm{H}^+]$ and in the presence of initially added succinimide, with the approximations $k_{-1}[\text{Succinimide}] > k_2$ and $k_1k_2/k_{-1}[\text{Succinimide}] > K_\mathrm{a}k_3/[\mathrm{H}^+]$, the composite rate law (Eq. 1) reduces to rate law (4).

$$-\mathrm{d[NBS]}/\mathrm{d}t = k_1k_2[\text{NBS}][\text{Acid}]/k_{-1}[\text{Succinimide}] \tag{4}$$

The second-order rate constant,

$$k = k_1k_2/k_{-1}[\text{Succinimide}].$$

Linear plot of k versus $1/[\text{Succinimide}]_0$ almost through the origin (Fig. 6, r=0.9666, s=0.0629, intercept=0.017 $\mathrm{dm^{-3}mol^{-1}s^{-1}}$) confirms rate law (4). The visualization of the formation of an intermediate in steady state concentration accounts for the inhibition by succinimide. If $\mathrm{Ph\overset{+}{C}HCHBrCOOH}$ were to be the intermediate and were to undergo rate-limiting nucleophilic attack by methanol the reaction rate, contrary to the experimental findings, should increase

$$\mathrm{PhCH{=}CHCOOH \overset{K_a}{\rightleftharpoons} PhCH{=}CHCOO^- + H^+}$$

$$\mathrm{(CH_2CO)_2NBr + PhCH{=}CHCOO^- \xrightarrow{k_3} Ph\overset{+}{C}HCHBrCOO^- + (CH_2CO)_2N^-} \quad \text{slow}$$

$$\mathrm{Ph\overset{+}{C}HCHBrCOO^- + CH_3OH \longrightarrow PhCH(OCH_3)CHBrCOO^- + H^+} \quad \text{fast}$$

$$\mathrm{PhCH(OCH_3)CHBrCOO^- + H^+ \rightleftharpoons PhCH(OCH_3)CHBrCOOH}$$

$$\mathrm{(CH_2CO)_2N^- + H^+ \longrightarrow (CH_2CO)_2NH} \quad \text{fast}$$

Scheme 2.

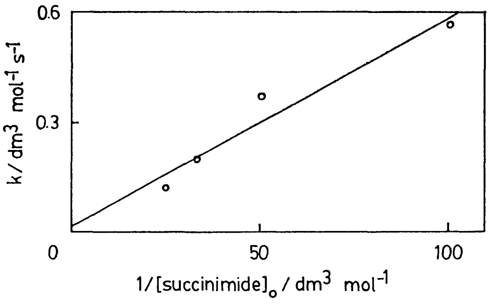


Fig. 6. Dependence of k on $1/[\text{Succinimide}]_0$.

Table 2. The Percentage of the Reaction through Scheme 2 at Different pH in 50% Aqueous Methanol at 35 °C[a)]

pH	1.21	1.35	1.47	1.79	2.22	2.36	2.94
%	1.7	2.5	3.0	6.5	14	17	48

a) $[\mathrm{NBS}]_0=[\mathrm{Acid}]_0=2\times10^{-3}$ mol dm^{-3}.

with increase in methanol content of the medium. From the slopes and intercept the kinetic constants at 35 °C are found as

$$k_1=1.82\ \mathrm{dm^3\,mol^{-1}\,s^{-1}},$$
$$K_ak_3=1.91\times10^{-3}\ \mathrm{s^{-1}},$$
$$k_2/k_{-1}=3.17\times10^{-3}\ \mathrm{mol\,dm^{-3}}.$$

The percentage of the reaction through Scheme 2 at different pH is given in Table 2. The high negative entropy of activation is in agreement with the formation of a positively charged cyclic intermediate. The low enthalpy of activation is in accordance with the rate-limiting breakdown of weak bond.

Experimental

Materials. *N*-Bromosuccinimide was prepared by the bromination of succinimide and recrystallized. Analytical grade methanol was purified by the usual procedure. Analytical grade perchloric acid and sodium perchlorate were used as such. Succinimide (Merck) was recrystallized before use. Cinnamic acid was purified by recrystallization in aqueous ethanol.

Stoichiometry. NBS in slight excess (4.7×10^{-3} mol dm^{-3}) was allowed to react with cinnamic acid (2.0×10^{-3} mol dm^{-3}) in 50% (v/v) aqueous methanol in presence of perchloric acid (2.0×10^{-2} mol dm^{-3}) at 35 °C and iodometric estimation of unreacted NBS after 3, 6, 12, and 24 hours showed that 1 mole of cinnamic acid consumed 1 mole of NBS. Due correction for the decomposition of NBS in the medium was given by carrying out simultaneously a blank experiment.

Kinetics. Aqueous solutions of NBS and perchloric acid of desired concentrations were prepared. Cinnamic acid was dissolved in methanol. Required volumes of the reactants were mixed in reaction stills blackened from outside at constant temperature, and the progress of the reaction was followed from 20 to 80% completion by iodometric estimation of unreacted NBS; 2ml aliquots of the reaction mixture at different time intervals were drained into a mixture of 5 ml of 2.5 M sulphuric acid (1 M=1 mol dm^{-3}) and 5 ml of 2% potassium iodide and 0.3 mol dm^{-3} sodium hydrogen carbonate, and the liberated iodine was titrated against thiosulphate to the starch end point. The second-order rate constant (k) was calculated from the slopes of the plots of ln ($[\mathrm{NBS}]_0[\mathrm{Acid}]/[\mathrm{Acid}]_0[\mathrm{NBS}]$) against time when $[\mathrm{NBS}]_0\neq[\mathrm{Acid}]_0$, and $[\mathrm{NBS}]_{\mathrm{consumed}}/[\mathrm{NBS}]$ against time when $[\mathrm{NBS}]_0=[\mathrm{Acid}]_0$ by the method of least square. The error quoted in k is the 95% confidence limit of a Student's t-test. The $[\mathrm{H^+}]$ was calculated from pH measurements.

Product Analysis. To cinnamic acid (0.05 mole) in 50% aqueous methanol (100 ml) in presence of perchloric acid (0.1 mol dm^{-3}) at 65 °C NBS (0.05 mole) was added. After cooling it was treated with saturated solution of sodium hydrogen carbonate, and succinimide was filtered off. The bromomethoxy acid was regenerated with mineral acid, filtered (yield: 60%), recrystallized in 50% aqueous ethanol and identified as 2-bromo-3-methoxy-3-phenylpropionic acid by IR, ^{1}H NMR and MS. IR (Nujol) 2910 (O-H), 2840 ($O\text{-}CH_3$), 1700 (C=O), and 1105 (C-O-C) cm^{-1}: ^{1}H NMR (270 MHz) δ=3.11 (3H, s, OCH_3), 4.42 (1H, d, J=9.9 Hz), 4.52 (1H, d, J=9.9 Hz), 7.37—7.43 (5H, aromatic), and 13.34 (b, carboxyl). MS (in the decreasing order of abundance) m/z 121 ($C_6H_5\text{-}CH{=}\overset{+}{O}\text{-}CH_3$), 77 ($C_6H_5^+$), 91 ($C_7H_7^+$), 103 [M-($CH_3OBr$ and COOH)], 147 [M-(HBr and OCH_3)], 148 (M-CH_3OBr), 131 [M-(CH_3OBr and OH)], 227 and 229 (M-OCH_3), 179 (M-Br), and 181 and 183 (M-C_6H_5).

The authors thank Dr. K. Ganapathy for providing facilities. Thanks are also due to SIF, Bangalore for running ^{1}H NMR spectrum and RSIC, Lucknow for providing mass spectrum.

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