JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2001; **14:** 684–690
DOI:10.1002/poc.415

Mechanistic studies of the oxidation of substituted phenethyl alcohols by *N*-metallo-*N*-haloarylsulphonamides: kinetic isotope studies

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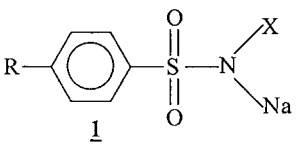
Received 15 May 2000; revised 15 December 2000; accepted 9 May 2001

ABSTRACT: The oxidation of *para*-substituted phenethyl alcohols (PEA, **2**) by *N*-metallo-*N*-haloarylsulphonamides (**1**) in the presence of dilute HCl to the corresponding phenacetaldehydes (**4**) is first order with respect to oxidant (**1**) and [H^+] and a fractional order each in [PEA] and [Cl^-]. Addition of the reaction product (**3**), ionic strength variations and variation of dielectric constant of the medium had no effect on the rate. The oxidation of $PhCH_2CD_2OH$ (**2**) exhibited a substantial primary kinetic isotope effect ($k^H/k^D = 5.83$). The rates correlate satisfactorily with the Hammett free energy relationship. The activation parameters $\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$ and log*A* were calculated for the reaction. The proposed mechanism is consistent with the observed results. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: substituted phenethyl alcohols; oxidation; *N*-metallo-*N*-haloarylsulphonamides; mechanism; kinetic isotope effect

INTRODUCTION

The *N*-metallo-*N*-haloarylsulphonamides (**1**) are a class of compounds capable of producing halonium cations, hypohalites and N-anions which behave both as bases and as nucleophiles, depending on the reaction conditions. The subject has been extensively reviewed by Campbell and Johnson[1] and Bremner.[2] These oxidants contain a strongly polarized N-linked halogen which is in the +1 state (X = Cl or Br, bonded to nitrogen is positive). Generally they undergo a two-electron change to form the respective halide ions and the corresponding sulphonamides (**3**). Depending on the pH of the medium, these oxidants (**1**) furnish different types of reactive species. Since these oxidants react with a wide variety of functional groups, they are used as reagents in analytical chemistry.[3–6] The important aspects of the chemistry of these oxidants are that (i) they perform very specific and selective oxidations and (ii) they can also be used as mild oxidants. For example, mild oxidation of alcohols to carbonyl compounds is a very important operation in organic synthesis. During a detailed study[7,8] of the primary and secondary kinetic isotope effects for *E*2 reactions, it was anticipated that the oxidation of substituted phenethyl alcohols (**2**) with the halosulphonamides **1** could shed light on the mechanism of oxidation of **2**. Therefore, with the available data, it is important to report the detailed kinetic isotope effects for the oxidation of **2** by **1** in an aqueous homogeneous medium. It is found that addition of HCl catalyses the reaction, indicating simultaneous catalysis by H^+ and Cl^- ions. Attempts have been made to correlate the structure–reactivity relationships for these reactions through Hammett plots.



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R = H or CH_3; X = Cl or Br

When (i) R = CH_3; X = Cl → Chloramine-T (CAT)
R = CH_3; X = Br → Bromamine-T (BAT)

(ii) R = H; X = Cl → Chloramine-B (CAB)
R = H; X = Br → Bromamine-B (BAB)

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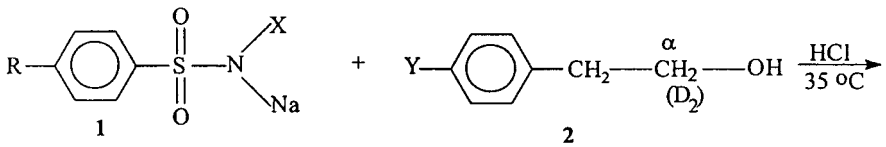
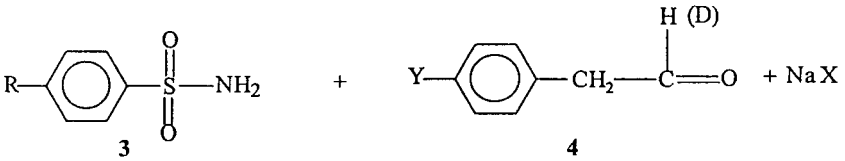
Contract/grant sponsor: Department of Science and Technology, New Delhi; *Contract/grant number:* SP/S1/GO5/97.

RESULTS AND DISCUSSION

Oxidation of **2** by **1** revealed that 1 mol of **1** was



(1)



consumed by 1 mol of **2** as shown in Eqn. (1) and the product is the corresponding phenacetaldehyde (**4**).

With the substrate (PEA, **2**) in excess, at constant [HCl] and $[PEA]_0$, plots of log[ox] vs time were linear ($r = 0.999$), indicating a first-order dependence of rate on $[ox]_0$. Further, the values of k' were unaltered with variation of $[ox]_0$ (0.0002–0.002 M) confirming the first-order dependence of rate on $[oxidant]_0$. The rate initially increases with increase in $[PEA]_0$ (0.005–0.05 M). Plots of log k' vs log $[PEA]_0$ were linear (Fig. 1, $r = 0.998$) with fractional slopes, thus showing a fractional order dependence on $[substrate]_0$.

The rate increases with increase in [HCl] (0.08–0.4 M) and plots of log k' vs log[HCl] were linear (Fig. 2, $r = 0.9986$) and the slopes (order) are given in Table 1. At constant $[Cl^-] = 0.4$ M, maintained by adding NaCl, the rate increased with increase in $[H^+]$ (0.1–0.4 M), which was varied on adding HCl and plots of log k′ vs log $[H^+]$ were linear (Fig. 3, $r = 0.9986$) with slopes of unity. At constant $[H^+] = 0.4$ M, the rate increased with addition of NaCl and plots of log k' vs log $[Cl^-]$ were linear ($r = 0.998$) with fractional slopes (Fig. 4, Table 1). Addition of the reaction product **3** (0.0005–0.002 M) had a negligible effect on the rate, indicating that it is not involved in a pre-equilibrium to the rate-limiting step.

Variation of the ionic strength of the medium was carried out by adding $NaClO_4$ (0.2–1.0 M) and the rate was unaffected.

The dielectric constant of the medium was varied by adding methanol (0–40%, v/v) to the reaction mixture but the rates were not significantly altered. The kinetic orders observed in the present set of experiments are summarized in Table 1. The reaction was studied at different temperatures and from the Arrhenius plots of log k' vs

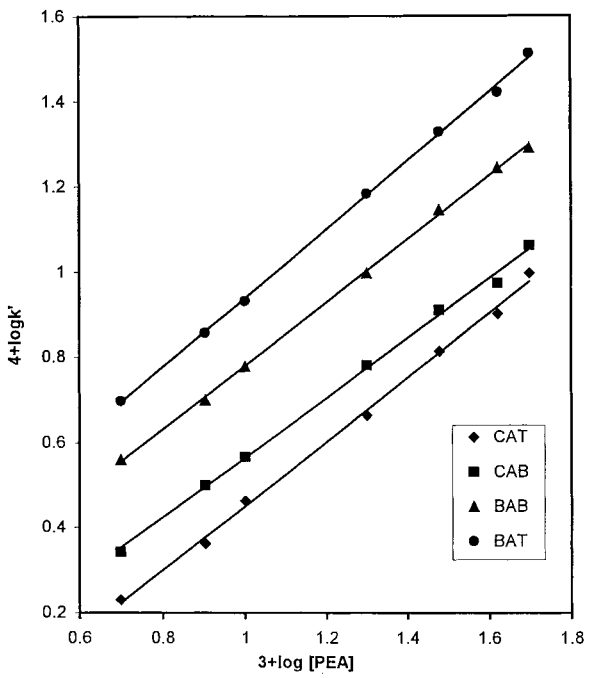


Figure 1. Plot of logk' vs log[PEA] at 308 K

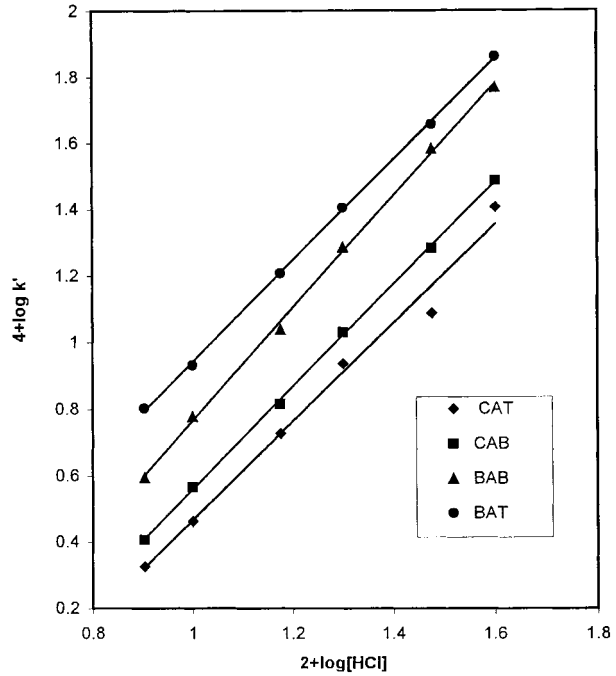


Figure 2. Plot of logk' vs log [HCl] at 308 K

Table 1. Kinetic data for the oxidation of substituted phenethyl alcohols (**2**) by *N*-metallo-*N*-haloarylsulphonamides (**1**), with [**1**] = 0.0005 mol dm^{-3}, [**2**] = 0.001 mol dm^{-3}, [HCl] = 0.1 mol dm^{-3}, μ = 0.5 mol dm^{-3}, T = 35 °C

	N-Metallo-*N*-haloarylsulphonamide			
Observed order w.r.t	CAT	CAB	BAT	BAB
[**1**]	1.00	1.00	1.00	1.00
[**2**]	0.75	0.72	0.80	0.77
[HCI]	1.54	1.60	1.50	1.60
[H^+]	1.00	1.00	1.00	1.00
[CI^-]	0.56	0.65	0.58	0.70
[**3**]	No effect			
Ionic strength (μ)	No effect			
Dielectric constant (D) variation	No effect			

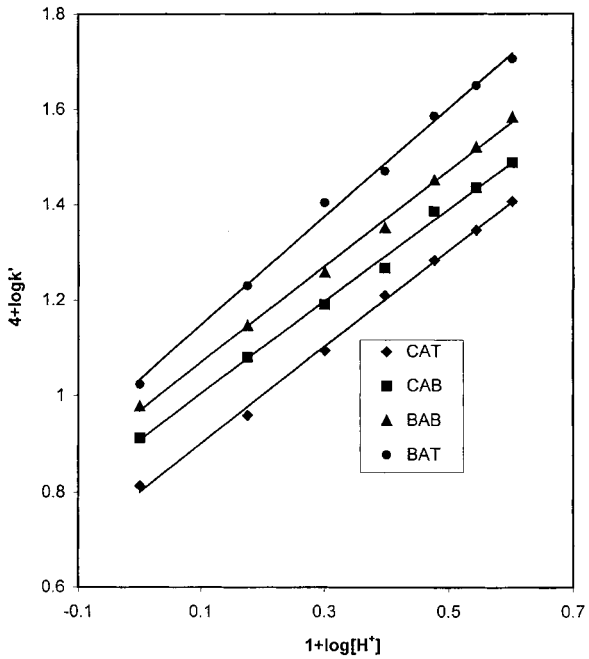


Figure 3. Plot of log[H^+] vs logk' at 308 K

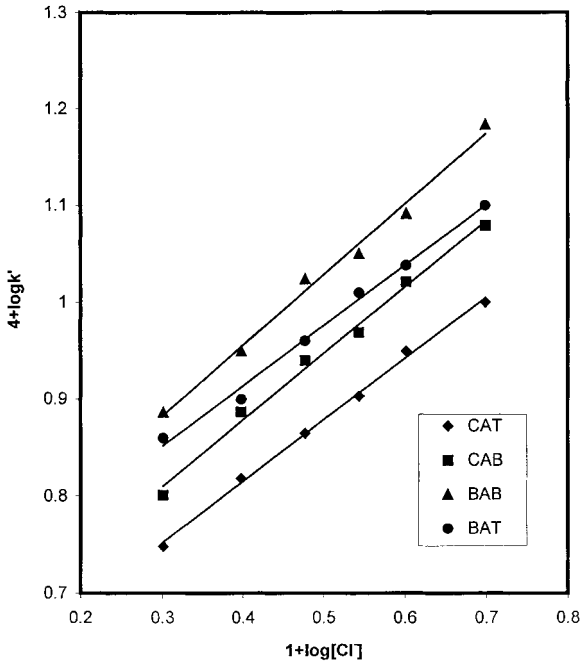


Figure 4. Plot of log[CI^-] vs logk'

1/T, values of the activation parameters for the composite reaction were calculated and these are shown in parentheses in Table 2.

Tests for free radicals

Addition of acrylamide to the reaction mixture did not initiate polymerization, showing the absence of free radical species.

Discussion

N-Metallo-*N*-haloarylsulphonamides (**1**) act as oxidizing agents in both acidic and alkaline media. Regarding the oxidizing species, it has been thoroughly discussed from our work[3–5] and that of others[1,2] and shown in the case of

Table 2. Activation parameters for the rate-limiting step of Scheme 1, with $[ox]_0 = 5.0 \times 10^{-4}$ mol dm^{-3}, $[PEA]_0 = 10.0 \times 10^{-3}$ mol dm^{-3}, [HCl] = 0.1 mol dm^{-3}, μ = 0.5 mol dm^{-3}

Oxidant	E_a (kJ mol^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J K^{-1} mol^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})	Log A
CAT	81.3	78.8	−45.4	93.0	10.3
	(54.6)[a]	(52.1)	(−144)	(96.9)	(8.80)
CAB	66.9	64.4	−87.8	91.6	11.7
	(59.8)	(57.2)	(−125)	(95.9)	(9.80)
BAT	68.3	65.7	−90.3	93.7	11.6
	(57.4)	(54.8)	(−125)	(93.8)	(9.80)
BAB	74.4	71.8	−73.2	94.5	12.6
	(60.8)	(58.2)	(−116)	(91.9)	(11.2)

[a] Values in parentheses refer to the parameters calculated for the overall reaction (1).

chloramine-T (CAT; **1**, R = CH_3, X = Cl) that it behaves like a strong electrolyte in aqueous solutions and dissociates according to

$$RNClNa \rightleftharpoons (RNCl)^- + Na^+ \quad (2)$$

The anion picks up a proton in acidic solutions to give the free acid monochloramine-T, RNHCl (*N*-chloro-*p*-toluenesulphonamide):

$$(RNCl)^- + H^+ \rightleftharpoons RNHCl \quad (3)$$

$$K_a = 2.82 \times 10^{-5}$$

Although the free acid has not been isolated, there is experimental evidence for its formation in acidic solutions. It undergoes disproportionation giving rise to *p*-toluenesulphonamide (RNH_2) and dichloramine-T ($RNCl_2$):

$$2RNHCl \overset{K_d}{\rightleftharpoons} RNH_2 + RNCl_2 \quad (4)$$

$$K_d = 6.1 \times 10^{-2} \text{ at } 25^\circ C$$

The dichloramine-T and the free acid hydrolyse to give hypochlorous acid (HOCl):

$$RNCl_2 + H_2O \overset{K_h}{\rightleftharpoons} RNHCl + HOCl \quad (5)$$

$$K_h = 8.0 \times 10^{-7} \text{ at } 25^\circ C$$

$$RNHCl + H_2O \overset{K_h'}{\rightleftharpoons} RNH_2 + HOCl \quad (6)$$

$$K_h' = 4.88 \times 10^{-8}$$

Finally, HOCl ionizes according to

$$HOCl \overset{K_a}{\rightleftharpoons} H^+ + OCl^- \quad (7)$$

$$K_a = 3.3 \times 10^{-8} \text{ at } 25^\circ C$$

In the light of the above, we can show that the oxidation potential of the oxidant–**3** couple is pH dependent and decreases with increase in the pH of the medium. Depending on the pH of the medium, **1** furnishes[3–5] different types of reactive species in solutions such as RNHX, RNX_2, HOX and possibly H_2O^+X (R = CH_3 $C_6H_4SO_2^-$ or $C_6H_5SO_2^-$). If RNX_2 were to be the oxidant, the reaction predicts a second-order dependence on $[oxidant]_0$, which is not observed experimentally. Similarly, the absence of a retardation effect on the rate by the added sulphonamide rules out the involvement of HOX or H_2O^+X. The results obtained in the present investigation (around pH 0–3) show that RNHX is the active oxidant, in the present oxidations. Since both H^+ and Cl^- ions catalyze the reaction, Scheme 1 can be proposed for the oxidation of **2** by **1**, involving simultaneous catalysis by both these ions.

$$RNHX + H^+ + Cl^- \overset{K_1}{\underset{(i)}{\rightleftharpoons}} \underset{(X')}{RNH_2X \cdots Cl^-} \quad \text{fast}$$

$$Y\text{-}PEA + X' \overset{K_2}{\underset{(ii)}{\rightleftharpoons}} X'' \quad \text{fast}$$

$$X'' + H_2O \xrightarrow[(iii)]{k_3} \text{products} \quad \text{slow rate-determining step}$$

Scheme 1

Scheme 1 assumes the formation of a tight[9] ion pair (X′), which is an intermediate and at the same time indicates simultaneous catalysis by H^+ and Cl^- ions. This ion pair reacts with PEA through an equilibrium step to form a complex (X″) which decomposes in a rate-limiting step to the products. The Michaelis–Menten kinetics obeyed by the substrate indicate a pre-equilibrium step (ii) in Scheme 1. Assuming $[OX]_t = [RNHX] + [X'] + [X'']$, rate law (9) can be derived for the oxidation of **2** by **1**.

$$\text{rate} = -\frac{d[ox]}{dt} = k_3[X''] \quad (8)$$

$$-\frac{d[ox]}{dt} = \frac{k_3K_1K_2[ox]_t[H^+][Cl^-][PEA]_0}{1 + K_1[H^+][Cl^-]\{1 + K_2[PEA]_0\}} \quad (9)$$

Equation (9) can be transformed into

$$\frac{1}{k'} = \frac{1}{k_3K_2[PEA]}\left\{\frac{1}{K_1[H^+][Cl^-]} + 1\right\} + \frac{1}{k_3} \quad (10)$$

From the double reciprocal plots of k' vs $[PEA]_0$ and k' vs $[HCl]^2$, since $[H^+] = [Cl^-] = [HCl]$, values of k_3, K_1 and K_2 can be evaluated (Table 3). Using k_3 values (obtained by varying $[PEA]_0$ at each temperature), activation parameters can be determined for the rate-limiting step (Table 2).

Kinetic isotope effect

To ascertain the importance of the cleavage of the C_α—H bond in the rate-determining step, the oxidation of $YC_6H_4CH_2CD_2OH$ (**2**, Y = H) was studied. The observed substantial primary kinetic isotope effect (Table 4) in the oxidation of **2** by **1** confirms the cleavage of the C_α—H bond in the rate-determining step. The intermediate (X″) loses X^- (Scheme 2) creating O^+ species, which in turn makes C_α—H more acidic. Therefore, the formation of an electron-deficient reaction centre in the activated com-

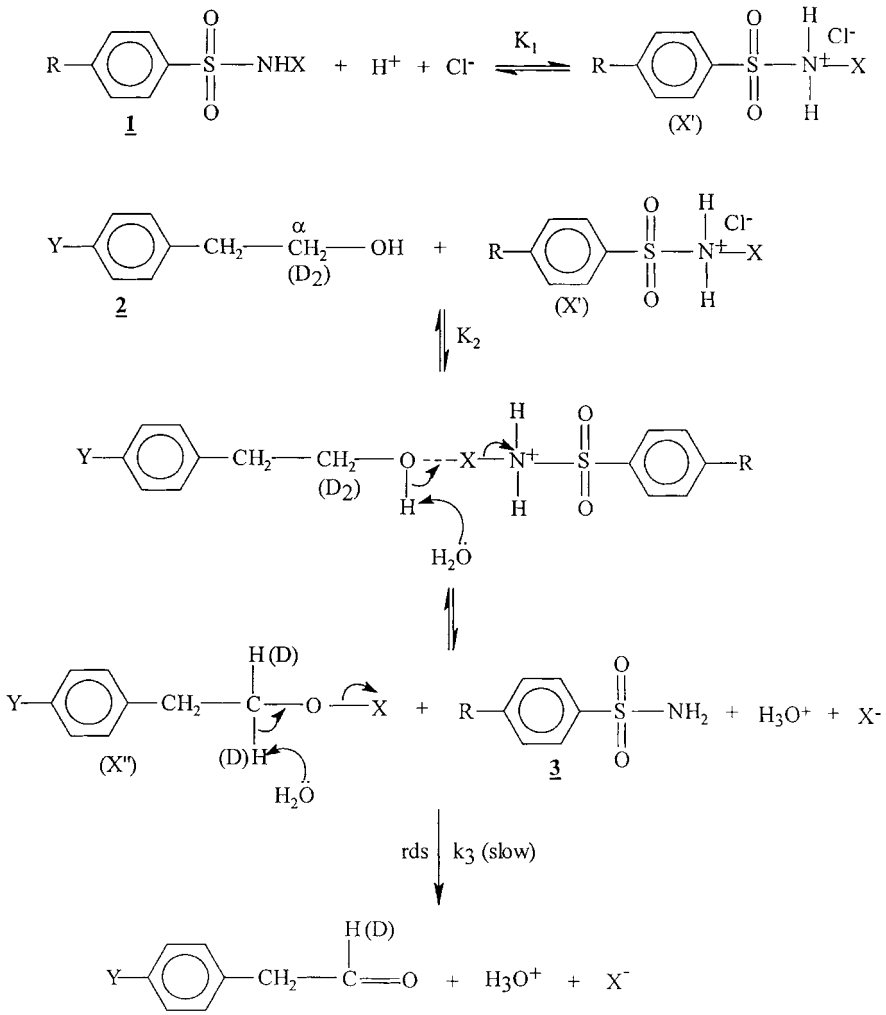
Table 3. Values of formation constants, K_1 and K_2, and decomposition constant, k_3, for the oxidation of PEA by arylhaloamines (Scheme 1), with $[ox]_0 = 5.0 \times 10^{-4}$ mol dm^{-3}, $[PEA]_0 = 10.0 \times 10^{-3}$ mol dm^{-3}, [HCl] = 0.1 mol dm^{-3}, $\mu = 0.5$ mol dm^{-3}, $T = 35$ °C

Oxidant	K_1(mol^{-2} dm^6)	K_2(mol^{-1} dm^3)	$k_3 \times 10^3$ (s^{-1})			
			303 K	308 K	313 K	318 K
CAT	10.9	266	0.66	1.25	2.00	3.33
CAB	3.50	890	1.34	1.67	2.86	5.00
BAT	4.90	500	3.57	5.00	6.25	10.0
BAB	4.40	568	1.66	2.94	5.00	6.25

Table 4. Kinetic isotope effect in the oxidation of phenethyl alcohols by arylhaloamines, with $[ox]_0 = 5.0 \times 10^{-4}$ mol dm^{-3}, $[PEA]_0 = 10.0 \times 10^{-3}$ mol dm^{-3}, [HCl] = 0.1 mol dm^{-3}, $\mu = 0.5$ mol dm^{-3}, $T = 35$ °C

[PEA] (mol dm^{-3})	10^2 k^H l mol^{-1} s^{-1}				10^3 k^D l.mol^{-1}.s^{-1}				k^H/k^D			
	CAT	CAB	BAT	BAB	CAT	CAB	BAT	BAB	CAT	CAB	BAT	BAB
0.005	3.40	4.40	9.96	7.24	5.86	7.65	17.0	12.5	5.80	5.75	5.85	5.79
0.010	2.90	3.68	8.52	5.98	4.96	6.20	14.7	10.1	5.84	5.93	5.78	5.89
0.050	9.90	2.30	6.49	3.90	1.72	4.00	11.0	6.67	5.80	5.75	5.90	5.84
Average[a]									5.81 ± 0.02	5.81 ± 0.10	5.84 ± 0.06	5.84 ± 0.05

[a] Mean $k^H/k^D = 5.83 \pm 0.02$.



Scheme 2

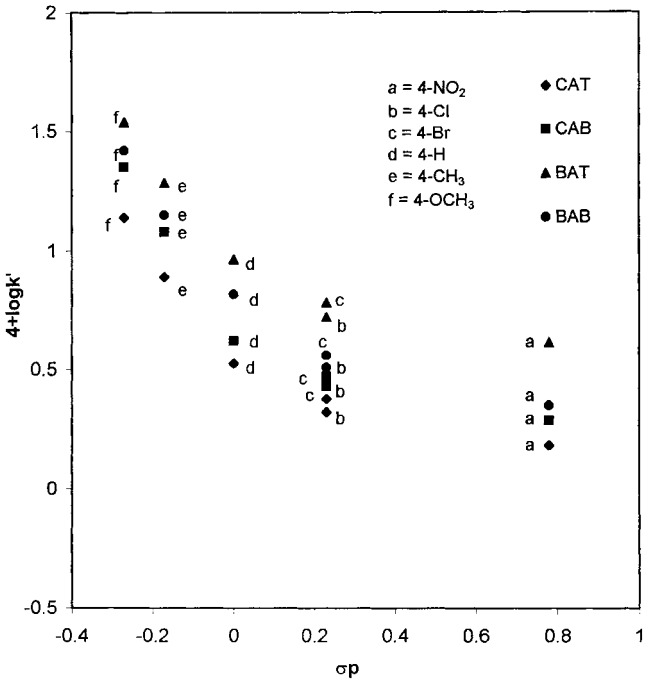


Figure 5. Hammet plot ($4 + \log k'$ vs σp) for the reaction of Y-PEA with **1**

plex indicates that the cleavage of the C_α—H bond is ahead of the formation of the C=O bond. Detailed kinetic isotope studies were performed with different oxidants and at different concentrations and the results are shown in Table 4.

The activation parameters were calculated with the help of k_3 values for the rate-determining step, obtained by Michaelis–Menten kinetics. The values of k_3 and the formation constant K_1 K_2 for all the oxidants were calculated and are given in Table 3.

A Hammett plot[10] of log k' vs σp was drawn (Fig. 5) to correlate the structure–reactivity for these reactions. The rate increased with electron-donating groups and decreased with respect to electron-withdrawing groups. Swain and Langsdorf[11] and other workers[12] have studied various reactions of this type and observed similar behaviour. The results showed lower rates with respect to electron-withdrawing groups and higher rates with electron-donating groups (Table 5). Electron-donating substituents stabilize a transition state having a carbocation centre by resonance. This facilitates the bond-breaking process in the transition state. On the other hand, an electron-withdrawing substituent increases the capacity of the carbocation ion centre, suggesting the development of a loose or partial positive charge at the transition state, which in turn helps the bond-making process, thus leading to a decrease in rate.

A plot of $\Delta H^{\neq}$ vs $\Delta S^{\neq}$ gave a very good correlation, which supports the existence of a similar mechanism for the oxidation of substituted phenethyl alcohols. These

Table 5. Rate constants for the reaction of phenethyl alcohols with arylhaloamines, with $[ox]_0 = 5.0 \times 10^{-4}$ mol dm^{-3}, $[PEA]_0 = 10.0 \times 10^{-3}$ mol dm^{-3}, [HCl] = 0.1 mol dm^{-3}, $\mu = 0.5$ mol dm^{-3}, $T = 35$ °C

	$k' \times 10^4$ (s^{-1})			
Y-PEA: Y =	CAT	CAB	BAB	BAT
OCH_3	24.0	29.5	44.7	60.3
CH_3	10.4	13.2	20.0	28.2
H	2.90	3.68	5.98	8.52
Br	1.67	2.60	4.10	5.88
Cl	1.55	2.30	3.80	5.37
NO_2	1.25	1.74	2.69	1.97

substrates follow a Michaelis–Menten plot and yielded definite intercepts, which supports the proposed mechanism. The presence of a substantial primary kinetic isotope effect indicates that the rupture of the C—H bond occurs after the O—H bond cleavage, creating a carbocation centre or a positive character in the transition state, which is stabilized by the electron-donating groups, and the decrease in rate with electron-withdrawing groups is in agreement with this observation. The rate of oxidation decreased in the order BAT > BAB > CAB > CAT (Table 5).

Detailed studies were carried out by changing R = H or CH_3, X = Cl or Br and Y = *p*-NO_2, *p*-Cl, *p*-Br, *p*-H, *p*-CH_3 or *p*-OCH_3 in reaction (1) to ascertain the proposed mechanism and confirm the conclusions drawn. Similar results were obtained in supporting the proposed mechanism.

The detailed mode of oxidation of **2** by **1** and the probable structures of the intermediates are shown in Scheme 2. Overall, the mechanistic scheme appears to be of *E*2 type.

EXPERIMENTAL

Materials. Phenethyl-1,1-d_2 alcohol was prepared[7,8] by the reduction of phenethyl acetate with lithium aluminium deuteride[13] in dry diethyl ether by the method of Amundsen and Nelson.[13] The isotopic purity, determined by ^{1}H NMR spectroscopy, was 95 ± 3%. The oxidants (CAT, CAB, BAT and BAB) were prepared by the reported procedure.[14–16] An aqueous solution of the compound was prepared, standardized iodimetrically and stored in brown bottles to prevent photochemical deterioration. All other chemicals were of analytical-reagent grade. Triply distilled water was used for preparing aqueous solutions. The ionic strength of the reaction mixture was kept at high with a concentrated solution of $NaClO_4$.

Product analysis. The reaction products were subjected to column chromatography on silica gel (60–200 mesh)

using gradient elution (from dichloromethane to chloroform). After initial separation, the products were further purified by recrystallization. Materials were identified by comparison with commercially available samples.

Phenacetaldehyde. Recrystallized from diechloromethane–light petroleum, m.p. 32–33 °C, known m.p. 33–34 °C (Merck Index, 11 2236). Phenacetaldehyde was further purified as its 2,4-dinitrophenylhydrazone (2,4DNP) derivative, which was recrystallized from ethanol (recovery 68%) and was found to be identical with the DNP derivative of an authentic sample.

p-*Toluenesulphonamide or benzenesulphonamide (**3**).* Recrystallized from dichloromethane–light petroleum. The sulphonamide (PTS or BSA) was detected by TLC and confirmed[17] by IR, ^{1}H NMR and GC–MS methods.

Kinetic measurements. The reaction was carried out in glass-stoppered Pyrex boiling tubes whose outer surface was coated black to eliminate photochemical effects.[18] Solutions containing appropriate amounts of PEA, HCl and water (to keep the total volume constant for all runs) were placed in the tube and thermostated at 35 °C. A measured amount of oxidant solution, also thermostated at the same temperature, was rapidly added to the mixture. The progress of the reaction was monitored by withdrawing aliquots from the reaction mixture at regular time intervals and determining the unreacted oxidant iodimetrically. The course of the reaction was studied up to two half-lives. The calculated pseudo-first-order rate constants k' were reproducible to within $\pm 3\%$.

Acknowledgements

I thank the Department of Science and Technology (DST), New Delhi, for financial support (SP/S1/GO5/97). The technical assistance given by Mr N. D. Dinesh is gratefully acknowledged.

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