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Kinetics and mechanism of the oxidation of substituted benzylamines by hexamethylenetetramine-bromine

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ABSTRACT: The oxidation of substituted benzylamines by hexamethylenetetramine-bromine (HABR) to the corresponding aldimines is first order with respect to each the amine and HABR. It is proposed that HABR itself is the reactive oxidizing species. The oxidation of deuterated benzylamine ($PhCD_2NH_2$) indicated a substantial kinetic isotope effect ($k_H/k_D = 5.60$ at 293 K). This confirmed the cleavage of an α-C—H bond in the rate-determining step. Correlation analyses of the rates of oxidation of 20 monosubstituted benzylamines were performed with various single- and multi-parametric equations. The rates of the oxidation showed excellent correlations in terms of the Yukawa–Tsuno and Brown equations. The polar reaction constants were negative. The oxidation exhibited extensive cross-conjugation, in the transition state, between the electron-donating substituents and the reaction centre. A mechanism involving a hydride ion transfer from the amine to HABR, in the rate-determining step, is proposed.

KEYWORDS: kinetics; mechanism; oxidation; benzylamines; correlation analysis

INTRODUCTION

Hexamethylenetetramine-bromine (HABR) was first reported as a synthetic reagent for the oxidation of alcohols to carbonyl compounds in 1994.[1] 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.[2–6] It seems that there are no reports about the oxidation of aromatic amines by HABR. However, the kinetics of the oxidation of aromatic amines by many reagents have been studied, e.g. by permanganate,[7] *N*-chlorosuccinimide (NCS),[8] *N*-bromoacetamide (NBA),[9] *N*-chloroacetanilide,[10] acid bromate[11] and periodate.[12] The oxidation of benzylamines presents interesting possibilities. It is known to yield a number of products including those resulting from condensation of the intermediate products of oxidation with the parent amine.[13] In addition, benzamide, benzaldehyde and benzoic acid are also formed.[13] In this paper, the kinetics of the oxidation of 20 monosubstituted benzylamines by HABR in dimethyl sulfoxide (DMSO) as a solvent are reported. Attempts were made to correlate rate and structure in this reaction. A suitable mechanism is proposed.

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RESULTS

The oxidation of benzylamines by HABR results in the formation of corresponding aldimines. Analyses of products indicate the following overall reaction:

$$2ArCH_2NH_2 + (CH_2)_6N_4Br_4 \rightarrow 2ArCH = NH + (CH_2)_6N_4 + 4H^+ + 4Br^- \quad (1)$$

Rate laws

The reactions were found to be first order with respect to HABR. The individual kinetic runs were strictly first order in HABR. Further, the pseudo-first-order rate constants, k_{obs}, do not depend on the initial concentration of HABR. The reaction rate increases linearly with increase in the concentration of the amine (Table 1). Thus the reaction is first order with respect to amines also.

Spectral studies

The UV–visible spectra of HABR (0.001 mol dm^{-3}) and

Table 1. Rate constants for the oxidation of benzylamine by HABR at 303 K

[Amine] (mol dm^{-3})	10^3[HABR] (mol dm^{-3})	10^5 k_{obs} (s^{-1})
0.1	1.0	9.62
0.2	1.0	19.6
0.3	1.0	28.5
0.5	1.0	49.0
1.0	1.0	95.8
1.5	1.0	150
2.0	1.0	204
2.0	1.0	200[a]
1.0	2.0	96.2
1.0	4.0	94.8
1.0	6.0	97.0
1.0	8.0	96.0
1.0	1.0	96.2[b]
1.0	1.0	95.7[c]

[a] Contains 0.005 mol dm^{-3} acrylonitrile.
[b] Contains 0.02 mol dm^{-3} HXA.
[c] Contains 0.02 mol dm^{-3} sodium bromide.

an equivalent amount of bromine (0.002 mol dm^{-3}), in DMSO at ~293 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 300–310 nm and for bromine there is a peak at 278 nm. Their optical densities showed large variations (Fig. 1). Hexamethylenetetramine (HXA) had no appreciable absorption in this range. Further, the spectrum of HABR did not show any change during the experimental time period (ca 2 h). When a solution of HABR in DMSO was evaporated to dryness under reduced pressure, HABR was recovered unchanged. This confirmed that HABR retained its integrity in DMSO.

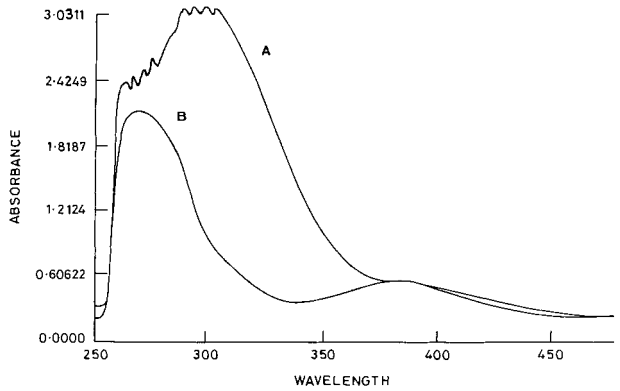


Figure 1. UV–visible spectra of (A) 0.001 mol dm^{-3} HABR and (B) 0.002 mol dm^{-3} bromine; Temperature, 293 K; solvent, DMSO

Induced polymerization of acrylonitrile

The oxidation of benzylamine, in an atmosphere of nitrogen, failed to induce the polymerization of acrylonitrile. Further, the addition of acrylonitrile had no effect on the rate of oxidation (Table 1).

Effect of hexamethylenetetramine

Addition of HXA had no effect on the rate of oxidation (Table 1).

Table 2. Rate constants for the oxidation of substituted benzylamines by HABR and the activation parameters

Substituent	10^4 k_2 (dm^3 mol^{-1} s^{-1}) 293 K	303 K	313 K	323 K	ΔH^* (kJ mol^{-1})	ΔS^* (J mol^{-1} K^{-1})	ΔG^* (kJ mol^{-1})
p-NO_2	0.23	0.62	1.70	3.98	72.8 ± 0.7	−86 ± 2	98.2 ± 0.6
p-CF_3	0.26	0.66	1.74	4.07	70.0 ± 0.7	−94 ± 2	98.0 ± 0.5
p-CO_2Me	0.48	1.23	2.95	7.24	68.4 ± 0.6	−95 ± 2	96.5 ± 0.6
p-Br	2.24	5.12	12.9	27.5	63.9 ± 1.0	−97 ± 3	92.8 ± 0.8
p-Cl	2.88	6.76	13.8	28.2	57.0 ± 0.6	−119 ± 2	92.2 ± 0.5
H	4.20	9.62	21.5	45.0	59.8 ± 0.3	−106 ± 1	91.2 ± 0.2
p-F	6.61	14.1	30.9	66.1	58.0 ± 0.9	−109 ± 3	90.2 ± 0.7
p-Me	18.0	33.9	70.8	138	51.3 ± 1.2	−123 ± 4	87.9 ± 1.0
p-OMe	214	354	631	1050	39.5 ± 0.8	−143 ± 3	81.9 ± 0.7
p-NH_2	5240	7080	10000	12000	19.8 ± 1.0	−183 ± 3	74.2 ± 0.8
p-NMe_2	16600	20000	31700	40800	22.3 ± 2.0	−166 ± 7	71.5 ± 1.6
m-NO_2	0.11	0.30	0.79	1.95	74.2 ± 0.1	−88 ± 1	100 ± 1.0
m-CF_3	0.49	1.20	2.95	6.92	67.0 ± 0.7	−99 ± 2	96.5 ± 0.5
m-CO_2Me	0.54	1.38	3.31	7.76	67.4 ± 0.3	−97 ± 1	96.2 ± 0.2
m-Cl	0.63	1.62	3.89	8.89	66.8 ± 0.1	−98 ± 1	95.8 ± 0.1
m-I	0.68	1.78	4.27	9.66	67.2 ± 0.3	−96 ± 1	95.6 ± 0.3
m-F	0.71	1.86	4.47	11.0	69.0 ± 0.6	−89 ± 2	95.5 ± 0.5
m-OMe	2.45	5.75	13.2	27.7	61.3 ± 0.3	−105 ± 1	92.5 ± 0.2
m-Me	5.62	12.6	28.8	60.3	60.0 ± 0.5	−103 ± 2	90.5 ± 0.4
m-NH_2	8.91	19.1	42.7	88.7	58.0 ± 0.6	−106 ± 2	89.4 ± 0.6

Table 3. Kinetic isotope effect in the oxidation of benzylamine by HABR

Compound	$10^4\ k_2$ (dm^3 mol^{-1} s^{-1}) 293 K	303 K	313 K	323 K	ΔH^* (kJ mol^{-1})	ΔS^* (J mol^{-1} K^{-1})	ΔG^* (kJ mol^{-1})
$PhCH_2NH_2$	4.20	9.62	21.5	45.0	59.8 ± 0.3	-106 ± 1	91.2 ± 0.2
$PhCD_2NH_2$	0.75	1.77	4.05	8.70	61.8 ± 0.3	-113 ± 1	95.5 ± 0.2
k_H/k_D	5.60	5.44	5.31	5.17			

Effect of bromide ion

The rate of oxidation of the amine was not affected by the addition of added sodium bromide (Table 1).

Kinetic isotope effect

To ascertain the importance of the cleavage of the α-C—H bond in the rate-determining step, the oxidation of [1,1-$^2H_2$]benzylamine ($PhCD_2NH_2$) by HABR was studied. The results (Table 3) showed the presence of a substantial primary kinetic isotope effect ($k_H/k_D = 5.60$ at 293 K).

Effect of substituent

The rates of oxidation of benzylamine and 19 mono-substituted benzylamines were determined at different temperatures and the activation parameters were calculated (Table 2).

DISCUSSION

The values of logk_2 at 293 K for the oxidation of 20 benzylamines are linearly related to logk_2 at 323 K (slope = 0.8174 ± 0.0059; $c^2 = 0.9990$). The value of the isokinetic temperature, calculated by Exner's[14] method, is 597 ± 19 K. A linear isokinetic relationship implies that all the compounds so correlated react by the same mechanism. Further, the linear relationship is also a necessary condition for the validity of linear free energy relationships.[15]

In solution, HABR may dissociate to form molecular bromine and HXA:

$$(CH_2)_6N_4Br_4 \rightleftharpoons 2Br_2 + (CH_2)_6N_4 \qquad (2)$$

The observed effects of added HXA or bromide ion on the rate of oxidation are reminiscent of the results obtained earlier in the oxidation of other reductants by HABR,[5,6] and indicate that the reactive oxidizing species is HABR itself. This is supported by the spectral data and isolation of unchanged HABR.

Correlation analysis of reactivity

The rate constants for the oxidation of the *meta*- and *para*- substituted compounds were correlated in terms of the Hammett[16] equation [Eqn. (3)], but no significant correlation was obtained. We used the standard deviation (sd), the coefficient of determination (C^2 or c^2) and Exner's[17] parameter ψ as the measures of goodness of fit:

$$\log k_2 = -(3.03 \pm 0.21)\sigma - 2.65 \qquad (3)$$

$c^2 = 0.9238$; sd $= 0.37$; $n = 20$; $\psi = 0.28$; $T = 303$ K

The main deviating points correspond to *para*-substituents capable of electron donation by resonance, viz. methoxy, amino and dimethylamino. Their rates are higher than those required by their Hammett σ values. This indicates that in the transition state of the reaction, there is an electron-deficient centre, which is stabilized by cross-conjugation with the electron-donating substituents at the *para*-position. The substituent effects in such systems can be described by the Yukawa–Tsuno[18] equation:

$$\log k_2 = \rho\sigma^\circ + \rho r(\sigma^+ - \sigma^\circ) + \log k_0 \qquad (4)$$

Where σ° is the normal substituent constant, which does not involve any additional π-electronic interaction between the substituent and the reaction centre, $\sigma^+ - \sigma^\circ$ is the resonance substituent constant measuring the capability for π-delocalization of the π-electron donor substituent and r is characteristic of the given reaction measuring the extent of resonance demand, i.e. the degree of resonance interaction between the aryl group and the reaction centre in the rate-determining transition state.

The correlation of the rate of oxidation of the *para*- and *meta*-substituted benzylamines in terms of Eqn. (4) is excellent (Table 4) with the value of ρ ranging from -1.72 to -2.03 and the value of r being ~1.03. The value of r indicates that the resonance demand is slightly more than that for the model reaction[19] for σ^+ values, i.e. solvolysis of 2-aryl-2-chloropropanes for which the value of r is, by definition, 1.0. In view of this, an attempt was made to correlate the rates of the oxidation of *meta*- and *para*-substituted amines with Brown's σ^+ values. The correlation is very good [Eqn. (5)]. In fact, the

Table 4. Correlation of rates of oxidation of *meta*- and *para*-substituted benzylamines by HABR in terms of the Yukawa–Tsuno equation[a]

Temperature (K)	ρ	r	C^2	sd	ψ
293	-2.03 ± 0.09	1.06 ± 0.08	0.9939	0.09	0.08
303	-1.91 ± 0.08	1.05 ± 0.09	0.9941	0.07	0.08
313	-1.81 ± 0.08	1.03 ± 0.08	0.9933	0.08	0.09
323	-1.73 ± 0.08	0.98 ± 0.08	0.9926	0.08	0.09

[a] No. of data points = 19.

significance of the two correlations is almost equal.

$$\log k_2 = -(1.95 \pm 0.04)\sigma^+ - 3.03 \qquad (5)$$

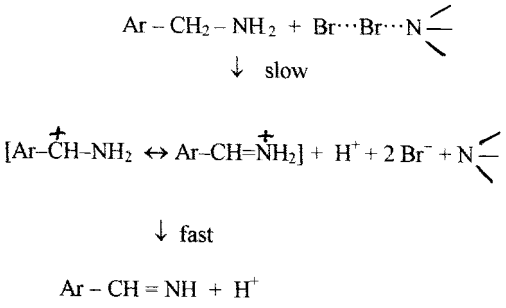
$$c^2 = 0.9939,\ \text{sd} = 0.08,\ n = 19,\ \psi = 0.08,\ T = 303\ \text{K}$$

The data for the *p-N,N*-dimethylamino compound were not included in the correlations with Eqn. (4) and Brown's σ^+ values, as the substituent constants are not available.

Mechanism

The absence of any effect of the radical scavenger on the reaction rate and the failure to induce polymerization of acrylonitrile point against a one-electron oxidation, giving rise to free radicals.

The presence of a substantial kinetic isotope effect in the oxidation of [1,1-$^2H_2$]benzylamine confirmed the cleavage of the α-C—H bond in the rate-determining step. The large negative values of the reaction constants and a significant resonance interaction between the aryl group and the reaction centre in the rate-determining transition state suggest that the activated complex has a considerable carbocationic character. Therefore, transfer of a hydride ion from the methylene group of the amine to HABR, in the rate-determining step, is indicated. Formation of a benzylic carbocationic activated complex generally leads to higher magnitudes of reaction constants, e.g. in the bromination of styrene[20] in acetic acid at 298 K, the values of ρ and r are -4.61 and 1.25, respectively. The relatively lower magnitudes of the reaction constants in the present reaction may well be due to the presence of an electron-donor group (NH_2) adjacent to the cationic carbon. The non-bonded pair of electron on nitrogen can delocalize the positive charge on the carbon and, therefore, reduce the electronic demand of the reaction centre. In the acid-catalysed solvolysis of acetophenone acetals,[21] where electron-donating alkoxy and methyl groups are present adjacent to the cationic carbon, the values of ρ and r are -1.7 and 0.6, respectively.



Scheme 1.

The mechanism depicted in Scheme 1 accounts for the experimental results. The values of activation parameters support the proposed mechanism. The large negative entropy of activation indicated a rigid activated complex in the transition state. When two species come together to form a single activated complex, they lose the independence to move singly and there is a loss of entropy. Further, as the charge separation takes place in the transition state, the charged ends become highly solvated. This results in the immobilization of a large number of solvent molecules. This also results in a loss of entropy. The large enthalpies of activation indicated that the formation of the activated complex involves a greater degree of bond cleavage.

It is of interest to compare the results of this investigation with earlier reports on the oxidation of benzylamine. In the permanganate[7] ion oxidation and Ru(III)-catalysed oxidation by acid bromate,[11] the reaction constants are -0.28 and 0.87, respectively, indicating the possibility of a one-electron oxidation. The oxidations by NCS[8] and NBA[9] exhibited large negative polar reaction constants and substantial primary kinetic isotope effects. The mechanism proposed for the oxidation by NBA, NCS and HABR is essentially same, i.e. transfer of a hydride ion from the amine to the oxidant resulting in the formation of a cationic species in the rate-determining step.

EXPERIMENTAL

Materials. HABR was prepared by the reported method[1] and its purity was checked by an iodimetric method and melting-point determination. Contrary to the earlier report,[1] we found that, in DMSO solution, the active bromine content of this complex is 2 mol per mole of the

reagent. [1,1-$^2H_2$]Benzylamine was prepared by the reduction of phenyl cyanide with lithium aluminium deuteride.[22] Its isotopic purity, determined from the ^1H NMR spectrum, was $93 \pm 2\%$. *m*-Aminobenzylamine was prepared by the reported method.[23] The other amines were commercial products and were purified by distillation. DMSO was purified by the usual method.[24]

Product analysis. The oxidation of benzylamines leads to the formation of the corresponding aldimines. Quantitative product analysis was carried out under kinetic conditions. In a typical experiment, benzylamine (0.1 mol) and HABR (0.01 mol) were made up to 50 ml of DMSO and kept in the dark for ~12 h to ensure completion of the reaction. The amount of aldimine formed was then determined by the reported 2,4-dinitrophenylhydrazine method.[25] According to this method, the aldimine is hydrolysed to the aldehyde and then isolated as the 2,4-dinitrophenylhydrazone (DNP), vacuum dried, weighed, recrystallized from ethanol and weighed again. The yields of DNP before and after recrystallization were 5.5 g (96%) and 4.5 g (78%), respectively. The DNP was found to be identical (m.p. and mixed m.p.) with the DNP of benzaldehyde. In similar experiments with the other substituted benzylamines the yields of DNP, after recrystallization, were in the range 70–81%. Attempts were made to detect the formation of bromination products in amines containing electron-donating substituents. The results indicated that no noticeable amount of bromination product was formed.

Kinetic measurements. The reactions were studied under pseudo-first-order conditions by keeping an excess (×20 or greater) of the amine over HABR. The solvent was DMSO. The reactions were studied at constant temperature (±0.1 K) and were followed by monitoring the decrease in [HABR] spectrophotometrically at 380 nm for up to 80% reaction. Beer's law was found to be valid within the concentration range used in our experiments. 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 ±3%.

Spectral analysis. UV–visible spectra of HABR, hexamethylenetetramine (HXA) and bromine were obtained on a Hewlett-Packard diode-array rapid scanning spectrophotometer (Model 8452A) with a scanning speed of 600 nm s^{-1}. The solvent was DMSO and the temperature was ~293 K.

Acknowledgements

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