Asian Journal of Chemistry Vol. 13, No. 2 (2001), 395–402

Kinetics and Mechanism of Bromination of 1-Hetera-4-Cyclohexanones by N-Bromobarbitone

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Kinetics of bromination of substituted 1-hetera-4-cyclohexanones by N-bromobarbitone [NBB] has been studied in aqueous acetic acid medium in the presence of $HClO_4$ and mercuric acetate. The reaction is acid and mercuric acetate catalysed exhibiting first order dependence each in [acid], [$Hg(OAc)_2$] and [substrate] and zero order in [NBB]. This supports the acid catalysed enolisation of ketone as the rate determining step and reaction between enol and NBB as the first step. The decrease in dielectric constant of the medium enhances the rate of reaction. Arrhenius activation parameters have been computed. A plausible mechanism based on these observations is proposed. The effect of the various substituents on the rates of bromination has been rationalized on the basis of their inductive and steric effects.

INTRODUCTION

Kinetics of oxidation of aliphatic, aryl aliphatic and cyclic ketones by a variety of oxidants like Ce(IV), V(V), $[S_2O_8]^{2-}$, $[MnO_4]^-$, Pb(IV), CAT, NBA and NBSA has received considerable attention[1–6]. However, to our knowledge no systematic investigation of bromination of various substituted 1-hetera-4-cyclohexanones by N-bromobarbitone (NBB) has been carried out. The present investigation is an attempt to do this and our results have enabled us to correlate reaction rate with substituent and to postulate a plausible mechanism of bromination of these substrates.

EXPERIMENTAL

The 1-heteracyclohexan-4-ones used in the present investigation were prepared following literature procedure[7–9]. N-Bromobarbitone was prepared by treating monosodium barbitone with bromine in alkaline medium as the method of preparation of NBSA[10]. Acetic acid AR (BDH) was refluxed over CrO_3 and used as solvent[11, 12]. All other chemicals used were of reagent grade (BDH). Pseudo-zero-order condition was maintained by taking a large excess of substrate. In order to avoid photocatalysis, the reaction, were run in the dark. Solutions of the

substrate and NBB were separately thermostated at 35 ± 0.05°C for 30 min before mixing. The reaction was followed by taking aliquots (2 mL) of the reaction mixture, pouring into a known excess of standard KI solution and titrating the liberated iodine against standard thiosulphate solution using starch as indicator. The reaction were followed to at least 70% converstion of NBB. The results were reproducible to within ±5%. To obtain the activation parameters, the reactions were run at several temperatures. Following the Eyring equation (1), ln (K_1/T) was plotted against (1/T) and the enthalpy of activation ($\Delta H^{\#}$) and entropy of activation ($\Delta S^{\#}$) were evaluated from the slope and intercept, respectively, of the straight-line plot.

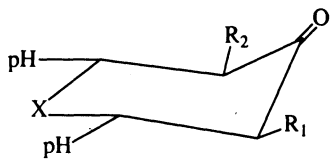
$$\ln (K_1/T) = \ln (K/h) + \Delta S^{\#}/R - \Delta H^{\#}/R(1/T) \quad (1)$$

The bromination of piperidone by NBB resulted in the formation of the corresponding α-bromo derivative as the product. A solution (50 mL) containing piperidone (0.5 mol dm^{-3}), NBB (0.05 mol dm^{-3}), perchloric acid (3.5 mol dm^{-3}) and mercuric acetate (1.5 millimol dm^{-3}) in aqueous acetic acid (80% v/v) was heated to 80–90°C for 2 h, cooled and the acid neutralized by the addition of dilute ammonia. Water (50 mL) was then added and the insoluble barbitone was filtered off. The filtrate was extracted with ether (3 × 50 mL) and the combined ether extracts were dried with Na_2SO_4 and evaporated. The residue was dissolved in the minimum amount of benzene and chromatographed over a column of neutral alumina. The bromopiperidone isolated (yield 30%) was analaysed by ^{1}H NMR. spectroscopy. The product from **(8)** gave signals at 0.85 (d, 3H, J7Hz, 3Me), 1.85 (s, 3H, N-Me), 3.00 (m, 1H, 3-H), 3.80 (d, 1H, J11 Hz, 2-H), 4.00 (d, 1H, J10 Hz, 6H), 5.60 (d, 1H, J10 Hz, 5-H) and 7.3–7.7 (m, 10H, 2- and 6-ph). The product from **(11)** gave signals at 0.85 (d, 3H, J 7Hz, 3-Me), 1.50 (s, 3H, 5-Me), 1.85 (s, 3H, N-Me), 3.00 (m, 1H, 3-H), 3.80 (m, 2H, 2- and 6-H) and 7.3–7.7 (m, 10H, 2- and 6-ph).

RESULTS AND DISCUSSION

The kinetics of bromination of piperidine-4-ones **(1–12)** by NBB in $HClO_4$-aqueous acetic acid mixture in the prence of mercuric acetate have been investigated under pseudo-zero-order condition, with the substrate in large excess and the results are presented in Tables 1 and 2. The order in [substrate] is unity as revealed by the unit slope of the linear plot of log k_0 *vs.* log [substrate] at varying initial [substrate] (Table-3). Similar linear plot with unit slope each between log k_0 and log [H^+]; and log k_0 and log [$Hg(OAc)_2$] at different initial [H^+] and [$Hg(OAc)_2$] indicate first order dependences on [H^+] and [$Hg(OAc)_2$] (Tables 4 and 5). Such first order dependences have already been observed in the oxidation of ketones by Te(III) acetate[13] and also by CAT[4].

Increase in the percentage of acetic acid increases the rate and the plot of $\log k_0$ versus 1/D is linear indicating ion-dipole type of reaction (Table-6). Activation parameter was obtained by running the reaction at several temperatures (Table-7).



Sl.No.	X	R_1	R_2
(1)	NH	H	H
(2)	NH	CH_3	H
(3)	NH	C_2H_5	H
(4)	NH	C_3H_7-i	H
(5)	NH	CH_3	CH_3
(6)	NH	C_2H_5	CH_3
(7)	NCH_3	H	H
(8)	NCH_3	CH_3	H
(9)	NCH_3	C_2H_5	H
(10)	NCH_3	C_3H_7-i	H
(11)	NCH_3	CH_3	CH_3
(12)	NCH_3	C_2H_5	C_2H_5

TABLE-1
EVALUATION OF THE ZERO-ORDER RATE CONSTANT FOR SUBSTRATE (1)[a]

Time/min	$[NBB]_0-[NBB]_t$ (10^{-4} M)	
0	0	
5	0.25	
10	1.25	
20	2.50	
50	6.00	$k_0 = 11.79 \times 10^{-5}$ mol l^{-1} min^{-1}
80	9.75	
100	12.15	
120	13.00	

[substrate] = 12.58 mM; [NBB] = 1.19 mM; $[HClO_4]$ = 0.31 M; $[Hg(OAc)_2]$ = 1.58 mM; Solvent HOAc-H_2O (80 : 20 v/v); I = 231.9 mM; T = 35°C

TABLE-2
PSEUDO-ZERO-ORDER AND FIRST ORDER RATE CONSTANTS FOR THE BROMINATION OF VARIOUSLY SUBSTITUTED PIPERIDIN-4-ONES BY NBB*

Compound	10^5 k_0/mol L^{-1} min^{-1}	10^3 k_1/min^{-1}
(1)	11.79	9.37
(2)	12.22	9.72
(3)	12.50	9.94
(4)	8.82	7.02
(5)	3.04	2.42
(6)	5.00	3.98
(7)	18.00	14.37
(8)	18.40	14.68
(9)	20.00	16.01
(10)	16.45	13.08
(11)	7.05	5.60
(12)	12.58	8.43

*See footnote to Table-1.

TABLE-3
DEPENDENCE OF RATE ON SUBSTRATE CONCENTRATION, SUBSTRATE (3)

10^2 [substrate]/mol L^{-1}	10^5 k_0/mol L^{-i} min^{-1}	10^3 k_1/min^{-1}
1.19	4.40	3.68
1.79	6.53	3.64
2.39	8.73	3.65
2.99	10.85	3.63

Except for [substrate], data as in footnote Table-1.

TABLE-4
EFFECT OF VARYING ACID CONCENTRATION ON THE REACTION RATE SUBSTRATE (5)*

[$HClO_4$]/mol L^{-1}	10^5 k_0/mol L^{-1} min^{-1}	10^2 k_1/min^{-1}
0.31	3.04	9.77
0.82	8.34	10.23
1.22	11.69	10.42
1.78	19.05	10.71

*[$HClO_4$] given above; other data as in footnote to Table-1.

TABLE-5
EFFECT OF VARYING CONCENTRATION OF MERCURIC ACETATE ON THE RATE OF BROMINATION OF SUBSTRATE (2)*

$[Hg(OAc)_2]$/millimol L^{-1}	10^5 k_0/mol L^{-1} min^{-1}	10^2k_1/min^{-1}
0.63	4.69	7.45
0.80	6.10	7.62
1.58	12.22	7.70
3.34	26.14	7.82
6.33	50.00	7.90

*Except for $[Hg(OAc)_2]$, data as in footnote to Table-1.

TABLE-6
EFFECT OF VARYING SOLVENT POLARITY ON THE REACTION RATE*

Substrate	10^5k_0/mol L^{-1} min^{-1} at HOAc-H_2O (v/v)			
	20–80	40–60	60–40	80–20
(5)	2.50	2.62	2.78	3.04
(6)	3.82	4.26	4.56	5.00
(10)	8.33	9.26	12.68	16.45
(12)	1.93	3.34	4.48	7.04

*Except for HOAc-H_2O ratio, data as in footnote to Table-1.

TABLE-7
ACTIVATION PARAMETER FOR THE BROMINATION OF PIPERIDIN-4-ONES BY NBB IN AQUEOUS ACETIC ACID (80% v/v) IN THE PRESENCE OF $HClO_4$ (0.31 M) AND $Hg(OAC)_2$ (1.58 mM)

Piperidin-4-one	$\Delta H^{\#}$/kJ mol^{-1}	$\Delta S^{\#}$/J mol^{-1} K^{-1}
(2)	7.87	60.76
(3)	13.74	41.47
(5)	61.22	101.03
(6)	53.68	80.45
(8)	8.89	54.19
(11)	22.52	17.76

Correlation of enolisation and free energy relationship

The reaction between piperidin-4-ones and NBB have been carried out in perchloric acid-aqueous acetic acid mixtures in the presence of mercuric acetate. Enolisation of piperidin-4-ones is the rate-determining step and it consists of two consecutive steps: (a) equilibrium protonation of carbonyl group and (b) deprotonation of α-carbon of the conjugate acid. Depending on the relative magnitudes of these two factors, the rate of enolisation will be affected. In general,

the first is aided by the electron releasing groups and the second is influenced by the electron withdrawing groups. Here both the steps (a) and (b) are controlling the rates of enolisation. Such operation of both steps has been invoked earlier in Te(III) acetate oxidation of acetophenones[13].

Mechanism and rate law

In all the cases investigated, the observed zero-order kinetics with respect to NBB and first order each in [substrate], $[H^+]$ and $[Hg(OAc)_2]$ show that NBB is not taking part in the rate-determining step. Taking these observations in view the mechanism in the scheme for the reaction is proposed and the rate law for this mechanism is given in equation (2). With a large excess of substrate,

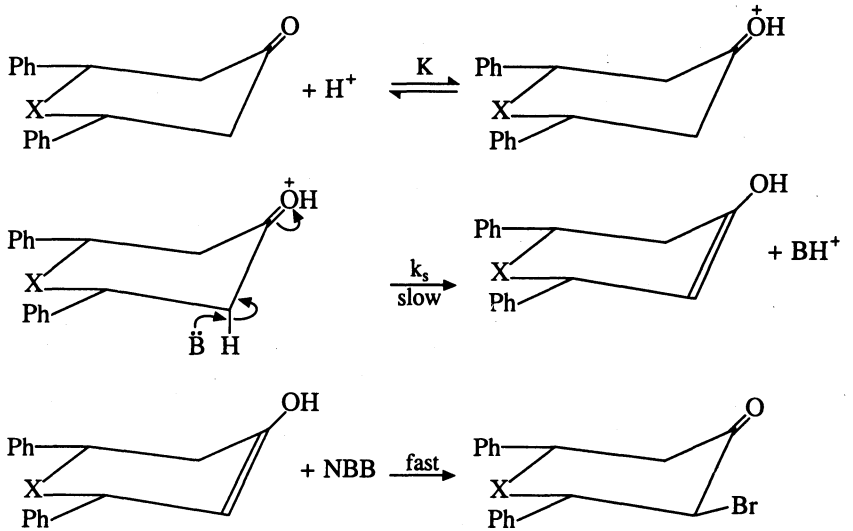
$$\text{Rate} = \frac{-d[NBB]}{dt} = k_s K[\text{substrate}][H^+][Hg(OAc)_2] \qquad (2)$$

Its concentration thus remaining virtually constant, and the concentration of H^+ and $Hg(OAc)_2$ remaining constant during the entire run, the rate law reduces to equation (3)

$$\text{Rate} = k_0 \qquad (3)$$

where $k_0 = k_s K$ [substrate] $[H^+]$ $[Hg(OAc)_2]$.

SCHEME



In the case of unsubstituted and 3,5-dialkyl substituted substrates only one enol form is possible, while in the case of 3-alkyl substituted substrates 4,5-unsaturated enol form alone is possible because the electron releasing inductive effect of the alkyl group reduces the acidity of α-hydrogen and the same alkyl group sterically hinders the approach of the proton abstract. ^1H NMR analysis of the products obtained from **(8)** and **(11)** also confirms the above fact and indicates that the incoming bromine has become attached to unsaturated α-carbon and occupies the

equatorial position in the case of 3-alkyl piperidin-4-ones and the axial position in the case of 3,5-dialkyl piperidin-4-ones.

Structure and Reactivity

All the piperidin-4-ones investigated have been shown from their ^{1}H- and ^{13}C-NMR studies to exist in the chain conformation with the phenyl and alkyl substitution occupying the least strained equatorial position[7, 14, 15].

The effect of the alkyl substituents on the rates of bromination in the N-Me series parallels their effect in the N-H series. A combination of both steric and electronic factors seems to be responsible for the observed trend in the rates. The slight increase in the rate in going from **(1)** to **(2)** and from **(7)** to **(8)** is understandable on the basis of the inductive effect of the distant alkyl substituents on the rate of proton abstraction from the unsubstituted α-carbon by a general base in the enol formation step. As the methyl group is more electron releasing than the ethyl group[16], it discourages the abstraction of a proton, But the small observed rate increase in going from **(2)** to **(3)** and from **(8)** to **(9)** is probably due to the considerable separation of the alkyl substituent from the abstraction site.

When alkyl substituents are introduced at positions 3 and 5 (α, α′ to the carbonyl functional group) a significant reduction in the rate of bromination is observed. This can be estimated by comparing the rates of **(2)**, **(3)**, **(8)** and **(9)** with those of **(5)**, **(6)**, **(11)** and **(12)** respectively. The larger reduction observed is understandable on the basis of the proximity of the electron releasing alkyl group to the site of proton abstraction and the steric interaction of this group with the approaching basic species. This agrees with Wigfield's results for the BH_4^- addtion to α-substituted cyclones and is presumably due to steric hindrance to approach of the reactant[17]. The slight increased rates of **(6)** and **(12)** when compared with those of **(5)** and **(11)**, respectively, reveal that the methyl substituent is more electron releasing than the ethyl substituent in spite of the fact that a methyl group is less bulky and hence less retarding sterically than the ethyl group.

Since the replacement of a more electron-releasing methyl group by a less electron-releasing ethyl group enhances the rate, one would expect a further enhancement when an isopropyl group is introduced in place of methyl group[16]. On the contrary, a reduction of rate has been observed in both the N-H series as well as the N-Me series. Compare the rate of **(4)** with that of **(2)** or **(3)** and the rate of **(10)** with that of **(8)** or **(9)**. The reason for this reduction is probably that the steric factor of the bulky isopropyl group outweighs the electronic factor and hence hinders the approach of the base in the rate limiting enolisation step.

A comparison of rate constants of bromination indicates that the N-Me compounds react faster than their corresponding N-H compounds. It may be reasoned on the basis of conformational effects, *i.e.*, a change in orientation of the nitrogen lone pair because it is difficult to rationalize based on the inductive effect of the N-methyl group. It has been shown, based on nitrogen lone pair axial-equatorial equilibrium data calculated from dipole moments measured, that the hydrogen has a small preference for the equatorial position in NH-piperidines

whereas the methyl is found to be lagely in the equatorial positon in the NCH_3-piperidones[18]. Likewise, therefore, in the NH-piperidones, the lone pair is preferentially equatorial and this orientation probably affects the transannular effect, *i.e.*, 1,3-interaction between the lone pair and the axial hydrogens at positions 3 and 5 could enhance the ground-state energy of the reactant and consequently lead to a lowering of activation energy, whereas in NCH_3-piperidones, the lone pair is preferentially axial[19] below the average plane of the cycle.

ACKNOWLEDGEMENTS

We thank Dr. B. Sampathkumar, Principal and Prof. D.K.P. Varadarajan, Secretary, P.S.G. College of Arts and Science, Coimbatore and Mr. G.R. Karthikeyan, M.B.A., Managing Trustee, P.S.G. Institutions, Coimbatore, for constant encouragement and facilities provided.

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(*Received*: 25 August 2000; *Accepted*: 16 November 2000) AJC-2195