Kinetics and Mechanism of the Oxidation of Some Heterocyclic Secondary Alcohols by *N*-Bromoacetamide in Acid Medium †

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The kinetics of oxidation of 12 epimeric pairs of 1-hetera-2,6-diphenylcyclohexan-4-ols by *N*-bromoacetamide in the presence of perchloric acid in aqueous acid have been investigated. The oxidation is first-order in both oxidant and substrate and of minus-one-order in acetamide (an intermediate in the reaction) at constant acid concentration. The order with respect to H_3O^+ is observed to be unity at constant ionic strength in perchloric acid. Based on the observed deuterium kinetic isotope effect in the case of the epimeric pairs, 2,6-diphenyl-3,*N*-dimethylpiperidin-4-ols and 2,6-diphenyl-3-ethyl-*N*-methylpiperidin-4-ols, a mechanism involving the participation of an O–H bond in the rate-limiting step is proposed. The reactivities of various 1-heteracyclohexan-4-ols towards oxidation have been rationalised on the basis of conformational differences. The effect of solvent polarity on the rate has been studied. Activation parameters have also been evaluated.

The use of *N*-bromoacetamide (NBA) as an oxidant has been the subject of several publications.[1–4] However, to our knowledge, no systematic investigation of the oxidation of heterocyclic alcohols by NBA has been carried out. The present investigation is an attempt to do this, and our results have enabled us to correlate reaction rate with conformation.

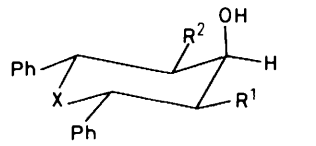
Results and Discussion

The kinetics of oxidation of variously substituted 1-heteracyclohexan-4-ols (**1**)—(**28**) by NBA were investigated in aqueous acetic acid in the presence of perchloric acid, acetamide, and mercuric acetate and the results are recorded in Tables 1—6. In the absence of mercury(II) acetate there exists the possibility of oxidation with molecular bromine (resulting from the interaction of NBA and Br^-) interfering with, and running parallel to, the oxidation by NBA. By forming complexes such as $HgBr_2$ and $HgBr_4^{2-}$ with Br^-, mercury(II) acetate prevents the oxidation by molecular bromine. Thus, in the presence of mercury(II) acetate, the reaction is expected to follow simpler kinetics.

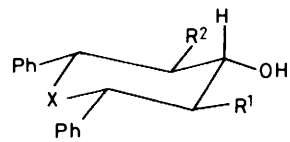
The first-order dependence of the rate on the substrate concentration can be seen from Table 1. Recorded in Table 2 are the rate constants obtained for the various 1-heteracyclohexan-4-ols at constant acid concentration. The data in Table 3 confirm the first-order dependence of rate on $[H_3O^+]$.

The effect of solvent polarity on the reaction rate is presented in Table 4. The rate is found to be inversely proportional to solvent polarity and this suggests that the transition state is less polar than the initial state. The activation parameters obtained for some of the compounds are given in Table 5. The negative entropy of activation indicates an orderly arrangement of the reacting species in the transition state. As is evident from the data in Table 6 no deuterium kinetic isotope effect is observed.

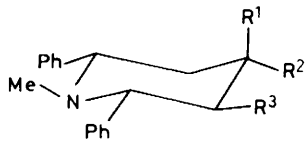
The reaction mixture in the oxidation of alcohols by NBA failed to induce polymerisation of acrylamide. This excludes the possibility of formation of free-radical intermediates during the reaction.



	X	R^1	R^2
(**1**)	O	H	H
(**2**)	O	Me	H
(**3**)	O	Et	H
(**4**)	O	Me	Me
(**5**)	NMe	H	H
(**6**)	NMe	Me	H
(**7**)	NMe	Et	H
(**8**)	NMe	Pr^i	H
(**9**)	NMe	Me	Me
(**10**)	SO_2	H	H
(**11**)	SO_2	Me	H
(**12**)	SO_2	Et	H



	X	R^1	R^2
(**13**)	O	H	H
(**14**)	O	Me	H
(**15**)	O	Et	H
(**16**)	O	Me	Me
(**17**)	NMe	H	H
(**18**)	NMe	Me	H
(**19**)	NMe	Et	H
(**20**)	NMe	Pr^i	H
(**21**)	NMe	Me	Me
(**22**)	SO_2	H	H
(**23**)	SO_2	Me	H
(**24**)	SO_2	Et	H



	R^1	R^2	R^3
(**25**)	OH	D	Me
(**26**)	D	OH	Me
(**27**)	OH	D	Et
(**28**)	D	OH	Et

Mechanism and Rate law.—Based on the above observations, we propose the mechanism in the Scheme for the oxidation. The rate law for this mechanism can be written as (1). With the substrate taken in large excess, thus maintaining its concentration virtually constant and the concentration of $HClO_4$

† This paper is an account of part of the work described in the thesis of M. Jambulingam.

Table 1. Dependence of rate on the concentration of *t*-2,*t*-6-diphenyl-*c*-3-ethyl-*N*-methylpiperidin-*r*-4-ol (**7**)[a]

10^3[Substrate]/mol l^{-1}	10^5k_1/mol l^{-1} min^{-1}	10^3k_2/min^{-1}
8.02	7.908	9.86
10.06	10.201	10.14
18.28	18.004	9.85
29.56	29.781	10.07
41.24	42.686	10.35
		Mean 10.05 ± 0.16

[a] Reaction conditions: i, solvent aq. AcOH (90% v/v); ii, [NBA] 1.23 × 10^{-3}M; iii, [$Hg(OAc)_2$] 3.26 × 10^{-3}M; iv, [Acetamide] 1.28 × 10^{-3}M; v, [$HClO_4$] 0.3M; vi, ionic strength 0.5M; vii, *t* 30 °C.

Table 2. The k_2 rate coefficients for the NBA oxidation of various 1-heteracyclohexan-4-ols[a]

Compd.	10^3k_2/min^{-1}	Compd.	10^3k_2/min^{-1}
(1)	8.05	**(13)**	9.18
(2)	6.54	**(14)**	8.45
(3)	4.09	**(15)**	6.75
(4)	13.58	**(16)**	15.89
(5)	13.39	**(17)**	14.84
(6)	12.56	**(18)**	13.79
(7)	10.04	**(19)**	12.01
(8)	7.21	**(20)**	8.52
(9)	16.56	**(21)**	18.86
(10)	8.01	**(22)**	8.87
(11)	7.45	**(23)**	8.83
(12)	6.51	**(24)**	7.14

[a] Reaction conditions as in Table 1.

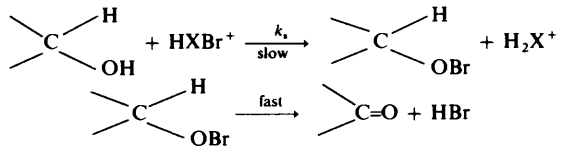
Table 3. Effect of varying acid concentration on the reaction rate of *c*-2,*c*-6-diphenyl-*t*-3-isopropyl-*N*-methylpiperidin-*r*-4-ol (**20**)[a]

10[$HClO_4$]/mol l^{-1}	10^5k_1/mol l^{-1} min^{-1}
1.50	4.408
2.25	6.710
3.00	9.438
3.75	11.780

[a] [Substrate] 10.75 × 10^{-3}M; all other conditions as in Table 1.

$$MeCONHBr + HX \underset{\text{solvent}}{\overset{K_1}{\rightleftharpoons}} MeCONH_2 + XBr$$

$$XBr + H_3O^+ \overset{K_2}{\rightleftharpoons} HXBr^+ + H_2O$$



Scheme.

$$\text{Rate} = \frac{-d[NBA]}{dt} = \frac{k_s K_1 K_2\,[\text{substrate}]\,[H_3O^+]\,[NBA]}{[\text{Acetamide}]} \quad (1)$$

$$\text{Rate} = \frac{-d[NBA]}{dt} = k_1 \frac{[NBA]}{[\text{Acetamide}]} \quad (2)$$

$$k_1 = k_s K_1 K_2\,[\text{substrate}]\,[H_3O^+] \quad (3)$$

Table 4. Effect of varying solvent polarity on the reaction rate of *c*-2,*c*-6-diphenyl-*t*-3-methyl-*N*-methylpiperidin-*r*-4-ol (**18**)[a]

HOAc–H_2O (% v/v)	10^3k_2/min^{-1}
75–25	1.20
80–20	4.45
85–15	9.85
90–10	13.79

[a] [Substrate] 10.34 × 10^{-3}M; [NBA], [$Hg(OAc)_2$], [Acetamide], [$HClO_4$], ionic strength, and *t* as in Table 1.

Table 5. Activation parameters for the oxidation of 1-heteracyclohexan-4-ols by NBA[a]

Compd.	$\Delta H^‡$/kJ mol^{-1}	$\Delta S^‡$/J mol^{-1} K^{-1}
(2)	68.5	−61.4
(5)	64.8	−38.6
(6)	65.4	−37.4
(10)	83.8	−30.1
(11)	84.1	−36.5
(12)	86.5	−8.1
(17)	69.4	−6.5
(18)	71.1	−29.9

[a] [Substrate] 11.26 × 10^{-3}M; all other conditions as in Table 1.

Table 6. Kinetic isotope effect on the oxidation of 1-heteracyclohexan-4-ols[a]

Compd.	10^3k_2/min^{-1}	Compd.	10^3k_2/min^{-1}	k_H/k_D
(6)	12.56	**(25)**	11.96	1.05
(18)	13.79	**(26)**	14.01	0.98
(7)	10.05	**(27)**	10.32	0.97
(19)	12.01	**(28)**	12.14	0.99

[a] Reaction conditions as in Table 1.

remaining constant during the run, equation (1) reduces to (2) where k_1 is given by (3).

The concentration of acetamide at any time is equal to the sum of its initial concentration and that formed during the reaction, the latter being equal to the concentration of NBA reacted. Bearing this in mind, integration of equation (2) yields (4) where [Acetamide]$_o$ and [NBA]$_o$ are the initial concentra-

$$([\text{Acetamide}]_o + [NBA]_o) \ln\left(\frac{[NBA]_o}{[NBA]_t}\right) - ([NBA]_o - [NBA]_t) = k_1 t \quad (4)$$

tions of acetamide and NBA respectively and [NBA]$_t$ is the concentration of NBA at time *t*. A plot of the left-hand side of equation (4) against *t* should yield a straight line and indeed this was observed (Figure). This confirms that the reaction is first-order in NBA and is minus-one-order in acetamide. The mechanism in the Scheme is also consistent with the observation that the reaction is first-order with respect to both substrate and H_3O^+.

As shown in the Scheme, the rate-determining step brings two species together, and hence the transition state is more organised than the reactants. This explains the observed negative entropy of activation. Also the non-participation of the C–H bond in the rate-determining step accounts for the absence of kinetic isotope effect.

Structure and Reactivity.—The substituted 1-heteracyclohexan-4-ols (**1**)—(**3**), (**5**)—(**8**), (**10**)—(**15**), (**17**)—(**20**), and (**22**)—

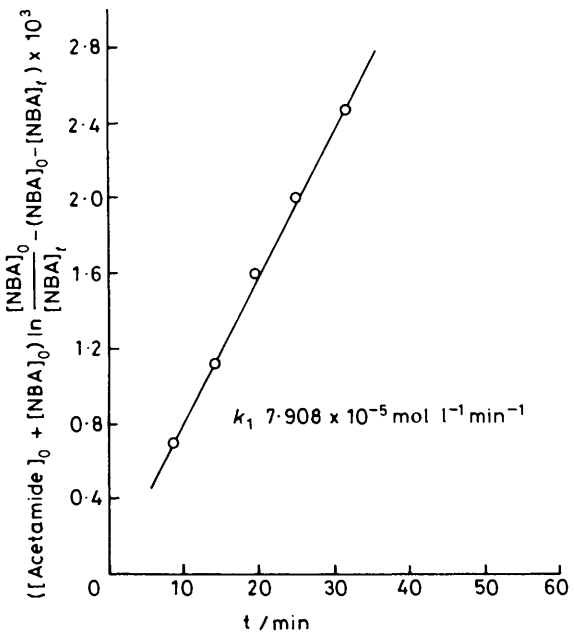


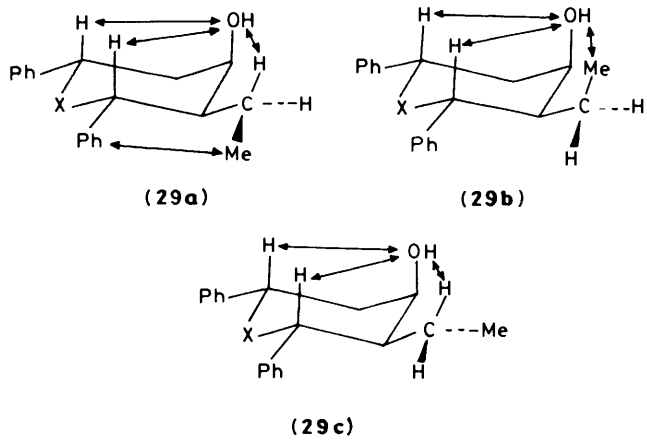
Figure. Pseudo-first-order plot for oxidation of (**7**) in acid medium at 30 °C. Solvent AcOH (90% v/v); [Substrate] 8.02 × 10^{-3}M; [NBA]$_0$ 1.23 × 10^{-3}M; [Hg(OAc))$_2$] 3.26 × 10^{-3}M; [Acetamide]$_0$ 1.28 × 10^{-3}M; [$HClO_4$] 0.3M; ionic strength 0.5M

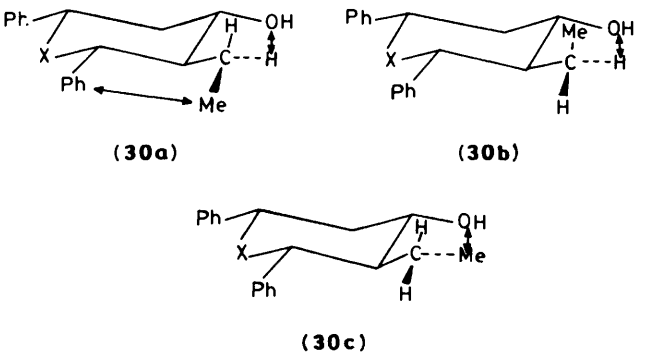
(**28**) have been shown to exist in the chair conformation, with the alkyl and phenyl groups in the most stable equatorial positions.[5-10] A perusal of their rate coefficients in Table 1 indicates that axial alcohols are oxidised at a slower rate than their equatorial counterparts. This is contrary to what has been observed in the case of epimeric alicyclic alcohols and piperidin-4-ols.[11-13] The reason for this difference is, probably, due to the difference in the mechanism of oxidation. As shown in the Scheme, the rate-limiting step involves the formation of a hypobromite ester. Any interference in the formation of this ester may be expected to retard the reaction. Compared with an equatorial hydroxy group, an axial hydroxy group is subjected to two additional 1,3-diaxial H–OH interactions. The resultant additional steric strain is thus the cause for the reduced rate of oxidation of axial alcohols.

The presence of an equatorial alkyl group in the 3-position lowers the rate of oxidation of both axial and equatorial alcohols. This is in accord with the proposed mechanism. An alkyl group vicinal to a hydroxy group engages in non-bonded gauche interactions with the latter irrespective of whether the hydroxy group is axial or equatorial. The consequent increase in strain will retard the rate of formation of the hypobromite ester in the rate limiting step. As expected, increasing the size of the alkyl group results in a decrease in the rate. Thus, a 3-isopropyl compound reacts at a slower rate than a 3-ethyl compound, which in turn reacts slower than a 3-methyl compound.

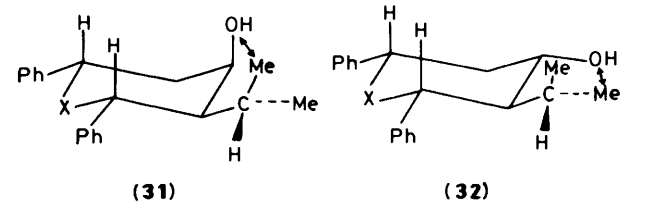
The possible conformations for 1-hetera-*t*-2,*t*-6-diphenyl-*c*-3-ethylcyclohexan-*r*-4-ol are (**29a—c**). Excluding conformation (**29a**) on the grounds of severe steric interaction between the phenyl and methyl groups, the other two conformations may be expected to be present as an equilibrium mixture. Whereas conformation (**29c**) has three H–OH interactions, conformation (**29b**) has two H–OH interactions and one Me–OH interaction. It is the presence of this Me–OH interaction that makes this conformation and hence the equilibrium mixture react at a slower rate than a 3-methyl or a 3-unsubstituted compound.

A similar explanation holds good in the case of 1-hetera-*c*-2,*c*-6-diphenyl-*t*-3-ethylcyclohexan-*r*-4-ols. The possible conformations are (**30a—c**). Excluding (**30a**) for the same reason as above, the other two conformations may be expected to exist as an equilibrium mixture. The presence of the Me–OH interaction in (**30c**) lowers the rate of oxidation of a 3-ethyl compound compared with that of a 3-methyl or a 3-unsubstituted compound.





The preferred conformation for 1-hetera-*t*-2,*t*-6-diphenyl-*c*-3-isopropylcyclohexan-*r*-4-ol-and 1-hetera-*c*-2,*c*-6-diphenyl-*t*-3-isopropylcyclohexan-*r*-4-ol are (**31**) and (**32**), respectively. The substantial reduction in the rates of the 3-isopropyl compound is attributed to the inevitable presence of the Me–OH interaction in these compounds.



Since the presence of a 3-methyl group was observed to reduce the rate of oxidation of both axial and equatorial alcohols (due to gauche interactions), one would expect the rates of oxidation of 1-hetera-2,6-diphenyl-3,5-dimethylcyclohexane-4-ols to be lower than those of the corresponding 1-hetera-2,6-diphenyl-3-methylcyclohexan-4-ols. The observed rates of oxidation, much higher than expected, are indicative of a decreased non-bonded interaction and hence the possible existence of these compounds in a twist conformation. A twist conformation for these compounds has been proposed by other workers.[5,6,12]

Experimental

Materials.—All compounds used in this study were prepared following literature procedures.[8-10,12] Acetic acid (AnalaR; B.D.H.) was refluxed over CrO_3 and used as solvent. Other chemicals used were of AnalaR grade. *N*-Bromoacetamide was prepared and purified as described in the literature.[14]

Kinetic Measurements.—All the kinetic runs were made by keeping the substrate and acid concentrations always in large excess over that of NBA. The ionic strengths of the reaction mixtures were kept constant by the addition of sodium perchlorate. To avoid photocatalysis, the reactions were carried out in darkened flasks in a room lit with a sodium vapour lamp. The reaction was followed by withdrawing portions (2 ml) of the reaction mixture at suitable intervals, pouring into an excess of KI solution containing 0.5M-$NaHCO_3$, and titrating the liberated I_2 against standard $Na_2S_2O_3$ using starch indicator. All the reactions were followed to at least 70% conversion of the oxidant and the results were found to be reproducible within ±2.5% error.

To calculate the activation parameters, the reactions were run at 30, 35, 40, 45, and 50 °C. A plot of log (k_2/T) *versus* $(1/T)$ gave a straight line. The enthalpy of activation ($\Delta H^{\ddagger}$) and the entropy of activation ($\Delta S^{\ddagger}$) were calculated from the slope and intercept respectively, following the Eyring equation (5).

$$\log (k/T_2) = \log (k/h) + \Delta S^{\ddagger}/2.303R - \Delta H^{\ddagger}/2.303T \quad (5)$$

Product Analysis.—A mixture of (**3**) (1.5 g, 0.005 mol), *N*-bromoacetamide (0.9 g, 0.006 mol), and mercury(II) acetate (1.2 g, 0.004 mol) in aqueous acetic acid (90% v/v) (100 ml) was heated in a darkened round bottom flask fitted with a water condenser on a boiling water-bath for 4 h. The mixture was left at room temperature for 24 h and was then poured onto crushed ice, filtered off, washed, and dried. Crystallisation from ethanol gave *r*-2,*cis*-6-diphenyl-*trans*-3-ethyloxan-4-one (1.32 g, 88%), m.p. 104—105 °C (lit.,[8] 104—105 °C). Similar product analysis was done for alcohols (**20**) and (**24**) and the product was found to be identical with the corresponding heterocyclic ketones.

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