Kinetics of Oxidation of Heterocyclic Secondary Alcohols by *N*-Chloro-*r*-2,*c*-6-Diphenyl-*t*-3 Methyl Piperidin-4-one (NCP) in Perchloric Acid Medium

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Abstract

An investigation of the kinetics of oxidation of epimeric piperidin-4-ols, oxan-4-ols, and cyclohexanol by *N*-chloro-*r*-2, *c*-6-diphenyl-*t*-3-methylpiperidin-4-one (NCP) in aqueous acetic acid in the presence of perchloric acid shows that the reaction is first-order each in substrate and oxidant. Both H_3O^+ and Cl^- which catalyze the reaction, exhibit a fractional order kinetics. While increase in ionic strength increases the rate slightly, an inverse dependence is observed between rate and solvent polarity. Addition of *r*-2-*c*-6-diphenyl-*t*-3-methylpiperidin-4-one, one of the reaction products, did not influence the rate. Also, no kinetic isotope effect has been observed. A plausible mechanism consistent with these observations is proposed and the relative reactivities of the substrates are explained on conformational grounds.

Introduction

N-Haloimides have been widely used as both oxidizing and chlorinating agents for a variety of organic substrates [1–3]. *N*-Chloro-*r*-2-*c*-6-diphenyl-*t*-3-methylpiperidin-4-one (NCP) is a recent addition to the list of *N*-halocompounds [4]. The present investigation is aimed at exploring the potential of NCP as an oxidant for heterocyclic secondary alcohols, understanding the mechanism of oxidation and correlating reactivity with structure.

Experimental

Materials

All the heterocylic alcohols used in the present investigation were prepared following literature procedures [5–8]. Acetic acid (AnalaR-Qualigens) was refluxed over CrO_3 before use. NCP was prepared and purified as described in the literature [4]. All other chemicals used were of AnalaR grade.

Kinetic Measurements

Pseudo-first-order conditions were maintained for all the kinetic runs by keeping the substrate and perchloric acid concentration always in large excess over that of

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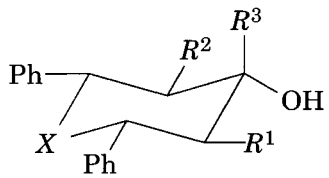
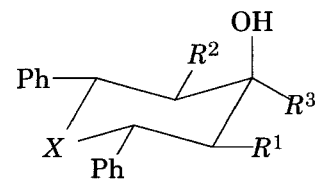
NCP. The ionic strength of the reaction medium was kept constant by the addition of sodium perchlorate. The progress of the reaction was followed by taking aliquots (2 ml) of the reaction mixture at suitable intervals and estimating the unused NCP iodometrically. Activation parameters were evaluated by running the reaction at 308, 313, 318, 323, and 328 K.

Product Analysis

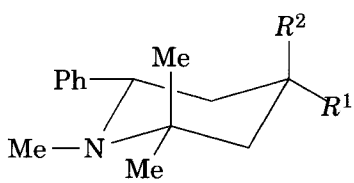
By separately reacting the substrates with NCP under the same conditions at which the kinetic runs were made, isolating the reaction products through chromatography and identifying them (from their melting points), it has been found that, in all the cases investigated, the secondary alcohols were converted to the corresponding ketones.



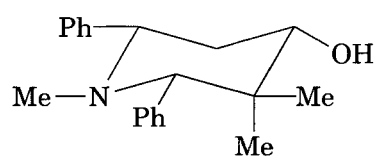
	X	R^1	R^2	R^3
1)		Cyclohexanol		
2)	NMe	H	H	H
3)	NMe	Me	H	H
4)	NMe	Et	H	H
5)	NMe	Pr^i	H	H
6)	NMe	Me	Me	H
7)	NMe	H	H	D
8)	NMe	Me	H	D
9)	NMe	Et	H	D
10)	NMe	Pr^i	H	D
11)	NMe	Me	Me	D
12)	O	H	H	H
13)	O	Me	H	H
14)	O	Et	H	H
15)	O	Me	Me	H



	X	R^1	R^2	R^3
16)	NMe	H	H	H
17)	NMe	Me	H	H
18)	NMe	Et	H	H
19)	NMe	Pr^i	H	H
20)	NMe	Me	Me	H
21)	NMe	H	H	D
22)	NMe	Me	H	D
23)	NMe	Et	H	D
24)	NMe	Pr^i	H	D
25)	NMe	Me	Me	D
26)	O	H	H	H
27)	O	Me	H	H
28)	O	Et	H	H
29)	O	Me	Me	H



	R^1	R^2
30)	OH	H
31)	H	OH
32)	D	OH



(33)

Results and Discussion

The kinetics of oxidation of secondary alcohols (1)–(33) by NCP have been investigated in aqueous acetic acid in the presence of perchloric acid and the results

TABLE I. Dependence of rate on the concentration of substrate.

10^2[substrate]/M	$10^5 k_1/s^{-1}$	$10^4 k_2/M^{-1}s^{-1}$
1.693	4.083	24.12
2.201	5.258	23.89
2.709	6.506	24.02
3.217	7.780	24.18
3.725	8.926	23.96
4.233	10.10	23.86

Substrate: *t*-2, *t*-6-diphenyl-*c*-3, *c*-5,*N*-trimethylpiperidin-*r*-4-ol (20)
[NCP] = 1.668×10^{-3} M; Solvent = aq. AcOH (70% v/v)
[$HClO_4$] = 0.2 M; T = 313 K

are recorded in Tables I–VI. The first-order dependence of the rate on substrate concentration can be seen from Table I. The data in Table II show that the reaction is susceptible to acid catalysis and the order with respect to [H_3O^+] is fractional. The sodium perchlorate added to the reaction mixture, to maintain a constant ionic strength, produced an induction period of about half an hour, after which the reaction followed a smooth first-order kinetics. The induction period vanished in the presence of Cl^-. Hence, the effect of [H_3O^+] and ionic strength variations have been studied in the presence of Cl^-.

The data in Table II also show an increase in reaction rate with increase in ionic strength. The linear plot that results when $\ln k_2$ is plotted against ionic strength (μ) suggests the involvement of neutral molecule or a dipole and a positive ion in the rate-limiting step [9]. The inverse dependence of rate on solvent polarity is evident from the data in Table III. A linear plot with a positive slope that results when $\ln k_2$ is plotted against the reciprocal of the dielectric constant further confirms the interaction of a positive ion and a dipole or neutral molecule in the slow step of the reaction [10,11].

While addition of *r*-2, *c*-6-diphenyl-*t*-3-methylpiperidin-4-one, the reduction product from NCP, has no effect on the rate, addition of Cl^- to the reaction mixture enhanced the rate of the reaction (Table IV). The order with respect to [Cl^-] is found to be

TABLE II. Effect of varying acid concentration and ionic strength on the reaction rate.

[$HClO_4$]/M	[$NaClO_4$]/M	$10^3 k_2/M^{-1}s^{-1}$
0.20	0.10	3.601
0.20	0.15	4.561
0.20	0.20	5.264
0.20	0.25	6.283
0.20	0.30	7.599
0.25	0.20	7.160
0.30	0.15	7.895
0.35	0.10	8.551
0.40	0.05	9.123

Substrate: *c*-2, *c*-6-diphenyl-*N*-methylpiperidin-*r*-4-ol (2)
[Substrate] = 1.870×10^{-2} M; [NCP] = 1.668×10^{-3} M;
[Cl^-] = 8.212×10^{-4} M; Solvent = aq. AcOH (70% v/v)
T = 313 K.

TABLE III. Dependence of rate on the polarity of the medium.

%AcOH–%H_2O (v/v)	$10^3 k_2/M^{-1}s^{-1}$
65–35	1.858
70–30	2.412
75–25	3.488
80–20	5.556
85–15	10.54

Substrate: *t*-2, *t*-6-diphenyl-*c*-3, *c*-5,*N*-trimethylpiperidin-*r*-4-ol (20)
[Substrate] = 1.693×10^{-2} M; [NCP] = 1.668×10^{-3} M
[$HClO_4$] = 0.2 M; T = 313 K.

TABLE IV. Effect of added sodium chloride on the reaction rate.

10 [Cl^-]/M	$10^3 k_2/M^{-1}s^{-1}$
8.212	3.499
10.27	3.823
12.32	4.048
16.43	4.375
20.53	4.627
24.64	4.803

Substrate: *c*-2, *c*-6-diphenyl-*t*-3, *t*-5.*N*-trimethylpiperidin-*r*-4-ol (6)
[Substrate] = 1.693×10^{-2} M; [NCP] = 1.668×10^{-3} M;
[$HClO_4$] = 0.2 M; Solvent = aq. AcOH (70% v/v)
T = 313 K.

fractional. The closeness (within experimental error) of the rate constants obtained for α-deuterated piperidinols and those for the corresponding undeuterated alcohols suggests the absence of any kinetic isotope effect. The nonparticipation of any free radical intermediate in the reaction is evidenced by the failure of the reaction mixture to induce polymerization of acrylamide. All the reactions show a negative entropy of activation (Table V).

TABLE V. Activation parameters for the oxidation of alcohols.

Compound	$\Delta H^{\#}$/ KJ mol^{-1}	$\Delta S^{\#}$/ J mol^{-1} K^{-1}	Compound	$\Delta H^{\#}$/ KJ mol^{-1}	$\Delta S^{\#}$/ J mol^{-1} K^{-1}
(1)	89.76	−48.42	(17)	85.09	−47.46
(2)	79.79	−48.80	(18)	79.79	−49.67
(3)	75.57	−48.23	(19)	81.72	−49.76
(4)	78.85	−48.80	(20)	78.16	−50.34
(5)	77.62	−49.48	(26)	73.64	−49.57
(6)	77.93	−49.38	(27)	72.84	−48.42
(12)	75.10	−48.23	(28)	76.15	−48.42
(13)	72.84	−47.46	(29)	75.57	−49.19
(14)	76.59	−47.27	(30)	82.07	−50.53
(15)	76.15	−48.23	(31)	88.17	−50.53
(16)	95.74	−45.80	(33)	79.79	−50.15

[NCP] = 1.668×10^{-3} M; Solvent = aq. AcOH (70% v/v);
[$HClO_4$] = 0.2 M

Mechanism

Based on the above discussion, a mechanism (Scheme I) involving the formation of a hypochlorite and its rapid decomposition is proposed.

The rate law of the proposed mechanism is given as (1)

$$\text{Rate} = \frac{-d[\text{NCP}]}{dt} = \frac{k_s K_1[\text{substrate}][\text{NCP}]_T[\text{H}_3\text{O}^+]}{1 + K_1[\text{H}_3\text{O}^+]} \quad (1)$$

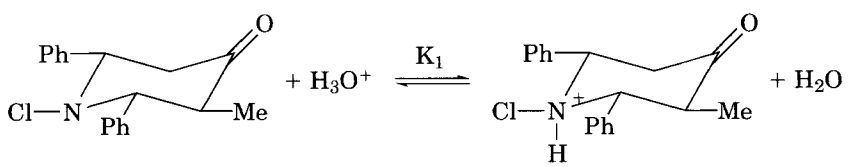
The observed pseudo-first-order rate constant k_1 is given by (2).

$$k_1 = \frac{k_s K_1[\text{substrate}][\text{H}_3\text{O}^+]}{1 + K_1[\text{H}_3\text{O}^+]} \quad (2)$$

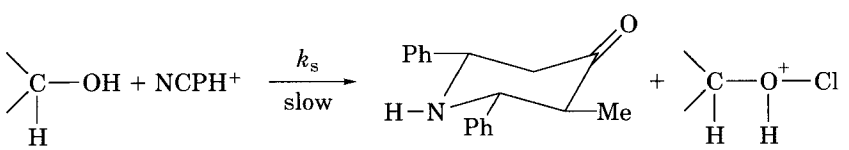
or

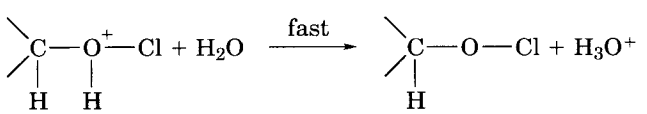
$$\frac{1}{k_1} = \frac{1}{k_s K_1[\text{substrate}][\text{H}_3\text{O}^+]} + \frac{1}{k_s[\text{substrate}]} \quad (3)$$

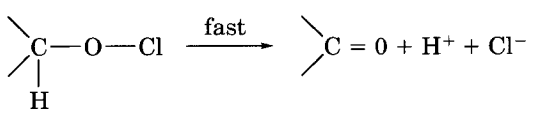
Equation (1) explains the observed order with respect to [NCP] and [substrate]. Equation (3) demands that at constant substrate concentration, a plot of $1/k_1$ vs. $1/[\text{H}_3\text{O}^+]$ should be linear and this has been found to be so.



(NCP) (NCPH$^+$)







Scheme I

To account for the influence of added Cl^- ion on the rate of the reaction, the mechanism outlined in Scheme II is proposed.

The rate law may be given as

$$\text{rate} = \frac{-d[\text{NCP}]}{dt} = \frac{k_s K_1 K_2[\text{substrate}][\text{NCP}]_T[H_3O^+][Cl^-]}{1 + K_1K_2[H_3O^+][Cl^-] + K_1[H_3O^+]} \tag{4}$$

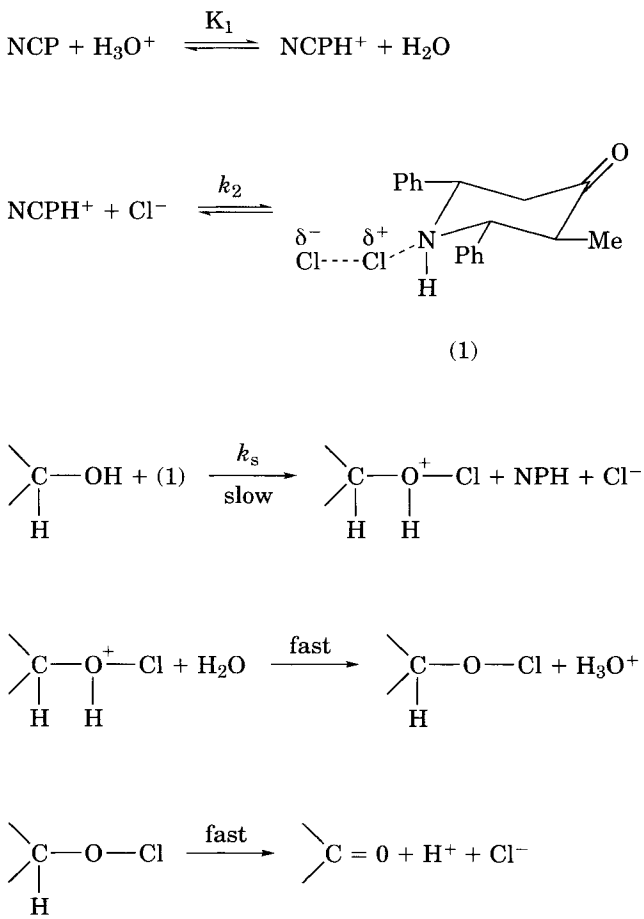
and

$$k_1 = \frac{k_s K_1 K_2[\text{substrate}][H_3O^+][Cl^-]}{1 + K_1K_2[H_3O^+][Cl^-] + K_1[H_3O^+]} \tag{5}$$

or

$$\frac{1}{k_1} = \frac{1}{k_s K_1 K_2[\text{substrate}][H_3O^+][Cl^-]} + \frac{1}{k_s K_2[\text{substrate}][Cl^-]} + \frac{1}{k_s[\text{substrate}]} \tag{6}$$

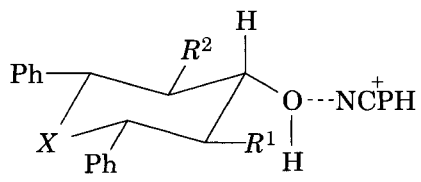
Equation (6) requires that plots of $1/k_1$ against $1/[Cl^-]$ at constant substrate and acid concentration and $1/k_1$ against $1/[H_3O^+]$ at constant substrate and Cl^- concentrations should both be linear and this has been observed.

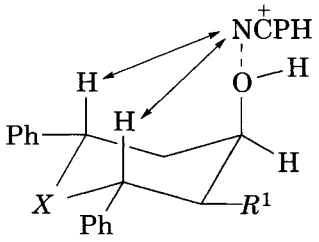


Scheme II

Structure and Reactivity

The substituted 1-heteracyclohexan-4-ols (2) to (6), (12) to (20), (26) to (31) and (33) have been shown to exist in the chair conformation with alkyl and phenyl groups in the most stable equatorial positions [5–7,12–14]. In compounds (30), (31), and (33) one of the methyl groups must necessarily be placed in the axial position. A perusal of rate coefficients in Table VI indicates that the equatorial alcohols react at a faster rate than axial counterparts. This is contrary to what has been observed earlier in the case of epimeric alicylic and several heterocyclic alcohols [8,15,16]. This is not surprising. As outlined in Scheme I, the rate limiting step involves the approach of $\overset{+}{N}CPH$ towards the —OH group of the substrate and the subsequent formation of hypochlorite. The reaction should naturally be subjected to steric approach control (SAC), and approach of $\overset{+}{N}CPH$ from the less hindered equatorial side is more favored over that from the more hindered (due to 1,3-diaxial interaction) axial side.





The presence of an equatorial group at C_3 may influence the rate of oxidation of both axial and equatorial alcohols in two ways: (i) Owing to the inherent inductive effect of alkyl groups, the electron density on the oxygen of O—H increases and this in turn facilitates the attack by the oxidant and (ii) Nonbonded gauche interaction exists between the vicinal alkyl group and the —OH group whether the latter is axial or equatorial. Consequently the imposed strain will retard the rate of formation of hypochlorite of both axial and equatorial alcohols in the rate determining step.

TABLE VI. The k_2 rate coefficients for the NCP oxidation of various alcohols.

Compound	$10^3 k_2/M^{-1}s^{-1}$		Compound	$10^3 k_2/M^{-1}s^{-1}$	
(1)	2.368		(17)	2.959	
(2)	2.773	(3.019)[a]	(18)	2.607	
(3)	3.323	(6.883)[a]	(19)	2.551	
(4)	3.014	(4.122)[a]	(20)	2.412	
(5)	2.839	(2.921)[a]	(26)	2.958	
(6)	2.731	(3.010)[a]	(27)	3.389	
(12)	3.390		(28)	3.185	
(13)	3.888		(29)	2.889	
(14)	3.674		(30)	2.112	(2.412)[a]
(15)	3.334		(31)	1.850	
(16)	2.473		(33)	2.337	(2.870)[a]

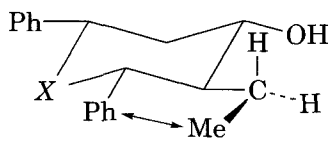
[NCP] = 1.668×10^{-3} M
Solvent = aq. AcOH (70% v/v)
[$HClO_4$] = 0.2 M; T = 313 K
[a] k_2 values in presence of [Cl^-] = 8.212×10^{-4} M.

Thus any correlation between the rate of oxidation and the nature of the equatorial alkyl group at C_3 should take into account both the electronic and steric factors.

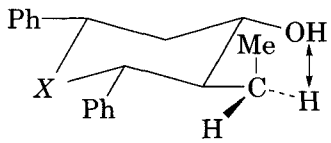
The observation that *c*-2, *c*-6, diphenyl-*t*-3-alkyl-*N*-methyl-peperidin-*r*-4-ols (3)–(5) and *t*-2, *t*-6-diphenyl-*c*-3-alkyl-*N*-methyl-piperidin-*r*-4-ols (17)–(19) react faster than *c*-2, *c*-6-diphenyl-*N*-methylpiperidin-*r*-4-ol (2) and *t*-2, *t*-6-diphenyl-*N*-methyl-piperidin-*r*-4-ol (16), respectively, indicates the dominance of the electronic effect over steric factor in these cases.

Among the compounds (3)–(5) and (17)–(19) the order of reactivity is found to be 3 > 4 > 5 and 17 > 18 > 19. This is in accordance with the operation of both inductive and steric effect of the 3-substituent on the rate of oxidation. Ethyl is less electron releasing than methyl [17]. Further, the possible conformation of 1-hetera-*c*-2 *c*-6-diphenyl-*t*-3-ethylcyclohexan-*r*-4-ol are (4a–c). Excluding conformation (4a) on the ground of severe steric interaction between the phenyl and the methyl group, the other two conformations may be expected to be present as an equilibrium mixture. Whereas conformation (4b) has one H—OH interaction, conformation (4c) has one Me—OH interaction.

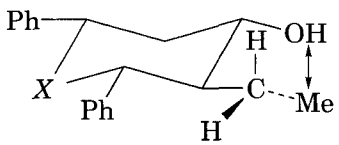
(4a)



(4b)



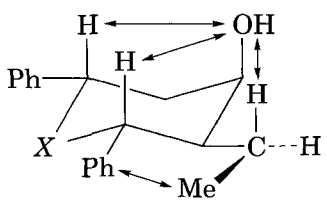
(4c)



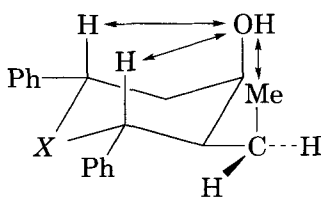
It is the presence of this Me—OH interaction that makes this conformation and hence the equilibrium mixture to react at a slower rate than the 3-methyl compound.

A similar explanation holds good in the case of 1-hetera-*t*-2, *t*-6-diphenyl-*c*-3-ethyl cyclohexan-*r*-4-ols. The possible conformations are (18a–c). Excluding (18a) for the same reason as above, the other two conformations may be expected to exist as an equilibrium mixture.

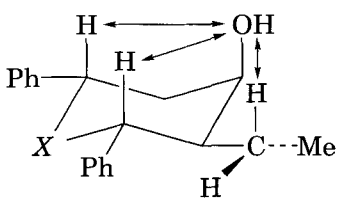
(18a)



(18b)



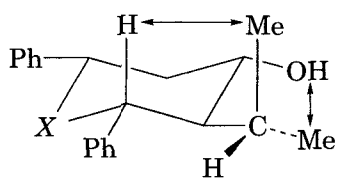
(18c)



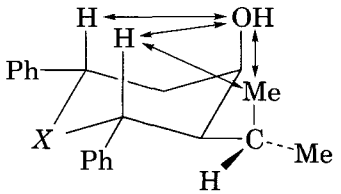
The presence of the Me—OH interaction in (18b) lowers its rate of oxidation compared to that of 3-methyl compound.

The preferred conformations of 1-hetera-*c*-2, *c*-6, diphenyl-*t*-3-isopropylcyclohexan-*r*-4-ol and 1-hetera-*t*-2, *t*-6, diphenyl-*c*-3-isopropylcyclohexan-*r*-4-ol are (5) and (19), respectively. Both contain the Me—OH interaction.

(5)



(19)



Further an isopropyl group is less electron releasing than an ethyl group [17]. Hence, the observed order of reactivity of 3-isopropyl compounds.

Comparison of rates of (6) with (2) and (20) with (16) suggests that the presence of two methyl groups at C_3 and C_5 has no influence on the rate of oxidation. This may perhaps be due to the cancellation of inductive acceleration by steric retardation. On the other hand, when both the methyl groups are attached to the same carbon as in (33), there is considerable reduction in rate due, probably, to the dominant influence of steric factor.

The reduced rates observed in the case of epimeric alcohols (30) and (31) may also be due to steric effect.

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