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A Study of Conformational Effects on Oxidation Kinetics of *N*-H- and *N*-Methyl-4-piperidones with *N*-Bromosuccinimide : A Comparative Analysis

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A comparative oxidation kinetics of six pairs of *N*-H and *N*-methyl-2,6-diphenyl-4-piperidones with *N*-bromosuccinimide (NBS) in aqueous acetic acid medium (20–80%, v/v) at constant ionic strength in presence of mercuric acetate has been investigated. The effect of alkyl substituents on the rates of oxidation in N–Me series parallels their effects in *N*–H series. The enhanced rates N–Me compounds compared to their N–H counterparts and the least reactivity of 3,5-dimethyl-2,6-diphenyl-4-piperidones have been rationalised on the basis of their conformation. The reactions are second order, first order each in [piperidone] and [NBS]. Negative salt effect, positive dielectric effect and nil succinimide effect have been observed suggesting NBS itself as the reactive species. A mechanism involving formation of a cyclic transition state by the interaction between the enol form of piperidone and NBS, consistent with reaction stoichiometry has been proposed.

Kinetics of oxidation of 2,6-diphenyl-4-piperidones by various oxidants has been the subject matter of several publications[1,2]. However, the interesting conformational aspects of 4-piperidones and lack of study on NBS as oxidant with heterocyclic ketones initiated the present study. The object of the study is to compare the oxidation kinetics of *N*-H- and *N*-methyl-2,6-diphenyl-4-piperidones to bring out the role of conformational effects.

Results and Discussion

The following are the salient features of this investigation. (i) The reaction is first order in NBS as revealed by the linear plots of log [NBS] vs time ($r >$ 0.99). The pseudo-first order rate constants remain constant at different initial [NBS] (Table 1). (ii) The rate of the reaction increases with increase in [substrate]. The values of k_1/ [substrate] give the second order rate constants (k_2) which are found to be constant (Table 2). Hence, the reaction between piperidone and NBS is governed by the simple rate expression,

$$\frac{-d[NBS]}{dt} = k_2\,[\text{piperidone}][NBS]$$

(iii) A small but progressive drop in magnitude of rate constants observed when ionic strength ($NaClO_4$) was changed from 0.1 to 0.3 *M*, indicates dipole-dipole interaction (Table 3). (iv) The increase in water content of aqueous acetic acid medium increases the rate of oxidation (Table 4),

TABLE 1–DEPENDENCE OF RATE ON [NBS]

[P] = 1.0 $\times 10^{-2}$ mol dm^{-3}, [$NaClO_4$] = 0 2 mol dm^{-3}, HOAc = 80% (v/v), [$Hg(OAc)_2$] = 2 0 $\times$ 10^{-3} mol dm^{-3}

10^3[NBS] mol dm^{-3}	$10^4 k_1$ (s^{-1})			
Substrate (P)	0.75	1.00	1.25	1 50
3-H[a]	3.32	3.51	3.26	3.25
3-Me[b]	2.57	2.72	2.46	2.21
3-Et[b]	3.72	3.64	3.53	3.42
3-i-Pr[b]	3.23	3.24	3.21	3.02
3,3-diMe[c]	2.51	2.44	2 43	2.37
3,5-diMe[d]	1.36	1.34	1.32	1 27
1-Me[e]	2.38	2.51	2.44	2.25
1,3-diMe[a]	2.27	2.24	2.03	2 16
1-Me-3-Et[a]	3.64	3.50	3.38	3.35
1-Me-3-i-Pr[a]	2.57	2.52	2.56	2 36
1,3,3-triMe[c]	2.60	2.60	2.64	2.47
1,3,5-triMe[f]	2.11	2.06	1.96	2.03

[a]25°, [b]35°, [c]30°, [d]50°, [e]20°, [f]40°.

TABLE 2–DEPENDENCE ON RATE ON [PIPERIDONE]

[NBS] = 1.0×10^{-3} mol dm^{-3}, [$NaClO_4$] = 0.2 mol dm^{-3}, HOAc = 80% (v/v), [$Hg(OAc)_2$] = 2.0×10^{-3} mol dm^{-3}

Substrate (P)	10^2 [P] mol dm^{-3}	$10^4 k_1$ s^{-1}	$10^2 k_2$ dm^{3}mol^{-1}s^{-1}
3-H[a]	0.5	1.73	3.47
	1.0	3.51	3.51
	1.5	5.30	3.53
	2.0	7.07	3.53
3-Me[b]	0.5	1.30	2.59
	1.0	2.72	2.72
	1.5	4.23	2.82
	2.0	5.68	2.83
3-Et[b]	0.5	1.84	3.68
	1.0	3.64	3.64
	1.5	5.30	3.54
	2.0	7.44	3.72
3-i-Pr[b]	0.5	1.66	3.31
	1.0	3.24	3.24
	1.5	4.80	3.20
	2.0	6.43	3.21
3,3-diMe[c]	0.5	1.20	2.40
	1.0	2.44	2.44
	1.5	3.56	2.37
	2.0	4.70	2.35
3,5-diMe[d]	0.5	0.70	1.40
	1.0	1.34	1.34
	1.5	1.96	1.31
	2.0	2.76	1.38
1-Me[e]	0.5	1.30	2.60
	1.0	2.51	2.51
	1.5	3.74	2.49
	2.0	5.07	2.53
1,3-diMe[a]	0.5	1.09	2.19
	1.0	2.24	2.24
	1.5	3.03	2.02
	2.0	4.27	2.14
1-Me-3-Et[a]	0.5	1.76	3.51
	1.0	3.50	3.50
	1.5	5.07	3.38
	2.0	7.07	3.53
1-Me-3-i-Pr[a]	0.5	1.30	2.61
	1.0	2.52	2.52
	1.5	3.74	2.49
	2.0	4.90	2.45
1,3,3-triMe[c]	0.5	1.31	2.62
	1.0	2.6	2.60
	1.5	3.8	2.56
	2.0	5.10	2.55
1,3,5-triMe[f]	0.5	1.07	2.14
	1.0	2.06	2.06
	1.5	3.03	2.02
	2.0	4.09	2.05

[a]25°, [b]35°, [c]30°, [d]50°. [e]20°, [f]40°.

TABLE 3–DEPENDENCE OF RATE ON [$NaClO_4$] AT DIFFERENT IONIC STRENGTHS

[P] = 1.0×10^{-2} mol dm^{-3}, HOAc = 80% (v/v), [NBS] = 1.0×10^{-3} mol dm^{-3}, [$Hg(OAc)_2$] = 2.0×10^{-3} mol dm^{-3}

	$10^4 k_1$ (s^{-1})			
Substrate (P)	0.1 *M*	0.15 *M*	0.2 *M*	0.3 *M*
2,6-Diphenyl-4-piperidone (P)	5.24	3.94	3.51	3.17
3-Me	3.73	3.15	2.72	2.14
3-Et	4.28	3.82	3.64	2.86
3-i-Pr	4.27	3.75	3.24	2.28
3,3-diMe	3.34	2.84	2.44	2.08
3,5-diMe	1.80	1.60	1.34	1.08
1-Me	3.45	3.00	2.51	2.06
1,3-diMe	3.00	2.54	2.24	1.62
1-Me-3-Et	3.96	3.80	3.50	2.91
1-Me-3-i-Pr	3.43	2.93	2.52	1.71
1,3,3-triMe	3.49	2.93	2.60	2.13
1,3,5-triMe	3.43	2.44	2.06	1.52

TABLE 4–EFFECT OF SOLVENT COMPOSITION

[P] = 1.0×10^{-2} mol dm^{-3}, [$NaClO_4$] = 0.2 mol dm^{-3}, [NBS] = 1.0×10^{-3} mol dm^{-3}, [$Hg(OAc)_2$] = 2.0×10^{-3} mol dm^{-3}

	$10^4 k_1$ (s^{-1})			
%AcOH	60	70	80	90
D	32.2	25.0	18.7	12.5
Substrate (P)				
2,6-Diphenyl-4-piperidone (P)	3.93	3.78	3.51	3.29
3-Me	3.89	3.16	2.72	2.22
3-Et	4.46	4.04	3.64	2.43
3-i-Pr	4.58	3.70	3.24	2.28
3,3-diMe	3.36	2.84	2.44	1.71
3,5-diMe	2.47	1.73	1.34	1.07
1-Me	2.88	2.78	2.51	2.33
1,3-diMe	2.73	2.31	2.24	1.77
1-Me-3-Et	4.31	3.89	3.50	2.38
1-Me-3-i-Pr	3.53	3.08	2.52	1.68
1,3,3-triMe	3.99	3.31	2.60	1.59
1,3,5-triMe	3.35	2.84	2.06	1.85

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$$

The equilibrium shifts towards right producing more of H^+ necessary to enolise the ketone. The positive

TABLE 5–EFFECT OF ADDED [$HClO_4$] (mol dm^{-3})

[P] = 1 0 × 10^{-2} mol dm^{-3}, [$NaClO_4$] = 0 2 mol dm^{-3}, [NBS] = 1.0 × 10^{-3} mol dm^{-3}, HOAc = 80% (v/v), [Hg(OAc)] = 2 0 10^{-3} mol dm^{-3}

[$UClO_4$] mol dn^3	$10^4 k_1$ (s^{-1})					
Substrate (P)	0.50	1.00	1.25	1.50	1.75	2.00
2,6-Diphenyl-4-piperidine (P)	-	-	1.43	2.38	3 16	3.80
3-Me	0.90	2.33	-	3.33	-	5 21
3-Et	-	2.35	-	3 51	3.97	4 94
3-i-Pr			3.73	5.12	5.97	7.67
3,3-diMe			1.99	2.35	3.23	3.51
3,5-diMe			5.34	6.91	8.39	10 21
1-Me			1.03	1.36	1 67	2.13
1,3-diMe			0 79	1 02	1.26	1 51
1-Me-3-Et			1.06	1.18	1.47	2.02
1-Me-3-i-Pr			1.92	2.03	2.56	3.59
1,3,3-triMe			1.01	1.20	1.51	2.07
1,3,5-triMe			1.01	1.48	1.75	2.62

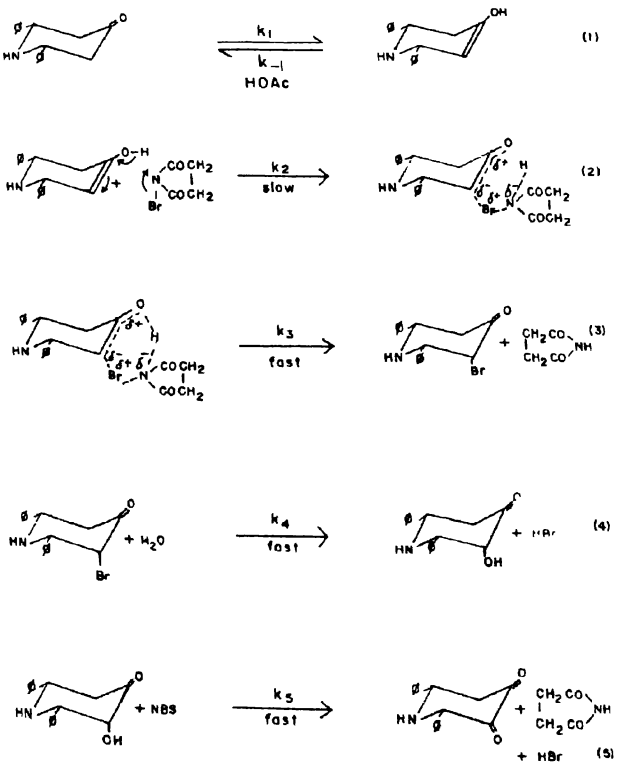
TABLE 6–RATE AND ACTIVATION PARAMETERS

[P] = 1 0 × 10^{-2} mol dm^{-3}, [$NaClO_4$] = 0.2 mol dm^{-3}, [NBS] = 1.0 × 10^{-3} mol dm^{-3}, [$Hg(OAc)_2$] = 2.0 × 10^{-3} mol dm^{-3}, HOAc = 80% (v/v)

Substrate	E_a kJ mol^{-1}	$\Delta H^{\neq}$ kJ mol^{-1}	$\Delta G^{\neq}$ kJ mol^{-1}	$\Delta S^{\neq}$ JK^{-1} mol^{-1}	log A	k_2 at 308 K dm^3 mol^{-1} s^{-1}
2,6-Diphenyl-4-piperidone (P)	92.5	89.9	80.7	29.9	14.9	13.4
3-Me	74.1	71.5	84.8	-42.8	11.0	2.72
3-Et	87.5	84 9	84.0	3.0	13.4	3.64
3-i-Pr	91.9	89.3	84.3	16.3	14.1	3.24
3,3-diMe	99.8	97.2	83.6	33.4	15.0	4.21
3,5-diMe	83.8	80.7	90.3	-3.1	11.6	0.31
1-Me	100.7	98.2	79.8	59.5	16.3	18.73
1,3-diMe	81.6	79.0	82.5	-11.3	12.6	6.59
1-Me-3-Et	82.3	79.8	81.6	-57.8	12.9	9.51
1-Me-3-i-Pr	72.8	70.2	82.4	-39.6	11.2	6.87
1,3,3-triMe	86.5	84.0	84.3	-0.9	13.3	3.31
1,3,5-triMe	107.6	105.1	87.3	57.8	16.4	1.03

dielectric effect also shows that there is charge development in the transition state[3]. (v) Added succinimide has no influence on the reaction rate–a feature which helps to ascertain the nature of the oxidising species. (vi) All the investigations were made in the presence of mercuric acetate in order to avoid any possible bromine oxidation. Mercuric acetate acts as scavenger for Br^- formed in the reaction and exist as $HgBr_4^{2-}$ and unionised $HgBr_2$ and thus ensuring only NBS oxidation[4]. (vii) The increase in added mineral acid [$HClO_4$] enhances the rate of oxidation. This may be due to increase in the enol content of the piperidone which is the participating reactive species (Table 5). (viii) An almost constant value of $\Delta G^{\neq}$ for all the twelve piperidones may be indicative of the operation of the same mechanism of oxidation (Table 6). (ix) The reaction stoichiometry 1 : 2 (piperidone : NBS) in the case of 3-H and 3-alkylpiperidones (**1–5** and **7–11**) and 1 : 1 in the case of 3,5-dimethylpiperidones (**6** and **12**) yielding α-diketone and α-ketol (characterised by tlc, ir and nmr spectral data and spot tests) are in accordance with the proposed mechanism. (x) Absence of induced poylymerisation by the addition of methyl methacrylate under nitrogen atmosphere rules out free radical mechanism (Scheme 1).

The proposed mechanism involves the formation of enol in the first equilibrium step. NBS being a two-electron oxidant, prefers to attack the enol form[5] in a



Scheme 1

slow second step leading to a cyclic transition state. In the third fast step bromine enters the α-axial position[6] of the piperidone yielding an unstable intermediate α-bromo compound. Further, the carbonyl oxygen lends anchimeric assistance to the faster nucleophilic solvolysis (step 4) ending in α-ketol. The first stage oxidation product, the α-ketol could not be isolated as it readily oxidised to α-diketone in agreement with the stoichiometric results 1 : 2. In the case of 3,5-dimethylpiperidone, the oxidation was limited to the first stage, as the α-ketol is a tertiary alcohol and hence resistant to further oxidation. The above mechanism is quite satisfactory in explaining different kinetic aspects and non-kinetic factors of the present investigation.

Relative reactivity and substituent effect : N–H and N–Me series provide an excellent comparative study of oxidation kinetics. Conformation exerts its place in determining the rates of oxidation. 3-H- and 3-alkyl-2,6-diphenyl-4-piperidones and their N–Me derivatives exist in a single anchored chair conformation with the phenyl and alkyl substituents occupying the least strained equatorial positions[7]. In the 3,3-dimethyl compounds (**5** and **11**), however, one of the methyl groups must necessarily be placed in the axial position. In the 3,5-dimethyl compounds (**6** and **12**) there are too many *gauche* interactions which are relieved when the molecule adopts a non-chair conformation. The assignment of such non-chair conformation derives support from pmr and ^{13}C nmr chemical shifts[8]. It is of interest to note that H-attached to nitrogen in piperidone is axial[9]. The replacement of H from nitrogen atom by Me group changes the picture by enchancing the ability to undergo oxidation. This is caused by the axial orientation of lone-pair as the bulky methyl group prefers the equatorial position[10]. The 1,3-interaction between the lone-pair and axial hydrogens at positions--3 and -5 could enhance the ground state energy of the reactant[11]. This accounts for the greater vulnerability of all the members of N–Me series to NBS oxidation than their N–H counterparts. However the kinetic behaviour is entirely analogous.

Comparable order of reactivity is obtained in both cases with the exception of 3,3-dimethyl, 3-H > 3,3-diMe > 3-Et > 3-i-Pr > 3-Me > 3,5-diMe in N–H series and 3-H > 3-Et > 3-i-Pr > 3-Me > 3,3-diMe > 3,5-diMe in N–Me series. The free access of the oxidant molecule to the reaction centre to form the transition state in the absence of alkyl group in position-3 substantiates the highest rate constants observed for 3-unsubstituted-2,6-diphenyl-4-piperidones in both N–H and N–Me series. 3-Alkyl substituents considerably affect the properties of the functional group in position-4 of 2,6-diphenylpiperidine ring system[12]. Stereoelectronic effects play a dominant role within the series. In the present study, 3-methyl substituent is found to retard the rate of oxidation to a strikingly considerable extent. Here the steric interaction of 3-Me which causes the destabilisation of the transition state is responsible for rate-retarding effect.

When 4-piperidone with 3-alkyl group undergoes enolisation, two enöls (I and II) may result (Fig. 1). The transition state of elementary slow step in the reaction can be considered as (III) for oxidation of (I) and (IV) for the oxidation of (II). The R groups may not facilitate the formation of a cyclic structure by the oxidant on the substrate. Particularly in structure (I) the R and OH groups are oriented in *cis* fashion[2]. In this geometry the R group will sterically inhibit any reagent attacking the OH function. Both these transition states are less stable than that with R = H.

If steric effect were the only factor governing the oxidative reaction rates, ethyl and isopropyl substitu-

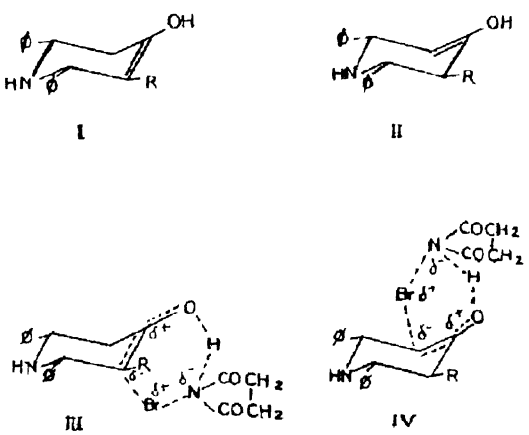
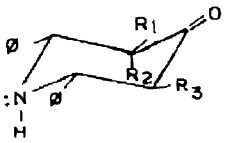
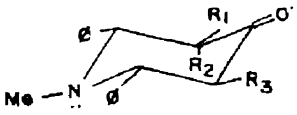


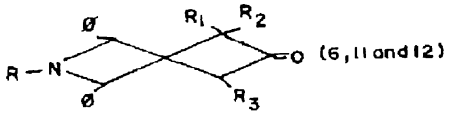
Fig. 1



(1–5)



(7–10)



(6, 11 and 12)

	R	R_1	R_2	R_3
1,	H	H	H	H
2,	H	Me	H	H
3,	H	Et	H	H
4,	H	i-Pr	H	H
5;	H	Me	Me	H
6,	H	Me	H	Me
7,	Me	H	H	H
8,	Me	Me	H	H
9,	Me	Et	H	H
10,	Me	i-Pr	H	H
11,	Me	Me	Me	H
12,	Me	Me	H	Me

ents should decrease the rate further. On the contrary, these substituents are found to enhance the rate. This may be attributed to the fact that the higher electron-releasing inductive effect of ethyl and isopropyl group does not favour hydrogen abstraction from position-3 to form enol (I) and favour indirectly the formation of enol (II) and hence resulting in the more stable transition state (IV). This accounts for the higher oxidation rates in the case of 3-ethyl and 3-isopropyl compared with 3-methyl. The subtle difference in size accounts for the slightly lower oxidation rate of 3-isopropyl than 3-ethyl.

The least reactivity of 3,5-dimethyl may be attributed to the non-chair conformation in which the non-bonded interaction of hydroxyl with adjacent methyl groups is relieved in the ground state itself[13] In the case of 3,3-dimethyl in N–H series, the high 1 : 3 interaction due to axial methyl group gets relieved when the product α-diketone is formed accounting for the high reactivity. Due to too many *gauche* interactions between two phenyl and three methyl groups the 3,3-dimethyl compound in N–Me series acquires a non-chair conformation to get steric relief[14] in the ground state itself which accounts for its low reactivity.

Experimental

Solutions of NBS (G.R., Loba Chemie) in distilled acetic acid were prepared fresh and their strengths checked iodometrically. All the 4-piperidones (**1–12**) were prepared by the reported procedure[15]. Glacial acetic acid unaffected by chromic acid was distilled and used. All other reagents were of A.R. grade. Conductivity water was used throughout.

Kinetics of NBS oxidation of N-H and *N*-methyl-2,6-diphenyl-4-piperidones were studied in 80% (v/v) acetic acid-water medium maintaining the ionic strength by adding 0.2 *M* $NaClO_4$ in the presence of mercuric acetate (2.0×10^{-3} *M*) and in the absence of mineral acid at a suitable optimum temperature. Pseudo-first-order condition was maintained by taking [piperidone] always ten-fold excess over [NBS]. The progress of reaction was studied by determining unconsumed NBS iodometrically at different time intervals. All the reactions were carried out in the blackened flasks in order to aviod photocatalysis. The reactions were followed upto 50% consumption of NBS. The rate constants calculated by the method of least squares were reproducible within ± 2%.

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