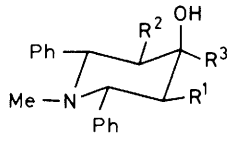
Reactivity of Certain Piperidin-4-ols Towards Oxidation with Cerium(IV)

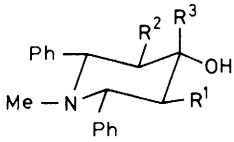
Chenniappan Vasantha Devi, Kuppusamy Selvaraj,* and Kondareddiar Ramalingam
Department of Chemistry, PSG College of Arts and Science, Coimbatore-641 014, India
Krishnasamy Ramarajan *
Department of Chemistry, CBM College, Coimbatore-641 042, India

Kinetics of the oxidation of six pairs of epimeric piperidin-4-ols by cerium(IV) in the presence of sulphuric acid in an aqueous acetic acid medium at 60 °C have been investigated. The corresponding α-deuteriated piperidin-4-ols have been prepared and their oxidation rates measured. The oxidation is first-order in both oxidant and substrate at constant acid concentration. Mechanisms involving free-radical intermediates are proposed. The observed kinetic isotope effect in the case of *t*-2, *t*-6-diphenyl-*c*-3-isopropyl-*N*-methylpiperidin-*r*-4-ol (4) (k_H/k_D = 6.26) suggests that the C–H (or C–D) bond of the carbinol carbon is involved in the rate-determining step. An alternative mechanism involving the participation of the O–H bond in the rate-limiting step is proposed to account for the absence of a kinetic isotope effect (k_H/k_D = 1.00) in the oxidation of *t*-2, *t*-6-diphenyl-*c*-3, *c*-5,*N*-trimethylpiperidin-*r*-4-ol (5) and *c*-2,*c*-6-diphenyl-*t*-3, *t*-5,*N*-trimethylpiperidin-*r*-4-ol (14). It is probable that both mechanisms operate simultaneously in the oxidation of those piperidin-4-ols which show a kinetic isotope effect of *ca.* 2.00. The conformational effects on the rates of oxidation are discussed.

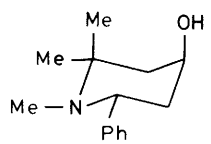
Cerium(IV) is a versatile oxidising agent and its use in the oxidation of a host of organic compounds is well known.[1] Although the oxidation of a variety of alcohols by cerium(IV) has been the subject of various publications,[2-13] no systematic investigation on the oxidation of heterocyclic alcohols, in general, and of piperidin-4-ols, in particular, has appeared. Kinetics of the oxidation of piperidin-4-ols by chromium(VI) [14] and vanadium(V) [15] have already been carried out. The present investigation is an attempt to study the oxidation kinetics of piperidin-4-ols by cerium(IV), as well as correlating conformation with reactivity.



	R^1	R^2	R^3
(1)	H	H	H
(2)	Me	H	H
(3)	Et	H	H
(4)	Pr^i	H	H
(5)	Me	Me	H
(6)	Me	H	D
(7)	Et	H	D
(8)	Pr^i	H	D
(9)	Me	Me	D



	R^1	R^2	R^3
(10)	H	H	H
(11)	Me	H	H
(12)	Et	H	H
(13)	Pr^i	H	H
(14)	Me	Me	H
(15)	Me	H	D
(16)	Et	H	D
(17)	Pr^i	H	D
(18)	Me	Me	D



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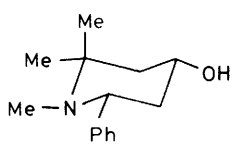

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Results and Discussion

Kinetics of the oxidation of piperidin-4-ols (1)—(5), (10)—(14), (19), and (20) and of α-deuteriated piperidin-4-ols (6)—(9) and (15)—(18) by cerium(IV) have been investigated in aqueous acetic acid in presence of sulphuric acid.

The effect of varying substrate concentration on the pseudo-first-order rate constant has been studied for *t*-2, *t*-6-diphenyl-*c*-3-isopropyl-*N*-methylpiperidin-*r*-4-ol (4) and the results are shown in Table 1. The pseudo-first-order rate constant, k_1, increases linearly with increase in piperidinol concentration, suggesting a first-order dependence of rate on substrate.

Oxidation of the piperidinol (4) was studied with different concentrations of sulphuric acid (1—2.5M) in 60% aqueous acetic acid with $[Ce^{IV}] = 2.5 \times 10^{-3}$M at 60 °C and the results are recorded in Table 2. The increase in acid concentration is found to increase the rate of oxidation. Hence the reaction is acid catalysed.

The effect of solvent polarity on the rate of oxidation of the piperidinol (4) was studied by carrying out the reaction in different binary solvent mixtures of acetic acid–water (Table 3). The rate is found to increase on decreasing the solvent polarity, suggesting a greater dispersal of charge in the transition state.

The reaction mixture of each piperidinol was found to induce polymerisation of acrylamide and this indicates the formation of free-radical intermediates during oxidation.

A deep yellow colour is produced immediately after the admixture of the pale yellow acid solution of Ce^{IV} with piperidinols. Therefore, one may visualise the reaction as taking place through the formation of an intermediate complex between the reacting species. It has already been reported that the formation of the Ce^{IV}–alcohol complex is an important step in the oxidation of alcohols.[16,17] Balasubramanian and Venkatasubramanian have also reported such complex formation in the oxidation of various substituted alcohols.[13] However, in the present investigation complex formation is not kinetically detectable, since the straight line obtained from the plot of $1/k_1$ *versus* 1/[piperidinol] has no intercept.

The data in Table 4 indicate that the deuteriated piperidinols react at a slower rate than the corresponding undeuteriated piperidinols. The k_H/k_D values range from 1.8 to 6.3. The existence of the large isotope effect (k_H/k_D = 6.26) in the case of *t*-2, *t*-6-diphenyl-*c*-3-isopropyl-*N*-methylpiperidin-*r*-4-ol (4) indicates that the oxidation step involves one-electron transfers within a cyclic alcohol–cerium(IV) complex as in mechanism I. But the low isotope effect ($k_H/k_D \simeq 2$) observed for a number of other piperidinols may, probably, be due to the

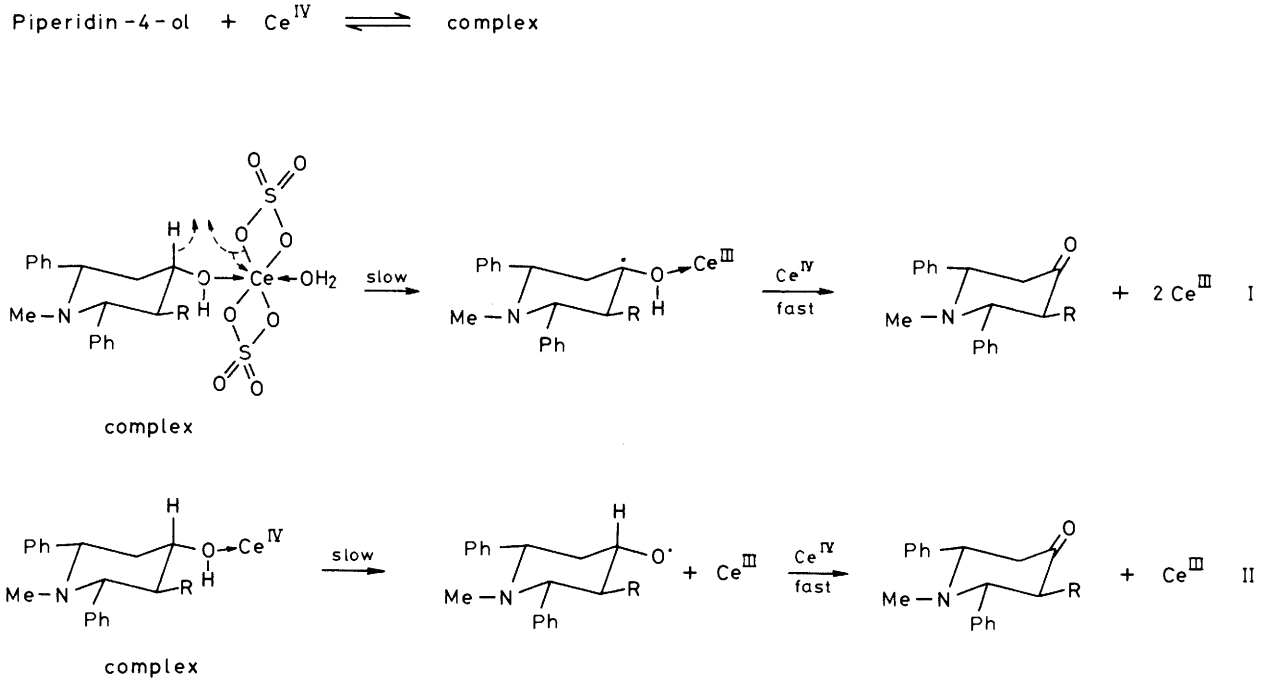

Table 1. Dependence of rate on the concentration of *t*-2, *t*-6-diphenyl-*c*-3-isopropyl-*N*-methylpiperidin-*r*-4-ol (4) (S). [Cerium(IV)] = 2.5×10^{-3}M; temperature = 60 °C; solvent = 60% HOAc–40% H_2O (v/v); [H_2SO_4] = 2M

10^3[S]/mol l^{-1}	$10^5k_1/s^{-1}$	10^4k_2/l mol^{-1} s^{-1}
31.86	21.59	67.76
33.91	23.03	67.90
38.92	24.95	64.09
44.15	28.78	65.21
55.40	37.00	66.78

Table 2. Effect of varying the concentration of H_2SO_4 on the rate of oxidation of *t*-2, *t*-6-diphenyl-*c*-3-isopropyl-*N*-methylpiperidin-*r*-4-ol (4). [Cerium(IV)] = 2.5×10^{-3}M; temperature = 60 °C; solvent = 60% HOAc–40% H_2O (v/v)

[H_2SO_4]/mol l^{-1}	10^3[S]/mol l^{-1}	$10^5k_1/s^{-1}$	10^4k_2/l mol^{-1} s^{-1}
1.0	30.20	15.86	52.53
1.5	30.26	17.55	57.86
2.0	31.86	21.59	67.76
2.5	30.38	24.90	81.87

Table 3. Effect of changing the solvent composition on the rate of oxidation of *t*-2,*t*-6-diphenyl-*c*-3-isopropyl-*N*-methylpiperidin-*r*-4-ol (4). [Cerium(IV)] = 2.5×10^{-3}M; temperature = 60 °C; [H_2SO_4] = 2M

HOAc–H_2O (% v/v)	10^3[S]/mol l^{-1}	$10^5k_1/s^{-1}$	10^4k_2/l mol^{-1} s^{-1}
50–50	34.35	13.16	38.31
55–45	31.32	21.44	43.19
60–40	31.86	21.59	67.76
65–35	29.73	23.03	77.47

Table 4. Second-order rate constants of various piperidin-4-ols and kinetic isotope effects. [Cerium(IV)] = 2.5×10^{-3}M; temperature = 60 °C; solvent = 60% HOAc–40% H_2O (v/v); [H_2SO_4] = 2M

Compd.	10^4k_2/l mol^{-1} s^{-1}	Compd.	10^4k_2/l mol^{-1} s^{-1}	k_H/k_D
(1)	14.26			
(2)	15.08	(6)	6.28	2.40
(3)	16.44	(7)	7.20	2.28
(4)	67.76	(8)	10.83	6.26
(5)	7.24	(9)	7.17	1.00
(19)	22.36			
(10)	10.40			
(11)	13.27	(15)	5.87	2.26
(12)	12.46	(16)	7.02	1.77
(13)	11.93	(17)	5.76	2.07
(14)	6.27	(18)	6.25	1.00
(20)	14.48			

simultaneous operation of an acyclic mechanism, II, which involves the O–H bond in the rate-limiting step. The k_H/k_D values suggest that mechanism II predominates in the oxidation of piperidinols having alkyl substituents in positions 3 and/or 5. Similar concurrent mechanisms have been reported for the oxidation of cyclohexanol with cerium(IV).[12] The absence of isotope effect in *t*-2,*t*-6-diphenyl-*c*-3,*c*-5,*N*-trimethylpiperidin-*r*-4-ol (5) and *c*-2, *c*-6-diphenyl-*t*-3, *t*-5, *N*-trimethylpiperidin-*r*-4-ol (14) is probably due to the operation of mechanism II. Since compounds (5) and (14) are the least reactive substrates, the absence of a kinetic isotope effect in these cases can also be explained by assuming the complex formation as the rate-limiting step.

Structure and Reactivity.—Piperidinols (1)—(4), (10)—(13), (19), and (20) were shown to exist in chair conformations with the alkyl- and phenyl-groups in the most stable equatorial positions.[18–20] The second-order rate constants of piperidin-4-ols (Table 4) reveal that the piperidinols with an axial hydroxy-group are oxidised faster than the corresponding piperidinols with an equatorial hydroxy-group. This behaviour is strikingly similar to the observations in the oxidation of epimeric alicyclic alcohols,[21,22] steroid alcohols,[23] and piperidin-4-ols [14]

by chromium(VI) and piperidin-4-ols by vanadium(V).[15] The difference in reactivity between axial and equatorial alcohols can be explained as being due to the differences in non-bonded steric interactions. An axial $^{-}$OH group has two additional H^{-}OH 1,3-interactions when compared with an equatorial $^{-}$OH group. This additional strain is the cause for the enhanced oxidation rate of axial alcohols as this strain is released in the product.

The data in Table 4 indicate that the axial and the equatorial piperidinols behave differently when there is an alkyl-group adjacent to the reaction centre. The reactivity of the 3-alkylpiperidin-4-ols reflects the combined influence of the following two opposing factors: (i) steric assistance and (ii) steric hindrance.

(i) An alkyl group vicinal to the $^{-}$OH group can cause steric interactions with the latter. The resulting increase in strain would increase the rate of oxidation.

(ii) On the other hand, the same alkyl-group would hinder the approach of cerium(IV) species and this would result in a decrease in the oxidation rate.

t-2,*t*-6-Diphenyl-*c*-3-alkyl-*N*-methylpiperidin-*r*-4-ols (2)—(4) and *c*-2,*c*-6-diphenyl-*t*-3-alkyl-*N*-methylpiperidin-*r*-4-ols (11)—(13) react at a faster rate than *t*-2,*t*-6-diphenyl-*N*-methylpiperidin-*r*-4-ol (1) and *c*-2,*c*-6-diphenyl-*N*-methylpiperidin-*r*-4-ol (10), respectively. This trend is expected when the first effect, *i.e.* steric assistance, is the predominating factor.

An increase in size of the 3-alkyl-substituent should increase the rate of oxidation if the steric assistance takes precedence over the steric hindrance. This is found to be so in the piperidinols (2)—(4) with an axial $^{-}$OH group where the decreasing reactivity is in the order (4) > (3) > (2). On the other hand, if the steric hindrance overshadows the steric assistance, the rate would decrease with an increase in size of the 3-alkyl-group. Thus, for the piperidinols (11)—(13) with an equatorial $^{-}$OH group, the decreasing order of reactivity is (11) > (12) > (13).

Examination of the data in Table 4 shows that the epimeric 2,6-diphenyl-3,5-dimethyl-*N*-methylpiperidin-4-ols (5) and (14) react at a slower rate than 2,6-diphenyl-*N*-methylpiperidin-4-ols (1) and (10), respectively. The decrease in rate is presumably steric in origin. The initial approach of the oxidant species itself is made more difficult owing to the presence of bulky methyl-groups at both 3 and 5 positions.

The epimeric 2,2-dimethyl-6-phenyl-*N*-methylpiperidin-4-ols (19) and (20) are oxidised at a faster rate than 2,6-diphenyl-*N*-methylpiperidin-4-ols (1) and (10), respectively. This is due to the large strain resulting from the non-bonded steric interactions of $^{-}$OH group in (19) or H in (20) with the axial methyl-group at the C(2) carbon.

Experimental

Materials.—The piperidin-4-ols (1)—(5), (10)—(14), (19), and (20) included in the present study were prepared by reducing piperid-4-ones appropriately.[24-26] The deuteriated piperidinols (6)—(9) and (15)—(18) were prepared by reducing 4-piperidones with lithium aluminium deuteride.[15] Acetic acid (AnalaR, BDH) was refluxed over CrO_3 and used as a solvent.[27] Other chemicals used were of reagent grade.

Kinetic Measurements.—Pseudo-first-order principles were followed to obtain the first-order rate constants k_1 by maintaining the concentration of piperidin-4-ol always in excess. Ionic strength of the medium was kept constant by the addition of a calculated amount of sodium sulphate. The reaction was followed by taking 2 ml aliquots of the reaction mixture at different intervals of time, pouring into a known excess of Fe^{II} solution and titrating the unused Fe^{II} against potassium dichromate solution using barium diphenylaminesulphonate as indicator. The reactions were followed for at least 60% conversion of the oxidant. The first-order rate constant k_1 was obtained from the slope of the straight-line graph obtained when log[oxidant] was plotted against time *t*. The results were found to be reproducible to within ±3%.

Product Analysis.—In the oxidation of piperidin-4-ol by cerium(IV), the corresponding piperid-4-one was identified as the product. A solution (50 ml) containing piperidinol (0.75 mol), cerium(IV) (0.05 mol), and sulphuric acid (2M) in 60% aqueous acetic acid was kept at 60 °C for 24 h. The solution was neutralised with aqueous ammonia, extracted with ether, and the ether extract evaporated. The residue was dissolved in a minimum amount of cold benzene and chromatographed over a column of neutral alumina. Light petroleum (b.p. 60—80 °C)–benzene eluates, on evaporation, gave a solid which after recrystallisation with light petroleum (b.p. 60—80 °C) was found to be identical with the piperid-4-one, since it gave no m.p. depression on admixture with the authentic sample.

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