Conformation and Reactivity of Some Substituted Oxan-4-ols in the Oxidation with Cerium(IV)

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The kinetics of the oxidation of some substituted oxan-4-ols by cerium(IV) in an aqueous acetic acid medium at 60 °C in the presence of sulphuric acid have been investigated. The reaction is first-order each in oxidant and substrate at constant acid concentration. *t*-2,*t*-6-Diphenyl-*c*-3,*c*-5-dimethyloxan-*r*-4-ol, an axial alcohol, reacts slower than the corresponding equatorial epimer, *c*-2,*c*-6-diphenyl-*t*-3,*t*-5-dimethyloxan-*r*-4-ol. This anomalous observation and the reactivity of other oxanols towards oxidation have been discussed on the basis of conformational differences.

Much valuable information on the oxidation of a variety of alcohols by cerium(IV) is on record.[1-13] A systematic study on the oxidation of piperidin-4-ols by cerium(IV) which correlates conformation and reactivity has been reported recently from our laboratory.[14] In continuation of our interest in the oxidation of heterocyclic alcohols we now report kinetic data for the oxidation of oxan-4-ols by cerium(IV). In this paper we also discuss the reactivity of oxan-4-ols towards oxidation in terms of conformational differences.

Results and Discussion

The kinetics of oxidation of oxan-4-ols (1)—(9) by cerium(IV) (1.0 × 10^{-3}M) have been investigated in 50—60% aqueous acetic acid in presence of 0.5—1.0M-sulphuric acid at 60 °C. These reaction conditions were chosen because of the poor solubility of both substrate (below 50% aqueous acetic acid) and oxidant (above 60% aqueous acetic acid).

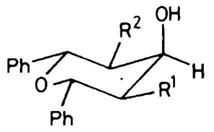
Pseudo-first-order conditions have been maintained to obtain the first-order rate constants k_1. The pseudo-first-order rate constant k_1 increases linearly with increase in oxanol concentration indicating a first-order dependence of rate on substrate. A representative example for the oxidation of *c*-2,*c*-6-diphenyl-*t*-3-methyloxan-*r*-4-ol (6) is recorded in Table 1.

The data in Table 2 indicate the effect of varying the sulphuric acid concentration (0.5—1.0M) on the rate of oxidation of oxan-4-ol (6). The increase in acid concentration is found to increase the rate of oxidation. Hence the reaction is acid catalysed.

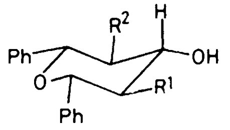
Inspection of the data in Table 3 shows that the reaction is susceptible to changes in solvent polarity. The rate decreases with increase in solvent polarity, suggesting that the transition state is less polar than the initial state.

The formation of a deep yellow colour immediately after the admixture of the pale yellow acid solution of cerium(IV) with a solution of oxan-4-ol indicates that the reaction proceeds through the formation of the intermediate complex between the reacting species. Such complex formation in the oxidation of alcohols has already been reported.[13-16]

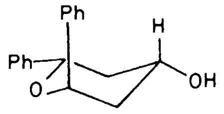
The reaction mixture of each oxanol was found to induce the polymerisation of acrylamide. This indicates the formation of free-radical intermediates during oxidation.



	R	R
(1)	H	H
(2)	Me	H
(3)	Et	H
(4)	Me	Me



	R	R
(5)	H	H
(6)	Me	H
(7)	Et	H
(8)	Me	Me



(9)

Table 1. Dependence of rate on the concentration of *c*-2,*c*-6-diphenyl-*t*-3-methyloxan-*r*-4-ol (6) (S). [Cerium(IV)] 1.0 × 10^{-3}M; temperature 60 °C; solvent 60% HOAc–40% H_2O (v/v); [H_2SO_4] 0.5M

10^3[S]/mol l^{-1}	10^5k_1/s^{-1}	10^3k_2/l mol^{-1} s^{-1}
11.97	15.22	12.71
15.05	18.95	12.59
17.98	22.73	12.64
23.01	28.99	12.60
		Mean 12.64 ± 0.05

Table 2. Effect of varying the concentration of H_2SO_4 on the rate of oxidation of *c*-2,*c*-6-diphenyl-*t*-3-methyloxan-*r*-4-ol (6). [Cerium(IV)] 1.0 × 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}	10^3k_2/ l mol^{-1} s^{-1}
0.50	11.97	15.22	12.71
0.75	11.90	18.15	15.25
1.00	11.90	22.34	18.77

Mechanism.—Two alternative mechanisms have been suggested for the oxidation of piperidin-4-ols by cerium(IV).[14] It has been confirmed by kinetic isotope effect studies that the two mechanisms are simultaneously operating in oxidation. Similar concurrent mechanisms have also been reported for the oxidation of cyclohexanol with cerium(IV).[12] By analogy with the above investigations, the concurrent mechanisms (I) and (II) can be suggested for the oxanol oxidation. These mechanisms involve the formation of a complex between oxan-4-ol and cerium(IV) species followed by its decomposition in a slow step, to give a radical which subsequently reacts with another cerium(IV) species in a fast step to yield the product.

Conformation and Reactivity of Oxan-4-ols.—The relationship between conformation and chemical reactivity was first

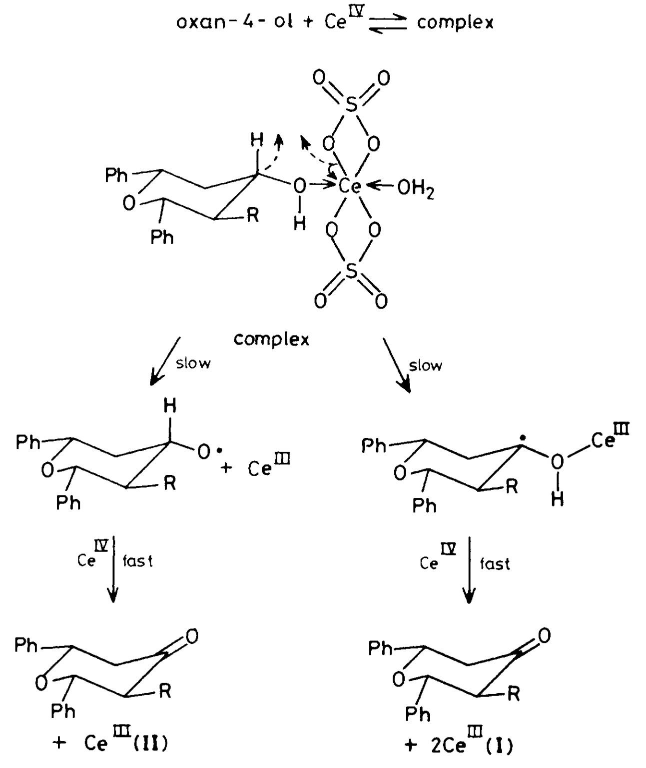


Table 3. Effect of changing the solvent composition on the rate of oxidation of *c*-2,*c*-6-diphenyl-*t*-3-methyloxan-*r*-4-ol (**6**). [Cerium(IV)] 1.0 × 10^{-3}M; temperature 60 °C; [H_2SO_4] 0.5M

HOAc-H_2O % v/v	10^3[S]/mol l^{-1}	10^5k_1/s^{-1}	10^3k_2/ l mol^{-1} s^{-1}
60—40	11.96	15.22	12.71
55—45	11.90	13.50	11.34
50—50	11.90	9.59	8.06

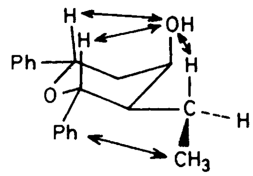
pointed out by Barton in 1950.[17] Many reports on the reactivity of epimeric cyclic alcohols in oxidation reactions are available.[14,18–22] The kinetics of oxidation of epimeric alicyclic alcohols[18,19] and steroid alcohols[20] by chromium(VI) and piperidin-4-ols by chromium(VI),[21] vanadium(V),[22] and cerium(IV)[14] have been investigated. All these reactions have one feature in common, *i.e.*, axial alcohols (crowded) are oxidised faster than equatorial alcohols (uncrowded).

Compounds with equatorial substituents are generally more stable (because of less steric crowding) than compounds with corresponding axial substituents. An axial hydroxy-group has two additional H–OH 1,3-interactions when compared with an equatorial hydroxy-group. Therefore the ground state energy level of an axial alcohol is higher than that of an equatorial alcohol. In other words, an axial alcohol is more crowded or strained than an equatorial alcohol in the ground state. This strain is relieved in the product as well as in the transition state leading to it and therefore the transition state energy levels of the crowded (axial) and uncrowded (equatorial) alcohols do not differ appreciably. Hence, the situation of steric acceleration results.

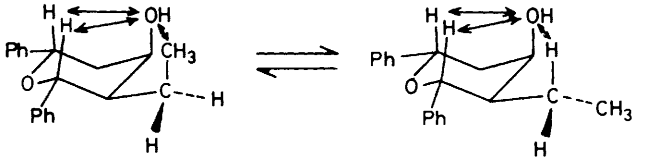
The rate-determining step in the oxidation of an alcohol generally involves the abstraction of the hydrogen on the carbinol carbon. In the axial alcohol the carbinol hydrogen, being equatorial, is more susceptible for abstraction than the axial carbinol hydrogen in the equatorial alcohol.

Table 4. Second-order rate constants of various oxan-4-ols. [Cerium(IV)] 1.0 × 10^{-3}M; temperature 60 °C; solvent 60% HOAc–40% H_2O (v/v); [H_2SO_4] 0.5M

Compound	10^3k_2/l mol^{-1} s^{-1}
(**1**)	12.60
(**2**)	13.55
(**3**)	21.34
(**4**)	5.90
(**5**)	10.76
(**6**)	12.64
(**7**)	10.46
(**8**)	9.30
(**9**)	16.43



(**3a**)



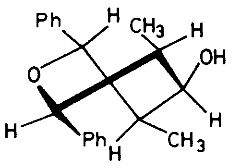
(**3b**) (**3c**)

In the present investigation, quite similar observations have been found (Table 4). The axial oxanols (**1**), (**2**), and (**3**) are oxidised at a faster rate than the corresponding epimeric equatorial alcohols (**5**), (**6**), and (**7**) respectively. It is a pleasant surprise to note that *t*-2,*t*-6-diphenyl-*c*-3,*c*-5-dimethyloxan-*r*-4-ol (**4**), an axial alcohol, reacts slower than the corresponding equatorial epimer *c*-2,*c*-6-diphenyl-*t*-3,*t*-5-dimethyloxan-*r*-4-ol (**8**). This difference in behaviour will be discussed later.

An interesting observation in the present study is the effect of the 3-alkyl group, situated adjacent to the reaction centre, on the rate of oxidation. An alkyl group adjacent to the hydroxy-group can produce non-bonded steric interactions (*gauche*-interactions) with the hydroxy-group. The resulting increase in strain is relieved during oxidation. Hence 3-alkyl-substituted oxan-4-ols should undergo oxidation at a faster rate than the corresponding 3-unsubstituted oxanols. This is found to be so in the axial series wherein *t*-2,*t*-6-diphenyl-*c*-3-alkyloxan-*r*-4-ols (**2**) and (**3**) react faster than *t*-2,*t*-6-diphenyloxan-*r*-4-ol (**1**). An increase in size of the 3-alkyl substituent should also increase the rate of oxidation since there is an increase in strain (due to the *gauche*-interaction between the alkyl group and hydroxy-group). Thus *t*-2,*t*-6-diphenyl-*c*-3-ethyloxan-*r*-4-ol (**3**) reacts faster than *t*-2,*t*-6-diphenyl-*c*-3-methyloxan-*r*-4-ol (**2**).

In *t*-2,*t*-6-diphenyl-*c*-3-ethyloxan-*r*-4-ol (**3**), the ethyl group can have preferred conformation with respect to the C-3 alkyl bond. The conformations (**3a**—**c**) are possible for the ethyl group in oxan-4-ol (**3**). The conformation (**3a**) is precluded because there is a severe interaction between phenyl and methyl groups as shown. The other two conformations (**3b** and **c**) place the methyl group away from the phenyl side and should exist as an equilibrium mixture of (**3b** and **c**). Conformation (**3b**) has got one CH_3–OH interaction (with high energy) in addition to two H–OH interactions and (**3c**) has got three H–OH interactions. Hence the rate of oxidation of (**3**) is higher than that of either the 3-methyl or 3-H alcohol.

On the other hand, in the equatorial series *c*-2,*c*-6-diphenyl-



(4a)

t-3-methyloxan-*r*-4-ol (**6**), as expected, undergoes oxidation faster than *c*-2,*c*-6-diphenyloxan-*r*-4-ol (**5**). But *c*-2,*c*-6-diphenyl-*t*-3-ethyloxan-*r*-4-ol (**7**) reacts as fast as the oxanol (**5**). This is rather unexpected. A decelerating effect must also be operative in the case of 3-ethyloxanol (**7**) which is steric in origin. The bulky ethyl group may cause steric hindrance to the approach of cerium(IV) species. This retarding effect may counterbalance the other effect (due to steric strain) and this explains the above observation.

The behaviour of the epimeric 2,6-diphenyl-3,5-dimethyloxan-4-ols (**4**) and (**8**) appears to be still more complex. Since the higher oxidation rates of 2,6-diphenyl-3-methyloxan-*r*-4-ols compared with those of 2,6-diphenyloxan-*r*-ols (both axial and equatorial) are mainly due to the *gauche*-interaction of the hydroxy-group with the 3-methyl group, one would expect the oxidation rates of the epimeric 2,6-diphenyl-3,5-dimethyloxan-*r*-4-ols (**4**) and (**8**) to be higher than those of the corresponding 2,6-diphenyl-3-methyloxan-4-ols (**2**) and (**6**) (because in the chair conformation of 2,6-diphenyl-3,5-dimethyloxan-*r*-4-ols the hydroxy-group has *gauche*-interactions with both the adjacent equatorial methyl groups).

But the rate constants for the oxidation of the epimeric 2,6-diphenyl-3,5-dimethyloxan-*r*-4-ols (**4**) and (**8**) are less than those of the corresponding 2,6-diphenyl-3-methyloxan-*r*-4-ols (**2**) and (**6**). The rate constants also indicate that the epimeric 2,6-diphenyl-3,5-dimethyloxan-*r*-4-ols (**4**) and (**8**) react more slowly than the 3,5-unsubstituted oxanols (**1**) and (**5**), respectively. This lowering in rate for the epimeric 2,6-diphenyl-3,5-dimethyloxan-*r*-4-ols (**4**) and (**8**) is presumably steric in orgin. The initial complex formation itself is made more difficult due to the equatorial methyl group at the 3 and 5 positions.

Now we shall consider the anomalous behaviour of the oxanols (**4**) and (**8**). Generally, a crowded alcohol (axial) undergoes faster oxidation when compared with the corresponding uncrowded alcohol (equatorial). The results of the present investigation in the case of oxanols (**4**) and (**8**) are not in conformity with the general view. The results indicate that the ground state energy level of the axial oxanol (**4**) should be lower than that of the equatorial epimer (**8**). This is possible only when the axial oxanol (**4**) exists in the non-chair conformation (**4a**), since in such a conformation the interactions between the hydroxy-group and methyl group are greatly reduced in the ground state. But, the ^{1}H and ^{13}C n.m.r. data[23,24] for this compound do not endorse such a conclusion. However, it may be assumed that the axial oxanol (**4**) exists in a non-chair conformation, in aqueous acetic acid, the solvent used for the kinetic study.

Inspection of the data in Table 4 shows that *t*-2,*c*-6-diphenyloxan-*r*-4-ol (**9**) reacts at a faster rate than *c*-2,*c*-6-diphenyloxan-*r*-4-ol (**5**). This enhancement in rate is due to the large strain resulting from the non-bonded 1,3-steric interactions of the axial phenyl group with the axial hydrogens.

Experimental

Materials.—The oxan-4-ols (**1**)—(**9**) included in the present study were prepared by following the reported procedures.[24] Other chemicals used were of reagent grade.

Kinetic Measurements.—Pseudo-first-order conditions were used to obtain first-order rate constants k_1 by maintaining the concentration of oxan-4-ol in excess. The 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 portions of the reaction mixture at different intervals, pouring into a known excess of Fe^{II} solution, and titrating the unused Fe^{II} against potassium dichromate using barium diphenylaminosulphonate as indicator. The reactions were followed for at least 60% conversion of the oxidant. The first-order rate constants k_1 were obtained from the slope of the straight line obtained when log [oxidant] was plotted against time. The results were found to be reproducible to within ±3%.

Product Analysis.—In the oxidation of oxan-4-ol by cerium(IV), the corresponding oxan-4-one was identified as the product. In a typical experiment, a solution (50 ml) containing oxanol (0.5 mol), cerium(IV) (0.03 mol), and sulphuric acid (0.5M) 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 the 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 oxan-4-one.

Polymerisation Tests with Acrylamide.—The existence of free radicals in the reaction mixture was detected from the induced polymerisation of acrylamide. The following solutions were prepared: (1) 0.015M-substrate, 0.5M-H_2SO_4 and 0.001M-cerium(IV) in 60% HOAc (v/v); (2) 0.015M-substrate and 0.5M-H_2SO_4 in 60% HOAc (v/v); (3) 0.5M-H_2SO_4 and 0.001M-cerium(IV) in 60% HOAc (v/v); and (4) 0.5M-H_2SO_4 in 60% HOAc (v/v). Each solution (5 ml) was treated with a saturated solution of acrylamide (10 ml) in aqueous acetic acid (60% v/v) and the resulting mixture was kept in a thermostat (60 °C) for a day. A thick polymer was seen only in the flask containing solution (1) and acrylamide, indicating the formation of free radicals during the reaction.

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