Steric Effects in the Oxidation of Oxan-4-ols and Thian-4-ols by Vanadium(v)

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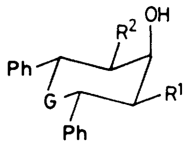
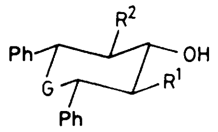
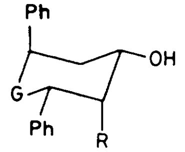
The rates of oxidation of 20 heterocyclic alcohols by vanadium(v) have been measured at 60 °C in aqueous acetic acid medium in the presence of sulphuric and perchloric acid. The data indicate an overall second-order reaction at constant acid concentration, first-order each in alcohol and oxidant. The conformational effects on the rates of oxidation of various heterocyclic alcohols are discussed. An interesting observation in the present study is that *t*-2,*t*-6-diphenyl-*c*-3,*c*-5-dimethyloxan-*r*-4-ol, an axial alcohol, reacts slower than corresponding equatorial epimer, *c*-2,*c*-6-diphenyl-*t*-3,*t*-5-dimethyloxan-*r*-4-ol, which is contrary to general expectations.

The relationship between conformation and reactivity had been of interest since 1950.[1] The kinetics of chromic acid oxidations[2–5] have been used as an important tool to elicit corroborative evidence in determining the structures of various cyclic alcohols since an axially orientated hydroxy group behaves differently from an equatorially orientated hydroxy group during oxidation. Recently, systematic investigations of the oxidation of heterocyclic alcohols, particularly piperidin-4-ols, by vanadium(v)[6] and cerium(IV)[7] have been carried out. We now report the results of oxidation kinetics of some substituted oxan-4-ols and thian-4-ols by vanadium(v) and discuss the reactivity of these substrates in the light of their conformational differences.

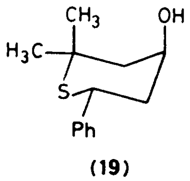




	G	R¹	R²		G	R¹	R²
(1)	O	H	H	(8)	O	H	H
(2)	O	CH_3	H	(9)	O	CH_3	H
(3)	O	C_2H_5	H	(10)	O	C_2H_5	H
(4)	O	CH_3	CH_3	(11)	O	CH_3	CH_3
(5)	S	H	H	(12)	S	H	H
(6)	S	CH_3	H	(13)	S	CH_3	H
(7)	S	C_2H_5	H	(14)	S	C_2H_5	H



	G	R		G	R
(15)	O	H	(17)	S	CH_3
(16)	S	H	(18)	S	C_2H_5



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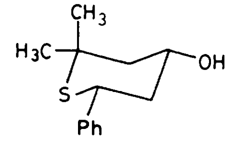


(20)

Results and Discussion

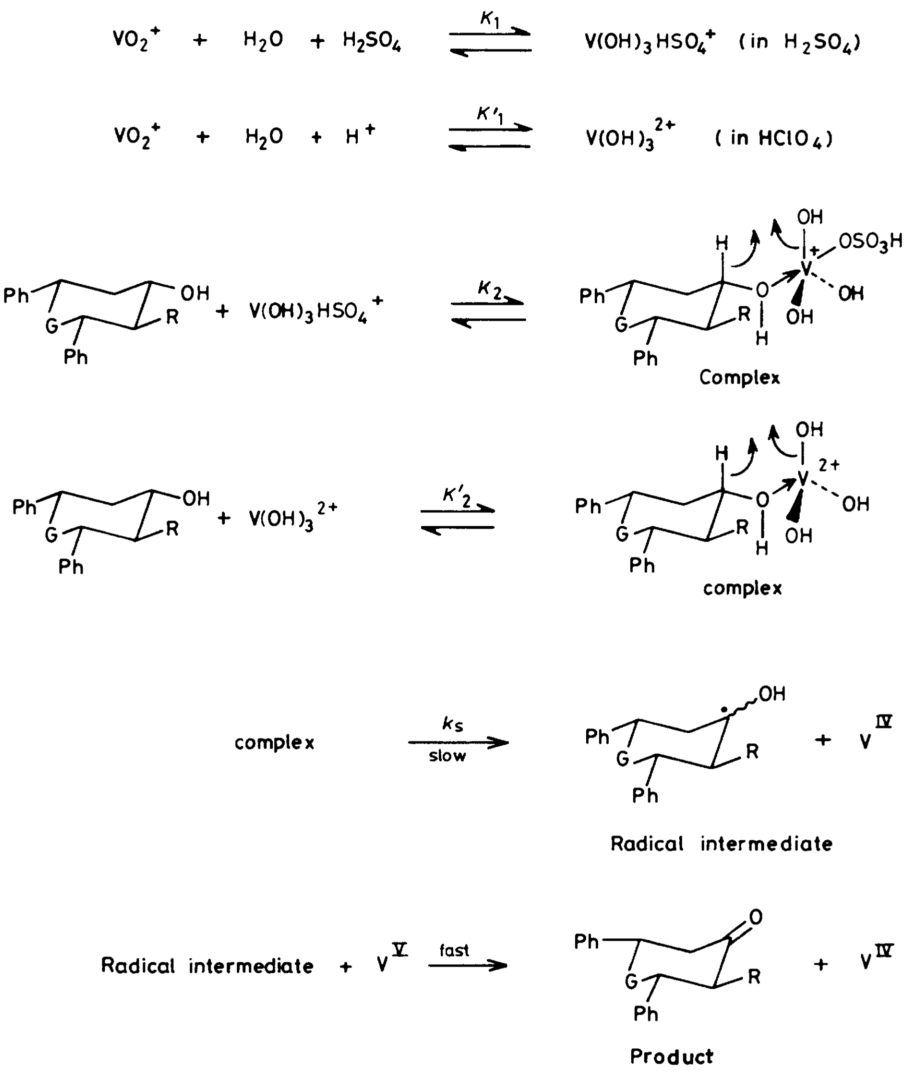
Oxidation kinetics of heterocyclic alcohols (**1**)—(**20**) by vanadium(v) have been investigated in 80% aqueous acetic acid medium in the presence of sulphuric and perchloric acid and the results are given in Tables 1—4.

The data in Table 1 indicate a first-order dependence of the rate on alcohol concentration. The effect of varying the concentration of the acid on the rate of oxidation can be seen from Table 2. The rate is found to increase with an increase in concentration of the acid. The rates of oxidation of oxanols (**1**)—(**4**), (**8**)—(**11**), and (**15**) have been measured in both sulphuric and perchloric acid. These oxanols except (**15**) react faster in sulphuric than in perchloric acid for the same molar concentration of acid, indicating that the active species of vanadium(v) is different in different acids and that the vanadium(v) species in sulphuric acid is more effective in bringing about oxidation than that in perchloric acid. The behaviour of *t*-2,*c*-6-diphenyloxan-*r*-4-ol (**15**) may presumably be steric in origin. The active species of vanadium(v) may be assumed to be $V(OH)_3^{2+}$ and $V(OH)_3HSO_4^+$ in perchloric and sulphuric acid, respectively.[8,9] The active species would experience a non-bonded steric interaction with the axial phenyl group during the abstraction of the hydroxy hydrogen. Since the active species of vanadium(v) in sulphuric acid is bulkier than that in perchloric acid, the steric interaction would be severe in the case of $V(OH)_3HSO_4^+$ and hence the rate would be slower in sulphuric acid.

A change in solvent polarity is found to alter the rate of oxidation (Table 3). The rate increases with decrease in solvent polarity, indicating the greater dispersal of charge in the transition state.

The reaction mixture of each alcohol is found to induce polymerisation of acrylamide, indicating the formation of free-radical intermediates during oxidation. When an acid solution of vanadium(v) which is pale yellow in colour is added to the alcohol solution the colour deepened. This may be an indication of complex formation between alcohol and vanadium(v) species. The mechanism in the Scheme can be suggested for the oxidation which is consistent with all the foregoing observations. A similar mechanism has been proposed for the oxidation of piperidin-4-ols by vanadium(v).[6]

Structure and Reactivity.—Careful examination of the data in Table 4 reveals the following. (i) In general axial alcohols are oxidised more rapidly than the corresponding equatorial epimers. However, the observation 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-



Scheme.

dimethyloxan-*r*-4-ol (**11**) is rather unexpected. (ii) The presence of an alkyl group adjacent to the alcoholic function alters the rate of oxidation. (iii) A marked influence in rate is observed when an axial methyl–phenyl is present in the γ-position with respect to the alcoholic function. These observations can be rationalized on conformational grounds.

Difference in reactivity between axial and equatorial alcohols. Earlier investigations[2–7,10] on the oxidation of epimeric cyclohexanols and heterocyclanols indicate that the axial alcohols are oxidised more readily than the equatorial alcohols. A similar observation is found in the present case. The difference in reactivity between axial and equatorial alcohols can be rationalized as follows.

An axial hydroxy group has two additional H–OH 1,3-interactions when compared with an equatorial hydroxy group. This additional strain is the cause for the enhancement in the oxidation rate of an axial alcohol as this strain is relieved in the product as well as in the transition state leading to it, since the transition state energy levels of the strained (axial) and the unstrained (equatorial) alcohols do not differ very much and the situation of steric enhancement results. Further, since the rate-determining step of oxidation is the abstraction of the hydroxy hydrogen, the axial alcohol wherein the hydroxy hydrogen is equatorial is more susceptible to oxidation than the equatorial epimer in which the hydroxy hydrogen is axial.

Effect of introducing an alkyl group adjacent to the reaction centre on the rate. The introduction of an alkyl group adjacent to the alcoholic function may affect the reactivity in two different ways. (i) An alkyl group vicinal to the hydroxy group can produce non-bonded steric interaction (*gauche*) with the hydroxy group. The resulting increase in strain would be relieved during oxidation and hence there would be an enhancement in the rate of oxidation (steric acceleration). (ii) On the other hand, the alkyl group would retard the formation of the complex between the alcohol and the vanadium species and this would result in a decrease in oxidation rate (steric retardation).

So the reactivity of 3-alkyl-substituted alcohols must be examined carefully, taking into account the two opposing effects.

In the present investigation the first effect, namely steric acceleration, dominates over the second, namely steric retardation. Thus *t*-2,*t*-6-diphenyl-*c*-3-alkyloxan-*r*-4-ols (**2**) and (**3**), *c*-2,*c*-6-diphenyl-*t*-3-alkyloxan-*r*-4-ols (**9**) and (**10**), *t*-2,*t*-6-diphenyl-*c*-3-alkylthian-*r*-4-ols (**6**) and (**7**), and *c*-2,*c*-6-diphenyl-*t*-3-alkylthian-*r*-4-ols (**13**) and (**14**) react at a faster rate than the corresponding 3-H alcohols (**1**), (**8**), (**5**), and (**12**), respectively.

An increase in size of the 3-alkyl substituent should increase the rate of oxidation if steric acceleration takes precedence over steric retardation. This is found to be so in the oxan-4-ols (**9**)

Table 1. Dependence of rate on the concentration of alcohol (S). [Vanadium(v)] 1.0 × 10^{-3}M; temperature 60 °C; solvent 80% HOAc–20% H_2O (v/v)

10^3[S]/M	10^5 k_1/s^{-1}	10^3 k_2/l mol^{-1} s^{-1}
c-2,*c*-6-Diphenyl-*t*-3-ethyloxan-*r*-4-ol (**10**) [H_2SO_4] 2M		
11.40	34.27	30.06
14.25	43.86	30.78
16.08	48.19	29.97
20.00	60.68	30.34
		Mean 30.29 ± 0.32
t-2,*t*-6-Diphenyl-*c*-3-ethylthian-*r*-4-ol (**7**) [H_2SO_4] 0.5M		
10.87	11.13	10.24
13.85	14.35	10.36
16.17	17.27	10.68
18.93	19.04	10.06
		Mean 10.34 ± 0.23

Table 2. Effect of varying the concentration of acid on the rate of oxidation. [Vanadium(v)] 1.0 × 10^{-3}M; temperature 60 °C; solvent 80% HOAc–20% H_2O (v/v)

[Acid]/M	10^3 [S]/M	10^5k_1/s^{-1}	10^3k_2/l mol^{-1} s^{-1}
t-2,*t*-6-Diphenyl-*c*-3-ethyloxan-*r*-4-ol (**3**)			
		[Na_2SO_4] 0.1M	
Acid	H_2SO_4		
0.5	11.58	2.53	2.18
1.0	11.47	7.26	6.33
1.5	11.67	19.19	16.44
2.0	11.29	44.44	39.36
		[$NaClO_4$] 0.1M	
Acid	$HClO_4$		
0.5	11.86	1.40	1.18
1.0	11.73	3.20	2.73
1.5	11.73	7.60	6.48
2.0	11.49	21.84	19.01
t-2,*t*-6-Diphenyl-*c*-3-methylthian-*r*-4-ol (**6**)			
		[Na_2SO_4] 0.1M	
Acid	H_2SO_4		
0.5	11.63	10.12	8.70
0.75	11.54	14.21	12.31
1.0	11.67	20.45	17.52

Table 3. Effect of varying the solvent composition on the rate of oxidation. [Vanadium(v)] 1.0 × 10^{-3}M; temperature 60 °C

HOAc–H_2O (% v/v)	10^3[S]/M	10^5k_1/s^{-1}	10^3k_2/l mol^{-1} s^{-1}
c-2,*c*-6-Diphenyl-*t*-3-ethyloxan-*r*-4-ol (**10**)			
	[H_2SO_4]2M		
60–40	11.38	1.42	1.25
70–30	11.30	4.18	3.70
75–25	12.30	10.10	8.21
80–20	11.40	34.27	30.06
2,2-Dimethyl-*t*-6-phenylthian-*r*-4-ol (**19**)			
	[H_2SO_4] 0.5M		
60–40	14.59	11.50	7.92
70–30	15.11	28.22	18.68
75–25	14.56	28.34	19.46
80–20	14.51	56.60	38.94

Table 4. Second-order rate constants of various heterocyclic alcohols. [Vanadium(v)] 1.0 × 10^{-3}M; temperature 60 °C; solvent 80% HOAc–20% H_2O (v/v)

Compound	10^3k_2/l mol^{-1} s^{-1}		Compound	10^3k_2/l mol^{-1} s^{-1}	
	H_2SO_4*	$HClO_4$ (2M)		H_2SO_4*	$HClO_4$ (2M)
1	16.51	10.63	8	8.86	5.87
2	40.32	18.51	9	12.11	8.09
3	39.36	19.01	10	30.29	17.37
4	16.22	4.40	11	47.94	15.82
5	7.64		12	2.16	
6	8.70		13	3.48	
7	10.34		14	2.35	
19	38.94		20	4.06	
			15	45.08	58.52
			16	4.30	
			17	6.52	
			18	17.41	

* For oxanols [H_2SO_4] 2.0M and for thianols [H_2SO_4] 0.5M.

and (**10**) and in the thian-4-ols (**6**) and (**7**) where the alcohols with a 3-ethyl substituent [(**7**) and (**10**)] react faster than the alcohols with a 3-methyl substituent [(**6**) and (**9**)] respectively.

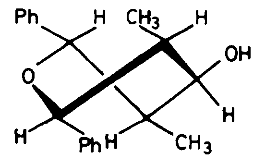
However, *c*-2,*c*-6-diphenyl-*t*-3-ethylthian-*r*-4ol (**14**) reacts slower than *c*-2,*c*-6-diphenyl-*t*-3-methylthian-*r*-4-ol (**13**) though there is an increase in the size of the 3-alkyl substituent. This result is indicative of the dominance of the second effect (steric retardation) over the first (steric acceleration). The second-order rate constants of *t*-2,*t*-6-diphenyl-*c*-3-methyloxan-*r*-4-ol (**2**) and *t*-2,*t*-6-diphenyl-*c*-3-ethyloxan-*r*-4-ol (**3**) do not differ appreciably. In this case, probably the two effects may counterbalance each other.

Effect of an axial methyl or phenyl group in the γ *-position with respect to the hydroxy group.* An axial methyl substituent at C-2 can cause non-bonded steric interaction with the other axial substituents. This would result in an increase in strain and therefore would react at a faster rate. Thus 2,2-dimethyl-*t*-6-phenylthian-*r*-4-ol (**19**) and 2,2-dimethyl-*c*-6-phenylthian-*r*-4-ol (**20**) react at a faster rate than *t*-2,*t*-6-diphenylthian-*r*-4-ol (**5**) and *c*-2,*c*-6-diphenylthian-*r*-4-ol (**12**), respectively.

Inspection of the data in Table 4 shows that *c*-2,*t*-6-diphenylthian-*r*-4-ol (**16**) and *c*-2,*t*-6-diphenyl-*c*-3-alkylthian-*r*-4-ols (**17**) and (**18**) react faster than *c*-2,*c*-6-diphenylthian-*r*-4-ol (**12**) and *c*-2,*c*-6-diphenyl-*t*-3-alkylthian-*r*-4-ols (**13**) and (**14**), respectively. Similar observation is also found in the oxanols. This behaviour may presumably be due to an increase in strain in the molecule.

The conformation of the thian-4-ols (**16**)—(**18**) has been confirmed by *X*-ray studies.[11] In this conformation, there are two additional phenyl–hydrogen (1,3 interactions) and one alkyl–hydrogen interaction and these would be responsible for the enhancement in rate. Among the thian-4-ols (**16**)—(**18**) the rate falls in the order (**18**) > (**17**) > (**16**) as expected.

Anomalous behaviour of the epimeric pair of oxan-4-ols (**4**) and (**11**). An axial alcohol, generally, undergoes oxidation faster than the corresponding equatorial alcohol because of steric reasons. But in the present investigation, the axial axanol (**4**) reacts slower than the equatorial oxanol (**11**). This epimeric pair



(**4a**)

react similarly with cerium(IV) oxidant.[10] The ^1H[12] and ^{13}C n.m.r.[13] spectra of these oxanols show that they exist in the chair conformation, in deuteriochloroform, the solvent used for n.m.r. studies. The anomaly in the present investigation can be explained if we assume a non-chair conformation (**4a**) for oxanol (**4**) in aqueous acetic acid, the solvent used for kinetic studies. In such a non-chair conformation, the interactions between the hydroxy and methyl groups are greatly reduced in the ground-state itself and hence the rate may be slower.

It is also possible that the oxanol (**4**) may undergo a conformational twist during the formation of the oxanol–vanadium complex and thereby relieve the steric strain which does not assist the oxidation.

Experimental

Materials.—The oxan-4-ols (**1**)—(**4**), (**8**)—(**11**), and (**15**) were prepared as reported.[12] The thian-4-ols (**5**)—(**7**), (**12**)—(**14**), and (**16**)—(**20**) were prepared by reducing thian-4-ones appropriately.[11] Acetic acid (AnalaR; B.D.H.) was refluxed over CrO_3 and used as a solvent. Other chemicals used were of reagent grade.

Kinetic Measurements.—Pseudo-first-order conditions were maintained for all the kinetic runs by keeping the substrate and acid concentration always in excess over that of vanadium. The ionic strengths of the reaction mixtures were kept constant by the addition of sodium sulphate in sulphuric acid and sodium perchlorate in perchloric acid. The reaction was followed by taking portions (2 ml) of the reaction mixture at suitable intervals, pouring into a known excess of Fe^{II} solution, and titrating against potassium dichromate using barium diphenylaminesulphonate as indicator. The reactions were followed to at least 60% conversion of the oxidant. The pseudo-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 oxan-4-ol by vanadium(V), the corresponding oxan-4-one and of thian-4-ol, the corresponding thian-4-one, was identified as the product. In a typical experiment, a solution (50 ml) containing alcohol (0.5 mol), vanadium(V) (0.03 mol), and sulphuric acid (0.5M) in 80% aqueous acetic acid was kept at 60 °C for 24 h. After the removal of acetic acid under reduced pressure, the solution was neutralized 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 recrystallization was found to be identical with the ketone since it gave no m.p. depression on admixture with an authentic sample.

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-vanadium(V) in 80% HOAc (v/v); (2) 0.015M-substrate and 0.5M-H_2SO_4 in 80% HOAc (v/v); (3) 0.5M-H_2SO_4 and 0.001M-vanadium(V) in 80% HOAc (v/v); (4) 0.5M-H_2SO_4 in 80% HOAc (v/v).

Each solution (5 ml) was treated with a saturated solution of acrylamide (10 ml) in aqueous acetic acid (80% 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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