The Selectivity of Attack by the Hydroxyl Radical on Myoinositol, and the Importance of Stereoelectronic Factors upon Radical Rearrangement: an Electron Spin Resonance Conformational-analysis Study

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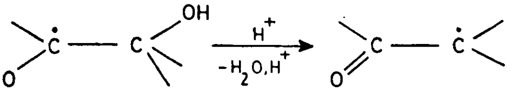
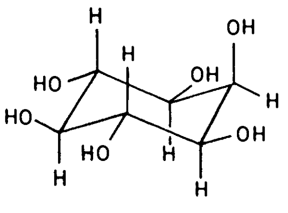
E.s.r. spectroscopy has been employed to show that the reaction of ·OH with the model substrate myoinositol is unselective; at pH 4, e.s.r. signals of all possible radicals produced by C–H abstraction are detected. A conformational analysis based on the hyperfine splittings is presented. The rates of acid-catalysed rearrangement of the radicals have been measured; the radical with an axial β-hydroxy-group is shown to lose water with a rate constant (*ca.* 3 × 10^6 dm^3 $mol^{-1}s^{-1}$) which is considerably greater than those of the radicals with only equatorial β-hydroxy-groups. This is interpreted in terms of a significant stereoelectronic requirement for rearrangement.

It has previously been shown that e.s.r. spectroscopy, in conjunction with the use of a flow system employing the radiomimetic Ti^{III}–H_2O_2 couple, provides a useful means for studying the reactions of the hydroxyl radical with some monosaccharides and related compounds;[1-3] the spectra of first-formed, and in some cases rearranged, radicals have been described. In particular, the acid-catalysed elimination of water from αβ-dihydroxy-substituted radicals [*cf.* reaction (1)[4]] has been characterized.

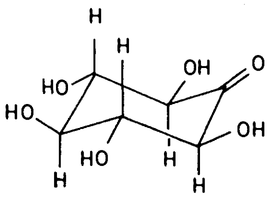


(1)

It has been claimed[5,6] as a result of a product study of the reaction of myoinositol [mesoinositol (1)] with the hydroxyl radical (generated by u.v. photolysis[5] or γ-irradiation[6] of water) that attack takes place predominantly at the sole equatorial hydrogen atom with, ultimately, specific formation of myoinos-2-one (2) rather than other inosose isomers. The suggestion has also been made, on the basis of an earlier e.s.r. study,[1] that reaction with ·OH occurs preferentially at the equatorial C–H bond. Such specificity in the position of attack of the very reactive hydroxyl radical (which abstracts hydrogen atoms from sites activated by an adjacent hydroxy-group at rates approaching the diffusion-controlled limit[7]) would not have been expected.



(1)



(2)

Further, product studies of the reaction of radiolytically-produced hydroxyl radicals on D-glucose suggest that attack is more or less indiscriminate.[8]

We have commenced a detailed e.s.r. study of the selectivity of attack of ·OH on a variety of mono- and poly-saccharides with a view to making use of the advantages possessed by e.s.r. in the recognition, conformational analysis and quantitative analysis of mixtures of radicals produced in primary processes. We chose to study initially the reaction between ·OH and the model compound myoinositol in an attempt to rationalize the apparent anomalies reported for the selectivity of ·OH in these systems and to determine the factors affecting both the site of attack and the ease of rearrangement.

RESULTS

(a) *E.s.r. Results at* pH ca. 4.—The e.s.r. spectrum obtained from the reaction of ·OH (from Ti^{III}–H_2O_2) and myoinositol in a three-way continuous flow system[9] at pH *ca.* 4 (in the presence of EDTA to sequester titanium) is shown in Figure 1a. Careful analysis of this spectrum, which was obtained under conditions of moderate modulation amplitude, shows that there are *four* different types of radicals present, all of which are characterized as hydroxy-conjugated[10] on the basis of their *g* value (2.003 1); previously,[1] only one radical had been characterized. Of these radicals, three have spectra which are overlapping triplets with *a*(2H) *ca.* 3.0 mT; such a splitting is typical of the interaction of the unpaired electron with two *axial* β-protons which make a small dihedral angle θ with the orbital of the unpaired electron and hence give rise to a large β-proton splitting [β-proton splittings are generally believed[10] to be proportional to $\cos^2\theta$; comparison of these splittings with that of 2.0 mT for[11] ·CMe_2OH, in which the methyl groups are freely rotating, so that $\langle\cos^2\theta\rangle = \frac{1}{2}$, leads to a value of θ for the myoinositol radicals of *ca.* 30°, which is as expected for a perfect chair geometry]. Other small splittings were detected in all of these spectra, especially when low modulation was employed; the individual assignments of these three spectra to the three different radicals with two axial β-protons (3)—(5) † is justified subsequently.

The fourth component of the spectrum is assigned to the isomeric radical (6) (presumably present in both enantiomeric forms) on the basis of the doublet splittings of 3.313 and 0.625 mT, typical of axial and equatorial protons, respectively, in radicals in six-membered rings. Dihedral angles of *ca.* 25 and 67°, respectively, are calculated for the C–H

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† Enantiomeric structures (5a and b) [or (6a and b)] will not be distinguishable by e.s.r. spectroscopy.

bonds; the value for the (pseudo) equatorial proton indicates that the adjacent OH group occupies an axial position, more or less eclipsing the orbital of the unpaired electron. This radical also shows other splittings which produce a pattern resembling a 1 : 3 : 3 : 1 quartet of *ca.* 0.1 mT and a small triplet splitting of 0.03 mT which becomes better resolved under conditions of low modulation. When the oxidation was carried out in solution in ^2H_2O the ' quartet ' pattern was replaced by a doublet [$a(^1H)$ 0.130 mT], indicating that two of the three protons responsible for this pattern are of OH type (the smallest splittings of 0.033 mT would probably not have been resolved under these conditions, even if exchange had not occurred). Careful simulation of the spectrum from myoinositol itself indicates that the three hydrogens have different splittings, of 0.130, 0.105, and 0.075 mT, of which the last two are hydroxy-protons. These may well be those from the β-axial and α-OH groups, as judged by the occurrence of similar hydroxy splittings in •CH(OH)CH$_2$OH, in which the β-hydroxy-group not only eclipses the orbital of the unpaired electron (as found here) but also induces a significant amount of conformational locking, with distortion; [12] an

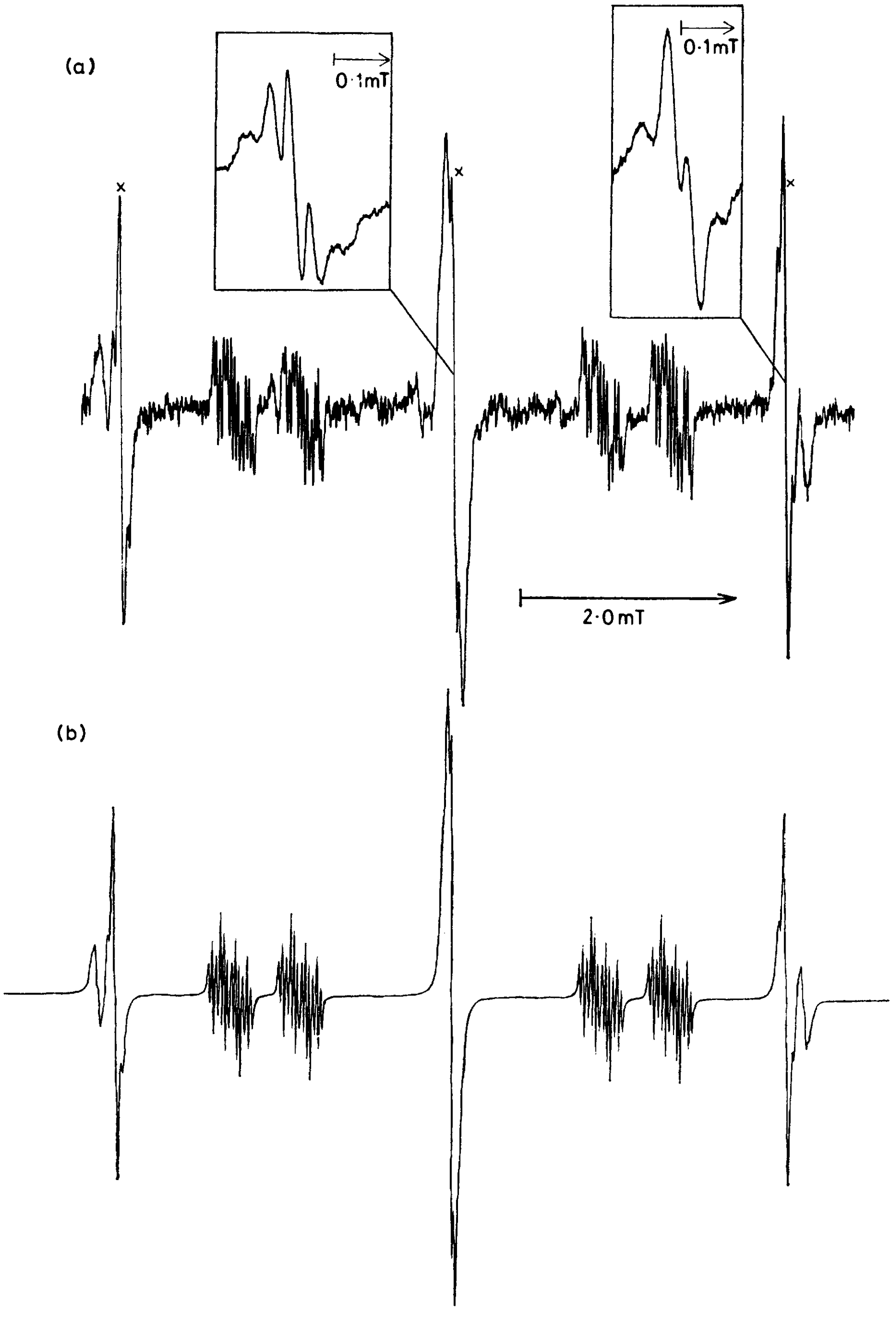
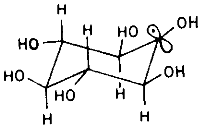
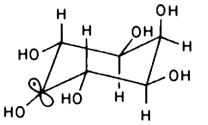
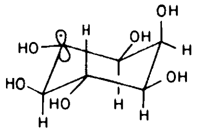
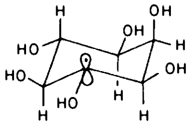
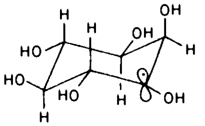
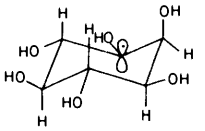


FIGURE 1 a, E.s.r. spectra of radicals (3)—(6) obtained by reaction of •OH with myoinositol at pH 4. Lines marked × are from radical (5); signals shown inset are those from radical (5) recorded under conditions of higher resolution. b, Spectral simulation for radicals (3)—(6) obtained using the splittings, line-widths, and relative concentrations given in Table 1 appreciable β-OH splitting is also detected in the analogous radical obtained [13] by abstraction of C(2)–H in α-glucose (but not in the analogous radical from β-glucose). The origin of the remaining small splittings is not clear (but see later).

Double integration [14] of signals recorded under conditions of high resolution established that the steady-state concentration of this fourth radical is, within experimental error, one-half that of the sum of the radicals (3)—(5). This is as anticipated if attack on (1) is indiscriminate, as long as all the myoinositol radicals have similar radical–radical termination rate constants (as would be expected).

Table 1

E.s.r. spectra of radicals from myoinositol and ·OH at pH 4 [a]

	Hyperfine splittings (mT) [b,c] ΔH/mT [b]		Relative intensity [b]
	a (β-H)	a (other)	
 (3)	3.003(2)	0.062 (2γ-H_{ax})	1
 (4)	3.160(2)	0.031 (2γ-H_{ax}) 0.029 (δ-H_{eq})	1
 (5a)  (5b)	3.020(1) 2.984(1)	0.036 (γ-H_{ax})	2
 (6a)  (6b)	3.313(1) 0.625(1)	0.130 (γ-H_{ax}) 0.105 (OH) 0.075 (OH) 0.033 (2H)	2

[a] All have g 2.0031 ± 0.0001. [b] Data employed for spectrum simulation shown in Figure 1b. [c] ±0.005, except for small splittings (see text)

The assignment of the spectra of the individual radicals with two axial β-protons (3)—(5), and the estimation of their relative steady-state concentrations, was made on the following basis. The main feature of the spectra from (3)—(5) is the relatively sharp and dominant triplet with the lines marked × in Figure 1. On closer inspection, under conditions of very low modulation, especially at somewhat lower pH when the concentration of these radicals is lower, it is revealed that the end lines of this spectrum are doublets with a(H) 0.036 mT and that the central line appears as a triplet, again with a(H) 0.036 mT [see the insets on Figure 1a]. The extra splitting on the central line must be due to a slight non-equivalence in the splittings from the two β-protons, and spectrum simulation confirms this (*n.b.* any second-order splitting will be significantly less than 0.03 mT). This indicates that the two β-protons are magnetically non-equivalent which is a feature expected for (5) but not the more symmetric radicals (3) and (4). Further, a (relatively) strong signal would be expected for this isomer compared with (3) and (4), if ·OH attack is indeed largely indiscriminate.

The other spectra, from (3) and (4), comprise large triplets, one with a further small triplet splitting (0.062 mT) and the other with a pattern which appears to indicate further interactions with three protons [a(2H) 0.031, a(1H) 0.029 mT] as confirmed by spectrum simulation. These small splittings did not appear to be susceptible either to broadening *via* acid-catalysed exchange at low pH (down to pH *ca.* 1) or removal in ^2H_2O and we therefore believe that they are from C–H rather than O–H protons. The detailed, though nevertheless tentative, assignment of these to (3) and (4), respectively, follows from the analysis of long-range coupling to γ- and δ-protons in model compounds; although spectra from the cyclohexyl radical [15] itself and from *e.g.*, 1-hydroxycyclohexyl [16] do not allow clear distinctions to be drawn, the spectrum from the cyclic nitroxide piperidine 1-oxyl (which, like the radicals in question, has an oxygen substituent at the radical centre and a chair geometry [17]) shows long-range coupling from axial γ-protons and the equatorial δ-proton [*cf.* also INDO calculations [18] on six-membered rings of related type, in which the equatorial δ-proton is predicted to have a much larger splitting than the axial δ-proton, and the general expectation for significant interaction with a δ-equatorial proton held in a **W** type relationship with the orbital of the unpaired electron (see *e.g.* ref. 19)]. For (3) the long-range interaction is thus suggested to be with the *axial* γ-protons, whereas for (4) there is, in addition, a δ-H coupling. [On a similar basis, the single small coupling in (5) is assigned to the single axial γ-proton; in the case of (6) the geometry is evidently modified somewhat by the presence of the (eclipsing) axial β-OH group (as for ·$CHOHCH_2OH$), and long-range interaction is evidently facilitated; we speculate that the large coupling of 0.13 mT is from the axial γ-H adjacent to the axial β-OH.]

Good agreement between observed and simulated spectra for (3)—(5) and (6) was obtained using the hyperfine parameters shown in Table 1 and a statistical distribution of radicals [*i.e.* 1 : 1 : 2 : 2 for (3) : (4) : (5) : (6)]. It should be stressed that the appearance of the overall simulated spectrum proved fairly sensitive to variations in the ratios of the individual radicals; thus, although agreement is not perfect (it is possible, for example, that line-shape variation could improve matching), we believe that there is no cause for regarding the relative concentrations as being significantly removed from those expected on a statistical basis.

(b) *E.s.r. Results at Lower* pH.—When the pH was lowered, clear changes in the spectra took place; the results obtained were also dependent upon the presence or absence of EDTA. In experiments at *ca.* 20 °C at pH 2.6 in the absence of EDTA the signal from (6) was only approximately half its concentration at pH 4 (see above) whereas the spectra from (3)—(5) were barely diminished in intensity; in addition, traces of a new signal appeared. As the pH was lowered further, the spectrum from (6) disappeared, signals from (3)—(5) decreased somewhat (being reduced to about half their initial intensity by pH 1.5), and the new signal was clearly visible and analysable (see Figure 2). This has doublet splittings of 1.76, 3.69, 0.275, and 0.075 mT, with g 2.004 4 and, as recognized previously,[1,3] it is a carbonyl-conjugated radical formed *via* rearrangement reaction (1). We should note at this stage that the largest proton splitting is typical of an axial β-proton and that the splitting of 0.275 mT is typical of a γ-proton situated next to the carbonyl group in cyclic radicals of related type (see *e.g.* refs. 20 and 21). At very low pH a further very similar spectrum, presumably from an isomer, was detectable, though the concentration was low and only a tentative analysis is possible [a(1H) 1.76, 3.69, 0.275, and 0.22 mT, g 2.004 4]. The overall signal intensity at low pH (*ca.* 1.0) proved significantly lower (*ca.* 30%) than at pH 4, which may well reflect a contribution to radical termination of reduction by Ti^{III} [*cf.* a previous e.s.r. study of the ease of reduction of carbonyl-conjugated radicals ($-\dot{C}-CO-$) by[22] Ti^{III} and Fe^{II}]. In experiments in the presence of EDTA, the reduction in intensity proved more marked as the pH was lowered (though the overall behaviour was otherwise the same); this probably reflects the faster reduction of carbonyl-conjugated radicals by Ti^{III} (EDTA) complexes[22] compared with hydrated titanium(III).

Table 2 shows the structures of the radicals which could be formed *via* loss of water from the first-formed radicals (3)—(6) (again ignoring the distinction between enantiomers). Thus (3) will give (7), and its enantiomer, and (4) will give (8) and its enantiomer. Radical (5) can give either or both (9) and (10), depending on which hydroxy-group is lost, and (6) can give either or both (7) and (11). Table 3 lists the types of C–H bond (axial, equatorial) in these radicals in easily recognizable form; our problem is to assign the observed signals to the appropriate radicals.

First, we note that the only radicals detected at low pH possess an axial β-C–H proton; no signals with a small β-H splitting as expected for an equatorial proton [as in (9)] could be identified. Such signals may be obscured by the resonances from the central groups of lines in the overall 1 : 1 : 1 : 1 pattern, though it is also possible that radical (5) rearranges primarily to (10) rather than (9).

The two new signals detected both possess a significant γ-hydrogen splitting across the carbonyl group (0.275 mT); this is evidently due to an axial $\dot{C}-CO-CH$ γ-proton [a common feature for structures (7)—(10)], and such a sizeable interaction presumably reflects the operation of a hyperconjugative interaction with spin density in a $p(\pi)$ orbital on carbonyl carbon (with an expected $\cos^2\theta$-type dependence). Since γ-proton couplings across carbonyl are normally smaller than this, it suggests that the appro-

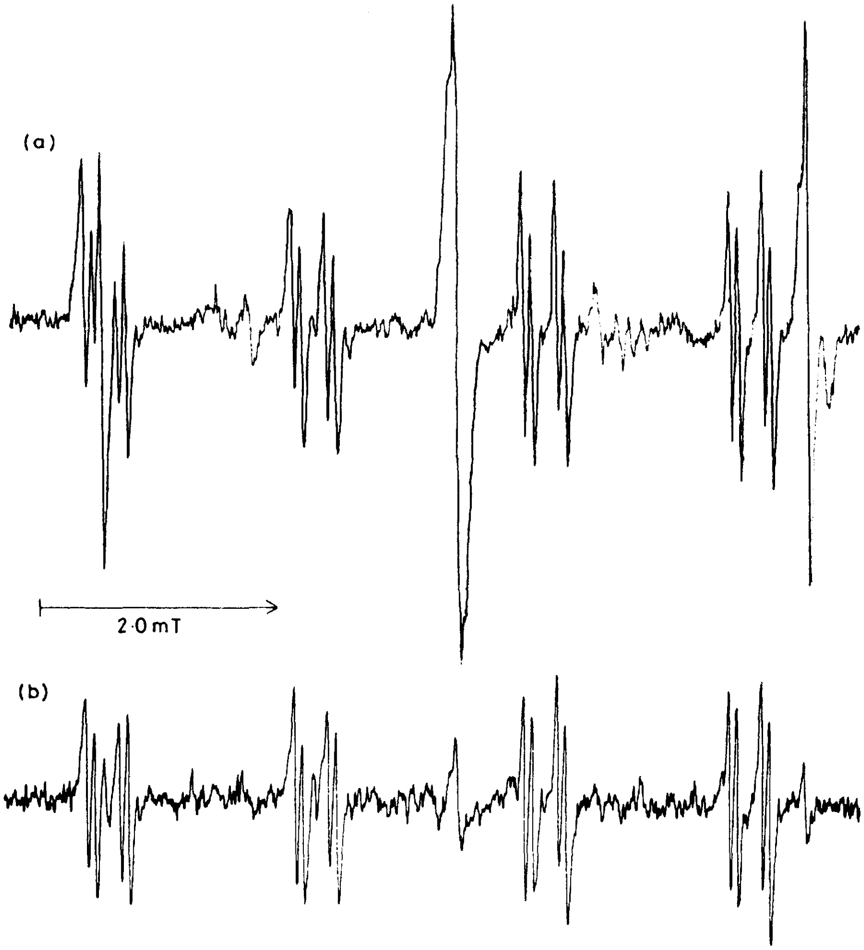
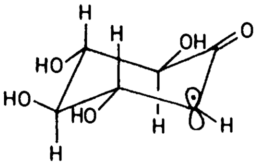


FIGURE 2 E.s.r. spectra of radicals obtained from the reaction of •OH and myoinositol: (a) at pH *ca.* 1.6; (b) at pH *ca.* 0.6

priate equatorial γ-proton would have a splitting of near zero (as expected on the basis of a $\cos^2\theta$ dependence); accordingly we believe that no spectrum attributable to (11) is detectable. This is understandable if radical (6) rearranges primarily by loss of the axial hydroxy group, to give predominantly radical (7), the first carbonyl-conjugated species detected as the pH is lowered. The pH-dependence of the signals, and the kinetic analysis (see later), also supports this interpretation.

TABLE 2

Structures of radicals which may possibly result from acid catalysed rearrangement of radicals (3)—(6)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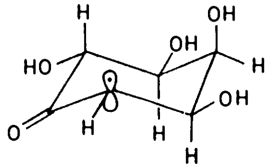
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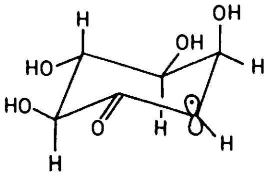
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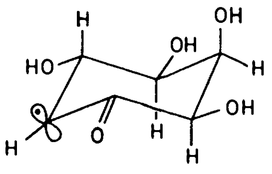
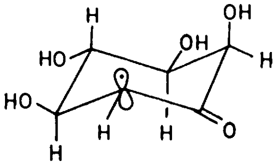

(10)


(11)

Major signal detected [a 1.76 (1 H), 3.69 (1 H), 0.275 (1 H), 0.075 (1 H) mT] is assigned to (7) and (10)

Minor signal detected [a 1.76 (1 H), 3.69 (1 H), 0.275 (1 H), 0.220 (1 H) mT] is assigned to (8)

The major signal observed then is attributed to radical (7), formed from rearrangement of radicals (6) and (3); as explained earlier, these precursors correspond to *ca.* 50% of the initial radical mixture. It also seems likely that, of the two remaining radicals (8) and (10), one [probably (10), with the axial γ-proton, like (7)] has a closely similar spectrum, while the other is somewhat different. Accordingly we suggest that the minor radical detected is (8), though the distinction between (8) and (10) cannot be clearly made without further evidence regarding the angular dependence of γ- and δ-proton splittings.

TABLE 3

Stereochemical arrangement of C–H bonds in radicals (7)—(11)

	β	γ(CO)	γ	δ	Possible precursor(s)
(7)	a	a	a	a	(3) and (6)
(8)	a	a	e	a	(4)
(9)	e	a	a	a	(5)
(10)	a	a	a	e	
(11)	a	e	a	a	(6)

(c) *E.s.r. Results at Higher* pH.—As the pH was raised from pH 4, signals from radicals (3)—(6) disappeared, that from (6) again being removed first. No signals at all were detected above pH 7. We interpret these findings in terms of the rearrangement of radicals (3)—(6) *via* base-catalysed loss of water [*cf.* reaction (1)] to give carbonyl-conjugated radicals which themselves are destroyed by rapid reaction with Ti^{III} (EDTA) complexes.[22]

(d) *Kinetic Studies.*—We believe that it is particularly significant that the spectrum from (6) is the first to be reduced in intensity as the pH is either lowered or raised from 4 (see earlier). This implies that the acid-catalysed (and base-catalysed) loss of a β-OH group proceeds more readily from this radical than from (3)—(5); the conclusion that this corresponds to loss of the axial OH group adjacent to the radical centre [a feature present in (6), but not in (3)—(5)] is supported by our detection from (6) of the rearranged radical (7), but not (11) (which would require loss of the equatorial OH group). We have previously argued [23] that for the radical $\cdot CH(OH)CH_2OH$ the rearrangement to $\cdot CH_2CHO$ is facilitated by the adoption in the radical of a geometry in which the β-hydroxy-group eclipses the orbital of the unpaired electron, but evidence on the angular dependence of the requirement in rearrangements of this type has previously proved elusive.

We have measured the rates of rearrangements of radicals (3)—(6) in the following way, which depends upon obtaining the rates of termination for these radicals under conditions where there is no detectable rearrangement (pH *ca.* 4) and estimating the relative effectiveness of the two competing modes of decomposition as the pH is lowered. An analysis is possible since, as has been previously demonstrated [23-25] in kinetic studies employing the Ti^{III}–H_2O_2 system, a pseudo-steady-state system is established in the cavity for short-lived radicals formed when $\cdot OH$ is completely scavenged by the substrate.

Reactions (2)—(7) form the basis of the analysis. Reaction (2) is simply the radical initiation step, reaction (3) is the attack of $\cdot OH$ on myoinositol (MH) to give a variety of radicals $\cdot R_i$, $\cdot R_j$, reactions (4) and (5) describe the bimolecular termination reactions of these (self-destruction and cross-termination, respectively), and reaction (6) is the acid-catalysed rearrangement of any given radical to a new radical ($\cdot S_i$). Radical abstraction reactions of $\cdot R_i$ with myoinositol to give $\cdot R_j$ will be too slow to contribute to radical destruction or formation under these conditions and can be ignored here (see ref. 7 for typical rate constants for reactions of aliphatic radicals with saturated substrates).

$$Ti^{III} + H_2O_2 \xrightarrow{k_{in}} Ti^{IV} + HO^- + HO\cdot \tag{2}$$

$$\cdot OH + MH \xrightarrow{k_i} \cdot R_1 + \cdot R_2 \ldots \cdot R_i + \cdot R_j \tag{3}$$

$$\cdot R_i + \cdot R_i \xrightarrow{k_{ii}} \text{molecular products} \tag{4}$$

$$\cdot R_i + \cdot R_j \xrightarrow{k_{ij}} \text{molecular products} \tag{5}$$

$$\cdot R_i + H^+ \xrightarrow{k_r} \cdot S_i \tag{6}$$

$$\cdot R_i + \cdot S_i \xrightarrow{k_{ii}'} \text{molecular products} \tag{7}$$

Employing the steady-state relationship for that one of the myoinositol radicals $\cdot R_i$ which undergoes rearrangement as well as bimolecular termination allows us to equate the rate of formation [equation (8)] with the rate of destruction [equation (9)]; in equation (8), the subscript t refers to concentrations of reagents in the cavity and R is a fraction which accounts for the selectivity of ·OH in producing the particular radical $\cdot R_i$ rather than isomeric radicals.

$$\text{Rate of generation of } \cdot R_i = k_{in}[H_2O_2]_t[Ti^{III}]_t R \quad (8)$$

$$\text{Rate of removal of } \cdot R_i = 2k_{ii}[\cdot R_i]^2 + k_{ij}[\cdot R_i]\Sigma[\cdot R_j] + k_{ii}'[\cdot R_i][\cdot S_i] + k_r[H^+][\cdot R_i] \quad (9)$$

$$\text{Thus } k_{in}[H_2O_2]_t[Ti^{III}]_t R = 2k_{ii}[\cdot R_i]^2 + k_{ij}[\cdot R_i]\Sigma[\cdot R_j] + k_{ii}'[\cdot R_i][\cdot S_i] + k_r[H^+][\cdot R_i] \quad (10)$$

Since the radical–radical termination rates should be, to a first approximation, independent of structure (this should certainly be true for $\cdot R_i + \cdot R_j$ and is probably also a reasonable approximation for $\cdot R_i + \cdot S_i$, since all radicals concerned have similar size and shape) we can write $2k_{ii} = k_{ij} = k_{ii}'$, so that equation (10) becomes simplified to (11) and (12) where $[\cdot R_{tot}]$ is the total radical concentration. Equation (13) follows.

$$k_{in}[H_2O_2]_t[Ti^{III}]_t R = 2k_{ii}[\cdot R_i]([\cdot R_i] + \Sigma[\cdot R_j] + [\cdot S_i]) + k_r[H^+][\cdot R_i] \quad (11)$$

$$k_{in}[H_2O_2]_t[Ti^{III}]_t R = 2k_{ii}[\cdot R_i][\cdot R_{tot}] + k_r[H^+][\cdot R_i] \quad (12)$$

$$[R_i\cdot] = \frac{k_{in}[H_2O_2]_t[Ti^{III}]_t R}{2k_{ii}[\cdot R_{tot}] + k_r[H^+]} \quad (13)$$

This equation, which should be applicable when $[\cdot R_{tot}]$ stays approximately constant (*i.e.* when there has been relatively little rearrangement and hence little contribution to termination of radical reduction by Ti^{III}), leads to the prediction that there should be a linear relationship between $1/[\cdot R_i]$ and $[H^+]$ for experiments with constant initiation conditions and also that as the pH is varied $[R_i]$ should drop to half its value in the absence of rearrangement when $2k_{ii}[\cdot R_{tot}] = k_r[H^+]$.

In a series of experiments with $[H_2O_2]_t$ and $[Ti^{III}]_t$ constant (with $[H_2O_2]_0$ 0.016 mol dm^{-3}, $[Ti^{III}]_0$ 0.002 7 mol dm^{-3},* and a constant flow rate with a mixing time of *ca.* 60 ms) we confirmed that equation (13) holds for radical (6) in the pH range 4—2.5. We have also measured $[\cdot R_{tot}]$ in these experiments by comparison of doubly integrated spectra with those from vanadyl sulphate under conditions of identical machine settings. $2k_{ii}$ was measured by comparison of the intensity of the (doubly integrated) signal from the myoinositol radicals (recorded under conditions of no rearrangement) with that from $\cdot CH_2OH$ generated under identical conditions from the reaction between ·OH and CH_3OH. Since the radical generation rate should be the same in the two systems, we can equate the rates of radical destruction, as in equation (14).

$$2k_t[\cdot CH_2OH]^2 = 2k_{ii}[\cdot R_{tot}]^2 \quad (14)$$

In experiments at 20 °C with $[Ti^{III}]_0$ 0.002 7 mol dm^{-3}, $[H_2O_2]_0$ 0.016 mol dm^{-3}, a mixing time of *ca.* 60 ms, and identical recording conditions, we measured $[\cdot CH_2OH]$ as 8.5×10^{-6} mol dm^{-3} (by comparison with the signal from a standard solution of vanadyl sulphate), and $[\cdot R_{tot}]$ as 2.4×10^{-5} mol dm^{-3}. Taking $2k_t$ for $\cdot CH_2OH$ as [26] 2.4×10^9 dm^3 mol^{-1} s^{-1} we obtained a value for $2k_{ii}$ of 2.9×10^8 dm^3 mol^{-1} s^{-1} (a value which, by comparison with the value of $2k_t$ for $\cdot CHOHCH_2OH$ of 6.7×10^8 dm^3 mol^{-1} s^{-1},[27] suggests that a bulk effect is important here). Knowledge of $2k_{ii}$, $[\cdot R_{tot}]$, and the value of $[H^+]$ for half-removal of $R_i\cdot$ [*i.e.* radical (6)] leads to a value of 2.8×10^6 dm^3 mol^{-1} s^{-1} for the appropriate rearrangement (at 20 °C). Although the detailed analysis would not be expected to hold precisely at very low pH, when radicals (3)—(5) rearrange (since the total radical concentration is then significantly affected by the occurrence of radical reduction), the approximate rate constant for the appropriate rearrangement is indicated by the pH for half-removal (*ca.* 1.5); thus k_r for radicals (3)—(5) is calculated as 2.2×10^5 dm^3 mol^{-1} s^{-1}.

It might be expected that loss of an axial OH group would be intrinsically faster than loss of an equatorial group on account of the steric acceleration expected for the former; thus, for example,[28] of the two isomers of 4-t-butylcyclohexyl tosylate, the *cis*-isomer (with the tosyl group axial) reacts *via* S_N1 solvolysis *ca.* 3 times faster than the *trans*-isomer (with the tosyl group equatorial). We suggest that the significantly greater acceleration detected here for the relatively small hydroxy leaving group in the axial position implies that the reaction is facilitated by the overlap of the axial C–O bond and the orbital of the unpaired electron. Thus we believe that our results provide further evidence for the importance of stereoelectronic requirements in certain radical reactions (*cf.* a similar requirement for overlap between the bond to be broken and the half-occupied orbital in examples of homolytic cleavage reactions [29]).

EXPERIMENTAL

E.s.r. spectra were recorded on Varian E-104 and E-4 spectrometers, both of which were equipped with X-band klystrons and 100 kHz modulation. Splitting constants were generally measured to within 0.005 mT as described previously [9] and were checked by spectrum simulation (for most of the small splittings the accuracy is considered to be greater than this); g values were measured by comparison with that for $\cdot CH_2OH$ (2.003 3 [30]) generated by reaction of methanol with ·OH *in situ*. Most of the experiments employed an aqueous flat cell and mixing chamber which allowed three reagent streams to be mixed simultaneously; solutions were pumped through the cell with a Watson–Marlowe H.R. flow inducer and the time between mixing and observation was typically 60 ms (determined as explained previously [9]). The three reactant solutions contained, typically, 0.008 mol dm^{-3}-titanium(III) [prepared from Fisons technical grade titanium(III) chloride, 12.5% w/v solution], 0.05 mol dm^{-3}-hydrogen peroxide (prepared from Fisons 100-volume hydrogen peroxide solution), and 0.03 mol dm^{-3}-myoinositol (Sigma), respectively. For spectra recorded at pH values above 2, the disodium salt of EDTA (3 g dm^{-3}) was added to the titanium(III) solution, together with the amount of ammonia (*d* 0.880) required for the final pH; for pH values below 2, the required amount of concentrated sulphuric acid was added together with, in some cases, the disodium salt of EDTA. pH Values were recorded for the mixed effluent solution with a Pye–Unicam PW 9410 digital pH meter equipped with a Russell electrode. All solutions were thoroughly deoxygenated prior to use by bubbling nitrogen through. The experiments employing ^2H_2O (Aldrich, 99.8 atom %) were carried out using a two-way flow system with titanium chloride, disodium ethylenediaminetetra-acetate and ammonia in one stream and hydrogen peroxide and myoinositol in the other (the concentrations after mixing being as for the three-way

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* Concentrations referred to in the text are those after mixing.

flow system). All chemicals employed were commercially available samples, used as supplied.

The spectrum simulation program, which includes allowance for second-order effects and employs Lorentzian line-shapes, was kindly provided by Dr. M. F. Chiu and was executed on the DEC-10 computer at the University of York. This was used to confirm estimates of relative radical concentrations obtained by inspection of the spectra from mixtures of radicals from myoinositol (see text). Absolute radical concentrations (for myoinositol and for $\cdot CH_2OH$) were obtained by comparison of doubly integrated signals with that from vanadyl sulphate (10^{-3} mol dm^{-3}-$VOSO_4 \cdot H_2O$) obtained under identical spectrometer settings.

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