

### 321. *Periodate Oxidation of 1,2-Diols, Diketones, and Hydroxyketones: The Use of Oxygen-18 as a Tracer.*

By C. A. BUNTON and V. J. SHINER, jun.

The oxygen atom of the acetone from oxidation of pinacol and 2-methylpropane-1,2-diol by periodic acid comes from the 1,2-diol, in agreement with the suggestion that an intermediate is formed by electrophilic attack of the periodate. In contrast to this, the additional oxygen atom of acetic acid, formed by oxidation of biacetyl by periodate in basic solution, comes from the periodate. The mechanism is a nucleophilic attack by periodate upon the carbonyl-carbon atom, and does not seem to involve the hydrates of the ketone as intermediates. In the oxidation of methylacetoin by periodic acid the oxygen of the acetone comes from the hydroxyl group of the hydroxyketone, and the additional oxygen atom of the acetic acid comes from the periodate. The mechanism probably involves nucleophilic attack by the periodate ion upon the carbonyl group, and co-ordination of the hydroxyl group on to the iodine atom of the periodate.

KINETIC evidence has suggested that, whereas the oxidation of 1,2-diols by periodic acid (or its ions) involved co-ordination of the hydroxyl groups to the iodine atom,<sup>1</sup> that of  $\alpha\beta$ -diketones was by an entirely different path. Contrary to general belief, the hydrate of the  $\alpha\beta$ -diketone played no direct part in the reaction, and the mechanism appeared to involve direct nucleophilic attack of the periodate ion upon the carbonyl group.<sup>2</sup> Our aim was to test these views by the use of oxygen-18 as a tracer, and to obtain evidence on the oxidation of an  $\alpha$ -hydroxyketone.

The experimental problem was complicated by the exchange of oxygen atoms between water on the one hand and the periodate,  $\alpha\beta$ -diketone, or  $\alpha$ -hydroxyketone, and the ketonic product on the other.<sup>3</sup> Because our experimental methods were chosen to evade the consequence of the exchanges, *i.e.*, equilibration of the tracer between reactants and products, we discuss the three classes of compound separately.

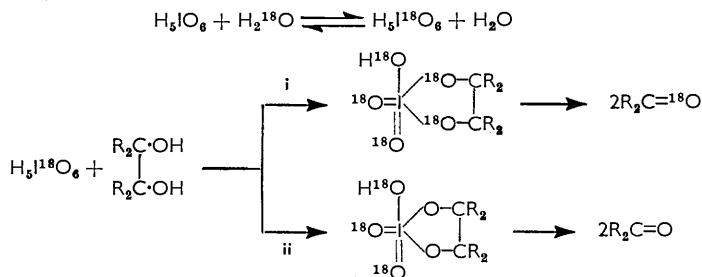
$\alpha\beta$ -Diols.—Aldehydes exchange their oxygen atoms very rapidly with water, ketones less rapidly.<sup>3</sup> Therefore it was necessary to choose diols which would give a readily removable ketone as product, and to do the experiment under conditions in which the oxidation would be rapid and the exchange with the ketone slow. The former condition was satisfied by using diols which gave acetone, and removing this by evaporation, the latter by using the pH range 4—7 where periodate is in isotopic equilibrium with water. The oxidation of  $\alpha\beta$ -diols is thought to involve a cyclic intermediate, and it was suggested

<sup>1</sup> (a) Duke, *J. Amer. Chem. Soc.*, 1947, **69**, 3054; Duke and Bulgrin, *ibid.*, 1954, **76**, 3803; (b) Buist and Bunton, *J.*, 1954, 1406; Buist, Bunton, and Miles, *J.*, 1957, 4567, 4574.

<sup>2</sup> Shiner and Wassmuth, *J. Amer. Chem. Soc.*, 1959, **81**, 37.

<sup>3</sup> Cohn and Urey, *J. Amer. Chem. Soc.*, 1938, **60**, 679; Lauder, *Trans. Faraday Soc.*, 1948, **44**, 729; Bell and Darwent, *ibid.*, 1950, **46**, 34.

that this could be formed by (i) nucleophilic attack by periodate upon the carbon atom<sup>4</sup> or, more probably, (ii) by co-ordination of the hydroxyl groups to periodate, as shown.



In our first experiments we used pinacol and isolated acetone whose <sup>18</sup>O abundance was much less than that required for mechanism (i).<sup>5</sup> The small enrichment of the acetone came from exchange with the water during isolation. Pinacol was somewhat unsatisfactory, because its kinetic form of oxidation is different from that of the simple αβ-diols,<sup>1,4</sup> and we therefore did other experiments with 2-methylpropane-1,2-diol, whose kinetic form of oxidation is typical of the mechanism involving an intermediate between the periodate and the diol.<sup>1b</sup> The acetone from this compound was also isotopically normal (except for a small adventitious exchange). The formaldehyde was not isolated, because it would be in isotopic equilibrium with the water *via* its hydrate.<sup>3</sup> The results (Table 1) show that the oxygen of the ketone produced comes from the hydroxyl groups of the diols. The experiments with pinacol were at room temperature initially, those with 2-methylpropane-1,2-diol at 0° initially.

TABLE 1. Oxidations of pinacol and 2-methylpropane-1,2-diol by periodic acid in water.

	Pinacol				2-Methylpropane-1,2-diol	
pH .....	3.5	7—11	3.5 *	5.0 *	7—11	7 *
N(H <sub>2</sub> O) (atom % excess) .....	0.710	0.727	0.727	0.926	0.78	0.78
N(COMe <sub>2</sub> ) (atom % excess) .....	0.440	0.141	0.313	0.144	0.115	0.20

\* Control experiments. Experiments in which the acetone was not aspirated out immediately, but allowed to exchange, gave samples with isotopic abundances between 97% and 102% of those of the water, for both pinacol and 2-methylpropane-1,2-diol. Isotopic abundances N are all in atom % excess above normal.

*αβ-Diketones.*—Although the spectral changes associated with the hydration of biacetyl (butane-2,3-dione) are essentially instantaneous in water and *ca.* 70% of the compound is hydrated, it seems that the hydrate is not reactive to periodate. The oxidation appears to be a direct nucleophilic attack of the periodate upon the carbonyl group.<sup>2</sup> This initial attack is probably followed by a ring closure, to give a cyclic intermediate which decomposes rapidly to the products. This requires that some of the oxygen of the acetic acid produced must come from the diketone, and some from the periodate. In principle it should be possible to confirm this directly by tracer experiments, but these are complicated by oxygen exchange between water and both reactants. Biacetyl is rapidly and extensively hydrated in water; therefore it must exchange its oxygen atoms very rapidly. However, periodate ion should exchange its oxygen atoms only through the singly ionised form, because only in this ionisation stage in aqueous solution are two stable species, differing in degree of hydration, known.<sup>6</sup> Thus in solutions of high pH the exchange of oxygen atoms between water and periodate ions should be slowest. There is the further advantage that the rate of oxidation is highest at these high pH values.<sup>2</sup>

<sup>4</sup> Price and Knell, *J. Amer. Chem. Soc.*, 1942, **64**, 552.

<sup>5</sup> Buist, Bunton, and Shiner, *Research*, 1953, **6**, 45.

<sup>6</sup> Chrouthamel, Hayes, and Martin, *J. Amer. Chem. Soc.*, 1951, **73**, 82.

Therefore our experiments were carried out with very concentrated basic solutions of periodate in isotopically normal water. These solutions were added to excess of biacetyl which had been left to exchange its oxygen atoms in  $^{18}\text{O}$  water. It was hoped that oxidation would be faster than oxygen exchange of the periodate. Because the alkali metal salts of periodic acid are sparingly soluble in strongly basic solution we used the tetraethylammonium salt. This was extremely soluble in water, and for this reason it may be useful for preparations in which concentrated reagents are required. When reaction was complete the acetic acid was isolated as its silver salt. The results are given in Table 2.

TABLE 2. Oxidation of  $^{18}\text{O}$ biacetyl by periodate in  $\text{H}_2^{18}\text{O}$ .

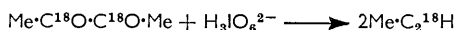
$[\text{Et}_4\text{N}]\text{OH}$ (mmoles $^c$ ) .....	5.06	10.2	15.1	17.6	25.0	18.2 $^b$
$N(\text{H}_2\text{O})$ (atom % excess $^a$ ) .....	0.99	0.99	0.97	0.93	0.89	0.00
$N(\text{AcOH})$ (atom % excess $^a$ ) ...	1.00	1.06	0.86	0.70	0.66	0.016

$^a$  Calc. for complete reaction, dilution being assumed by normal oxygen in  $\text{H}_2\text{O}$  and periodic acid, and in biacetyl. Initially  $N(\text{H}_2\text{O}) = 1.05$  atom % excess.  $^b$  All reagents isotopically normal.  $^c$  In all experiments *ca.* 5.0 mmoles of periodate and *ca.* 25 c.c. of water were present initially.

Because the biacetyl was in isotopic equilibrium with the oxygen of the water, and acetic acid does not exchange (except at high acidities), the acetic acid would be fully enriched if oxidation was through the dihydrate of biacetyl, or if the periodate had exchanged before oxidation. If, however, the periodate oxidised the biacetyl directly much faster than it exchanged its oxygen atoms, then the acetic acid would have one of its oxygen atoms isotopically labelled. The various possible reactions are (iii)—(v).

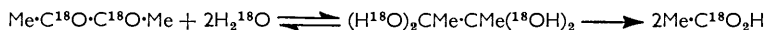


(iii) Direct attack by periodate upon the carbonyl group:



This requires a second-order rate law and 50% enrichment of the acetic acid.

(iv) Reaction with the dihydrate:



This involves complete enrichment of the acetic acid.

(v) Reaction with the monohydrate:



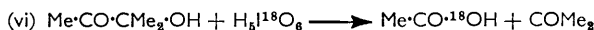
This involves 75% enrichment of acetic acid.

The reactions done with base equivalent to the periodate (or twice that amount) give fully enriched acetic acid, but an increasing amount of base gives progressively less enrichment of the acetic acid. Thus with these larger amounts of base an appreciable amount of the oxygen in the product has come from the periodate directly. This rules out reaction of the dihydrate, (iv).

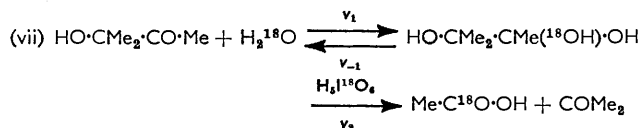
If reaction were by nucleophilic attack upon the carbonyl group of the monohydrate, together with co-ordination of a hydroxyl group to the iodine atom, then the acetic acid would be 75% enriched (v). The values with the highest concentration of base are close to this: with  $[\text{OH}^-]$  five times the [periodate] the value is 74%, on the basis of dilution of the  $^{18}\text{O}$  water by the oxygen of the periodate, and 73% without such dilution. However, the known exchange between periodate and water would be expected to force our experimental values of  $^{18}\text{O}$  abundance above the values predicted for no exchange of periodate, and so the results favour mechanism (iii), *i.e.*, direct nucleophilic attack by periodate upon both the carbonyl groups of the diketone. They do not rule out the dihydrate as an intermediate at lower pH, but the complete enrichment of the acetic acid from these experiments at lower pH seems to be more readily explained in terms of a rapid exchange between periodate and water, which is faster than the reaction between diketone and water, except at the highest pH.

We had hoped to test this point by examining the isotopic abundance of the iodate product, although it has been reported that iodate did exchange its oxygen atoms readily with water.<sup>7</sup> The iodate isolated at the end of the reaction as its silver salt had the same isotopic abundance as the solvent water, confirming that iodate ion exchanged its oxygen with water. The direct method of examining the exchange of oxygen between water and periodate in our strongly basic solution was not feasible, because the tetraethylammonium salt was too hygroscopic for isolation and the sodium or potassium salt insufficiently soluble.

*α-Hydroxy-ketones.*—Completion of this oxygen tracer study of the periodate oxidation of bifunctional compounds containing oxygen required experiments on an  $\alpha$ -hydroxy-ketone. Methylacetoin (3-hydroxy-3-methylbutan-2-one) was chosen because it gives as products acetic acid and acetone which are both readily isolated. The effects of pH changes on the rate of its oxidation by periodate are different from those observed with the  $\alpha\beta$ -diols and  $\alpha\beta$ -diketones. The rate is of first order with respect to both reactants and has a maximum value at pH 8.<sup>8</sup> Addition of isotopically normal methylacetoin to isotopically enriched periodate at pH 8 in <sup>18</sup>O water gave acetone with very little enrichment, and acetic acid whose enrichment was approximately half that of the water [ $N(\text{H}_2\text{O}) = 1.04$  atoms % excess,  $N(\text{AcOH}) = 0.575$  atom % excess,  $N(\text{COMe}_2) = 0.07$  atoms % excess]. This reaction probably involves co-ordination of the tertiary hydroxyl group to the iodine atom, as is postulated for the oxidation of  $\alpha\beta$ -diols.<sup>1</sup> One of the oxygen atoms of the acetic acid must have come from the carbonyl group of the hydroxy-ketone, because both the water and the periodate are isotopically enriched. The other must have come from either the water or the periodate. These results require oxygen exchange of the carbonyl-oxygen atom of the hydroxy-ketone to be slower than oxidation by periodate. Again we can write various possible reactions, *e.g.*:



This would involve nucleophilic attack by periodate upon the carbonyl-carbon atom, and co-ordination of the hydroxyl group to iodine.



(a) If  $v_{-1} > v_2$  (second-order kinetic form), the hydrate and therefore the acetic acid will be fully enriched.

(b) If  $v_{-1} < v_2$  (rate independent of periodic acid), then the acetic acid will be 50% enriched.

There are two interpretations of our tracer results, scheme (vi), which is a direct nucleophilic attack by periodate upon the carbonyl group, or scheme (vii**b**) in which the hydrate is very rapidly attacked by periodate, so that only one of the two adjacent hydroxyl groups is isotopically labelled. The latter scheme seems to us to be unsatisfactory because it requires the rate of reaction to be of zero order with respect to periodate.

Although the kinetic law is not known for solutions as concentrated as those of the tracer experiment, there is no deviation from a second-order kinetic law in dilute solution.<sup>8</sup> Also there seems to be no reason why the hydrate of an  $\alpha$ -hydroxy-ketone should be very reactive towards periodate, and if we interpret our results by scheme (vii**b**) it would have to be considerably more reactive than are the simple  $\alpha\beta$ -diols, whose rates of oxidation are in all cases within the region of convenient measurement.<sup>1</sup>

Therefore we prefer the interpretation in terms of a nucleophilic attack by periodate

<sup>7</sup> Hoering, Butler, and McDonald, *J. Amer. Chem. Soc.*, 1956, **78**, 4829.

<sup>8</sup> Shiner and Wassmuth, unpublished results.

upon the carbonyl group, and oxidation of the hydroxyl group, probably by co-ordination to the periodate. Our results, of themselves, do not exclude the hydrate as an intermediate with certainty, nor do they give any information of the timing of the various steps.

#### EXPERIMENTAL

*Materials.*—Biacetyl (B.D.H.) was fractionally distilled through a 20 × 100 mm. column packed with glass helices. The middle fraction, b. p. 88—90°, was used.

Tetraethylammonium hydroxide was prepared from the iodide, carbonate-free sodium hydroxide, and silver nitrate, in the usual way. Care was taken to exclude carbon dioxide. The solution was evaporated under reduced pressure.

Methylacetoin, prepared by hydration of 2-methylbut-3-yn-2-ol in dilute sulphuric acid containing mercuric sulphate,<sup>9</sup> had b. p. 74—78°/100 mm. It gave a single peak on a gas-liquid chromatogram.

2-Methylpropane-1,2-diol, prepared from isobutene by the action of *t*-butyl hydroperoxide and osmium tetroxide,<sup>10</sup> had b. p. 79—81°/11 mm.,  $n_D^{25}$  1.4305.

Pinacol and orthoperiodic acid were commercial samples.

*Oxidation of  $\alpha\beta$ -Diols.*—Solutions of periodate were allowed to equilibrate isotopically with <sup>18</sup>O water. Experiments with the sodium salt showed that at pH ~7 the exchange was complete within the time required for dissolution and isolation of the periodate. The isotopic abundance of the periodate was determined by mass-spectrometric analysis of the oxygen liberated when the solid periodate was heated.

The  $\alpha\beta$ -diol was added to the periodate solution, and the ketone swept out by a stream of air under reduced pressure. The following procedure was typical. 2-Methylpropane-1,2-diol (10 g.) was added to a solution of tetraethylammonium periodate (0.09 mole) in 100 c.c. of <sup>18</sup>O water at 0°, under reduced pressure. The temperature rose rapidly, and the distillate was trapped at -80°. After 5 min., the distillate was redistilled under reduced pressure at 0°; the distillate, after three such distillations, was fractionated through a column (150 × 6 mm.) with a low hold-up. The acetone collected had b. p. 55—56° and gave a single peak on gas-liquid chromatography. Control experiments were carried out in a similar manner.

When the initial pH of the reactants is *ca.* 4 it does not change during reaction, because the periodate is present mainly as  $\text{IO}_4^-$ , and this is reduced to  $\text{IO}_3^-$ . This is not so at higher pH, where the periodate is present mainly as  $\text{H}_3\text{IO}_6^{2-}$ .

The procedure for isolation of acetone after oxidation of pinacol was slightly different from that described above. The distillate was cooled to -80° before final fractionation, to remove traces of water. The latter seems here to be unnecessary.

The isotopic analysis of the acetone isolated from the oxidation of pinacol was made by allowing known amounts of acetone, water, and carbon dioxide to come to isotopic equilibrium in a vacuum. This takes *ca.* 3 weeks at room temperature, and the isotopic abundance of the carbon dioxide was followed until it reached a constant maximum value. From this, and the known amounts of oxygen present, the isotopic abundance of acetone was calculated, any isotopic fractionation between water and acetone being neglected. The acetone obtained by oxidation of 2-methylpropane-1,2-diol and of methylacetoin was analysed by pyrolysis to carbon monoxide over carbon *in vacuo*, the monoxide being analysed mass-spectrometrically.

*Oxidation of Biacetyl.*—A concentrated solution of isotopically normal tetraethylammonium periodate was added to isotopically enriched biacetyl in <sup>18</sup>O water. The following experiment illustrates the procedure. Orthoperiodic acid  $\text{H}_5\text{IO}_6$  (0.0053 mole) was dissolved in a solution (*ca.* 3 c.c.) of tetraethylammonium hydroxide (0.025 mole) in isotopically normal water; to this solution was added, rapidly and with stirring, a solution of biacetyl (2.5 c.c.) in <sup>18</sup>O water (25 c.c.) (this solution had been kept for 1 hr. to allow oxygen exchange between water and biacetyl). The temperature rose to 42°, and the solution darkened because of condensation of the excess of biacetyl. Concentrated nitric acid was then added dropwise to bring the pH to 5. The precipitate of biacetyl condensate was removed and silver nitrate (0.0057 mole) in <sup>18</sup>O water added to the solution. The silver iodate was removed, washed with water, and dried in a vacuum-desiccator. The pH of the residual solution was adjusted to *ca.* 6 by addition of ammonia (*d* 0.88), and silver acetate precipitated by addition of silver nitrate; the yield of

<sup>9</sup> Bernard and Cologne, *Bull. Soc. chim. France*, 1945, **12**, 347.

<sup>10</sup> Milas and Sussman, *J. Amer. Chem. Soc.*, 1936, **58**, 1302.

dried silver iodate was 0.0052 mole and of dried silver acetate 0.0044 mole. The silver acetate was found to be free from carbonate; it was decomposed thermally to carbon dioxide *in vacuo*, and this was analysed mass-spectrometrically. The silver iodate was decomposed thermally, *in vacuo*, to oxygen, and this was analysed mass-spectrometrically.

*Oxidation of Methylacetoin.*—Methylacetoin (0.11 mole) was oxidised by periodic acid, and the acetone collected by the procedure outlined for 2-methylpropane-1,2-diol. The pH of the solution was adjusted to 3 by addition of concentrated sulphuric acid, and the solution distilled, almost to dryness, in a vacuum. The distillate was neutralised by sodium hydroxide (to pH 6), and silver acetate was precipitated by silver nitrate.

*Exchange of Iodate.*—In the first experiments, potassium iodate was dissolved in  $^{18}\text{O}$  water, and after 5 min. silver nitrate was added to precipitate silver iodate; a portion of this was washed with isotopically normal water, the rest with isotopically enriched water; both samples were *ca.* 70% exchanged. Because it was possible for silver nitrate to be catalysing the exchange, a further exchange experiment was made. Potassium iodate was dissolved in isotopically enriched water, at room temperature, and the solution freeze-dried as rapidly as possible; the isolated potassium iodate was *ca.* 80% exchanged.

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