# 296. *Periodate Oxidation of Deoxy-hexoses and Their Derivatives.*

By J. B. Lee.

There are numerous examples of periodate oxidation of activated methylene groups [1] and the appearance of free iodine has been regarded as accompanying this process [2] although no iodine was liberated in the oxidation of malondialdehyde and related compounds.[3] Hydroxylation of the methylene compound is postulated as the intermediate stage,[4] and

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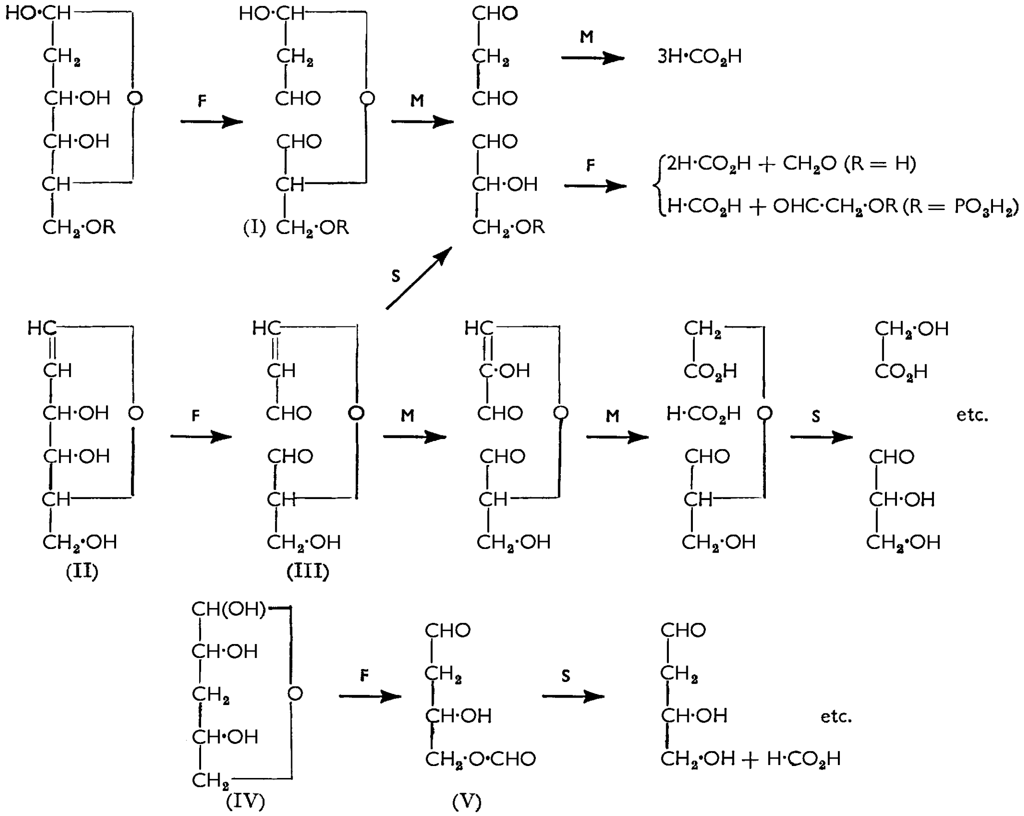
[1] Ness, Fletcher, and Hudson, *J. Amer. Chem. Soc.*, 1951, **73**, 3742; Wolfrom, Thompson, O'Neill, and Galkowski, *ibid.*, 1952, **74**, 1062.

[2] Williams and Woods, *J. Amer. Chem. Soc.*, 1937, **59**, 1408; Head, *Nature*, 1950, **165**, 236; Sarkar, *ibid.*, 1951, **168**, 122; Halsall, Hirst, and Jones, *J.*, 1947, 1427; Fletcher, Ness, and Diel, *J. Amer. Chem. Soc.*, 1954, **76**, 3029.

[3] Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621.

[4] Courtois and Ramet, *Bull. Soc. Chim. biol.*, 1945, **27**, 610; 1947, **29**, 240; Head and Hughes, *J.*, 1954, 603; Lemieux and Bauer, *Canad. J. Chem.*, 1953, **31**, 814; McKeown and Hayward, *ibid.*, 1955, **33**, 1392.

some proof of this has been offered.[5] When we tried to confirm the structures of some 2-deoxyhexose phosphates by periodate titration the results prompted examination of the reaction with the parent sugars.



F = Fast; M = moderate; S = slow.

2-Deoxy-D-glucose, -D-altrose, and -D-galactose at 20—25° rapidly consumed 1 mol. of periodate. If the reaction was then stopped the same dialdehyde (I; R = H) was obtained from each sugar; this probably indicates that each had reacted in the same anomeric pyranose form. The small proportion of furanose and/or open-chain form was indicated by the low yield of formaldehyde. If set aside for 48 hours, or briefly warmed, the solution contained malondialdehyde.

An excess of periodate caused over-oxidation and, at completion, the products were formic acid (~5 mols.) and formaldehyde (<1 mol.), approximately 6 mols. of oxidant being consumed. The appearance of formaldehyde on over-oxidation is also in agreement with a predominantly pyranose form in the original solution.

After the initial rapid uptake of 1 mol., the rate decreases slowly with no marked break.

Similarly, with 2-deoxyhexose 6-phosphates an initial rapid uptake of 1 mol. is followed by slower over-oxidation. From the mixture after the initial rapid reaction D-glyceraldehyde 3-phosphate was isolated. When reaction was complete, mainly glycollaldehyde phosphate and formic acid were found.

Both free sugars and phosphate esters initially yield a dialdehyde (I; R = H or $PO_3H_2$ respectively). Fission on the hemiacetal link must occur (possibly activated by the methylene group [6]) as the next step. The second oxidation stage for the free sugar will

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[5] Schwarz and McDougall, *J.*, 1956, 3065.

[6] Cf. Overend, *J.*, 1950, 671, 1433; 1951, 2063.

involve mainly fission of glyceraldehyde to glyoxal and formaldehyde, with concomitant slower oxidation of malondialdehyde; in agreement, formic acid is produced largely in the later stages of reaction (see Figs. 1 and 2).

Formaldehyde is only partly released by 2 mols. of oxidant; also, glyceraldehyde releases formaldehyde more quickly than it is released in this reaction: it is likely that the rate of hemiacetal bond fission determines the rate of production of glyceraldehyde and hence largely the rate of oxidation in the second step.

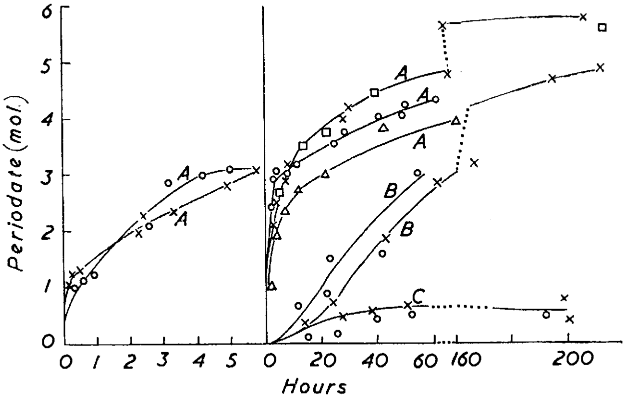

Fig. 1. *Oxidation of* 0·0035M-*sugar by* 0·035M-*periodate.*

*A, Periodate uptake.*
*B, Formation of formic acid.*
*C, Formation of formaldehyde.*
× 2-*Deoxy*-D-*galactose.*
○ D-*Galactal.*
□ 2-*Deoxy*-D-*altrose.*
△ 2-*Deoxy*-D-*glucose* 6-*phosphate.*

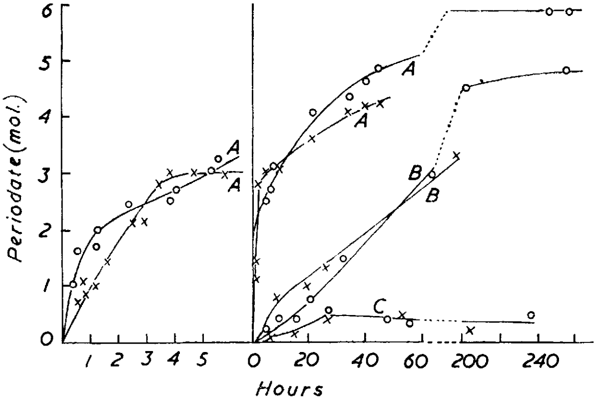

Fig. 2. *Oxidation of* 0·0031M-*sugar by* 0·029M-*periodate.*

*A, B, C as Fig.* 1.
× D-*Glucal.*
○ 2-*Deoxy*-D-*glucose.*

It should be noted that malondialdehyde and the dialdehyde (I; R = H) rapidly decolorise 2 mols. of iodine in the presence of sodium hydrogen carbonate, but not in acid conditions, and unreliable results are obtained in the earlier parts of the oxidation unless periodate uptake is measured at low pH, *viz.*, by using acidified potassium iodide and thiosulphate.[7]

As malondialdehyde and other 1,3-dicarbonyl derivatives tend to exist in the enolic form [8] it was of interest to compare the periodate oxidation of glycals. These, by analogy, should yield the enol derivative of malondialdehyde in the first stage (II ⟶ III). Extensive over-oxidation occurs on treatment of D-galactal and other glycals with periodate. For hexals there is initial rapid consumption of 1 mol. of oxidant, with later slower oxidation. However, comparison of 2-deoxyglucose with glucal shows an interesting steric effect. The glycals in each case are oxidised more slowly than the 2-deoxyhexoses (Figs. 1 and 2).* Since it seems likely, although not rigidly proved, that attack by periodate

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* Note, however, the rate inversion at 1—3 mol. and sharp break in the curve at 3 mol. for glycals.

[7] Gottlieb, Caldwell, and Hixon, *J. Amer. Chem. Soc.*, 1940, **62**, 3342; Taylor, *ibid.*, 1953, **75**, 3912; Whistler and Hickson, *ibid.*, 1954, **76**, 1671.

[8] Diekmann and Platz, *Ber.*, 1904, **37**, 4638; Pino, *Gazzetta*, 1947, **77**, 283; 1950, **80**, 768.

involves formation of a cyclic intermediate [9] similar to that propounded by Criegee [10] for oxidation by lead tetra-acetate, and since in the glycals the four atomic centres O, C(1), C(2), C(3) must be coplanar,[11] the transition stage in this case will involve fusion of a five- and a six-membered ring with more consequent strain than in the similar fusion involving the more flexible pyranose rings of 2-deoxyglucose and 2-deoxygalactose.

The main formation of formaldehyde occurs slowly after consumption of 1 mol. of oxidant (only small amounts are released before this) and is only slight after consumption of 3 mol. Whilst it is known [5, 12] that formaldehyde condenses with malondialdehyde and its derivatives in these conditions, after complete removal of free formaldehyde at this stage, more is regenerated in the medium, indicating that the slow fission of the hemiacetal bond is again the rate-controlling step for oxidation of the glyceraldehyde portion of the molecule (III).

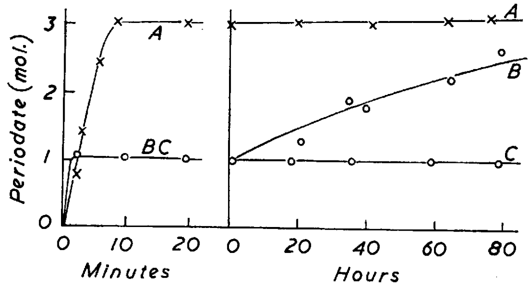

FIG. 3.

*A, B, At* 20—25°; *C, at* 0°.
× 0·0014M-2-*Deoxy*-D-*sorbitol and* 0·008M-*periodate.*
○ 0·0037M-3-*Deoxy*-D-*xylose and* 0·022M-*periodate.*

Release of iodine did not occur in any of the above reactions. However, when the dialdehyde (I; R = H) or malondialdehyde was kept, in daylight, in contact with sodium iodate at pH 2—4, slow release of iodine was observed, presumably involving attack on the methylene group.

Over-oxidation involving hydroxylation of a methylene group has been shown to require two flanking $>$C=O groups, and even so will not proceed readily in acyclic systems if both groups are ketonic.[3] The oxidation of some 2-deoxyhexitols has provided further support for this generalization.[13] 2-Deoxysorbitol rapidly consumed 3 mols. of oxidant, negligible further oxidation occurring. β-Hydroxypropionaldehyde is therefore not readily oxidized under these conditions.

Periodate oxidation of a 3-deoxypentose (xylose) was examined. At 0° reaction was rapid, with consumption of 1 mol. of oxidant, but further oxidation was very slow. At higher temperatures further oxidation occurred, finally yielding formic acid and formaldehyde. Use of 2 mols. of oxidant under these conditions permitted isolation of some malondialdehyde, but only small yields of formaldehyde were obtained, and it is likely that hydrolysis of a formate ester is the rate-controlling step, further oxidation of the malondialdehyde occurring even under these conditions (IV $\longrightarrow$ V).

## EXPERIMENTAL

2-Deoxy-D-glucose and 2-deoxy-D-galactose were recrystallized commercial samples. 2-Deoxy-D-altrose was prepared by reduction of the 2-deoxy-2-iodo-derivative [14] followed by hydrolysis of protecting groups. The corresponding 6-phosphates were prepared by essentially

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[9] Duke, *J. Amer. Chem. Soc.*, 1947, **69**, 3504; Buist and Benton, *Research*, 1953, **6**, 55; *J.*, 1954, 1436.

[10] Criegee, *Sitzber. Beförd. Ges. Natürwiss. Marburg*, 1934, **69**, 25; *Chem. Abs.*, 1935, **29**, 6820; Criegee, Krafft, and Rank, *Annalen*, 1933, **507**, 159.

[11] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 77.

[12] O'Dea, *Chem. and Ind.*, 1953, 1338.

[13] Unpublished work, and example quoted.

[14] Richards and Wiggins, *J.*, 1953, 2443; Jeanloz, Prins, and Reichstein, *Helv. Chim. Acta*, 1946, **29**, 371.

the method of Foster *et al.*[15] Oxidations were carried out with unbuffered sodium metaperiodate solutions. Formaldehyde was determined [16] as its dimedone derivative after being removed from the reaction mixture in carbon dioxide. Formic acid was determined by titration.[17] Chromatography [18] was on Whatman No. 3 paper with propan-1-ol–ammonia solution (*d* 0·88)–water (6 : 3 : 1).

Weighed portions of the compound were dissolved in water, and the required volume of freshly prepared sodium periodate solution added, the mixture being rapidly diluted to a measured volume. The mixtures were kept in darkness, in glass-stoppered vessels at 20—25°. Aliquot portions were removed from time to time for determinations.

*Oxidation of* 2-*Deoxy*-D-*glucose*.—(*a*) 2-Deoxy-D-glucose [19] (0·058 g.) (recrystallized from ethyl alcohol) was treated in water (2 ml.) with periodate solution (1 mol.). After 30 min. no periodate remained, and the iodate was precipitated (as the barium salt). Passage of carbon dioxide removed formaldehyde (0·02—0·05 mol.). One portion of solution was added to Brady's reagent, and the bright red bis-2,4-dinitrophenylhydrazone was collected and recrystallized from chloroform–methanol to constant, m. p. 212—214° (17 mg.) (Found: C, 41·6; H, 3·5. $C_{18}H_{18}O_{11}N_8$ requires C, 41·4; H, 3·5%). A second portion was warmed to 50° for 5 min., cooled, and extracted with several portions of chloroform. The combined extracts, a portion of which gave a bright red colour with ferric chloride solution, were treated with aniline to yield malondialdehyde dianil (2 mg.), m. p. 113—116° (Claissen [20] reports m. p. 115°). The extracted aqueous solution was treated with 2,4-dinitrophenylhydrazine solution. D-Glyceraldehyde 2,4-dinitrophenylhydrazone was obtained, having m. p. 158—159° (from ethanol) (lit., m. p. 155—156°). A third portion of solution was added to cupric acetate solution, giving slowly the copper derivative of malondialdehyde (Found: Cu, 30·6. Calc. for $C_6H_6O_4Cu$: Cu, 30·9%). Preheating of the solution hastened formation of the precipitate.

(*b*) 2-Deoxy-D-glucose (14 mg., 1 mol.) in water (3 ml.) was treated with 0·035N-periodate solution (2 mol). Negligible formation of formaldehyde occurred in the first 30 min.; thereafter slow liberation occurred (0·4 mol.). A slight amount of titratable acid was formed. Some malondialdehyde was detectable after complete oxidation. Attempts to isolate glyoxal were unsuccessful.

(*c*) 2-Deoxy-D-glucose (28·5 mg., 1 mol.) completely reduced 0·035N-periodate (6 mols.) in 5 days. Production of formaldehyde (0·4—0·5 mol.) and formic acid (4·3—4·8 mols.) was measured.

(*d*) Portions of 2-deoxy-D-glucose were treated with excess of periodate. The rates of production of formaldehyde and formic acid, and of disappearance of oxidant, are summarized graphically.

*Oxidation of* 2-*Deoxy*-D-*galactose*.—(*a*) 2-Deoxy-D-galactose [21] (0·063 g.) (recrystallized from methanol; m. p. 109°) was treated in water (2 ml.) with 0·035N-sodium periodate (1 mol.). When reaction was complete (30 min.) the iodate was removed, also the small proportion of formaldehyde. One portion of solution was treated with Brady's reagent. The bright red precipitate had m. p. 210—214°, undepressed on admixture with that from 2-deoxy-D-glucose. The remaining solution, after filtration, was held at 50° for 10 min., cooled, and treated with a second portion of periodate solution (1·5 mols.). Rapid formation of formaldehyde (0·6 mol.) was observed; attempts to isolate malondialdehyde from the solution were not successful.

(*b*) 2-Deoxy-D-galactose (0·037 g.) was treated with a solution of 0·035N-sodium periodate (1 mol.) and set aside for 1 hr. Iodate was removed and the solution was added to warm cupric acetate solution. This gave the copper derivative of malondialdehyde (Found: Cu, 29·9%).

(*c*) Rate measurements on periodate–2-deoxy-D-galactose mixtures are recorded graphically.

*Oxidation of* 2-*Deoxy*-D-*altrose*.—(*a*) 2-Deoxy-D-altrose (0·013 g.) was treated in water (2 ml.) with 0·035N-aqueous periodate (1 mol.). No periodate remained after 1 hr. Then ions were

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[15] Foster and Overend, *J.*, 1951, 980.

[16] Karrer and Pfeiler, *Helv. Chim. Acta*, 1934, **17**, 766; 1937, **20**, 79; Caldwell and Hixon, *J. Biol. Chem.*, 1938, **123**, 595; Nicolet and Shinn, *ibid.*, 1941, **138**, 91.

[17] Jorpes, Werner, and Åberg, *J. Biol. Chem.*, 1948, **176**, 277; Myrbäck and Jorneström, *Arkiv Kemi*, 1941, **1**, 129; Rankin and Jeanes, *J. Amer. Chem. Soc.*, 1954, **76**, 4435.

[18] Cf. Baddiley, *Chem. Soc. Special Publ.*, No. 8, 1957, p. 153.

[19] Overend, Stacey, and Stanek, *J.*, 1949, 2481.

[20] Claissen, *Ber.*, 1903, **36**, 3668.

[21] Overend, Shafizadeh, and Stacey, *J.*, 1950, 671.

removed with bio-deminrolite, and the solution was divided into two portions. To one was added Brady's reagent, giving the same precipitate as above. The remaining portion of solution was warmed at 50° for 20 min., cooled, and added to a solution of cupric acetate, giving the copper derivative of malondialdehyde.

(*b*) 2-Deoxy-D-altrose was treated with an excess of aqueous sodium periodate. The results are presented graphically.

*Oxidation of* 2-*Deoxy*-D-*glucose* 6-*Phosphate*.—(*a*) Aqueous sodium periodate (0·237 g.) was added to 2-deoxy-D-glucose 6-phosphate in water (0·018 g. in 2 ml.). The solution was set aside for 10 days, iodate and excess of periodate were removed with sodium hydrogen sulphite, and the solution was chromatographed on paper by the ascending method. Spraying[22] revealed the presence of free orthophosphate and glycollaldehyde phosphate. Attempts to isolate derivatives of the latter were unsuccessful.

(*b*) 2-Deoxy-D-glucose 6-phosphate (0·008 g.) and 0·029M-sodium periodate (1 mol.) were mixed and set aside for 1 hr. Iodate was removed and the solution divided into two parts. Addition to one part of cupric acetate yielded a small portion of blue precipitate, soluble in dilute acid and giving only a very faint phosphate reaction. D-Glyceraldehyde 3-phosphate was detected in the remaining portion by paper-chromatographic comparison with an authentic sample.

(*c*) Periodate uptake and formic acid production are recorded in Fig. 1. Difficulty was encountered in obtaining consistent results in acid titrations, owing to the buffering effect of the phosphate present.

*Oxidation of* D-*Galactal*.—Comparison of the oxidation of this compound under identical conditions with 2-deoxy-D-galactose is given graphically. D-Glucal and 2-deoxy-D-glucose are similarly compared.

*Oxidation of* 2-*Deoxy*-D-*sorbitol*.—2-Deoxy-D-sorbitol (0·0087 g.) in water (2 ml.) and sodium periodate (0·036 g.) in water (3 ml.) were mixed and the volume made up to 10 ml. After 30 min. no further oxidation was occurring (3·05 mols. reacted). Further uptake was negligible (3·10 mol. after 78 hr.).

*Oxidation of* 3-*Deoxy*-D-*xylose*.—This is recorded graphically (see text).

*Reaction of Dialdehyde* (I; R = H) *and of Malondialdehyde with Sodium Iodate*.—A solution of the dialdehyde was prepared by the interaction of 2-deoxy-D-glucose with sodium periodate (1 mol), and an excess of sodium iodate was added. Approximately 0·16 mol. of iodine was released in 80 hr. at room temperature. A similarly treated solution of malondialdehyde also yielded iodine.

*Reaction of the Dialdehyde* (I; R = H) *and Malondialdehyde with Iodine*.—Solutions of dialdehyde were prepared by oxidation of 2-deoxy-D-glucose followed by removal of iodate. Malondialdehyde was prepared by shaking the copper derivative with water and ion-exchange resin. (*a*) Portions of these solutions were buffered with sodium hydrogen carbonate and titrated with standard iodine solution. In each case about 1·5 mols. of iodine were rapidly removed, further reaction being slow. (*b*) Portions were titrated directly; in each case about 0·05 mol. of iodine reacted. (*c*) Portions were acidified with dilute sulphuric acid. Negligible reaction occurred with iodine.

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[22] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.