Oxidative Decarboxylation of Aldonolactones by Cerium(IV) Sulphate in Aqueous Sulphuric Acid; Synthesis of D-Arabinose

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Oxidations of D-glucono-1,5-lactone, D-glucono-1,4-lactone, calcium D-gluconate, and 3-deoxy-D-*arabino*-hexono-1,4-lactone by cerium(IV) sulphate in sulphuric acid were studied at 25 and at 37 °C, with various concentrations of reactants and acidities. The results indicated that it is the aldonic acid that undergoes oxidation; the stoicheiometry requires two cerium(IV) ions for the oxidation of one molecule of aldonic acid to the next lower sugar. The rate of disappearance of cerium(IV) ions depended directly on its concentration, but the dependence on the organic substrate concentration suggested the existence of an intermediate complex: this was proved by a spectrophotometric method. The complex undergoes slow unimolecular decomposition to a free radical, which reacts with Ce^{IV} to afford the products. The reaction rate was proportional to 1/[SO$_4$H$_2$]^2. A preparative experiment with D-glucono-1,5-lactone gave crystalline D-arabinose in 94% yield.

WE have recently reported[1] a convenient synthesis of 2-deoxy-D-*erythro*-pentose by oxidative decarboxylation of 3-deoxy-D-*arabino*-hexono-1,4-lactone with cerium(IV) sulphate in M-sulphuric acid. The reagent had not been used previously for synthetic purposes although its oxidizing action on organic substances has been widely studied.[2-10]

In the carbohydrate field, Mehrotra[11,12] investigated the degradation of aldoses by cerium(IV) sulphate in aqueous sulphuric acid and Pottenger and Johnson[13] studied the mechanism of cerium(IV) oxidation of glucose and cellulose in M-perchloric acid.

We report here a study of the kinetics and mechanism of oxidation of D-gluconolactones and D-gluconic acid, carried out in order to establish whether the reaction could be controlled to avoid further degradation of the sugar and thus be useful for the synthesis of aldoses with one less carbon atom than the starting material.

RESULTS AND DISCUSSION

D-Glucono-1,5-lactone was oxidized with cerium(IV) sulphate in M-sulphuric acid at 37 °C. The yields of arabinose were determined at various times and with various molar proportions of lactone to oxidant (Figure 1). Similar experiments were carried out with D-glucono-1,4-lactone, calcium D-gluconate, and 3-deoxy-D-*arabino*-hexono-1,4-lactone. The aldose yields indicated a 2 : 1 stoicheiometry of Ce^{IV} to lactone, in accord with the stoicheiometry[5] for mandelic acid. In order to confirm the consumption of 2 mol of Ce^{IV} per mol of oxidized lactone or acid, three parallel experiments were

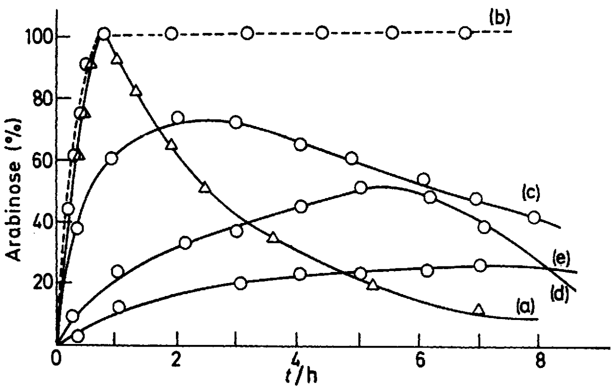

FIGURE 1 Oxidation of D-glucono-1,5-lactone with cerium(IV) sulphate in M-sulphuric acid at 37 °C; molar ratios (a) 1 : 2; (b) 1 : 2 (N$_2$ atmosphere); (c) 1 : 1.5; (d) 1 : 1; (e) 1 : 0.5

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[1] R. M. de Lederkremaer and L. F. Sala, *Carbohydrate Res.*, 1975, **40**, 385.

[2] F. R. Duke and R. F. Bremer, *J. Amer. Chem. Soc.*, 1951, **73**, 5179.

[3] M. Ardon, *J. Chem. Soc.*, 1957, 1811.

[4] G. Mino, S. Kaizerman, and E. Rasmussen, *J. Amer. Chem. Soc.*, 1959, **81**, 1494.

[5] B. Krishna and K. C. Tewari, *J. Chem. Soc.*, 1961, 3097.

[6] S. S. Muhammad and K. V. Rao, *Bull. Chem. Soc. Japan*, 1963, **36**, 943.

[7] R. N. Mehrotra and S. Gosh, (*a*) *Z. phys. Chem.*, 1963, **224**, 57; (*b*) 1965, **230**, 231.

[8] A. McAuley, *J. Chem. Soc.*, 1965, 4054.

[9] P. S. Sankhla and R. N. Mehrotra, *J. Inorg. Nuclear Chem.*, 1972, **34**, 3781.

[10] P. S. Sankhla and R. N. Mehrotra, *J. Inorg. Nuclear Chem.*, 1973, **35**, 891.

[11] R. N. Mehrotra, *Z. phys. Chem.*, 1965, **230**, 221.

[12] R. N. Mehrotra and E. S. Amis, *J. Org. Chem.*, 1974, **39**, 1788.

[13] C. R. Pottenger and D. C. Johnson, *J. Polymer Sci.*, 1970, **8**, 301.

run with D-glucono-1,5-lactone, calcium D-gluconate, and L-arabinose and a known excess of cerium(IV) sulphate. When the oxidation mixtures were left at 37 °C for 1 week to achieve complete degradation, both D-glucono-1,5-lactone and calcium D-gluconate consumed twelve Ce^{IV} equivalents per mole, whereas arabinose consumed ten equivalents.

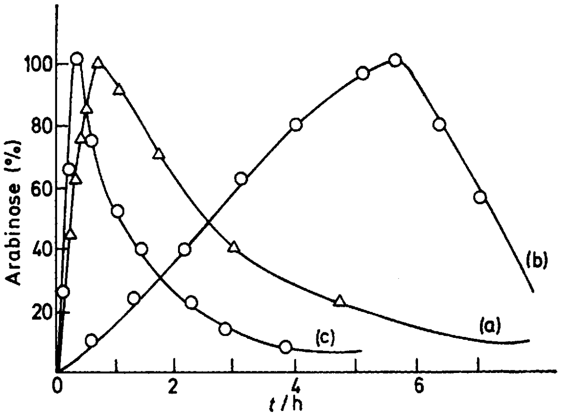

FIGURE 2 Stoicheiometric oxidation in M-sulphuric acid by cerium(IV) sulphate of (a) D-glucono-1,5-lactone, (b) D-glucono-1,4-lactone, (c) calcium D-gluconate

The modes of stoicheiometric oxidation of D-glucono-1,5-lactone, D-glucono-1,4-lactone, and calcium D-gluconate (Figure 2) suggested that it is the aldonic acid that undergoes oxidation, since the 1,5-lactone has an oxidation rate greater than that of the 1,4-lactone, in accord with the relative rates of hydrolysis of the respective gluconolactones to gluconic acid.[14]

Degradation of the arabinose produced was observed when the reaction was allowed to proceed after the maximum was reached. Erythrose and glyceraldehyde were detected by paper chromatography and g.l.c. of the alditol acetates, in comparison with authentic samples. This could be explained by reoxidation of Ce^{III} to Ce^{IV} by air.[15] Indeed, cerium(IV) could be detected after the maximum was achieved, by qualitative tests with brucine in glacial acetic acid or acetanilide.[15] The degradation of arabinose could be avoided by passing nitrogen continuously through the reaction mixture (Figure 1).

No further degradation was observed in the formation of 2-deoxy-D-*erythro*-pentose from 3-deoxy-D-*arabino*-hexono-1,4-lactone, in accord with participation of the C-2 hydroxy-group in the decomposition of the intermediate complex.[12]

In mixtures containing an excess of calcium D-gluconate or D-glucono-1,5-lactone, the rate of disappearance of cerium(IV) was proportional to the cerium(IV) concentration, *i.e.* the reaction is first order with respect to cerium(IV). The values of the first order rate constant (k_1) at various aldonic acid and lactone concentrations, at 25 and at 37 °C, are shown in Table 1.* The dependence of k_1 on substrate concentration, however, was non-linear, as it would be for a bimolecular mechanism. The plot showed a downwards concavity passing through the origin (Figure 3), indicating the participation of intermediate complexes.

Evidence for the formation of stable co-ordination complexes has been obtained by kinetic and spectrophotometric methods for cerium(IV) oxidations of many compounds in perchloric and nitric acids.[2,6,13,16] Complex formation in cerium(IV) oxidations in sulphuric acid solutions, however, has been indicated only in a few studies,[11,17] and in none of these was spectrophotometric evidence provided for the complex.

In the co-ordination complex mechanism a stable complex is formed between cerium(IV) and the aldonic acid, in a rapid preliminary equilibration step. The complex then disproportionates unimolecularly in the rate-determining step forming cerium(III) and a free radical. These reactions are followed by a very fast reaction of the free radical with more cerium(IV); this accounts for the observed 2 : 1 stoicheiometry.

The theory for oxidations involving co-ordination complexes was first applied to cerium(IV) oxidations by Duke and Bremer,[2] and has been discussed more recently in detail by Hintz and Johnson.[16] If this theory applies, the first-order constant k_1 is related to the equilibrium constant K for complex formation and to the rate constant k for complex disproportionation by the expression $1/k_1 = 1/k + 1/kK[S]$, where [S] is the substrate concentration.

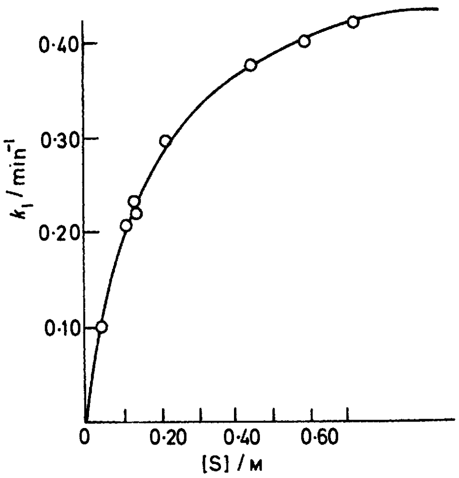

FIGURE 3 Effect of D-gluconic acid concentration on the first-order rate constant at 37 °C; $[Ce(SO_4)_2]_0$ 0.019 2M

A linear relationship with a positive intercept in a plot of $1/k_1$ against $1/[S]$ for the reactions of D-glucono-

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* Tables 1—3 are available as Supplementary Publication No. SUP 21963 (5 pp.) (see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue).

[14] H. S. Isbell and C. S. Hudson, *J. Res. Nat. Bur. Stand.*, 1932, **8**, 327.

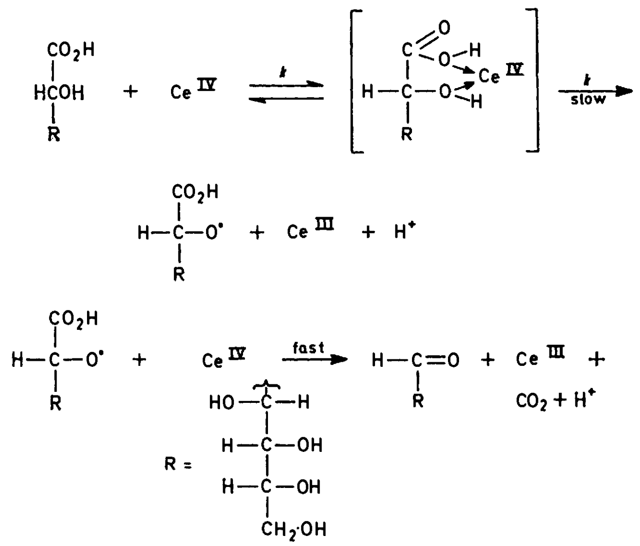
[15] F. J. Welcher, ' Organic Analytical Reagents,' Van Nostrand New York, 1947, vol. 4, pp. 214, 313, 513.

[16] H. L. Hintz and D. C. Johnson, *J. Org. Chem.*, 1967, **32**, 556.

[17] J. S. Littler, *J. Chem. Soc.*, 1959, 4135.

1,5-lactone and calcium D-gluconate at 25 and at 37 °C gives kinetic evidence of complex formation. The values obtained from the plot for k and K at 25 and 37 °C are summarized in Table 2.

Complex formation was also indicated by a change of colour from the yellow of the cerium(IV) sulphate solution to purple-red in the presence of D-glucono-1,5-lactone, D-glucono-1,4-lactone, or calcium D-gluconate. This change can be related to the equilibrium constant for complex formation by the method developed by Ardon [3] as in equation (i), where A_0 is the initial absorbance, A_b the absorbance observed for a cerium(IV) solution of the same concentration without the organic substrate, $[\mathrm{Ce^{IV}}]_0$ the initial cerium(IV) concentration, and $\Delta\varepsilon$ the difference in the molar absorptivities of the complex and cerium(IV). The equilibrium constant for complex formation K was calculated from a plot of $1/(A_0 - A_b)$ against $1/[\mathrm{S}]$. The results for D-glucono-1,5-lactone and calcium D-gluconate are given in Table 2. Determinations were made only at 25 °C because the reaction is very rapid at 37 °C.



$$1/(A_0 - A_b) = 1/\Delta\varepsilon[\mathrm{Ce^{IV}}]_0 + 1/\Delta\varepsilon[\mathrm{Ce^{IV}}]_0K[\mathrm{S}] \quad \text{(i)}$$

Pottenger and Johnson [13] reported values for the equilibrium constants in 1.0M-perchloric acid at 20 °C for methyl-β-D-glucopyranoside and 1,5-anhydro-D-glucitol of 10.3 and 12.7 (kinetic data) and 6.2 and 12.7 (spectrophotometric data). Mehrotra [11] calculated for the oxidation of arabinose by cerium(IV) sulphate in 0.5N-sulphuric acid, on the basis of kinetic data, a value of K of 8.849 $\mathrm{l\ mol^{-1}}$ at 35 °C. However in his work on the oxidation of aldoses, Mehrotra [12] reported second-order kinetics, and a mechanism which involved an intermediate complex.

In reported studies on the oxidation of hydroxy-acids by cerium(IV) sulphate,[5,7,8] a first-order dependence on both cerium(IV) and the substrate is postulated, but in all cases the suggested mechanism involves a co-ordination complex between cerium(IV) and the substrate.

The values obtained for the equilibrium constant K for D-glucono-1,5-lactone and calcium D-gluconate (Table 2) indicate that the complex is the same in both cases, and their magnitude (*ca.* 6 $\mathrm{l\ mol^{-1}}$) suggests that the complex is really involved in the reaction. Further evidence that the same complex is formed from both the lactone and the acid is the agreement between the values of the true rate constants k.

The disproportionation of the complex to form a free radical was indicated by the rapid gelification of a solution of acrylamide in the presence of the oxidation mixture. The oxidation of acrylamide by cerium(IV) sulphate in sulphuric acid is negligible at 25 °C.

Experiments were carried out at various sulphuric acid concentrations (1M, 1.5M, 2.0M, and 2.5M). The disappearance of cerium(IV) was followed at 37 °C spectrophotometrically, with an excess of D-glucono-1,5-lactone always present. The first-order constants k_1 were calculated (Table 3), and the equilibrium constant K and the true rate constant k were derived from the positive intercept on the rate axis and the slope of the plot of $1/k_1$ against $1/[\mathrm{S}]$ as before. As expected, K has the same value in the four cases. On the other hand, k decreases with an increase in sulphuric acid concentration. The product $k[\mathrm{H_2SO_4}]^2$ is constant, indicating a linear relationship between k and $1/[\mathrm{H_2SO_4}]^2$ (Table 3). These results are in accord with those of Krishna and Tewari [5] for mandelic acid and by Mehrotra and Gosh for citric [7a] and tartaric acids.[7b]

Cerium(IV) sulphate was chosen instead of cerium(IV) perchlorate as oxidant because of its lower oxidation potential and the greater stability of its solutions. The high yield of crystalline D-arabinose in a preparative oxidation of D-glucono-1,5-lactone, in accord with the yield previously reported for the synthesis of 2-deoxy-D-*erythro*-pentose,[1] shows that the reaction can be of general use for the synthesis of sugars, with better yields than those obtained by Ruff degradation.[18,19]

EXPERIMENTAL

All chemicals used were of AnalaR quality. All aqueous solutions were prepared with twice-distilled water. Solutions of organic compounds were prepared by weighing out samples of pure substances, with care to prevent absorption of moisture by hygroscopic material. D-Glucono-1,4-lactone [14] and 3-deoxy-D-*arabino*-hexono-1,4-lactone [20] were synthesised as already described. The stock cerium(IV) solution was prepared by dissolving cerium(IV) sulphate (Carlo Erba) in M-sulphuric acid. The reactant solutions were brought to the desired temperature before mixing. Spectrophotometric measurements were made with a Beckmann DU spectrophotometer. Temperature was kept constant within ±0.1 °C.

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[18] O. Ruff, *Ber.*, 1899, **32**, 550.

[19] G. Y. Moody, *Adv. Carbohydrate Chem.*, 1964, **19**, 149.

[20] R. M. de Lederkremer, M. I. Litter, and L. F. Sala, *Carbohydrate Res.*, 1974, **36**, 185.

Stoicheiometry and Products.—Mixtures containing various proportions of D-glucono-1,5-lactone and cerium(IV) sulphate were analysed for arabinose in the presence and absence of air (nitrogen atmosphere), at convenient times. Samples were withdrawn, neutralized, with barium carbonate and filtered. The arabinose produced was determined by quantitative paper chromatography on Whatman No. 1 paper [butyl alcohol–pyridine–water (6 : 4 : 3) as solvent and aniline hydrogen phthalate [21] as reagent]. Parallel experiments were made with calcium D-gluconate and D-glucono-1,4-lactone, in a 1 : 2 molar relationship with cerium(IV) sulphate. The production of arabinose as a function of time is recorded in Figures 1 and 2. 3-Deoxy-D-*arabino*-hexono-1,4-lactone was oxidized in a similar manner at 37 °C in M-sulphuric acid. Samples were withdrawn at intervals and the reaction stopped by neutralization with an excess of barium carbonate. The 2-deoxy-D-*erythro*-pentose produced was determined by the Dische (diphenylamine) reaction.[22]

Degradation products of arabinose were analysed by paper chromatography with the following solvent systems: (*a*) butyl alcohol–pyridine–water (6 : 4 : 3) and (*b*) butyl alcohol–ethanol–water (10 : 4 : 4). Spots were detected with silver nitrate–sodium hydroxide [23] and aniline hydrogen phthalate.[21] The aldoses were reduced with sodium borohydride in aqueous solution to the corresponding alditols, which were acetylated with acetic anhydride–pyridine (1 : 1 v/v). G.l.c. of the alditol acetates was carried out on stainless steel columns (183 × 2.3 cm) packed with (1) 10% EGS on Chromosorb W (80—100 mesh) (injection temp. 270 °C, detector temp. 300 °C, column temp. 215 °C) or (2) 10% NPGS on Chromosorb G (injection temp. 270 °C, detector temp. 300 °C, column temp. 180—215 °C, programmed at 4 °C min^{-1}), with nitrogen flow rate 30 ml min^{-1}.

Rate Determinations.—The rates of reactions were determined by following the disappearance of cerium(IV) by measuring the optical density change at 380 nm.[24] At this wavelength all other reactants and products gave negligible absorption. The mixture always contained a large excess of D-glucono-1,5-lactone or calcium D-gluconate. The first-order constants k_1 were calculated from slopes of the plots of log c_0/c against time (t) (c_0 = [Ce^{IV}] at $t = 0$; c = [Ce^{IV}] at time t) (Table 1). Average values were obtained from duplicate or triplicate runs; the mean standard deviation is never greater than 2%.

Radical Mechanism Evidence.—To a buffered (pH 8.9) 19% solution (3 ml) of acrylamide was added 0.05M-D-glucono-1,5-lactone in 0.1M-cerium(IV) sulphate in M-sulphuric acid (4 ml). Polymerization was shown by gelification after 3—5 min at 25 °C.

Effect of Sulphuric Acid.—Rate determinations were effected at sulphuric acid concentrations of 1.0M, 1.5M, 2.0M, and 2.5M. In all cases an excess of D-glucono-1,5-lactone was present in order to obtain first-order rate constants, k_1, from which K and k were derived. Cerium(IV) consumption was determined spectrophotometrically (Table 3).

Isolation of D-*Arabinose from the Oxidation Mixture.*—D-Glucono-1,5-lactone (0.5 g) was oxidized with 0.192M-cerium(IV) sulphate solution (29 ml) (molar ratio 1 : 2) under nitrogen. After 45 min at 37 °C the reaction was stopped by neutralization with barium carbonate. The filtrate was evaporated to a syrup, which was extracted twice with small portions of hot methanol in order to remove salts. The methanolic solution was evaporated to a syrup, from which chromatographically pure D-arabinose (0.4 g, 94%) crystallized on addition of ethanol; m.p. and mixed m.p. 158—159°; $[\alpha]_D^{20}$ −107° (equilibrium value; c 1.0 in H_2O) {lit.,[25] m.p. 158—160°, $[\alpha]_D^{20}$ −105° ± 3° (H_2O)}.

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[21] C. M. Wilson, *Analyt. Chem.*, 1959, **31**, 1199.

[22] Z. Dische, *Mikrochemie*, 1930, **2**, 4.

[23] W. E. Trevelyan, D. P. Procter, and J. S. Harrison, *Nature*, 1950, **166**, 444.

[24] G. Haargreaves and L. H. Sutcliffe, *Trans. Faraday Soc.*, 1955, **51**, 1105.

[25] R. L. Whistler and J. N. BeMiller, *Methods Carbohydrate Chem.*, 1962, **1**, 71.