879. β-*Glucopyranosides of Hydroxymethyl- and Hydroxyethyl-ferrocene.*

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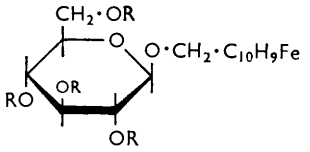
Synthesis and properties of ferrocenylmethyl and ferrocenylethyl β-D-glucopyranoside are described. The sensitivites of the compounds to dilute mineral acid have been investigated.

As a first step in the study of carbohydrate derivatives of ferrocene, ferrocenylmethyl β-D-glucopyranoside (Ia) has been prepared by the Koenigs–Knorr [1] reaction under the conditions recommended by Reynolds and Evans.[2]

Condensation of hydroxymethylferrocene with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver oxide and calcium sulphate yielded mainly ferrocenylmethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (Ib), with some di(ferrocenylmethyl) ether (II). Deacetylation gave yellow crystals of the glucoside (Ia) monohydrate. This was also prepared in low yield by reaction of D-glucose with hydroxymethylferrocene in the presence of toluene-*p*-sulphonic acid.[3]

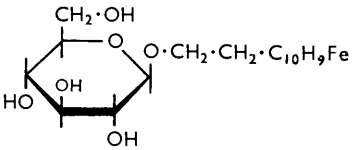
The structure of the glucoside (Ia) was proved by acidic and enzymic hydrolyses, methylation, and periodate oxidation. Potassium metaperiodate, in addition to reacting with the glucosyl residue, degraded the ferrocene nucleus, producing insoluble material which was probably a mixture of ferric hydroxide and ferric periodate or possibly potassium periodate adsorbed on ferric hydroxide. Ferric salts interfered with the periodate consumption (cf. Lang and Faude [4]), so the acetate (Ib) and the glucoside (Ia)



(I) a: R = H
b: R = Ac

$(C_{10}H_9Fe\cdot CH_2)_2O$

(II)



(III)

were oxidised in identical conditions and the periodate uptake by the glucosyl residue of (Ia) and the formaldehyde liberation were calculated by difference. In this way it was shown that the glucosyl group consumed 2 mol. of oxidant and produced no formaldehyde, consistently with a glucopyranoside structure. Methylation of the glucoside, followed by hydrolysis, yielded crystalline 2,3,4,6-tetra-*O*-methyl-D-glucose. Emulsin hydrolysed the glucoside to glucose and hydroxymethylferrocene, and this result together with the specific optical rotation of the compound ($[\alpha]_D^{22}$ −37·7°) confirms the view that the molecule is a β-glucopyranoside.

Table 1.

Hydrolysis of the glucoside (Ia; 0·0218M) in 0·048N-H_2SO_4.

Time (min.) ...	0	8	15	21	26	∞
α_D^{25}	−0·28° (calc.)	−0·04°	+0·05°	+0·11°	+0·13°	+0·18° (calc.)
k_1 (min.$^{-1}$)	—	0·088	0·083	0·088	0·084	—

0·048N-Sulphuric acid rapidly hydrolysed the glucoside at 25°, giving hydroxymethylferrocene, glucose, and di(ferrocenylmethyl) ether (II). The first-order rate constant for this reaction was $8·6 \times 10^{-2}$ min.$^{-1}$ (Table 1), which resembles the value for the hydrolysis

[1] Koenigs and Knorr, *Ber.*, 1901, **34**, 957.
[2] Reynolds and Evans, *J. Amer. Chem. Soc.*, 1938, **60**, 2559.
[3] Combs, McCloskey, Sundberg, and Coleman, *J. Amer. Chem. Soc.*, 1949, **71**, 276.
[4] Lang and Faude, *Z. anorg. Chem.*, 1937, **232**, 271.

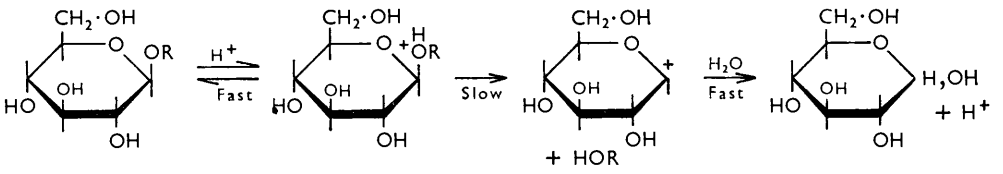
of a furanoside rather than a pyranoside.[5] The nature of the bond fission was therefore investigated by conducting the hydrolysis in the presence of $H_2{}^{18}O$. This indicated that the hydrolysis occurred predominantly by hexosyl–oxygen bond fission (Table 2). Similar results have been obtained by Bunton *et al.*[6,7] with methyl and phenyl glucopyranosides, methyl 2-deoxyglucopyranosides, and maltose. No conclusions can be drawn from the isotope experiments regarding the formation of the ether: it could be formed by direct reaction of a ferrocenylmethyl cation with the glucoside (Ia) or by further reaction of the hydroxymethylferrocene liberated in the hydrolysis.

TABLE 2.

	Fcn·CH_2·OH	Fcn·CH_2·O·CH_2·Fcn	Glucose *	Fcn·CH_2·OH (control)	Glucose (control)	Water
Abundance (atom %) †	0·35	0·25	0·93	0·18 ‡	0·18	1·11
Excess abundance (atom %) ...	0·17	0·07	0·74	0	0	0·93

* Calculated from the observed isotopic ratio on the assumption that only the 1-hydroxyl group was enriched. † ^{18}O atom % abundance is given by $100 - (2R + 1)$ when R is $[C^{16}O_2]/[C^{18}O^{16}O]$. ‡ Normal abundance.

Bunton *et al.*[6,7] have shown that the acidic hydrolysis of a number of glucopyranosides proceeds by the annexed mechanism. The alternative scheme whereby the cyclic oxygen atom is protonated and the carbonium ion is formed by ring-opening between $C_{(1)}$ and this oxygen atom is not favoured.



The rates of hydrolysis of some glucosides[8] increase as the aglycone residue is changed from a primary to a tertiary group. In some respects hydroxymethylferrocene has properties characteristic of a tertiary alcohol. For example, it is readily converted into an ether (II) in the presence of acid[9] and attempts to prepare its toluene-*p*-sulphonate in pyridine produce the 1-ferrocenylmethylpyridinium salt.[10] Bunton *et al.*[7] have recently shown that t-butyl D-glucopyranoside is rapidly hydrolysed by acid, but in this instance by alkyl–oxygen bond fission and not by the hexosyl–oxygen bond fission which occurs predominantly with ferrocenylmethyl β-D-glucopyranoside. Ferrocene has many properties characteristic of a highly activated benzene derivative,[11] so in the case of the glucoside (Ia) the ferrocene nucleus might be expected to increase the basicity of the exocyclic oxygen atom and thereby facilitate formation of the conjugate acid during hydrolysis. Nath and Rydon[12] showed that the introduction of electron-repelling groups into the aromatic ring of phenyl β-D-glucopyranoside increased the lability of this glucoside to acid, but comparatively slightly. Edward[13] suggested that phenyl glucosides are under strain. Thus the resulting lack of planarity may restrict the conjugate displacements in these molecules and the polar influences would then be small. A model of the glucoside (Ia) shows that there is no marked intramolecular steric pressure, and polar

[5] Pigman and Goepp. " Chemistry of the Carbohydrates," Academic Press Inc., New York, 1948, p. 206.
[6] Bunton, Lewis, Llewellyn, and Vernon, *J.*, 1955, 4419.
[7] Armour, Bunton, Patai, Selman, and Vernon, *J.*, 1961, 412.
[8] Veibel and Hjorth, *Acta Chem. Scand.*, 1952, **6**, 1353.
[9] Hauser and Cain, *J. Org. Chem.*, 1958, **23**, 2007.
[10] de Belder, Bourne, and Pridham, unpublished results.
[11] Pauson, " Non-Benzenoid Aromatic Compounds," Interscience Publ., Inc., New York, 1959, p. 123.
[12] Nath and Rydon, *Biochem. J.*, 1954, **57**, 1.
[13] Edward, *Chem. and Ind.*, 1955, 1102.

influences therefore presumably play the more important rôle in the stability of this compound to acid.

Ferrocenylethyl β-D-glucopyranoside, also prepared by the Koenigs–Knorr method, was virtually stable to 0·05N-sulphuric acid at 25° and was incompletely hydrolysed by this acid after 20 hr. at 70°. The greater stability of this glucoside (II) than of ferrocenylmethyl β-D-glucopyranoside (Ia) is presumably due to the additional carbon atom in the former which reduces the electrical influence of the ferrocene nucleus.

Further quantitative studies of the substitution of ferrocene and its derivatives may clarify the position and it is obvious that great care must be taken in assigning pyranoside or furanoside structures solely on the basis of stability to acid.

Experimental

Butan-1-ol–ethanol–water (4 : 1 : 5, v/v; organic layer) was used for the paper chromatography of sugars, and a system comprising two organic phases [14] for ferrocene derivatives.

Hydroxymethylferrocene.—This compound was prepared from (ferrocenylmethyl)trimethylammonium iodide,[15] as described by Hauser and Lindsay,[16] and, recrystallised from hexane, had m. p. 75—76° (lit.,[17] 76°).

Hydroxyethylferrocene.—Acetylferrocene was converted into this compound as described by Rinehart, Curby, and Sokol; [18] the product had m. p. 45—47° (lit.,[18] 49—50°) after recrystallisation from ether–hexane.

Ferrocenylmethyl 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside (Ib) (*Köenigs–Knorr Method*).—2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4·1 g.) in methylene chloride (30 ml.) was added slowly to a mixture of hydroxymethylferrocene (3·3 g.), silver oxide (9·2 g.), and calcium sulphate (5·0 g.) in methylene chloride (30 ml.), that was then shaken for 18 hr., filtered, and evaporated to dryness. The residue dissolved in hot methanol and on cooling gave a precipitate which when recrystallised from benzene–hexane afforded orange crystals of the *acetate* (Ib) (3·0 g., 54%), m. p. 183—185°, $[\alpha]_D^{21}$ −11·7° (*c* 1·0 in $CHCl_3$) (Found: C, 55·0; H, 5·8; Fe, 10·0; Ac, 31·3. $C_{25}H_{30}FeO_{10}$ requires C, 54·9; H, 5·7; Fe, 10·2; Ac, 31·5%).

Di(ferrocenylmethyl) Ether (II).—Fractionation of the methanolic filtrate from the Koenigs–Knorr reaction [remaining after the precipitation of the acetate (Ib)] on a column of alumina (with benzene, benzene–hexane, and benzene–chloroform) produced crystals of di(ferrocenylmethyl) ether (0·9 g.), m. p. 130—131° (lit.,[19] 129—130°) (Found: C, 63·3; H, 5·5. Calc. for $C_{22}H_{22}OFe_2$: C, 63·8; H, 5·4%).

Ferrocenylmethyl β-D-Glucopyranoside (Ia).—The acetate (Ib) (1·0 g.) was treated with 0·2N-sodium methoxide (1 ml.) in methanol–chloroform at room temperature for 24 hr. The resulting water-soluble fraction contained the *glucoside* (Ia) which after one recrystallisation from water was obtained as yellow plates of the monohydrate (0·4 g., 50%), m. p. 135—136°, $[\alpha]_D^{22}$ −37·7° (*c* 1·0 in H_2O) (Found: C, 51·8; H, 6·3; Fe, 14·1%; H_2O, 0·98 mol. $C_{17}H_{22}FeO_6,H_2O$ requires C, 51·5; H, 6·1; Fe, 14·1%).

Ferrocenylmethyl β-D-Glucopyranoside (Ia) (*Fischer Method*).—Hydroxymethylferrocene (0·1 g.), D-glucose (0·05 g.), and toluene-*p*-sulphonic acid (5 mg.) in dimethylformamide (5 ml.) were heated for 6 hr. at 80—90°. Fractionation of the mixture by partition chromatography on Whatman No. 3MM paper yielded a small specimen of the glucoside (Ia), m. p. 133—136°.

Hydrolysis of the Glucoside (Ia).—(a) *With Amberlite* IR-120 (H^+ *form*) *resin.* The glucoside (50 mg.) in 90% aqueous ethanol was shaken with the resin for 2 hr. at 80—90°. The resulting glucose and hydroxymethylferrocene were identified by paper chromatography.

(b) *With emulsin.* The glucoside (5 mg.) was incubated with emulsin solution (3 ml.) at 30° for 18 hr., and the products, glucose and hydroxymethylferrocene, were characterised by paper chromatography.

Methylation of the Glucoside (Ia).—Silver oxide (0·5 g.) was added during 30 min., with continual agitation, to the glucoside (0·2 g.) in dimethylformamide (5 ml.) and methyl iodide (1 ml.). Shaking was continued for 18 hr. and the product isolated by partition between water

[14] de Belder, Bourne, and Pridham, *Chem. and Ind.*, 1959, 996.
[15] Osgerby and Pauson, *J.*, 1958, 656.
[16] Hauser and Lindsay, *J. Org. Chem.*, 1956, **21**, 382.
[17] Broadhead, Osgerby, and Pauson, *J.*, 1958, 650.
[18] Rinehart, Curby, and Sokol, *J. Amer. Chem. Soc.*, 1957, **79**, 3420.
[19] Graham, Lindsey, Parshall, Peterson, and Whitman, *J. Amer. Chem. Soc.*, 1957, **79**, 3416.

and chloroform. The methylation was repeated and the product isolated as a syrup (0·1 g.) that was dissolved in N-hydrochloric acid (10 ml.); steam was passed through this solution for 30 min. After cooling, hydroxymethylferrocene was removed by extraction with ether. The hydrolysate was then saturated with sodium sulphate and extracted with chloroform. The chloroform solution was decolorised with charcoal, dried ($MgSO_4$), and concentrated to a syrup. 2,3,4,6-Tetra-*O*-methyl-D-glucose (40 mg.), m. p. 96—97°, mixed m. p. 95—97°, was obtained from a light petroleum (b. p. 40—60°) solution of this, and its identity was confirmed by paper chromatography.

Periodate Oxidations.—The glucoside (Ia) (10—20 mg.) was dissolved in dioxan (20 ml.), and 0·02M-potassium metaperiodate (30 ml.; adjusted to pH 7) was added. Samples (3 ml.) were removed at intervals and the periodate uptake and formaldehyde liberation determined by the methods of Fleury and Lange [20] and O'Dea and Gibbons,[21] respectively. The experiment was repeated with the acetate (Ib).

Time (hr.)	5	8	10
Periodate consumed (mol.) : acetate (Ib)	10·5	11·5	11·5
glucoside (Ia)	12·0	13·5	13·5

Kinetic Measurements.—The acidic hydrolysis at 25° was followed by dissolving the glucoside (Ia) in water (25 ml.), then adding N-sulphuric acid (1·25 ml.). At intervals samples (5 ml.) were withdrawn, neutralised with 0·05N-ammonia, and centrifuged and the optical rotations of the solutions were then measured. The hydrolysis was carried out with the glucoside at 0·0218M-concentration (Table 1). Errors between calculated and observed values by this procedure were generally less than 4%.

Hydrolysis of Glucoside (Ia) *in the Presence of* $H_2{}^{18}O$.—The glucoside (*ca.* 0·4 g.) was dissolved in ^{18}O-enriched water (30 ml.; 0·8 atom %). N-Sulphuric acid (1·5 ml.) was added. The solution was left at room temperature for 45 min., then extracted with benzene. The aqueous layer was shaken with an excess of barium carbonate, filtered, and treated with Biodeminrolit (carbonate form). After filtration and freeze-drying the resulting glucose crystallised from methanol–water–propan-2-ol (m. p. 149—152°). The benzene layer was washed with water and dried (K_2CO_3). Fractionation on an alumina column yielded hydroxymethylferrocene (40 mg.), m. p. 74—76°, and di(ferrocenylmethyl) ether (50 mg.), m. p. 130—131°.

Control experiments with β-D-glucose and hydroxymethylferrocene were carried out under the same conditions.

All compounds were analysed isotopically as carbon dioxide.[22]

Ferrocenylethyl β-D-*Glucopyranoside* (III).—Hydroxyethylferrocene (0·39 g.) in methylene chloride (3 ml.) was added to 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0·62 g.), silver oxide (0·5 g.), and calcium sulphate (0·5 g.) in methylene chloride (5 ml.), and the mixture was shaken for 20 hr. Filtration followed by removal of the solvent left a residue which was dissolved in methanol. 0·1N-Sodium methoxide (1 ml.) was then added and the products were partitioned between water and chloroform. The aqueous layer was freeze-dried and the residual *glucoside* (0·1 g.) (III) crystallised from water; it had m. p. 174°, $[\alpha]_D^{23} - 28°$ (*c* 0·3 in H_2O) (Found: C, 55·3; H, 6·1. $C_{18}H_{24}FeO_6$ requires C, 55·1; H, 6·2%).

Hydrolysis of Glucoside (III).—(a) *With acid.* The glucoside (10 mg.) was dissolved in 0·05N-sulphuric acid (10 ml.) at 25° and samples (1 ml.) were removed at intervals, neutralised with barium carbonate, and examined for glucose on paper chromatograms. This experiment was repeated at 70°.

(b) *With emulsin.* This was carried out under the conditions described for the hydrolysis of the glucoside (Ia). The resulting glucose and hydroxyethylferrocene were identified by paper chromatography.

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[20] Fleury and Lange, *J. Pharm. Chim.*, 1933, **17**, 107.
[21] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.
[22] Doering and Dorfman, *J. Amer. Chem. Soc.*, 1953, **75**, 5595.