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Note

The Hofer–Moest decarboxylation of D-glucuronic acid and D-glucuronosides

Jonathan A. Stapley† and James N. BeMiller*

Whistler Center for Carbohydrate Research, Purdue University, 745 Agriculture Mall Drive, West Lafayette, IN 47906-2009, USA

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Dedicated to the memory of Professor Nikolay K. Kochetkov

Abstract—Research was undertaken to effect the oxidative decarboxylation of glycuronosides. Experiments with free D-glucuronic acid and aldonic acids were also executed. Both anodic decarboxylation and variants of the Ruff degradation reaction were investigated. Anodic decarboxylation was found to be the only successful method for the decarboxylation of glucuronosides. It was, therefore, proposed that glycuronosides can only undergo a one-electron oxidation to form an acyloxy radical, which decomposes to form carbon dioxide and a C-5 radical, that is, a Hofer–Moest decarboxylation. The radical is subsequently oxidized to a cation by means of a second one-electron oxidation. The cation undergoes nucleophilic attack from the solvent (water), whose product (a hemiacetal) undergoes a spontaneous hydrolysis to yield a dialdose (*xylo*-pentodialdose from D-glucuronosides).

Keywords: Decarboxylation; D-Glucuronic acids; D-Glucuronosides; *xylo*-Pentodialdose; Xylitol

von Euler et al.[1] reported that uronoside polymers were decarboxylated by Ruff's reagent, but our attempts to decarboxylate poly(galacturonic acid) using Ruff degradation conditions[2,3] were unsuccessful. These unsuccessful attempts to apply the Ruff degradation to the decarboxylation of uronic acid-containing substances led us to consider the Hofer–Moest reaction[4] (Chart 1) for the oxidative decarboxylation of uronosides.

Both aldonic acids and uronosides were decarboxylated by the Hofer–Moest reaction.[5] In the case of uronopyranosides, the ring oxygen atom is electron withdrawing, and the resulting cation (C-5) is stabilized as a carboxonium ion. The uronoside structure thus facilitates the reactions of the Hofer–Moest type. Chart 2 presents the mechanism as applied to a D-glucuronopyranoside (I). In this scheme, intermediate II is a hemiacetal, which upon hydrolysis (ring opening), by the concerted mechanism shown, produces III (*xylo*-pentodialdose) spontaneously. Electrolytic decarboxylation, that is, the Hofer–Moest reaction, has been exploited in the production of xylitol via reduction of *xylo*-dialdose produced by the decarboxylation of glucuronosides.[6]

Using the crude apparatus described in the Experimental section of this paper, methyl β-D-glucuronopyranoside (aqueous solution) was converted into *xylo*-pentodialdose at a rate of 1.5×10^{-3} mol/h at a current efficiency of 1.8 kW mol/h. (Decarboxylations of sodium D-glucuronate and L-glucuronate in water, methanol, and aqueous methanol were somewhat more facile.)

Kitagawa and Yoshikawa,[7] in a review of uronic acid glycoside cleavage, discussed the anodic decarboxylation of 2,3,4-tri-*O*-methyl-D-glucuronopyranosides in methanol. Their reaction products and proposed mechanism are consistent with Chart 1 ($R^2 = Me$). Francisco et al.[8] chemically decarboxylated similar starting materials and reported analogous products, proposing the same mechanism. Weiper and Schäfer[9] reported the decarboxylation of 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hex-2-ulopyranosonic acid and 2,3:4,6-di-*O*-iso-

* Corresponding author. Tel.: +1 765 494 5684; fax: +1 765 494 7953; e-mail: bemiller@purdue.edu
† Present address: Dynamic Food Ingredients Corp., 127 10th Street, Kirkland, WA 98033, USA.

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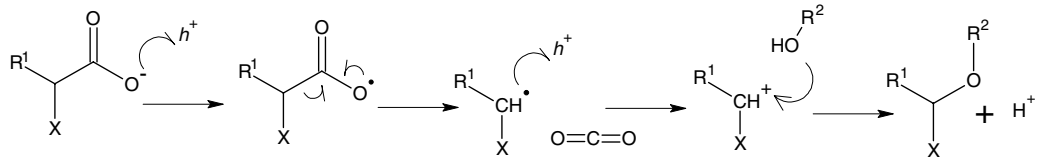

Chart 1. Hofer–Moest decarboxylation; h^+ symbolizes an anode.

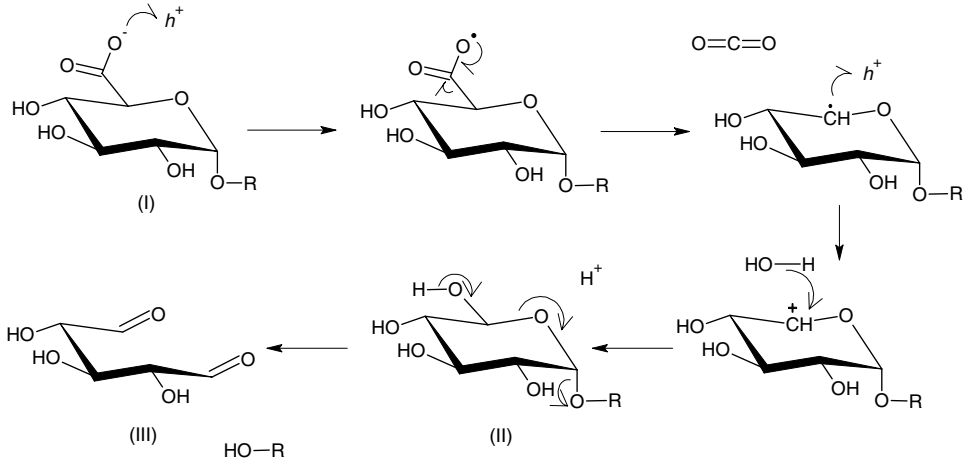

Chart 2. Hofer–Moest decarboxylation of a D-glucuronopyranoside.

propylidene-β-L-*xylo*-hex-2-ulofuranosonic acid in methanol to yield ortho-esters. Kitagawa et al.[10–12] oxidized D-glucuronic acid (IV) in methanol anodically and obtained V (Chart 3), which was used as a synthetic intermediate. [In water, the ring of V would open (analogously to II → III, the methoxyl of C-1 and the hydroxyl of C-5 being reversed) yielding *xylo*-pentodialdose.] Renaud et al.[13] reported that the electrolytic decarboxylation of α-hydroxy acids in methanol yields aldehydes.

First, we examined the efficacy of the standard [Fe(II)] Ruff reagent for the decarboxylation of D-glucuronic acid. HPLC chromatograms (not given) indicated that no decarboxylation occurred, that is, that D-glucuronic acid is resistant to decarboxylation by both Fe and Cu variations of the reaction. Extended reaction times (135 and 146 min for a complete consumption of hydrogen peroxide, respectively, more than 10 times the duration of the Cu(II)–D-gluconate reaction) suggested that the hydrogen peroxide is not decomposed as a result of a Ruff degradation type of reaction.[14]

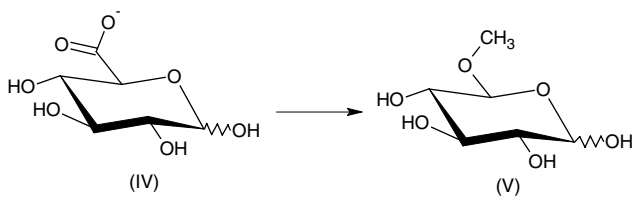

Chart 3. Methanolic Hofer–Moest decarboxylation of D-glucuronic acid.[8–10]

Both methyl β-D-glucuronopyranoside and methyl α-D-glucuronopyranoside were subjected to the Cu(II) variant (the most efficient varient[14]) of the Ruff degradation reaction to determine whether uronosides might form stable complexes that are resistant to chemical decarboxylation and if the anomeric oxygen atom might participate in such complexes. In both cases, the reaction times were further extended (250 and 238 min for a complete consumption of hydrogen peroxide, respectively). Even so, HLPC indicated that no change in the carbohydrate occurred. It was thus determined that the configuration of the anomeric carbon atom (orientation of the aglycon) was not the impediment to the reaction of interest.

Colors of the reaction mixtures when Cu(II) was used as the catalyst suggested that a decarboxylation-resistant complex is formed. For example, equimolar solutions of sodium D-gluconate, sodium D-glucuronate, and the sodium salt of methyl D-glucuronopyranoside containing equimolar concentrations of Cu(II) ion were made; the pH of the solutions was adjusted to 7, and hydrogen peroxide was added. Upon the addition of hydrogen peroxide to the D-gluconate solution, it turned blue and effervescence occurred immediately. The D-glucuronate solution was blue-green; there was no effervescence upon addition of hydrogen peroxide. The methyl β-D-glucuronopyranoside solution was yellow-green;

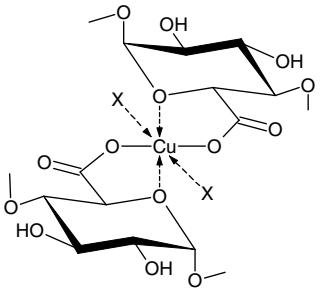

Chart 4. Potential structure of a mononuclear Cu(II) glucuronoside complex.[20]

neither did it effervesce upon the addition of hydrogen peroxide.

Uronates form complexes quite dissimilar from those of aldonates.[14] While hexuronic acids have a hydroxyl group adjacent to their carboxylic acid group, that α-hydroxyl group (C-5) becomes the endocyclic oxygen atom when the pyranose ring forms. The pyranose ring form is favored in aqueous solutions but is in constant equilibrium with its open chain state, as copper ions catalyze mutarotation.[15] Even so, no Ruff degradation occurs.

While there is conflicting data on D-glucuronate–Cu(II) systems,[16–20] there is consensus that D-glucuronate forms a complex with Cu(II) in such a manner that only the carboxylate group participates as a ligand. There is also a substantial amount of similar evidence that the endocyclic oxygen atom of the pyranose ring, but no hydroxyl groups, participate in the coordination, forming a complex similar to the salt bridges formed when polyuronates gel (Chart 4).

The observations that the Ruff degradation is successful on all aldonic acids and unsuccessful on uronic acids and their glycosides suggest that uronic acids and their glycosides cannot form the $M_1L_2H_{-2}$ complex necessary for decarboxylation.[14] We, therefore, turned to the actual Hofer–Moest reaction (oxidative decarboxylation at the anode of an electrochemical cell) to decarboxylate uronosides. As already stated, anodic oxidative decarboxylation was quite successful in removing the carboxylate carbon atom as CO_2 and producing an aldehydo group from the α-carbon atom (C-5).

1. Experimental

1.1. Equipment

A Dionex 500 Chromatography System equipped with a GP40 Gradient Pump, an ED40 Electrochemical Detector, and PeakNet chromatography systems management software (Dionex Corporation, Sunnyvale, CA) was equipped with a PA10 column, a PA10 guard column, and a 20-μL sample loop. Samples were prepared by dilution to ~0.1 mg/mL with double distilled (dd) water and filtering through a 0.2-μm filter. A gradient of (a) 0.100 M sodium hydroxide and (b) 0.100 M sodium hydroxide with 1.00 M sodium acetate was used for elution.

A 5890 Series II gas chromatograph (Hewlett–Packard Company, Palo Alto, CA) equipped with a J&W DB-5 30 m × 0.250-mm, 0.25-μm column (Agilent Technologies, Palo Alto, CA) was used. Samples were prepared by adding Tri-Sil reagent (200 μL, Pierce Chemical Co., Rockford, IL) to approximately 0.1 mg dried sample and heating 20 min at 80 °C. Reaction mixtures were then evaporated to dryness with air, dissolved in hexane (100 μL), dried again, and re-dissolved in hexane (100 μL).

1.2. *xylo*-Pentodialdose

Aspects of several different approaches[21–23] were combined in the preparation of a standard sample of *xylo*-pentodialdose. 1,2-*O*-Isopropylidene-α-D-glucofuranose (2.20 g) and sodium hydrogen carbonate (0.50 g) were added to a 25-mL beaker equipped with a stir bar. The reagents were dissolved in dd water (15 mL), after which sodium meta-periodate (2.36 g) was added portionwise. After 10 min, the soln remained oxidative (starch–iodide test). Sodium thiosulfate (0.05 g) was added until the soln was no longer oxidative. The soln was then filtered and extracted five times with chloroform. The extract was dried over anhydrous sodium sulfate and evaporated to dryness at 50 °C in a rotary evaporator. Trifluoroacetic acid soln (50 mL, 20% v/v) was added, and the soln was heated at 80 °C with stirring for 1 h and then evaporated to dryness in a rotary evaporator at 50 °C. Water (dd, 25 mL) was added, and subsequently evaporated to dryness at 50 °C. The dry residue was rinsed with 95% ethanol. Another 25 mL of dd water was added, and the soln was again evaporated to dryness at 50 °C in a rotary evaporator. One major HPLC peak was present.

Concentrated *xylo*-pentodialdose contains a mixture of hemiacetal forms. This preparation and those produced electrochemically from methyl β-D-glucuronopyranoside were reduced, both using sodium borohydride and by catalytic (Raney nickel) hydrogenation, to xylitol. Characterization via comparison of HLPC elution time (single peak), mp, and mixed mp (93–94 °C)[24] using an authentic xylitol standard indicated that the product was xylitol.

1.3. Electrolytic cell and electrolysis

The electrolytic cell used in this research was fabricated from a 50-mL polypropylene centrifuge tube. Two centimeters of a 7-cm graphite rod (0.312-12-GR008G, Graphtek, LLC., Buffalo Grove, IL) were electroplated

with copper. An insulated copper wire was soldered to the electroplate and secured with epoxy resin. This graphite rod was placed through two holes at the base of and through an axis of the centrifuge tube. The graphite rod was secured with epoxy resin.

A 5-cm piece of stainless steel rod (2 mm diam) was soldered to an insulated copper wire, which was secured with epoxy resin. The steel rod was placed through two holes close to the top of and though an axis of the centrifuge tube and secured with melted polypropylene. The inlet and outlet were fashioned from 250-μL pipette tips, which were affixed to holes in the centrifuge tube with epoxy resin just above the stainless steel cathode at the top and the graphite anode at the bottom of the tube. Glass wool was placed in the cell under the anode and at the inlet. Graphite pieces were created by crushing another piece of the graphite rod and sieving; 15 g of graphite pieces that were collected between No. 9 and No. 2 US sieves were placed into the cell.

Throughout the experiments a silver/silver chloride reference electrode (RE-5b, Bioanalytical Systems, Inc., West Lafayette, IN) was placed at a depth of 4 cm from the top of the cell. The anode and cathode were connected to a SP-2 potentiostat (SP-2, Bioanalytical Systems, Inc., West Lafayette, IN). The inlet and outlet were connected with tubing that passed through a peristaltic pump (Tris; Isco, Inc., Lincoln, NE).

The starting materials of the experiments were weighed into 150-mL Erlenmeyer flasks to which water (dd) was added. The reaction solution was then pumped from the Erlenmeyer flask in which it was prepared through the input of the electrolytic cell. After transferring an amount capable of sustaining constant flow, the pump was connected to the outlet. The amount of solution transferred was determined gravimetrically (i.e., by weighing the solution flask before and after the transfer). The reaction solution was circulated through the cell at a rate of 10 mL/min. The reactions were commenced by turning on the potentiostat. The solutions were electrolyzed for approximately 3 h. Temperature and pH readings were periodically taken by placing the potentiostat on a standby and immersing a pH electrode into the cell. In some cases, reaction mixtures were subjected to catalytic reduction after electrolysis. The reaction solutions were evacuated from the cell, pooled with rinses and brought to standard volumes. To approximately 30 mL of these solutions, freshly prepared Raney Nickel (1 g) was added. Hydrogen gas was subsequently bubbled through these mixtures at 50 °C for 1.5 h. Then, enough water (dd) was added to the reaction mixtures to bring them to 1 L. They were subsequently analyzed by HLPC. Reduction was complete in all cases.

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