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Partial Hydrolysis and Acetolysis of Cellotriose-1-C^{14} [1]

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Abstract: The chemical preparation and purification of cellotriose-1-C^{14} is described. Starting with inert cellotriose, the reaction sequence involved an oxidation to the aldonic acid followed by a Ruff degradation, cyanohydrin addition using sodium cyanide-C^{14}, hydrolysis of the resulting nitrile, lactonization, and subsequent reduction with sodium amalgam. The resulting cellotriose-1-C^{14}, after purification, was used in a series of experiments wherein the ratio of the hydrolysis rates of the two glycosidic bonds within the molecule was determined. The ratio was measured using 14.2 *N* (50%) sulfuric acid at 30° and 0.5 *N* sulfuric acid at both 90 and 120°; in all cases the ratio of the hydrolysis rate of the bond at the nonreducing end of the molecule (k_2) to that at the reducing end (k_1) was 1.5. At 120° in 0.5 *N* sulfuric acid, the hydrolysis rate of cellotriose ($k_1 + k_2$) was 0.126 min^{-1}. Thus k_1 = 0.050 min^{-1} and k_2 = 0.076 min^{-1}. When cellotriose-1-C^{14} underwent acetolysis, however, the ratio of cleavage rates was reversed, and a threefold preference was observed for cleaving the glycosidic bond at the reducing end of the molecule.

The hydrolysis of glycosides in acidic solution is a reaction well known to the organic chemist. From the numerous studies available concerning this reaction, it is evident that among conformationally stable glycosides, rate of hydrolysis depends on the structure of the glycone; inductive effects in the aglycone have but little effect on rate.[3] Recent critical reviews and interpretations[4-7] on this subject conclude that the major rate-controlling factors are steric diequatorial intramolecular interactions within the glycone. When the cellotriose molecule, which is composed of three β-D-glucopyranose units linked 1→4, is examined in the light of this conclusion, it is apparent that the two glycosidic bonds within the molecule are different. The prediction would be made that the rate of hydrolysis of the glycosidic bond at the nonreducing portion of the molecule, which is controlled by a D-glucopyranose structure, would be faster than that at the reducing end, the rate of which is controlled by a more bulky glycone containing two D-glucopyranose residues. It would also be expected that the rate of hydrolysis of the glycosidic bond at the nonreducing end of cellotriose would approximate that of cellobiose.

This communication reports a series of experiments wherein the above conclusions and predictions were tested. The experiments involved the measurement of the rate of hydrolysis of cellotriose in 0.5 *N* sulfuric acid at 120°, and measurement, under the same conditions, of the ratio of the hydrolysis rates of the two glycosidic bonds within the molecule. This ratio was also measured in 0.5 *N* sulfuric acid at 90° and in 14.2 *N* (50.0%) sulfuric acid at 30°. In order to measure the ratio of the two rate constants, it was necessary to employ a cellotriose molecule labeled specifically at one end.

The compound used was cellotriose-1-C^{14}, that is, the trisaccharide in which the reducing unit was D-glucose-1-C^{14}. It was synthesized from inert cellotriose obtained by a previously described method,[8] using essentially the procedures developed by Isbell, *et al.*, in their synthesis of specifically labeled disaccharides.[9] It was purified by acetylation and chromatographed on silica gel. The resulting crystalline acetate was deacetylated and the sugar further purified by preparative paper chromatography. The final cellotriose-1-C^{14} preparation, after dilution and crystallization, contained less than 0.5% of radiochemical contamination by mannose, glucose, and cellobiose. That it contained negligible epimer, which could have been produced during the cyanohydrin addition, was verified by the finding of insignificant quantities (less than 1%) of radioactive mannose in total hydrolysates of the material.

Labeled cellotriose was partially hydrolyzed to give a maximum yield of cellobiose in excess of 20%; ap-

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preciable quantities of cellotriose and D-glucose were also present. The hydrolysis mixture was acetylated and the resulting acetates were separated on a silica gel column. It was demonstrated with thin layer chromatography that both α- and β-cellobiose octaacetate and α- and β-cellotriose[10] hendecaacetate were all present in the acetylated hydrolysis mixture. However, the α anomers predominated in the charge to the column, and the crystallized products were the pure α-acetates in all cases.[11]

Like hydrolysis, acetolysis is frequently used to fragment glycosides, particularly to convert polysaccharides to fully acetylated monomers.[12] This reaction was applied to cellotriose-1-C^{14} using an isolation procedure similar to that used in the hydrolysis experiments. The ratio of the hydrolysis rates of the two bonds was calculated from the specific activities of the isolated acetates as above.

Results and Discussion

The specific activities of the homologous acetates obtained from the various experiments are given in Table I. All analyses were made on crystalline compounds, prepared by recrystallization of material separated by column chromatography. For each run, the particular time used was that thought to give the maximum yield of radioactive cellobiose, which is approximately 25%. The ratio listed, k_2/k_1, is the ratio of the cleavage rate of the bond at the nonreducing end to that of the bond at the reducing end. It was calculated from the specific activities of isolated acetate cellobiose and cellotriose using eq 5 of the Appendix.

Table I. Specific Activities of Oligosaccharide Acetates Obtained from the Cleavage of Cellotriose-1-C^{14}

	1[a]	2[a]	3[b]	4[c]	5[d]
Cellotriose hendecaacetate	0.218	0.216	0.212	0.220	0.218
Cellobiose octaacetate	0.135	0.127	0.131	0.129	0.055
D-Glucose pentaacetate	...	0.073	0.071	0.063	0.119
Ratio k_2/k_1	1.65	1.43	1.61	1.43	0.345

[a] Hydrolysis at 120°, 0.50 N H_2SO_4, 10 min. [b] Hydrolysis at 90°, 0.50 N H_2SO_4, 2.5 hr. [c] Hydrolysis at 30°, 14.2 N H_2SO_4 (50%), 19 hr. [d] Acetolysis at 27°, HOAc–Ac_2O–H_2SO_4 (10:10:1), 43 hr.

Since the same sample of cellotriose-1-C^{14} was used for all the experiments, the variability of the technique can be estimated from the variation in reported values for the specific activity of the radioactive cellotriose hendecaacetate for this was always recovered without dilution. The range of the variation for these samples is 0.008 μcurie/mmole, approximately 4% of the average value. The similar range for the dimers recovered from the hydrolysis runs is also 0.008 μcurie/mmole, with the maximum difference occurring between duplicate runs. It must be concluded that the specific activity of the dimer is constant, and differences in the individual ratios only reflect the chance differences of the experimental technique. The relative rate of cleavage of the two bonds is constant, varying neither with temperature nor acid concentration. The value calculated from the averaged values of the biose and triose acetates is 1.53, which is, as predicted, greater than unity. It is a small effect, however, even among the normally small variations encountered in glycoside hydrolysis.

The rate of disappearance of cellotriose was obtained indirectly by measuring the rate of increase of the reducing power of a hydrolyzing solution. Since this increase is partially due to the hydrolysis of cellobiose generated from the reacting cellotriose, it was also necessary to measure the stability of the dimer at the same conditions. By supposing the reactions to be kinetically first order, the hydrolysis rate for cellotriose, $k_1 + k_2$, can be obtained through eq 6 as described in the Appendix. The method is inherently inaccurate: errors in the direct determination are greatly magnified in the derived result, particularly in the early stages of hydrolysis. This was offset to some extent by increasing the number of data points. The procedure is inapplicable at high acid concentrations because of the formation of reversion products, but at the dilute acid level employed here this is unimportant.

The hydrolysis rate of cellotriose was found to be 0.126 min^{-1} at 120°, in 0.5 N sulfuric acid. Since the ratio of k_2/k_1 is 1.53, the individual bond dissociation rates are $k_1 = 0.050\ min^{-1}$ and $k_2 = 0.076\ min^{-1}$. Cellobiose under the same conditions had a decomposition rate of 0.088 min^{-1}. Thus, the stability of the glycosidic bond at the nonreducing end of cellotriose is somewhat greater than that of the cellobiose bond. This small increase of 14%, if significant, must be attributed to the difference in the aglucone. Whether it is the result of an electronic inductive effect or some steric interaction or shielding is unknown.

It is interesting that the bond cleavage ratio is the same for hydrolysis both in 50 and 5% sulfuric acid. This would indicate that the supposed conformational stability of the β-linked oligomer in dilute acid solution extends to strong acid medium, a fact of particular importance for the interpretation of cellulose hydrolysis data. From the standpoint of intramolecular interactions which might occur during hydrolysis, there are a number of structural similarities between cellotriose and cellulose in solution. Both are presumably conformationally stable compounds in which the glucose substituents possess the bulkiest groups in equatorial positions. The nonreducing end of the cellotriose molecule contains an unsubstituted D-glucopyranose residue, and the glycosidic bond adjacent to this end hydrolyzes fastest, while the hydrolysis rate of the bond at the reducing end of the molecule is slower and is partly controlled by a glucose residue containing more bulky residues. Such residues would also be expected to influence the hydrolysis of the soluble cellulose molecule, that is, the glycosidic bond at the nonreducing end would hydrolyze faster than the internal bonds, which would all hydrolyze at the same rate. Thus, the two kinetic constants, describing the hydrolysis of cellotriose, would completely describe the homogeneous hydrolysis of cellulose.

(10) The β anomer of this compound has never been reported. Its identity was assumed on the basis of its chromatographic flow rate and the fact that it was produced in conjunction with the known α anomer by acetylation of cellotriose.

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Freudenberg and Blomquist[13] measured the rate of hydrolysis of solubilized cellulose, cellotetraose, cellotriose, and cellobiose in 51% sulfuric acid. Measurements on the series were extended to cellopentaose and cellohexaose by Wolfrom and Dacons.[11] Although it was not possible for these investigators to obtain the individual bond cleavage rates, their data may be satisfactorily correlated with the above model assuming a rate ratio between 2.5 and 3.0. This is considerably greater than the value of 1.5 reported here. The presence of reversion products in the strong acid medium may have introduced serious errors into the work of these investigators.

No other measurements of the hydrolysis rates of this series of oligomers are available, although Holló, *et al.*,[14] found during the acid hydrolysis of isotopically labeled amylose that the glucose unit at the nonreducing end of the molecule was removed more rapidly than that at the reducing end. It also appeared that hydrolysis of the α-linked oligomers could not be described by as simple a model as that proposed here for the β-linked series.

The finding (Table I) that the acetolysis reaction shows a threefold preference for cleaving the glycosidic bond at the reducing end of the molecule is surprising and unexpected. This suggests that although both hydrolysis and acetolysis occur in acidic solution, the reaction mechanisms may not be the same. An examination of the reaction mixture (thin layer chromatography) showed the only visible products to be the fully acetylated α-D-glucose, α-cellobiose, and α-cellotriose. Reports have appeared concerning the presence of isolable quantities of acyclic heptaacetates in acetolysates of hexosans,[15] but no evidence of these structures could be seen in reaction mixtures encountered here. Thus, the fragments isolated and counted were representative products of the reaction.

Sufficient information concerning the character of glycosidic hydrolysis and acetolysis reactions is available to indicate that either the mechanism or the steric factors which control bond cleavage could be different. Available evidence now indicates that hydrolysis occurs through a cyclic carbonium ion intermediate.[3] This concept was recently strengthened by the findings of Capon[16] who found conclusively that the methyl D-glucosides are anomerized in fully deuterated methanolic methanesulfonic acid with virtually complete exchange with the solvent. Under acetolytic conditions, on the other hand, most glycopyranosides are anomerized (presumably intramolecularly) at a much faster rate than they are acetolyzed.[17] Lindberg has examined this reaction kinetically in some detail and has concluded that ring opening occurs prior to loss of the aglycone group. The acyclic intermediates can give rise to anomers or to open-chain acetates. Reaction sequences and intermediates such as these, which are very different from those that occur during hydrolysis, could account for the difference in specificity.

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(15) R. L. Whistler, E. Heyne, and J. Bachrach, *J. Am. Chem. Soc.*, 71, 1476 (1949).
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Experimental Section

Materials and Methods. Acetylated oligomers were chromatographically examined using silica gel thin layer plates with benzene–methanol (9:1) as irrigant. Spots were visualized by spraying with 10% sulfuric acid in ethanol followed by charring at 110°. Paper chromatography of oligosaccharides utilized the irrigants, ethyl acetate–acetic acid–water (3:1:1), ethyl acetate–pyridine–water (10:4:3), or ethyl acetate–acetic acid–water (3:1:3, upper phase), in connection with the usual spray reagents.[18,19] Quantitative paper chromatographic analyses were performed using the procedures of Saeman, *et al.*,[20] in conjunction with the colorimetric method described by Nelson.[21] Redistilled technical grade benzene and "99%" ethyl acetate were used in the column chromatographic separations. Specific activities of compounds were determined by scintillation counting using a Model No. 3003 Packard Tricarb spectrometer.

O-β-D-Glucopyranosyl-(1→4)-O-β-D-glucopyranosyl-(1→3)-D-arabinose (I). This compound was prepared from cellotriose using the procedure similar to that reported by Isbell and coworkers[22] for the conversion of D-glucose-6-C^{14} to D-arabinose-5-C^{14}. In this preparation, 900 mg of cellotriose, mp 192°, $[\alpha]^{25}D$ +21.7° (*c* 3.4, water), gave 180 mg of syrupy product. Paper chromatograms of this material showed a major spot having the same R_f value and color reactions that Beelik and Hamilton[23] report. Traces of glucose and arabinose were also visible, but no cellotriose was present. Complete acid hydrolysis of this compound produced glucose and arabinose (paper chromatography).

Cellotriose-1-C^{14}. The procedure followed in this synthesis was similar to that described by Frush and Isbell[9] for the synthesis of lactose-1-C^{14} without isolation of the intermediate products. Compound I (134 mg, 0.283 mmole) in 5 ml of water was treated with an equimolar quantity of sodium cyanide-C^{14} (330 μcuries) using a sodium carbonate buffer. After a 24-hr reaction, the resulting nitrile was hydrolyzed in solution by heating at 80° for 5 hr. The solution was then passed through a column of Dowex-50 (H) and the effluent repeatedly evaporated to dryness from Cellosolve. After vacuum desiccation overnight, the resulting syrup did not crystallize, but gave a positive lactone test. Paper chromatograms indicated that compound I had completely reacted. The syrup was dissolved in 5 ml of water containing 0.19 g of sodium hydrogen oxalate and reduced with 0.6 g of 5% sodium amalgam. Evaporation of the deionized reduction solution gave 30 mg of syrup which was found to be largely cellotriose. The syrup was diluted with 500 mg of carrier cellotriose and the mixture crystallized from water–ethanol. The dried crystals (480 mg) were acetylated by stirring with acetic anhydride (25 ml) containing zinc chloride (200 mg) at 50° for 2 hr. The resulting clear acetylation solution was evaporated to dryness; the residue was washed several times with cold water by decantation and dried. This material was dissolved in 30 ml of benzene–ethyl acetate (1:1), applied to a 6.5 × 60 cm silica gel column, and eluted with a total of 10 l. of the above solvent. Pertinent fractions were pooled and evaporated; the residue was crystallized from chloroform–ether to give hendeca-*O*-acetyl-α-cellotriose, 367 mg, mp 216–217°, 18.09 μcuries/mmole. Crystalline α-cellotriose was obtained by deacetylation.[11] Paper chromatographic analysis of both the cellotriose and acid hydrolysates thereof indicated that contaminating cellobiose-C^{14}, mannose-C^{14}, and glucose-C^{14} represented less than 1.5% of the total radiochemical activity of the preparation. Approximately 15% of the total activity was found at the origin on the paper chromatograms and persisted even after hydrolysis of the preparation. This impurity, which was not identified, was removed by preparative paper chromatography. Approximately 90 mg was streaked on four sheets of Whatman 3MM paper, each 20 cm in width, and eluted for 72 hr with ethyl acetate–acetic acid–water (3:1:1). The resulting syrup, obtained by elution from the paper, was diluted with 1.6 g of inert carrier and crystallized from water–ethanol to give 1.5 g of crystals, specific activity 0.206 μcurie/mmole. This material was used in all subsequent radiochemical experiments.

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Acid Hydrolysis. In a typical experiment, 200 mg of the above cellotriose-1-C^{14} was dissolved in 2 ml of 0.5 *N* sulfuric acid and sealed in four 4-mm glass tubes which were heated for 10.0 min at 120°. At the end of this time, the tubes were immersed in tap-water to quench the reaction and opened; the contents were washed into a 25-ml beaker and neutralized with an excess of barium carbonate. The resulting suspension was filtered through Celite, and the filtrate was evaporated to dryness. The residue was acetylated with acetic anhydride (10 ml) and zinc chloride (50 mg) as described above and the acetates of α-D-glucose, α-cellobiose, and α-cellotriose were obtained in crystalline form after chromatography on a 3 × 45 cm silica gel column with a total of 3 l. of irrigant (ethyl acetate–benzene, 1:1). Approximately 30 mg of each compound was obtained, and 10-mg samples were used in duplicate radiochemical assays. The results are tabulated in Table I. The same procedure was used for both the hydrolysis at 90° in 0.5 *N* sulfuric acid where a hydrolysis time of 50 min was used and for the reaction in 50% sulfuric acid which was done at 30° and required 25 hr.

Acetolysis. Cellotriose-1-C^{14} (200 mg) was slurried with 10 ml of a solution composed of acetic acid–acetic anhydride–sulfuric acid (10:10:1 v/v) and stirred at room temperature for 3 hr, when a clear solution was attained. After standing for a total of 43 hr, the solution was poured into ice water, and sufficient barium carbonate was added to neutralize the sulfuric acid present. The slurry was evaporated to dryness, the residue extracted with boiling acetone and filtered, and the filtrate evaporated to give an amorphous residue. This material was applied to a 3 × 45 cm silica gel column and the acetates were isolated as described for the hydrolysates. The results are tabulated in Table I.

Hydrolysis Rates of Cellobiose and Cellotriose. Aliquots of 0.023 ml of a solution of 0.5 *N* sulfuric acid containing 5% of the disaccharide or trisaccharide were quantitatively injected into 1.5-mm capillary tubes. The tubes were sealed and heated, completely immersed, in an oil bath at 120 ± 0.02°. Tubes were removed periodically for analysis; the total reaction time was 5 min (about 50% decomposition). Tubes were quenched in cold water immediately upon removal. The total content of each ampoule was analyzed for reducing power.[21] The first-order rate constant for cellobiose was found to be 0.0881 min^{-1}. Following the procedure outlined in the Appendix, the decomposition rate for cellotriose was calculated to be 0.1260 min^{-1}; 19 data points were used.

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Appendix

Define k_1 as the first-order velocity constant for the hydrolysis of the glycosidic bond at the reducing end of cellotriose, k_2 as the hydrolysis rate constant for the remaining bond in cellotriose, and k_3 as the rate constant for the disappearance of cellobiose. These are the usual apparent first-order rate constants, the product of the bimolecular rate constant and catalyst acid concentration.

Let $X_n(t)$ represent the moles of inert *n*-mer and $X_n^*(t)$ the moles of radioactive *n*-mer ($n < 3$).

Assume (1) glucose is stable at the conditions under consideration; (2) at initial time, $(X_1)_{t=0} \equiv X_{10} = X_{10}^* = X_{20} = X_{20}^* = 0$; (3) at all times, $X_n \gg X_n^*$, $n = 1, 2, 3$. The following equations may be derived.[24]

$$X_3/X_{30} = X_3^*/X_{30}^* = \exp(-\{k_1 + k_2\}t) \quad (1)$$

$$X_2/X_{30} = [(k_1 + k_2)(X_2^*/X_{30}^*)]/k_2 = ((-)k_1 + k_2)[\exp(-\{k_1 + k_2\}t) - \exp(-k_3t)] \quad (2)$$

$$X_1/X_{30} = 3 - \{(k_1 + k_2 - 3k_3) \times [\exp(-\{k_1 + k_2\}t)] + 2(k_1 + k_2) \times [\exp(-k_3t)]\}/(k_1 + k_2 - k_3) \quad (3)$$

$$X_1^*/X_{30}^* = 1 - \{(k_1 - k_3)[\exp(-\{k_1 + k_2\}t)] + k_2[\exp(-k_3t)]\}/(k_1 + k_2 - k_3) \quad (4)$$

From eq 2

$$(X_2^*/X_2)/(X_{30}^*/X_{30}) = R/(R + 1) \quad (5)$$

where $R \equiv k_2/k_1$.

Note that it is unnecessary to assume first-order kinetics to obtain eq 5. Its validity only requires that the cleavage products of cellotriose be cellobiose and glucose and $X_{30} \gg X_{30}^*$.

Consider, now, the hydrolysis of an inert cellotriose sample and the increasing reducing power as reaction proceeds. The reducing strength of the solution expressed as equivalent glucose is

$$P = r_3X_3 + r_2X_2 + X_1 = (r_3X_3/X_{30} + r_2X_2/X_{30} + X_1/X_{30})X_{30} \quad (6)$$

where r_2 and r_3 are, respectively, the molar reducing power of cellobiose and cellotriose relative to glucose. For the modified Nelson–Somogyi method,[21] they have the values 1.071 and 1.088.

Substituting for X_2/X_{30} and X_1/X_{30} from eq 2 and 3 and replacing $\exp(-\{k_1 + k_2\}t)$ with X_3/X_{30}, the right side of eq 6 becomes an expression containing X_3/X_{30}, t, and the parameters k_3, r_2, r_3, and X_{30}. By its use, a set of (P, t) values may be converted to equivalent $(X_3/X_{30}, t)$ values. Data thus transformed can be analyzed in the usual manner.

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