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Note

Partial acetylation of methyl α-D-glucopyranoside with 1-acetylimidazole*

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This work was undertaken to assess the possible use of 1-acetylimidazole as a selective acetylating agent for sugars and their derivatives. It is shown, however, that unimolecular acetylation of methyl α-D-glucopyranoside with this reagent affords no significant selectivity and leads to partial substitution at all four hydroxyl groups.

The relative reactivities of hydroxyl groups in carbohydrates[1] toward substitution reagents under kinetic and thermodynamic conditions is a subject of considerable theoretical complexity[2], but the practical utility of partial substitution-reactions displaying a measure of selectivity is evident if such reactions can be exploited to yield direct access to partially substituted derivatives otherwise available only by multi-step routes. Selective acetonation of sugars under kinetic conditions has been of particular interest in this regard[3]. Partial acetylation reactions of sugar derivatives have been the subject of frequent studies[4]. In previous work from this laboratory, the substitution pattern resulting from unimolecular acetylation of methyl α-D-glucopyranoside with acetic anhydride–pyridine was examined, and it was shown[5] that acetyl groups are distributed in the product to the extent of 40% at O-6 and 20% each at O-2, O-3, and O-4. In view of the literature reports[6] of greater selectivity of substitution by use of *N*-acylimidazoles, especially 1-benzoylimidazole[7], it was of interest to examine the behavior of 1-acetylimidazole[8] in its reaction with methyl α-D-glucopyranoside, to determine whether unimolecular acetylation with this reagent affords a substitution pattern substantially different from that produced[4] by acetic anhydride–pyridine. A reaction displaying specificity for the primary position (O-6) would be of high synthetic interest, especially in procedures for selective modification of carbohydrate antibiotics and of polysaccharides.

1-Acetylimidazole and methyl α-D-glucopyranoside in equimolar proportions were brought into reaction at 5° or below in a homogeneous medium of dry *N*,*N*-

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dimethylformamide, and the reaction was allowed to proceed for 48 h at ~25°. The product isolated proved to be mainly a mixture of monoacetates plus a small proportion of unchanged starting material; formation of polyacetylated products was negligible. To determine the proportional distribution of acetyl groups by substitution position in the product-mixture, the product was acetylated with an excess of acetic anhydride-d_6–pyridine under conditions that do not cause acetyl-group migration[9]. The crystalline methyl α-D-glucopyranoside tetraacetate thereby isolated was examined by ^{1}H-n.m.r. spectroscopy to determine the extent of substitution at each position effected by protioacetate in the reaction with 1-acetylimidazole. The values observed (30% at O-2, 15% at O-3, 20% at O-4, and 35% at O-6) differed somewhat from those encountered[5] when acetic anhydride–pyridine was used, but it is evident that the alternative reagent did not cause any major alteration in substitution-mode or selectivity. Lowering the reaction-temperature to −20° initially, with subsequent reaction for 12 h at −5°, led to approximately the same result. No significant differences were observed in the substituent-distribution according to whether or not methanol was added to the mixture before isolation of the reaction product.

When the reaction between equimolar amounts of methyl α-D-glucopyranoside and 1-acetylimidazole was conducted at higher temperatures (~70°), the product-mixture contained, in addition to monoacetylated products, a higher proportion of unreacted starting-material, together with a range of polyacetylated products, including even a trace of the tetraacetate. Clearly, the treatment at lower temperature was effective in restricting the reaction to the formation of monoacetates, but without especial selectivity for any individual position.

For selective acetylation at the primary position of carbohydrate derivatives, the reaction of per(trimethylsilyl)ated derivatives in carbon tetrachloride with acetic anhydride and a small proportion of acetic acid, followed by removal of secondary trimethylsilyl ether groups, offers an advantageous route[10], as shown with a range of monosaccharide derivatives[10], and also[11] with the polysaccharide amylose.

EXPERIMENTAL

1-Acetylimidazole. — A solution of 3.92 g (50 mmol) of freshly distilled acetyl chloride in anhydrous chloroform (25 mL) was added slowly at <5° to a stirred solution of 6.8 g (100 mmol) of imidazole (recrystallized from benzene after treatment with charcoal; m.p. 90–91°) in anhydrous chloroform (75 mL). Precipitation of imidazole hydrochloride began just before the end of the addition. After 15 min at ~25°, the stirred mixture was filtered, and the insoluble salt washed with chloroform. The filtrate was evaporated to give 1-acetylimidazole as a white powder that was dried at ~25° *in vacuo*; yield 5.3 g (96%), m.p. 104° (lit.[8] 104°).

Acetylation of methyl α-D-glucopyranoside with 1-acetylimidazole. — A solution of 1-acetylimidazole (0.55 g, 5 mmol) in anhydrous *N,N*-dimethylformamide (5 mL) was added at <5° to a stirred solution of methyl α-D-glucopyranoside (0.97 g, 5 mmol) in anhydrous *N,N*-dimethylformamide (10 mL). After 48 h at ~25°, an-

hydrous methanol (10 mL) was added, and the solution was stirred for 1 h. The solvents were then removed under diminished pressure (<1 torr) at ~40°. The resulting syrup was dissolved in anhydrous pyridine (5 mL) and a solution of acetic anhydride-d_6 (3 g) in dry pyridine (5 mL) was added slowly at 0° with stirring. After 12 h at ~25°, the solution was poured onto ice and extracted with dichloromethane. The extract was washed thoroughly with water, dried (magnesium sulfate), and evaporated. The crystalline residue (1.10 g, 80%; m.p. 99–101°, lit.[5] 101–101.5°) was analyzed by 100-MHz, n.m.r. spectroscopy in chloroform-*d* according to the procedure of Horton and Lauterbach[5].

From the spectral integrals (peak areas) in the acetate region, measured from spectra recorded at 50-Hz sweep-width, the following percentages (rounded to the nearest 5%) of protioacetate at the four positions of substitution were determined: 2-OAc, 30%; 3-OAc, 15%; 4-OAc, 20%; and 6-OAc, 35%.

A similar experiment was performed in which the methyl α-D-glucopyranoside and 1-acetylimidazole were mixed at −20°. The mixture was kept for 12 h at −5°, and then processed as before. The distribution of protioacetate in the product was essentially identical to that determined in the first experiment.

In separate experiments, the products of reaction of equimolar quantities of 1-acetylimidazole and methyl α-D-glucopyranoside under the foregoing conditions were analyzed by t.l.c. [Silica Gel G (Merck), 4:1 ethyl acetate–ethanol]. The chromatograms showed a main component having R_F 0.28, presumed to be a mixture of monoacetates, together with a minor component (R_F 0.24) corresponding to unreacted methyl α-D-glucopyranoside. When the reaction was conducted with the mixture heated for 24 h at ~70°, t.l.c. of the product mixture showed, in addition to the (difficultly resolved) unreacted, starting glycoside (R_F 0.24) and monoacetates (R_F 0.28), faster-migrating components (R_F 0.58, 0.75, and a very minor component at 0.85), presumed to be polyacetates. The authentic tetraacetate had R_F 0.86.

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