pressure to give a mixture of diastereomers **66–69**, which was purified by column chromatography (silica gel, 70–230 mesh, CH_2Cl_2/hexane).

***trans*-3-Acetyl-4-(methoxycarbonyl)-1-(4-methoxyphenyl)azetidin-2-one (74).** To a solution of β-lactams **66b–69b** (1 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C a solution of the HBF_4·Et_2O (1.2 mmol, 85% solution in Et_2O), and the mixture was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 (25 mL), washed with H_2O (1 × 25 mL) and NaCl (2 × 25 mL, saturated solution), and dried ($MgSO_4$). Evaporation of the solvent gave the corresponding silyl fluoride as an oil, which was mixed with a 32% solution of peracetic acid in acetic acid (4 mL) at 0 °C. Triethylamine (0.16 mL, 1.2 mmol) was slowly added, and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with 2 N HCl (1 × 20 mL), 40% aqueous $NaHSO_3$ (3 × 20 mL, 40% w/v solution), and aqueous $NaHCO_3$ (3 × 20 mL, saturated solution), dried ($MgSO_4$), and evaporated under reduced pressure to give the corresponding 3-(1′-hydroxyethyl) β-lactams **70b** and **72b** as main products and traces of **71b** and **73b**: yield 0.25 g (90%); IR (neat) ν 3439 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ **70b** 7.25 (d, 2 H, J = 7.3 Hz, Ar), 6.87 (d, 2 H, J = 7.3 Hz, Ar), 4.43 (d, 1 H, J = 2.4 Hz, H-4), 4.20 (qd, 1 H, J = 6.6 Hz, J' = 5.4 Hz, O—CH), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.37 (dd, 1 H, J = 5.4 Hz, J' = 2.4 Hz, H-3), 2.52–2.23 (s_b, 1 H, OH), 1.42 (d, 3 H, J = 6.6 Hz, CH_3); **72b** 7.25 (d, 2 H, J = 7.3 Hz, Ar), 6.87 (d, 2 H, J = 7.3 Hz, Ar), 4.60 (d, 1 H, J = 2.7 Hz, H-4), 4.33 (qd, 1 H, J = 6.5 Hz, J' = 4.1 Hz, O—CH), 3.79 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.35 (dd, 1 H, J = 4.1 Hz, J' = 2.7 Hz, H-3), 2.52–2.23 (s_b, 1 H, OH), 1.33 (d, 3 H, J = 6.5 Hz, CH_3). To a suspension of chromic nicotinic anhydride (NDC) (0.81 g, 3.68 mmol) in CH_2Cl_2 (3 mL) and pyridine (0.57 mL, 7 mmol) was added the crude mixture of β-lactams **70b–73b** obtained as above (0.35 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred overnight at room temperature and then was diluted with CH_2Cl_2 (25 mL) and filtered off through a pad of silica gel. The organic layer was washed with 6 N HCl (4 × 25 mL) and aqueous $NaHCO_3$ (2 × 25 mL, saturated solution), dried ($MgSO_4$), and evaporated under reduced pressure to afford the title compound: yield 0.095 g (98%); mp 103–104 °C (EtOH); IR (neat) ν 1754, 1716 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.24 (d, 2 H, J = 9.2 Hz, Ar), 6.87 (d, 2 H, J = 9.2 Hz, Ar), 4.97 (d, 1 H, J = 2.4 Hz, H-3), 4.40 (d, 1 H, J = 2.4 Hz, H-4), 3.80 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 2.41 (s, 3 H, CH_3). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.46; N, 5.05. Found: C, 61.04; H, 5.47; N, 5.10.

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Supplementary Material Available: Preparation and characterization data of additional compounds (16 pages). Ordering information is given on any current masthead page.

An Investigation of Intermediates in the Hydrolysis of Ortho Esters Derived from D-Glucose and D-Mannose

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The hydrolysis of a series of 1,2-ortho esters derived from α-D-glucopyranose and β-D-mannopyranose have been investigated by NMR and UV spectroscopy. When the hydrolysis of 1,2-*O*-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose (**6**) in CD_3CN (97.2 v %) and D_2O (2.8 v %) containing DCl (2.8×10^{-4} M) was followed by ^1H NMR spectroscopy, an intermediate was detected that may be the corresponding hemi ortho ester. Evidence was also obtained for the incursion of a hemi ortho ester in the hydrolysis of 1,2-*O*-(α-*exo*,4-dimethoxybenzylidene)-α-D-glucopyranose (**14**) under similar conditions. The proportions of the hydrolysis products of **6**, 1-*O*-acetyl-α-D-glucopyranose (**13**), and 2-*O*-acetyl-α-D-glucopyranose (**12**) depend on acid concentration with more of the former being formed at the higher acid concentrations. When the hydrolysis of **14** was studied at higher acid concentrations (DCl, 0.17 M) the intermediate cation **15** was detected. Evidence was obtained by ^{18}O-labeled studies for decomposition of this by attack of water at C-1 of the glucopyranose ring and by an attack at the *pro*-acyl carbon of the dioxolanylium ion depending on the reaction conditions. In the hydrolysis of the ortho esters derived from β-D-mannopyranose, tricyclic 1,2,6-ortho esters were detected in solvents of low water content and when the concentration of DCl was 0.33 M, the intermediate cation was also detected. The kinetics of hydrolysis of the two series of ortho esters were studied by UV spectrophotometry, and evidence was obtained that the 1,2-*O*-(α-*exo*-alkoxy-4-methoxybenzylidene)-α-D-glucopyranoses reacted with rate-limiting breakdown of intermediate hemi ortho ester at high acid concentrations. Evidence for similar behavior was obtained for the hydrolysis of the analogous glucose orthobenzoate esters and mannose 4-methoxyorthobenzoate esters, but the other compounds studied showed no evidence for a change in the rate-determining step of their hydrolyses or else showed complex kinetics on hydrolysis indicative that formation and breakdown of the hemi ortho ester were proceeding at comparable rates.

Introduction

Although there have been many kinetic and mechanistic studies on the hydrolysis of ortho esters,[1-3] there have been few investigations of this type on ortho esters derived from carbohydrates, despite these being important synthetic intermediates.[4-7] Apart from several early investigations carried our polarimetrically,[8-10] there appear to have been

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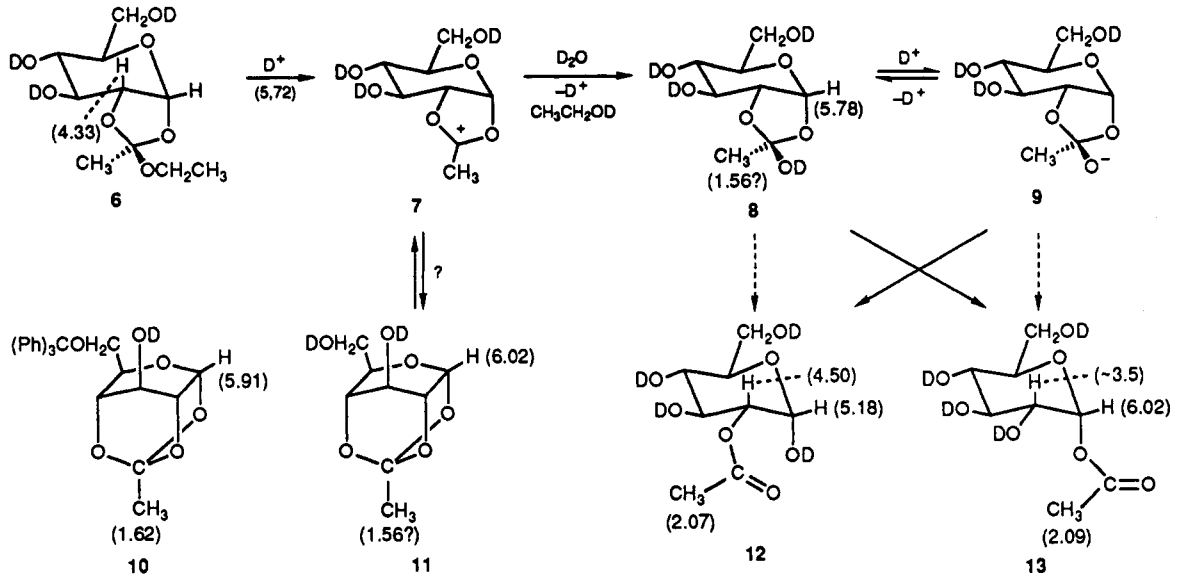
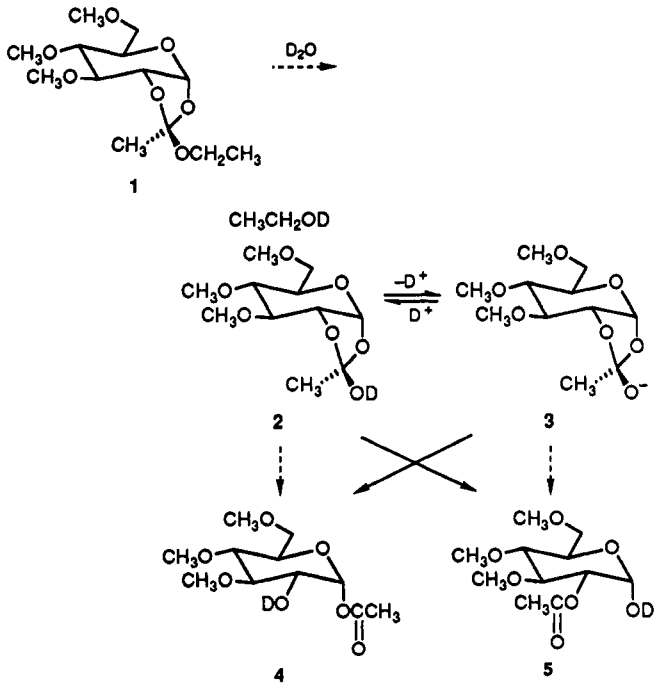
0022-3263/91/1956-4428$02.50/0

Scheme I



no kinetic investigations and in the last 20 years there has been only one significant mechanistic investigation, that of Schroeder, Hultman, and Johnson.[11] These workers made the important observation that the proportions of 2-*O*-acetyl- (**5**) and 1-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranose (**4**) formed on hydrolysis of 3,4,6-tri-*O*-methyl-1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose (**1**) depended on acid concentration, with more of the 1-*O*-acetyl derivative being formed the higher the acid concentration. This was attributed quite reasonably to a change in the product-forming intermediate from the hemi ortho ester (**2**) at high acid concentrations to its conjugate base (**3**) at low acid concentrations. Hemi ortho esters



derived from simpler systems have now been widely investigated,[1-3] and we wondered if it would be possible to detect hemi ortho esters derived from carbohydrates. This has only proved partially successful, but we have also been able to detect other types of intermediate.

Results and Discussion

Hydrolysis of 1,2-*O*-(1-*exo*-Ethoxyethylidene)-α-D-glucopyranose (6). This reaction was carried out in a mixture of CD_3CN (97.2 v %) and D_2O (2.8 v %) that contained DCl (2.8×10^{-4} M) at 25 °C. Two products and an intermediate were detected by ^1H NMR spectroscopy (see Scheme I). The initial spectrum of the ortho ester showed a doublet at δ 5.72 (J = 5.3 Hz) attributed to H-1, a triplet at δ 4.33 (H-2) and a singlet at δ 1.66 for the methyl group. Both products showed no signal at δ ca. 1.6 characteristic of an ortho ester type methyl group, but singlets at δ ca. 2 characteristic of acetyl methyl groups. One product showed a low-field signal for the anomeric proton at δ 6.02 with a coupling constant, J = 3.5 Hz, characteristic of the α-configuration and was considered to be 1-*O*-acetyl-α-D-glucopyranose (**13**). The second product showed a signal for the anomeric proton at δ 5.18 also with a coupling constant, J 3.5 Hz, characteristic of the α-configuration. This proton was shown by decoupling experiments to be coupled to a proton (H-2) with a signal which was a double doublet at δ 4.50 (3.5 and 9.6 Hz). This would be a very low chemical shift for a proton attached to a carbon which was attached to a hydroxyl group, and so this product was considered to be 2-*O*-acetyl-α-D-glucopyranose (**12**).

These results are very similar to those reported by Schroeder and his co-workers with the corresponding 3,4,6-tri-*O*-methyl derivatives, but in addition we observed a transient intermediate under our reaction conditions. This species, which was never present at a concentration greater than ca. 7% of initial concentration of ortho ester, showed signals with very similar chemical shifts. Thus there was a singlet at δ 1.56 and a doublet (J = 5.3 Hz) at δ 5.78 that is slightly upfield from that of the starting ortho ester. This could not be the endo ortho ester as its anomeric proton has a chemical shift downfield from that of the starting exo isomer.[12] Also this would require capture of the intermediate ion by ethanol, which is present at much lower concentration than D_2O. The two

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Scheme II

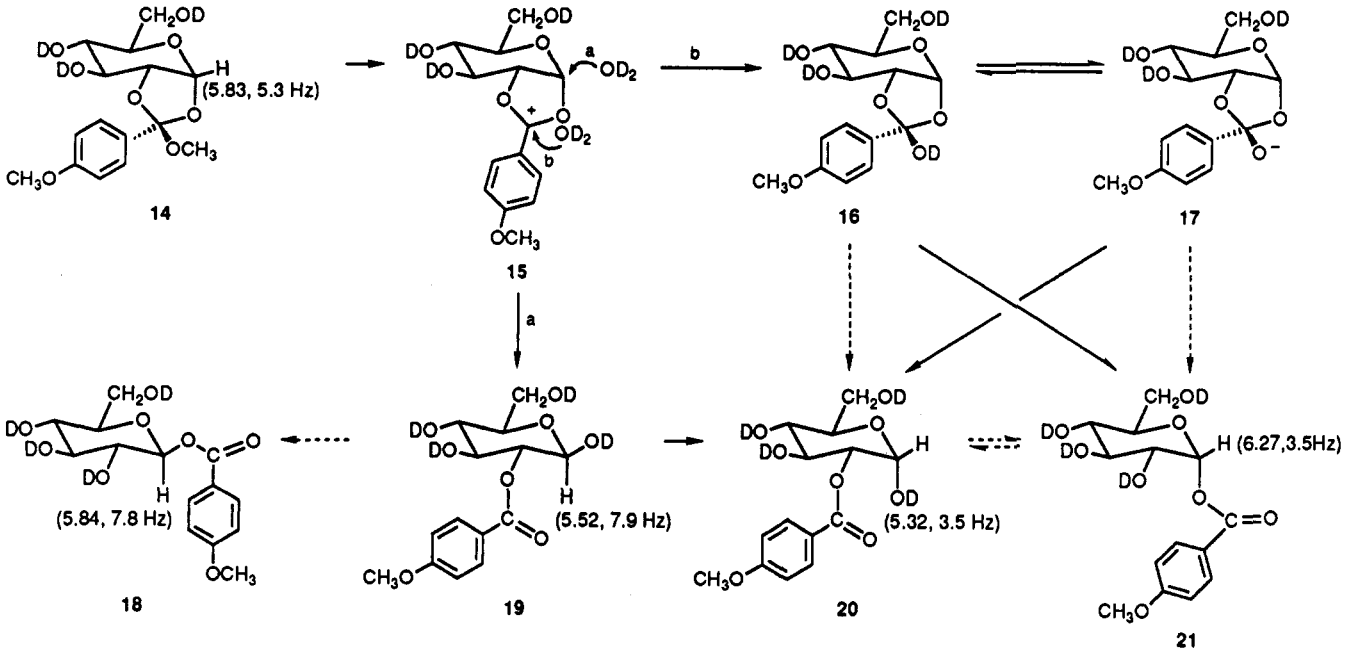

Table I. Effect of Acid Concentration of the Product Distribution in Hydrolyses of 1,2-*O*-(1-*exo*-Ethoxyethylidene)-α-D-glucopyranose (D_2O/CD_3CN = 10/350, v/v)[a]

acid concentration[b] (M)	% A[c]	% B[c]
2.9×10^{-4}	50	45
5.7×10^{-4}	70	30
6.2×10^{-4}	80	20
7.9×10^{-4}	90	10
5.9×10^{-3}	90	10
4.1×10^{-2}	90	10
6.4×10^{-2}	90	10

[a] Determined by ^1H NMR integration ratio of respective anomeric signals. [b] D^+ concentration. [c] A: 1-*O*-acetyl-α-D-glucopyranose. B: 2-*O*-acetyl-α-D-glucopyranose.

most likely structures for this species are the hemi ortho ester (8) and the tricyclic ortho ester (11). The former would be formed by capture of the intermediate cation by water and the latter by capture by the internal hydroxyl at C-4. Both structures are consistent with the observed chemical shifts as the anomeric proton and the methyl group of a hemi ortho ester would be expected to have chemical shift similar to the starting ortho ester 6, as found, and the reported chemical shifts for a closely related ortho ester 10 are similar to those observed.[13]

The relative proportions of products varied with acid concentration (Table I) with 2-*O*-acetyl-α-D-glucopyranose (12) being the predominent product at low acid concentrations and 1-*O*-acetyl-α-D-glucopyranose (13) the predominant product at high acid concentrations, which is similar to what was reported by Schroeder and co-workers[11] for the corresponding tri-*O*-methyl ortho ester. As they suggest, this behavior presumably results from the product being formed from the conjugate base of the ortho ester (e.g. 9) at low acid concentrations which results in expulsion of the anion of lowest pK_a[14] and from the acid-catalyzed decomposition of the un-ionized ortho ester at high acid concentrations. The formation of the product with the axial acetoxy group (13) under these latter conditions is similar to what is found on breakdown of five-membered cyclic hemi orthoacetates fused to cyclohexane rings which react with expulsion of the equatorial oxygen to form the hydroxy acetate with an equatorial hydroxy and an axial acetoxy group.[15] The steric[15] or stereoelectronic factors[16] previously postulated are presumably operating in our system, but in addition an electronic effect may favor expulsion of the more basic O-2 with acid catalysis over expulsion of the less basic O-1.

Hydrolysis of 1,2-*O*-(α-*exo*,4-Dimethoxybenzylidene)-α-D-glucopyranose (14). When the hydrolysis of this compound was followed by ^1H NMR spectroscopy using conditions similar to those described for compound 6 in the last section [CD_3CN (97.2 v %), D_2O (2.8%), DCl (2.8×10^{-4} M), 25 °C], similar results were obtained, except that no intermediate was directly detected. Nevertheless, the presence of an intermediate with an ^1H NMR spectrum almost identical with that of the starting material could be inferred by the observation that the disappearance of the ortho ester methoxy signal with concomitant formation of the signal of methanol was faster than the apparent disappearance of the other signals of the ortho ester 14 and formation of products 20 and 21. Thus, integration of the signals of the ortho ester methoxy group and methanol after 30 min indicated 67.5 (±2)% reaction whereas integration of the signals of the anomeric proton, the aromatic methoxy group and the ortho aromatic protons indicated 46.5 (±2)% reaction. Approximate rate constants calculated from the first-order rate expression were respectively 5.1 (±0.5) $\times 10^{-4}$ and 3.0 (±0.5) $\times 10^{-4}$ s^{-1}. These results suggest that when methanol is released another species is formed that has an almost identical NMR spectrum with that of the starting material 14. This is most probably the tetrahedral intermediate 16. Kinetic data obtained by UV spectrophotometry also indicates the accumulation of this species (see below). The reaction products were considered to be 1-*O*-(4-methoxybenzoyl)-α-D-glucopyranose (21) and 2-*O*-(4-methoxybenzoyl)-α-D-glucopyranose with signals in their ^1H NMR spectra assigned by decoupling experiments as shown in

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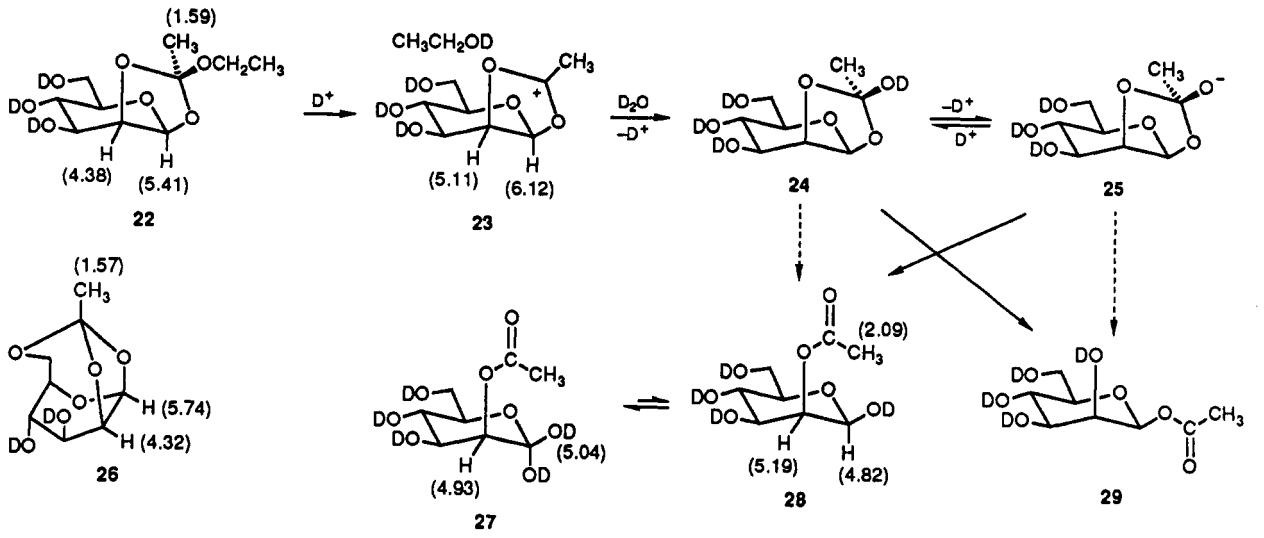
Scheme III



Scheme II. These were considered to be formed by way of the proposed tetrahedral intermediate 16 and its conjugate base 17 (pathway b of Scheme II).

When the hydrolysis of 14 was studied at a higher acid concentration and lower temperature [CD_3CN (97.2%), D_2O (28 v %), DCl (0.17 M), −30 °C], a completely different product was detected in the initial NMR spectrum. This appeared to be the only product under these conditions, and its spectrum showed signals for protons attached to the sugar ring at δ 5.52 (d, J = 7.9 Hz) and δ 5.04 (t, J = 7.9 Hz). The aromatic signals were an A_2B_2 system with two sets of signals centered at δ 7.02 and δ 8.02. The latter indicates that the ortho ester functional group had already decomposed to a 4-methoxybenzoyl group. Complete hydrolysis was also indicated by the disappearance of the signal of its methoxyl group (δ 3.15) and the formation of the signal of methanol (δ 3.27). The signals at δ 5.52 and 5.04 were shown to be coupled to one another by decoupling experiments and in view of the relatively large coupling constant (J = 7.9 Hz) were considered to be the signals of H-1 and H-2 of 2-*O*-(4-methoxybenzoyl)-β-D-glucopyranose (**19**). Also, if this were the species present it would account for the lowfield signal of H-2 since there is an acyl group attached to O-2. Further H-2 would have a diaxial coupling to the protons H-1 and H-3, which would have approximately the same coupling constant and hence should be a triplet, as found.

It was considered that this species (**19**) was formed by pathway a of Scheme II in which water attacks C-1 of the glucose ring of the ambident electrophile **15**.

Even at −30 °C 14 was unstable and was converted into the two products detected at lower acid concentration, **20** and **21**. In addition a small amount of a third product was also observed. This showed a signal in the ^1H NMR spectrum at δ 5.84 (d, J = 7.8 Hz) and was considered to be that of 1-*O*-(4-methoxybenzoyl)-β-D-glucopyranose (**18**). Therefore under these more strongly acidic condition it seems that both mutarotation an acyl migration can take place. The formation of **18** from **19** would involve an intermediate with a five-membered ring fused trans to a six-membered ring.

According to the above reaction schemes the products (**20** and **21**) formed in dilute acid (path b Scheme II) would incorporate oxygen from the solvent into the carbonyls of their *p*-methoxybenzoyl groups whereas those formed in more concentrated acid (path a Scheme II) would not. Reactions were therefore carried out using a mixture of acetonitrile and water enriched in ^{18}O ($^{18}O/^{16}O$ = 0.5) and the signals of the carbonyl groups in the ^{13}C NMR spectra of the products were examined. It has been shown that when ^{18}O is substituted in the carbonyl group of an ester it normally causes an upfield shift of ≥0.03 ppm in the ^{13}C signal of the carbonyl carbon, but a smaller shift (≤0.015 ppm) when it is substituted in the ether oxygen.[17,18]

The ^{13}C NMR spectrum of the products formed in dilute acid [CD_3CN (97.2%), H_2O ($^{18}O/^{16}O$ = 0.5, 2.8%), HCl (2.8 × 10^{-4} M), −25 °C] showed carbonyl signals for 1-*O*-(4-methoxybenzoyl)-α-D-glucopyranose (**21**) at δ 162.2 and for 2-*O*-(4-methoxybenzoyl)-α-D-glucopyranose (**20**) at δ 165.0ppm. Both were split into two signals with an isotopic shift of 0.038 ppm, in agreement with their being formed by path b of Scheme II.

When more concentrated acid was used [CD_3CN (97.2%), H_2O ($^{18}O/^{16}O$ = 0.5, 2.8 v %), HCl (2.8 × 10^{-2} M), −25 °C] both carbonyl signals were again observed, but whereas that for 1-*O*-(4-methoxybenzoyl)-α-D-glucopyranose (**21**) still showed an isotope shift (0.03 ppm), that for 2-*O*-(4-methoxybenzoyl)-α-D-glucopyranose (**20**) did not. The acid concentration used in this experiment was intermediate between those used in the ^1H NMR spectroscopic experiments and it is suggested that both pathways a and b of Scheme II are followed, but because the acid concentration is higher (2.8 × 10^{-2} M) than that used in the first isotopic-shift experiment (2.8 × 10^{-4} M), the hemi ortho ester breaks down exclusively with expulsion of O-2 to form 1-*O*-(4-methoxybenzoyl)-α-D-glucopyranose (**21**) and no 2-*O*-(4-methoxybenzoyl)-α-D-glucopyranose is formed by this route (see behavior of **6**). Instead it is formed by pathway a of Scheme II via its β-anomer, which would not lead to incorporation of oxygen from the solvent into the carbonyl group.

The two routes involve attack by water at different positions on cation **15** which is an ambident electrophile.[19]

Hydrolysis of 1,2-*O*-(1-*exo*-Ethoxyethylidene)-β-D-mannopyranose (22). This was carried out in a mixture of CD_3CN (95.9 v %) and D_2O (4.1 v %), which contained DCl (4.1 × 10^{-4} M) at 25 °C. After about 5 min complete conversion into the tricyclic ortho ester (see below), 1,2,6-*O*-orthoacetyl-β-D-mannopyranose (**26**), had taken place (see Scheme III). The signal of the methyl group of the starting ortho ester at δ 1.59 had been replaced by

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Table II. Rate Constants for the Hydrolysis at High pH of 1,2-*O*-(α-*exo*-Alkoxy-4-substituted-benzylidene)-D-hexopyranoses in Water at 25 °C (I = 1.0 M)

		α-D-gluco series		β-D-manno series	
4-substituent	alkoxy group	k_{H^+}, M^{-1} s^{-1} (sd)	$10^3k_{H_2O}$, s^{-1} (sd)	k_{H^+}, M^{-1} s^{-1} (sd)	$10^3k_{H_2O}$, s^{-1} (sd)
methoxy	CH_3CH_2O	613.1 (11.0)[a]	6.48 (1.84)	100.4 (1.3)[b]	0.185 (0.081)
methoxy	CH_3O	456.7 (12.7)[c]	4.17 (2.14)	86.9 (1.9)[d]	0.183 (0.108)
methoxy	$ClCH_2CH_2O$	120.5 (1.4)[e]	4.72 (0.67)	42.2 (0.7)[f]	0.190 (0.057)
hydrogen	CH_3CH_2O	133.0 (3.3)[g]	8.04 (1.43)	27.3 (0.5)[h]	-5.65 (0.98)
hydrogen	CH_3O	123.7 (3.9)[i]	3.96 (1.71)	23.9 (0.9)[j]	-6.05 (1.71)
hydrogen	$ClCH_2CH_2O$	39.7 (0.8)[k]	2.18 (0.47)	12.2 (0.3)[l]	-2.34 (0.88)
nitro	CH_3CH_2O	5.26 (0.04)[m]	0.635 (0.075)	0.729 (0.021)[n]	-0.411 (0.233)
nitro	CH_3O	4.51 (0.03)[o]	0.325 (0.041)	0.654 (0.019)[p]	-0.385 (0.209)

[a] pH range 3.52–4.51 (8 points). [b] pH range 3.99–4.91 (7 points). [c] pH range 3.52–4.51 (7 points). [d] pH range 3.96–5.21 (9 points). [e] pH range 3.98–5.63 (13 points). [f] pH range 3.75–5.02 (8 points). [g] pH range 3.16–4.41 (6 points). [h] pH range 2.52–3.20 (6 points). [i] pH range 3.15–4.16 (6 points). [j] pH range 2.52–3.21 (6 points). [k] pH range 3.04–3.69 (6 points). [l] pH range 2.03–3.20 (7 points). [m] pH range 2.49–3.24 (7 points). [n] pH range 1.74–2.74 (7 points). [o] pH range 2.70–3.61 (6 points). [p] pH range 1.74–2.74 (7 points).

a new singlet at δ 1.57, and the signals of its anomeric proton δ 5.41 (J = 2.2 Hz) and its H-2, δ 4.38, had been replaced by new signals at δ 5.74 (J = 5.7 Hz) and δ 4.32 (dd, J = 2.2, 5.7 Hz). Also the signal of the ethoxy group had changed to that of ethanol. After a further two hours the tricyclic ortho ester **26** had been converted into 2-*O*-acetyl-β-D-mannopyranose (**28**) whose ^{1}H NMR spectrum showed the presence of an acetylmethyl group at δ 2.09 and two ring protons at δ 5.19 (dd, J = 3.0, 1.3 Hz) and 4.82 (d, J = 1.3 Hz), which were attributed respectively to H-2 and H-1.

When hydrolysis of **22** was carried out using a higher acid concentration and lower temperature [CD_3CN (97.2 v %), D_2O (2.8 v %), DCl (8.3×10^{-2} M), -30 °C], two additional species were detected. One of these was an intermediate between the tricyclic ortho ester **26** and 2-*O*-acetyl-β-D-mannopyranose (**28**) and the other was a transformation product of the latter.

The intermediate whose maximum concentration was about 20% of the initial concentration of the starting material had signals in its ^{1}H NMR spectrum at very low fields for H-1 (δ 6.12, d, J = 1.3 Hz) and H-2 (δ 5.11, dd, J = 3.1, 1.3 Hz) and was considered to be the cation **23**. As discussed below in the 4-methoxyphenyl series, conversion to the analogous cation could be obtained quantitatively. After about 2 h at -30 °C this intermediate had decomposed and conversion into 2-*O*-acetyl-β-D-mannopyranose (**28**) was complete. On warming to room temperature, **28** was converted into another compound whose ^{1}H NMR spectrum has signals for H-1 at δ 5.04 (d, J = 1.8 Hz) and H-2 at δ 4.93 (dd, J = 1.8, 3.5 Hz). Its anomeric proton shows a lower chemical shift (δ 5.04) than its precursor, the β-anomer (δ 4.82), which is the usual relationship between the chemical shifts of equatorial and axial protons.[20] It is more stable than its β-anomer, which is what is normally found for mannose derivatives,[21] and the final product consists of more than 90% of this species **27**.

Hydrolysis of 1,2-*O*-(α-*exo*,4-Dimethoxybenzylidene)-β-mannopyranose (30). When this reaction was carried out in dilute acid solution in the presence of a small amount of D_2O [**30**, 0.014 M; CD_3CN (97.2 v %), D_2O (2.8%), DCl (2.8×10^{-3} M), 25 °C], results similar to those obtained with the corresponding orthoacetate (**22**) were obtained. The first ^{1}H NMR spectrum taken about 5 min after mixing showed formation of the tricyclic ortho ester **34**. Over the course of 20 min this decomposed into 2-*O*-(4-methoxybenzoyl)-β-D-mannopyranose (**36**), which then underwent mutarotation to yield 2-*O*-(4-methoxybenzoyl)-α-D-mannopyranose (**35**). The changes in the observed chemical shifts in the ^{1}H NMR spectrum were as shown in Scheme IV.

Table III. ρ Values (esd) for the Hydronium Ion Catalyzed Hydrolysis of 1,2-*O*-(α-*exo*-Alkoxy-4-substituted-benzylidene)-D-hexopyranoses in Water at 25 °C (I = 1.0 M)

alkoxy group	α-D-gluco series	β-D-manno series
ethoxy	-1.93 (0.13)	-2.03 (0.016)
methoxy	-1.90 (0.05)	-2.02 (0.015)
2-chloroethoxy	-1.79[a]	-2.00[a]

[a] Calculated from two points.

When the reaction was carried out in more concentrated acid solution [**30**, 0.014 M; CD_3CN (97.2 v %), D_2O (2.8 v %), DCl (0.33 M)] at 25 °C, the first spectrum taken after 10 min showed quantitative conversion into a new species considered to be the carbocation **31**. Its ^{1}H NMR spectrum showed signals for H-1 and H-2 at low field δ 6.22 (d, J = 1.8 Hz) and 5.36 (dd, J = 1.8, 3.5 Hz) and the ^{13}C NMR spectrum also showed a signal at low field δ 209.6, indicating the presence of a very electronegative center. Similar 1,3-dioxolan-2-ylium cations have been detected in the hydrolysis of simpler ortho esters by UV spectroscopy.[22]

Kinetics of Hydrolysis of Ortho Esters. The rate constants for the hydrolysis of the hexopyranose orthobenzoates were determined at these relatively high pHs by following the appearance of the benzoate esters by UV spectrophotometry. The variation of k_{obs} with [H^+] was fitted to equation by at least-squares method and the

$$k_{obs} = k_{H^+}[H^+] + k_{H_2O}$$

values of k_{H^+}, k_{H^2O} and their standard deviations are given in Table II. The high standard deviations for the k_{H_2O} values or their negative values indicate that they do not contribute significantly to the total rate except possibly with the glucopyranose 4-nitroorthobenzoates. The variation of k_{H^+} with leaving alkoxy group varies in the order $CH_3CH_2O > CH_3O > ClCH_2CH_2O$, which is similar to that reported for 2-alkoxy-2-phenyl-1,3-dioxolanes[22] and indicates that the rate-determining step involves cleavage of the exocyclic C–O bond of the starting ortho ester. The values of k_{H^+} also vary with the 4-substituent in the ortho ester group in the order MeO > H > NO_2. The three- or two-point Hammett plots yield negative values in the range -1.9 to -2.03 (see Table III). These are more negative than those for the hydrolysis methyl 4-substituted orthobenzoates (ρ -1.16) and 2-aryl-2-methoxy-1,3-dioxolanes (ρ -1.58, calculated from the results in refs 22 and 23).

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Scheme IV

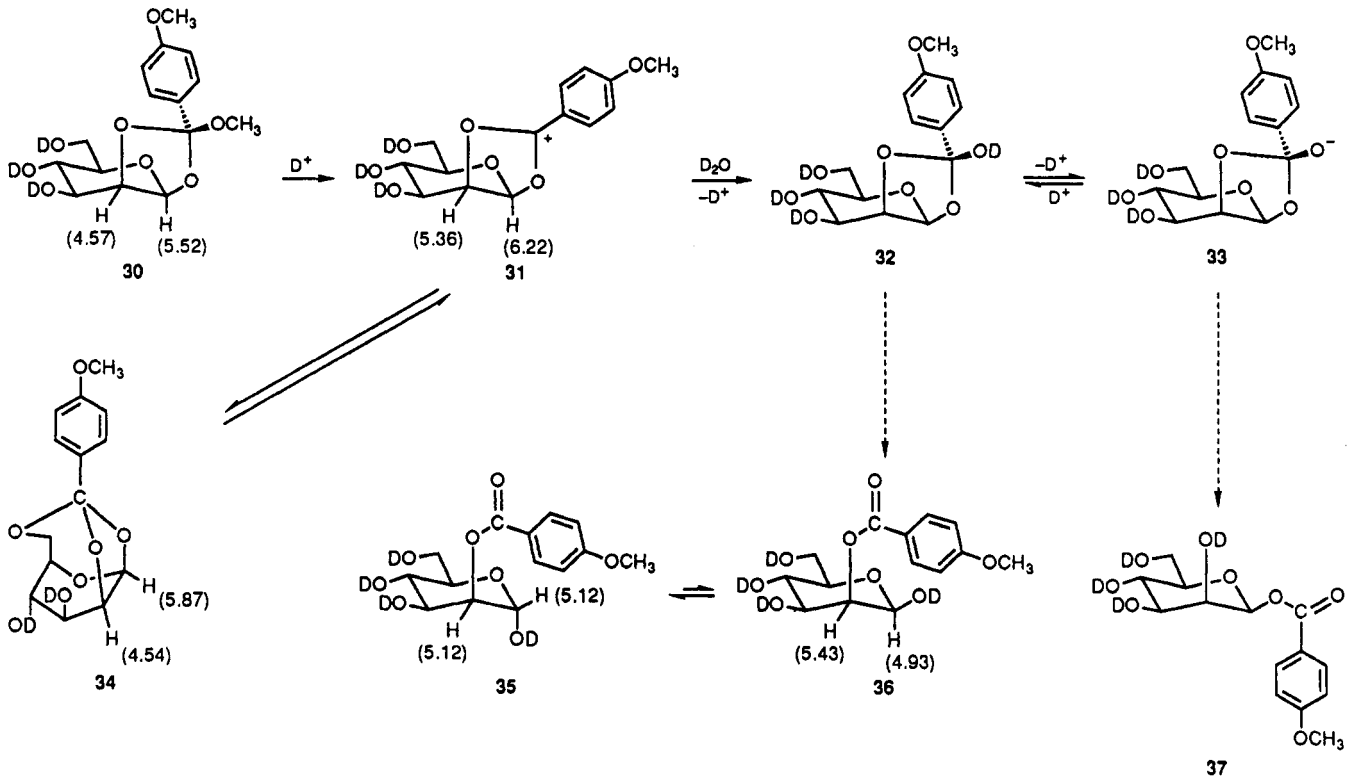


Table IV. Rate Constants for the Hydrolysis at Low pH of 1,2-*O*-(α-*exo*-Alkoxy-4-substituted-benzylidene)-D-hexopyranoses in Aqueous Hydrochloric Acid at 25 °C (I = 1.0 M)

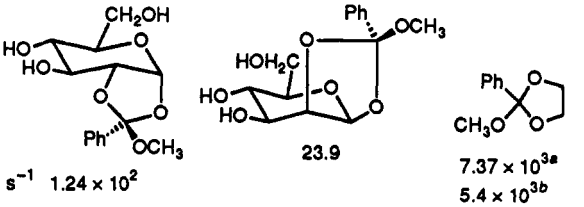
		α-D-gluco series		β-D-manno series	
4-substituent	alkoxy group	k_{H^+}, M^{-1} s^{-1} (sd)	k_{H_2O}, s^{-1} (sd)	k_{H^+}, M^{-1} s^{-1} (sd)	k_{H_2O}, s^{-1} (sd)
methoxy	CH_3CH_2O	101.0 (3.7)[a]	1.45 (2.0)	62.5 (±1.6)[b]	−0.24 (0.98)
methoxy	CH_3O	103.4 (3.1)[c]	4.65 (24)	63.5 (±1.7)[d]	0.07 (1.1)
methoxy	$ClCH_2CH_2O$	induction period[e]		induction period[f]	
hydrogen	CH_3CH_2O	46.3 (1.0)[g]	0.57 (0.66)	induction period[h]	
hydrogen	CH_3O	46.8 (1.0)[i]	0.96 (0.61)	induction period[j]	
hydrogen	$ClCH_2CH_2O$	induction period[k]		induction period[l]	
nitro	CH_3CH_2O	5.23 (0.13)[m]	0.11 (0.08)	0.749 (0.013)[n]	-1.48×10^{-2}
nitro	CH_3O	4.83 (0.14)[o]	0.21 (0.09)	0.694 (0.006)[p]	-1.35×10^{-2}

[a] [HCl] = 0.11–0.90 M (6 points). [b] [HCl] = 0.10–1.00 M (6 points). [c] [HCl] = 0.01–0.19 M (11 points). [d] [HCl] = 0.10–1.00 M (6 points). [e] [HCl] = 0.19–1.00 M (5 points). [f] [HCl] = (8.8×10^{-3})–(8.08×10^{-2}) M (8 points). [g] [HCl] = 0.10–1.00 M (5 points). [h] [HCl] = 0.10–1.00 M (6 points). [i] [HCl] = 0.10–1.00 M (6 points). [j] [HCl] = 0.10–1.00 M (6 points). [k] [HCl] = 0.10–1.00 M (6 points). [l] [HCl] = 0.10–1.00 M (6 points). [m] [HCl] = 0.10–1.00 M (6 points). [n] [HCl] = 0.10–1.00 M (6 points). [o] [HCl] = 0.10–1.00 M (6 points). [p] [HCl] = 0.10–1.00 M (6 points).

The glucose ortho esters react about 5 times more rapidly than the mannose ortho esters but about 50 times more slowly than the corresponding 2-aryl-2-methyl-1,3-dioxolanes (see Chart I). This and the more negative ρ values for the sugar ortho esters suggest that formation of a planar 1,3-dioxolan-2-ylium ion and the corresponding transition state is more difficult with the latter as a result of the dioxolan-2-ylium ion being fused to the six-membered hexopyranose ring.

The kinetics of hydrolysis of these ortho esters were also studied at higher acid concentrations when behavior similar to that reported by McClelland, Kresge, and coworkers[22] for the hydrolysis of 2-alkoxy-2-aryl-1,3-dioxolanes was observed (see Table IV). Thus under these conditions the rate constants (k_{H^+}) based on the rate of ester formation, for the hydrolysis of ethoxy- and methoxyglucose-4-methoxyorthobenzoates were within experimental error identical and 4–6 times smaller than those determined at low acid concentrations (Table II). This indicates that the rate-determining step is now breakdown of the hemi ortho ester intermediate. In agreement with this, the analogous ortho ester with the poorer 2-chloroethoxy leaving group shows complex kinetics with an induction period at these acid concentrations. Now steps 1 and 2 are occurring at similar rates. An induction period was also observed when the methoxyglucose 4-methoxy-

Chart I. A Comparison of the Rate Constants for Hydronium Ion Catalyzed Hydrolysis of Ortho Esters at 25.0 °C



k_{H^+} M^{-1} s^{-1} 1.24×10^2 23.9 7.37×10^{3a} 5.4×10^{3b}

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orthobenzoate was studied in 10^{-2} M HCl, an acid concentration intermediate between those given in Tables II and IV.

Similar behavior was found with the glucose orthobenzoate esters and the mannose 4-methoxyorthobenzoate esters, but under the high acid conditions used all the mannose orthobenzoate esters showed complex kinetics so there was never a complete change in rate-determining step to breakdown of the hemi ortho ester even when ethoxy was the leaving group.

In contrast to this behavior the ethoxy and methoxy 4-nitrobenzoate ortho esters in both series react at the high acid concentrations with different rate constants to one another, but within experimental error with the same rate constants as in the more dilute acid solutions. Therefore the deactivating nitro substituent is present, the slow step is always step 1, and breakdown of the hemi ortho ester does not become rate-determining at any of the acid concentrations that we have used.

There is a much larger effect (41-fold decrease) on $k^1_{H^+}$ on going from 2-methoxy-2-(4-methoxyphenyl)-1,3-dioxolanes to the analogous glucose ortho esters than there is on $k^3_{H^+}$ (7-fold decrease). Fusion of the carbohydrate ring on to the 1,3-dioxolane ring therefore has a greater destabilizing effect on the transition state for ionization than on that for ring opening. This contrasts with the effect of four methyl substituents at positions 4 and 5 of the dioxolane ring which enhances the rate of step 1 but causes a 23-fold decrease in the rate of step 3.[24]

Structure of 1,2,6-*O*-(4-Methoxyorthobenzoyl)-β-D-mannopyranose (34). This tricyclic ortho ester was isolated as a decomposition product of 1,2-*O*-(α-*exo*,4-dimethoxybenzylidene)-β-D-mannopyranose (**30**) (see the Experimental Section) and also detected as an intermediate in the hydrolysis of the latter in solvents of low water content (<5%). The product was clearly an ortho ester as the ^{13}C NMR spectrum showed a signal for the characteristic tertiary carbon at δ 122.5 and the ^1H NMR spectrum showed no signals at δ ca. 7.9 characteristic of the protons at position 2 of a 4-methoxybenzoyl group. As neither the ^1H nor the ^{13}C NMR spectrum showed signals characteristic of an ortho ester methoxyl group, it was concluded that this had been lost and that a new ortho ester had been formed with an internal hydroxyl group. The hydroxyls at C-3 and C-6 are on the right side of the ring to form an internal ortho ester. Formation of the O-6 ortho ester was preferred as the major change in the ^{13}C NMR spectrum was a shift of the C-6 signal from δ 61.8 to δ 71.2. The change in chemical shift of C-3 was much smaller, δ 72.8 to δ 72.2. The ^1H NMR spectrum is also consistent with this structure. From a consideration of molecular models it can be seen that the dihedral angles between H-1, H-2, and H-3 of 1,2-*O*-(α-*exo*,4-dimethoxybenzylidene)-β-D-mannopyranose are approximately 28° and 26°, respectively, and that on formation of 1,2,6-*O*-(4-methoxyorthobenzoyl)-β-D-mannopyranose that the dihedral angle between H-1 and H-2 should decrease to ca. 12° and that between H-2 and H-3 should increase to ca. 38°. Therefore the coupling constant $J_{1,2}$ should increase as observed (2.6 to 5.9 Hz) while $J_{2,3}$ should decrease, also as observed (3.5 to 2.2 Hz). The only previous member of this tricyclic ortho ester series, 3,4-di-*O*-acetyl-1,2,6-*O*-orthoacetyl-β-D-mannopyranose also shows a signal for the anomeric proton (δ 5.78, d, J = 6 Hz),[25] very similar to that found for **34** (δ 5.86, d, J = 5.7 Hz). On the other hand the only previously reported member of the 1,2,3-ortho ester series 1,2,3-*O*-orthoacetyl-6-*O*-(triphenylmethyl)-β-D-mannopyranose shows a signal for the anomeric proton at δ 5.46, which is a broad triplet.[13] It appears that this arises from the compound having a conformation in which there is an "M" relationship between H-1 and H-3, which leads to a large long-range coupling $J_{1,3}$.[26,27] The absence of such a coupling with the compound that we isolated argues against a 1,2,3-ortho ester structure.

Experimental Section

Melting points are uncorrected; 90-MHz ^1H and ^{13}C NMR spectra were measured on a JEOL FX-90Q spectrometer. Chemical shifts are given in δ, in ppm downfield from internal standard sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) in D_2O and tetramethyl silane (TMS) in other solvents. Low-resolution mass spectra were recorded on a VG 70-70F mass spectrometer by chemical ionization. Elemental analyses were carried out in the Amdel Australian Microanalytical Service, Melbourne. Optical rotations were measured on a AA-1000 optical activity polarimeter in 10^{-4} M NaOH aqueous solution or in chloroform.

Preparation of Ortho Esters. The acylated glucose and mannose ortho esters (Tables S3, S4 in the supplementary material) were prepared from the corresponding tetra-*O*-acyl-α-D-gluco- and -mannopyranosyl bromides (Tables S1, S2, supplementary material). For the preparation of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-*exo*-ethoxyethylidene)-α-D-glucopyranose, the method of Lemieux and Morgan[12] was used which involved reaction of the tetra-*O*-acetyl-α-D-glucopyranosyl bromide with ethanol in the presence of 2,4,6-collidine[28] and tetra-*n*-butylammonium bromide. A similar method was used for the preparation of 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-*exo*-ethoxyethylidene)-β-D-mannopyranose from the tetra-*O*-acetyl-α-D-mannopyranosyl bromide except that now no tetra-*n*-butylammonium bromide was needed to effect anomerisation.

The benzoyl and substituted-benzoyl glucose ortho esters were prepared by the reaction of the corresponding glucosyl bromide with the alcohol in nitromethane in the presence of 2,4,6-collidine[28] and tetra-*n*-butylammonium bromide. The corresponding mannose ortho esters were prepared similarly, but without the addition of the tetra-*n*-butylammonium bromide.

The acylated ortho esters were usually mixtures of the exo (>90%) and endo (<10%) isomers.[12] These were deacylated with sodium methoxide and methanol, and the pure exo isomers (Tables S5 and S6, supplementary material) were obtained by chromatography on neutral silica gel, eluting with acetonitrile. This was carried out as quickly as possible in order to avoid decomposition.

Decomposition of the mannose ortho esters occurred particularly easily so the product of decomposition was investigated. Pure 1,2-*O*-(α-*exo*,4-dimethoxybenzylidene)-β-D-mannopyranose (2.0 g) was dissolved in the minimum amount of acetonitrile and left on a column of neutral silica gel for 2 h. The decomposition product, identified as 1,2,6-*O*-(4-methoxyorthobenzoyl)-β-D-mannopyranose (**34**), was eluted by acetonitrile. The acetonitrile was removed by suction at 40 °C to yield a syrup, which was stored at −20 °C over sodium hydroxide pellets: yield 1.8 g; $[\alpha]^{20}_D$ −72.3° (*c* 1.0 in H_2O); ^1H NMR (CD_3CN) δ 5.86 (1 H, d, J = 5.7 Hz, H-1), 4.50 (1 H, dd, J = 2.2, 5.7 Hz, H-2), 3.2–3.8 (3 H, m, H-3, H-4, H-5), 4.06 (2 H, dd, J = 2.6, 48 Hz, H-6), 6.89, 7.50 (4 H, A_2B_2 system, aromatic protons), 3.78 (3 H, s, methoxyl); ^{13}C NMR δ 100.8 (d, C-1), 81.6 (d, C-2), 72.2 (d, C-3), 71.0 (d, C-4), 77.9 (d, C-5), 71.2 (t, C-6), 122.5 (s, ortho ester carbon), 131.1 (s, aromatic C-1), 128.7 (s, aromatic C-2s), 114.3 (s, aromatic C-3s), 161.4 (s, aromatic C-4), 56.1 (q, CH_3O).

Kinetic Measurements. For kinetics in the range of 10^{-2}–10^{-4} s^{-1}, 20 μL of stock solution, prepared as described, of the ortho esters (in anhydrous methanol) were added to 2.0 mL of the

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themally equilibrated reaction solution contained in the curvette in the thermostatted cell holder of a Shimadzu UV250 spectrophotometer as described before.[29]

Rate constants in the range of 0.1-1.0 s^{-1} were measured on a LKB 2238 UVICORD SII UV monitor which was coupled with a HI-TECH Scientific SFA-II Rapid Kinetics Accessory. Stock solution of ortho ester (ca. 1.5×10^{-4} M) in a 5×10^{-5} M sodium hydroxide solution and aqueous acidic buffer solution were introduced into two different reservoirs. After thermal equilibration, an equal volume of these solution was injected into the UV cell to initiate the hydrolysis experiment. The data were fed as voltage signals, via the interface and the analogue-digital converter, to an Apple II microcomputer.

Rate constants in the range from 1.0 to 100 s^{-1} were measured on HI-TECH SCIENTIFIC stopped-flow SF-51 spectrometer. The aqueous acidic buffer and the stock solution of ortho ester (ca. 1.5×10^{-4} M) in 5×10^{-5} M NaOH were loaded in two reservoirs, after thermal equilibration, an equal volume was injected into the curvette. The data collection was controlled by an Apple IIe microcomputer via an ADS-1 interface unit. The programs for controlling the data collection were purchased from HI-TECH. A DASAR system (data acquisition, storage and retrieval system) from HI-TECH was used to collect the data.

Reactions were normally followed to greater than 90% completion, and first-order rate constants were calculated using a generalized least-square method.[30] The standard deviations for most of the first-order rate constants were less than 4%. Second-order rate constant for the reactions were obtained as the slopes of plots of the first-order rate constants against $[H^+]/101^{-pH}$ using linear least-square method. Reaction solutions, whose ionic strengths were maintained constant with potassium chloride (I = 1.0 M), had their pHs adjusted with HCl and sodium acetate (1×10^{-4} M). The pHs of the solutions were checked constantly.

Supplementary Material Available: Tables of spectral data and ^1H NMR spectra (23 pages). Ordering information is given on any current masthead page.

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On the Structure and Reactivity of Lithium Diisopropylamide (LDA) in Hydrocarbon Solutions. Formation of Unsolvated Ketone, Ester, and Carboxamide Enolates

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Enolizations of ketones, *tert*-butyl esters, and carboxamides by solvent-free lithium diisopropylamide (LDA) in hexane or toluene are described. Enolates are isolated as spectroscopically pure, white (often crystalline) solids. Solubilities of the enolates in hexane range from highly soluble to completely insoluble. Enolizations of aldehydes, methyl esters, and acetone afford complex mixtures. Analysis of [^{6}Li]LDA and [^{6}Li,^{15}N]LDA in hexane by ^{6}Li and ^{15}N NMR spectroscopy show evidence of an equilibrium mixture of at least three cyclic oligomers.

Introduction

During the course of our investigations of the structure and reactivity of lithium diisopropylamide (LDA) and its propensity to form mixed aggregates with ketone enolates, we had occasion to make several observations. We rediscovered[1] that LDA has an appreciable solubility in hexane at ambient temperatures, which, in turn, affords a fairly efficient method of purification by recrystallization. Solutions of LDA in hexane readily supersaturate, affording transiently stable solutions exceeding 0.1 M even below -78 °C. As initially noted by Rathke[2a] and Lochmann[2b] during the course of metalations of hindered esters,[3,4] hydrocarbon solutions of unsolvated LDA afford solid (often crystalline) enolates of high purity when treated with carbonyl-containing substrates at ambient or elevated temperatures.[5] Noting that donor solvent-free lithiations could prove useful in a process research setting where ethereal solutions at cryogenic temperatures can be prohibitively costly, we describe a number of representative enolizations by donor solvent-free LDA.[2,5,6] We also include preliminary structural studies indicating that LDA in hexane resides as a distribution of at least three and possibly as many as five cyclic oligomers.[7]

Results and Discussion

Enolizations. The results of enolizations of standard carbonyl compounds are summarized in Table I. Spectroscopic data are summarized in Table II. Enolizations could be carried out using recrystallized (prepurified) LDA or LDA generated in situ from *n*-BuLi and diisopropylamine with little difference in the end result. The in situ

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