84602-80-2; **18**, 84602-81-3; **19**, 39188-96-0; 6-chloro-9-(2-tetrahydropyranyl)purine, 7306-68-5; 8-phenyl-9-methylpurine, 33833-45-3; 6-anilino-9-methylpurine, 84602-82-4; 6-anilino-9-(2-tetrahydropyranyl)purine, 84002-83-5; 5-amino-4-chloro-6-(methylamino)pyrimidine, 52602-68-3; 6-anilinopurine, 1210-66-8; 4-amino-5-(methylamino)pyrimidine, 3059-67-4; benzamidine, 618-39-3; 9-methyladenine (dianion), 84623-11-0; 7-methyladenine (dianion), 84623-12-1; 6-(methylamino)-9-methylpurine (dianion), 84602-84-6; methyl diethoxyacetate, 16326-34-4; potassium amide, 17242-52-3; bromobenzene, 108-86-1.

Acetolysis of Permethylated *O*-Alkyl Glycopyranosides: Kinetics and Mechanism[1-4]

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Acetolysis of permethylated methyl α- and β-glycopyranosides of D-glucose, D-galactose, and D-mannose was studied. It was found that α-glycosides of D-glucose and D-galactose acetolyze at a greater rate than the corresponding β anomers, contrary to the behavior of these substrates toward acid-catalyzed hydrolysis and contrary to previous findings on the acetolysis of peracetylated disaccharides. The results were rationalized as a consequence of the coplanar and trans-diaxial orientation of the C(1) to glycosidic oxygen bond and the axially oriented nonbonding electrons of the ring oxygen in α anomers, resulting not only in orbital mixing of the axial lone-pair electrons of the ring oxygen with the C(1) to the glycosidic oxygen antibonding orbital but also in a highly favorable geometry for an E1 elimination. The reversed behavior of permethylated methyl α- and β-D-mannopyranoside as compared to permethylated α- and β-D-gluco- and -galactopyranosides was explained to be the consequence of a much higher conformational energy of the β anomer.

In connection with other work, we wanted to hydrolyze the *O*-glycosidic bond of selected permethylated methyl glycopyranosides. Since the glycosidic bond of these sugars was remarkably resistant even at elevated temperatures to acid-catalyzed hydrolysis, we became interested in acetolysis[5] as an acceptable alternative.

Preliminary experiments with methyl 2,3,4,6-tetra-*O*-methyl-α- and -β-D-glucopyranosides indicated that at +2 and/or −20 °C, acetolysis of the glycosidic bond with acetic anhydride containing 1% (v/v) of concentrated sulfuric acid was very fast, giving an equilibrium mixture of α- and β-1-acetates as the only reaction products. The observation that the α-glycosidic bond was cleaved faster than the β-glycosidic bond was contrary to reported rates for glycosidic bond cleavage by acetolysis of several peracetylated disaccharides[6] as well as the reported rates for acid-catalyzed hydrolysis of the glycosidic bond in anomeric methyl D-glycopyranosides[7] and their permethylated derivatives.[8] This unexpected finding, together with a lack of available data on the influence of stereoelectronic factors other than neighboring group participation upon the acetolysis rates of alkyl α- and β-glycopyranosides, prompted us to undertake a detailed study of the acetolysis of permethylated methyl α-and β-glycopyranosides of D-glucose, D-galactose, and D-mannose. The chosen substrates are the only ones which do not have the O–O or C–O 1,3 nonbonding interactions in either α or β anomer of a given hexopyranoside. This is very important for the interpretation of the kinetic data since the presence of such interaction would enormously complicate the situation.

Because of its complexity, the progress of acetolysis of a glycosidic bond is difficult to follow by observing the

Table I. Experimental Conditions for Separation of Permethylated Methyl α- and β-Glycopyranosides 1-6 and the Corresponding 1-α- and 1-β-Acetates (7-11) by Reverse Phase HPLC

sugar	solvent CH_3CN/H_2O	flow rate, mL/min	retention time, min
Methyl 2,3,4,6-tetra-*O*-methyl			
α-D-glucopyranoside (1)	1:3	1.0	5.60
β-D-glucopyranoside (2)	1:3	1.0	7.40
α-D-galactopyranoside (3)	1:5	1.2	4.80
β-D-galactopyranoside (4)	1:5	1.2	5.45
α-D-mannopyranoside (5)	1:4	1.2	6.55
β-D-mannopyranoside (6)	1:4	1.2	4.86
1-*O*-Acetyl-2,3,4,6-tetra-*O*-methyl			
α-D-glucopyranose (7)	1:3	1.0	8.10
β-D-glucopyranose (8)	1:3	1.0	11.80
α-D-galactopyranose (9)	1:5	1.2	6.90
β-D-galactopyranose (10)	1:5	1.2	9.45
α-D-mannopyranose (11)	1:4	1.2	7.70

(1) Taken in part form the Ph.D. thesis of M.H.-M.
(2) Supported in part by Public Health Service Grant CA15483.
(3) Dedicated to the memory of Prof. Milivoje S. Lozanić.
(4) Presented at the Annual Meeting of the Society for Complex Carbohydrates, Hershey, PA, Sept 22–24, 1982, Abstract No. 9.
(5) For a review on acetolysis see: R. D. Guthrie and J. F. McCarthy, *Adv. Carbohydr. Chem.*, **22**, 11–23 (1967), and references cited therein.
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Table II. ^{1}H NMR Spectral Data of Permethylated Methyl Glycopyranosides

	^{1}H chemical shifts, ppm				coupling constants, Hz		
sugar	H-1	H-2	H-3	OCH_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
1	4.83	3.22		3.63, 3.54, 3.51, 3.42, 3.41	3.66	9.77	
2	4.14			3.62, 3.56, 3.53, 3.52, 3.41	7.63		
3	4.88			3.57, 3.52, 3.52, 3.42, 3.40	3.66		
4	4.15	3.31	3.15	3.58, 3.56, 3.52, 3.51, 3.41	7.63	9.77	3.05
5	4.80			3.52, 3.49, 3.48, 3.41, 3.38	1.83		
6	4.28			3.60, 3.50, 3.50, 3.47, 3.38	0.91		

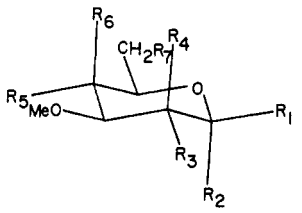
Table III. ^{1}H NMR Spectral Data of Permethylated Glycopyranose 1-Acetates

	^{1}H chemical shifts, ppm			
sugar	H-1	OCH_3	OAc	$J_{1,2}$, Hz
7	6.31	3.64, 3.56, 3.47, 3.40	2.13	3.66
8	5.45	3.64, 3.54, 3.54, 3.38	2.13	6.93
9	6.37	3.58, 3.54, 3.47, 3.39	2.12	3.66
10	5.45	3.58, 3.55, 3.54, 3.38	2.13	7.93
11	6.22	3.54, 3.52, 3.52, 3.40	2.11	1.83

change in optical rotation.[6,9-11] Thin-layer chromatography (TLC) in several solvents was likewise found to be unsatisfactory since, in addition to inherent inaccuracies, the R_f values of starting materials and reaction products were generally too close to permit reliable quantitation. Consequently, we developed a new general method for monitoring the progress of the acetolysis that allowed direct and accurate measurement of the concentrations of starting material and reaction products at any time during the reaction. This procedure involved adding samples of the acetolysis reaction mixture to a saturated aqueous $NaHCO_3$ solution containing 10% (v/v) methanol and, after the workup (vide infra), analyzing them by high-pressure liquid chromatography (HPLC) with a μ-Bondapak C_{18} column and the conditions given in Table I.

Experimental Section

Materials. Methyl 2,3,4,6-tetra-*O*-methyl-α- and -β-glycopyranosides of D-glucose (**1** and **2**), D-galactose (**3** and **4**), and D-mannose (**5** and **6**) were obtained by methylation of the corresponding parent sugar with methyl iodide–BaO/$Ba(OH)_2$ in *N*,*N*-dimethylformamide.[12] The permethylated methyl β-D-mannopyranoside **6** was obtained by alkaline hydrolysis (0.5 N NaOH in 80% aqueous methanol, room temperature, overnight, quantitative yield) of methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methyl-β-D-mannopyranoside (**12**)[13] followed by methylation[12] of the 3-*O*-methyl derivative **13**. The anomeric purity of all permethylated methyl glycopyranosides and the anomeric configuration of the permethylated glycopyranose 1-acetates were ascertained by ^{1}H NMR spectroscopy[14,15] (Tables II and III) and by measuring specific optical rotations. ^{1}H NMR spectra of deuteriochloroform solutions were recorded with a Brucker WM-360 spectrometer with tetramethylsilane as the internal standard. Chemical shifts are expressed in parts per milion (ppm). Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell.



1, $R_1 = R_4 = R_6 = H$; $R_2 = R_3 = R_5 = R_7 = OCH_3$
2, $R_1 = R_3 = R_5 = R_7 = OCH_3$; $R_2 = R_4 = R_6 = H$
3, $R_1 = R_4 = R_5 = H$; $R_2 = R_3 = R_6 = R_7 = OCH_3$
4, $R_1 = R_3 = R_6 = R_7 = OCH_3$; $R_2 = R_4 = R_5 = H$
5, $R_1 = R_3 = R_6 = H$; $R_2 = R_4 = R_5 = R_7 = OCH_3$
6, $R_1 = R_4 = R_5 = R_7 = OCH_3$; $R_2 = R_3 = R_6 = H$
7, $R_1 = R_4 = R_6 = H$; $R_2 = OAc$; $R_3 = R_5 = R_7 = OCH_3$
8, $R_1 = OAc$; $R_2 = R_4 = R_6 = H$; $R_3 = R_5 = R_7 = OCH_3$
9, $R_1 = R_4 = R_5 = H$; $R_2 = OAc$; $R_3 = R_6 = R_7 = OCH_3$
10, $R_1 = OAc$; $R_2 = R_4 = R_5 = H$; $R_3 = R_6 = R_7 = OCH_3$
11, $R_1 = R_3 = R_6 = H$; $R_2 = OAc$; $R_4 = R_5 = R_7 = OCH_3$
12, $R_1 = OCH_3$; $R_2 = R_3 = R_6 = H$; $R_4 = R_5 = R_7 = PhCOO$
13, $R_1 = OCH_3$; $R_2 = R_3 = R_6 = H$; $R_4 = R_5 = R_7 = OH$

Measured optical rotations of permethylated methyl glycopyranosides **1**–**6** and permethylated glycopyranose 1-acetate **11** were in excellent agreement with the reported values (for β-D-glucoside **2**,[17] α-D-galactoside **3**,[18] α-D-mannoside **5**,[17] β-D-mannoside **6**,[19] and α-D-mannopyranose 1-acetate **11**[22] within 2° and for α-D-glucoside **1**[16] and β-D-galactoside **4**[18] within 4°). There was, however, a large discrepancy between the reported[20] and measured $[\alpha]_D$ values of α- and β-D-glucopyranose 1-acetates **7** and **8**. For **7**, we have found $[\alpha]^{27}_D$ to be +131° (lit.[20] +165°) and for **8**, +10° (lit.[20] −17°) (both rotations were determined in a chloroform solution at a concentration of 1.43 for the former and 0.57 for the latter glycopyranose 1-acetate). The rather large difference between the reported[20] and determined $[\alpha]_D$ values for the sugars **7** and **8** is probably due to the fact that Van Dyke et al.[20] have not been able to obtain α- and β-D-glucopyranose 1-acetates **7** and **8** in the pure state. The $[\alpha]_D$ values reported in their paper were calculated from the $[\alpha]_D$ value of a mixture of **7** and **8**, the composition of which was determined by partial alkaline hydrolysis. Although the permethylated α- and β-D-galactopyranose 1-acetates **9** and **10** have been prepared,[20] their rotation has never been reported. We have prepared both permethylated α- and β-D-galactopyranose 1-acetates in pure form and determined for **9** $[\alpha]^{27}_D$ +118° (*c* 1.05, $CHCl_3$) and for **10** $[\alpha]^{27}_D$ +3° (*c* 1.00, $CHCl_3$).

Acetolysis. A permethylated glycoside (200 mg, 0.8 mmol) dissolved in acetic anhydride (0.2 mL) was heated to the desired reaction temperature (75 °C),[23] and the acetolysis reagent[24] (3.1

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(14) We are greatly indebted to Dr. Charles W. DeBrosse for recording the 360-MHz ^{1}H NMR spectra.
(15) For previous reports on the ^{1}H NMR spectra of permethylated methyl α- and β-D-gluco-, D-galacto-, and D-mannopyranosides see (a) J. Haverkamp, M. J. A. DeBie, and J. F. G. Vliegenthart, *Carbohydr. Res.*, **39**, 201 (1975); (b) D. G. Streefkerk and A. M. Stephen, *ibid.*, **49**, 13 (1976).
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(23) The acetolysis of permethylated methyl α- and β-glycopyranosides of D-glucose, D-galactose, and D-mannose with acetic anhydride containing 1% (v/v) of concentrated sulfuric acid or with a 1:1 (v/v) acetic anhydride–acetic acid mixture containing 1% (v/v) sulfuric acid at room temperature, 2 °C and even −20 °C was too fast for some glycosides to permit accurate kinetical measurements; however, at −60 °C, with the exception of permethylated methyl α-D-galactopyranoside, the acetolysis was too slow.

Table IV. Determination of the Amount of Pure Glycopyranose Derivatives 1-11 (moles) Corresponding to Unit Peak Area (cm^2)[a]

sugar	no. of samples	$10^7 \times$ mol/cm^2 (mean)	$10^8 \times$ standard deviation	% rel standard deviation
1	9	7.31	2.33	3.2
2	9	7.80	3.23	4.1
3	9	9.05	3.36	3.7
4	9	7.51	4.31	5.7
5	9	6.87	3.86	5.6
6	9	8.54	5.05	5.9
7	9	6.20	2.58	4.2
8	8	6.64	3.54	5.3
9	8	6.90	4.56	6.6
10	8	8.07	5.44	6.7
11	8	7.17	2.30	3.2

[a] The experimental conditions for individual determinations are identical with those given in Table I.

mL), after being heated to the same temperature, was added to the acetic anhydride solution of a glycopyranoside. At predetermined time intervals, aliquots (100 μL) were taken from the reaction mixture and added to test tubes containing saturated aqueous $NaHCO_3$ solution (1 mL) and methanol (0.1 mL). The test tube contents were shaken for approximately 10 min and the aqueous solutions extracted with chloroform (1 mL). The chloroform extracts were evaporated to dryness in a stream of nitrogen, the residues dissolved in acetone (50 μL), and the resulting solutions analyzed by HPLC chromatography.[25]

Kinetics: Measurements and Calculations. Samples (10 μL) were injected onto a μ-Bondapak C_{18} column (3.9 × 300 mm, 10-μm particle size, Waters Associates, Inc.) via a U6K universal injector (Waters Associates, Inc.); the effluent was monitored with R-401 differential refractometer (Waters Associates, Inc.). The composition of eluants, the eluant flow rates, and the corresponding retention times (in minutes) for individual determinations are given in Table I.

In all kinetic measurements, the progress of acetolysis was followed by monitoring the change of relative concentration, expressed in mole percents, of the permethylated methyl glycopyranoside, and assuming that at any moment during the acetolysis the sum of all components present in the reaction mixture is equal to 100 mol %. The justification for doing this was based on the fact that the acetolysis of permethylated methyl glycopyranosides 1–6 was a very clean reaction: at any moment during the acetolysis, in addition to starting material (before the completion of the reaction) only permethylated α- and β-D-glycopyranose 1-acetates in thermodynamic equilibrium could be detected in the reaction mixture. There were no detectable traces of side product(s) present.

Since the amounts of starting material and the reaction products in the acetolysis mixture were monitored with a differential refractometer, and various glycopyranose derivatives may and probably do have different refractive indices, for each glycopyranose derivative we determined the amount of sugar corresponding to a unit peak area (expressed in mol/cm^2) by injecting a known amount of a given glycopyranose derivative onto a HPLC column and measuring the obtained peak area. The peak areas were calculated by multiplying the peak height by half the base length since all the peaks were symmetrical and well-defined. As can be seen in Table IV, small differences in refractive index changes were observed for the different sugar derivatives.

For determination of the rate of acetolysis, the logarithm of mole percents of unreacted methyl glycopyranoside was plotted vs. time (seconds). The data were fitted to a straight line by least-squares regression analysis, whereby the correlation coefficients were within −0.96 and −1.00. The rate constant and half-life were then calculated from the slope. The numerical data for the acetolysis rate constants, half-lives, and the α/β 1-acetate ratios are given in Table V.

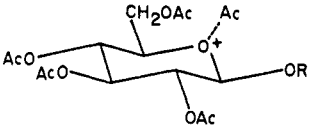
Table V. Kinetic Data for Acetolysis of Permethylated Methyl Glycopyranosides 1-6 (200 mg of Each) with Acetic Anhydride–Methanesulfonic Acid (30:1 v/v, 3.1 mL) at 75 °C

sugar	$10^3 k_1$, s^{-1}	$10^3 \times$ standard deviation	$10^{-2} t_{1/2}$, s	α/β ratio of 1-acetates
1	1.87	0.0734	3.71	3.17
2	0.12	0.00462	59.70	3.36
3	37.10	1.43	0.19	2.97
4	0.84	0.0709	8.27	3.22
5	1.08	0.0456	6.42	only α acetate
6	3.06	0.0631	2.24	only α acetate

The α to β ratio of glycopyranose 1-acetates obained by acetolysis of permethylated methyl α- and β-D-gluco- and -galactopyranosides was constant at all time intervals, suggesting that the two anomeric 1-acetates were in thermodynamic equilibrium throughout the acetolysis. This could be possible only if the anomerization of permethylated glycopyranose 1-acetates is a much faster reaction than the acetolysis. In order to check this conclusion, we compared, at 2 °C, the rate of acetolysis of permethylated methyl α-D-glucopyranoside with the rate of anomerization of permethyl-α-D-glucopyranose 1-acetate 7 under identical reaction conditions (99:1 acetic anhydride–concentrated H_2SO_4 and the same sugar concentration and reaction temperature). The anomerization was ca. 20 times faster than the acetolysis, giving the mixture of α- and β-1-acetates in approximately the same ratio as for the acetolysis.

Results and Discussion

The acetolysis of the glycosidic bond of methyl α- and β-D-glycopyranosides has thus far not been systematically studied.[26] Rather, the relative rates of glycosidic-bond cleavage by acetolysis have been inferred from studies of various polysaccharides. Rosenfeld and Ballou[6] attempted to elucidate the reaction mechanism by comparing the initial acetolysis rates of several peracetylated disaccharides. Without ruling out the Lemieux mechanism,[27] they concluded that Lindberg's mechanism,[10,11] postulated as an explanation for the acid-catalyzed anomerization of alkyl glycopyranosides, represented the most plausible pathway for acetolysis. According to their rationale, the acetylium $[CH_3CO]^+$ cation coordinates with the ring oxygen of the glycosidically bound sugar to give the intermediate 14, which, in the rate-determining step, undergoes



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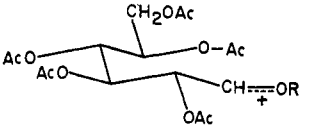

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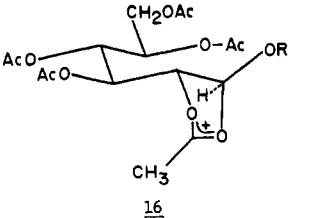

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ring opening to the acyclic resonance-stabilized carbonium ion 15. This, in turn, can be additionally stabilized by neighboring acetoxy group participation resulting in the

(24) The acetolysis reagent was made fresh prior to each reaction by dissolving methanesulfonic acid (0.1 mL) in acetic anhydride (3.0 mL).

(25) Direct analysis of chloroform extracts was impractical since with the solvent systems used (see Talbe I), chloroform is eluted from the column as a broad tailing peak over an interval of 10 min; thus a total of 38 min is needed to remove all the chloroform from the column.

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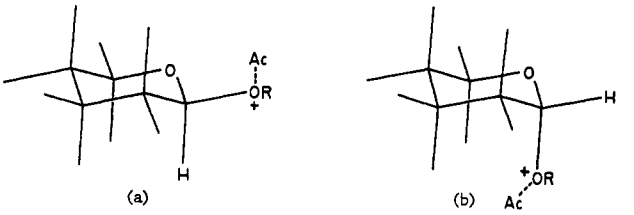
formation of the acyloxonium ion **16**. The carbonium ion intermediates **15** and **16**, once formed, can then cyclize with loss of acetylium cation to give either anomer (anomerization) or may be subjected to nucleophilic attack by acetic anhydride with concomitant loss of the acetylium cation to give acyclic products. Furthermore, the acetal group at C(1) may be attacked by O(5) with the elimination of either acetic anhydride (anomerization) or alkyl acetate (acetolysis); the second pathway represents the Rosenfeld and Ballou extension of Lindberg's mechanism.

The most serious objections to this mechanism are (a) that the anchimeric assistance of the C(2) acetoxy group may not only stabilize the positive charge at the C(1) carbon after heterolysis of the C(1)–O(5) bond (**16**) but also facilitate the rate-determining C(1) to ring oxygen bond cleavage if the C(2) acetoxy group is oriented trans to the ring oxygen, a fact which even Rosenfeld and Ballou recognized, (b) that, being acetylated, the C(5) oxygen of **15** or **16** is not nucleophilic and therefore cannot and/or will not attack the C(1) carbonium ion, and (c) that it is not clear why the final cyclization occurs with exclusive formation of the pyranose rather than the furanose 1-acetate, since, being kinetically controlled, it might be expected that the acetolysis would preferentially lead to five-membered-ring formation. In addition to the above objections, this mechanism is also in contradiction with the data reported in this paper.

From Table V it can be seen that the α anomers of permethylated methyl D-gluco- and D-galactopyranosides are acetolyzed faster than are the corresponding β anomers. In the case of permethylated methyl α- and β-D-mannopyranosides, the β anomer is acetolyzed (ca. 3 times) faster than the α anomer (vide infra). It is interesting to note that, whereas the ratio of acetolysis rates for the β anomers of permethylated D-gluco-, D-galacto-, and D-mannopyranosides (**2**, **4**, and **6**, respectively) are 1:7:25, the permethylated methyl α-D-galactopyranoside **3** is acetolyzed much faster than both the permethylated methyl α-D-glucopyranoside **1** (ca. 20 times) and the corresponding α-D-mannopyranoside derivative **5** (ca. 34 times; see Table V).

We will not attempt to compare the results of these studies with the kinetic data and conclusions of Rosenfeld and Ballou[6] because the substrates used in our kinetic measurements (the permethylated methyl α- and β-D-glycopyranosides of D-glucose, D-galactose, and D-mannose), unlike those used by Rosenfeld and Ballou, do not contain at the C-2 (or any other) carbon a group which could interfere in the rate-determining step. Further, we believe that our kinetic data, unlike those of Rosefeld and Ballou, are a direct result of stereoelectronic interactions inherent to a given glycon structure.

There is little doubt that the first step in the acetolysis of an *O*-glycosidic bond must be the coordination of the acetylium $[CH_3CO]^+$ cation with one of the two oxygens bonded to the C(1) carbon of a sugar glycoside. Contrary to Rosenfeld and Ballou, we believe that it is not the ring but rather the glycosidic oxygen (for the rationalization vide infra). The addition and loss of acetylium ion to the glycosidic oxygen is presumably a fast and reversible process so that the equilibrium concentration of the conjugate acid **17** is reached very quickly. However, the heterolysis of the C(1) to glycosidic oxygen bond is the rate-determining step. Thus the rate of acetolysis must depend upon both the concentration of the positively charged acetylium–glycoside complex **17** and upon the activation energy needed to convert the conjugate acid (**17**) into the transition-state intermediate, which is presumably



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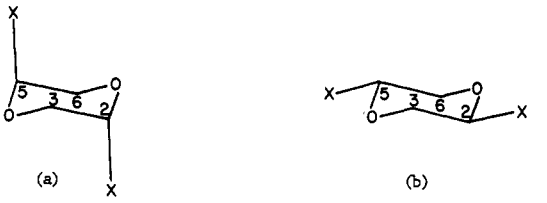
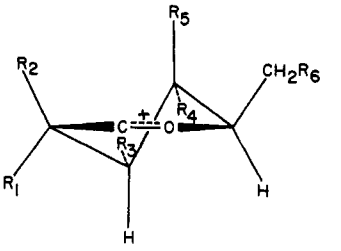


18, X = Cl, Br



19, $R_1 = R_3 = R_4 = R_6 = OCH_3$; $R_2 = R_5 = H$
20, $R_1 = R_3 = R_5 = R_6 = OCH_3$; $R_2 = R_4 = H$
21, $R_1 = R_5 = H$; $R_2 = R_3 = R_4 = R_6 = OCH_3$

the same for both anomers (**19**–**21**). Consequently, the heterolysis of a β-glycosidic bond may be actually slower than that of an α-glycosidic bond, but if the concentration of conjugate acid is sufficiently higher for the β (**17a**) than for the α anomer (**17b**), the observed rate of acetolysis of the β-glycosidic bond can be higher. Similarly, the concentration of conjugate acid may be lower for the α than for the β anomer, but if the activation energy is sufficiently higher for the β than for the α anomer, the α anomer could be acetolyzed at a higher rate.

The greater reactivity of anomers with equatorially oriented aglycons (e.g., β-D) has been ascribed[28,30] to their higher ground-state energy caused by dipolar interaction between the equatorially oriented C(1) alkoxy group and the two pairs of nonbonding electrons of the ring oxygen. Protonation of the glycosidic oxygen destroys this destabilizing interaction. Consequently, the concentration of conjugate acid **17** can be expected to be greater in the case of β than in the case of α anomers (for D sugars) which should result in a higher rate of heterolytic cleavage of the equatorially oriented C(1) to glycosidic oxygen bond. Similarly, Lemieux and Morgan[31] attributed the rate difference between equatorial and axial anomers in acid-catalyzed glycoside hydrolysis to additional stabilization of the conjugate acid by the equatorially oriented aglycon due to a reverse anomeric effect, resulting in an increase of the equilibrium concentration of the conjugate acid **17** and a higher hydrolysis rate.

These two rationalizations cannot explain the faster acetolysis rates of the α vs. the β anomers of permethylated methyl glycopyranosides **1**–**4**. There must therefore be another structural property(ies) of the glycon residue which

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is (are) responsible for the observed rate differences.

It is quite reasonable to assume that, in acetic anhydride as the solvent, electronic interactions must play an important role in determining the chemical behavior of the glycosidic bond, since acetic anhydride has a relatively low dielectric constant (E = 20.7° at 19 °C) and is aprotic. This conclusion is supported by findings that an acetic anhydride solution of D-glucose pentaacetate contains, after equilibration with sulfuric acid, approximately 87% of the α and 13% of the β anomer.[32]

It is known[33a] that in 2,5-dihalo-1,4-dioxanes (**18**) (a) the C(2)–O distance is shorter than the C(6)–O distance, which appears to be of normal length when compared with the C–O bond in aliphatic ethers, and (b) the axial C(2)–X (X = Cl, Br) bond (**18a**) seem to be somewhat longer than the corresponding equatorial bond (18b). These bond length "abnormalities" have been interpreted by postulating[33] that two nonbonding electrons of the ring oxygen are delocalized by mixing the oxygen's axial nonbonding p orbital with the antibonding σ^* orbital of the axially oriented C–X grouping. This type of delocalization would have a tendency to strengthen and consequently shorten the C(2)–O bond and to slightly weaken and consequently elongate the C–X bond, and it should be common to all glycopyranosides with an axially oriented glycosidic oxygen.[26b,c] We believe that such an electronic interaction is responsible for the observed faster acetolysis of the permethylated methyl α-D-glycopyranosides of D-glucose and D-galactose. Mixing of the "axially oriented" p orbital of the ring oxygen with the antibonding σ^* orbital of the axially oriented C(1) to glycosidic oxygen bond will make the ring oxygen more electropositive and thus less susceptible to electrophilic attack by the acetylium cation. However, as a consequence of this orbital mixing, the glycosidic oxygen becomes more electronegative and thus significantly more basic than the ring oxygen. This is why we assumed (vide supra) that the acetylium cation coordinates with the glycosidic and not with the ring oxygen. Another important structural property of glycopyranosides having an axially oriented glycosidic oxygen is their geometry: namely, the axially oriented "leaving group" at the C(1) carbon (methyl acetate in **17b**) and the axially oriented nonbonding p electrons of the ring oxygen are coplanar and trans oriented, having thus the optimal geometry for an E1 elimination. Obviously, none of the above stereoelectronic factors, which can accelerate the C(1) to glycosidic oxygen bond cleavage, exist in glycopyranosides with an equatorially oriented aglycon. If the proposed rationalization is true, then it can also be expected that the 1,3-dipolar interaction of the "axially oriented" nonbonding p electrons of the ring oxygen with an axially oriented electronegative substituent (e.g., oxygen) located on the same side of the pyranoside ring may additionally accelerate the cleavage of the axial C(1) to glycosidic oxygen bond since the extent of the n $\rightarrow \sigma^*$ orbital mixing could be further increased as a consequence of this dipolar interaction. Indeed, the permethylated methyl α-D-galactopyranoside is acetolyzed faster than the corresponding methyl α-D-glucopyranoside derivative.

The observed higher acetolysis rate of permethylated methyl β-D-mannopyranoside as compared to the α anomer (the α/β ratio being 0.35) may seem to contradict the above mechanism. However, there may be several reasons for such a behavior. First, the axial orientation of the C(2) methoxy group considerably increases the ground-state energy of the β anomer due to unfavorable torsional strain and electrostatic interactions. Second, the described n $\rightarrow \sigma^*$ orbital mixing in α anomers of D-glycopyranosides could be expected to be less favored if they have an axially oriented substituent at the C-2 carbon since the n $\rightarrow \sigma^*$ orbital mixing should result in flattening the pyranoside ring involving the C(5), O(5), C(1), and C(2) atoms which will increase the eclipsing of the equatorial C(3) and the axial C(2) methoxy groups (in the case of permethylated methyl α-D-mannopyranoside).

The faster acid-catalyzed hydrolysis of methyl α- and β-D-galactopyranosides as compared to the methyl α- and β-D-glucopyranosides, as well as the faster acetolysis of both permethylated methyl D-galactopyranosides and the slower acetolysis rate of permethylated methyl α-D-mannopyranoside as compared to that of permethylated methyl α-D-glucopyranoside, is in accord with the proposal of Chapman and Laird[34] that in the transition state the pyranoside ring adopts a half-chair conformation wherein the C(2), C(1), O(5), and C(5) atoms all lie in one plane in order to allow for maximal stabilization of the intermediate carbonium ion (**19–21**) through mesomeric interaction with the ring oxygen. However, the speculation[29,30,35,36] that the conversion of the $^4C_1$ ground-state pyranoside chair into the $^4H_3$ half-chair conformation of the transition-state intermediate (**19–21**) involves counterclockwise rotation about the C(2)–C(3) and the C(4)–C(5) bonds is not in full agreement with the kinetic data. Inspection of molecular models of methyl α- and β-D-galactopyranosides or their permethylated derivatives shows that counterclockwise rotation about the C(4)–C(5) [or C(5)–C(4)] bond increases the eclipsing of the C(5) hydroxymethyl (or methoxymethyl) and the axially oriented C(4) hydroxyl (or methoxyl) groups. The torsional strain between these two substituents reaches a maximal value in the $^4H_3$ half-chair conformation of the transition-state intermediate. It is therefore reasonable to expect that the acid-catalyzed hydrolysis of methyl α- and β-D-galactopyranosides should be slower than that of the methyl α- and β-D-glucopyranosides and, likewise, that the permethylated methyl α- and β-D-galactopyranosides should be acetolyzed at a slower rate than the corresponding permethylated methyl α- and β-D-glucopyranosides. Since the opposite was found, one can only conclude that counterclockwise rotation about the C(4)–C(5) bond does not take place during the conversion of the ground-state $^4C_1$ chair conformation of a D-galactopyranose (and possibly any hexopyranose) derivative into the $^4H_3$ half-chair conformation of the transition-state intermediate. However, counterclockwise rotation about the C(2)–C(3) bond may well be the route by which the $^4C_1$ ground-state chair conformation of a glycopyranoside is converted into the $^4H_3$ half-chair conformation of the transition-state intermediate (**19–21**). From inspection of molecular models, it is apparent that when the C(2) and C(3) substituents are cis oriented (e.g., D-manno- and D-allopyranosides), counterclockwise rotation about the C(2)–C(3) bond increases the eclipsing of these substituents and thus torsional strain. This should result in slower acid-catalyzed hydrolysis and slower acetolysis of the glycosidic bond in these sugars. Indeed, the acetolysis of

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(35) W. G. Overend in "The Carbohydrates, Chemistry and Biochemistry", Vol. IA, W. Pigman and D. Horton, Eds., 2nd ed., Academic Press, New York and London, 1972, p 326.
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permethylated methyl α-D-mannopyranoside is slower than the acetolysis of either permethylated methyl α-D-gluco- or α-D-galactopyranosides.

Therefore, it can be concluded that the conversion of the ground-state chair into the transition-state half-chair conformation of a glycopyranose derivative involves counterclockwise rotation about the C(2)–C(3) and the C(1)–O(5) bonds, analogous to the conversion of a cyclohexane chair into the C_2 half-chair conformation.

The faster acetolysis of permethylated methyl β-D-mannopyranoside as compared to β anomers of both permethylated methyl D-gluco- and D-glactopyranosides is probably due to a much higher ground-state energy of the former.

Registry No. 1, 605-81-2; 2, 3149-65-3; 3, 3149-64-2; 4, 2296-47-1; 5, 3149-62-0; 6, 3445-71-4; 7, 3554-77-6; 8, 3554-78-7; 9, 38986-86-6; 10, 38982-49-9; 11, 38986-87-7; 12, 54307-88-9; 13, 84580-16-5.

Reactions of Haloketenes with Allyl Ethers and Thioethers: A New Type of Claisen Rearrangement[1]

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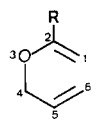
A new reaction of dichloroketene (2) with allylic ethers, sulfides, and selenide 1 has been observed. A [3,3] sigmatropic rearrangement takes place at room temperature, leading to α,α'-dichloro-γ,δ-unsaturated esters 3. The scope of this reaction was further investigated with dibromoketene (16), difluoroketene (17), electron-deficient chloroketenes, and different allylic systems. In the course of these studies, total syntheses of two naturally occurring macrolides, phoracantholide I and phoracantholide J, were achieved. Medium-ring conformations are discussed.

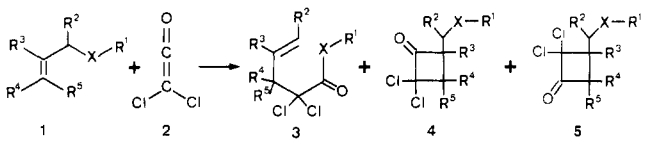
The utility of Claisen rearrangement in the synthesis of complex molecules has recently been reviewed.[3] This rearrangement has value because it proceeds through a highly ordered transition state, leading to unsaturated carbonyl compounds with high regio- and stereospecificity. Unfortunately, the desired transformation often requires temperatures too high for the survival of sensitive functional groups.

One solution to this problem has been to change the rate of Claisen rearrangement through appropriate substituents. Thus, with π-donor substituents at position C-2, the



temperatures for Claisen rearrangement can range from 200 °C to ambient temperature. The rates follow the usual order of donor strength: sodium or lithium enolates (R = $O^{-+}Na$[4] or $O^{-+}Li$[5]) > zinc enolate (R = $O^{-+}ZnBr$[6]) > amide acetal (R = NMe_2[7]) > ortho ester (R = OMe[8]) ≫ vinyl ether (R = H, Me[9]).

Scheme I



X = O, S, Se

Table I. Yields of Competitive Reactions of Allyl Sulfides 1a-f and Selenide 1g with Dichloroketene (2)

entry	X	R^1	R^2	R^3	R^4	R^5	% yield[a] of 3	% yield[b] of 4
a	S	Et	H	H	Me	Me	38	
b	S	Et	H	H	Me	H	45	
c	S	Et	H	Me	H	H	21	
d	S	Me	H	CN	H	H	26	
e	S	Me	H	H	H	H	25	
f	S	Ph	H	H	Me	Me	26	19
g	Se	Ph	H	H	Me	Me	38	19

[a] Yields of isolated products. [b] Yields calculated from integrated ^1H NMR spectra.

A positively charged heteratom at position 3 also lowers the activation energy of the rearrangement. For the Claisen rearrangement of allyl aryl ethers in the presence of boron trichloride, Schmid et al.[10] report that the "charge induction" causes an increase in the reaction rate of 10^{10}. The acceleration factors (k_{H^+}/k_Δ) calculated from the activation parameters of the acid-catalyzed rearrangement of *N*-allylaniline are also very large: 10^5–10^7.[11,12]

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