Experimental and Theoretical Evidence of Through-Space Electrostatic Stabilization of the Incipient Oxocarbenium Ion by an Axially Oriented Electronegative Substituent During Glycopyranoside Acetolysis

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The rate of acetolysis of methyl 2,3,6-tri-*O*-methyl-α-D-galacto- and -glucopyranosides depends strongly on the electronegativity of the C4 substituent. Thus, of the three derivatives studied (4-methoxy, 4-acetoxy, and 4-acetamido-4-deoxy derivatives of D-galacto- and D-glucopyranosides), the glycopyranosides bearing the most electronegative C4 substituent (methoxy group) acetolyze at the fastest rate, whereas those having the least electronegative C4 substituent (*N*-acetamido group) acetolyze at the slowest rate. Furthermore, whereas the influence of the electronegativity of the C4 substituent upon the acetolysis rate in the D-*gluco* series is relatively moderate (k_{max}/k_{min} = 2.9−3.5), this influence is very large in the D-*galacto* series (k_{max}/k_{min} = 44.4−58.6). We propose that this observation can only be explained by the existence of an electron donation process from the axially oriented electronegative substituent at the C4 carbon atom of the galactopyranoside ring to the forming oxocarbenium ion. Such a through-space phenomenon cannot occur in the glucopyranoside series where the C4 carbon substituent is oriented equatorially. *Ab initio* calculations of model molecules fully support the above conclusions.

Introduction

It is a widely accepted view that in structures R−Y−C−Z, where Y is a heteroatom (oxygen or sulfur) and Z is an electron-withdrawing group (such as a halogen atom or an alkyloxy group), the ligands R and Z will adopt the synclinal (gauche) conformation about the heteroatom−carbon (Y−C) bond, if the heteroatom Y has at least one pair of sp^3-hybridized nonbonding electrons which can assume an antiperiplanar orientation to the ligand Z. This preference for the synclinal conformation was explained to be due to the $n \rightarrow \sigma^*$ orbital mixing of this lone electron pair with the antibonding orbital of the C−Z bond (generalized anomeric effect, GAE).[5] The antiperiplanar lone pair hypothesis (ALPH)[6] goes one step further, postulating that the antiperiplanar relationship of the sp^3-lone pair orbital of Y and the cleavable C−Z bond results in lengthening and thus weakening of the cleavable carbon−heteroatom bond (kinetic anomeric effect). Hence, in the case of glycopyranosides, the α-anomers should be expected to be more susceptible to acid-catalyzed cleavage than the β-anomers. However, studies on the hydrolysis of glycopyranosides have shown the opposite; β-D-glycopyranosides hydrolyze ca. 2−3 times faster than α-D-glycopyranosides. Interestingly and surprisingly, no apparent relationship between the sugar structure and its reactivity was noted. Due to the absence of a kinetic anomeric effect in the hydrolysis of acetal derivatives, two alternative hypotheses were proposed as an explanation for the hydrolysis of glycopyranosides. One hypothesis was based on the principle of least nuclear motion[7] and completely rejects a universal relationship between the anomeric hyperconjugation and the reactivity of the glycosidic bond. The other hypothesis, known as synperiplanar lone-pair hypothesis[6b,8] (SLPH) advocates that as the reaction progresses *synperiplanar* (sp^3) lone pair interactions in the energetically accessible half-chair conformation of the β-anomer are equivalent to the *antiperiplanar* interactions in the half-chair of the α-anomer. Deslongchamps et al.[9] have recently provided the first experimental evidence for the synperiplanar stereoelectronic effect in the acid hydrolysis of acetals. Results described in this paper strongly support the ALPH as an explanation for the acid-catalyzed cleavage of acetal bonds in glycopyranosides by acetolysis.

Some time ago we reported[10] that the glycosidic bond of α-anomers was cleaved *much faster* than the glycosidic bond of the corresponding β-anomers in the acid-catalyzed acetolysis of permethylated methyl α- and β-D-gluco- and -galactopyranosides (for the α-D-gluco derivative: ca. 15 times faster, and for the α-D-galacto derivative, ca. 44 times faster). This finding was contrary

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(5) Thatcher, G. R. J. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993; pp 6−25.

(6) For a good discussion of stereoelectronic control of acetal hydrolysis and ALPH, see: (a) Deslongchamps, P. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993; pp 26−54. (b) Deslongchamps, P. ; Dory, Y. L.; Li, S. *Can. J. Chem.* **1994**, *72,* 2021.

(7) Sinnott, M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113. See also; Sinott, M. L. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993; pp 97−113.

(8) (a) Ratcliffe, A. J.; Mootoo, D. R.; Andrews, C. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 7661. (b) Andrews, C. W.; Fraser-Reid, B.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 8293. See also: Andrews, C. W.; Fraser-Reid, B.; Bowen, J. P. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993; pp 114−125.

(9) Li, S.; Kirby, A. J.; Deslongchamps, P. *Tetrahedron Lett.* **1993**, *34*, 7757.

(10) Miljković, M.; Habash-Marino, M. *J. Org. Chem.* **1983**, *48,* 855.

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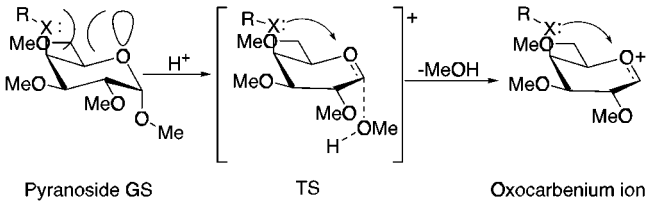
Scheme 1



to the well-known fact that β-D-glycopyranosides hydrolyze ca. 2−3 times faster than the corresponding α-anomers. We explained this large kinetic anomeric effect in terms of ALPH and argued that the reason for this discrepancy was that *the stereoelectronic effects and their influence upon the rate of the glycosidic bond cleavage can only be observed in aprotic and nonpolar solvents*. Our rationale was that protic solvents, such as water, due to extensive and unavoidable hydrogen bonding of solvent molecules to polar ligands on a glycopyranoside ring, such as oxygen or hydrogen atoms of hydroxyl groups, shield, if not completely destroy, the intrinsic electronic interactions present in a particular glycopyranoside structure. In addition, we suggested that polarity of solvents may also play an important role in determining the magnitude of electronic interactions in a sugar molecule, as observed previously.[11] For example, highly polar solvents, such as water (dielectric constant at 20° is $\epsilon = 80.20$), may decrease electronic interactions due to solvent−sugar dipolar interactions, whereas the solvents of lower polarity, such as acetic anhydride (dielectric constant for acetic anhydride at 19° is $\epsilon = 20.7$), may, due to the absence of such dipolar interactions, have a much smaller effect upon the magnitude of these electronic interactions. Thus we suggested that the acid-catalyzed acetolysis in acetic anhydride is a much better system than acid-catalyzed hydrolysis in aqueous solutions for studying the relationship between the reactivity of a glycosidic bond and the stereoelectronic interactions present in the glycopyranoside.

There were two reasons for choosing the permethylated methyl α- and β-D-gluco- and -galactopyranosides for our previous[10] as well as for this study: (a) methoxy groups are chemically inert under the reaction conditions chosen and (b) they are known to be "nonparticipating groups", thus eliminating the possibility that a substituent at the C2 or any other carbon of a glycopyranoside ring will interfere, via neighboring group participation, in the rate-determining step of the glycosidic bond cleavage, which is the scission of the C1−O1 bond. In our first study we suggested that the much faster acetolysis of methyl α-D-galactopyranoside as compared to the α-D-glucopyranoside (ca. 20 times) could be due to the electronic interaction between the strongly electronegative oxygen of the axially oriented C4 methoxy group and the axially oriented sp^3-lone pair electrons of the ring oxygen. The assumption was that this electronic interaction may influence the rate of acetolysis due to the electronic repulsion (destabilizing effect) in the ground state and electronic attraction (stabilizing effect) in the transition state and the oxocarbenium ion stage of reaction (see Scheme 1). One way to gain support for, or to disprove, this explanation was to examine the rates of acetolysis of various methyl 2,3,6-tri-*O*-methyl-α-D-galactopyranoside derivatives having different electronegative substituents at the C4 carbon. Hence, we decided to measure the rates of acetolysis of the methyl 4-*O*-methyl (**1**), 4-*O*-acetyl (**2**), and 4-acetamido-4-deoxy (**3**) 2,3,6-tri-*O*-methyl-α-D-galactopyranoside derivatives and to compare these rates with each other and with the acetolysis rates of methyl 4-*O*-methyl- (**4**), 4-*O*-acetyl- (**5**), and 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-glucopyranosides (**6**). The results of this study are reported in this paper.

Table 1. Range of Percentage Relative Standard Deviation (%RSD Range), Mean of Percentage Relative Standard Deviation (%RSD Mean), and Linear Correlation Coefficient for Concentration Curves of Various Glycopyranosides

glycopyranoside	%RSD range	%RSD mean	*R*
1	1.969−3.558	2.689	0.988
	0.538−4.792	1.933	0.989
2	1.740−4.693	3.595	1.000
	2.895−4.887	4.111	0.999
3	1.174−3.753	2.033	0.991
	1.447−3.876	2.367	0.996
4	0.647−3.176	1.639	0.982
	0.353−1.884	1.161	0.990
5	1.351−2.715	2.259	0.997
	0.753−3.688	2.577	0.999
6	1.538−1.622	1.591	0.994
	0.922−2.486	1.461	0.995

Materials and Methods

Methyl 2,3,4,6-tetra-*O*-methyl-α-D-galacto- and -glucopyranosides (**1** and **4**, respectively) were synthesized by direct methylation with dimethyl sulfate and sodium hydroxide in acetone of methyl α-D-galacto- and -glucopyranosides, as previously described.[12]

Syntheses of methyl 4-*O*-acetyl- and 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-galacto- (**2** and **3**) and -glucopyranosides (**5** and **6**) will be reported elsewhere.[13]

Concentration Curves. A sample of methyl 4-*O*-methyl-, 4-*O*-acetyl-, or 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-galacto- and/or -glucopyranoside was weighed into a 1.5 mL microfuge tube (50 or 100 mg). A solvent (acetone for permethylated sugars **1** and **4**, and methanol for 4-*O*-acetyl and 4-acetamido-4-deoxy derivatives **2**, **3**, **5**, and **6**) (250 or 500 μL, respectively) was added, and the solution was mixed on a vortexer, producing a stock solution with a final concentration of 200,μg sugar/μL solvent. This solution was stored on dry ice.[14] Aliquots of stock solutions (10 μL) were diluted with 40 μL solvent and briefly mixed on a vortexer, giving a 50 μL sample with the sugar concentration of 40 μg/μL solution. In a similar way, other samples (50 μL each) with the following sugar concentrations were prepared: 80 μg/μL solution, 120 μg/μL solution, 160 μg/μL solution, and 200 μg/μL solution.

From each sample, four 10 μL injections were made onto a μBondapak C18 reverse phase HPLC column(125 Å pore size, 10 μm particle size, 3.9 × 300 mm column size, Waters Corporation, Milford, MA) via a U6K injector (Waters Associates). Eluent was acetonitrile−water (see Table 1), and the

(11) Fuchs, B.; Ellencweig, A.; Tartakovsky, A.; Aped, P. *Angew. Chem., Int. Engl.* **1986**, *25*, 287.

(12) Glen, W. L.; Myers, G. S.; Grant, G. A. *J. Chem. Soc.* **1951**, 2568.

(13) Yeagley, D.; Miljković, M. *J. Serb. Chem. Soc.*, in press.

(14) Both microfuge tubes and microvials were used for the various runs. Initially microfuge tubes were used for the acetolysis study, as well as for the determination of concentration curves because they were of the proper size and easy to vortex and the water, after the chloroform extraction, was much easier to remove than from glass microvials. When it was determined that they leached smaller oligomers into the acetone solution or into the chloroform extract hplc chromatograms (retention time >50 min)] glass microvials were used instead. However, further studies showed that (1) the contamination of the acetone or chloroform solution coming from polyethylene microfuge tubes can be completely eliminated if the microfuge tubes were kept at −78 °C and (2) it had no effect upon the acetolysis results (direct comparison of kinetic values in experiments eriments using polyethylene microfuge tubes at −78 °C or glass microvials at room temperature gave identical results).

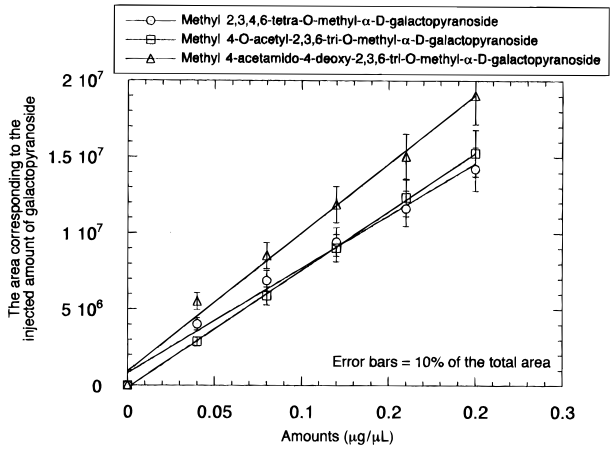


Figure 1. Concentration curves for 4-*O*-methyl, 4-*O*-acetyl, and 4-*O*-acetamido-4-deoxy derivatives of methyl 2,3,6-tri-*O*-methyl-α-D-galactopyranosides.

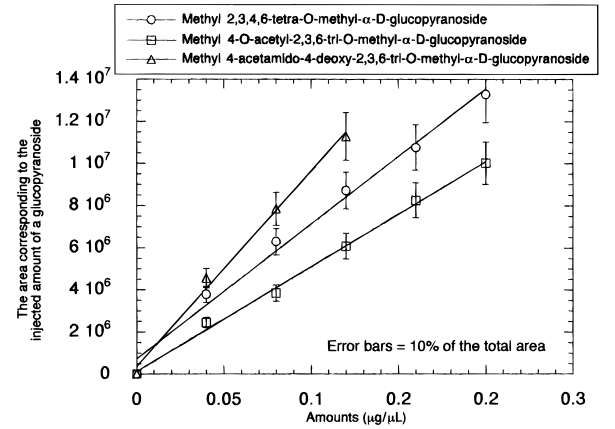


Figure 2. Concentration curves for 4-*O*-methyl, 4-*O*-acetyl, and 4-*O*-acetamido-4-deoxy derivatives of methyl 2,3,6-tri-*O*-methyl-α-D-glucopyranosides.

flow rate was 1.0 mL/min. The sugars were detected with a R401 differential refractometer (Waters Associates), and the obtained chromatograms were recorded using a Spectra Physics SP 4270 integrator. The calculated and reported areas under each peak were entered into the Kaleidagraph graphics program, and using the method of least squares, a straight line through the obtained points was determined. Figures 1 and 2 show a good linear relationship between the concentration of various glycopyranosides and the integrated area under the corresponding glycopyranoside peaks. Table 1 shows the statistical parameters for these concentration studies.

Acetolysis. The protocol used for kinetic measurements was essentially the same as described previously.[10] A sample of methyl 4-*O*-methyl-, 4-*O*-acetyl-, or 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-galacto- and/or -glucopyranoside (0.800 mM) was weighed into a 10 mL round-bottomed flask. To this were added acetic anhydride (200 μL) and a small magnetic stirring bar ("sugar solution"). To another 10 mL round-bottomed flask were added acetic anhydride (3.00 mL) and methanesulfonic acid (100 μL) ("reagent"). For acetolysis of 4-acetamido-4-deoxy derivatives **3** and **6** an additional amount of methanesulfonic acid (50 μL) was added.[15] The two flasks were immersed in the same oil bath, set at 75 °C, and heated for 10 min. After 9 min, a 100 μL aliquot of the "reagent" was removed and added to a 12−15 mL conical glass test tube containing methanol (100 μL) and saturated aqueous sodium bicarbonate solution (1.00 mL) and mixed by vortexing for approximately 5 s. After the solution was heated for 10 min, the "reagent" was added, in one portion, to the "sugar solution", the latter being continually mixed with a magnetic stirring bar. At set time intervals, 100 μL aliquots were removed and transferred into 12−15 mL conical glass test tubes containing methanol (100 μL) and saturated aqueous sodium bicarbonate solution (1.00 mL). After each sample was vortexed for approximately 5 s, it was kept for ca. 10 min at room temperature (at this point the release of carbon dioxide ceased) and each sample was vortexed for an additional 30 s. To each test tube was added chloroform (1.00 mL), and the unreacted starting material together with the acetolysis products was extracted by vortexing each test tube for 1 min. After the layers separated, the chloroform layer from each sample was removed by pipetting. Each organic phase was transferred into a 1.5 mL microfuge tube or to a 1.0 mL microvial. The aqueous solutions containing sodium bicarbonate and methanol to which the aliquots, taken at various times, were added were once more extracted with chloroform (0.5 mL) by vortexing each sample for 1 min. After the layers separated, the organic layer in each sample was transferred into the corresponding microfuge tube or microvial using the same disposable pipettes used for the first transfer. The chloroform solutions were first dried overnight at room temperature in a fume hood and then for at least 6 h in a vacuum desiccator over sodium hydroxide pellets to remove any residual water. Each vial was then capped and stored in a desiccator over sodium hydroxide pellets. Immediately prior to analysis, 50 μL of solvent was added to each aliquot and the reaction mixture was dissolved by vortexing. The permethylated glycopyranosides (**1** and **4**) and their acetolysis products were dissolved in acetone as in the previous study.[10] The 4-*O*-acetyl and the 4-acetamido-4-deoxy derivatives of methyl 2,3,6-tri-*O*-methyl-α-D-galacto- and -glucopyranosides (**2**, **3**, **5**, and **6**, respectively) eluted at the same time as acetone and therefore methanol was used to dissolve these compounds. Immediately after the reaction mixture was dissolved, a 10 μL sample was removed with a 25 μL Hamilton syringe, the microfuge tube, or microvial capped and stored on dry ice and kept there during all subsequent runs. The sample was injected, via a U6K injector (Waters Associates), onto the μBondapak column (Waters Corporation) . The individual components of the reaction mixture were separated by elution with acetonitrile−water (see Table 2) at a flow rate of 1.00 mL/min. The individual sugars were detected with the R401 differential refractometer (Waters Associates) and recorded and integrated with the Spectra Physics SP 4270 integrator. The amount of the remaining starting material versus time was plotted as a first-order reaction using the Levenberg−Marquardt algorithm incorporated into the Kaleidagraph graphics program.

Table 2. Eluents and Reaction Times for Kinetic Measurements of Acetolysis of Methyl Glycopyranosides

glycopyranoside	eluent acetonitrile−water	reaction time, min
1	1:5	2.0
2	1:3	10.0
3	1:3	15.0
4	1:3	20.0
5	1:9	60.0
6	1:9	60.0

Results and Discussion

With this study we wanted to answer two interrelated questions: (1) *does the 1,3-syn-diaxial electronic interaction between an axially oriented electronegative group at C4 of a galactopyranoside derivative with the axially oriented sp³ hybridized nonbonding electron pair of the*

(15) Assuming that the 4-acetamido group of **3** and **6** could also be protonated, under the used reaction conditions, we have decided to use 100% molar excess of methanesulfonic acid for the acetolysis of these two substrates since we wanted to be sure that the molar concentration of methanesulfonic acid available for the protonation of the glycosidic oxygen atom is identical to the amount of methanesulfonic acid used in kinetic studies with four other glycopyranosides (**1**, **2**, **4**, and **5**). However, if our assumption on protonation of the C4 acetamido group was wrong, then the determined acetolysis rates for these two glycopyranosides are possibly too high.

Table 3. Comparison of Present and Previous Acetolysis Rates of Methyl 2,3,4,6-Tetra-*O*-methyl-α-D-galacto- and -glucopyranosides

	$10^3 k_{app}$ (s^{-1})	
glycopyranoside	present	previous
1	24.37	37.10
4	1.64	1.87

Table 4. Kinetic Data Obtained for the Acetolysis of Methyl 4-*O*-Methyl, 4-*O*-Acetyl, and 4-Acetamido-4-deoxy Derivatives of Methyl 2,3,6-Tri-*O*-methyl-α-D-galacto- (1, 2, and 3, Respectively) and -Glucopyranosides (4, 5, and 6, Respectively)

			% RSD		
glycopyranoside	10^3k	% RSD[a] range	mean	R^b	intercept
1	22.18	1.74−11.44	5.95	0.999	8.43
	25.79	1.81−6.40	4.48	0.999	5.70
2	2.44	1.02−19.43	6.57	0.992	8.91
	2.39	1.32−13.00	6.49	0.994	8.59
3	0.44	1.89−22.02	5.16	0.986	10.60
	0.50	2.45−15.12	9.97	0.989	8.54
4	1.67	1.21−14.53	5.96	0.982	8.40
	1.63	1.06−9.56	3.43	0.984	6.97
5	0.63	0.73−6.04	3.01	0.983	6.04
	0.51	1.30−7.72	4.38	0.926	6.46
6	0.56	1.12−13.84	6.17	0.978	9.49
	0.47	1.01−14.66	4.54	0.916	8.20

[a] %RSD = % relative standard deviation. [b] R = linear correlation coefficient

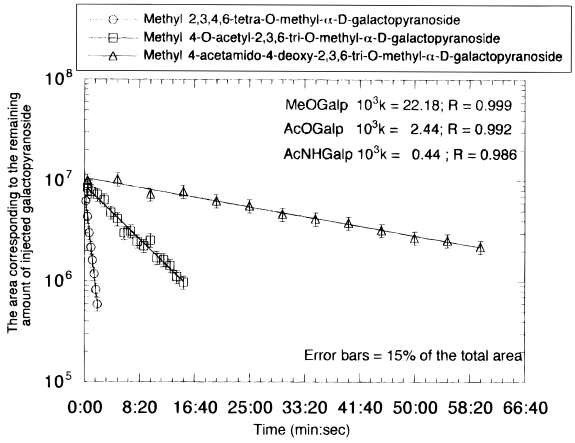


Figure 3.

ring oxygen exist and (2) if it does, is then this interaction responsible for the observed much higher acetolysis rate of methyl 2,3,4,6-tetra-O-methyl-α-D-galactopyranoside as compared to methyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside.[10]

Before undertaking the study on acetolysis of methyl 4-*O*-acetyl- and 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-galacto and -glucopyranosides, the previously published work[10] on the acetolysis of methyl 2,3,4,6-tetra-*O*-methyl-α-D-galacto- and -glucopyranosides was repeated. The protocol used was essentially the same as the one described in our previous study,[10] except that this time a Spectra Physics SP 4270 integrator was used for recording and integrating the peaks. The obtained results and the comparison of new with the previous results are given in Table 3. The results obtained in the current study are reported in Table 3 and 4 and Figures 3 and 4.

In the current study we found that methyl 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside cleaved 13.3−15.8 times faster than the methyl 2,3,4,6-tetra-*O*-methyl-α-

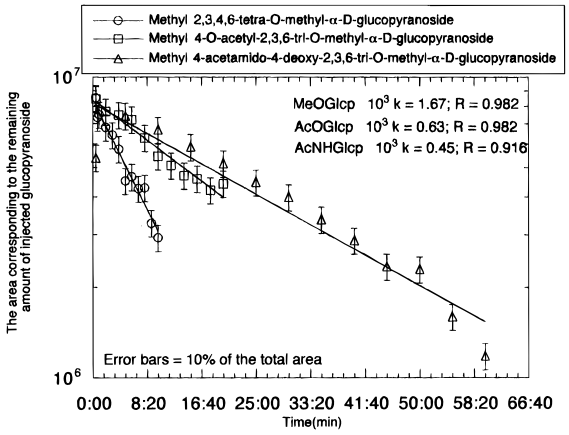


Figure 4.

D-glucopyranoside, as compared to ca. 20 times, the figure we reported in our previous study (Table 3). It should be noted, however, that the present study shows generally a somewhat slower rate of acetolysis of both permethylated compound than was previously found. The most likely reason for this could be that the thermometers used for determining the temperature of oil baths in which the acetolysis reactions were performed in previous and in this study were different.

As can be seen from Table 4, the relative standard deviations [%RSD (range)] for each data point were typically less that 15%, although some were as high as 22%. The linear correlation coefficient (R) was better than 0.92 for each curve, indicating the linearity of data. Aliquots for each acetolysis reaction were collected until the reaction was at least 70% complete.

From comparison of the rates of acetolysis of methyl 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside (**1**), methyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl-α-D-galactopyranoside (**2**), and methyl 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-galactopyranoside (**3**) (Table 4 and Figure 3), it is clear that the greater the electronegativity of the C4 substituent of the glycopyranoside ring, the faster the rate of acetolysis. Thus, the 4-*O*-methyl derivative (**1**) acetolyzes ca. 10 times faster than the 4-*O*-acetyl derivative (**2**), which acetolyzes ca. 5 times faster than the 4-acetamido-4-deoxy derivative (**3**). When the C4 substituent is equatorial, as is the case in the D-glucopyranoside series, the influence of the changes in the electronegativity of the C4 substituent on acetolysis rates is much smaller. Thus, methyl 2,3,4,6-tetra-*O*-methyl-α-D-glucopyranoside (**4**) acetolyzes only 2.9 and 3.3 times faster than methyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl- (**5**) and 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-glucopyranoside (**6**), respectively. *In the D-gluco series, the dependence of acetolysis rates upon the electronegativity of the C4 substituent can only be explained as a "through-bond" interaction (inductive effect) with the ring oxygen, which is apparently rather small.* However, in the D-*galacto* series, the very large influence of the electronegativity of the axially oriented C4 substituent on the acetolysis rate cannot be ascribed to this small through-bond interaction. *The only possible explanation for the unusually large kinetic effect observed in the D-galacto series is a strong through-space electron donation of the axially oriented electronegative substituent at C4 into the oxocarbenium ion under formation. This effect, which is destabilizing in the neutral galactopyrannoside due to electrostatic repulsion, becomes very stabilizing as the oxocarbenium species appears.*

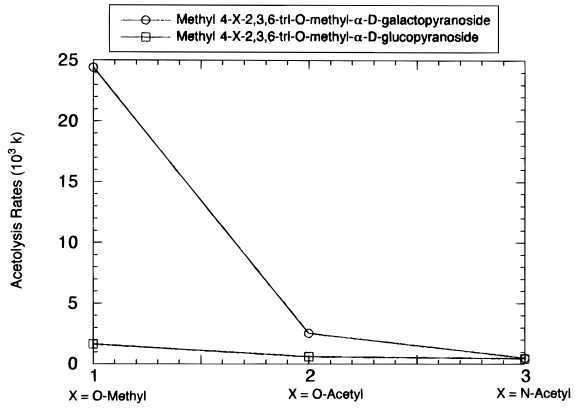


Figure 5.

In that case the acetolysis rate increase is readily explained via destabilization of the ground state of the starting material and stabilization of the transition state which resembles the final oxocarbenium ion. In the D-*gluco* series, the acetal ground state is not destabilized and the corresponding transition state is not stabilized; thus, the rate of acetolysis is smaller. As can be seen from Table 4, there is no significant difference in acetolysis rates between methyl 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-galactopyranoside (**3**), methyl 4-*O*-acetyl-2,3,6-tri-*O*-methyl-α-D-glucopyranoside (**5**), and methyl 4-acetamido-4-deoxy-2,3,6-tri-*O*-methyl-α-D-glucopyranoside (**6**).

It is interesting that, by acetylation, the C4 oxygen of a galactopyranoside loses most of its electronegativity. That could be the reason why the axial acetoxy groups, except for the 1,3-syn-diaxial nonbonding steric interactions, are not introducing additional destabilization into the given conformation.

The relationship between the electronegativity of the C4 substituent and the rate of acetolysis is presented in Figure 5.

From comparison of acetolysis rates of **3** and **6**, it seems that **3** acetolyzes slightly slower than **6** (the values are too close for any definitive conclusion), suggesting that, instead of the usual repulsion expected in **1** and **2**, there could exist an electrostatic attraction between the slightly positive axially oriented C4 nitrogen atom of the acetamido group and the axially oriented sp^3-hybridized nonbonding electron pair of the ring oxygen in the ground state as well as an electronic repulsion between that nitrogen and the oxocarbenium ion in the transition state.

Since the solvent used in acetolysis studies (acetic anhydride) is much less polar than water and is aprotic, we thought that molecular modeling would be very meaningful and that the obtained results could either support or disprove our hypothesis on the existence of a destabilizing 1,3-syn-diaxial electronic interaction between an electronegative axial C4 substituent and the axially oriented sp^3 hybridized nonbonding electron pair on the ring oxygen of a glycopyranoside, as well as the stabilizing electron donation of the axially oriented electronegative C4 substituent to the forming oxocarbenium ion.

The presence of an amido group in some of the molecules we wanted to examine by *ab initio* calculations dictated the choice of basis set: the 6-31G** [16] level of calculation was chosen. The size of the basis set chosen for our calculation made it impossible to study the actual carbohydrate structures. Hence we designed simplified model molecules that would permit us to conduct the calculation in a much shorter time but would also allow us to determine whether the electronic interactions, which we postulated as an explanation for our kinetic results, exist. The three equatorial substituents, the C2 and the C3 methoxy groups and the C5 methoxymethyl group of glycopyranosides **1**−**6**, were replaced with hydrogen atoms so that only substituents that remained in our model compounds were at the C4 and C1 carbons. The removal of the C2, C3, and C5 substituents should have an identical effect on all studied glycopyranosides and therefore should not affect our overall conclusions regarding the mechanism of acetolysis reactions.

Since the reactions are kinetically driven, the transition structures should be ideally localized, but again, the size of our system rendered that task difficult.

In order to correctly probe the electronic interactions involved, we considered the transition states to be late and consequently close to oxocarbenium ions.[6b,17] Thus the oxocarbenium ions **7**−**12** were calculated with GAMESS[18] (Table 5). The obtained results clearly showed that the chosen model compounds are good models for the actual carbohydrate molecules **1**−**6**[19] because the experimental trend is correctly found.

Since the conformational energies of our model molecules represent the sum of electronic and steric interactions, *ab initio* calculations of olefins **13**−**18** (Table 6) were carried out in order to evaluate the magnitude of steric interactions in oxocarbenium ions **7**−**12**.

Finally, it was assumed that the electronic interaction between the oxocarbenium ion (>C═O^+—) and the axially oriented C4 heteroatom should be energetically opposite to the same electronic interaction in the corresponding neutral acetals. Thus, the electronic repulsion between the axial methoxy group and the axial sp^3-hybridized lone pair of electrons on the ring oxygen in methyl 2,3,4,6-tetra-*O*-methyl-α-D-galactopyranoside (**1** in Figure 6) should become an attraction in the corresponding oxocarbenium ion. Accordingly, the acetals **19**−**24** were calculated at the 6-31G** level of theory (Table 7).

For each of 18 structures **7**−**24**, three rotamers about the C4−X bond are theoretically possible; nevertheless a conformational search revealed that of these only two rotamers were feasible, meaning that 36 energy minimizations had to be carried out. In the case of neutral acetals **19**−**24** in addition to the C4−X rotamers, there were two more rotamers about the C1−O1 bond. However, only rotamers that allowed the exocyclic oxygen lone

(16) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; De Frees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654.

(17) (a) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 604. (b) Deslongchamps, P. *Pure Appl. Chem.* **1993**, *65*, 1161. (c) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238. (d) Bennett, A. J.; Sinnott, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 7287.

(18) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(19) ***Ab Initio* Computational Procedure.** All the calculations were done at the RHF 6-31G** level using natural internal coordinates.[20] In the case of structures **7a** and **8b** the Hessian matrices were computed at the 6-31G** level of theory yielding the following respective ZPE: 0.15976 and 0.15947 au (applied scale factor of 0.89). Due to the very small resulting energy correction (0.18 kcal/mol) and to system limitations, the Hessian matrices of the other struc- tures were not computed.

(20) Fogarasi, G.; Zhou, X.; Taylor, P. W.; Pulay, P. *J. Am. Chem. Soc.* **1992**, *114*, 8191.

Table 5. Geometric and Energetic Characteristics of Oxocarbenium Ions 7−12

	X	R	τ	d	E (au)	rel E (kcal/mol)
7a[a]	O(ax)	Me	90.6	2.88	−383.089 05	0
7b			152.6	2.84	−383.088 84	0.13
8a	O(eq)		−102.3	3.65	−383.081 72	4.60
8b[a]			−152.3	3.61	−383.082 58	4.06
9a[a]	O(ax)	Ac	78.8	2.96	−495.854 89	0
9b			155.0	2.90	−495.853 45	0.90
10a[a]	O(eq)		−77.0	3.68	−495.850 29	2.89
10b			−158.1	3.62	−495.849 73	3.24
11a[a]	NH(ax)	Ac	68.8	3.02	−476.026 96	0
11b			170.5	2.96	−476.023 74	2.02
12a[a]	NH(eq)		−75.8	3.73	−476.026 64	0.20
12b						

[a] Conformers used in the discussion; "a" and "b" represent different rotamers around the C4−X bond. τ = RX−C4C5 dihedral angle (in deg). d = X−O distance (in Å).

Table 6. Geometric and Energetic Characteristics of Alkenes 13−18

	X	R	τ	d	E (au)	rel E (kcal/mol)
13a[a]	O(ax)	Me	81.2	3.12	−346.915 62	0.91
13b			163.4	3.07	−346.915 52	0.97
14a	O(eq)		−74.4	3.75	−346.917 02	0.03
14b[a]			−156.2	3.70	−346.917 07	0
15a[a]	O(ax)	Ac	82.1	3.10	−459.689 56	0.62
15b			155.9	3.07	−459.689 38	0.73
16a[a]	O(eq)		−82.3	3.74	−459.690 39	0.10
16b			−155.1	3.71	−459.690 55	0
17a[a,b]	NH(ax)	Ac	85.0	3.16	−439.858 90	0.93
17b			153.8	3.11	−439.860 28	0.07
18a[a]	NH(eq)		−84.7	3.80	−439.860 25	0.20
18b			−151.5	3.78	−439.860 39	0

[a] Conformers used in the discussion; "a" and "b" represent different rotamers around the C4−X bond. [b] Not a minimum on the PES, τ was held at 85°. τ = RX−C4C5 dihedral angle (in deg). d = X−C2 distance (in Å).

Table 7. Geometric and Energetic Characteristics of Acetals 19−24

	X	R	τ	d	E (au)	rel E (kcal/mol)
19a[a]	O(ax)	Me	72.2	2.94	−497.807 92	0.88
19b			159.7	2.90	−497.807 59	1.09
20a	O(eq)		−85.2	3.64	−497.808 92	0.26
20b[a]			−161.1	3.59	−497.809 33	0
21a[a]	O(ax)	Ac	79.9	2.92	−610.582 21	0
21b			155.1	2.89	−610.581 36	0.53
22a	O(eq)		−84.0	3.65	−610.581 84	0.55
22b[a]			−156.5	3.60	−610.5820 09	0.08
23a[a]	NH(ax)	Ac	155.6	2.88	−590.754 18	0
23b			156.6	2.88	−590.754 05	0.08
24a[a]	NH(eq)		−85.1	3.70	−590.753 31	0.55
24b			−84.5	3.70	−590.753 25	0.58

[a] Conformers used in the discussion; "a" and "b" represent different rotamers around the C4−X bond. τ = RX−C4C5 dihedral angle (in deg). d = X−O(ring) distance (in Å).

pair donation into the C1−O5 bond were retained (O5C1−OCH_3 torsion angle $\tau \approx 60°$) (due to the exo-anomeric effect).

Results of our calculations are given in Tables 5−7. When considering only the low-energy conformers of acetals **19**−**24**, it can be seen from Table 7 that the compound in which the C4 methoxy group is equatorially oriented (**20b**) is 0.88 kcal/mol more stable than the compound **19a** having the C4 methoxy group axial. This trend is reversed for the C4 acetamido derivatives: axial isomer **23a** is now more stable, by 0.55 kcal/mol, than the equatorial isomer **24a**. The C4 acetates fall between these two extremes since the equatorial and axial acetates (**22b** and **21a**, respectively) are almost equally stable. These observations are in complete agreement with the idea of repulsion between an electron rich C4 axial substituent and the axially oriented sp^3-hybridized lone pair of electrons on the ring oxygen. In the case of acetamido acetal there exists an electronic attraction between the axially oriented sp^3-hybridized lone pair of electrons on the ring oxygen and the axially oriented C4 amido nitrogen (H bond, see structure **23a** in Figure 8) since the axial isomer is preferred. The most likely reason for this is that the nitrogen atom has a partial-

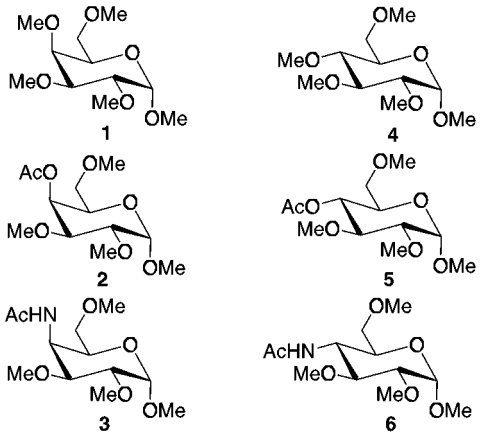


Figure 6.

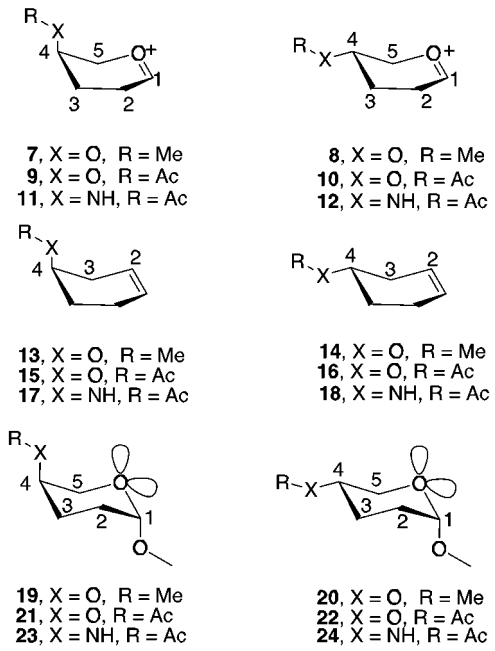


Figure 7.

positive charge due to donation of its nonbonding pair of electrons to the carbonyl oxygen of the acetamido group through delocalization involving carbonyl carbon and carbonyl oxygen. As the electron density on the heteroatom X increases, its axial position becomes less stable. This is very evident from the distance between the C4 axial heteroatom and the ring oxygen because this distance increases with the increase of electronegativity of the X atom.

While the electronic interactions are rather small in neutral acetals, they are much more significant in corresponding oxocarbenium ions which are both geometrically and energetically very similar to the acetolysis transition structures. Thus, the oxocarbenium ion having the C4 methoxy group axially oriented (**7a**) was found to be 4.06 kcal/mol more stable than the oxocarbenium ion with the C4 methoxy group equatorially oriented (**8b**). The same electronic interaction can be seen in the oxocarbenium ions having the C4 acetoxy group axially oriented (**9a**); however, it is somewhat smaller: the axial isomer is now favored by 2.89 kcal/mol over the equatorial isomer (**10a**). In the case of acetamido derivatives, this interaction seems to no longer exist. Thus the oxocarbenium ions having the C4 acetamido group axially or equatorially oriented (**11a** and **2a**, respectively) have very similar energies; the axial isomer, however, is again favored, but only by 0.20 kcal/mol. *It is interesting that while the nitrogen atom is sp²-hybridized in all acetamido compounds* (**12**, **17**, **18**, **23**, and **24**) *as expected, in two oxocarbenium ions* **11a** and **11b** *in which the C4 acetamido group is axially oriented the nitrogen atom exhibits a high degree of sp³ hybridization* (Figure 8) *and the nitrogen lone pair points toward the oxocarbenium ion.*

This fact alone provides a strong support for the existence of the electronic interaction proposed in this work. The sp^3 hybridization of the amido nitrogen, observed only when the acetamido group is axially oriented, most likely occurs because the nonbonding electrons of the nitrogen atom, normally delocalized over carbonyl carbon and carbonyl oxygen due to the mesomeric structure $-N-C=O \leftrightarrow -N^+=C-O^-$ of the acetamido group, becomes more localized on the nitrogen atom in the oxocarbenium ion, so that it can now stabilize the oxocarbenium ion.

The existence of the proposed electronic interaction is evident also from interatomic distances between the axial heteroatom X and the ring oxygen of the corresponding oxocarbenium ion. This distance is shortest when the axial substituent is a methoxy group (**7a**) (2.88 Å), in which case the attraction is at maximum. When the methoxy group is replaced with an acetoxy group (**9a**), the interatomic distance increases (2.96 Å), and it is

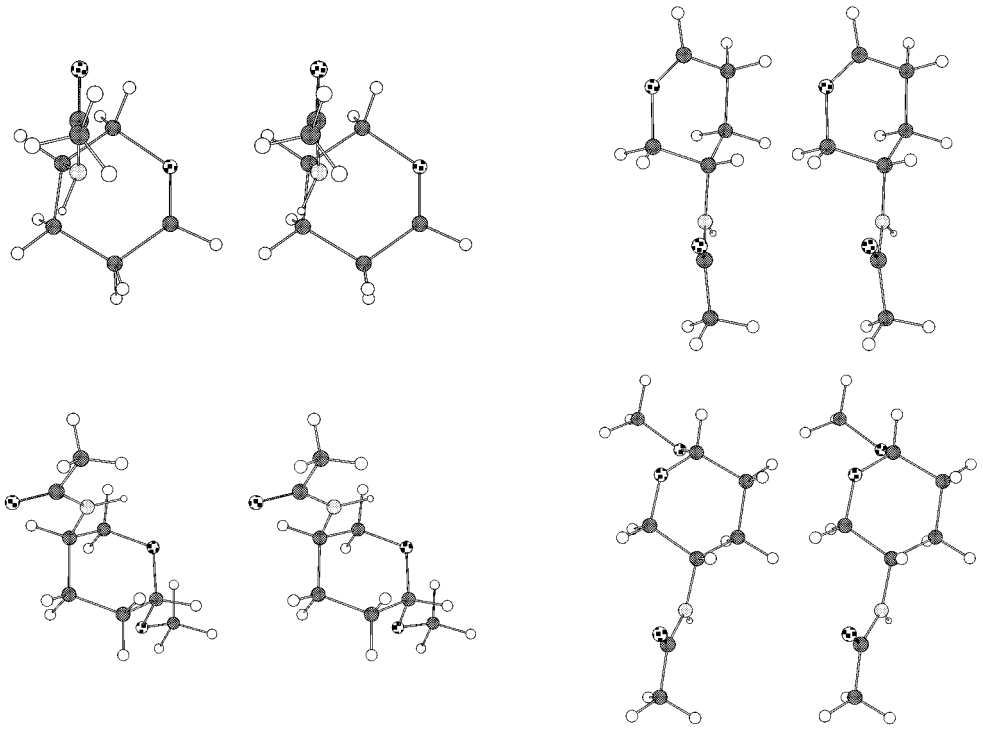


Figure 8. Selected 6-31G** optimized structures: **11a** (top left), **12a** (top right), **23a** (bottom left) and **24a** (bottom right).

longest when the C4 substituent is an acetamido group (**11a**) (3.02 Å).

In order to be able to evaluate the magnitude of these electronic interactions in model oxocarbenium ions **7**−**12**, we had first to calculate the ground state conformational energies of alkenes **13**−**18** and to optimize them at the 6-31G** level of theory. This operation should allow us to separate the electronic and steric parts of the whole effect present in the oxocarbenium ions because the alkene geometries should give a fair estimate of the steric contributions. Thus we found that the electronic interactions are the largest when the C4 substituent was a methoxy group [4.97 kcal/mol = $(E_{\mathbf{7a}} - E_{\mathbf{13a}}) - (E_{\mathbf{8b}} - E_{\mathbf{14b}})$], smaller when the C4 substituent was an acetoxy group [3.41 kcal/mol = $(E_{\mathbf{9a}} - E_{\mathbf{15a}}) - (E_{\mathbf{10a}} - E_{\mathbf{16a}})$], and smallest when the C4 substituent was an acetamido group [1.14 kcal/mol = $(E_{\mathbf{11a}} - E_{\mathbf{17a}}) - (E_{\mathbf{12a}} - E_{\mathbf{18a}})$]. In all three cases the axial isomer was less stable than the corresponding equatorial one.

Finally, having experimental data for the acetolysis rates of six glycopyranosides, we decided to correlate the measured values to theoretical calculations. Thus, assuming that the acetolysis $\Delta E^{\ddagger}$ is directly related to ΔE (late transition state approximation), the calculations gave the following figures for $\Delta\Delta E^{\ddagger}$ between the axial and equatorial isomers within each series:

1. MeO_{series} 4.94 kcal/mol $[(E_{\mathbf{8b}} - E_{\mathbf{20b}}) - (E_{\mathbf{7a}} - E_{\mathbf{19a}})]$

2. AcO_{series} 2.81 kcal/mol $[(E_{\mathbf{1a}} - E_{\mathbf{22b}}) - (E_{\mathbf{9a}} - E_{\mathbf{21}})]$

3. $AcNH_{series}$ −0.35 kcal/mol $[(E_{\mathbf{12a}} - E_{\mathbf{24a}}) - (E_{\mathbf{11a}} - E_{\mathbf{23a}})]$

These results clearly indicate that the acetal **19**, in which the C4 methoxy group is axially oriented, should acetolyze much faster than the corresponding equatorial isomer **20**. The acetal **21**, in which the C4 substituent is acetyl should behave in a similar fashion, namely, the isomer having the C4 acetyl group axially oriented, should react faster than its equatorial counterpart **22**, but the difference should be considerably smaller. However, when the C4 substituent is an acetamido group, this trend is reversed: the acetal **23** having the acetamido group axially oriented should acetolyze slightly slower than the acetal **24** having the C4 acetamido group equatorially oriented. Again the theory fully supports our conclusions based on experimental results (Figures 1−5).

Conclusion

It has been experimentally observed that the α-D-glucopyranosides **4**−**6** and the 4-acetamido-α-D-galactopyranoside **3** undergo acetolysis at similar rates. The 4-acetoxy-α-D-galactopyranoside **2** acetolyzed faster and the 4-methoxy-α-D-galactopyranoside **1** much faster.

These experimental facts and theoretical calculations support the existence of a weak 1,3-syn-diaxial electronic interaction between an axially oriented electronegative substituent and the axially oriented ring oxygen sp^3-hybridized lone pair of electrons. On its own this effect could not be strong enough to account for the acetolysis rate differences observed between the various α-D-gluco- and galactopyranosides.

The 6-31G** calculations on oxocarbenium ions (**7**−**12**) related to the previous glycopyranosides and structurally close to the rate-limiting transition states (late transition state approximation) have revealed that electron rich axially oriented groups are able to feed electrons into the electron deficient cation.

Consequently, the more electronegative the 4-axial substituent, the more stabilized the transition state becomes. A 4-equatorial substituent has virtually no effect regardless of its electronegativity, except for inductive through-bond interactions.

In Figures 6 and 7 are given the structures of various glycopyranosides used in our study as well as the proposed stereoelectronic interactions discussed in this work.

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