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Carbohydrates

Acceleration of Acetal Hydrolysis by Remote Alkoxy Groups: Evidence for Electrostatic Effects on the Formation of Oxocarbenium Ions[**]

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Abstract: *In contrast to observations with carbohydrates, experiments with 4-alkoxy-substituted acetals indicate that an alkoxy group can accelerate acetal hydrolysis by up to 20-fold compared to substrates without an alkoxy group. The acceleration of ionization in more flexible acetals can be up to 200-fold when compensated for inductive effects.*

Studies of the relative reactivities of glycosyl donors, often determined by measuring the kinetics of acetal hydrolysis,[1,2] provide critical information used for designing iterative oligosaccharide synthesis.[3] These experiments reveal that the relative rates of substitution reactions of carbohydrate-derived acetals[3–6] depend upon the stereochemical configurations of substituents. For example, the methyl acetal of galactose (**2**) hydrolyzed five times faster than the glucose-derived acetal **1**, which differs only in the stereochemical configuration at C4 (Figure 1).[1,7–10] This difference in rate has been attributed to favorable electronic interactions between the electron-rich oxygen atom at C4 and the developing positive charge at C1 in the transition state for hydrolysis.[7,11,12] This stabilizing electrostatic effect, however, does not compensate for the electron-withdrawing influence of the oxygen atom at C4: inductive destabilization by the hydroxy group slows hydrolysis by 4–30 times compared to reactions where the alkoxy group was replaced with a substituent which is not electron withdrawing (for example, **3**; Figure 1).[7,13,14]

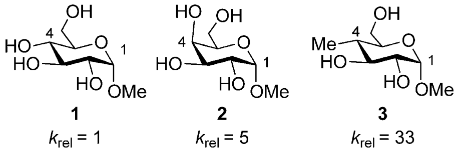
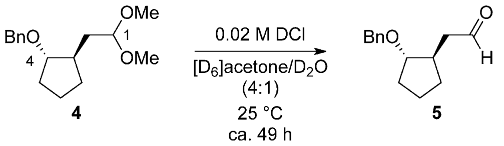


Figure 1. Relative rates of hydrolysis of α-methyl pyranosides (2.0 M HCl, 74 °C).[7]

Herein we provide evidence that the electrostatic stabilization conferred by an alkoxy group four carbon atoms away from an acetal group, the arrangement found in the pyranosides **1** and **2**, can overcome inductive effects and accelerate acetal hydrolysis if the system is more conformationally flexible than carbohydrates are. Flexibility likely allows the alkoxy group to approach the acetal functional group during substitution to provide up to a 20-fold increase in the rate of acetal hydrolysis compared to substrates that do not have an alkoxy group. When rates are compensated for inductive destabilization of the transition state for hydrolysis, through-space electrostatic stabilization of the developing charge can accelerate hydrolysis by up to 200-fold.

To evaluate the difference in reactivity exerted by a 4-alkoxy group based upon its position in space, a series of 4-alkoxy-substituted acetals resembling **4** [Eq. (1)] were synthesized and their rates of acetal hydrolysis were measured.



(1)

These compounds were designed so the ability of the alkoxy group to approach the acetal carbon atom could be varied systematically. The two key functional groups were arrayed around a ring, just as for the carbohydrate systems (Figure 1), so entropic effects[15] would be similar for all substrates. Protection of the alkoxy group as the benzyl ether was chosen because the fate of the benzyl group could reveal the structures of reactive intermediates. The hydrolysis reactions follow the reaction conditions depicted in Equation (1).[16]

The relative rates of acid-catalyzed hydrolysis are summarized in Figure 2, listed in order of increasing rate. Relative rates were normalized to the rate of hydrolysis of the alkyl acetal **8**. This simple acetal should be sterically equivalent to the other β-substituted acetals because the two-carbon side-chains of the acetals **4**, **6**, and **10**–**12** should adopt conformations where the acetal groups are oriented away from the alkoxy groups.[17,18] Comparison of the rates of ionization of the α-branched acetal **9** and β-branched acetal **8** indicates that steric effects play only a minor role in the hydrolysis of acetals in this series.[19]

The acetal models illustrated in Figure 2 share trends in reactivity with their carbohydrate relatives. The presence of

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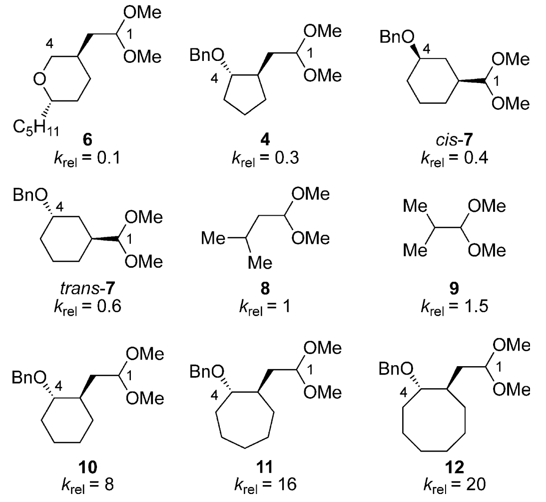


Figure 2. Relative rates of hydrolysis of acetals by DCl in $[\mathrm{D}_6]$acetone/$\mathrm{D}_2\mathrm{O}$ (4:1), listed in order of increasing rate.

an alkoxy group in the acetals *cis*- and *trans*-**7** decreased the rate compared to that of branched acetal **9** because an alkoxy group would inductively destabilize positively charged intermediates.[13,20] The relative reactivity of the acetals *cis*- and *trans*-**7** is also reminiscent of the carbohydrate systems: the slower-reacting acetal *cis*-**7** positions the alkoxy group at C4 further from the acetal carbon atom (Figure 3), much as the slower-reacting glucose isomer does (Figure 1).[21] The small difference between the rates of the stereoisomers likely reflects the fact that the alkoxy group in *trans*-**7** is far enough away to exert little stabilization of the transition state for hydrolysis.[22,23]

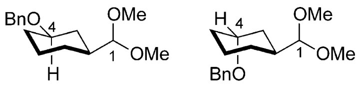


Figure 3. Chair conformations of the acetals *cis*- and *trans*-**7** illustrating the distances between the alkoxy groups and the acetal carbon atoms.

In contrast to the results exemplified in Figure 1,[24] an alkoxy group positioned at C4 can accelerate hydrolysis of an acetal. Whereas the cyclopentane-derived acetal **4** is less reactive than the alkyl acetal **8**, the larger cycloalkyl-containing acetals **10**–**12** reacted up to 20 times faster (Figure 2). This trend is consistent with the idea that a larger, more flexible ring[25] allows the alkoxy group to approach the acetal carbon atom more closely in the transition state for ionization[1] without incurring additional strain (**13**; Figure 4). As observed for galactosides compared to glucosides (Figure 1),[7] the closer the alkoxy group can approach the acetal carbon atom,[11,12] the faster hydrolysis occurred.

The slow hydrolysis of the tetrahydropyran-derived acetal **6** reinforces the importance of flexibility on the rates of hydrolysis of a 4-alkoxy-substituted acetal. If there were any interaction of the oxygen atom of the ring of acetal with the protonated acetal group during hydrolysis (**14**; Figure 4), the ring would need to adopt an orientation resembling a strained bicyclic structure[26] with substituents in disfavored axial orientations.[27] These energetic penalties and the inductive destabilization of the alkoxy group[13,20] must outweigh any benefit the alkoxy group can confer on hydrolysis. The hydrolysis of this compound provides a point of comparison for the hydrolysis of the other alkoxy-substituted acetals. By using the rate of hydrolysis of the constrained acetal **6** to control for inductive effects, it can be estimated that electrostatic effects imparted by an alkoxy group can accelerate hydrolysis by up to 200-fold.[28]

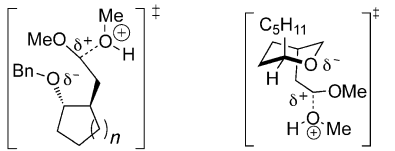
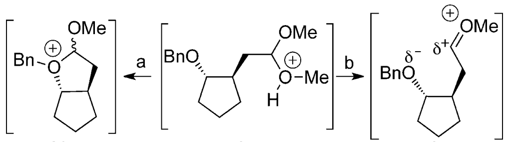


Figure 4. Structural requirements for acceleration of acetal hydrolysis by an alkoxy group.

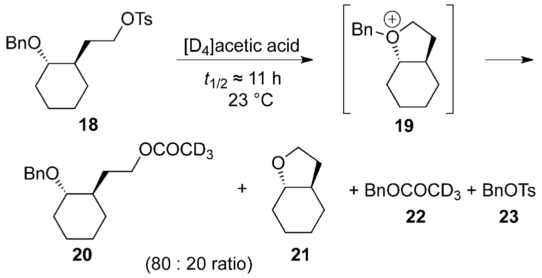
The relatively slow ionization of the cyclopentane-derived acetal **4** suggests the origin of the accelerating influence of an alkoxy group on the hydrolysis in acetals. Two types of interactions of an alkoxy group during hydrolysis can be envisioned (illustrated in Scheme 1 for **4**). At one limit, a new covalent bond would form between the alkoxy group and the acetal carbon atom in the transition state for hydrolysis (pathway a, Scheme 1), as occurs in neighboring-group participation during solvolytic displacement reactions.[29] Alternatively, the alkoxy group might only approach the acetal carbon atom in the transition state (pathway b, Scheme 1) without forming a new covalent bond (as suggested for the influence of acyl groups on the hydrolysis of 2-acyloxy-substituted acetals[24]). If formation of an intermediate oxonium ion such as **16** were required, ionization of **4** would form a strained *trans*-bicyclo[3.3.0]octane ring system.[26,30] In contrast, ionization of the cyclohexane-derived acetal **10** would form a much less strained oxonium ion (by about 10 kcal mol^{-1} [26,30]). Consequently, **10** should hydrolyze much faster than **4**. The difference in rate is only 20-fold, however, which is small considering the large difference in strain.



Scheme 1. Interaction of an alkoxy group during hydrolysis: a) Formation of a new covalent bond in the transition state. b) Electrostatic stabilization in the transition state.

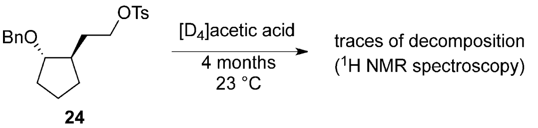
Electrostatic stabilization of the oxocarbenium ion **17** which forms upon hydrolysis is consistent with the relative rates (Scheme 1, pathway b).[11,12] Electrostatic stabilization would require the alkoxy group to be close to the acetal carbon atom,[11,12] but the carbon–oxygen bond distances would be much longer[31] than they would be for an oxonium ion.[32] As a result, the relative rates of hydrolysis should not track the ring strain closely because a new ring would not be fully formed.

Other observations also suggest that oxonium ion intermediates are not involved in acetal hydrolysis. In none of the hydrolyses were products consistent with loss of a benzyl group observed, as might be expected if an oxonium ion had formed.[33] In contrast, solvolysis of the 4-alkoxy-substituted tosylate[34] **18** reveals that the model ring systems can form oxonium ions if required for solvolysis (Scheme 2). The presence of significant quantities of the cyclized, debenzylated product **21** along with benzyl esters **22** and **23** implicates the formation of the oxonium ion **19** during solvolysis.[34]



Scheme 2. Solvolysis of the tosylate **18** resulted in benzyl substitution products. Ts = 4-toluenesulfonyl.

The tosylate model system also showed how large the difference in rates can be between similar substrates if oxonium ions were reactive intermediates. In contrast to the relatively rapid solvolysis of cyclohexane-derived tosylate **18**, the cyclopentane-derived tosylate **24** was resistant to solvolysis: after four months at 23 °C, a sample of **24** in [D$_4$]acetic acid showed only traces of decomposition [Eq. (2)]. The low reactivity of this tosylate can be attributed to the difficulty of engaging in neighboring-group participation during solvolysis[34] through a highly strained *trans*-bicyclo[3.3.0]octane-like oxonium ion resembling **16** (Scheme 1).[26] The fact that the acetal substrates do not show as large a difference in solvolysis rate as the tosylates provides additional evidence against the formation of an oxonium ion during acetal hydrolysis.



(2)

Experiments with alkoxy-substituted acetals suggest that an alkoxy group can accelerate the ionization of acetals. The accelerating influence of the alkoxy group can be attributed to electrostatic stabilization of the developing oxocarbenium ion intermediate, and can outweigh the decelerating inductive effect by about 200-fold.

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