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Steric Effects Are Not the Cause of the Rate Difference in Hydrolysis of Stereoisomeric Glycosides

Henrik Helligsø Jensen and Mikael Bols*

Department of Chemistry, University of Aarhus, Langelandsgade 140, DK-8000 Aarhus C, Denmark

mb@chem.au.dk

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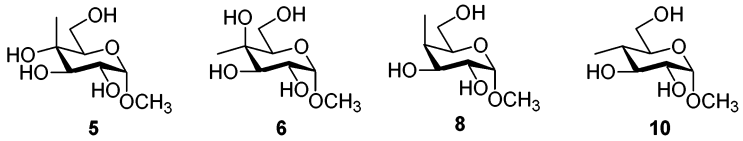
ABSTRACT



A long-lived and plausible explanation as to why glycosides with axial substituents are more reactive than those with equatorial substituents was given in 1955 by Edward based on sterical hindrance being relieved in the transition state. Using model compounds 5, 6, 8, and 10, we here show conclusively that sterical hindrance not is the controlling factor in glycoside hydrolysis.

Nonenzymatic hydrolysis of alkyl glycopyranosides is a much-studied reaction with a well-established mechanism.[1,2] The process is specific-acid-catalyzed where the rate-determining step is the formation of a cyclic oxacarbenium ion intermediate (**1a**) (Scheme 1). Rate constants (k_{obs}) of this reaction are an expression of the energy difference between the neutral reactant state and the transition state leading to this oxacarbenium ion.

It has been known for many years[3] that stereoisomeric glycosides hydrolyze with increasing rate depending on the number of axial hydroxyl groups. On the basis of available data and some assumptions on pyranoside reactant-state conformations and the mechanism of hydrolysis, J. T. Edward gave in 1955 a very plausible explanation to this phenomenon.[4,5] His rationale as to why guloside **3** reacts faster than galactoside **2**, which again reacts faster than glucoside **1** (Figure 1), was based on relief of steric strain. He envisioned that axial substituents would ease the rotation around the C2−C3 and C4−C5 bonds and thereby facilitate the transformation from reactant into intermediate, which was assumed to possess a more flattened half-chair conformation.

Previous experimental results published by Withers and co-workers show that field effects dictate the rate of hydrolysis. Replacement of a hydroxyl group with fluorine decreases the reactivity, whereas deoxygenation enhances the reactivity.[6,7] This is evidently due to destabilization of the incipient oxacarbenium ion in the transition state by electron-withdrawing groups. Withers and co-workers' study, however, was limited as to only study field effects within groups of glycosides with conserved stereochemistry. Recent results from our group go one step further.[8,9] They show a sizable

(1) Bennet, A. J.; Kitos, T. E. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1207−1222. Bochkov, A. F.; Zaikov, G. E. *Chemistry of the O-Glycosidic Bond*; Pergamon: Oxford, 1979. Capon, B. *Chem. Rev.* **1969**, *69*, 407−498. Feather, M. S.; Harris, J. F. *J. Org. Chem.* **1965**, *30*, 153−157.

(2) Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429−3440.

(3) Armstrong, H. E.; Glover, W. H. *Proc. R. Soc. London B* **1908**, *80*, 312−331.

(4) Edward, J. T. *Chem. Ind. (London)* **1955**, 1102−1104.

(5) This celebrated article is perhaps mostly known for the observation that pyranosides having axial anomeric substituents appear to be more stable than their equatorial counterparts. This effect was given the name *the anomeric effect* but has later been found to operate in many systems other than carbohydrates.[5a] Another name suggested for this general effect has in fact been *the Edward-Lemieux effect*.[5b] (a) *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993. (b) Wolfe, S.; Shi, Z. *Isr. J. Chem.* **2000**, *40*, 343−355. Wolfe, S.; Rauk, A. Tel, L. M.; Csizmadia, I. G. *J. Chem. Soc. B.* **1971**, 136−145.

(6) Withers, S. G.; Percival, M. D.; Street, I. P. *Carbohydr. Res.* **1989**, *187*, 43−66.

(7) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270−1277.

(8) Jensen, H. H.; Lyngbye, L.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3447−3449.

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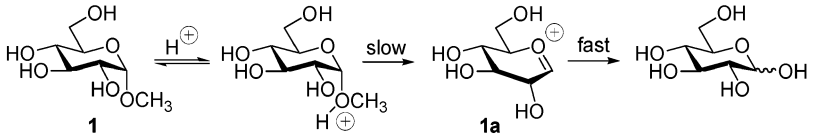
Scheme 1



difference in the de facto electron-withdrawing properties of axially and equatorially placed hydroxyl groups. This could be an alternative explanation to the higher reactivity of a galactoside (**2**) (axial 4-OH) compared to a glucoside (**1**) (equatorial 4-OH).

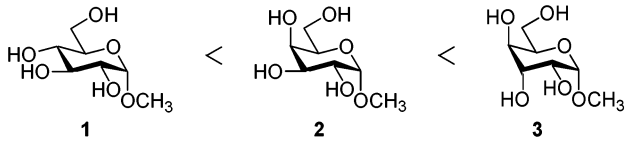


Figure 1.

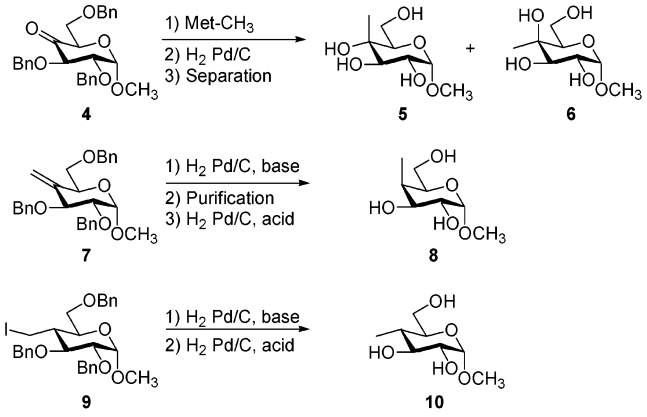
This result was obtained from Hammett-like plots where σ-values were derived from studies of base strengths of hydroxylated piperidines (azasugars).[10] These could be correlated to oxacarbenium ion stability relative to reactant-state stability, i.e., glycoside hydrolysis rates. Because of this connection between base strengths of azasugars and reaction rates of glycosides it seemed questionable that steric effects would be the controlling factor of the latter. This was, however, what was proposed by Edward.[4]

On the basis of molecular mechanics calculations in the gas phase, an electronic argument has also been given by Woods et al. to account for the variation in reactivity of glycosides undergoing hydrolysis.[11] Miljkovic and co-workers have published a related result based on ab initio calculations where they addressed the reactivity difference of galactosides and glucosides in acetolysis.[12]

Despite the above suggestions that electronic factors do play an important role, no rigorous experimental study had been conducted to clarify to which extent glycopyranoside reactivity was controlled by sterics or electronics.[13] As a consequence, we decided to prepare modified glycosides and test our hypothesis independently of earlier results. Our study was to focus on the noteworthy difference in reactivity of galactosides and glucosides. Substitution at C4 was therefore to be investigated.

Introduction of a sterically demanding methyl group in the 4-position of methyl gluco- and galactopyranoside (**5**/**6**) would expectedly reverse the order of reactivity if sterical hindrance were to be the major factor controlling rate of hydrolysis. Glycosides with hydroxyl groups replaced for methyl groups (**8**/**10**) were also of interest in this context, as it was anticipated from Edward's hypothesis[4] that the galactoside **8** would hydrolyze considerably faster than the glucoside **10**, which was known from unmodified sugars.[2]

Scheme 2



These four modified glycosides were prepared in a few steps from known intermediates. Tertiary alcohols **5**/**6** were prepared via methyl addition (CH_3MgI or CH_3Li) to the known ketone **4**.[14] The selectivity, however, was not as high as when trityl was used instead of benzyl protection of O6 (Scheme 2).[15]

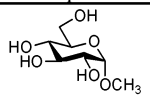
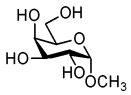
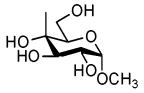
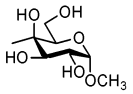
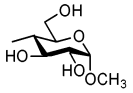
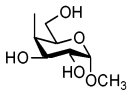
4-Deoxy-4-methylgalactoside **8** was obtained as the major product of hydrogenation of the known olefin **7**,[14] whereas the epimeric glycoside (**10**) (minor product) could not be obtained in satisfactory purity even after protecting group removal or exchange for acetyl groups. 4-Deoxy-4-methyl-glucoside **10** was obtained through reduction of primary iodide **9** (Scheme 2).[14] All compounds were characterized by NMR that in every case suggested the pyranoside conformation to be $^4C_1$.

Acidic hydrolysis in 2.0 M HCl of the 4 synthesized glycosides and unmodified methyl glucoside and galactoside were assumed to proceed by identical mechanisms. The

(9) Bols, M.; Liang, X.; Jensen, H. H. *J. Org. Chem.* **2002**, *67*, 8970−8974.
(10) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem. Eur. J.* **2002**, *8*, 1218−1226.
(11) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859−864.
(12) Miljkovic, M.; Yeagly, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.
(13) For a study of torsional effects on the reactivity of glycosyl transfer, see: Dean, K. E. S.; Kirby, A. J.; Komarov, I. V. *J. Chem. Soc., Perkin Trans. 2*, **2002**, 337−341.
(14) Preuss, R.; Jung, K.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 377−382.
(15) Sato, K.; Kubo, K.; Hong, N.; Kodama, H.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 938−942.

hydrolyses of glycosides were followed by optical rotation carried out at 74°C in a polarimeter cell. To ensure that the expected products had formed, a mass spectrum was recorded after each run and only masses corresponding to the expected hemiacetal were detected. The observed α-values could be fitted to an exponential decay curve, and rate constants (k_{obs}) were thereby obtained. Averaged values are listed in Table 1. In the case of **1** and **2**, good agreement was found with calculated rate constants obtained from kinetic parameters measured by Overend et al.[2] From Table 1, it can been seen that only a slight change in rate of hydrolysis occurs by incorporation of an additional methyl group in the 4-position, i.e., the galactoside **6** is still the most reactive of the pair of 4-*C*-glycosides **5**/**6**.

Table 1. Rate Constants Determined by Polarimetry at 74 °C in 2.0 M HCl[a]

compound	number	$10^5\ k_{obs}/s^{-1}$	$k_{obs,rel}$
	**1**	6.07 ± 0.03	1
	**2**	30.5 ± 0.1	5.2
	**5**	4.13 ± 0.05	0.68
	**6**	27.0 ± 0.3	4.4
	**10**	199 ± 2	33
	**8**	127 ± 1	21

[a] Rate constants are the average of four independent experiments. Values relative to glucoside **1** given as $k_{obs,rel}$.

Removal of the 4-hydroxyl group from the modified glycosides **5**/**6** resulted in a great rate enhancement, which is known to be a result of deoxygenation (vide supra).[7] In addition, the *gluco*-configured glycoside (**10**) reacts slightly faster than its *galacto*-configured isomer (**8**).

Altogether, these results disprove the previous hypothesis given by Edward.[4] It is clear that in this case the reactivity is governed by the configuration of hydroxyl groups and not sterical effects. If the latter were to be the controlling factor, the order of reactivity of **5**/**6** and **8**/**10** would have been the opposite of that observed. In addition, the difference in reactivity between galactoside **8** and glucoside **10** should have been greater than 5.2 in favor of **8**, which is not the case.

A few explanations of the nature of the electronic effect controlling glycoside reactivity have been offered. We have suggested that the field effect imposed by an electron-withdrawing group is less when placed axially than equatorially (vide supra). This, together with the fact that methyl groups either placed axially or equatorially impose a negligible electronic effect, could be an explanation.[8−10]

It may appear inconsistent that while a rather small difference in reactivity is seen between galactosides **2** and **6** (1.18), the differences between sets **1**/**5** and **10**/**8** are somewhat larger (1.5−1.6). However, this phenomena can be explained by the likely influence of an axial methyl group on the rotamer population around the C5−C6 bond. A methyl substituent placed axially in the 4-position (**5** and **8**) would be expected to lower the population of the gg conformer, thereby increasing the population gt and tg conformers. Due to the anti relationship between O5 and O6 in the tg conformer, the oxacarbenium ion-like transition state will be destabilized compared to when O5 is close in space to O6 (as in gg and gt). The somewhat lower reactivity of **5** and **8** compared to **1** and **10**, respectively, could therefore be caused by a somewhat higher population of the tg conformer in these compounds.

In conclusion, we have prepared and hydrolyzed four modified glycopyranosides and compared their rates of acid-catalyzed hydrolysis. We have thereby demonstrated, that an electronic rather than a steric effect of remote substituents on glycosides dictates their rates of hydrolysis.

Acknowledgment. We acknowledge the financial support of the SNF and the Lundbeck Foundation.

Supporting Information Available: Experimental details for the synthesis and data for the hydrolysis experiments, including representative progress curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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