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The Influence of Neighboring Group Participation on the Hydrolysis of 2-O-Substituted Methyl Glucopyranosides

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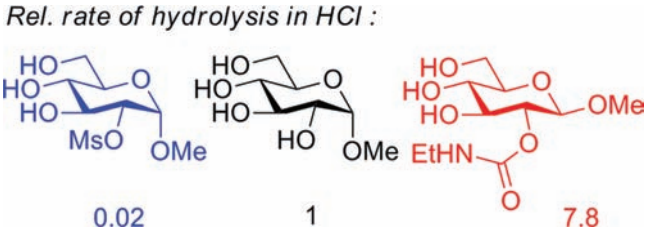
ABSTRACT



Does neighboring group participation actually enhance the reactivity of the anomeric center when the participating group is inherently disarming? To investigate the influence of the neighboring group effect from a 2-O protective group on acidic glycoside hydrolysis, 10 methyl glucosides having different protective groups on O2 have been synthesized and a clear trend between anomeric configuration, participation of the protective group, and the rate of hydrolysis could be observed.

The influence of 2-O-protective groups in carbohydrates on the stereochemical outcome of glycoside bond formation has been known for decades. Ester type protective groups participate in the glycosylation reaction to form 2-O-acyl oxonium ions, which lead preferentially to the *trans* coupling products, while ether type protective groups cannot participate and result in low α/β selectivity. Yet the precise rate increase obtained from such neighboring group participation is much more qualitative. Obviously some acceleration would be anticipated, or neighboring group participation would not be a favorable path, but it has never been quantified. In contrast Paulsen[1] and Fraser-Reid[2] observed the generally enhanced reactivity of benzylated vs acylated glycosyl donors and emphasized the importance of the protective group on position 2 as the most influential. It was therefore surprising when Demchenko,[3] in contrast to the above, observed that perbenzylated donors with a 2-*O*-benzoyl were significantly more reactive than the fully benzylated counterpart. Similarly he noted that the perbenzoylated 2-*O*-benzyl donor was less reactive than the fully benzoylated donor. This was apparently a case where neighboring group participation was enhancing reactivity by overriding inductive effects. This was clarified by Crich[4] who demonstrated that anchimeric assistance caused the 1,2 *trans* (β) 2-*O*-benzoyl to be more reactive than the 1,2-*trans*-2-*O*-benzyl, while the 1,2 *cis* (α) 2-*O*-benzoyl in fact was less reactive than the 1,2 *cis* (α) 2-*O*-benzyl.

The significant rate accelerations observed in Demchenko's work prompted us to speculate if neighboring group participation could be used to facilitate glycoside hydrolysis as well. Glycoside degradation methodologies are becoming increasingly important with the growing need to efficiently convert biomass. However, despite the many studies[5] carried out on hydrolysis of glycosides since the Fisher era only very little quantitative information about anchimeric assistance or neighboring group participation is available. The inductive effect of a C2 substituent has of course been studied and has a profound influence: The relative rate for

(1) Paulsen, H.; Richter, A.; Sinnwell, V.; Stenzel, W. *Carbohydr. Res.* **1978**, *64*, 339–264.

(2) (a) Mootoo, D. R.; Konradson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583. (b) Fraser-Reid, B.; Wu, Z.; Udodong, U.; Ottoson, H. *J. Org. Chem.* **1990**, *55*, 6068. (c) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowrinski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434–1435.

(3) Kamat, M. N.; Demchenko, A. V. *Org. Lett.* **2005**, *7*, 3215–3218. Premathilake, H. D.; Mydock, L. K.; Demchenko, A. V. *J. Org. Chem.* **2010**, *75*, 1095–1100.

(4) Crich, D.; Li, M. *Org. Lett.* **2007**, *9*, 4115–4118.

(5) Capon, B. *Chem. Rev.* **1969**, *69*, 407–498.

(6) *Chemistry of the O-Glycosidic Bond: Formation & Cleavage*; Bochkov, A. F., Zaikov, G. E.; Pergamon Press: Oxford, 1979.

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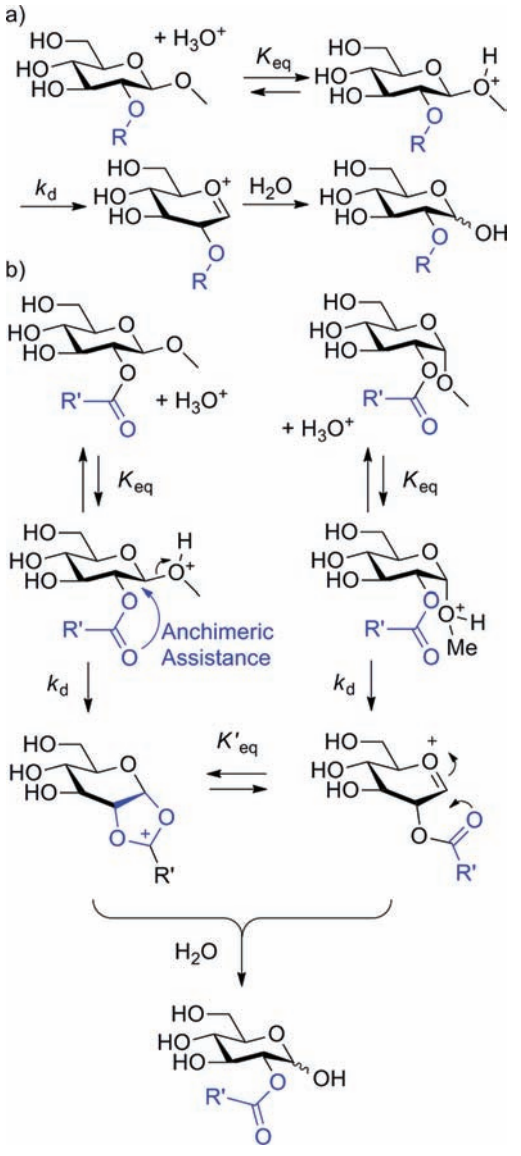


Figure 1. Mechanism for acid-catalyzed hydrolysis of methyl glucosides having different protective groups on O2. R being H or alkyl; R′ a side chain on a carbonyl (ester, carbamate, carbonate, etc.).

the deoxy is 2500 and 2-chloro 0.042 as compared with the parent 2-OH sugar.[6] The general considerations are as follows:[6] First, electron-withdrawing groups on O2 reduce the nucleophilicity of O1 and O5 and thereby slow the first step (Figure 1a). Second, the intermediate conjugated acid is destabilized by electron-withdrawing groups and hence decomposes faster to the oxacarbenium ion, as compared with the unprotected or alkylated equivalent. Under normal conditions the second step is the rate-determining step. Third, the oxacarbenium ion may be resonance stabilized by a participating group on O2 (Figure 1b); this can, according to the Bell–Evans–Polanyi principle, lead to a faster rate.[6,7] The rate enhancement should be the same for both anomers and depend on the ability of the neighboring group to stabilize the oxacarbenium ion. Finally, if "back-side attack" (anchimeric assistance) is at play, only the β-anomer (1,2 *trans*) would be affected and hence be reacting significantly faster than the α-anomer (1,2 *cis*), where the protective group on O2 cannot participate in a "back-side" attack to push out the aglycon.[8]

In this work the goal was to see if and how acidic glycoside hydrolysis was influenced by neighboring group participation and therefore a series of methyl glucosides were prepared with a 2-O-protective group with the ability to perform anchimeric assistance. Solubility in water and stability in acidic media were also necessary, and pivaloyl, ethyl carbamoyl,[9] and ethoxycarbonyl turned out to be groups that met these requirements. The 2-*O*-mesyl and 2-*O*-methyl derivatives were selected for comparison as two groups unable to perform neighboring group participation,[10] but with widely different electronic effects.

Synthesis of model compounds was carried out using selective protective group manipulations. Methyl α-D-glucopyranoside was 4,6-benzylidene protected to give the known diol **1**.[11] Inspired by Jeanloz and Jeanloz,[12] **1** was reacted with PivCl to give the corresponding 2-O-protected derivative in modest yield (24%) together with the 3-O-derivatives (Scheme 1). Treatment of the diol with ethylisocyanate and pyridine only showed a minor conversion of the starting material; this was overcome by using the CuCl promoted reaction in DMF[13] which gave the product in 32% yield. Debenzylidenation of the 2-O protected compounds using Pd/C and hydrogen gave the model compounds in quantitative yields (Scheme 3). Mesylation gave an inseparable mixture of products, and to overcome this the 3-OH was selectively benzylated using the method developed by Hung and co-workers[14] followed by mesylation or methylation and finally palladium-catalyzed hydrogenolysis to give the desired product **11** and **12** in an overall good yield (66 and 92% respectively from the mono-ol **4**) (scheme 1). Reaction of **4** with ethyl chloroformate in dichloromethane and TMEDA as base gave **5**, which was hydrogenolyzed to give **8**.[15]

(7) Brückner, R. *Reaktionsmechanismen: Organische Reaktionen, Stereochemie, Moderne Synthesemethoden 3. Auflage*; Elsevier GmbH: München, 2004.

(8) Winstein, S.; Grunwald, E.; Buckles, R. E.; Hanson, C. *J. Am. Chem. Soc.* **1948**, *70*, 816–821.

(9) Motokucho, S.; Sudo, A.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 4459–4464.

(10) There is plenty of evidence that sulfonate is nonparticipating; see: Srivastava, V. K.; Schuerch, C. *Carbohydr. Res.* **1980**, *79*, C13–C16. Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121–1126. Crich, D.; Picione, J. *Org. Lett.* **2003**, *5*, 781–784. Crich, D.; Hutton, T. K.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron: Assymmetry* **2005**, *16*, 105–119. Abdel-Rahman, A. A. –H.; Jonke, S.; Ashry, E. S. H. E.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2972–2974.

(11) Commercially avaliable.

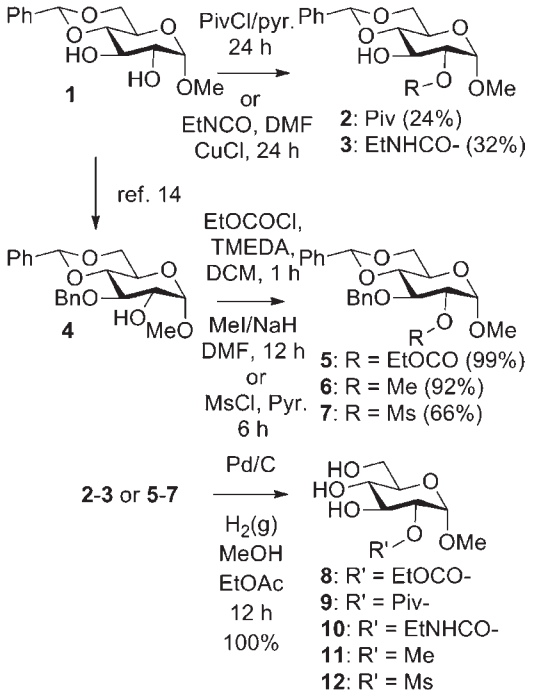
(12) Jeanloz, R. W.; Jeanloz, D. A. *J. Am. Chem. Soc.* **1957**, *79*, 2579–2583.

(13) Duggan, M. E; Imagire, J. S. *Synthesis* **1989**, 131–132.

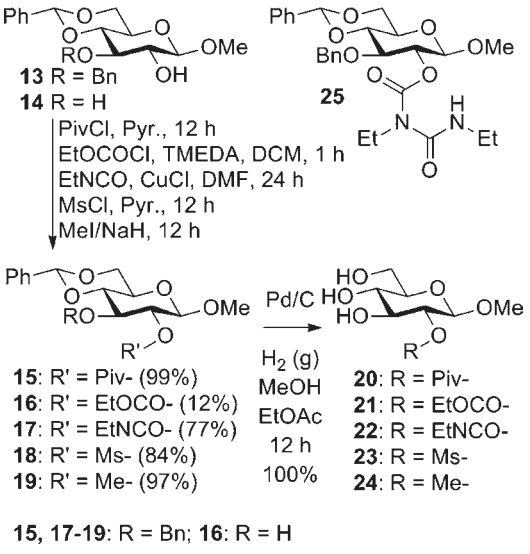
(14) Wang, C.; Lee, J.; Luo, S.; Fan, H.; Pai, C.; Yang, W.; Lu, L.; Hung, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2360–2362.

(15) The methyl 2-*O*-methoxycarbonyl-α/β-D-glucopyranoside was prepared as well, but methanol formed from hydrolysis of the methyl carbonate complicated the rate measurements. See Supporting Information.

Scheme 1. Synthesis of 2-O-protected Methyl-α-D-glucosides



Scheme 2. Synthesis of 2-O-Protected Methyl β-D-Glucopyranosides



The β-model compounds were prepared from the commercially available methyl β-D-glucopyranoside, which was 4,6-benzylidene protected followed by selective 3-O-benzylation via a tin-acetal intermediate to give the mono-ol **13**[16] ready for further functionalization. Compounds **15**–**19** were obtained using standard conditions with an excess of reagents (Scheme 2). Excess ethylisocyanate, however, resulted in the side product **25**, and therefore only 1 equiv of ethylisocyanate was used. Reaction of the substrate with ethyl chloroformate in pyridine did not go to completion. Instead, TMEDA was found superior as base for the synthesis of **16** from the diol **14**. Finally palladium-mediated removal of the benzylidene and benzyl groups gave the model compounds **20**–**24** in excellent yield.

With all model compounds in hand hydrolysis rates could be determined by following the conversion using NMR spectroscopy. The reactions were carried out in D_2O containing DCl (2.0 M), and the development of the methanol peak was followed in the initial part of the reaction (see Supporting Information). By plotting the integral vs time a rate was determined for the hydrolysis of each of the model compounds (Table 1).

The hydrolysis products of complete hydrolysis were, however, also determined.[17] The products 2-*O*-methyl and 2-*O*-ethylcarbamoyl glucose were obtained from **10**, **11**, **22**, or **24**, which were isolated in 30% and 22% yield, respectively (see Supporting Information). From **8**, **9**, **20**, and **21**, the end hydrolysis product was glucose, but 2-*O*-pivaloyl glucose could be observed as an intermediate in the hydrolysis of the pivalates. From the ethyl carbonates only glucose could be observed. From **12** and **23**, 2-*O*-mesyl glucose was the final product, but the reaction was so slow that no complete conversion of starting material was observed after many days.

When comparing the anomers a clear trend is observed; the β-anomer is 1.5 to 3 times faster than the corresponding α. Such difference in reactivity between the anomers is well-known; it is usually in the range 1.5–5 with β being the more reactive,[6,18] and can to a large extent be explained by the anomeric effect making the α-anomer more stable in the ground state.

This difference in rate coefficient between the anomers is essentially independent of the 2-O protective group, and the small difference between the nonparticipating and the participating groups suggests that "back-side attack" anchimeric assistance plays a negligible role in the rate enhancement of the 1,2-*trans* configurated methyl glucosides. This is in line with the observations by Paulsen and Meyberg,[19] who observed that 1,2-*trans* acetates in cyclohexane do not participate in a "back-side" anchimeric assistance[20] due to their equatorial–equatorial relationship; it should be emphasized that this study was carried out under water-free conditions.

Another remarkable observation is the small difference between "arming" nonparticipating groups and the "disarming" carbonyl-containing participating groups, where the difference is within a factor of 5; far from the examples of anchimeric assistance in the literature, where a factor of

(16) Murphy, P. V.; O'Brien, J. L.; Smith, A. B., III. *Carbohydr. Res.* **2001**, *334*, 327–335.

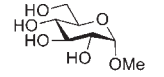
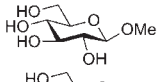
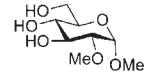
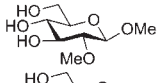
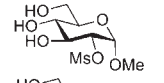
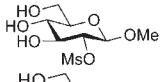
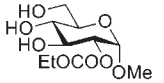
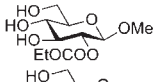
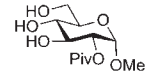
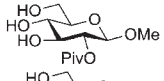
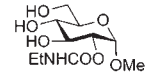
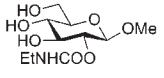
(17) Defined as when starting material was essentially gone.

(18) Ex. Lemieux *in situ* anomerization procedure: Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, 4056–4062.

(19) Paulsen, H.; Meyborg, H. *Tetrahedron Lett.* **1972**, *38*, 3973–3976.

(20) Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2780–2787.

Table 1. Rate Constants and Relative Rates of Hydrolysis of 2-O-Substitued Glucopyranosides in 2 M DCl at 60 °C

compound	$k10^5$ (s^{-1})	rel. rate	F	NB[a] rate increase
	1.883	1	0	-
	2.877	1.5	0	-
	0.911	0.5	0.01	-
	2.457	1.3	0.01	-
	0.033	0.02	0.59	-
	0.066	0.04	0.59	-
	0.629	0.3	0.34	x 3
	0.748	0.4	0.34	x 2
	2.448	1.3	0.26	x 7
	7.714	4.1	0.26	x 13
	4.662	2.5	0.35	x 25
	14.70	7.8	0.35	x 45

[a] NB = neighboring group. Rate increase estimated as a result of neighboring group particitation. This value was determined by using the Hammett and Swain and Lupton equations ($\log(k/k_o) = fF$) to calculate a rate solely based on induction (field) effects to see how much higher the experimental value were.[25]

2000 is a classical example of the rate enhancement caused by neighboring group participation from an ester.[8] The relative rates are picturing the stability of the formed cyclic intermediate, i.e. by the Bell–Evans–Polanyi principle. The acyloxonium ion that is generated from the carbamate is resonance stabilized and therefore most stable. Pivaloyl is second in stability because of the electron donation from the *tert*-butyl substituent. The carbonate is less nucleophilic and cannot stabilize a positive charge as well. This results in a small deactivation due to the inductive effect overriding neighboring group participation. The mesylates are, as expected, the least reactive toward acidic hydrolysis, due to the intense inductive destabilization of the intermediate oxacarbenium ion. Methylated and nonfunctionalized O-2 are of about the same reactivity, with the latter being slightly more reactive due to the more electron-donating capacity of H compared with a methyl group (electronegativity of 2.176 vs 2.472 on the Pauling scale).[21] No correlation between the rate coefficients and Hammett parameters or field effects (F)[22] (Table 1) was observed, which shows that inductive effects are not the only factor involved.[23] To obtain an estimate of the degree of neighboring group participation[24] we calculated the presumed rate of the acyl and carbamoyl derivatives if only field effects played a role and compared it with the experimental values.[25] This showed that these derivatives hydrolyze 2–45 times more rapidly than predicted from the F value (Table 1) and that the neighboring group effect has this magnitude.

From this study we conclude that participating groups indeed enhance the hydrolysis rate of methyl glucosides, but not due to a S_N2 type back-side assisted push out of methanol, but rather by stabilization of the intermediate developing positive charge where the Bell–Evans–Polanyi principle is operating. The magnitude of this stabilization is not large (2–45 times) and is mostly absorbed by the inherent electron-withdrawing effect of the neighboring group. The difference in rate between anomers is not caused by neighboring group effects but mainly by the greater stability of the α- over β-anomer due to the anomeric effect.

Acknowledgment. We thank FTP for supporting this work.

Supporting Information Available. Experimental details for preparation of new compounds, NMR spectra, and kinetics plots. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Inamoto, N.; Masuda, S. *Chem. Lett*. **1982**, 1003–1006.
(22) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev*. **1991**, *91*, 165–195.
(23) Similar conclusions were drawn from the work on C5 substituents: Timell, T. E.; Enterman, W.; Spencer, F.; Soltes, E. J. *Can. J. Chem*. **1965**, *43*, 2296–2305.
(24) Crich, D.; Hu, T.; Cai, F. *J. Org. Chem*. **2008**, *73*, 8942–8953.
(25) This was done by using the Hammett and the Swain and Lupton equations: $\log k/k_o = f \cdot F$. The parameter f was obtained from the data of the 2-OH and 2-O-mesylate and was −2.9 for the α-series and −2.7 for β.