JOC Article

Equatorial Contra Axial Polar Substituents. The Relation of a Chemical Reaction to Stereochemical Substituent Constants

Mikael Bols,* Xifu Liang, and Henrik H. Jensen

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

mb@chem.au.dk

Received August 12, 2002

The established rates of glycoside hydrolysis reactions were analyzed using free energy relationship plots based on substituent constants that depend on whether the substituent is axial or equatorial. In all cases good correlations were found when assuming either that the transition state had a charged ring-oxygen atom or that it had a charged anomeric carbon atom. The spontaneous hydrolysis of 2,4-dinitrophenyl β-glycopyranosides and the acidic hydrolysis of methyl β-D-glycopyranosides were found to give a good correlation, when 100% charge at the ring-oxygen in the transition state of these reactions is assumed. The acidic hydrolysis of methyl α-glycopyranosides was found to give good correlations regardless of whether 100% charge at the ring-oxygen or 100% charge at the anomeric carbon was assumed. The findings clearly demonstrate how crucial the stereochemistry of even remote polar substituents is for their electronic effect on chemical reaction.

Introduction

The Hammett free energy relationship is a useful method of investigating reaction mechanism.[1,2] The slope of such Hammett plots provides information about the electronic properties of reaction transition states, and the analysis has been applied to both aromatic and aliphatic systems.[3,4] The substituent effect can be divided into several components, some of which act through space, making the spacial position of the substituent crucial.[5−7] It is therefore in principle obvious that the stereochemistry of a substituent should be important for its electron withdrawing/donating effect on a chemical reaction. However, to our knowledge stereochemical substituent contributions have not previously been used in Hammett correlations.

Recently it was observed that the basicities of piperidines and hexahydropyridazines (Figure 1) were systematically affected by the axial or equatorial position of hydroxyl or ester groups.[8,9] An equatorial hydroxyl group was found to be three times more electron withdrawing than an axial hydroxyl group. The substituent contributions were very reliable, and a set of axial/equatorial substituent constants was extracted (Table 1) and used to predict piperidine basicity with high precision. The large variations in substituent effect as a result of substituents being equatorial and axial should be important in many reactions. They are likely to be caused, at least partially, by the varying hyperconjugative acceptor abilities of the substituent C−X σ bonds[10] in diffent configurations.

Carbohydrates, the most abundant biomolecules, consist mainly of monomers that are linked together with glycosidic bonds. Since each carbohydrate molecule owes many of its properties to the glycosidic linkages it contains, and because formation and cleavage of these bonds are involved in any carbohydrate synthesis or breakdown, the study of the chemistry of glycoside bond cleavage and formation is an important problem. Though spectacular progress has been made,[11,12] the effect of functional groups on rate cannot be considered to be well understood yet. The effects of stereochemistry on methyl glycoside hydrolysis rate were noted early: Methyl glycosides with many axial groups present were more reactive than were those with equatorial groups.[13,15,16] The same effect was observed on the reactivity of stereo-

* To whom correspondence should be addressed. Telephone: +45 89423963, Fax: +45 86196199.

(1) Alder, R. W.; Baker, R.; Brown, J. M. *Mechanisms in Organic Chemistry*; Wiley: London, 1971.
(2) Hammett, L. P. *Chem. Rev.* **1935**, *17*, 125.
(3) Taft, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 1045.
(4) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.
(5) Lowry, T. H.; Richardson, K. S. *Mechanisms and Theory in Organic Chemistry*, 3rd ed.; Harper Collins Publishers: New York, 1987.
(6) Grob, C. A.; Schlageter, M. G. *Helv. Chim. Acta* **1976**, *59*, 264−276.
(7) Grob, C. A.; Rich, R. *Helv. Chim. Acta* **1979**, *62*, 2793−2801.
(8) Jensen, H. H.; Lyngbye, L.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3447−3449.
(9) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem. Eur. J.* **2002**, 1218−1226.
(10) Alabugin, I. V.; Zeidan, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 3175−3185.
(11) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Stowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434−1435.
(12) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270−1277.
(13) Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429−3440.
(14) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753.
(15) Edward, J. T. *Chem. Ind. (London)* **1955**, 1102−1104.
(16) Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.

10.1021/jo0205356 CCC: $22.00
Published on Web 11/13/2002

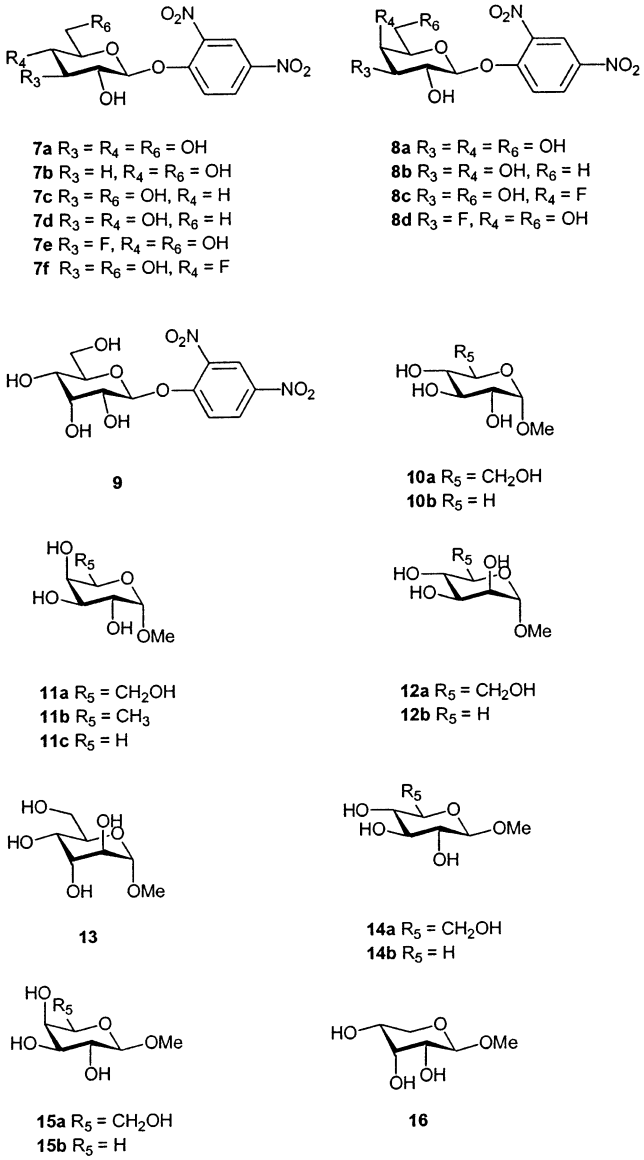


FIGURE 1. Substrates for the glycoside hydrolysis reactions studied.

TABLE 1. Stereochemical Substituent Constants of Various Substituents in a Six-Membered Ring in Chair Conformation[9]

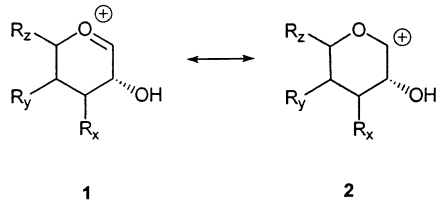
substituent	σ_α[a]	σ_β	σ_γ
H	0	0	0
OH(eq)		1.3	0.6
OH(ax)		0.5	0.2
CH_2OH(eq)	0.7	0.4	
CH_2OH(ax)		0.5	
Me(eq)	−0.1	−0.1	
F(eq)		2.3	1.0[b]
F(ax)		1.5[b]	

[a] α, *β*, and *γ* relate the position of the substituent relative to a ring atom. [b] Value determined in this paper.

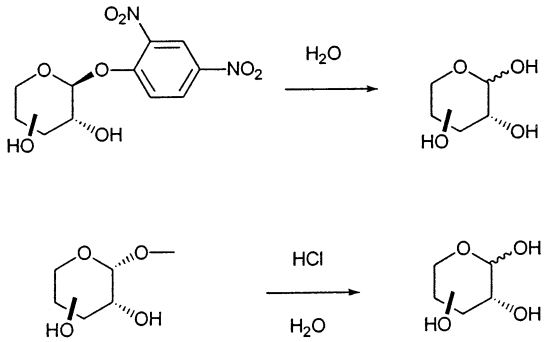
isomeric glycosyl donors.[14] This phenomenon has been explained as an effect caused by axial groups causing unfavorable sterical interactions in the ground state that are relieved in the transition state.[15]

The glycoside hydrolysis reaction (Scheme 1) is a good model to test the stereochemical dependence of substituent effects on a chemical reaction, because a large body of kinetic data exists on many stereoisomers: data that often are not available for other reactions. A problem with this reaction is that there may be significant charge in the transition state both at C1 and the ring-oxygen. It is therefore necessary to be able to relate the substituent effects to both C1 and ring-oxygen. We recently reported a preliminary study in which the basicity of stereoisomeric piperidines of the isofagomine-type was found to correlate with the rate of hydrolysis of methyl glycosides.[8] This suggests that the rate differences observed in hydrolysis of stereoisomeric glycosides are caused by a difference in substituent effect of axial and equatorial groups. The study also suggested that the transition state of methyl α-glycoside hydrolysis had considerable charge on the anomeric carbon. However, this study was limited as to the direct comparison of related compounds, and due to lack of related reference compounds, a direct correlation that considered charge at the ring-oxygen could not be made. However, the subsequent development[9] of a set of substituent constants (Table 1) that can be applied to carry out Hammett-type free energy relationship plots makes it now possible to do a refined analysis of the problem, which is the subject of this paper. This work constitutes to our knowledge the first example of a Hammett plot where stereochemical substituent constants are used (Scheme 2).

SCHEME 1 Oxocarbenium Ion Intermediate of Glycoside Hydrolysis Consisting of Resonance Forms 1 and 2



SCHEME 2. Two Glycoside Hydrolysis Reactions for Which Kinetic Data Are Available[a]

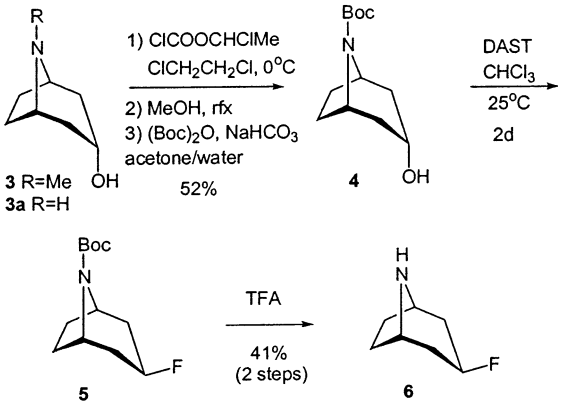


[a] The spontaneous hydrolysis of 2,4-dinitrophenylglycosides was performed at 37 °C and pH 6.5,[12] while the hydrolysis of methyl glycosides was performed in 2 M HCl solution at 40−80 °C.[13]

Results and Discussion

Substituent Constants for Fluorine. Published kinetic data were used in this study. Kinetic data of hydrolysis of stereoisomeric glycosides are available for either the hydrolysis of α- or *β*-methyl glycosides[13] or the hydrolysis of 2,4-dinitrophenyl *β*-glycosides (Scheme 1).[12]

SCHEME 3. Synthesis of Fluorinated Amine 6 and nor-Methyltropine 3b



However, Withers' very complete set of data contains kinetic constants for several deoxyfluoroglycosides which would be desirable to include in the analysis. The contributions for $3F_{eq}$ and $4F_{eq}$ had been determined to 2.3 and 1.7, respectively, but were based on a single set of literature pK_a values and might be unreliable.[9] It was particularly disturbing that the decrease in substituent effect was relatively small when the F atom was moved from the 3- to 4-position. In a recent study of fluorinated piperidines, the pK_a values of several stereo- and regioisomeric compounds were disclosed.[17] This paper supported that a $3F_{eq}$ substituent decreased basicity more than 2 pH units but also suggested that the substituent effect from a 4F substituent was less than 1, and thus far from 1.7. Because of this inconsistency, we decided to carry out an independent determination and synthesized the 4-fluorotropane **6** from tropinol **3** as outlined in Scheme 3. The tropine skeleton was chosen in order to have a rigid piperidine that can be relied on not to change conformation. The pK_a value of **6** was measured to be 9.8 and was compared to that of **3a**, which was determined to be 10.6. This means a difference of 0.8 between a $4F_{eq}$ and $4OH_{ax}$, giving a substituent contribution of $4F_{eq}$ of 1.0. This value, which is lower than the original value of 1.7, was used in this study.

Hammett Analysis. (a) Analysis of Dinitrophenyl *β*-Glycoside Hydrolysis. The two sets of literature kinetic data were fitted to the equation $pk = a\Sigma\sigma_s + b$ assuming either that the transition state had 100% charge at O and resembled resonance form **1** or that it had 100% charge on C and resemble resonance form **2**. Only variation of the 3-, 4-, and 5-positions was considered (*x*, *y*, and *z*, respectively) with the 2-substituent being kept constant in the series of compounds compared. Table 2 shows the calculation of $\Sigma\sigma_s$ for the hydrolysis of dinitrophenyl *β*-glycosides assuming charge distribution extreme **1**, and Table S1 (Supporting Information) shows a similar calculation assuming charge distribution extreme **2**. Parts a and b of Figure 2 are plots of p*k* versus $\Sigma\sigma_s$ for the two cases. The correlation corresponding to charge at oxygen (Figure 2a) is very good ($r^2 = 0.98$, slope = 1.06), while the correlation corresponding to charge at carbon (Figure 2b) is clearly poorer ($r^2 = 0.54$, slope = 0.85). This supports Withers' finding that charge is primarily located on oxygen in the transition state of this reaction. The slope of the correlation with oxygen charge is almost unity, which shows a direct correlation between the effect of a substituent on piperidine basicity and its effect on glycoside hydrolysis. It is noteworthy that the influence of the 2-substituent cannot be correlated to stereochemical substituent effects. The dinitrophenyl mannoside is 5 times less reactive than the glucoside even though one would expect the axial 2-OH to be less destabilizing to charge at ring-oxygen. Furthermore, the 2-deoxy-analogues are far more reactive than one would expect on the basis of substituent effects alone, particularly when charge is developing at oxygen. Sterical

TABLE 2. Calculation of p*k* and Σ*σ* for Hydrolysis of 2,4-Dinitrophenyl *β*-Glycopyranosides Assuming Charge at Ring-Oxygen

compd	k ($\times 10^6$)	p*k*	*σ*(*x*) 3-position	*σ*(*y*) 4-position	*σ*(*z*) 5-position	Σ*σ*[a]
glc (**7a**)	5.58	5.25	0.6	1.3	0.7	2.6
gal (**8a**)	26.1	4.58	0.6	0.5	0.7	1.8
all (**9**)	11.8	4.93	0.2	1.3	0.7	2.2
3dglc (**7b**)	22.3	4.65	0	1.3	0.7	2.0
4dglc (**7c**)	125	3.90	0.6	0	0.7	1.3
6dglc (**7d**)	26	4.59	0.6	1.3	−0.1	1.8
6dgal (**8b**)	161	3.79	0.6	0.5	−0.1	1.0
3Fglc (**7e**)	0.823	6.08	1.0	1.3	0.7	3.0
4Fglc (**7f**)	0.374	6.43	0.6	2.3	0.7	3.6
4Fgal (**8c**)	3.36	5.47	0.6	1.5	0.7	2.8
3Fgal (**8d**)	10.4	4.98	1.0	0.5	0.7	2.2

[a] Σ*σ* is obtained by addition of substituent contributions assuming the charge distribution of **1**. *k* is taken from ref 12. p*k* is −log *k*.

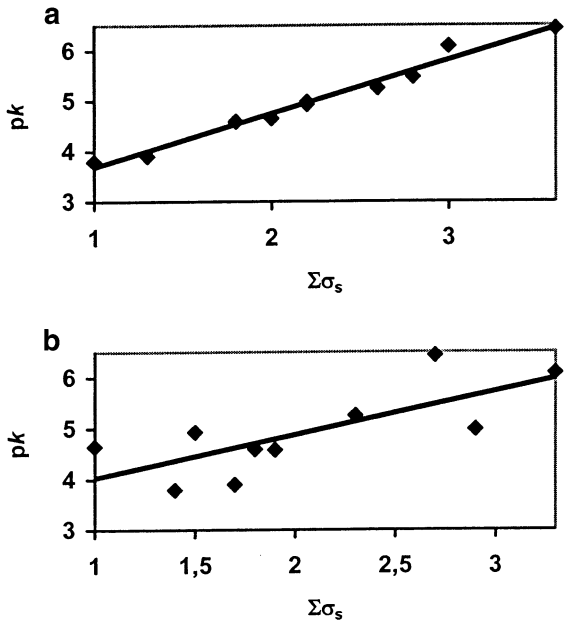


FIGURE 2. (a) Plot of p*k* versus Σ*σ* for hydrolysis of 2,4-dinitrophenyl *β*-glycopyranosides assuming charge at ring-oxygen in the transition state (similar to structure **1**). Data can be fitted to the equation $pk = 1.06\Sigma\sigma_s + 2.62$ with a coefficient of variation of $r^2 = 0.98$. (b) Plot of p*k* versus Σ*σ* for hydrolysis of 2,4-dinitrophenyl *β*-glycopyranosides assuming charge at anomeric carbon in the transition state (similar to structure **2**). Data can be fitted to the equation $pk = 0.85\Sigma\sigma_s + 3.18$ with a coefficient of variation of $r^2 = 0.54$.

(17) van Niel, M. B.; Collins, I.; Beer, M. S.; Broughton, H. B.; Cheng, S. K. F.; Goodacre, S. C.; Heald, A.; Locker, K. L.; MacLeod, A. M.; Morrison, D.; Moyes, C. R.; O'Connor, D.; Pike, A.; Rowley, M.; Russell, M. G. N.; Sohal, B.; Stanton, J. A.; Thomas, S.; Verrier, H.; Watt, A. P.; Castro, J. L. *J. Med. Chem.* **1999**, *42*, 2087−2104.

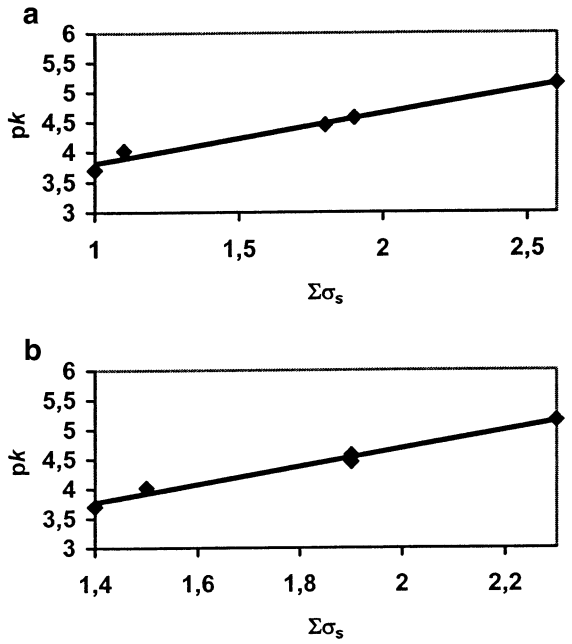


FIGURE 3. (a) Plot of pk versus $\Sigma\sigma$ for hydrolysis of methyl glycosides with an axial OMe group and an equatorial 2-OH assuming charge at ring-oxygen in the transition state (similar to structure **1**). Data can be fitted to the equation p$k = 0.84\Sigma\sigma_s + 2.97$ with a coefficient of variation of $r^2 = 0.98$. (b) Plot of pk versus $\Sigma\sigma$ for hydrolysis of methyl glycosides with an axial OMe group and an equatorial 2-OH assuming charge at anomeric carbon in the transition state (similar to structure **2**). Data can be fitted to the equation p$k = 1.52\Sigma\sigma_s + 1.64$ with a coefficient of variation of $r^2 = 0.98$.

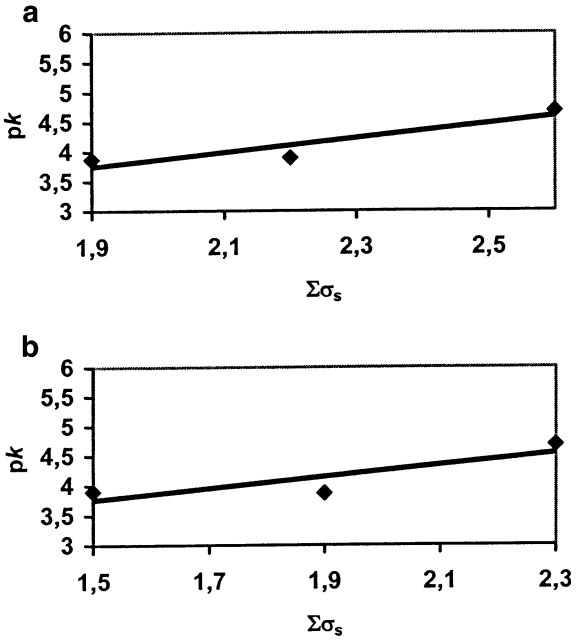


FIGURE 4. (a) Plot of pk versus $\Sigma\sigma$ for hydrolysis of methyl glycosides with an axial OMe group and an axial 2-OH assuming charge at ring-oxygen in the transition state (similar to structure **1**). Data can be fitted to the equation p$k = 1.2\Sigma\sigma_s + 1.46$ with a coefficient of variation of $r^2 = 0.84$. (b) Plot of pk versus $\Sigma\sigma$ for hydrolysis of methyl glycosides with an axial OMe group and an axial 2-OH assuming charge at anomeric carbon in the transition state (similar to structure **2**). Data can be fitted to the equation p$k = 0.98\Sigma\sigma_s + 2.3$ with a coefficient of variation of $r^2 = 0.72$.

hindrance may be playing a role for these substituents due to the proximity of the reaction site.

(b) Analysis of Methyl α-Glycoside Hydrolysis. In the analysis of methyl glycoside hydrolysis, the 2-substituents were therefore similarly kept constant due to the unclear influence of the stereochemistry of the 2-position. It should also be mentioned that we have only included data where the rate at 60° was available from Arrhenius plots, and we have not used data from hydrolysis at a single temperature. It was found that attempts to employ these data by comparing them with rate constants recalculated to their temperature gave poorer fits, which might be caused by the assumptions associated with recalculation or the greater error associated with these single temperature determinations. The plots of pk versus $\Sigma\sigma_s$ for α-glycosides with equatorial 2-OH are shown in Figure 3, and the corresponding data are in Tables S2 and S3 (Supporting Information). It should be noted that methyl β-L-arabinopyranoside has been included as an α-glycoside because it is predominantly in a conformation where the 1-OMe group is axial. The correlation to structure **1** (Figure 3a) was good ($r^2 = 0.98$, slope = 0.84), but so was the correlation to structure **2** ($r^2 = 0.98$, slope = 1.52, Figure 3b). A significant point here is, however, that the slopes of the two plots are quite different. When a slope is less than 1, as in Figure 3a, this means that the variation in glycoside hydrolysis rate is less than expected on the basis of substituent effects, while if the slope is greater than 1, as in Figure 3b, substituent effects cannot account for the entire variation in rate. In this case the data could be explained by a transition state with considerable charge at both oxygen and carbon. If the data are fitted to a weighted intermediate of the $\Sigma\sigma_s$ for **1** or **2**, it is found that with 65% charge at O a slope of 0.99 is found ($r^2 = 0.98$, plot not shown). So while the data are in accordance with the previous finding that anomeric carbon was charged in the transition state of this reaction,[8] two-thirds of the charge is resting on ring-oxygen. This is in agreement with results by Bennett et al. that α-glycosides have less positive charge buildup on ring-oxygen in the transition state than the corresponding β-glycoside.[18]

A similar evaluation of methyl α-glycosides with an axial 2-OH group is shown in Figure 4. The limited data available for this case gave a fair correlation (Figure 4a, $r^2 = 0.84$, slope = 1.2) to charge at oxygen and a slightly poorer fit to **2** (Figure 4b, $r^2 = 0.72$, slope = 0.97). The interpretation of these data must be that they also support a transition state with charge at both positions, similar to the cases of other α-glycosides.

(c) Analysis of Methyl β-Glycoside Hydrolysis. An analysis of acidic hydrolysis of methyl β-glycosides based on Overend's data[13] is shown in Figure 5. Similar to the analysis above, methyl α-L-arabinopyranoside has been included here. As in the case of the hydrolysis of nitrophenyl glycosides, good correlation (Figure 5a, $r^2 = 0.96$, slope = 0.7) to charge at oxygen is obtained, as is a clearly poorer fit to **2** (Figure 5b, $r^2 = 0.66$, slope = 0.7). The interpretation is therefore that there is at least some charge at oxygen in this case.

(18) Bennet, A.; Sinnott, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7287−7294.

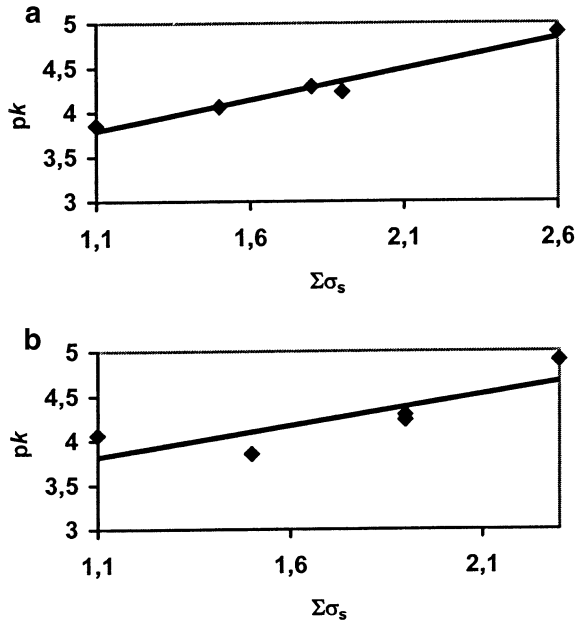


FIGURE 5. (a) Plot of p*k* versus Σσ for hydrolysis of methyl glycosides with an equatorial OMe group and an equatorial 2-OH assuming charge at ring-oxygen in the transition state (similar to structure **1**). Data can be fitted to the equation pk = 0.70Σσ_s + 3.03 with a coefficient of variation of r^2 = 0.96. (b) Plot of p*k* versus Σσ for hydrolysis of methyl glycosides with an equatorial OMe group and an equatorial 2-OH assuming charge at anomeric carbon in the transition state (similar to structure **2**). Data can be fitted to the equation pk = 0.70Σσ_s + 3.04 with a coefficient of variation of r^2 = 0.66.

This study clearly shows that the variations in electron-withdrawing effect of axial and equatorial polar groups can account for the variation in rate of hydrolysis of stereoisomeric glycosides. In fact, since slopes are often close to unity, it appears that the rate differences are mainly caused by electronic effects, though it is not clear from this study to what extent other effects such as the relief of 1,3-diaxial strain also play a role.

It may be argued, since the transition state does not have a chair conformation, that axial and equatorial substituent constants for chair conformations will not be applicable. However, the good correlations found in this study show that the importance of the geometry difference is minor for substituents in the 3-, 4-, and 5-positions. Perhaps the geometry difference between the transition state and a chair can explain why substituent effects from the 2-position are poorly correlated.

Second, it is possible to interpret the data as to where charge is positioned in the ring. The data are most clear for 2,4-dinitrophenyl β-D-glycoside hydrolysis, where they clearly support Withers' findings that oxygen appears to be bearing the charge in the transition state. The acidic hydrolysis of methyl β-glycosides also gives the best correlation when assuming charge on oxygen. For the α-glycosides, however, the data support charge being in both positions equally well, which is in accordance with our previous study that found correlation to charge at C1 for α-glycosides.[8] These results, which appear to contradict the commonly accepted stereoelectronic effects regarding glycoside cleavage according to which axial glycosides receive more assistance from ring-oxygen than equatorial glycosides, should probably not be overemphasized. Nevertheless, it is noteworthy that the results are in accordance with kinetic isotope effect studies by Bennet and Sinnott which showed more charge on oxygen in β-glycoside hydrolysis than in the α-glycoside case.[18]

Experimental Section

The kinetic data were taken from refs 12 and 13. The synthesis of **6** is included as Supporting Information.

Supporting Information Available: Synthetic procedures for the preparation of **6**, ^{1}H NMR spectrum of **6**, and Tables S1−S7 showing the data calculations for Figures 3−9. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0205356