The Acid-Catalyzed Hydrolysis of Glycopyranosides[1]

M. S. FEATHER AND J. F. HARRIS

Forest Products Laboratory,[2] Forest Service, U. S. Department of Agriculture, Madison, Wisconsin

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An interpretive review of the factors affecting the rate of hydrolysis of glycopyranosides is presented. Conformational analysis indicates that the stereochemistry of the glycoside is an extremely important factor. The orientation of the aglycone, equatorial or axial, and the resistance to rotation about the C-2–C-3 and C-4–C-5 bonds appear to be major rate-determining factors. In addition to the previously recognized effects of changing the character of the aglycone, which includes steric, electronic, and mechanistic effects, it is pointed out that the aglycone may change the conformation of the glycone, thereby effecting a change in the hydrolysis rate. The relative rates of a large number of glycosides were examined in light of this rationale and no anomalous cases were found.

Many workers[3-5] have been involved in experimental work designed to elucidate the mechanism of glycoside hydrolysis, and some[6-8] have also commented on the various steric and electronic factors which affect the rate of hydrolytic reactions. Although an abundance of data concerning glycoside hydrolysis is available, little is definitely known about the mechanism of hydrolysis or the factors which affect hydrolysis rates. Fortunately, much of the compiled data on this subject lends itself well to a theoretical treatment, and it is toward this subject that this manuscript is directed.

Table I provides a comparison between the rate of hydrolysis of anomers and the orientation of the methoxyl group. The particular pairs presented have been chosen because the stable conformer of each member of the pair is similar. The stable conformer of each of the first 11 members listed has been determined experimentally.[9] The stable conformation for the remaining members was assigned using the instability factors of Reeves[9] and Hassel and Ottar[10]; no questionable assignations occurred. The position, equatorial or axial, of the methoxyl group in the stable conformer is readily determined from the configuration and conformation. It should be remembered that, although the assigned conformation is more stable than other possible conformations, the molecule is not compelled to react as if it were in this conformation or that it is rigidly fixed in any way.

For each pair listed, the anomer having an equatorial methoxyl group hydrolyzes more rapidly than the anomer containing an axially oriented group. Thus, for anomeric methyl pyranosides, the conformation of the initial state determines the hydrolysis rate. It cannot be deduced if the anomers hydrolyze *via* different transition states or if the initial conformation determines the concentration of the rate controlling species. The ratio of the rates for anomers is approximately twofold, which is small compared with the large differences in rates between pairs.

The greater reactivity of glycosides containing the aglycone equatorially oriented is contrary to the usual order of conformational stabilities. This has been explained[11-13] on the basis of differing degrees of hindrance introduced by neighboring groups in the two positions. This interpretation is analogous to that proposed to explain the reactivity of the *cis*-cyclohexane-1,2-diols in which the axial hydroxyls are more difficult to esterify and the esters more difficult to hydrolyze than those in the corresponding *trans* isomer.[14,15] During esterification, the hydroxyl group of the diol attacks an electron-deficient carbon atom, and the differences in rates are supposed to be due to differences in accessibility; equatorial substituents are considered to be more accessible than those in axial positions. Although the reaction mechanism of hydrolysis is very different, it is likely that it involves the transfer of a proton from a hydronium ion to the oxygen atom of the glycosidic linkage; similar reasoning suggests that an equatorial group would hydrolyze more readily than an axial group.

Edward[6] attributes the greater reactivity of the equatorial substituent to the dipole moment of the ring oxygen. The nonbonding orbitals of this atom have a resultant dipole lying in closer proximity to an equatorial C-1 substituent than to one positioned axially. The repulsion between the lone pairs of electrons on the geminal oxygens of C1 will be greatest when the aglycone group assumes an equatorial position. Support for this explanation of opposing dipoles is found in the "$\Delta 2$ effect" of Reeves.[9] The configurational requirements for this effect allow the oxygen atoms neighboring the glycosidic oxygen to attain a juxtaposition which would result in maximum repulsion.

The hydrolysis rates of the anomers of methyl 2,4-di-*O*-methyl-3,6-anhydro-D-glucopyranoside have been supposed to support[16] the hypothesis that an equatorially positioned methoxyl group is more susceptible to hydrolytic fission than the axially positioned group, since the α-anomer hydrolyzes 30 times faster than the β-form.[17] The hydrofuran ring was thought to retain the pyranose ring in the 1C conformation placing an α-substituent in an equatorial position, while a β-substituent would be in the unreactive axial position. Examination of scale models, however, indicates that the β-anomer would adopt a slightly distorted 1B con-

(1) Presented at the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964.
(2) In cooperation with the University of Wisconsin.
(3) C. A. Bunton, T. A. Lewis, D. R. Llewellyn, and C. A. Vernon, *J. Chem. Soc.*, 4419 (1955).
(4) B. E. C. Banks, Y. Meinwald, A. J. Rhind-Tutt, I. Sheft, and C. A. Vernon, *J. Chem. Soc.*, 3240 (1961).
(5) R. L. Whistler and T. Van Es, *J. Org. Chem.*, **28**, 2303 (1963).
(6) J. T. Edward, *Chem. Ind.* (London), 1102 (1955).
(7) A. B. Foster and W. G. Overend, *ibid.*, 556 (1955).
(8) B. Capon and W. G. Overend, *Advan. Carbohydrate Chem.*, **15**, 11 (1960).
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(10) O. Hassel and B. Ottar, *Acta Chem. Scand.*, **1**, 929 (1947).
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(13) F. A. Shafizadeh, *Advan. Carbohydrate Chem.*, **13**, 9 (1958).
(14) D. H. R. Barton, *Experimentia*, **6**, 316 (1950).
(15) G. Vavon, *Bull. soc. chim.*, **49**, 937 (1931).
(16) S. G. Sunderwirth and G. G. Olson, *J. Chem. Ed.*, **39**, 410 (1962).
(17) W. N. Haworth, L. N. Owen, and F. Smith, *J. Chem. Soc.*, **88** (1941).

TABLE I

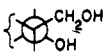
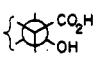
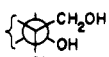
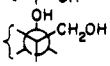
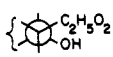
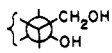
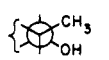
HYDROLYSIS RATES OF SOME ANOMERIC METHYL PYRANOSIDES[a]

Methyl pyranoside of	Relative rate[b]	Conditions of comparison: Acid	Temp., °C.	Ref.	Stable conformation	Orientation of methoxyl
α-D-Glucose β-anomer	1.0	0.5 *N* HCl	75	*c*	Cl	Axial
	1.9				Cl	Equatorial
α-D-Mannose β-anomer	2.4	0.5 *N* HCl	75	*c*	Cl	Axial
	5.7				Cl	Equatorial
α-D-Galactose β-anomer	5.2	0.5 *N* HCl	75	*c*	Cl	Axial
	9.2				Cl	Equatorial
α-D-Xylose β-anomer	4.5	0.5 *N* HCl	75	*c*	Cl	Axial
	9.1				Cl	Equatorial
α-L-Rhamnose β-anomer	8.3	0.01 *N* HCl	100	*c*	1C	Axial
	19.0				1C	Equatorial
α-L-Arabinose β-anomer	13.1	0.5 *N* HCl	75	*c*	Cl	Equatorial
	9.0				Cl	Axial
α-D-Glucuronic acid β-anomer	0.47	0.47 *M* H_2SO_4	75	*d*	Cl	Axial
	0.62				Cl	Equatorial
D-*glycero*-α-L-*manno*-Heptose β-anomer	1.4	0.05 *N* HCl	98	*c*	Cl	Axial
	3.2				Cl	Equatorial
2-Deoxy-α-D-glucose β-anomer	2090	0.01 *N* HCl	58	*f*	Cl	Axial
	5125[e]				Cl	Equatorial
2,3,4,6-Tetra-*O*-methyl-α-D-glucose β-anomer	0.16	0.01 *N* HCl	95–100	*g*	Cl	Axial
	0.40				Cl	Equatorial

[a] For a listing of additional compounds see F. Shafizadeh and A. Thompson, *J. Org. Chem.*, **21**, 1059 (1956). [b] Ratio of the rate constant for the hydrolysis of the methyl aldopyranoside to that of methyl α-D-glucopyranoside at the conditions specified (extrapolated when necessary). [c] As quoted by H. S. Isbel and H. L. Frush, *J. Res. Natl. Bur. Std.*, **24**, 125 (1940). [d] J. Nakano and B. G. Rånby, *Svensk Papperstid.*, **65**, 29 (1962). [e] This value obtained by extrapolation of data given in ref. 26. [f] Ref. 26. [g] W. N. Haworth and E. L. Hirst, *J. Chem. Soc.*, 2615 (1930).

TABLE II

THE EFFECT OF GLYCOSYL GROUP ON HYDROLYSIS RATE

Methyl pyranoside of	C-2–C-3	C-5–C-4	Relative rate	Conditions of comparison: Acid	Temp., °C.	Ref.
β-D-Xylose			9.1	0.5 *N* HCl	75	*a*
β-D-Ribose			12.3	2 *N* HCl	60	*b*
β-D-Glucose			1.9	0.5 *N* HCl	75	*a*
β-D-Mannose			5.7	0.5 *N* HCl	75	*a*
2-Deoxy-β-D-glucose			5125	0.01 *N* HCl	58	*b*
β-D-Glucuronic acid			62	0.47 *M* H_2SO_4	75	*c*
β-D-Glucose			1.9	0.5 *N* HCl	75	*a*
β-D-Galactose			9.2	0.5 *N* HCl	75	*a*
β-D-Xylose			9.1	0.5 *N* HCl	75	*a*
α-L-Arabinose			13.5	2.0 *N* HCl	60	*b*
β-D-*glycero*-L-*manno*-Heptose			3.2	0.05 *N* HCl	98	*a*
β-D-Mannose			5.7	0.5 *N* HCl	75	*a*
β-D-Rhamnose			19.0	0.01 *N* HCl	100	*a*

[a] Table I, ref. *c*. [b] Ref .26. [c] Table I, ref. *d*.

formation, which places the methoxyl group in an equatorial position. This explains its high rate of hydrolysis compared with methyl α-D-glucopyranoside—approximately seven times as fast. The very high rate of hydrolysis of the α-compound, which is 200 times greater than that of methyl α-D-glucopyranoside, can be attributed to the fact that it is greatly strained in all possible conformations.

TABLE III

THE EFFECT OF AGLYCONE ON HYDROLYSIS RATE

Pyranoside	Relative rate α-anomer	Relative rate β-anomer	Conditions of comparison Acid	Temp., °C.	Ref.
Methyl D-gluco-	1.0	1.9	0.5 *N* HCl	75	*a*
Ethyl D-gluco-	...	2.1	0.5 *M* H_2SO_4	60	*b*
n-Propyl D-gluco-	...	2.5	0.5 *M* H_2SO_4	60	*b*
t-Butyl D-gluco-	...	1960	3.3 *M* $HClO_4$	25	*c*
Benzyl D-gluco-	2.0	2.97	0.05 *N* HCl	60	*d*
Phenyl D-gluco-	61.5	18.0	0.05 *N* HCl	60	*d*
p-Nitrophenyl D-gluco-	35.8	4.1	2.0 *N* HCl	60	*e*
Phenyl D-gluco-		11.1	0.1 *N* HCl	60	*f*
o-Nitrophenyl D-gluco-		16.0			
m-Nitrophenyl D-gluco-		3.9			
p-Nitrophenyl D-gluco-		3.2			
Ethyl D-galacto-	10.7	7.1	2.0 *N* HCl	60	*e*
Phenyl D-galacto-	181	34.6			
Phenyl D-gluco-	...	8.0	1.0 *N* HCl	60	*g*
D-galacto-	...	28.2			
D-xylo-	...	93.7			
p-Chlorophenyl D-gluco-	...	6.1	1.0 *N* HCl	60	*g*
D-galacto-	...	21.2			
D-xylo-	...	86.5			
o-Nitrophenyl D-gluco-	...	8.5	0.01 *N* HCl	65	*h*
D-galacto-	...	19.4			
L-arabo-	88.6	...			
p-Nitrophenyl D-gluco-	...	2.5	0.01 *N* HCl	65	*h*
D-galacto-	...	5.4			
L-arabo-	23.4	...			
Cellobiose	...	6.2	1.0 *M* H_2SO_4	90	*i*
Cellobiouronic acid	...	0.18			
Pseudocellobiouronic acid	...	6.2			

[a] Table I, ref. *c*. [b] Ref. 27. [c] Ref. 32. [d] L. J. Heidt and C. B. Purves, *J. Am. Chem. Soc.*, **66**, 1385 (1944). [e] Ref. 26. [f] Ref. 28. [g] B. N. Stepanenko and O. G. Serdyuk, *Dokl. Acad. Nauk SSSR*, **139**, 1132 (1961); *Chem. Abstr.*, **56**, 1561 (1962). [h] Ref. 31. [i] Ref. 30.

The very rapid hydrolysis of glycosides of the 2-deoxy sugars and the enhanced rate of hydrolysis of methyl pentosides compared with methyl hexosides was noted by Riiber and Sørensen.[18] The subsequent explanations given for the order of stability toward acid of the various classes of methyl pyranosides (that is, hexopyranosides, pentopyranosides, deoxyhexopyranosides, and so on) have not been completely satisfactory, for anomalous examples may be cited to each explanation.[6,8,19] A slight variation of an explanation originally proposed by Edward,[6] however, appears to satisfactorily correlate the relative hydrolysis rates of various pyranosides.

Rates for several groups of methyl glycopyranosides are compared in Table II. These glycosides are all conformationally stable; that is, the energy difference between the stable conformer and any other form is large enough to ensure that the molecule may be considered to be in only the stable conformation. In addition, the aglycone of each is equatorially oriented in the stable conformation. The arrangement of the substituents on C-2, C-3, C-4, and C-5 when the molecule is in its stable conformation is shown in the Newman projections. In interpreting these formulas, it should be remembered that the C-2 and C-5 atoms are projected in front of the plane of the paper, while C-3 and C-4 are behind. The vertical lines represent axial bonds, while those which are slightly above or below the horizontal axis are bonds equatorially oriented. The bonds on the right in the C-2–C-3 column and those on the left in the C-5–C-4 column are bonds in the pyranose ring.

(18) C. N. Riiber and N. A. Sørensen, *Kgl. Norske Videnskab. Selskabs Skrifter*, **No. 1**, 1 (1938); *Chem. Abstr.*, **33**, 4962 (1939).

(19) F. Shafizadeh, *Tappi*, **46**, 381 (1963).

An examination of Table II indicates that there is a direct relationship between the hydrolysis rate and the ease of rotation about the C-2–C-3 and C-5–C-4 bonds. The ease of rotation depends not only on the extent of interaction of the groups on C-2 relative to C-3 and C-4 relative to C-5, but also on 1,3-type interactions.[20] It has not been possible to find suitable data to evaluate the effect of the latter. The data in Table II show that the rate is decreased by increased opposition of substituents on C-2, *vis-a-vis* those on C-3 when rotation is in the direction which tends to eclipse the equatorial groups. The rate is also decreased by increased opposition of substituents on C-5, *vis-a-vis* those on C-4 for the same reasons.

Assuming the hydrolysis rates of glycosides containing equatorially oriented aglycones to be related to the ease of rotation about the C-2–C-3 and C-4–C-5 bonds, the relative ability of members of various classes may be predicted. For example, the order of stability for some common glycopyranosides should be heptosides > hexosides > 6-deoxyhexosides > pentosides, glycosides > mannosides > 2- and 3-deoxyglucosides > 2,3-dideoxyglycosides, and D-glucosides > D-galactosides > D-xylosides > L-arabinosides.

The available data for methyl β-glycosides listed in Table II conforms fully to these predictions, and addi-

(20) The type of interaction implied here is analogous to that which produces restricted rotation about a single bond. It is assumed in this case that the physical size of the substituents (steric hindrance) is the major contributor to these interactions. Electrostatic effects, however, should not be ignored, particularly in cases where substituents are highly electronegative (such as carboxyl groups). For more complete discussion of the origin of barriers to restricted rotation about single bonds, see D. J. Millen, "Progress in Stereochemistry," Vol. 3, P. B. D. de la Mare and W. Klyne, Ed., Butterworth, Inc., Washington, D. C., 1962, p. 138.

tional examples are shown in Table III. These principles also explain numerous qualitative observations reported, such as the high stability of methyl 2-*O*-methylsulfonyl-3,4-*O*-isopropylidene-β-D-arabinoside.[21]

It should be noted that, in part, support for the conclusion reached above rests on a comparison of the relative rates measured under a variety of conditions. These comparisons are justified only if the compounds concerned show similar variations of rate with changes in catalyzing acid, acid concentration, and temperature. It is known that glycoside hydrolysis is strongly acid catalyzed, and, for the compounds for which data are available, rates of hydrolysis parallel acidity closely.[3,8] Thus, comparison of rate ratios measured at different acidities is probably quite valid. The reported activation energies for the hydrolysis of various glycosides differ, however, and consequently, the rate ratios vary with temperature. Timell[22] has measured the activation energies for seven methyl pyranosides and found the range to be narrow with values varying from 32.0 to 35.1 kcal./g. mole. The similar compounds of Table II should fall within this range, in which case, the error introduced would not affect the conclusion.

The mechanism of glycoside hydrolysis is still in doubt,[13,19] but many workers[3,4,23] concerned with this area consider the reaction rate to be controlled by heterolysis of the glycoside conjugate acid to a cyclic C-1 carbonium ion. Since this ion has the probable conformation of cyclohexene (a half chair),[24] its formation involves a net counterclockwise rotation about the C-2–C-3 and C-4–C-5 bonds. Edward[6] has discussed the hydrolysis mechanism on the basis of this net rotation, and although he was able to explain most observations, anomalies were noted. As shown above, these are resolved by considering the hydrolysis rate to be controlled by the resistance to rotation counter to the net effect. It is probable that transient structural distortions are responsible for this behavior. Perhaps the conjugate acid assumes a structure at C-1 similar to that of a classical carbonium ion, planar in structure with bond angles of 120°. Such a phenomenon could conceivably result in the equatorial interactions discussed.

In addition to the stereochemical effects discussed, it is probable that various electronic effects, particularly inductive effects, are also important in determining glycoside hydrolysis rate. The presence of polar groups at C-2 would be expected to have a particularly large effect on hydrolysis rate.

The extremely rapid hydrolysis rates exhibited by the methyl 2-deoxy-D-glucopyranosides may be partly due to the absence of an inductive effect which normally arises from the hydroxyl group situated at C-2. Evidence that these rapid rates are due partly, but not entirely, to inductive effects has been given by Richards.[25] He has found that methyl 3-deoxy-α-D-glucopyranoside and α-D-mannopyranoside hydrolyze, respectively, 7.4 and 11.5 times as fast as methyl α-D-glucopyranoside. These rates, while faster than the analogous hexoside, are considerably slower than those quoted for the 2-deoxyglucosides (Table I) and are in the expected direction and of the expected magnitude for rate changes due to inductive effects. On the other hand, it has been found[26] that the rate of hydrolysis of methyl 4-deoxy-α-D-glucoside is faster than the 3-deoxy analog by a factor of two, an increase in rate not attributable to inductive effects. Likewise, it is diffiult to attribute rate changes arising from the presence of 6-deoxy groups to inductive effects—the group in question being far removed from the active site and the rate changes being relatively large.

The hydrolysis rate of the glycosidic bond is profoundly affected by the nature of the aglycone. The effect is due to several causes which are, however, difficult to separate for experimental study, and, thus, difficult to demonstrate. The difficulty is compounded when using the available data from the literature, since large differences exist in values reported by different investigators; rate constants reported for the familiar methyl glucosides vary threefold. Inconsistencies are apparent in Table III, but the variation of rate with the nature of the aglycone, to be discussed, is readily apparent.

It is well known that the *O*-aryl glycosides hydrolyze more rapidly than the *O*-alkyl glycosides, supporting the hypothesis that an increase in the electronegativity of the aglycone enhances the rate by weakening the glycosyl–oxygen bond. It has been noted, however,[3] that the electron density on the glycosidic oxygen may affect the reaction rate in two opposing ways: first, by changing the equilibrium concentration of the conjugate acid, and, secondly, by changing the rate of breakdown. The over-all effect of changing the electronegative character of the aglycone may be expected to be small, and this has generally been found to be the case. Timell[27] recently studied the hydrolysis of some alkyl β-D-glucopyranosides in which the aglycone contained various electron-withdrawing polar groups and found the rate only slightly increased as the electronegativity was increased. On the other hand, Nath and Rydon[28] made a study of substituted phenyl β-D-glucopyranosides and found that, certain exceptions apart, the acid-catalyzed hydrolysis rate was slightly decreased as the electronegativity of the substituents was increased. The introduction of negative substituents into the aromatic ring of phenyl β-D-xylosides was found by Hibbert and associates[29] to have little effect on the acid hydrolysis rate.

Johansson and co-workers[30] measured the rates of hydrolysis of cellobiouronic acid [4-*O*-(β-D-glucopyranosiduronic acid)-D-glucose], pseudocellobiouronic acid [4-*O*-(β-D-glucopyranosyl)-D-glucuronic acid], and cellobiose (Table III). Since two of the compounds contain carboxyl groups each at the same distance from the glycosidic oxygen, the results effectively demonstrate the difference in magnitude of the effect of an electronegative group in the "aglycone," and the same group in the sugar molecule. The rate of hydrolysis for cellobiose and pseudocellobiouronic acid was identical, in-

(21) J. K. N. Jones and W. H. Nicholson, *J. Chem. Soc.*, 3050 (1955).
(22) T. E. Timell, *Can. J. Chem.*, **42**, 1456 (1964).
(23) C. Bamford, B. Capon, and W. G. Overend, *J. Chem. Soc.*, 5138 (1962).
(24) D. H. R. Barton and coworkers, *Chem. Ind.* (London), 21 (1954).
(25) G. N. Richards, *ibid.*, 228 (1955).
(26) W. G. Overend, C. W. Rees, and J. S. Sequeira, *J. Chem. Soc.*, 3429 (1962).
(27) T. E. Timell, *Chem. Ind.* (London), 1208 (1963).
(28) R. L. Nath and H. N. Rydon, *Biochem. J.*, **57**, 1 (1954).
(29) J. H. Fisher, W. L. Hawkins, and H. Hibbert, *J. Am. Chem. Soc.*, **63**, 3031 (1941).
(30) I. Johansson, B. Lindberg, and O. Theander, *Acta Chem. Scand.*, **17**, 13 (1963).

dicating the inductive effect to be negligible in this case. The very slow hydrolysis rate for cellobiouronic acid probably results from the hindrance to rotation about the C-5–C-4 bond.

Several investigators[28,29,31] have observed that *ortho*-substituted phenyl β-D-glucosides exhibit relatively high hydrolysis rates compared with those containing *meta*- and *para*-substituted aglycones. The nature of this phenomena is not, at present, clear. It has been suggested[28] that intramolecular association may be partly responsible.

The very high rate of hydrolysis of *t*-butyl β-D-glucoside would indicate that the inductive effect is more important than indicated above. It has been shown,[32] however, that the hydrolysis of this compound involves alkyl–oxygen bond cleavage with the formation of an alkyl carbonium ion rather than a glycopyranosyl carbonium ion. A similar change in reaction mechanism has been demonstrated in the case of ester hydrolysis.[33] The position of fission presumably depends on the relative stability of the two carbonium ions.

It has frequently been observed that the α-anomers of *O*-aryl glycosides hydrolyze more rapidly than the corresponding β-anomers, but this fact has not been satisfactorily explained. It can be readily explained by conformational analysis. The stable conformer of the β-anomer has the glycone in the C1 conformation with the aglycone in an equatorial position. A phenyl α-glycoside in a C1 conformation, however, contains an axial phenoxyl group. Scale molecular models of such compounds show that considerable axial–axial interactions result when the molecule is in the C1 conformation. This is largely removed if the aglycone is in an equatorial position; this is true when the glycone assumes the 1C, B1, 2B, or 3B conformation. The α-anomer would then be expected to hydrolyze more rapidly than the β-anomer, as the resistance to rotation about the C-2–C-3 and C-5–C-4 bonds of any of these conformers is less than that of the C1 conformer. This effect, where the aglycone apparently changes the conformation of the glycone, is apparent for several of the compounds listed in Table III.

In the case of the benzyl glucosides, the interaction between the glycone and aglycone portions of the molecule is much less than that for the phenyl glucosides because of the intervening methylene group. This is reflected in the smaller ratio of the hydrolysis rates of the α- and β-anomers. The instability of the C1 conformer of galactose, contrasted with glucose, is apparent, since the effect described is much greater for galactosides.

The possibility of the aglycone changing the conformation of the glycone, and thus affecting the hydrolysis rate, has not been previously noted. Its importance in interpreting the relative hydrolysis rates of di- and oligosaccharides is obvious.

Examination of the hydrolysis rates of the *p*-chlorophenyl glycopyranosides in Table III reveals, however, that the rate changes among different sugars having the same aglycone can be explained, as with the methyl glycopyranosides, on the basis of equatorial interaction.

The previous portion of this discussion has been spent on the hydrolysis of methyl glycopyranosides which exist largely in one conformation. Information is also available on the hydrolysis of some unstable glycoside pairs; that is, glycosides which, when in solution, exhibit appreciable concentrations of both chair conformations.

It is difficult to interpret the sometimes unpredictable hydrolysis rates of these glycosides because several variables are involved in each case. Some general observations indicate that certain structural similarities exist among the glycosides in this series.

The methyl glycopyranosides of α- and β-D-glucose and α- and β-D-*glycero*-D-*gulo*-heptose have composite[8] rate constants of 58.1, 19.0, 20.9, and 6.7. In both cases, the α-anomer hydrolyzes approximately three times faster than the β-. Both α-anomers would be expected to produce appreciable amounts of 1C conformer in solution. This conformation possesses an equatorial methoxyl group and, undoubtedly, represents a high energy form relative to the conformationally stable analog. Since previous evidence was presented which indicates that glycosides having equatorial anomeric methoxyl groups hydrolyze faster than those having axial ones, it is probable that the α-D-gulopyranosides undergo hydrolysis at extremely rapid rates because of the position of the aglycone and the additional energy content of the form involved. In addition, each α-anomer, when in a 1C conformation, possesses a Δ2 instability factor. According to Reeves,[9] such a factor when present renders a particularly large amount of strain on the molecule.

The methyl glycopyranosides of α- and β-D-lyxose have composite rate constants of 14.5 and 46.4, respectively, and also represent a conformationally unstable pair of anomers. Of significance in this case is the abnormally rapid hydrolysis rate of the β-anomer which hydrolyzes three times faster than the α-glycoside. This glycoside, when in a C1 conformation like the α-gulosides, possesses both an equatorial methoxyl group and a Δ2 instability factor.

As in the case of an equatorial anomeric methoxyl group, the effect of a Δ2 instability factor on hydrolysis rate cannot be definitely defined. It appears, however, from the examples cited above, that such a factor may have the effect of increasing the hydrolysis rate. The prediction might be made that the methyl glycosides of β-D-idose and β-D-talose may behave similarly, since both of these glycosides possess conformational instability and a Δ2 factor when the methoxyl group is equatorial to the sugar ring.

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