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An Evaluation of the Factors Influencing the Hydrolysis of the Aldosides[1]

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The hydrolysis of the aldosides is discussed and evidence is presented that it may proceed through an acyclic carbonium ion. The variation in the rates of hydrolysis of the aldosides is related to their conformational features and to the nature of the substituents in their molecules. In the sugar series, it appears that an acyclic carbonium ion preferably forms a five-membered ring.

The reversible reactions concerned with the formation and hydrolysis of the glycosides of aldoses have been the subject of numerous investigations.[4] The nature of the factors influencing the course of these reactions can be interpreted on the basis of recent developments in organic chemistry.

The hydrolysis of the glycosides of the aldoses (I), according to Bunton and associates[5] and in analogy with the well established mechanism of acetal hydrolysis,[6-11] proceeds through the carbonium ion IV (IVa or IVb; Fig. 1) and the intermediates II, VII, and X or through the carbonium ion V and the intermediates III and VIII. Since the reaction is reversible, the proposed hydrolysis mechanism should also account for the production of the glycosides from the free aldoses. During the course of glycoside formation, the free aldoses, normally existing in the pyranose forms (IX), provide a mixture of aldofuranosides (VI) and aldopyranosides (I), in which the less stable aldofuranoside forms first predominate.[12,13] Thus, glycosidation, and consequently hydrolysis, must involve an opening of the oxygen ring which very probably proceeds through the intermediate carbonium ion IV. It must be noted that the cleavage of the cyclized bond in preference to the glycosidic bond, in several instances,[14-16] has been suggested as the only alternative consistent with the experimental results. The presence of such an acyclic intermediate (IV) in the equilibria is supported by numerous well established facts. The rings in the methyl tri-*O*-acetyl-D-arabinopyranosides are ruptured without loss of the methoxyl group to form a penta-*O*-acetyl-D-arabinose methyl hemiacetal[17] in an acetic anhydride solution of zinc chloride. Methyl β-D-glucopyranoside tetraacetate yields *aldehydo*-D-glucose

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heptaacetate in the presence of anomerizing catalysts in acetic anhydride.[16,18] The dimethyl acetals of D-glucose and D-galactose are converted to the methyl pyranosides by methanolic hydrogen chloride in a complex reaction involving intermediate forms.[19] *aldehydo*-D-Galactose heptaacetate and *aldehydo*-D-xylose hexaacetate have been isolated from the acetolysis products of guaran triacetate and xylan diacetate, respectively.[20]

In the hydrolysis of the aldosides through cleavage of the internal or cyclized bond, the crucial stage is the formation of the high energy carbonium ion IV (Fig. 1) and the rate of reaction to a large

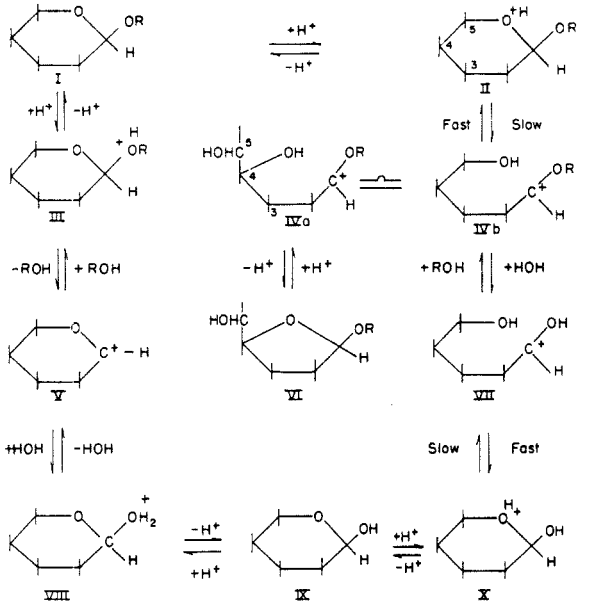

FIG. 1.—POSTULATED INTERMEDIATES IN GLYCOSIDE FORMATION AND HYDROLYSIS.

extent is a function of the difference of energies associated with II and IV, herein designated as ΔE_p. The same consideration also applies to the aldofuranosides, the rate of hydrolysis of which should be a function of the corresponding factor ΔE_f. The free energy associated with the strained furanoside form of an aldoside is generally greater than that of the staggered pyranoside form,[21,22] and since they both provide the same acyclic carbonium ion, then ΔE_p is greater than ΔE_f. This readily accounts for the fact that the aldofuranosides are hydrolyzed much more readily than the corresponding aldopyranosides. For a similar reason, those stereoisomeric aldopyranosides which have a higher free energy because of the non-bonded interaction of axial groups or other conformational instability factors (Δ2 arrangement, Fig. 2)[21] are hydrolyzed faster.

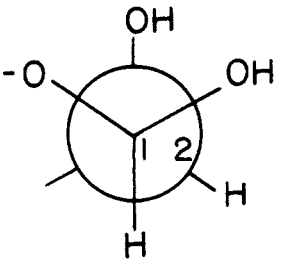

FIG. 2.—ARRANGEMENT (Δ2) OF OXYGEN ATOMS ABOUT CARBONS 1 AND 2; NEWMAN CONVENTION.[25]

The equilibrium between I and II should be affected by the ability of the medium to transfer a proton[5] (Hammett's acidity factor, H_0, which in dilute acid solutions is equivalent to pH[23]) and the extent of amenability of the aldoside to form the conjugate acid II. Thus, in aqueous solutions, the relative accessibility of the ring oxygen to the approach of hydronium ions also plays a significant part in controlling the rate of hydrolysis. This factor is related to the conformational features of the aldopyranoside. The glycopyranoside ring can theoretically assume two chair forms (C1 and 1C, Fig. 3) and six boat forms. The energy requirements

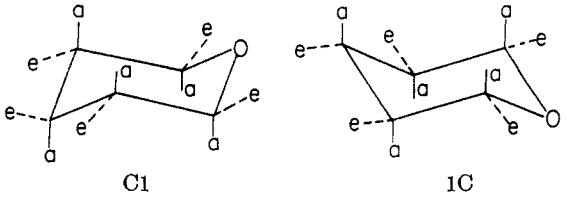

FIG. 3.—THE CHAIR CONFORMATIONS OF THE PYRANOSE RING.

exclude the boat forms as large contributing factors in the equilibrium, and result in the predominate formation of C1, 1C, or a large portion of both conformations, as in D-glucose, α-D-idose,[21] and D-gulose, respectively. It should be noted that the strong tendency of the large —CH_2OH substituent on carbon 5 to occupy an equatorial position will enhance the formation of the C1 conformation unless it is overbalanced by a preponderance of axial hydroxyl groups. The study of scale models indicates that in the C1 conformation of the methyl aldohexopyranoside series, the *beta* form is more accessible to attack than is the *alpha* anomer.[24] This results in a more rapid hydrolysis of the *beta* form, the converse being true for the 1C conformations.

A special case will arise when an axial hydroxyl

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(23) Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 267.
(24) Foster and Overend, *Chemistry & Industry*, 566 (1955).

group on carbon 2 of an aldopyranoside bisects the oxygen valences of carbon 1 (Δ2 arrangement, shown in Fig. 2 by the Newman Convention).[25] This will cause an enhanced instability[21] and will also present a more accessible arrangement. The above theoretical considerations can be correlated with the significant differences in the rates of hydrolysis of a number of methyl aldopyranosides[26-28] as shown in Table I.

The quantitative data upon which the calculations in Table I were made, were obtained under somewhat different hydrolytic conditions. Methyl α-D-mannopyranoside was used as a standard for the calculations of the values k/k' under each of the reaction conditions. Inspection of the table indicates that the values k/k' obtained throughout this range of conditions, do not vary grossly and thus afford a reasonable basis of comparison. A composite column has also been included in the table, in which the ratios k/k' have been altered by a factor which gives methyl α-D-glucopyranoside a value of 1.0 (0.5 *N* HCl, 75°C.). These values were obtained under reaction conditions of 0.5 *N* HCl and 75°C. when the data were available, otherwise data from one of the other columns were used.

It has been noted that in the C1 conformation, the methyl β-D-glycopyranosides are hydrolyzed faster than the α-D-anomers due to the higher accessibility of the latter forms. Despite this, a large aglycon group in the axial position will introduce a measure of instability large enough to reverse the situation. Thus, phenyl α-D-glucopyranoside, maltose, and isomaltose are hydrolyzed faster than phenyl β-D-glucopyranoside,[5] cellobiose[29] and gentiobiose,[29,30] respectively.

TABLE I

CONFORMATIONAL FEATURES AND RELATIVE RATES OF HYDROLYSIS OF METHYL ALDOPYRANOSIDES

Methyl glycopyranoside of:	k/k' 0.01 *N* HCl, 100°C.[a]	k/k' 0.05 *N* HCl, 98°C.[a]	k/k' 0.5 *N* HCl, 75°C.[a]	Computed Composite Values[b]	Axial Substituents[c] C1	Axial Substituents[c] 1C
α-D-Xylose			1.9[d,f]	4.5	1	Δ2, 3, 4
β-D-Xylose			3.8[d,f]	9.0		1, 2, 3, 4
α-D-Glucose	0.48[d,e,f]		0.42[d,e,f]	1.0	1	Δ2, 3, 4, 5
β-D-Glucose	1.0[d,e,f]		0.80[d,e,f]	1.9		1, 2, 3, 4, 5
D-*glycero*-α-L-*gluco*-Heptose		0.24[f]		0.6	1	Δ2, 3, 4, 5
α-D-Lyxose		5.4[f]	6.1[f]	14.5	1, 2	3, 4
β-D-Lyxose		19.5[f]		46.4	Δ2	1, 3, 4
α-L-Rhamnose	4.0[d,f]			9.5	1, 2	3, 4, 5
β-L-Rhamnose	9.2[d,f]			21.9	Δ2	1, 3, 4, 5
α-D-Mannose	1.0[d,f]	1.0[f]	1.0[f]	2.4	1, 2	3, 4, 5
β-D-Mannose		2.4[f]	2.4[f]	5.7	Δ2	1, 3, 4, 5
D-*glycero*-α-L-*manno*-Heptose		0.55[f]		1.3	1, 2	3, 4, 5
D-*glycero*-β-L-*manno*-Heptose		1.25[f]		3.0	Δ2	1, 3, 4, 5
α-D-Gulose		18.1[f]	24.4[f]	58.1	1, 3, 4	Δ2, 5
β-D-Gulose		8.3	8.0[f]	19.0	3, 4	1, 2, 5
D-*glycero*-α-D-*gulo*-Heptose		7.0[f]	8.8[f]	20.9	1, 3, 4	Δ2, 5
D-*glycero*-β-D-*gulo*-Heptose		3.2[f]	2.8[f]	6.7	3, 4	1, 2, 5
α-L-Arabinose			3.8[d,f]	9.0	1, 2, 3	4
β-L-Arabinose			5.5[d,f]	13.1	Δ2, 3	1, 4
α-D-Galactose			2.2[d,e,f]	5.2	1, 4	Δ2, 3, 5
β-D-Galactose			3.9[d,e,f]	9.3	4	1, 2, 3, 5

[a] Ratio of the rate constant for the hydrolysis of the methyl aldopyranoside (k) to that of methyl α-D-mannopyranoside (k') under the reaction conditions indicated. [b] Ratios calculated on the basis of methyl α-D-glucopyranoside equal to 1.0, see discussion. [c] The arabic numerals represent carbon positions on which the substituent other than hydrogen is axial; on positions omitted the substituent is equatorial.[21] [d] Riiber and Sørensen, ref. 27. [e] Armstrong, ref. 28. [f] Isbell and Frush, ref. 26.

The nature of the substituent on carbon 5, being adjacent to the cyclized oxygen bond, exerts a marked effect on the stability of the molecule. For example, in the series D-lyxose, L-rhamnose, D-mannose and D-*glycero*-L-*manno*-heptose, having a common lyxopyranoside structure, the rate of hydrolysis decreases[26] as the size of the group on carbon 5 increases (see Table I.)

Likewise, the nature of the other substituent groups in the aldofuranose and aldopyranose rings materially affect the energy differences associated with the transition states, and hence the rate of hydrolysis. The effect of neighboring groups in the hydrolysis of acetals has been recently investigated.[8,31] Kreevoy and Taft[8] have shown that the constants (k) for the rate of hydrolysis of the diethyl acetals of chloroacetaldehyde and hydroxyacetalde-

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

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(30) Wolfrom, Lassettre, and O'Neill, *J. Am. Chem. Soc.*, **73**, 595 (1951).

(31) Taft, Jr., *J. Am. Chem. Soc.*, **75**, 4231 (1953).

hyde (glycolaldehyde) differ from that of the diethyl acetal of acetaldehyde by a factor of 4.1×10^{-5} and 3.4×10^{-3}, respectively. These authors attribute this, in the first place, to the polar effect of the substituent (OH or Cl) and in the second place, to the difference in the number of the α-hydrogen atoms which tend to stabilize the transition states involved in these reactions. Furthermore, it has been shown[31] that the polar effect of the substituents in the carbon chain is additive. These considerations offer an explanation for the well established higher rates of hydrolysis of the 2-deoxyglycosides (as compared with those of the corresponding normal sugars),[32,33] the slightly higher rate of hydrolysis of some methyl 3-deoxyhexopyranosides,[34] and the fact that ethyl 2,3-dideoxy-α-D-*erythro*-aldohexopyranoside is hydrolyzed faster than ethyl 2-deoxy-α-D-*arabino*-aldohexopyranoside.[32]

As noted before, treatment of the aldoses with alcoholic hydrogen chloride results in the predominant initial formation of furanosides[12,13] and the eventual formation of an equilibrium favoring the more stable pyranosides. Such a preferable initial formation of a five-membered ring from an acyclic carbonium ion has its counterpart in other reactions. The formation of thioglycofuranosides by the reaction of aldose thioacetals with mercuric chloride,[4] proceeds through a similar mechanism. A further example is the deamination of 2-amino-2-deoxy-D-gluconic acid which provides an acyclic transitory compound with a carbonium ion at position 2, and results in the formation of 2,5-anhydro-D-gluconic acid.

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(33) Overend, Shafizadeh, and Stacey, *J. Chem. Soc.*, 671 (1950).

(34) Richards, *Chemistry & Industry*, 228 (1955).