664. *The Acid Hydrolysis of Tetrahydropyran Derivatives.**

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As a model for glycoside hydrolyses, the rates of acid hydrolysis of tetrahydro-2-methoxypyran and three 6-derivatives of it have been determined. From these results and others in the literature the effect of each hydroxyl group in a glucoside has been calculated.

It is known that substitution in the pyranose ring influences the rate of hydrolysis of glycosides in a manner dependent on the electronegative character of the substituent group.[1] Variations in the aglycone portion also affect the rate of reaction.[2-4] However, as has been pointed out,[1] predictions of the rate of hydrolysis of the glycosides are complicated by the presence of several hydroxyl groups. Fundamentally, comparisons of the effects of substituting groups are best made with reference to the simplest model, tetrahydro-2-methoxypyran. Stepwise increase of the substituent complexity or number then allows quantitative evaluation of the influence of each substituent on the rate of acid hydrolysis.

The present study aims at making this evaluation by quantitative observations of the acid hydrolysis of tetrahydro-2-methoxypyran and its 6-hydroxymethyl, 6-carboxy-, and 6-ethoxycarbonyl derivative and of tetrahydro-3-hydroxy-2-methoxypyran.

Experimental

Tetrahydro-2-methoxypyran.—When prepared according to the procedure of Woods *et al.*,[5] the substance had a b. p. 126—128°, n_D^{24} 1·4255 (Found: C, 61·4; H, 11·0. Calc. for $C_6H_{12}O_2$: C, 62·1; H, 10·3%).

Ethyl Tetrahydro-6-methoxypyran-2-carboxylate.—The intermediate Diels–Alder adduct, ethyl 3,4-dihydro-2*H*-pyran-2-carboxylate, from acraldehyde and ethyl acrylate, was obtained as described previously.[6] Addition of methanol across the double bond yielded the desired product.[6] The adduct was also obtained as follows: To dry sodium 3,4-dihydro-2*H*-pyran-2-carboxylate (50 g.; obtained from Shell Chemical) in dry dimethylformamide (200 ml.) at 65—70°, ethyl iodide (100 ml.) was added, and the mixture was kept at 65° for 18 hr. Addition of water to the cooled mixture gave two liquid layers. The lower layer was washed twice with water and dried (Na_2SO_4). Removal of the solvent (ethyl iodide), followed by fractional distillation, yielded ethyl 3,4-dihydro-2*H*-pyran-2-carboxylate (24 ml.), b. p. 71—76°/3·5 mm. (Found: C, 60·7; H, 7·7. Calc. for $C_8H_{12}O_3$: C, 61·5; H, 7·7%). Its infrared spectrum was identical with that obtained previously,[6] and the derived amide [6] had m. p. 115·5—116°.

Tetrahydro-6-methoxypyran-2-carboxylic Acid.—Ethyl tetrahydro-6-methoxypyran-2-carboxylate was saponified as previously described.[6] The resulting free acid was impure, but did not reduce Fehling solution, indicating the absence of hydrolysis of the 6-methoxy-group (Found: C, 49·1; H, 7·1; OMe, 17·9%; equiv., 170. Calc. for $C_7H_{12}O_4$: C, 52·5; H, 7·5; OMe, 19·3%; equiv., 160).

Tetrahydro-3-hydroxy-2-methoxypyran.—The action of perbenzoic acid in wet ether on 2,3-dihydro-4*H*-pyran, according to the procedure of Barker *et al.*,[7] yielded a thick syrup. This (5 ml.) was heated under reflux with 2% methanolic hydrogen chloride (180 ml.) for 4 hr.

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[1] Shafizadeh, *Adv. Carbohydrate Chem.*, 1958, **13**, 9.
[2] Bunton, Lewis, Llewellyn, and Vernon, *J.*, 1955, 4419.
[3] Shafizadeh and Stacey, *J.*, 1957, 4612.
[4] Butler, Laland, Overend, and Stacey, *J.*, 1950, 1433.
[5] Woods and Kramer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246.
[6] Glaudemans, *J. Org. Chem.*, 1961, **26**, 1295.
[7] Barker, Brimacombe, Foster, Whiffen, and Zweifel, *Tetrahedron*, 1959, **7**, 10.

Neutralization with silver carbonate, followed by filtration and concentration, gave tetrahydro-3-hydroxy-2-methoxypyran, b. p. 42—45°/0·9 mm. (2·5 ml.), n_D^{22} 1·4553. The infrared spectrum indicated a reduction in the intensity ratio OH : CH as compared with that for the parent diol (Found: C, 54·9; H, 9·45; OMe, 23·7. Calc. for $C_6H_{12}O_3$: C, 54·5; H, 9·1; OMe, 23·5%).

Hydrolysis Procedure.—An accurately weighed sample (0·06—0·12 g.) of the compound to be hydrolysed was placed in a flask and immersed in a bath at 30° ± 0·1°. After 30 min., 20 ml. of 0·001N-hydrochloric acid (pH 3·10) which had previously been equilibrated at 30°, were added. Aliquot parts (1 or 2 ml.) were removed at different times, run into water (20 ml.), and immediately adjusted to a slightly basic pH with a dilute sodium hydroxide solution. To this were added dropwise, and in alternating 3 and 2 ml. portions, respectively, a buffer solution (0·1M-NaOH–0·05M-Na_2HPO_4: pH 12—13) and a solution of iodine in potassium iodide (0·01N). The solution was set aside for 2—3 min., and 5N-sulphuric acid (5 ml.) was added. The liberated iodine was over-titrated with sodium thiosulphate, and the excess was back-titrated with iodine in potassium iodide, starch being the indicator. The method was standardized with both glucose and tetrahydro-2-hydroxypyran, and was found to be quantitative and independent of the initial concentration of the compound.

By assuming first-order kinetics for the hydrolysis of the model tetrahydropyrans,[2] the rate constant, k, was obtained from the slope of the line in the plot of log C/C_0 against t, where C is the concentration at time t, and C_0 the initial concentration. Runs were made at pH 3·10, which is equal to an H_0 value (Hammett acidity function) of 3·10. For comparative reasons, runs at other pH values were reduced to this same H_0, as described below. The rate constants listed in Table 1 are averages of several measurements for each sample and are precise to ±7%.

For hydrolyses of this type, where the rate-controlling step is the formation of the conjugate acid,[2, 8] it has been shown that log $k = A + H_0$. Therefore, a plot of log k against H_0 yields a line with a slope of unity. Accordingly, the rate constants from the literature for various glycosides (for ref. see Table 2), adjusted to 30° by means of the Arrhenius equation (E = 34 kcal./mole), were plotted as their logarithm against H_0 and a line with a slope of unity drawn through them. Interpolation to a standard H_0 yielded the desired rate constant.

TABLE 1.

Kinetic results on the hydrolysis, at H_0 +3·10, of some substituted tetrahydro-2-methoxypyrans at 30°.

6-Subst.	10^2k (min.$^{-1}$)	$10^2[k_x/k_1]$ *
H	1·14	100
CH_2·OH	0·37	32·5
CO_2H	0·133	11·7
CO_2Et	0·018	1·58

* This ratio is a comparison with k for the " unsubstituted " parent, *i.e.*, the first of the four.

TABLE 2.

Comparison of the effects of the various hydroxyl groups in the pyranose ring of sugars on the rates of acid hydrolysis at 30° and H_0 +0·40.

Compound,*	Reference	k (min.$^{-1}$)	$10^6[k_x/k_1]$ *
Tetrahydro-2-methoxypyran	This paper	565 × 10^{-2}	1,000,000
Tetrahydro-3-hydroxy-2-methoxypyran	,,	0·52 × 10^{-2}	922
Me 2-deoxy-α-D-glucopyranoside	10	0·2 × 10^{-2}	364
Me α-D-xylopyranoside	14	11·6 × 10^{-7}	0·206
Me 3-deoxy-α-D-glucopyranoside	13	6·1 × 10^{-7}	0·108
Me α-D-glucopyranoside	2, 10, 13, 14	1·8 × 10^{-7}	0·0319

* See note to Table 1.

RESULTS AND DISCUSSION

Since it has been shown [2, 8] that hydrolysis of glycosides generally proceeds by glycosyl–oxygen fission, the same type of cleavage would probably prevail with the acetals of tetrahydro-2-hydroxypyrans. Accordingly, electronegative substitution at the 6-position should decrease the rate. The rates of hydrolysis for the tetrahydro-2-methoxypyrans carrying a 6-substituent of increasing electronegativity are compared in Table 1 at the

[8] Banks, Meinwald, Rhind-Tutt, Sheft, and Vernon, *J.*, 1961, 3240.

same temperature and H_0 value. As predicted, there is a substantial decrease (about sixty-fold) in the rate of hydrolysis in going from the first to the last, *i.e.*, in the direction of increasing electronegativity. The order of magnitude of the observed changes in rate constants is more than is attributable purely to conformational and/or configurational differences (cf. below). In the present case it can be said that electron-transfer to the exocyclic oxygen atom [8] is impeded, and the effect has been called the " stabilizing inductive effect " [9] in the hydrolysis of glycosides.

Several workers have drawn attention to the relatively fast hydrolysis of methyl 2-deoxyglycosides,[3, 4, 10-12] and quantitative data have recently become available.[10] It was of interest, therefore, to compare the rate of hydrolysis of tetrahydro-3-hydroxy-2-methoxypyran with that of tetrahydro-2-methoxypyran. The observed rate for the former (Table 2) is some 1100 times the slower. The direction of the effect is in accord with the simple inductive mechanism outlined above. Richards [13] suggests that in acid medium the oxygen of a hydroxyl group tends to become protonated. This additional effect would help to inhibit the approach of a hydronium ion to form the conjugate acid at the exocyclic oxygen, the initial step in the hydrolysis.[8]

The tetrahydropyrans studied here were derived from the reaction products obtained by a Diels–Alder addition of ethyl acrylate and acraldehyde [6] (except for tetrahydro-3-hydroxy-2-methoxypyran), and the addition of ROH to the 5,6-double bond of dihydropyran may not be stereospecific. Since it is known that alkyl α- and β-glycosides are hydrolysed at different rates,[1] part of the differences observed may be due to having different anomers of the pyrans. However, the magnitude of the variations in k found here for the different tetrahydropyran derivatives overshadows the effects usually encountered for a pair of anomers. Also, the last three compounds in Table 1 are structurally related, since the first two of them are derived from the last.

In the case of tetrahydro-3-hydroxy-2-methoxypyran, as compared with tetrahydro-2-methoxypyran, however, there seems to be a greater possibility for different symmetry at position 2. The latter compound was prepared by the addition of methanol to the double bond of 2,3-dihydro-4*H*-pyran, whereas the former was prepared by treatment of the same starting material with moist perbenzoic acid, followed by methanolysis of the resulting glycol. This last reaction is almost certainly different from the addition of an alcohol to the double bond. The ratio of the rate constants (Table 2) for the hydrolysis of these two compounds, is, however, much too large to be accounted for solely by a difference in structure at position 2.

It is now possible to give a fairly complete picture of the relative effect of each hydroxyl group in a glucoside on the rate of acid hydrolysis at a given H_0 value. The data have been collected in Table 2 for the methyl α-glucopyranosides. The last column lists the rates relative to that of tetrahydro-2-methoxypyran, and it may be seen that methyl α-D-glucopyranoside is hydrolysed some 31×10^6 times more slowly than is this reference compound. This stabilizing influence of the hydroxyl groups on the hydrolysis of 2-acetals of tetrahydropyrans is also illustrated by the fact that hydrolysis of these compounds proceeds at a conveniently measurable rate in 10^{-3}M-hydrochloric acid at room temperature.

By means of the factors from the last column of Tables 1 and 2, it is possible to calculate exactly the relative rate of hydrolysis of methyl α-xylopyranoside and of methyl 3-deoxy-α-glucopyranoside. Since some of the factors involved in this calculation were derived

[9] Ranby and Marchessault, *J. Polymer Sci.*, 1959, **36**, 561; Marchessault and Ranby, *Svensk Papperstdn.*, 1959, **62**, 230.
[10] Armour, Bunton, Patai, Selman, and Vernon, *J.*, 1961, 412.
[11] Overend, Stacey, and Stanek, *J.*, 1949, 2841.
[12] Overend, Shafizadeh, and Stacey, *J.*, 1950, 671.
[13] Richards, *Chem. and Ind.*, 1955, 228.
[14] Riiber and Sorensen, as cited by Pigman and Goepp, " The Chemistry of the Carbohydrates," Academic Press, Inc., New York, 1948, p. 204.

by comparing sugars other than those for which the rate was calculated, the method requires that each hydroxyl group contributes an effect independently of the presence or absence of neighbouring hydroxyl groups. An estimate of the retarding influence of the 4-hydroxyl group can also be made, and it appears that removal of this group causes a 126-fold rate increase, an effect second only to that of the removal of the 2-hydroxyl group. A rate constant of hydrolysis of 227×10^{-7} (at $H_0 = +0{\cdot}40$) is predicted for methyl 4-deoxy-α-D-glucoside.

It has been suggested that the rate of hydrolysis is increased when the aglycone portion of a disaccharide becomes more electronegative than the glycosyl portion.[9] Work is in progress to test this with model compounds.

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