# 675. *Reactions at Position 1 of Carbohydrates. Part III.*[1] *The Acid-catalysed Hydrolysis of Glycosides.*

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The rates of acid-catalysed hydrolyses of a range of glycopyranosides (see Table 1), and of one glycofuranoside, have been measured, mostly at three or more temperatures; the activation parameters have been calculated.

The steric and electronic effects of changes in the sugar configuration, and in the nature and configuration of the aglycone, upon the rates of hydrolysis are discussed; the most significant changes are found in the entropy of activation and an explanation of these is proposed.

For hydrolysis of all the pyranosides studied the entropies of activation are positive and relatively large, supporting an A-1 mechanism, whereas for the furanoside it is negative, suggesting an A-2 mechanism. Independent evidence for the A-1 mechanism, based on the products of hydrolysis of methyl α- and β-D-glucopyranoside, is presented.

This extensive kinetic investigation of the acid-catalysed hydrolysis of simple glycosides was undertaken with three primary objectives: determination of (i) the reaction mechanism and (ii) the effect of steric and electronic changes in both the sugar and the aglycone upon hydrolysis rate, and (iii) provision thereby of a basis, in terms of simple model compounds, for investigations of the controlled partial hydrolysis of polysaccharides. A certain amount of quantitative information was available at the outset, mainly as a result of the work of Armstrong and Glover,[2] Moelwyn-Hughes,[3] Riiber and Sørensen,[4] Heidt and Purves,[5] and more recently of Nath and Rydon,[6] and Bunton and Vernon and their co-workers;[7-9] reviews of this work and subsequent discussions are available.[10-12] Most of the rate measurements reported were for various selections of glycosides (mostly glucopyranosides), determined under different conditions, and although valuable in providing reactivity sequences they are often inadequate for calculation of reliable energies and entropies of activation (see ref. 13). Furthermore, simple polarimetric methods unsupported by chemical analysis generally have been used, and possible side reactions have been ignored; this has led to an over-simplified view of the reaction. In the present work first-order rate coefficients for the hydrolysis of 31 glycosides in aqueous hydrochloric acid have been determined polarimetrically, mostly at three or more temperatures, at least 20° apart, and this method has been supplemented by chemical analysis.

## Experimental

*Materials.*—The properties of the glycosides used in the kinetic measurements were as shown in Table 1. The compounds were prepared by standard methods, often modified,[41] and their properties agreed well with those reported (see references). Special attention was paid to purity rather than yield in the preparations.

[1] Part II, Capon, Overend, and Sobell, *J.*, 1961, 5172.
[2] Armstrong and Glover, *Proc. Roy. Soc.*, 1908, B, **80**, 312.
[3] Moelwyn-Hughes, *Trans. Faraday Soc.*, 1928, **24**, 309, 321; 1929, **25**, 81, 503.
[4] Riiber and Sørensen, *Kgl. norske Videnskab. Selskabs Skrifter*, 1938, **1**, 1.
[5] Heidt and Purves, *J. Amer. Chem. Soc.*, 1944, **66**, 1385.
[6] Nath and Rydon, *Biochem. J.*, 1954, **57**, 1.
[7] Bunton, Lewis, Llewellyn, and Vernon, *J.*, 1955, 4419.
[8] Rhind-Tutt and Vernon, *J.*, 1960, 4637.
[9] Armour, Bunton, Patai, Selman, and Vernon, *J.*, 1961, 412.
[10] Shafizadeh, *Adv. Carbohydrate Chem.*, 1958, **13**, 9.
[11] Capon and Overend, *Adv. Carbohydrate Chem.*, 1960, **15**, 33.
[12] Wolfrom and Thompson, in " The Carbohydrates," ed. Pigman, Academic Press, Inc., New York, 1957, p. 208.
[13] Purlee, Taft, and De Fazio, *J. Amer. Chem. Soc.*, 1955, **77**, 837.

TABLE 1.

Properties of glycosides used.

| Glycosides | Crystn. solvent | M. p. | $[\alpha]_D^{21}$ ($c$ in $H_2O$) | Ref. |
|---|---|---|---|---|
| D-*Glucopyranoside* | | | | |
| Me α- | MeOH | 165—166° | +158° (1·5) | 14 |
| Me β- | EtOAc | 108—110° | −32·8° (4·91) | 7 |
| Et β- | — | — | — | * |
| Ph α- | $H_2O$ | 169—171° | +178° (2·0) | 15 |
| Ph β- | $H_2O$ | 173—174° | −70·7° (2·0) | 15 |
| *p*-Nitrophenyl α- | $H_2O$ | 213—215° | +221° (1·0) | 16 |
| *p*-Nitrophenyl β- | $H_2O$ | 164° | −107° (1·0) | 16 |
| Me 2-deoxy-α- | EtOH–EtOAc | 90° | +136° (0·5) | 17 |
| Me 2-deoxy-β- | EtOAc | 121—122° | −43·4° (1·0) | 18, 19 |
| Ph 2-deoxy-α- | — | 162—163° | +159° (0·55) | 20 |
| Me 4,6-*O*-benzylidene-3-deoxy-α- | $CHCl_3$–Pet. ether | 177—180° | +121·6° | 21 |
| Me 3-deoxy-α- | — | Syrup | +125·1° (2·3) | 22 |
| Me 4-deoxy-α- | EtOAc | 90° | +168·2° (0·86 †) | 23 |
| Me 4,6-*O*-benzylidene-α- | MeOH | 162—163° | +105° (2·0 ‡) | 24 |
| D-*Galactopyranoside* | | | | |
| Me α- | 97% EtOH | 105—108° | +177·3° (2·0) | 25—27 |
| Me β- | 97% EtOH | 177—178° | +0·25° (2·0) | 27—29 |
| Et α- | EtOH | 138—139° | +182·6° (2·0) | 25 |
| Et β- | EtOH | 159—161° | −6° (2·0) | 30 |
| Ph α- | $H_2O$ | 140° | +210° (1·0) | 31 |
| Ph β- | $H_2O$ | 150° | −40·5° (2·5) | 32 |
| Me 6-deoxy-α- | EtOAc | 150—151° | | 33 |
| *Various* | | | | |
| Et β-D-galactofuranoside | EtOAc | 86—87° | −104° (1·0) | 34 |
| Me α-D-mannopyranoside | EtOH | 193—194° | +80° (2·5) | 35 |
| Me α-D-altropyranoside | EtOAc | 108° | +121·3° (1·0) | 24 |
| Me 4,6-*O*-benzylidene-α-D-idopyranoside | EtOAc | 146—148° | +52·1° (1·0 ‡) | 36 |
| Me α-L-arabinopyranoside | EtOAc | 128° | +15° (4·0) | 37 |
| Me β-L-arabinopyranoside | MeOH | 169° | +241·7° (2·0) | 37 |
| Me α-D-xylopyranoside | COMeEt | 90° | +153° (2·0) | 37 |
| Me β-D-xylopyranoside | MeOH | 156° | −63·4° (2·0) | 37 |
| Me β-D-ribopyranoside | EtOAc | 82—83° | | 38 |
| Me α-D-lyxopyranoside | EtOAc | 105° | | 39 |

* Et β-D-glucopyranoside was obtained as a very hygroscopic solid by Zemplen deacetylation of Et 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside.[40] † In MeOH. ‡ In $CHCl_3$.

References: [14] Patterson and Robertson, *J.*, 1929, 300. [15] Fischer and von Meckel, *Ber.*, 1916, **49**, 2813. [16] Montgomery, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 690. [17] Hughes, Overend, and Stacey, *J.*, 1949, 2846. [18] Fischer, *Ber.*, 1920, **53**, 509. [19] Bergmann, Schotte, and Lechinsky, *Ber.*, 1922, **55**, 158; 1923, **56**, 1052. [20] Shafizadeh and Stacey, *J.*, 1957, 4612. [21] Vis and Karrer, *Helv. Chim. Acta*, 1954, **37**, 378. [22] Hedgley, Ph.D. Thesis, Birmingham, 1956. [23] Hedgley, Mérész, Overend, and Rennie, *Chem. and Ind.*, 1960, 938. [24] Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1727. [25] Fischer and Beensch, *Ber.*, 1894, **27**, 2478. [26] Riiber, Minsas, and Lyche, *J.*, 1929, 2173. [27] Dale and Hudson, *J. Amer. Chem. Soc.*, 1930, **52**, 2534. [28] Fischer, *Ber.*, 1895, **28**, 1145. [29] Mowery and Ferrante, *J. Amer. Chem. Soc.*, 1954, **76**, 4103. [30] Fischer and Armstrong, *Ber.*, 1902, **35**, 3153. [31] Helferich and Appel, *Z. physiol. Chem.*, 1932, **205**, 231. [32] Helferich, Demant, Goerdeler, and Bosse, *Z. physiol. Chem.*, 1948, **283**, 179. [33] MacPhillamy and Elderfield, *J. Org. Chem.*, 1939, **4**, 150. [34] Green and Pacsu, *J. Amer. Chem. Soc.*, 1937, **59**, 1205, 2569. [35] Cadotte, Smith, and Spriestersbach, *J. Amer. Chem. Soc.*, 1952, **74**, 1501. [36] Sorkin and Reichstein, *Helv. Chim. Acta*, 1945, **28**, 1. [37] Hudson, *J. Amer. Chem. Soc.*, 1925, **47**, 265. [38] Jackson and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1229. [39] Kent and Ward, *J.*, 1953, 416. [40] Ferguson, *J. Amer. Chem. Soc.*, 1932, **54**, 4086.

*Kinetic Measurements.*—(1) *Polarimetric method.* A Hilger standard polarimeter Mk. III and centre-filling jacketed polarimeter tubes (0·5, 1, and 2 dm.) were used. Water from a thermostat-bath was rapidly circulated through the polarimeter jackets, heavily lagged by a paste of asbestos powder and sodium silicate solution baked at 120°. The connecting rubber tubing was also lagged with asbestos and insulating tape. The inlet of the polarimeter tube was fitted with two concentric pieces of Polythene tubing carrying the thermometer so that this could be lowered or raised without introduction of air bubbles. To allow for the temperature gradient, the temperature of the thermostat-bath was adjusted to give that required

[41] Sequeira, Ph.D. Thesis, London, 1960.

for the reaction in the polarimeter tube. As a blank a solution was used containing the quantity of free sugar that would result from complete hydrolysis of the glycoside dissolved in preheated 2·0N-hydrochloric acid. This provided a check on the " infinity " optical rotation obtained in the kinetic runs. (Control experiments could not be done for methyl α-D-altropyranoside, methyl α-D-idopyranoside, and methyl 3- and 4-deoxy-D-glucopyranoside as the corresponding free sugars were not available. It is appreciated that in the hydrolysates of methyl α-D-altroside, and of methyl 4,6-*O*-benzylidene-α-D-idoside, the 1,6-anhydro-β-D-hexapyranose will exist in significant amount, but its existence was not sought and no allowance was made in calculations for the formation of this substance.) α- and β-D-Glucose gave identical values in these experiments, showing that mutarotation was instantaneous under the hydrolysis conditions. 2·0N-Hydrochloric acid was used throughout, except for the 2-deoxy-glucopyranosides when 0·10N-acid was used. Polarimeter tubes of suitable lengths were chosen to give observed differences of not less than 1·5° between the initial and final rotations whenever possible. A 0·10M-glycoside solution in hydrochloric acid was prepared at the reaction temperature and immediately transferred to the polarimeter tube, and the rotation and time were noted when thermal equilibrium was attained. This normally corresponded to 5—10% of the reaction and was used as the initial reading for the rate equation. Observations were continued to about 75% of complete reaction and infinity readings were taken after ten half-lives. These infinity rotations, needed for calculation of the rate coefficients, agreed very well with those of the free sugar solutions mentioned above. Usually reaction rates were measured at three temperatures over a 20° range. More dilute solutions (0·05M) were used for the sparingly soluble *p*-nitrophenyl α-D-glucopyranoside and less readily available methyl 2-deoxy-α- and -β-D-glucopyranoside, α-D-altropyranoside, α-D-fucopyranoside, and 3-deoxy-D-glucopyranoside.

Modification for 4,6-*O*-benzylidene derivatives: Methyl 3-deoxy-α-D-glucopyranoside and α-D-idopyranoside were available in crystalline form only as their 4,6-*O*-benzylidene derivatives, but advantage was taken of the much faster acidic hydrolysis of the benzylidene group [42] than of the glycosyl bond. The reaction solution was prepared as before, held at 60° for 5 min., and then cooled and the benzaldehyde was removed with ether. The change in optical rotation of the aqueous solution was then measured as before. By this method good agreement (2—3%) was obtained for the rates of glycosidic hydrolysis of methyl α-D-glucopyranoside and its 4,6-*O*-benzylidene derivative and for syrupy methyl 3-deoxy-α-D-glucopyranoside and its crystalline benzylidene derivative.

The detailed kinetic runs tabulated are typical.

*Me β-D-glucopyranoside* (0·10M) *in* 2·0N-*hydrochloric acid at* 71·7° (2 *dm. tube*)

| Time (min.) | 0 | 10 | 21 | 30 | 45 | 60 | 80 | 100 | 120 |
|---|---|---|---|---|---|---|---|---|---|
| α | −1·08° | −0·95° | −0·83° | −0·71° | −0·54° | −0·38° | −0·19° | −0·02° | +0·15° |
| $10^5k_1$ (sec.$^{-1}$) | — | 7·44 | 7·29 | 7·37 | 7·40 | 7·44 | 7·39 | 7·33 | 7·40 |
| Time (min.) | 140 | 170 | 210 | ∞ | | | | | |
| α | +0·31° | +0·50° | +0·72° | +1·90° | | | | | |
| $10^5k_1$ (sec.$^{-1}$) | 7·33 | 7·41 | 7·35 | — | | | | | |

Mean $k_1 = 7·38 \times 10^{-5}$ sec.$^{-1}$; mean deviation = 0·5%; difference between extreme values = 1·5%.

*Me α-D-altropyranoside* (0·05M) *in* 2·05N-*hydrochloric acid at* 60·2° (2 *dm. tube*)

| Time (min.) | 0 | 13 | 20 | 30 | 40 | 52 | 61 | 76 | 90 |
|---|---|---|---|---|---|---|---|---|---|
| α | +2·10° | +1·70° | +1·50° | +1·25° | +1·02° | +0·72° | +0·52 | +0·30° | +0·05° |
| $10^4k_1$ (sec.$^{-1}$) | — | 1·35 | 1·36 | 1·33 | 1·31 | 1·36 | 1·37 | 1·31 | 1·33 |
| Time (min.) | 101 | 135 | 157 | 190 | ∞ | | | | |
| α | −0·10° | −0·56° | −0·76° | −1·00° | −1·90° | | | | |
| $10^4k_1$ (sec.$^{-1}$) | 1·32 | 1·35 | 1·33 | 1·31 | — | | | | |

Mean $k_1 = 1·34 \times 10^{-4}$ sec.$^{-1}$; mean deviation = 1·5%; difference between extreme values = 4·5%.

*Me 2-deoxy-β-D-glucopyranoside* (0·05M) *in* 0·10N-*hydrochloric acid at* 49·7° (2 *dm. tube*)

| Time (min.) | 0 | 7 | 15 | 21 | 30 | 38 | 45 | 58 | 76 |
|---|---|---|---|---|---|---|---|---|---|
| α | −0·73° | −0·64° | −0·55° | −0·47° | −0·38° | −0·30° | −0·23° | −0·14° | −0·02° |
| $10^4k_1$ (sec.$^{-1}$) | — | 1·49 | 1·43 | 1·53 | 1·49 | 1·49 | 1·51 | 1·45 | 1·54 |
| Time (min.) | 94 | 131 | 170 | 228 | ∞ | | | | |
| α | +0·10° | +0·30° | +0·42° | +0·55° | +0·76° | | | | |
| $10^4k_1$ (sec.$^{-1}$) | 1·44 | 1·50 | 1·51 | 1·43 | — | | | | |

Mean $k_1 = 1·48 \times 10^{-4}$ sec.$^{-1}$; mean deviation = 2·3%; difference between extreme values = 7·4%.

[42] Capon, Overend, and Sobell, *Tetrahedron*, 1962, **18**, 106.

*Ph* α-D-*glucopyranoside* (0·10M) *in* 2·0N-*hydrochloric acid at* 59·5° (1 *dm. tube*)

| Time (min.) | 0 | 3 | 5 | 8 | 10·5 | 13 | 15 | 20 | 25 |
|---|---|---|---|---|---|---|---|---|---|
| α | +3·83° | +3·67° | +3·58° | +3·42° | +3·32° | +3·21° | +3·16° | +2·92° | +2·78° |
| $10^4k_1$ (sec.$^{-1}$) | — | 3·19 | 3·04 | 3·21 | 3·11 | 3·12 | 2·95 | 3·18 | 3·04 |

| Time (min.) | 30 | 35 | 42 | 50 | 60 | 75 | 90 | 105 | ∞ |
|---|---|---|---|---|---|---|---|---|---|
| α | +2·63° | +2·48° | +2·31° | +2·14° | +1·97° | +1·73° | +1·53° | +1·41° | +0·96° |
| $10^4k_1$ (sec.$^{-1}$) | 3·01 | 3·03 | 2·99 | 2·96 | 2·90 | 2·92 | 2·99 | 2·94 | — |

Mean $k_1 = 3·04 \times 10^{-4}$ sec.$^{-1}$; mean deviation = 2·6%; difference between extreme values = 10·2%.

*Me* α-D-*xylopyranoside* (0·10M) *in* 1·98N-*hydrochloric acid at* 69·7° (1 *dm. tube*)

| Time (min.) | 0 | 13 | 24 | 33 | 46 | 60 | 80 | 100 | 136 |
|---|---|---|---|---|---|---|---|---|---|
| α | +2·39° | +2·23° | +2·11° | +1·98° | +1·85° | +1·73° | +1·54° | +1·43° | +1·17° |
| $10^4k_1$ (sec.$^{-1}$) | — | 1·04 | 1·02 | 1·13 | 1·11 | 1·08 | 1·07 | 1·06 | 1·12 |

| Time (min.) | 165 | 208 | ∞ |
|---|---|---|---|
| α | +1·04° | +0·86° | +0·35° |
| $10^4k_1$ (sec.$^{-1}$) | 1·09 | 1·11 | — |

Mean $k_1 = 1·08 \times 10^{-4}$ sec.$^{-1}$; mean deviation = 2·9%; difference between extreme values = 10·2%.

(2) *Titrimetric method.* Hydrolysis rates for methyl α- and β-D-glucopyranoside were also obtained by titrimetric titration of the glucose liberated, by measuring its reduction of alkaline potassium ferricyanide, by Nath and Rydon's method [6] with minor modifications.[41] Reproducible results were obtained only by careful calibration and use of a rigorously standardised procedure. This method was also used to investigate the effect of 2N-hydrochloric acid on D-glucose, alone and in admixture with each of the glucosides. After ten half-lives (" infinity ") aliquot parts of the reaction mixtures, diluted twice as much as in the standardised procedure, gave titrations which were always 5—10% less than the value obtained by interpolation in the linear calibration curve. The following details of a run with methyl α-D-glucopyranoside (0·10M) in 2N-hydrochloric acid at 72·1° are typical:

| Time (min.) | 35 | 65 | 95 | 125 | 170 | 220 | 280 | 340 | 420 | 511 | ∞ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Titre (ml. of 0·005N-$Na_2S_2O_3$) | 0·72 | 1·36 | 1·97 | 2·52 | 3·24 | 4·06 | 4·86 | 5·65 | 6·39 | 6·99 | 9·52 * |
| $10^5k_1$ (sec.$^{-1}$) | 3·75 | 3·95 | 4·07 | 4·11 | 4·08 | 4·21 | 4·25 | 4·41 | 4·37 | 4·22 | — |

Mean $k_1 = 4·14 \times 10^{-5}$ sec.$^{-1}$; mean deviation = 3·6%; difference between extreme values = 16%.

* The corresponding value, interpolated from calibration curve = 10·54 ml.

## Results

*Polarimetric Method.*—Good first-order rate coefficients were obtained in all cases except for methyl 4,6-*O*-benzylidene-α-D-idopyranoside (see above) where they fell steadily ($2·5 \times 10^{-4}$ to $2·0 \times 10^{-4}$ sec.$^{-1}$ during 0—50% reaction), and calculated and observed infinity readings agreed well. The kinetic results and derived quantities for hydrolyses in 2·0N-hydrochloric acid are summarised in Table 2. Also shown is $k_1$ at 60° calculated from the Arrhenius parameters. For hydrolyses in 0·10N-hydrochloric acid these values are given in Table 3. The entropy of activation was calculated according to $\Delta S^{\ddagger} = (E - \boldsymbol{R}T - 2·303\boldsymbol{R}T \log kT/h + 2·303\boldsymbol{R}T \log k_2)/T$, where $k_2 = k_1/h_0^{25}$, since for these reactions [7] the rate $= k_2$[glycoside]$h_0^{25}$. Duplicate determinations of $k_1$ agreed to within experimental error. For methyl α-D-galactopyranoside, rate coefficients were measured at five temperatures over a 40° range and the plot of log $k_1$ against $1/T$ gave a straight line.

*Titrimetric Method.*—In Table 4 the first-order rate coefficients calculated by using the measured " infinity " titre, with and without initially added glucose, are presented together for comparison with those determined polarimetrically. They agreed with the polarimetric rate coefficients much more closely than those calculated by using the theoretical " infinity " titre read from the calibration curve.

*Hydrolyses in Heavy Water.*—The rates of hydrolysis of methyl α-D-glucopyranoside were measured polarimetrically at 59·2° and 70·6° in 2·17N-hydrochloric acid in heavy water and in 2·175N-hydrochloric acid in isotopically normal water. The former solution was prepared

TABLE 2.

Rate coefficients and kinetic parameters for the hydrolysis of glycosides in 2·0N-hydrochloric acid.

| | Temp. | $10^5k_1$ (sec.$^{-1}$) | Deviation from mean (%) | $10^5k_1$ at 60° (sec.$^{-1}$) | $E$ (kcal. mole$^{-1}$) | log $A$ | $\Delta S^\ddagger$ at 60° (cal. deg.$^{-1}$ mole$^{-1}$) |
|---|---|---|---|---|---|---|---|
| *Pyranosides* | | | | | | | |
| Me α-D-gluco- | 61·2° | 0·859 | 2·0 | 0·708 | 34·1 ± 1·0 | 17·2 | +14·8 |
| | 71·9 | 4·04 | 1·5 | | | | |
| | 79·6 | 12·4 | 1·8 | | | | |
| Me β-D-gluco- | 59·1 | 1·07 | 1·6 | 1·26 | 34·3 ± 0·4 | 17·6 | +16·5 |
| | 71·7 | 7·38 | 0·5 | | | | |
| | 71·9 | 7·51 | 1·3 | | | | |
| | 79·7 | 22·4 | 0·7 | | | | |
| Et β-D-gluco- (a syrup) | 69·8 | 7·07 | 2·4 | | | | |
| | 81·0 | 36·8 | 4·1 | | | | |
| Ph α-D-gluco- | 40·8 | 1·82 | 2·2 | 38·0 | 31·1 ± 2·0 | 16·9 | +13·3 |
| | 47·0 | 4·31 | 3·3 | | | | |
| | 51·0 | 7·87 | 1·2 | | | | |
| | 59·5 | 30·4 | 2·6 | | | | |
| Ph β-D-gluco- | 39·2 | 0·402 | 6·8 | 9·33 | 31·0 ± 1·2 | 16·3 | +10·8 |
| | 51·8 | 3·18 | 1·8 | | | | |
| | 55·6 | 5·02 | 1·1 | | | | |
| | 60·8 | 9·66 | 2·9 | | | | |
| | 64·7 | 17·2 | 1·9 | | | | |
| *p*-Nitrophenyl α-D-gluco- | 51·6 | 6·95 | 1·1 | 25·1 | 30·3 ± 1·6 | 16·3 | +10·5 |
| | 57·4 | 15·1 | 1·3 | | | | |
| | 65·3 | 47·1 | 2·1 | | | | |
| *p*-Nitrophenyl β-D-gluco- | 51·0 | 0·889 | 1·9 | 2·88 | 30·3 ± 1·8 | 15·4 | +6·4 |
| | 51·0 | 0·858 | 1·2 | | | | |
| | 60·5 | 3·10 | 1·2 | | | | |
| | 70·6 | 12·8 | 2·3 | | | | |
| Me α-D-galacto- | 40·0 | 0·119 | 3·4 | 3·55 | 34·0 ± 0·3 | 17·8 | +17·7 |
| | 48·45 | 0·575 | 2·5 | | | | |
| | 48·45 | 0·557 | 3·5 | | | | |
| | 59·4 | 3·27 | 1·5 | | | | |
| | 69·2 | 14·4 | 1·2 | | | | |
| | 81·1 | 74·8 | 1·1 | | | | |
| Me β-D-galacto- | 48·95 | 1·01 | 1·3 | 5·13 | 32·3 ± 0·6 | 16·9 | +13·3 |
| | 59·65 | 4·97 | 1·2 | | | | |
| | 69·7 | 21·4 | 2·8 | | | | |
| Et α-D-galacto- | 49·45 | 1·59 | 1·0 | 7·58 | 33·0 ± 1·5 | 17·5 | +16·4 |
| | 59·9 | 7·43 | 1·7 | | | | |
| | 70·0 | 34·5 | 2·0 | | | | |
| Et β-D-galacto- | 50·8 | 1·34 | 1·8 | 5·01 | 31·6 ± 1·0 | 1 | +11·2 |
| | 59·8 | 4·85 | 1·9 | | | | |
| | 69·7 | 20·2 | 3·2 | | | | |
| Ph α-D-galacto- | 29·8 | 1·33 | 1·2 | 128 | 30·2 ± 0·4 | 16·9 | +13·5 |
| | 39·3 | 6·00 | 2·2 | | | | |
| | 49·7 | 29·3 | 1·5 | | | | |
| Ph β-D-galacto- | 29·8 | 0·351 | 3·2 | 24·5 | 28·1 ± 0·1 | 14·8 | +4·1 |
| | 29·8 | 0·348 | 4·5 | | | | |
| | 39·9 | 1·58 | 1·1 | | | | |
| | 50·1 | 6·60 | 2·3 | | | | |
| Me 6-deoxy-α-D-galacto- | 50·4 | 4·43 | 6·8 | 20·0 | 33·9 ± 0·6 | 18·5 | +20·8 |
| | 60·2 | 20·3 | 2·4 | | | | |
| | 70·1 | 91·1 | 2·4 | | | | |
| Me α-D-manno- | 60·7 | 2·38 | 3·0 | 2·09 | 31·9 ± 0·4 | 16·2 | +10·4 |
| | 71·1 | 10·0 | 1·6 | | | | |
| | 79·35 | 31·5 | 1·4 | | | | |
| Me α-D-altro- | 40·1 | 0·618 | 2·9 | 12·6 | 31·7 ± 1·0 | 16·9 | +13·5 |
| | 50·0 | 2·80 | 1·9 | | | | |
| | 60·2 | 13·4 | 1·5 | | | | |
| Me α-D-xylo- | 50·2 | 0·581 | 1·5 | 2·69 | 33·5 ± 0·9 | 17·4 | +15·7 |
| | 59·7 | 2·46 | 0·5 | | | | |
| | 69·7 | 10·8 | 2·9 | | | | |
| Me β-D-xylo- | 50·0 | 1·26 | 5·2 | 5·89 | 33·6 ± 0·9 | 17·8 | +17·5 |
| | 59·0 | 5·00 | 1·6 | | | | |
| | 69·6 | 25·1 | 3·1 | | | | |

TABLE 2. (*Continued.*)

| | Temp. | $10^5k_1$ (sec.$^{-1}$) | Deviation from mean (%) | $10^5k_1$ at 60° (sec.$^{-1}$) | $E$ (kcal. mole$^{-1}$) | log $A$ | $\Delta S^\ddagger$ at 60° (cal. deg.$^{-1}$ mole$^{-1}$) |
|---|---|---|---|---|---|---|---|
| Me α-L-arabino- | 49·2 | 3·05 | 2·1 | 14·1 | 30·6 ± 0·4 | 16·2 | +10·2 |
| | 60·6 | 15·3 | 2·3 | | | | |
| | 70·15 | 55·7 | 2·5 | | | | |
| Me β-L-arabino- | 49·2 | 1·86 | 1·5 | 9·55 | 32·5 ± 0·6 | 17·3 | +15·2 |
| | 49·2 | 1·78 | 0·2 | | | | |
| | 59·9 | 9·18 | 2·3 | | | | |
| | 69·9 | 39·9 | 0·9 | | | | |
| Me β-D-ribo- | 50·1 | 1·98 | 7·5 | 8·71 | 31·4 ± 0·9 | 16·5 | +11·8 |
| | 59·5 | 8·19 | 3·5 | | | | |
| | 69·7 | 32·4 | 2·7 | | | | |
| Me α-D-lyxo- | 51·4 | 3·68 | 3·5 | 13·5 | 31·2 ± 1·0 | 16·6 | +12·1 |
| | 59·3 | 11·7 | 2·9 | | | | |
| | 70·1 | 54·2 | 2·2 | | | | |
| Me 3-deoxy-α-D-gluco- | 58·4 | 10·5 | 2·1 | — | — | — | — |
| *Various* | | | | | | | |
| Me 4-deoxy-α-D-glucoside | 58·1 | 21·2 | 2·8 | — | — | — | — |
| Me 4,6-*O*-benzylidene α-D-glucoside | 70·0 | 3·14 | 1·6 | — | — | — | — |
| | 72·7 | 5·02 | 0·8 | | | | |
| Me 4,6-*O*-benzylidene-3-deoxy-α-D-glucoside | 58·1 | 10·4 | 1·2 | — | — | — | — |
| Me 4,6-*O*-benzylidene-α-D-idoside | 58·1 | 20·25 | — | — | — | — | — |
| Et β-D-galactofuranoside | 19·8 | 2·56 | 1·3 | 288 | 22·7 ± 0·2 | 12·4 | −7·1 |
| | 29·1 | 8·72 | 0·9 | | | | |
| | 39·7 | 31·1 | 3·1 | | | | |

TABLE 3.

Rate coefficients and kinetic parameters for the hydrolysis of 2-deoxyglucosides in 0·10N-hydrochloric acid.

| | Temp. | $10^5k_1$ (sec.$^{-1}$) | Deviation from mean (%) | $10^5k_1$ at 60° (sec.$^{-1}$) | $E$ (kcal. mole$^{-1}$) | log $A$ | $\Delta S^\ddagger$ at 60° (cal. deg.$^{-1}$ mole$^{-1}$) |
|---|---|---|---|---|---|---|---|
| Me 2-deoxy-α-D-gluco-pyranoside | 40·15° | 1·50 | 3·0 | 30·9 | 31·7 ± 0·2 | 17·3 | +23·0 |
| | 49·5 | 6·52 | 2·8 | | | | |
| | 60·1 | 31·4 | 3·0 | | | | |
| Me 2-deoxy-β-D-gluco-pyranoside | 40·15 | 3·69 | 1·0 | 63·6 | 29·9 ± 0·5 | 16·4 | +19·0 |
| | 49·7 | 14·8 | 2·3 | | | | |
| | 60·05 | 63·6 | 2·8 | | | | |
| Ph 2-deoxy-α-D-gluco-pyranoside | 19·8 | 5·10 | 2·6 | 955 | 25·2 ± 0·8 | 14·5 | +10·4 |
| | 25·9 | 14·2 | 2·8 | | | | |
| | 29·35 | 23·8 | 1·2 | | | | |
| | 31·35 | 27·6 | 4·4 | | | | |
| | 39·15 | 75·3 | 3·3 | | | | |

TABLE 4.

Hydrolysis of methyl α- and β-D-glucopyranoside in 2·0N-hydrochloric acid.

| | | $10^5k_1$ (sec.$^{-1}$) | | | | $10^5k_1$ (sec.$^{-1}$) | |
|---|---|---|---|---|---|---|---|
| | Temp. | Polarimetric | Titrimetric | | Temp. | Polarimetric | Titrimetric |
| Me α-D-glucopyranoside | 61·2° | 0·86 | — | Me β-D-glucopyranoside | 61·4° | 1·51 | 1·57 |
| | 61·4 | — | 0·77 | | 71·9 | 7·51 | — |
| | 72·1 | 4·04 | 4·14 | | 72·1 | — | 7·11 |
| Me α-D-glucopyranoside + D-glucose (0·10M) | 72·0 | — | 4·05 | Me β-D-glucopyranoside + D-glucose (0·10M) | 72·0 | — | 7·18 |

from anhydrous hydrogen chloride and deuterium oxide (99%; from Imperial Chemical Industries Limited). The results were:

59·2°: in $H_2O$, $k_1 = 5{\cdot}75 \times 10^{-6}$; in $D_2O$, $k_1 = 11{\cdot}13 \times 10^{-6}$.
$k_{D_2O}/k_{H_2O} = 1{\cdot}9$.
70·6°: in $H_2O$, $k_1 = 3{\cdot}83 \times 10^{-5}$; in $D_2O$, $k_1 = 6{\cdot}87 \times 10^{-5}$.
$k_{D_2O}/k_{H_2O} = 1{\cdot}8$.

*Chromatography of a Reaction Mixture.*—The hydrolysis of methyl α-D-glucopyranoside (0·1M) in 2N-hydrochloric acid was investigated by descending paper chromatography. The following solutions were applied to Whatman No. 1 paper: aqueous methyl α-D-glucopyranoside (0·1M), aqueous D-glucose (0·1M), the hydrolysate, and two possible reversion products 1,6-anhydro-D-glucose and D-gentiobiose. The chromatogram was developed for 48 hr. with butanol–ethanol–water (4 : 1 : 5) and sprayed with aqueous silver nitrate and sodium hydroxide. The hydrolysate contained D-glucose and a substance chromatographically very similar to D-gentiobiose. Methyl α-D-glucopyranoside showed only a very faint spot after long storage and 1,6-anhydro-D-glucose could not be detected. It has been stated [43] that this reagent reacts slowly with the latter.

Methyl α-D-glucopyranoside (1·94 g.) in 2N-hydrochloric acid (100 ml.) was heated at 70° for 40 hr. The cooled solution was diluted to 300 ml. with water and poured on a column of ion-exchange resin (De-acidite FF, $OH^-$ form). The column was eluted with water (1 l.), and the eluant was evaporated at 40° to a syrup which crystallised on nucleation with D-glucose. The solid {0·2 g., $[\alpha]_D$ +52·1° (equilib. in $H_2O$)} obtained was chromatographically indistinguishable from D-glucose.

## Discussion

*Products of the Reaction.*—Hitherto it has been assumed in investigations of the reaction rate that D-glucose is the only sugar product of the acidic hydrolysis of methyl α- and β-D-glucoside. We find that although glucose is the major product there is at least 5—10% of a second product, formed by reaction of the glucoside with liberated glucose. After complete hydrolysis of methyl α- and β-D-glucoside (0·10M) in 2N-hydrochloric acid at 72° the amount of reducing sugar liberated, as determined titrimetrically, was consistently 5—10% less than the theoretical value, the experimental error being ±0·5%. Chromatographic evidence for the presence of a disaccharide in the hydrolysate of the α-anomer was therefore sought and was found (see Experimental section). When D-glucose (0·10M) was treated exactly as were the glucosides its reducing power remained constant (±0·5%), although the formation of a substance with chromatographic characteristics similar to those of the above disaccharide was indicated. Presumably reaction between glucose and the glucoside occurred in the acid medium. When the glucosides were hydrolysed as before but with D-glucose (0·01M) added initially, the amount of reducing sugar liberated in the reaction was now less than previously (85—89% of theoretical), but the rate of hydrolysis was unchanged. This observation is considered to provide further support for the unimolecular mechanism (see A), more fully discussed in the next section.

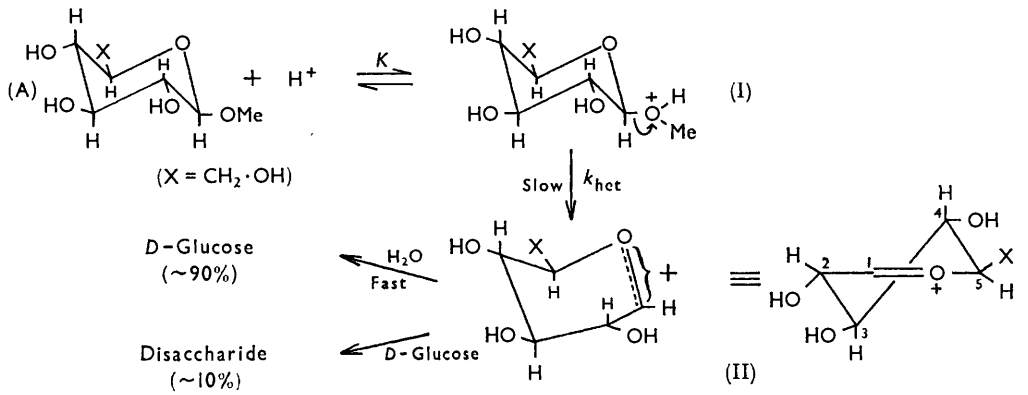
In this mechanism (A) the products are formed in fast reactions after the slow rate-determining heterolysis. If the rate-determining step were bimolecular attack of water or glucose on the glucoside conjugate acid, different proportions of products would be expected to be formed at different rates.

In spite of this demonstration that, at least with the methyl glucosides, hydrolysis is not the only reaction occurring in aqueous acid, our present discussion of reaction mechanism and dependence of reactivity upon structure is confined to this major reaction.

*Reaction Mechanisms.*—Bunton, Lewis, Llewellyn, and Vernon [7] have established, by isotopic tracer methods and by the criterion of molecularity based on Hammett's acidity function, that the acid-catalysed hydrolysis of methyl and phenyl α- and β-D-glucopyranoside proceeds by unimolecular heterolysis of the conjugate acids with fission of the glucosyl–oxygen bond. Our results entirely support this A-1 mechanism for all the pyranosides investigated.

[43] Peat, Whelan, Edwards, and Owen, *J.*, 1958, 586.

Additional evidence for a rapid pre-equilibrium protonation of the glycoside, and for specific acid-catalysis, was obtained in the case of methyl α-D-glucopyranoside, S, by measuring the reaction rate in water and in heavy water as solvents. The ratio of rates in $D_2O$ and $H_2O$ was 1·8 and 1·9 in duplicate experiments. The faster reaction in $D_2O$ follows from the greater concentration of $SD^+$ ions in $D_2O$ than $SH^+$ in $H_2O$, since deutero-acids have smaller dissociation constants than the corresponding proto-acids,[44] and also from the smaller autoprotolysis constant of $D_2O$ compared with $H_2O$ [45] which allows S to compete with solvent for deuterons in $D_2O$ more effectively than for protons in $H_2O$.



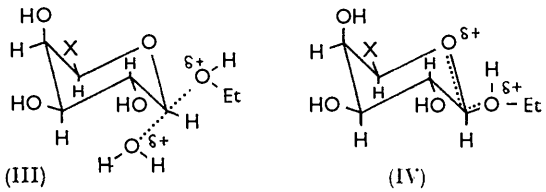

Evidence for the unimolecularity of these hydrolyses [7] additional to that based on the Hammett–Zucker hypothesis was considered desirable in view of the doubts associated with the use of rate–acidity correlations generally for predicting molecularity.[46,47] This may be afforded by the magnitude of the entropy of activation,[48] $\Delta S^{\ddagger}$, which is a measure of the difference in the restriction on the freedom of motion of the molecules in the ground and the transition state. If the reaction is bimolecular, the reactants will become more highly ordered as the transition state is approached, the entropy will decrease, and $\Delta S^{\ddagger}$ will tend to be negative; if the reaction is unimolecular the structure will be less ordered in the transition state than is the conjugate acid, the entropy will increase, and $\Delta S^{\ddagger}$ should be positive and probably large.* The A-1 mechanism suggested by the rate–acidity correlation in the acid-catalysed hydrolysis of epoxides,[50] for example, was supported by the values of $\Delta S^{\ddagger}$ found [48] for this reaction.

In the present study, $\Delta S^{\ddagger}$ values at 60° have been calculated for the hydrolysis of 24 pyranosides; all are positive, ranging from 4·1 to 23·0 e.u., all but two are greater than 10·0 e.u., and the mean is 13·7 e.u. (see Tables 2 and 3). They may be compared with the values at 25° reported [48] for the acid-catalysed hydrolysis of sucrose (+7·9 e.u.), ethyl orthoformate (+5·8 e.u.), and ethylal (+7·3 e.u.), all of which are known to proceed by the A-1 mechanism, and the values calculated by Capon and Overend [11] from Heidt and Purves's results [5] for hydrolysis of methyl, benzyl, and phenyl α- and β-D-glucopyranoside (mean +13·6 e.u.). They are in striking contrast with the value of −7·1 e.u. for ethyl

* Although negative values for $\Delta S^{\ddagger}$ indicate the A-2 mechanism fairly strongly, positive values cannot be regarded as proof of the A-1 mechanism, because of the positive value of the standard entropy change in the proton-transfer reaction.[49]

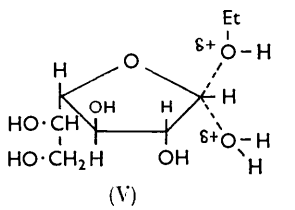
[44] Wiberg, *Chem. Rev.*, 1955, **55**, 713.
[45] Wynne-Jones, *Trans. Faraday Soc.*, 1938, **34**, 245.
[46] Long, *Proc. Chem. Soc.*, 1957, 220.
[47] Koskikallio, Pouli, and Whalley, *Canad. J. Chem.*, 1959, **37**, 1360.
[48] Long, Pritchard, and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 2362.
[49] Whalley, *Trans. Faraday Soc.*, 1959, **55**, 798.
[50] Pritchard and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 2667.

β-D-galactofuranoside, the only furanoside investigated. This is 20·8 units lower than the mean value for the pyranosides and 18·3 units lower than that for ethyl β-D-galactopyranoside, and this large difference strongly suggests a complete change in mechanism, from uni- to bi-molecular, for the furanoside hydrolysis. This difference in $\Delta S^{\ddagger}$ agrees well with that (20—30 e.u.) which characteristically separates A-1 and A-2 mechanisms, within the same class of compounds, as remarked by Long, Pritchard, and Stafford.[48] As this result for the furanoside is an isolated one, only tentative conclusions can be drawn from it, but an explanation of the change in mechanism can be given in terms of stereochemical differences of the furanoid and pyranoid rings. With the pyranosides the bimolecular mechanism would clearly be unfavourable owing to the considerable non-bonded interaction in the transition state (III) and the unimolecular decomposition (IV)



(III) (IV)

Ethyl β-D-galactopyranoside (X = $CH_2 \cdot OH$)

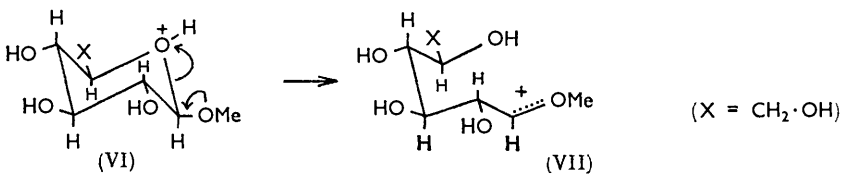


(V)

Ethyl β-D-galactofuranoside

would be correspondingly favoured. With the furanoside the conformation of the 5-membered ring would result in a much less strained transition state (V) for the bimolecular mechanism and it is not surprising to find this mechanism more important here. The low entropy of activation for this bimolecular hydrolysis is more than offset by the much lower energy of activation of 22·7 (compared with 31·6 kcal.) for ethyl β-D-galactopyranoside; at 60° the furanoside is hydrolysed nearly 60 times faster than this pyranoside, in agreement with the unstrained transition state (V) proposed.

For the unimolecular mechanism one major problem remains. The conjugate acid protonated on the methoxyl substituent (I) may undergo slow heterolysis to give a cyclic ion (II). Alternatively the ring oxygen can be protonated (VI) and this conjugate acid may be heterolysed to give the acyclic ion (VII), all subsequent reactions being fast:



(VI) (VII) (X = $CH_2 \cdot OH$)

These two possibilities were considered by Bunton *et al.*[7] who noted the difficulty of distinguishing between them experimentally. Circumstantial evidence for the " open-chain " mechanism [10] has been refuted.[11] Although we have no proof of which process is favoured, we find that all our results relating structure and reactivity are readily explained on the basis of the " cyclic " mechanism, which we favour at the present time. Banks *et al.*[51] have very recently presented evidence in favour of this mechanism based on analogy with the acid-catalysed methanolysis of phenyl glucopyranosides and the demonstration of an oxygen-isotope effect in the hydrolysis of methyl α-D-glucopyranoside.

*Structure and Reactivity.*—(*a*) *Electronic effects.* The electronic effects of substituents on reaction rate will be composite, resulting from changes in the equilibrium constant, $K$, for the formation of the conjugate acid and the rate coefficient, $k_{het}$, for its heterolysis.

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

In principle, electronic effects, chosen with due regard to steric factors, could distinguish between the mechanism involving cyclic and open-chain ionic intermediates; in both, $K$ would be affected in the same sense, though to a different extent, whilst $k_{het}$ would be affected oppositely in the two mechanisms since they involve migration of the electrons in opposite directions in the slow heterolysis stage. However, owing to their composite nature, it is also possible that the observed electronic effects could be the same on either mechanism, and this is unfortunately the case with all the available results.

The relative rates of hydrolysis of some phenyl glucopyranosides in 2·0N-hydrochloric acid at 60° are: phenyl α-D-glucopyranoside 13·2; *p*-nitrophenyl α-D-glucopyranoside 8·7; phenyl β-D-glucopyranoside 3·2; *p*-nitrophenyl β-D-glucopyranoside 1·0. In the " cyclic " mechanism the introduction of the *p*-nitro-group would decrease the concentration of conjugate acid but increase its rate of heterolysis, both to a considerable extent, and thus the effect on reaction rate could not be predicted, but it could be quite small, as is found. In the " open-chain " mechanism this nitro-group would decrease both the concentration and the rate of decomposition of the conjugate acid, both presumably less than before since the site of protonation and bond-breaking is more remote. Thus a slower rate for the nitrophenyl glucosides would result, as is found, though a rather bigger effect might have been expected on the basis of this mechanism. In general, a decrease in rate caused by *meta-* or *para*-substitution of an electron-withdrawing group, or an increase in rate similarly caused by an electron-releasing group, can be explained on either mechanism. If the reverse were ever observed the " open-chain " mechanism would be disproved, at least for the particular compounds involved. Nath and Rydon's results [6] for acid-catalysed hydrolyses of a wide range of substituted phenyl β-D-glucopyranosides are particularly interesting in this connection. From our analysis of the effects on rate of chloro-, cyano-, methoxyl-, methyl-, and nitro-groups in the *meta-* and *para*-positions, which they report, either mechanism could be operating.

Electronic effects undoubtedly contribute to the greatly enhanced lability to acid of 2-deoxyglucosides,[52,53] removal of the inductive effect of the 2-hydroxyl group enhancing both the formation and the decomposition of the conjugate acid, on either mechanism. The results of Armour *et al.*[9] for aqueous perchloric acid and ours for aqueous hydrochloric acid show that methyl 2-deoxy-α-D-glucopyranoside is hydrolysed 2000 times faster than methyl α-D-glucopyranoside. The former workers showed by analogy that the inductive effect could easily account for at least a 100-fold difference in rate, and suggested that the additional factor of about 20 could be due to an inductive effect on the conjugate-acid concentration or to conformational effects. We believe that a factor of about 20 is just that to be expected from conformational effects (see below) common to 2- and 3-deoxy-glucopyranosides. The increase in hydrolysis rates of 6-deoxymannosides compared with mannosides is less than the corresponding increase in 2-deoxyglucosides compared with glucosides; this was claimed by Richards [53] to indicate that the ring-oxygen is not protonated as the " open-chain " mechanism would require. If protonation were the only relevant factor this would be strong evidence against this mechanism, but when the effect on ease of bond-fission is also considered it is seen that this difference in rate-ratios can be explained by either mechanism.

(*b*) *Steric effects.* The effect of variation of sugar configuration on the hydrolysis rate of a number of methyl glycosides has been measured by Isbell and Frush,[54] and Riiber and Sørensen,[4] and discussed by Foster and Overend [55] and by Edward [56] on the basis of the " cyclic " mechanism, and by Shafizadeh and Thompson [57] on the basis of the " open-chain " mechanism. Our relative reactivities agree quite well with the earlier work and

[52] Overend, Shafizadeh, and Stacey, *J.*, 1950, 671.
[53] Richards, *Chem. and Ind.*, 1955, 228.
[54] Isbell and Frush, *J. Res. Nat. Bur. Standards*, 1940, **24**, 125.
[55] Foster and Overend, *Chem. and Ind.*, 1955, 566; see also *Proc. Chem. Soc.*, 1957, 10.
[56] Edward, *Chem. and Ind.*, 1955, 1102.
[57] Shafizadeh and Thompson, *J. Org. Chem.*, 1956, **21**, 1059.

are readily explained in terms of release of steric strain between axial substituents as the half-chair conformation of the oxonium ion (II) is adopted.[56] Relative rates at 60° for hydrolysis of the methyl α-D-hexopyranosides, for example, parallel the number of axial hydroxyl substituents in the sugar when this is in the most stable, C1, conformation; these relative rates for methyl α-D-gluco-, -manno-, -galacto-, -altro-, and -ido-pyranoside are 1, 2·8, 5·0, 17·7, and ~30, respectively, though the last compound will presumably not be in the C1 conformation, where it would have three axial hydroxyl groups. However it should be noted that these, fairly small, differences in reactivity often result from changes in the entropy of activation so that the idea of relief of repulsive strain energy in the transition state must be something of a simplification.

Methyl β-D-glycopyranosides are more rapidly hydrolysed than the corresponding α-anomers.[12] Our work supports this observation and extends it to 2-deoxy-α- and -β-D-glycopyranoside, but shows that the rate differences are small (about 2-fold) and when a methyl is replaced by an ethyl group, in the galactopyranosides, the rates are reversed. Furthermore, these small differences in rate coefficient result from opposing changes in the energy and entropy of activation, with the latter predominating, and detailed discussion of these reactivity sequences is not justified. In view of the recent discussion by Bollenback [58] it is worth noting that our difference (0·2 kcal. mole$^{-1}$) in energy of activation for the hydrolysis of methyl α- and β-D-glucopyranoside is much smaller than that (4·5 kcal. mole$^{-1}$) found in some early work,[3] and in contrast with the earlier report our rate ratio, $k_1^{\beta} : k_1^{\alpha}$, varies very little with temperature. For none of the anomeric pairs of compounds studied here was the difference in activation energy greater than 2 kcal. mole$^{-1}$. The greater reactivity of the β-anomers has been ascribed by Edward [56] to their higher free energy in the ground state caused by polar interaction between the equatorial methoxyl group and the lone pairs of electrons of the ring-oxygen atom. This repulsive interaction will, of course, be destroyed on protonation and thus from this viewpoint the concentration of conjugate acid would be greater for the β-anomer, with the rate, $k^{\beta}_{het}$, of its decomposition little affected; indeed $k^{\beta}_{het}$ may well be less than $k^{\alpha}_{het}$, as would be predicted in the absence of this special interaction.

Edward [56] recognised that with a bulky aglycone steric factors would again predominate and the α-axial anomer would be hydrolysed more rapidly because of its higher free energy in the ground state. This is borne out by the relative rates now reported for phenyl α- and β-D-glucopyranoside and -galactopyranoside, *p*-nitrophenyl α- and β-D-glucopyranoside, and ethyl α- and β-D-galactopyranoside. The α-anomers are all more reactive than the β-, and the differences between the methyl and phenyl glycosides are much greater for the α- than for the β-anomers. However inspection of the following results reveals an interesting factor:

| | $10^5 k_1$ at 60° (sec.$^{-1}$) | $E$ | $\Delta S^{\ddagger}$ |
|---|---|---|---|
| Phenyl α-D-glucopyranoside | 38·0 | 31·1 | 13·3 |
| Phenyl β-D-glucopyranoside | 9·33 | 31·0 | 10·8 |
| *p*-Nitrophenyl α-D-glucopyranoside | 25·1 | 30·3 | 10·5 |
| *p*-Nitrophenyl β-D-glucopyranoside | 2·88 | 30·3 | 6·4 |
| Phenyl α-D-galactopyranoside | 128 | 30·2 | 13·5 |
| Phenyl β-D-galactopyranoside | 24·5 | 28·1 | 4·1 |

The rate differences between the anomeric pairs are seen to result from differences in the entropy rather than the energy of activation; the latter is the same, within experimental error, for each pair of glucosides and the difference in it for the galactosides is overshadowed by the much larger difference in $\Delta S^{\ddagger}$. The same is true for the ethyl galactopyranosides. This suggests that, with other than the smallest aglycones, the α-anomers are more highly orientated than the β-anomers in the ground state and their increased reactivity is associated with greater loss of molecular order, compared with the β-anomers, on passing to the transition state. That is, the important factor is not the increase in potential

[58] Bollenback, "Methyl Glucoside," Academic Press Inc., New York, 1958, p. 31.

energy of the molecule owing to repulsive interaction between the aglycone and axial 3- and 5-substituents, but a decrease in entropy caused by the restriction imposed upon rotation of the aglycone by these substituents.

The rates of hydrolysis of the methyl deoxy-α-glucosides relative to the parent glucoside, at 58°, are as follows:

| | |
|---|---|
| Methyl α-D-glucopyranoside | 1 |
| Methyl 2-deoxy-α-D-glucopyranoside | 2090 |
| Methyl 3-deoxy-α-D-glucopyranoside | 20 |
| Methyl 4-deoxy-α-D-glucopyranoside | 40 |

As noted earlier, removal of the inductive effect of the 2-hydroxyl group would be expected to increase the rate approximately 100-fold;[9] the further increase of about 20-fold observed for the 2-deoxy-compound is the same as the increase observed on removal of the 3-hydroxyl group. This is entirely reasonable since conversion of the chair into the half-chair conformation (II) in the " cyclic " mechanism [55] will be facilitated by a decrease in opposition of 2- relative to 3-substituents, and this decrease should be the same whether the hydroxyl group is removed from C-3 or from C-2. Removal of the 4-hydroxyl group facilitates the reaction similarly, but to a greater extent since this group is in opposition to the bulkier 5-hydroxymethyl group.

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