[Chem. Pharm. Bull. 31(11)3902—3905(1983)]

Rates of Acidic and Alkaline Hydrolysis of Substituted Phenyl α- and β-D-Mannopyranosides

SHIGEHISA KYOSAKA, SANAE MURATA, and MITSUYA TANAKA*

School of Pharmaceutical Science, Toho University, 2-2-1, Miyama, Funabashi 274, Japan

(Received March 23, 1983)

The rates of hydrolysis of substituted phenyl α- and β-D-mannopyranosides were measured in acidic and alkaline solutions. In 0.11 N hydrochloric acid solution, the α-mannosides were hydrolyzed faster than the corresponding β-anomers. The rates of hydrolysis for the α-mannosides were unaffected by substitution in the phenyl group (Hammett reaction constant $\rho = -0.07 \pm 0.065$ (S.D.)), and those for the β-mannosides were slightly enhanced by the introduction of electron-releasing substituents ($\rho = -0.25 \pm 0.082$).

In sodium hydroxide solution, the α-mannosides liberated their aglycones, phenols, much faster than the corresponding β-anomers and the rates were enhanced by the introduction of electron-withdrawing substituents ($\rho = +2.7 \pm 0.14$ for the α-, $+3.1 \pm 0.46$ for the β-mannosides, each in 3.93 N NaOH). Phenyl α-mannoside was hydrolyzed much faster than phenyl β-glucoside, though both have *trans*-1,2 configuration, indicating the importance of a 1,2-diaxial orientation for the reaction.

Keywords——aryl α-mannopyranoside; aryl β-mannopyranoside; acid hydrolysis; alkaline hydrolysis; Hammett plot

Although many kinetic studies have been carried out on the hydrolysis of glycosides, no comparative study on the acidic and alkaline hydrolysis rates of both series of substituted phenyl α- and β-D-mannopyranosides (aryl α- and β-mannosides) has yet been done, as the synthesis of β-anomers with *cis*-1,2 configuration was difficult. Garegg *et al.*,[1] however, provided a useful method for the synthesis of aryl β-mannosides by condensation of *O*-dicyclohexylidene-α-mannopyranose with phenol using triphenylphosphine and azodicarboxylate as condensing reagents. In our work on the transglycosylation observed in the hydrolysis of aryl β-mannosides by a β-mannosidase, we wished to know the stability of the aryl mannosides in order to estimate the rate of product formation and to manipulate the products. Another aim of this study was to examine the effect of the difference in configuration at the 2-position between aryl mannoside and glucoside on the hydrolysis rate.

The substituted phenyl α- and β-mannosides were stable in neutral aqueous solution with the exception of *p*-nitrophenyl α- and β-mannoside. The pseudo-first-order reaction rate constants, k_{obs}, at 100 °C for *p*-nitrophenyl α- and β-mannosides were 3.2×10^{-5} and 2.0×10^{-5} min^{-1}, respectively. The k_{obs} values for phenyl α- and β-mannosides, estimated from the liberation of phenol after hydrolysis at 100 °C for 42 h were less than 6.3×10^{-6} min^{-1} assuming pseudo-first-order reaction kinetics.

The k_{obs} values (min^{-1}), k_{acid} for the acid-catalyzed hydrolysis in 0.11 N hydrochloric acid and k_{alk} for the base-catalyzed hydrolysis in 0.1 and 3.93 N sodium hydroxide, were determined. Table I shows the k_{acid} and k_{alk} values for the aryl α- and β-mannosides together with the values for related glycosides for comparison. When tested by the Somogyi method, only *o*- and *p*-nitrophenyl mannosides exhibited strong reducing power (Table I).

TABLE I. Hydrolysis Rates of Substituted Phenyl α- and β-D-Mannopyranosides and Related Glycosides

Substituent (σ value)[a]	$10^4 k_{acid}$[b]		$10^4 k_{alk}$[b]		$10^4 k_{alk}$			Reducing power[c] (%)	
Concn. of HCl or NaOH (N)	0.11		0.1		3.93				
Temp. (°C)	70 α-	70 β-	100 α-	120 β-	70 α-	70 β-	120 β-	α-	β-
Substituted phenyl D-mannopyranoside									
p-CH_3O (−0.268)	16.3	15.5	9.5	0.08	35.1	0.15	7.1	0.07	0.09
p-CH_3 (−0.170)	14.0	10.7	10.4	0.18	31.7	0.09	4.9	0.13	0.07
m-CH_3 (−0.069)	21.8	14.6	16.1		63.5	0.15		0.08	0.06
H (0)	19.9	8.6	16.8	0.55	71.7	0.21	11.8	0.20	0.10
p-Cl (+0.227)	18.1	11.4	59.2	0.67	288.9	0.23	26.7	0.34	0.10
m-Cl (+0.373)		14.8		1.87		0.66	86.6		0.05
p-NO_2 (+1.27)[a]	13.5	5.1	128000	Lag[d]	300400	2360		55.8	29.3
m-NO_2 (+0.71)		8.6				372			0.67
o-NO_2		12.7							33.3
Substituted phenyl D-glucopyranoside									
H (0)	14.9 (11.7)[e]	4.7 (1.15)[f]			(0.06)[e]	4.5 (2.54)[f]			
p-NO_2 (+1.27)[a]	11.0 (10.1)[e]	(0.33)[f]			(18000)[e]	(5000)[f]			
Phenyl 2-acetamido-2-deoxy-D-mannopyranoside									
H (0)	22.2	12.7			0.19	0.06			

a) For the p-nitro group, σ^- was used as in the previous study with glycosides.[3,4]
b) Pseudo-first-order rate constants (min^{-1}) in acidic (k_{acid}) and in alkaline (k_{alk}) solutions. Data in parentheses were taken from the literature for comparison.
c) Determined by the Somogyi method and represented as a percentage of the value calculated for complete hydrolysis.
d) k_{alk} was not determined as the rate increased with time at low temperatures.
e) Reported values in 0.1 N hydrochloric acid or 3.9 N sodium hydroxide, each at 70 °C.[3]
f) Reported values in 0.1 N hydrochloric acid or 4.0 N sodium hydroxide, each at 60 °C.[4]

Acid Hydrolysis

The effects of aglycone and glycone structures on the hydrolysis rates of glycosides were reviewed.[2] Acid hydrolysis of glycosides involves the protonation of the glycosidic oxygen to form the conjugate acid followed by the rate-determining step of heterolysis to give a cyclic planar carbonium–oxonium ion which has a half-chair conformation. The generally accepted concept[2] predicts that aryl α-mannosides are hydrolyzed faster than the corresponding aryl α-glucosides, owing to the ability of an axial hydroxyl group at the 2-position of the mannoside in Cl conformation to facilitate the formation of the half-chair conformation. It also predicts that the α-mannosides are hydrolyzed faster than the corresponding β-anomers, since generally aryl α-glycosides are "more highly oriented in the ground state" as manifested in their larger $\Delta S^{\neq}$ values in hydrolysis as compared with those of the β-anomers.

In the present study, the hydrolysis rates of the α-mannosides were 1.2 to 1.7 times larger than those reported for the corresponding α-glucosides,[3] and 1 to 2.7 times larger than those of the corresponding β-mannosides, as expected. The rates of acid hydrolysis of aryl α-mannosides were unaffected by substitution in the phenyl group; the Hammett reaction constant, ρ, was -0.07 ± 0.065 (S.D.). In the β-anomers, the acid hydrolysis was slightly facilitated by electron-releasing substituents: $\rho = -0.25 \pm 0.082$. Rydon *et al.* reported ρ values of −0.006[3] (at 70 °C) and −0.66 (at 60 °C),[4] for a series of substituted phenyl α- and

β-D-glucosides, respectively. The reasons for the vanishingly small ρ value for the α-series and the somewhat larger ρ value for the β-series were discussed.[2] The somewhat larger ρ value for the β-series was ascribed to a partial mutual cancellation of two opposite effects; electron-releasing substituents facilitate the formation of the conjugate acid (protonation of glycosidic oxygen) while hindering the process of cleavage to the onium ion. Rydon and co-workers suggested that the vanishingly small ρ value for the α-series was due to the involvement of a different mechanism, with a stereochemically controlled diaxial elimination between ring *O*-proton and the aryloxy group in the conjugate acid.[2,3]

In the case of phenyl 2-acetamido-2-deoxy-D-mannopyranosides, the α-anomer was hydrolyzed twice as fast as the β-anomer, in contrast to their 2-epimers, phenyl 2-acetamido-2-deoxy-D-glucopyranosides, of which the β-anomer is exceptionally hydrolyzed faster than the α-anomer.[5]

Alkaline Hydrolysis

Unlike acid hydrolysis, the alkaline hydrolysis of the substituted phenyl α- and β-mannosides was facilitated by electron-withdrawing substituents. The ρ values calculated by including (omitting) the nitrophenyl compounds were $+2.7\pm0.14$ ($+2.0\pm0.31$) for the α-anomers and $+3.1\pm0.46$ ($+3.2\pm0.82$) for the β-anomers, each in 3.93 N sodium hydroxide at 70 °C. ρ values of +4.0 (+2.8, when calculated without the *p*-nitrophenyl compound) for α-glucosides at 70 °C in 3.9 N sodium hydroxide,[3] and +2.48 (very similar values with or without *p*-nitrophenyl glucoside) for β-glucosides at 60 °C in 4.0 N sodium hydroxide were reported.[4] In contrast to aryl glucosides, whose β-anomers are hydrolyzed much faster than the α-anomers,[3,4] the aryl α-mannosides having *trans*-1,2 configuration were hydrolyzed about 100 to 1000 times faster than the corresponding β-mannosides. Several mechanisms have been proposed for the alkaline hydrolysis (or degradation) of aryl glycosides.[2,6] It has been shown that aryl β-glucosides[4] having *trans*-1,2 configuration react at a much faster rate than the corresponding α-anomers[3] presumably by a mechanism involving neighboring C-2 oxyanion participation.[7] In the present study, phenyl α-mannoside was hydrolyzed much faster than phenyl β-glucoside, although both have *trans*-1,2 configuration. This relation should also hold between other aryl α-mannosides and β-glucosides, since both series exhibit similar ρ values. The above observation may be explained in terms of the ease with which the α-mannoside takes *trans*-diaxial orientation at the 1- and 2-position.

Phenyl 2-acetamido-2-deoxy-α-D-mannopyranoside, which has no hydroxyl group at the 2-position, is hydrolyzed much more slowly than phenyl α-mannoside, indicating a remarkable C-2 oxyanion participation in the alkaline hydrolysis of aryl α-mannosides.

Experimental

Materials——The substituted phenyl α-D-mannopyranosides[8] were prepared by the method of Helferich.[9] The β-mannosides were prepared according to the method of Garegg *et al.*,[1] but the aryl di-*O*-cyclohexylidene-β-mannopyranosides were directly hydrolyzed to free aryl β-mannosides without purification. A solution of diethyl azodicarboxylate (0.0185 mol) in dry toluene (25 ml) was added to a stirred solution of 2,3 : 4,6-di-*O*-cyclohexylidene-α-mannose (0.0135 mol), triphenylphosphine (0.020 mol) and an appropriate phenol (0.02 mol) in dry toluene (100 ml) at room temperature. After being stirred overnight, the reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 90% aqueous trifluoroacetic acid (50 ml), and kept for 30—60 min in ice water. The reaction mixture was concentrated to a syrup under reduced pressure. The syrup was dissolved in water, and the solution was washed with chloroform. The aqueous phase was evaporated to dryness under reduced pressure, and the residue was recrystallized from water or ethanol. The purity of the products, especially the contamination with the corresponding anomer, was tested by thin layer chromatography on Merck Kieselgel $60F_{254}$ with ethyl acetate–isopropyl alcohol–water (9 : 4 : 2 (v/v/v)), and by proton magnetic resonance spectroscopy at 100 MHz on a JEOL JNM 4H-100 spectrometer in dimethyl sulfoxide-d_6. Chemical shifts of the anomeric proton (H1) given in ppm from tetramethylsilane (δ) are: α-anomer: *p*-methoxy, 5.21 (d, $J=2$ Hz); *p*-methyl, 5.27 (d, $J=2$ Hz); *m*-methyl, 5.35 (d, $J=2$ Hz); H, 5.37 (d, $J=2$ Hz); *p*-chloro, 5.36 (d, $J=2$ Hz); *p*-nitro, 5.60

(d, $J=1$ Hz); β-anomer: *p*-methoxy, 5.0 (s); *p*-methyl, 5.04 (s); *m*-methyl, 5.09 (s); H, 5.12 (s); *p*-chloro, 5.11 (s); *m*-chloro, 5.18 (s); *o*-nitro, 5.29 (s); *m*-nitro, 5.33 (s); *p*-nitro, 5.36 (s). The singlet signal resolved into a doublet ($J=2$ Hz) when examined at 130 °C with *p*-tolyl β-mannoside.

The properties of new compounds were as follows (all melting points are uncorrected and specific rotations are those at room temperature; yields were calculated with respect to dicyclohexylidene-α-mannoside used). *p*-Methoxyphenyl β-mannopyranoside, mp 168—170 °C (from water), $[\alpha]_D$ −69.3° ($c=1.0$, water), yield, 22%. *Anal.* Calcd for $C_{13}H_{18}O_7 \cdot 1/2H_2O$: C, 52.88; H, 6.49. Found: C, 52.84; H, 6.43. *p*-Tolyl β-mannopyranoside, mp 162 °C (from ethanol), $[\alpha]_D$ −69.5° ($c=1.0$, water), yield, 20%. *Anal.* Calcd for $C_{13}H_{18}O_6 \cdot 1/2H_2O$: C, 55.91; H, 6.86. Found: C, 55.81; H, 6.56. *m*-Tolyl β-mannopyranoside, mp 157 °C (from ethanol), $[\alpha]_D$ −69.2° ($c=1.0$, water), yield, 40%. *Anal.* Calcd for $C_{13}H_{18}O_6 \cdot 1/4H_2O$: C, 56.82; H, 6.79. Found: C, 56.98; H, 6.99. The pure β-mannoside was obtained by carbon celite column chromatography using 30% EtOH as an eluant; the β-anomer was eluted first. *p*-Chlorophenyl β-mannopyranoside, mp 166 °C (from ethanol), $[\alpha]_D$ −71.7° ($c=1.0$, water), yield, 29%. *Anal.* Calcd for $C_{12}H_{15}ClO_6 \cdot 2/3H_2O$: C, 47.61; H, 5.44. Found: C, 47.68; H, 5.40. *m*-Chlorophenyl β-mannopyranoside, mp 132 °C (from ethanol), $[\alpha]_D$ −72.1° ($c=1.0$, water), yield, 26%. *Anal.* Calcd for $C_{12}H_{15}ClO_6$: C, 49.58; H, 5.20. Found: C, 49.22; H, 5.28.

Rate Measurements——The hydrolysis was carried out in separate sealed tubes placed in a thermostated bath (±0.2 °C). Samples (5 mM glycoside) were removed at intervals (every 10—15 min) and analyzed for liberated phenol. *p*-Nitrophenols were estimated by the method of Levvy and Conchie[10] and other phenols by the method of Folin and Ciocalteu.[11] A maximum of 10—15% hydrolysis was allowed. The rates of alkaline hydrolysis of the nitrophenyl glycosides were extremely fast and were estimated by linear extrapolation from 3 to 4 data points at low temperatures (21 to 41 °C) on the basis of the Arrhenius law. On the other hand, the rates for β-mannosides, except for *p*-nitrophenyl β-mannosides, were very slow and the rate constants were roughly estimated from the phenol liberated after hydrolysis for 42 h.

Acknowledgement The authors are grateful to Dr. T. Morikawa for elemental analyses and to Miss Y. Sakamoto for NMR measurements.

References

1) *a*) P. J. Garegg, T. Iversen, and T. Norberg, *Carbohydr. Res.*, **73**, 313 (1979); *b*) K. Åkerfeldt, P. J. Garegg, and T. Iversen, *Acta Chem. Scand., Ser. B*, **33**, 467 (1979).
2) W. G. Overend, "The Carbohydrates," Vol. IA, 2nd Ed., ed. by W. Pigman, D. Horton, Academic Press, New York and London, 1972, p. 279.
3) A. N. Hall, S. Hollingshead, and H. N. Rydon, *J. Chem. Soc.*, **1961**, 4290.
4) R. L. Nath and H. N. Rydon, *Biochem. J.*, **57**, 1 (1954).
5) M. Tanaka, S. Kyosaka, and Y. Ito, *Chem. Pharm. Bull.*, **21**, 1971 (1973).
6) C. E. Ballou, *Advances in Carbohydrate Chemistry*, **9**, 59 (1954).
7) R. C. Gasman and D. C. Johnson, *J. Org. Chem.*, **31**, 1830 (1966).
8) A. Vervoort and C. K. De Bruyne, *Carbohydr. Res.*, **12**, 277 (1970).
9) B. Helferich and S. Winkler, *Chem. Ber.*, **66**, 1556 (1933).
10) G. A. Levvy and J. Conchie, *Methods in Enzymology*, **8**, 577 (1968).
11) O. Folin and V. Ciocalteu, *J. Biol. Chem.*, **73**, 627 (1927).