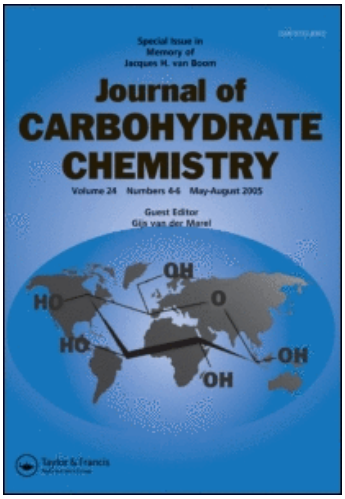

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The Stability of the N-glycosidic bond of N-aryl-D-pentopyranosylamines

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The stability of the N-glycosidic bond of N-aryl-D-pentopyranosylamines

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ABSTRACT

Some representative N-aryl-D-pentopyranosylamines have been synthesized and their structures confirmed by ^{13}C NMR. The kinetics of their acid-catalyzed hydrolyses have been studied at various temperatures by UV and HPLC techniques. The influence of the changes in the aglyconic and sugar moieties has been examined. The rates of hydrolyses increased as the pH of the solution decreased and the base strength of the parent amine increased. The lability of the C_1N bond increased in the order xyloside < lyxoside < riboside < arabinoside. A bimolecular A-2 mechanism is suggested for the acid-catalyzed hydrolysis of N-aryl-D-pentopyranosylamines, involving the formation of a Schiff base intermediate.

INTRODUCTION

The reactivity of the glycosidic bond can be discussed on the basis of its sensitivity to acids, and as a consequence, the mechanism of the acidic hydrolysis of glycosides has been the subject of much research. [3-6, 11-29, 30-39, 40-48] According to Cordes, [18,19] the acid-catalyzed hydrolysis of acetals proceeds by the A-1 mechanism. The same mechanism has been proposed for methyl glycopyranosides. [3-6, 11-16, 20, 23, 32, 39, 42-47] where the slow, rate-limiting step of the acid-catalyzed hydrolysis involves a unimolecular heterolysis of the

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glycoside conjugate acid to form a cyclic carbenium-oxenium ion, which then reacts with water. For the corresponding glycofuranosides [16, 32, 43] the bimolecular mechanism A-2 was suggested.

The A-1 mechanism was accepted for the acid-catalyzed hydrolysis of adenine nucleosides [26, 36], although the mechanism for pyrimidine nucleosides solvolysis in acidic media was not definitively proved. [25]

The diversity of mechanisms suggested for the glycopyranosylamines, [14, 21, 29, 30, 33, 48] may well only reflect variations in the experimental conditions of the hydrolysis reactions. The most probable mechanism seems to be the one proposed by Capon, Connet [14] and Simon, Palm. [48] These authors, examining the acid-catalyzed hydrolyses of N-aryl-D-glucopyranosylamines, [14] considered that the glycosylamines formed Schiff-base intermediates which were decomposed by addition of water in the rate-limiting step. A similar mechanism had been already advocated by Kenner [35] for the acid solvolysis of purine nucleosides (A-2 mechanism). The acid-lability of these compounds was related to the nature of both the base and the sugar.

This paper presents the mechanism of the acid hydrolysis of N-aryl-D-pentopyranosylamines and analysis of all the factors influencing the stability of N-glycosidic bond C_1N.

The synthetic compounds described in the experimental section (Tables 1 and 2) were submitted to various acid hydrolysis conditions (Table 3).

EXPERIMENTAL

The N-p-chlorophenyl- and N-p-tolyl- compounds were prepared by the method of Ellis and Honeyman, [21] the N-phenyl-D- ribopyranosylamine according to Berger and Lee, [7] and the N-p-nitrophenyl-

D-pentopyranosylamines by Weygand [51] and Magnin [37] methods. The compounds obtained were crystallized from ethanol or ethanol-ether except the N-p-chloro-phenyl-D-arabinopyranosylamine which was recrystalized from pyridine and dried in vacuo.

These derivatives showed the expected properties | melting-point, optical rotation, composition, and ^{1}H and ^{13}C NMR (Tables 1 and 2)|.

The spectrometric data were compatible with those of Imbach et al. [17]

Acid hydrolyses were conducted in ethanolic-aqueous HCl (Table 3). The rates were estimated by monitoring the changes in UV absorption using the $n \rightarrow \Pi^*$ transition of the protonated amine, λ_{max} 285, 290, 300 and 310 nm, for aniline, p-toluidine, p-chloro- and p-nitroaniline respectively (Table 3).

The probable protonation of the nitrogen atom in these glycosides (1 $\rightleftharpoons$ 2a . Scheme I) was not detected with the UV spectrophotometry method. The measured value of UV absorption at a given wavelength for the N-glycosides examined in a corresponding mixture of $EtOH/H_2O$ without catalyst was identical with Ao = the zero-time absorption, approximated from the plot log A = f(t), where t = time of reaction.

The pseudo-first order rate constants k at 21°, 31°, 41°C were calculated with the help of a K 202 computer from the results obtained by UV spectrophotometry and HPLC techniques. The rate constants were independent of the ionic strength. The Arrhenius activation energies Ea were calculated from the slope of plots log k.vs.1/T, where k = the rate constant for the hydrolysis reaction, T = temperature °K. The enthalpies and entropies of activation ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) were calculated from known thermodynamic relationships (Table 4). The Hammett's reaction constant ρ was obtained from a linear plot of log k.vs. $\sigma\rho^{+}$,

Table 1. Analytical Data for N-aryl-D-pentopyranosylamine.

Compound	m.p. (°C)	$\lvert\alpha\rvert_D^{20}$. a.b			Formula Mass	Elemental Analyses Calc. (%) Found (%) C	H	N
RpCl	129-130	+167.3[a]			$C_{11}H_{14}O_4NCl.\frac{1}{2}EtOH$	51.03	6.02	4.98
		+167.3	⟶	+ 9.5	282.2	50.82	5.95	5.00
ApCl	120-122	-82.8[a]			$C_{11}H_{14}O_4NCl.C_5H_5N$	56.72	5.61	8.27
		-82.8	⟶	- 5.5	338.5	56.76	5.67	8.28
XpCl	139-140	-70.6[b]			$C_{11}H_{14}O_4NCl.\frac{1}{2}EtOH$	51.03	6.02	4.98
		-70.6	⟶	+ 6.4	282.5	51.03	5.90	4.93
LpCl	168-169	-154.6[a]			$C_{11}H_{14}O_4NCl$	50.90	5.39	5.39
		-154.6	⟶	- 24.7	259.2	50.92	5.42	5.37
$RpNO_2$	190-191	+282.8[a]			$C_{11}H_{14}O_6N_2.\frac{1}{2}EtOH$	49.10	5.78	9.55
		+282.8	⟶	+ 49.5	293.2	49.07	5.78	9.63

$ApNO_2$	205-206	-135.2[c]		$C_{11}H_{14}O_6N_2.\frac{1}{2}EtOH$	49.10	5.78	9.55
		-135.2	+ 60.5	293.2	48.97	5.86	9.47
$XpNO_2$	188-189	+284.2[a]		$C_{11}H_{14}O_6N_2.\frac{1}{2}EtOH$	49.10	5.78	9.55
		+284.2	+ 30.0	293.2	48.94	5.80	9.47
$LpNO_2$	149-150	-254.0[a]		$C_{11}H_{14}O_6N_2.H_2O$	45.83	5.55	9.72
		-254.0	- 2.4	288.2	45.92	5.59	9.69
RpT	142-143	+117.0[a]		$C_{12}H_{17}O_4N$	60.23	7.12	5.86
		+117.0	+ 7.4	239.0	60.25	7.23	5.85
R_A	135-136	+146.6[a]		$C_{11}H_{15}O_4N.\frac{1}{2}H_2O$	56.41	6.84	5.98
		+146.6	+ 12.9	234.0	56.37	6.87	5.97

Abbreviations explained in footnote. | $\alpha|_D^{20}$ (c 0.5); a: in ethanol; b: in pyridine

Table 2. ^{13}C NMR Data for N-aryl-D-pentopyranosylamines

Compound	%	C-1	Δ C-1	C-2	C-3	C-4	C-5	C_{base} C-1	C_{base} C-3,5	C_{base} C-4	C_{base} C-2,6	Other chemical shifts
RpCl[b]	β 51	83.04	0.49	72.02	71.82	68.74	64.82	147.02	129.01	121.88	115.48	71.702
	α 49	82.55		70.95	71.60	69.03	63.86	145.74		122.12	115.37	
ApCl[c]	β	86.49		69.68	71.50	74.60	67.42	146.88	129.95	122.34	116.25	125.69
XpCl[c]	β	86.73		70.07	78.47	71.06	67.28	146.77	129.99	122.56	116.22	115.96 129.68 146.66
LpCl[c]	β	83.44		70.36	72.17	69.43	65.67	146.95	129.99	122.75	116.54	
				71.03	74.99	68.29	66.39	146.08		122.40	116.25	

$RpNO_2$[c]	α		81.97		70.76	71.03	68.98	64.69	154.04	127.03	138.68	113.87	
$ApNO_2$[c]	β		85.45		69.24	71.44	75.13	67.22	154.04	126.14	138.47	112.89	
$XpNO_2$[c]	α		81.63		71.46	71.80	70.71	64.13	154.61	126.93	138.65	113.95	
$LpNO_2$[c]	β		82.68		70.27	74.81	68.19	66.51	154.13	127.00	138.70	114.00	
RpT[b]	α		82.97		71.38	71.72	69.25	64.24	144.58	129.81	126.79	114.43	64.16 CH_3[20.45]
XpT[b]	β	90	87.59	4.55	74.46	79.17	71.22	67.54	145.61	127.11	123.70	114.69	135.86
	α	10	83.04		72.38	73.40	70.81	64.09	145.45	129.78	126.82	114.41	CH_3[20.46]
R_A[b]	β	42	83.14	0.56	71.96	71.16	68.81	64.05	148.09	129.23	117.91	114.14	114.44
	α	58	82.58		71.57	71.87	69.12	63.98	146.83	129.28	118.12	114.22	84.77

Abbreviations explained in footnote. ^{13}C NMR spectra were recorded at 25.2 MHz with XL 100 VARIAN spectrometer. C_5D_5N [**b**] or $DMSO_{d\_}$ [**c**] was used as the solvent.

Table 3. The conditions of Hydrolysis Reaction and Kinetic Measurements.

Method	Compound	Concentration of N-glycoside (mole.dm^{-3})	Temp. of Hydrolysis (°C)	Concentration of HCl (mole dm^{-3})	Amount of H_2O (%)	λ_{max} (nm)
	RpCl	5×10^{-4}	21, 31, 41	0.0005-0.05	5, 50, 80	300
	ApCl	5×10^{-4}	21, 31, 41	0.0005-0.02	5, 50, 80	300
	XpCl	5×10^{-4}	21, 31, 41	0.0005-0.02	5, 50, 80	300
	LpCl	5×10^{-4}	21, 31, 41	0.0005-0.02	5, 50, 80	300
U.V	$RpNO_2$	2.5×10^{-4}	21, 31, 41	0.02-0.2	5, 50, 80	310
	$ApNO_2$	2.5×10^{-4}	31	0.05-0.2	5, 50, 80	310
	$XpNO_2$	2.5×10^{-4}	31	0.05-0.2	5, 50, 80	310
	$LpNO_2$	2.5×10^{-4}	31	0.05-0.2	5, 50, 80	310
	RpT	5×10^{-4}	21, 31, 41	0.0005-0.05	5, 50, 80	290
	R_A	5×10^{-4}	21, 31, 41	0.0005-0.05	5, 50, 80	285
H.P.L.C. [a]	RpCl	10^{-2}	21	0.02-0.1	5	

Abbreviations explaines in footnote: a: 10 µm LICHROSORB NH_2 (3.6x200 mm) column, Mobile System: CH_2Cl_2 95%, MeOH 5%, UV Detector (λ 254), Flow rate 2 cm^3/min.

Table 4. Pseudo-first order rate constant (10^3k, sec^{-1}) and thermodynamic parameters for acid-catalysed hydrolysis of N-aryl-D-pentopyranosylamines in ethanolic-aqueous solutions.

C_{H_2O} %	C_{HCl} mole.dm^{-1}	$10^3\bar{k}$, sec^{-1} 21°	31°	41°	Parameters for $\bar{k}_{31}$ $\Delta H^{\neq}$ [a] kcal mole^{-1}	$\Delta S^{\neq}$ [b] cal.deg^{-1} mole^{-1}
	N-p-chlorophenyl-D-ribopyranosylamine RpCl					
5	0.002	0.035	0.083	0.217	16.2	-24.2
	0.005	0.088	0.207	0.546	16.2	-22.3
	0.01	0.165	0.444	1.065	16.5	-19.6
	0.02	0.329	0.865	1.984	15.9	-20.3
	0.05	0.808	2.126	4.869	15.9	-18.6
50	0.0005	0.075	0.154	0.414	15.1	-26.5
	0.001	0.132	0.329	0.737	15.3	-24.3
	0.002	0.243	0.572	1.372	15.3	-23.1
	0.05	5.217	11.680	28.670	15.1	-18.0
80	0.0005	0.228	0.487	1.169	14.6	-25.4
	0.001	0.387	0.865	1.938	14.2	-25.9
	0.002	0.656	1.310	3.072	13.8	-27.1
	N-p-chlorophenyl-D-arabinopyranosylamine ApCl					
5	0.002	0.060	0.146	0.349	15.6	-26.7
	0.005	0.150	0.374	0.963	16.5	-20.1
	0.01	0.291	0.748	1.713	15.7	-21.4
	0.02	0.623	1.528	3.341	14.8	-22.8
50	0.0005	0.073	0.205	0.441	15.9	-23.1
	0.001	0.168	0.367	0.840	14.2	-27.7
	0.002	0.319	0.731	1.423	13.1	-29.8
80	0.0005	0.237	0.472	1.032	12.9	-31.4
	0.001	0.462	0.859	1.528	10.4	-38.5
	0.002	0.859	1.713	2.911	10.6	-36.4

Table 4 cont.

Table 4 cont.

	N-p-chlorophenyl-D-xylopyranosylamine XpCl					
5	0.002	0.017	0.049	0.131	18.2	-20.8
	0.005	0.048	0.117	0.322	16.9	-21.1
	0.01	0.090	0.244	0.672	17.9	-16.4
	0.002	0.165	0.487	1.310	18.4	-13.2
50	0.0005	0.036	0.076	0.165	13.6	-32.6
	0.001	0.068	0.137	0.287	12.8	-34.8
	0.002	0.119	0.280	0.571	13.8	-29.5
80	0.0005	0.131	0.262	0.510	11.9	-35.9
	0.001	0.198	0.487	0.886	19.2	-30.5
	0.002	0.361	0.789	1.540	12.7	-30.9
	N-p-chlorophenyl-D-lyxopyranosylamine LpCl					
5	0.002	0.026	0.074	0.209	18.4	-16.9
	0.005	0.065	0.178	0.437	18.4	-15.2
	0.01	0.126	0.347	0.912	18.2	-14.5
	0.02	0.245	0.692	1.698	18.2	-13.2
50	0.0005	0.044	0.105	0.251	15.6	-25.9
	0.001	0.089	0.214	0.479	15.7	-24.1
	0.002	0.151	0.407	0.794	15.7	-22.7
80	0.0005	0.174	0.372	0.724	12.5	-33.2
	0.001	0.316	0.692	1.288	12.3	-32.6
	0.002	0.575	1.148	2.455	12.7	-30.2
	N-p-methylphenyl-D-ribopyranosylamine RpT					
5	0.002	0.112	0.263	0.617	15.1	-28.7
	0.005	0.229	0.562	1.230	14.8	-24.7
	0.01	0.417	0.955	2.138	14.6	-24.4
	0.02	0.676	1.585	3.467	14.4	-24.0
	0.05	1.413	3.311	7.079	14.2	-23.2
50	0.0005	0.501	0.891	1.585	10.0	-39.8
	0.001	0.912	1.585	2.884	10.0	-38.6
	0.002	1.584	2.818	4.677	9.6	-38.4
	0.05	19.050	31.620	54.950	9.1	-35.4
80	0.0005	1.660	2.754	4.266	8.1	-43.8
	0.001	2.818	4.677	7.586	8.5	-41.8
	0.002	4.365	7.943	12.590	8.3	-41.0

Table 4 cont.

	N-phenyl-D-ribopyranosylamine				R_A	
5	0.002	0.053	0.125	0.280	14.7	-28.2
	0.005	0.134	0.314	0.771	15.5	-23.7
	0.01	0.267	0.656	1.470	15.1	-23.6
	0.02	0.521	1.339	2.673	14.4	-24.3
	0.05	1.309	3.069	7.362	15.3	-19.9
50	0.0005	0.199	0.395	0.752	11.6	-35.9
	0.001	0.369	0.736	1.435	11.9	-33.9
	0.002	0.656	1.167	2.383	11.3	-35.0
	0.05	10.400	18.930	37.760	11.2	-30.7
80	0.0005	0.598	1.040	1.726	9.1	-42.2
	0.001	1.115	1.936	3.365	9.6	-39.8
	0.002	1.893	3.606	6.123	10.2	-36.3
	N-p-nitrophenyl-D-ribopyranosylamine				$RpNO_2$	
5	0.02	0.022	0.054	0.138	16.3	-24.6
	0.05	0.053	0.130	0.312	15.7	-24.8
	0.1	0.109	0.292	0.610	15.2	-24.7
	0.2	0.212	0.597	1.397	16.7	-18.4
50	0.05	0.153	0.368	0.717	13.8	-29.6
	0.1	0.306	0.669	1.366	13.1	-29.9
	0.2	0.669	1.497	2.921	12.9	-29.0
80	0.05	0.557	0.945	2.020	11.2	-35.5
	0.1	1.110	2.020	3.850	10.8	-35.3
	0.2	2.267	4.319	8.618	11.7	-31.0

k was calculated from the equation $A_t - A_\infty = [A_o - A_\infty]e^{-kt}$, where A_∞ and A_t - are the measured ultraviolet spectrophotometric absorbance, final A_∞ and at any time A_t, of the to N-D-pentopyranosides examined, A_o was estimated from the plot $\log [A_t - A_\infty] = f(t)$ for $t = 0$ initial absorbance, a) calculated from the Arrhenius equation $k = A_e^{-\Delta Ha/RT}$ and $\Delta H^{\neq} = \Delta H_a - RT$.

b) Calculated from the rearranged absolute rate expression:

$\Delta S^{\neq} = 2.303\ R\ [\log \bar{k}_{31} - \log kT/h] + \Delta H^{\neq}/T$ where $k = 1.3805 \times 10^{-16}$ erg.deg^{-1}, $h = 6.6256 \times 10^{-27}$ erg. sec, $R = 1.986$ cal deg^{-1} mole^{-1}, $T = 304.2°$, $\bar{k}_{31}$ - middle rate constant at 31°C, standard deviations calculated from the expression

$\pm\delta\bar{k} = \Sigma[k_i - \bar{k}]^2 / n - 1\ [2 - 5\ \%]$, $\pm\delta\Delta\bar{H}_{31} \neq 0.3$-$0.55$ kcal.mole^{1}

$\pm\delta\Delta S^{\neq}_{31} = 0.9 - 1.8$ cal mole^{-1} deg^{-1}

The activation free energy $\Delta G^{\neq}$ (kcal mole^{-1}) was calculated from the equation $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$ giving the values 20.6- 24.5 kcal mole^{-1} with standard deviations $\pm\delta\Delta S^{\neq}_{31} = 0.4$-$0.8$ kcal.mole^{-1}

where k is the rate constant of acid hydrolysis reaction of N-aryl-D-ribopyranosylamines. σp^+ is the substituent constant for p-CH_3, p-Cl, and p-NO_2 proposed by Biggs, Robinson, [8].

A linear enthalpy-entropy relationship was determined according to Exner [22] method, by plotting two sets of log k obtained at two different temperatures (Table 4), against each other, yielding as a result of regression analysis, the equation (1).

$$\log 10^3 \bar{k}_{(41°C)} = 0.604 + 0.874 \log 10^3 \bar{k}_{(21°C)} \quad (1)$$

with the slope b = 0.874 ± 0.050, isokinetic temperature β = 597 °K, T_1/T_2 = 0.936, n = 25, the correlation coefficient r = 0.992 and the standard error of the estimate $S_{y/x}$ = 0.032.

DISCUSSION

The dependence of the rate constants on the structure of the reacting molecules, or on other factors, especially solvent effects, is usually expressed in terms of activation parameters. The parameters used are either the activation energy Ea and the frequency factor A of the classical Arrhenius theory (equation 2), or the enthalpy of activation $\Delta H^{\neq}$ and the entropy $\Delta S^{\neq}$ of the activated complex theory (equation 3).

$$k = A \exp\left[-\frac{Ea}{RT}\right] \quad (2)$$

$$\log A = \frac{T_1}{T_1 - T_2}\left[\log k_1 - \frac{T_2}{T_1} \log k_2\right] \text{ when } T_1 > T_2 \quad (2a)$$

$$k = (RT/Nh) \exp\left[\frac{\Delta S^{\neq}}{R}\right] \exp\left[-\frac{\Delta H^{\neq}}{RT}\right] \quad (3)$$

The linear relationship between enthalpy and entropy of activation in a series of similar reactions cannot be proved directly from

the quantities $\Delta H^{\neq}$ and $\Delta S^{\neq}$, or Ea and log A neither graphically nor by means of a correlations calculus, as these aforementioned parameters are strongly dependent on the calculation of the kinetic data. According to Exner, [22] it can be done by plotting two sets of log k obtained at two different temperatures against each other. The kinetic measurements at different temperatures have been done (Tables 4 and 5) yielding approximately a linear dependence of log $\bar{k}_1$ on log $\bar{k}_2$ (equation 1, Experimental) confirming that the reactions studied herein, form, a so-called, reactions series i.e. they proceed to a certain extent with the same mechanism.

Since the individual values of the energy of activation Ea do not give useful information, as they are to a great extent parallel to the values of log k, therefore, the information obtained from kinetic measurements at different temperatures, within the reaction series examined, was the value of the slope b in the linear relationship (equation 4).

$$\log \bar{k}_{T_1} = a + b \log \bar{k}_{T_2} \quad (4)$$

According to Hinshelwood, [9] this value allows classification in one of three groups:

1. At constant log A (equation 2), the rate constant is controlled by changes of Ea. The slope b is equal to T_2/T_1 and the isokinetic temperature β is infinite.

2. At constant Ea, the rate constant is controlled by changes of log A, the slope $b = 1$, and $\beta = 0$.

3. Both activation parameters are variable and partially compensate each other, $b < T_2/T_1$ and $\beta > T$.

The slope $b = 0.874$ (equation 1, Experimental) is positive and smaller than $T_2/T_1 = 0.936$. The isokinetic temperature $\beta = 597°K$

Table 5. Pseudo-first order rate constant (10^3 k, sec^{-1}) for acid-catalyzed hydrolysis of N-p-nitrophenyl-D-pentopyranosylamines in ethanolic-aqueous solutions at 31°C.

Compound	C_{HCl} $mole.dm^{-1}$	10^3K, sec^{-1} Amount of H_2O % 5	50	80
ApNO$_2$	0.05	0.134	0.328	1.060
	0.1	0.272	0.717	2.216
	0.2	0.624	1.720	4.736
XpNO$_2$	0.05	0.070	0.164	0.485
	0.1	0.139	0.299	1.085
	0.2	0.285	0.717	1.929
LpNO$_2$	0.05	0.112	0.302	0.850
	0.1	0.190	0.489	1.546
	0.2	0.388	1.022	2.750

Abbreviations explained in footnote.

is greater than T_1 = 314°K. This corresponds to the third group, so according to Hinshelwood, [9] one can suspect solvent or steric rather than purely electronic effects.

The Hammett [29] plots (Figures 1 and 2) illustrate the substituent effect on reaction rate k (equation 5).

$$\log (k/k_o) = \sigma\rho \quad .$$

The observed ρ value (Fig. 1) slightly increased with temperature, in agreement with the Hammett equation (5), but decreased with increasing amounts of water in an ethanol-water solution, at constant temperature and catalyst-concentration for all the reactions examined.

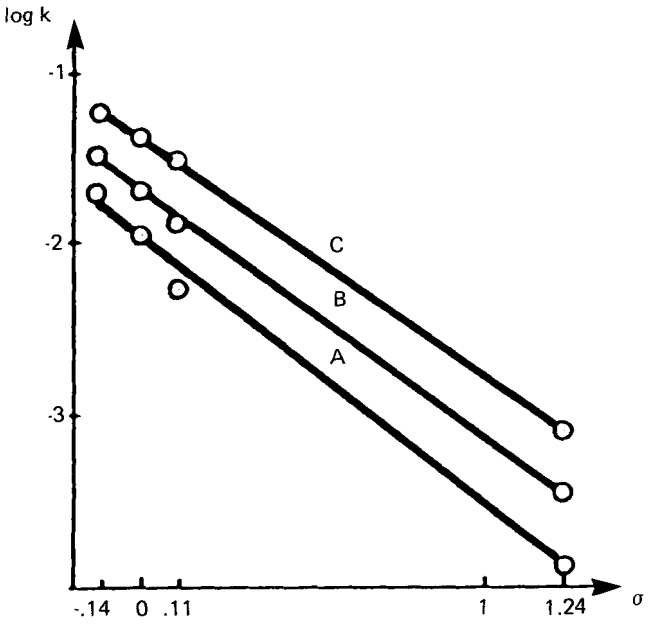

Fig. 1. The relationship between log k and the Hammett constant $\sigma\rho^+$ for acid-catalyzed hydrolysis of p-substituted N-phenyl- α-D-ribopyranosides. where C_{HCl} = 0.005 mole cm^{-1}, C_{H_2O} = 5%. A: 21°C. ρ_A = 1.48. B: 31°C. ρ_B = 1.42. C: 41°. ρ_C = - 1.38.

The ρvalue -1.05 for 5 % and -1.42 for 50 % of water can be explained by changes in solvent polarity. The increase of the dielectric constant, is accompanied by a decrease of ρ value, according to the expression log k.vs $1/\varepsilon$. [45] The changes in the acid-concentration (Fig. 2), which did not influence the ρ constant, when its value was smaller than 1, could be explained by a two-step reaction, [45] a fast equilibrium K_1 (eq.6) followed by a rate-limiting conversion k_2 (eq. 7)

$$PA + H_3O^+ \overset{K_1}{\rightleftharpoons} PAH^+ + H_2O \quad (6)$$

$$PAH^+ + H_2O \xrightarrow{k_2} POH + AH + H^+ \quad (7)$$

where P is the pentopyranosyl moiety and A the aglycone. The rate

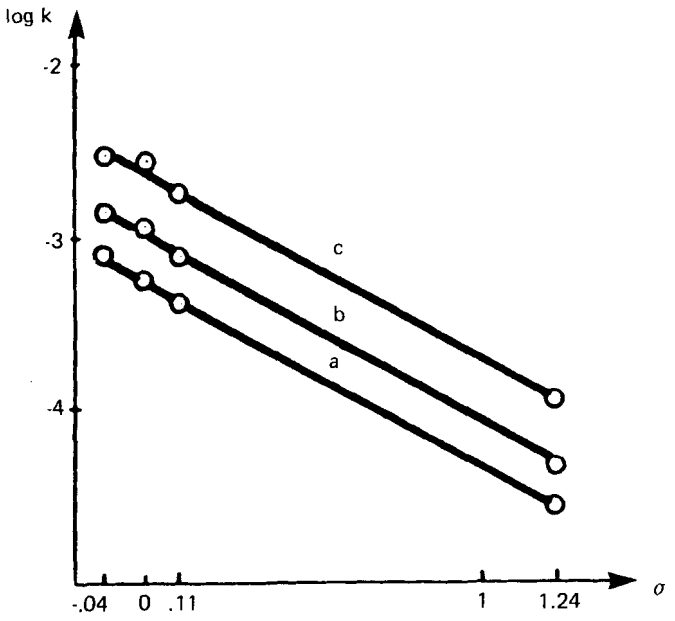

Fig.2. The relationship between log k and the Hammett constants $\sigma\rho^{\circ}$ for acid-catalyzed hydrolysis of p-substituted N-phenyl- α -D-ribopyranosides. where C_{H_2O} = 5 % temp = 31°C. a = 0.01 N HCl. b = 0.02N HCl. c = 0.05N HCl. $\rho_a = \rho_b = \rho_c = -1.05$

constant k is $k = K_1 k_2$ (8) and the Hammett equation, correspondingly:

$$\log (k/k_0) = \log (K_1/K_{1_0}) + \log (k_2/k_{2_0}) = (\rho_1 + \rho_2)\sigma = \rho\sigma \quad (9).$$

Taking into account the fact that the reactions with nucleophiles, where the electron density in the reaction center increases, have a positive ρvalue, [40, 50] (corresponding to ρ_2 in eq. 9) and that the calculated ρvalue is less than -1, one can expect the ρ_1 value to be negative.

In the reactions examined in this manuscript, the influence of the phenyl substituents on K_1 resulted in a ρ_1 value, which seems to be larger than on k_2 , i.e. the effect on protonation seems to be dominating.

The observed negative ρ value may indicate the formation of a positively charged carbenium ion, [41] which permits the nucleophilic attack of the water molecule (scheme I). The existence of such a carbenium ion as the intermediate, in the mechanism of the reactions examined, is indicated by better correlation of log k vs σp^+ rather than log k.vs $\sigma\rho$ [9,10, 34] (Fig. 1 and 2).

The bimolecular mechanism A_2 [14] (equations 6 and 7) appears to obey the linear Hammett equation, as was discussed above. It also seems to indicate that the rate constant k is proportional to the acid concentration (Zucker-Hammett criterion)[54], and to have a calcultated negative value for the entropy of activation $\Delta S^{\neq}$ [45] (Table 4).

The influence of the aglycone on the acid-hydrolysis of the p-substituted α -N-phenyl-D-ribopyranosides can be explained by the basicity of the parent amines. The rate constant $\bar{k}$ of the hydrolysis reactions of the compounds examined increased as the base strength K_b of the parent amine increased.

$\bar{k}$ ↗	$RpNO_2$	< $RpCl$	< R_A	< $RpCH_3$
$10\,K_b$	0.01	0.95	3.8	14.8

The increasing basicity of the corresponding glycosides favours the addition of the proton, resulting in a higher concentration of the protonated intermediate (eq. 6 and 7) as in the methyl-, phenyl- and thioglucopyranosides. [27, 30, 43] for which the rates of hydrolyses increased. The effect of the sugar moiety on the lability of C-N bond in the glycosylnucleoside base compounds, has been explained on the basis of the degree of steric interaction between the base and the 2'and/or 3'-hydroxyl of the sugar moiety.[24, 26, 36] The case of N-aryl-D-pentopyranosylamines seems to be more complicated because of their special behaviour in solution,[14,48] resulting in anomerisation of the compounds being studied during acid-catalyzed hydrolysis reactions.

It has been found experimentally, that the lability of C_1N bond of the compounds examined, increased in the following order

D-xyloside < D-lyxoside < D-riboside > D-arabinoside.

Assuming that the reactivity of N-glycosidic bond increases with the increase of N-glycoside free energy and the behaviour in solution of the N-aryl-D-pentopyranosylamines is similar to that of the D-pentopyranoses, [49] moreover considering that they have the same or similar energy of activation for all the isomers, in the rate limiting step, of the hydrolysis reaction (eq. 7), one can try to express the instability factor in a value of the standard, conformational free energy G° of D-pentopyranoses.[1,2]

For all the possible structures undergoing the hydrolysis reaction, the structure with the highest conformational free energy is more likely, the one hydrolysing by the easiest process, placing the D-pentopyranoses in the following order:

D-xylose < D-lyxose < D-arabinose < D-ribose

The discrepancy with the experimental results can be explained only on the basis of the bimolecular mechanism A 2 (Scheme 1).

The rate constant k of the hydrolysis reaction depends on K_1 and k_2 (eq. 8) and simultaneously on the concentration of the Schiff base intermediate (eq. 10).

$$k_2 = k' \text{(Schiff-base)} \qquad (10)$$

The substituent effect on the rate constant for the hydrolysis of the Schiff-base form according to Willi, Robertson should be small.[52,53]

Thus the concentration of the Schiff-base which depends to a certain degree on the substituent, can be easily explained by the observed relationship of the rate constant k, and the basicity of the amines.

On the other hand, the highest concentration of the Schiff-base intermediate, is expected, in a case of an arabino-compound (in comparison to the other pentoses) because of its high stability in an acyclic zigzag conformation,[31] conditioned by the lack of 1,3 syndiaxial interactions.[49] Such an observation can be the explanation of the previously shown glycoside-order found experimentally.

In proposing the bimolecular mechanism A2 for the acid catalyzed hydrolyses of the N-aryl-D-pentopyranosylamines (Scheme1) we postulate that the faster protonation of the ring oxygen of the sugar rather than the nitrogen in the N-glycoside molecules, has occured. (2a ⇌ 1 ⇌ 2).

In conclusion the mechanism proposed, proceeds with the fast O-protonation (2), opening of the sugar ring with the creation of a Schiff-base intermediate (3), followed by the nucleophilic attack of its mesomeric carbenium ion (4) by a water molecule to liberate the proton and the amine in a rate-determining step, hence creating the aldehyde and the cyclic form of D-pentose.

Footnote:

Abbreviations used: $RpNO_2$, RpCl, $RpCH_3$, RA:

N-(p-nitro, p-chloro, p-methyl) phenyl-D-ribopyranosylamine correspondingly. (X, L, R, A) p-Cl or (X, L, R, A) p-NO_2 :

N-(p-chloro or p-nitro) phenyl-D-(xylo, lyxo, ribo, arabino)pyranosylamine

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