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N-GLUCOSIDES OF AMINOBENZOIC ACIDS AND AMINOPHENOLS

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N-o-, -m-, *and* -p-*carboxyphenyl-D-glucosylamines and N*-o-, -m-, *and* -p-*hydroxyphenyl-D-glucosylamines were synthesized by reaction of D-glucose with* o-, m-, *and* p-*aminobenzoic acids and* o-, m-, *and* p-*aminophenols. It was demonstrated that both* β- *and* α-*anomers were formed by N-glycosylation of* o-, m-, *and* p-*aminobenzoic acids; only* β-*anomers, by N-glycosylation of* o-, m-, *and* p-*aminophenols.*

Key words: N-glucosides, carboxyphenylglucosylamines, hydroxyphenylglucosylamines.

The synthesis and properties of N-glucosides are under intense scrutiny. On one hand, these products play a key role in the formation of melanoidins [1], on the other, N-glucosylation is closely related to the metabolism of biologically active amines and proteins [2, 3]. These amines include also isomeric aminobenzoic acids and aminophenols. Aminophenols are often formed as metabolites of several pesticides. Formation of N-glycosides via direct reaction of unsubstituted monosaccharides with amines of moderate basicity (pKa 1-6) is a convenient method for preparative production of these compounds. We used this method [4-6] to investigate glycosylation of isomeric aminobenzoic acids and isomeric aminophenols. We prepared, isolated, and characterized via reaction of D-glucose with aminobenzoic acids and aminophenols in ethanol (96%) as solvent and glacial acetic acid as catalyst the N-glucosides: N-*o*-carboxyphenyl-D-glucosylamine (**1**), N-*m*-carboxyphenyl-D-glucosylamine (**2**), N-*p*-carboxyphenyl-D-glucosylamine (**3**), N-*o*-hydroxyphenyl-D-glucosylamine (**4**), N-*m*-hydroxyphenyl-D-glucosylamine (**5**), and N-*p*-hydroxyphenyl-D-glucosylamine (**6**).

The basicity of the starting amine is known to have a strong influence on the yield of the desired N-glycoside. The greater the basicity of the amine, the easier the resulting N-glycoside undergoes various conversions (hydrolysis, Amadori—Haynes rearrangement, formation of melanoidins, etc.) [7]. As a result, increasing the basicity of the starting amine decreases the preparative yield of the target N-glycoside. Such a trend was observed in our experiments, in which the pKa values of the amines used in the reactions and the yields of the corresponding N-glucosides were compared (Table 1).

The optimal conditions for the N-glucosylation were selected based on the amine properties. As a result, the target product could be isolated quantitatively from the reaction mixture. Under these conditions in ethanol (96%) using glacial acetic acid as a catalyst, the N-glucosides were obtained in greatest yield from *o*- and *p*-aminobenzoic acids and from *o*- and *m*-aminophenols (Table 1). After appropriate purification, the synthesized N-glucosides were identified by elemental analysis, IR spectra, and ^{13}C NMR spectra.

The analysis of the IR spectra should take into account the fact that most of the N-glycosides have cyclic pyranose because their spectral properties are consistent with the presence of an amine N and a carbohydrate ring and the lack of >C=N [8]. The following frequencies were observed for these N-glucosides: 750-760, 910-930 cm^{-1} (cyclic pyranose), 1010-1030 cm^{-1} (C_1–N stretching vibrations of the anomeric C_1), 1130-1170 cm^{-1} (carbohydrate ring vibrations), 1495-1515 cm^{-1} (absorption of N-glucoside bond), 2850-2950 cm^{-1} (glucose C–H stretching vibrations), 3200-3350 cm^{-1} (glucose O–H stretching vibrations).

We interpreted the ^{13}C NMR spectra taking into account that fact that the hemiacetal of the glucose hydroxyl is aminated in this reaction. Therefore, the substituent has the greatest effect on C_1 if the more electronegative O is replaced by a less electronegative N. Such a substitution increases the electron density on C_1. As a result, it shifts to strong field by 10-15 ppm. Therefore, this signal is easily identified from a group of signals and is located in the range 80-85 ppm. This resonant frequency of C_1 can be used as a specific indicator of C_1–N bond formation (N-glycoside formation).

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TABLE 1. Yields and Properties of Synthesized N-Glucosylamines

Compound	Yield, %	mp, °C	pKa of starting amine
1. N-*o*-carboxyphenyl-D-glucosylamine	~ 90	124-125	2.11
2. N-*m*-carboxyphenyl-D-glucosylamine	~75	113-114	3.12
3. N-*p*-carboxyphenyl-D-glucosylamine	~90	126-127	2.41
4. N-*o*-hydroxyphenyl-D-glucosylamine	~60	115-118	4.72
5. N-*m*-hydroxyphenyl-D-glucosylamine	~72	87-88	7.17
6. N-*p*-hydroxyphenyl-D-glucosylamine	~55	92	5.17

TABLE 2. Chemical Shifts (ppm) in ^{13}C NMR Spectra of Synthesized Phenyl-D-Glucosylamines

Atom	Compouns									
	1		**2**		**3**		**4**	**5**	**6**	
	β	α	β	α	β	α	β	β	β	α
Carbohydrate part										
C-1	83.4	81.37	84.93	82.40	84.08	81.59	85.8	85.19	82.98	81.34
C-2	73.51	73.07	73.12	74.89	73.02	71.81	73.13	73.09	75.7	
C-3	76.74	73.87	77.43	73.37	77.51	73.3	77.48	77.26	76.29	
C-4	70.1	70.25	70.16	70.35	70.12	70.56	70.35	70.15	70.5	
C-5	77.54	72.35	77.75	71.12	77.74	70.96	77.49	77.68	77.2	
C-6	61.21	60.84	60.94	61.28	60.93	61.94	60.99	60.93	63.31	63.03
Aromatic nucleus										
C-1′	149.75	149.86	147.49	147.78	151.6	151.5	135.7	148.6	142.05	
C-2′	111.1	111.5	114.1	114.5	112.6	112.3	144.1	100.25	115.6	
C-3′	131.28		131.3		131.3	131.0	112.1	157.0	113.7	113.8
C-4′	113.2	113.5	118.1	118.3	118.6		117.15	103.3	148.5	
C-5′	134.3		117.18	116.7	131.3	131.0	119.6	129.4	113.7	113.8
C-6′	116.1		129.0		112.6	112.3	13.65	104.6	115.6	
COOH	169.7	169.6	167.9		167.6					
Ratio of β- and α-anomers										
%	60.87	39.13	81.1	18.9	86.67	13.33	100	100	100	

Spectra of N-*o*-, -*m*-, and -*p*-carboxyphenyl-D-glucosylamines (**1**, **2**, and **3**, respectively) were separated into three principal ranges, of which C atoms bound to primary and secondary alcohols of the glucose resonate at strongest field. C atoms bound to two electronegative atoms (O–C–N) resonate at weakest field. The chemical shift of the β-conformer of any monosaccharide (except mannose) is known to be greater than that of the α-conformer [9-12]. Therefore, the signal located at 80-85 ppm at comparatively weak field belongs to the β-anomer of glucose; the signals located at comparatively strong field, to the α-anomer. Table 2 gives the ratios of β- and α-anomers calculated taking into account the duration of the reaction of the anomeric C and the strength of the signal and the assignments of the glucose C atoms in addition to the C atoms of the *o*-, *m*-, and *p*-aminobenzoic acids and *o*-, *m*-, and *p*-aminophenols of N-glucosides. Among the remaining signals, that of the C-5 ring defining the configuration of the glucose, the chemical shift of which is ~77 ppm for all glucose β-conformers, should be noted.

Compounds **4**-**6** were prepared by reaction of *o*-, *m*-, and *p*-aminophenols with glucose. They differ from **1**-**3** mainly in that exclusively the β-conformers are formed in the first instance.

EXPERIMENTAL

IR spectra were recorded on a Specord 75 IR spectrophotometer in KBr; ^{13}C NMR spectra, on a Bruker WM-250 MHz instrument. The standard was $(CD_3)_2SO$ with a shift of the central signal at 39.505 ppm for complete C–H decoupling. The sample size was 30 mg. Spectra were recorded at 60°C. Melting points were determined in a Kofler apparatus. The rate of temperature rise near the melting point was 4° per minute.

Synthesis of Carboxyphenyl- and Hydroxyphenyl-D-glucosylamines. A mixture of D-glucose (0.01 mol); *o*-, *m*-, *p*-aminobenzoic acid or *o*-, *m*-, *p*-aminophenol (0.0107 mol); ethanol (15 mL, 96%), water (0.5 mL), and glacial acetic acid (0.3 mL) was heated on a boiling-water bath with stirring until the starting materials dissolved completely. The mixture was cooled to room temperature, treated with diethylether (50 mL), stirred, and left overnight. The resulting crystalline precipitate was filtered off, ground with ethanol (96%), and treated with diethylether. After thorough mixing, the precipitate was filtered off. The resulting N-glucoside was purified by reprecipitation from alcoholic solution by diethylether. The purity of the compounds was monitored using TLC on Silufol UV-254 plates (dioxane:benzene, 1:4 for aminobenzoic acids; benzene:ethanol, 9:1 for aminophenols; $CHCl_3$:CH_3OH, 19:5 for glucose). Sugar was developed by alkaline $KMnO_4$ and sodium metaperiodate; aminobenzoic acids and aminophenols, by alchoholic 4-dimethylaminobenzaldehyde.

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