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Synthesis and characterization of bis(glycosylamino)benzenes based on reducing disaccharides*

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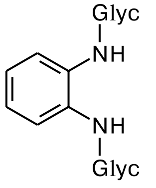
Synthesis of bis(glycosylamino)benzenes, derived from disaccharides lactose, maltose, and cellobiose, by direct condensation and their characterization are described.

Key words: bis(glycosylamino)benzenes, *N*-glycosylation, reducing disaccharides, *o*-, *m*-, and *p*-phenylenediamines, NMR spectroscopy, IR spectroscopy, chelation.

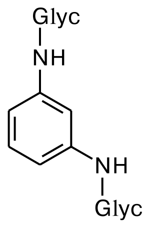
Glycosylamines belong to *N*-glycosides and are of interest for the food, textile, and rubber-processing industry.[1] Studies of properties of these carbohydrate derivatives will help understanding of the fundamental aspects of carbohydrate chemistry. Hence, investigations into chemistry of glycosylamines are of importance for the development of both basic and applied aspects of science.

To extend the array of *N*-glycosides, we synthesized and characterized bisglycosylamine derivatives **1—9**, in which *o*-, *m*-, or *p*-phenylenediamine residues serve as the aglycones, and the disaccharides lactose (compounds **1**, **4**, and **7**), maltose (**2**, **5**, and **8**), and cellobiose (**3**, **6**, and **9**) represent the glycosidic moieties.

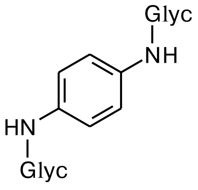
Compounds **1—9** were synthesized by direct condensation of diamines with carbohydrates in a molar ratio of 1 : 2. Taking into account poor solubilities of disaccharides in alcohols that are often used as solvents in glycosylation of amines[2—4] and lower reactivities of disaccharides in reactions with amines compared to monosaccharides,[5] the reactions were carried out in the absence of a solvent with heating and distillation of water. The rate of formation of bis(glycosylamino)benzenes **1—9** depends on steric factors, in particular, on the mutual arrangement of the amino groups in the phenylenediamine molecules. For example, bisglycosylation of *o*-phenylenediamine is completed in 6—8 h (depending on the disaccharide used), whereas the reactions with *m*- and *p*-phenylenediamines take, on the average, 3.5—4.5 h. Interestingly, glycosylation of *o*-phenylenediamine with monosaccharides in an ethanolic medium, on the contrary, occurs more rapidly than the reactions with *m*- and *p*-phenylenediamines. This difference can be attributed to the fact that the formation of 1,2-bis(glycosylamino)benzenes from monosaccharides occurs apparently *via* cyclic five-membered aminal,** unlike glycosylation of *m*- and *p*-phenylenediamines, which occurs *via* Schiff bases.[1] Apparently, the reactions of *o*-phenylenediamine with disaccharides as the glycosylating agents proceed by a standard mechanism, *i.e.*, *via* Schiff bases.[1]



1—3

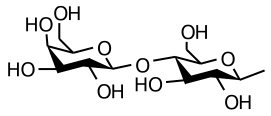


4—6

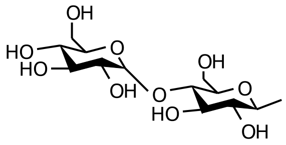


7—9

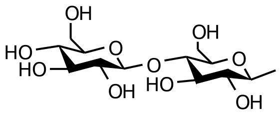
Glyc =



(**1**, **4**, **7**),



(**2**, **5**, **8**),



(**3**, **6**, **9**)

The composition and structures of the target products were confirmed by ^{13}C and ^{1}H NMR and IR spectroscopy. The ^{1}H NMR spectra of lactosylamines **1**, **4**, and **7**

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Table 1. Chemical shifts in the ^{1}H NMR spectra (δ) and the coupling constants (*J*/Hz) of compounds **1**, **4**, and **7** (DMSO-d$_6$)

Compound	Aglycone	Carbohydrate fragment				
		NH (d)	H(1) (t)	H(1′) (d)	H(2)—H(6) (H(6′)	OH
1	6.61 (2 H, HC(3), HC(6), $J = 6.0$); 6.71 (2 H, HC(4), HC(5), $J = 6.2$)	5.21 ($J = 9.0$)	4.35 ($J = 8.5$)	4.17 ($J = 6.5$)	3.28—3.73	4.39—5.08
4	5.66 (1 H, HC(2)); 5.82 (2 H, HC(4), HC(6)); 6.72 (1 H, HC(5))	5.45 ($J = 8.8$)	4.33 ($J = 8.2$)	4.24 ($J = 6.7$)	3.29—3.75	4.35—5.45
7	6.56 (4 H, HC(2), HC(3), HC(5), HC(6))	5.45 ($J = 8.8$)	4.32 ($J = 8.2$)	4.24 ($J = 6.7$)	3.28—3.73	4.35—5.45

(Table 1) contain signals for protons of the aromatic system and signals for protons of the disaccharide fragments. The assignment of the signals to the NH protons in molecule **1** and the anomeric protons of the disaccharide moiety was made using the COSY and HSQC techniques. The characteristic coupling constant $J_{1,2}$ = 8.2—8.5 Hz is indicative of the β configuration of the *N*-glycosidic bonds in the compounds synthesized. In the ^{13}C NMR spectra (Table 2), the assignment of the signals for all carbon atoms could be made. The signals for the anomeric carbon atoms of the *N*-glycosidic moieties of the disaccharide fragments are observed at δ 85—86, which also provides evidence for the β configuration of the glycosidic bonds.[1] The anomeric carbon atoms of the *O*-glycosidic fragments of the disaccharide residues are observed at *ca.* δ 101 (the maltose derivatives **2**, **5**, and **8**) and *ca.* δ 103 (the lactose and cellobiose derivatives).

The IR spectra of the resulting compounds have a broad band in the region 3550—3000 cm^{-1} (s) characteristic of OH and NH stretching vibrations as well as of CH stretching vibrations of the aromatic system. The position of this band is virtually independent of the nature of disaccharide. The characteristic bands at 1500—1390 and 1390—1290 cm^{-1} (s) correspond to OH bending vibrations of the disaccharide fragments. The intensity of the band at 1650—1565 cm^{-1} (s) corresponding to NH bending vibrations is very high due apparently to overlap of this band with variable-intensity bands corresponding to vibrations of the benzene ring. In the region 1200—985 cm^{-1}, C—O stretching bands are observed.

In spite of the fact that bis(glycosylamino)benzenes were synthesized using vacuum distillation of water that formed during condensation, compounds **1—9** were obtained as hydrates of various compositions. The amount of constitutional water was determined by Fischer titration, which demonstrated that these contain 1, 1.5, or 2 moles of water per mole of bis(glycosylamino)benzene. Drying of the hydrates for a long period did not afford anhydrous *N*-glycosides due apparently to the fact that water is involved in a stable chelate structure. Hydrate water can be removed by azeotropic distillation with benzene from solutions of *N*-glycoside hydrates in DMF. In our opinion, constitutional water is responsible for instability of bis(glycosylamino)benzenes during their heating or storage. For example, storage of compound **1** in DMSO-d$_6$ for 30 h led to its partial (20%) decomposition to give 2-[4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosylamino]aniline. The presence of the latter compound is evident from the characteristic signals in the ^{13}C NMR spectrum at δ 133.8 ($\underline{C}_{arom}$—NH—Glyc) and 136.2

Table 2. Chemical shifts in the ^{13}C NMR spectra (δ) of compounds **1—9** (DMSO-d$_6$)

Compound	Aglycone						Carbohydrate fragment											
							N-Glycosidic fragment						*O*-Glycosidic fragment					
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
1	135.0	135.0	113.2	119.0	119.0	113.2	85.4	70.7	73.3	81.1	75.4*	60.6	103.9	70.7	73.0	68.3	75.6*	60.6
2	135.1	135.1	113.3	119.2	119.2	113.3	85.6	73.5	76.9	79.9	75.8	61.0*	100.9	72.7	73.0	70.1	72.7	60.7*
3	136.1	136.1	113.2	118.9	118.9	113.2	85.7	72.9	73.4	80.7	75.4	61.1*	103.2	72.9	76.5	69.9	76.8	60.6*
4	147.9	99.2	147.9	102.0	129.1	102.0	85.1	71.4	74.5	81.0	74.7	60.5	103.8	69.8	72.1	69.0	75.9	60.5
5	147.7	99.6	147.7	102.4	129.4	102.4	85.4	74.9	75.7	81.3	75.1	60.3	100.9	70.0	72.5	68.6	71.8	60.3
6	147.8	98.3	147.8	103.9	128.9	103.9	85.0	70.6	73.3	80.9	75.5*	60.5	103.4	72.8	75.2	68.2	75.9*	60.5
7	139.0	114.4	114.4	139.0	114.4	114.4	86.2	70.6	73.2	81.0	75.8*	60.4	103.8	70.6	72.9	68.2	75.5*	60.4
8	139.8	113.9	113.9	139.8	113.9	113.9	85.8	75.2	75.9	81.6	75.4	60.5	100.8	70.4	72.7	68.3	72.1	60.5
9	139.5	114.2	114.2	139.5	114.2	114.2	86.3	70.8	73.0	81.3	75.7*	60.8	103.5	72.5	75.1	68.4	76.2*	60.8

* The assignment to the *N*- or *O*-fragments can be reverse.

Table 3. IR spectroscopic data for compounds **1**—**9** (ν/cm^{-1})

Compound	ν(OH, NH, CH_{arom})	ν(C=C)	δ(NH)	δ(C=C)	δ(OH)	ν(C—O)	ν(CH_{arom})
1	3300	1650	1600	1520	1435, 1360	1030	710
2	3300	1655	1600	1525	1430, 1360	1035	710
3	3350	1670	1600	1520	1440, 1365	1050	750
4	3300	1650	1590	1520	1445, 1365	1050	750
5	3350	1670	1600	1520	1445, 1360	1050	755
6	3350	1670	1600	1520	1440, 1360	1045	750
7	3350	1670	1605	1525	1440, 1360	1055	750
8	3350	1670	1600	1525	1445, 1360	1050	750
9	3350	1675	1600	1525	1400, 1360	1055	750

Table 4. Reaction time, yields, melting points, and elemental analysis data for compounds **1**—**9**

Compound	τ/h	Yield (%)	M.p./°C (decomp.)	Found / Calculated (%)			Molecular formula
				C	H	N	
1	6.5	86	199—201	45.78	6.56	3.60	$C_{30}H_{48}N_2O_{20} \cdot 2H_2O$
				45.45	6.61	3.53	
2	6	89	190—193	46.12	6.58	3.65	$C_{30}H_{48}N_2O_{20} \cdot H_2O$
				46.51	6.51	3.62	
3	8	86	203—205	46.21	6.61	3.60	$C_{30}H_{48}N_2O_{20} \cdot 1.5H_2O$
				45.98	6.56	3.57	
4	4	92	197—198	46.00	6.53	3.65	$C_{30}H_{48}N_2O_{20} \cdot H_2O$
				46.51	6.51	3.62	
5	3.5	85	198—200	46.85	6.64	3.60	$C_{30}H_{48}N_2O_{20} \cdot 1.5H_2O$
				45.98	6.56	3.57	
6	4.5	90	212—215	46.32	6.42	3.49	$C_{30}H_{48}N_2O_{20} \cdot H_2O$
				46.51	6.51	3.62	
7	4	85	190—193	46.58	6.68	3.49	$C_{30}H_{48}N_2O_{20} \cdot H_2O$
				46.51	6.51	3.62	
8	3.5	83	183—185	46.38	6.42	3.57	$C_{30}H_{48}N_2O_{20} \cdot H_2O$
				46.51	6.51	3.62	
9	4.5	90	209—211	46.44	6.48	3.56	$C_{30}H_{48}N_2O_{20} \cdot H_2O$
				46.51	6.51	3.62	

($\underline{C}_{arom}$—NH_2) and the signals at δ 113.5, 114.8, 117.6, and 119.2 characteristic of $C_{arom}(3)$—$C_{arom}(5)$. The second hydrolysis product, *viz.*, lactose, is easily identified from the characteristic signals in the ^{13}C NMR spectra (at δ 92.4 and 96.8 for the α- and β-anomeric forms of the disaccharide).

Interestingly, disaccharide-based bis(glycosylamino)benzenes, unlike monosaccharide analogs, are much less prone to anomerization of the *N*-glycosidic fragment, which may be associated with steric factors.*

Compounds **1**—**9** are readily soluble in DMF, DMSO, and $O=P(NEt_2)_3$, whereas dissolution of these compounds in water leads to their complete hydrolysis. Solutions of compounds **1**—**9** in pyridine and DMF are rapidly transformed from the liquid to the solid state, which resembles the properties of monosaccharide-based bis(glycosylamino)benzenes. We relate this transformation to chelation of the solvents with bis-*N*-glycosides. The chelation of pyridine with 1,2-bis(β-D-mannosylamino)benzene was confirmed by the formation of the 1 : 3 (Py : *N*-glycoside) complex.* Apparently, compounds **1**—**9** can also chelate molecules of certain compounds to form inclusion compounds.

Experimental

The ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer operating at 50 MHz with Me_4Si as the internal standard. The ^1H NMR spectra of compounds **1**, **4**, and **7** were

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* Unpublished data.

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measured on Bruker DRX-500 (500 MHz) and Bruker WM-250 (250 MHz) spectrometers with Me_4Si as the internal standard.

The IR spectra were recorded on a Specord IR-75 instrument in Nujol mulls using NaCl plates.

Preparation of bis(glycosylamino)benzenes 1—9 (general procedure). A mixture of lactose or maltose monohydrate (5 g, 13.89 mmol) or anhydrous cellobiose (14.6 mmol) and phenylenediamine (0.75 g, 6.93 mmol) was dissolved in water (3 mL). Then water was distilled off at 20 Torr and 45—50 °C for 1 h. The solid residue was heated at 90—100 °C (20 Torr) for 3.5—8 h. The mixture was triturated with methanol. The white precipitate was filtered off, washed with warm methanol, and dried *in vacuo*. The spectroscopic characteristics of compounds **1**—**9** are given in Tables 1—3. The yields, melting points, and elemental analysis data are listed in Table 4.

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