Preparation of some glycosyl derivatives of nitromethane

L. PETRUŠ, S. BYSTRICKÝ, T. STICZAY, and V. BÍLIK

Institute of Chemistry, Slovak Academy of Sciences,
842 38 Bratislava

Received 20 May 1981

Nitroalditols formed in the nitromethane synthesis with lactose, cellobiose, maltose, D-glucose, and D-galactose were converted to the corresponding glycosyl derivatives of nitromethane by intramolecular dehydration. β-Lactosylnitromethane, β-cellobiosylnitromethane, β-maltosylnitromethane, β-D-glucopyranosylnitromethane, and β-D-galactopyranosylnitromethane were isolated from the reaction mixtures as salts of a strongly basic anion exchanger in the OH cycle, from which they were liberated by carbon dioxide. Circular dichroism spectra of both disaccharide and monosaccharide glycosylnitromethanes confirmed their β-pyranoid structure.

Путем нитрометанового синтеза из лактозы, целлобиозы, мальтозы, D-глюкозы, и D-галактозы возникшие нитроальдитолы были интрамолекулярной дегидратацией превращены в соответствующие гликозилпроизводные нитрометана. β-Лактозилнитрометан, β-целлобиозилнитрометан, β-мальтозилнитрометан, β-D-глюкопиранозилнитрометан и β-D-галактопиранозилнитрометан были изолированы из реакционных смесей в виде солей с сильноосновным анексом в OH-цикле, из которого были освобождены с помощью двуокиси углерода. Корреляция полученных спектральных параметров кругового дихроизма дисахаридных и моносахаридных гликозилнитрометанов подтверждает их одинаковую β-пираноидную структуру.

The reaction of aldoses with nitromethane leads to acyclic 1-deoxy-1-nitroalditols which can be used for various purposes in carbohydrate chemistry. The 1-deoxy-1-nitroalditols give on intramolecular dehydration 2,6- and/or 2,5-anhydro derivatives, *i.e.* glycopyranosyl- and/or glycofuranosylnitromethanes. It is known that the reaction finally leads always to identical mixture of glycosyl derivatives of nitromethane regardless of the epimeric 1-deoxy-1-nitroalditol used as the starting compound [1]. From this one has inferred that 1,2-dideoxy-1-en-1-nitroalditol is the reaction intermediate which is immediately transformed to a mixture of cyclic isomeric glycosylnitromethanes, of which the pyranoid derivative having the bulky nitromethyl group in the equatorial position predominates [1, 2]. This route was used for preparation of the corresponding glycosylnitromethanes from a series of

monosaccharides [1—4]. In the present paper we describe application of the nitromethane synthesis to preparation of glycosylnitromethanes of (1 → 4) disaccharides and chiroptical properties of glycosylnitromethanes derived from mono- and disaccharides in a relation to the present stage of knowledge.

Sodium salts of the epimeric 5-*O*-β-D-galactopyranosyl-1-deoxy-1-nitroalditols obtained by nitromethane synthesis with lactose were deionized with a mixture of a cation exchanger and grounded solid carbon dioxide, and then, by heating in aqueous solution, converted to a cyclic lactose derivative, β-lactosylnitromethane (5-*O*-β-D-galactopyranosyl-2,6-anhydro-1-deoxy-1-nitro-D-*glycero*-D-guloheptitol). Isolation of the product from the reaction mixture containing also the starting disaccharide was done by binding β-lactosylnitromethane to a strongly basic anex in the OH cycle (nitrosaccharide pK_a values vary in the range 8.8—9.2 [2]). The ion exchanger was first washed with water to remove the starting lactose. Recycling to the HCO_3 cycle by excess of carbon dioxide liberated β-lactosylnitromethane (*I*) which was finally obtained in 37% yield. A similar procedure gave 34% of β-cellobiosylnitromethane (*II*) from cellobiose, 35% of β-maltosylnitromethane (*III*) from maltose, 53% of β-D-glucopyranosylnitromethane (*IV*) from D-glucose, and 62% of β-D-galactopyranosylnitromethane (*V*) from D-galactose. Preparative paper chromatography of the monosaccharide reaction mixtures followed by crystallization of the eluates afforded low amounts of additional isomeric glycosylnitromethanes (α-D-glucopyranosyl-, α-D-glucofuranosyl-, and β-D-glucofuranosylnitromethane from D-glucose, and α-D-galactopyranosyl-, α-D-galactofuranosyl-, and β-D-galactofuranosylnitromethane from D-galactose).

Stability of the products of nitromethane synthesis depends on structure of the starting aldose. The reaction mixtures generally contain preferably the epimeric alditol having the 2,4-*threo* configuration of hydroxyl groups (the Maltby rule). The epimer having the 2,4-*erythro* configuration of hydroxyl groups is, due to an interaction of these groups, less stable and, consequently, its yield is lower. In all saccharides tested here, D-glucose formed the reducing end unit. Therefore, for instance, lactose gave a mixture of 5-*O*-β-D-galactopyranosyl-1-deoxy-1-nitro-D-*glycero*-D-guloheptitol and 5-*O*-β-D-galactopyranosyl-1-deoxy-1-nitro-D--*glycero*-D-idoheptitol. The substitution of hydrogen of the C-5 hydroxyl group by the bulky glycosyl group in these nitroalditols causes a further decrease in stability, in a comparison to the unsubstituted derivatives prepared from D-glucose. All these factors contribute to reduction of yields of the nitromethane synthesis and accelerate decomposition of products to nitromethane and starting aldose. For these reasons the deionization of sodium salts of nitroalditols prepared from disaccharides was carried out in water saturated with carbon dioxide which immediately eliminated the alkalinity of solution. This step substantially increased the reaction yields (from 10—15% to 34—37%).

The mixtures of epimeric acyclic nitroalditols obtained from disaccharides

were then converted by intramolecular dehydration to 5-*O*-substituted 2,6-anhydro-1-deoxy-1-nitroalditols, *i.e.* glycosylnitromethanes. A removal of the starting saccharide from the reaction mixture prior this step is not reasonable because the elimination of water is accompanied by liberation of nitromethane from the acyclic nitroalditols affording additional amount of aldose. This was demonstrated during preparation of β-lactosylnitomethane from a mixture of pure nitroalditols. The β-derivative of lactose highly predominates in the final reaction mixture, while the α-derivative is formed in trace amounts only. The same situation occurs in the case of preparation of glycosylnitromethanes from cellobiose and maltose. The absence of larger amounts of α-derivatives may be due to the fact that the bulky nitromethyl group preferably occupies the equatorial position and the eventually formed α-derivative is *via* intermediary 1,2-dideoxy-1-en-1-nitroalditol converted to stable β-derivative. Contrary to the nitromethanes of monosaccharides existing in glycopyranosyl (2,6-anhydro ring) and glycofuranosyl (2,5-anhydro ring) forms, (1 → 4) disaccharides, due to 5-*O*-substitution of 1-deoxy-1-nitroalditols, can form only the glycopyranosylnitromethanes.

The nitro group linked to a saccharide enables to measure circular dichroism spectra giving information on structure of the molecule in the vicinity of the chromophore. Reports dealing with the chiroptical properties of 1-deoxy-1-nitroalditols [5, 6] pointed to a relation between signs of the Cotton effects and the absolute configuration of the asymmetric carbon atom adjacent to the nitromethyl group. A rule has been established according to which 1-deoxy-1-nitroalditols having the *S* configuration at C-2 exhibit in the long wavelength spectral region positive Cotton effects and the derivatives having the *R* configuration at C-2 negative Cotton effects.

The prepared disaccharide and monosaccharide β-glycopyranosylnitromethanes (*I*—*V*) as well as 1-deoxy-1-nitro-D-*glycero*-D-guloheptitol (*VI*), 1-deoxy-1-nitro-D-*glycero*-D-idoheptitol (*VII*), 1-deoxy-1-nitro-D-*glycero*-L-mannoheptitol (*VIII*), 1-deoxy-1-nitro-D-*glycero*-L-glucoheptitol (*IX*), the intermediates of the monosaccharides *IV* and *V*, were studied by circular dichroism (CD) and u.v. spectroscopy (Table 1). In the available region of measurements (lower limit 190 nm), three Cotton effects were observed. The first dichroic band in the long wavelength spectral region appearing at 310 nm as a shoulder on the second band, was not observed in the u.v. spectra. The second characteristic band with maximum at 275—280 nm has the same sign as the first band and in the CD spectra of nitro derivatives is assigned to the $n \rightarrow \pi^*$ electron transition. In u.v. spectrum this band appears as a shoulder on the third, by one order more intensive band. The third band in the CD spectra having maximum around 210 nm, being the most intensive band, has not been described yet. Its sign is opposite to the signs of the two former bands. Its intensity is the highest with acyclic forms where it attains a triple intensity of the band corresponding to the $n \rightarrow \pi^*$ transition (Table 1). Based

on its intensity (log $\varepsilon \sim 3.5$) the third band can be assigned to the $\pi \rightarrow \pi^*$ transition of the nitro group.

Nitro derivatives *IV* and *VI* (Fig. 1) have the same absolute configuration (*S*) on the asymmetric carbon atom adjacent to the chromophore. Their CD spectra show Cotton effects of the same sign. Qualitatively the same CD spectrum is also exhibited by compound *V* (Table 1) which has the *S* configuration on the closest

Table 1

UV and CD data of nitrosaccharides

No.	Compound	UV		CD		AC
		λ_{max}	log ε	λ_{max}	$\Delta\varepsilon$	
				Glycosylnitromethane		
I	β-Lactosyl-			310	+0.15	*S*
		271 sh	1.68	275	+0.50	
		199	3.64	208 sh	−0.59	
II	β-Cellobiosyl-			310	+0.16	*S*
		268 sh	1.68	274	+0.50	
		200	3.73	210 sh	−0.60	
III	β-Maltosyl-			310	+0.14	*S*
		270 sh	1.78	274	+0.62	
		199	3.71	210 sh	−0.61	
IV	β-D-Glucopyranosyl-			310	+0.27	*S*
		268 sh	1.63	275	+0.59	
		199	3.71	212 sh	−0.91	
V	β-D-Galactopyranosyl-			310	+0.27	*S*
		268 sh	1.66	275	+0.56	
		199	3.64	212 sh	−0.93	
				1-Deoxy-1-nitro-heptitol		
VI	-D-*glycero*-D-gulo-			310	+0.47	*S*
		269 sh	1.75	281	+0.59	
		200	3.67	208	−1.97	
VII	-D-*glycero*-D-ido-			310	−0.44	*R*
		267 sh	1.79	282	−0.52	
		200	3.74	208	+1.77	
VIII	-D-*glycero*-L-manno-			310	+0.46	*S*
		268 sh	1.79	280	+0.63	
		201	3.67	208	−2.02	
IX	-D-*glycero*-L-gluco-			310	−0.46	*R*
		270 sh	1.74	284	−0.52	
		201	3.73	208	+1.62	

AC — Absolute configuration of the asymmetric carbon atom adjacent to the chromophore; sh — shoulder.

asymmetric centre but differs only in the configuration at C-4 of the glycosyl residue. From the above said it follows that the configuration at C-4 of β-glycopyranosylnitromethanes derived from D-glucose or D-galactose does not

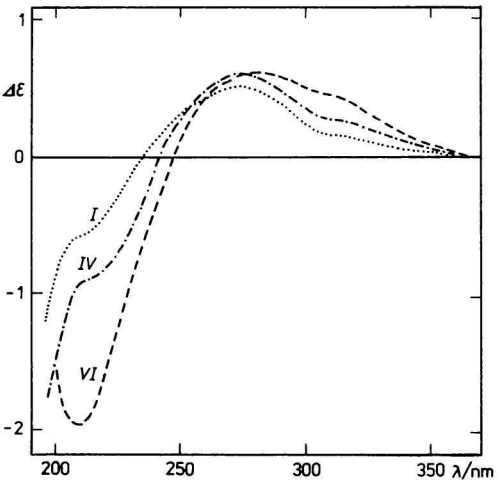

Fig. 1. Circular dichroism spectra of β-lactosylnitromethane (*I*), β-D-glucopyranosylnitromethane (*IV*), and 1-deoxy-1-nitro-D-*glycero*-D-guloheptitol (*VI*).

influence significantly their chiroptical properties. The CD spectra of nitro derivatives derived from (1 → 4)-linked disaccharides containing D-glucose in the reducing part (*I*—*III*) exhibit the same Cotton effects as the CD spectra of compounds *IV* and *V* (Fig. 1, Table 1). This served as an evidence that the nitro derivatives *I*—*III* have also the asymmetric centre adjacent to the chromophore in the *S* configuration, *i.e.* all studied cyclic nitro derivatives are β-glycopyranosylnitromethanes. (This information could not be obtained from 80 MHz ^{1}H-n.m.r. spectra.) The above chiroptical data of β-glycopyranosylnitromethanes, especially the signs of the Cotton effects corresponding to the $n \rightarrow \pi^*$ transition (Table 1), are in a consonance with the Satoh rule established for 1-deoxy-1-nitroalditols [5, 6]. Hence, the rule can be applied also to β-pyranoid structures of glycosylnitromethanes.

The spectra of cyclic nitrosaccharides *I*—*V* differ from the spectra of acyclic derivatives *VI*—*IX* in a lower intensity of the long wavelength dichroic band at 310 nm and of the band at 210 nm, assigned to the $\pi \rightarrow \pi^*$ transition. The decrease in band intensities is more pronounced with disaccharide derivatives *I*—*III*. Reduction of the intensity of the short wavelength dichroic band obviously leads to a shift of the maxima of the overlapping dichroic bands of opposite signs corresponding to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electron transitions, so the bands are drawn closer one to another.

Experimental

Specific rotations were measured on a Perkin—Elmer polarimeter, type 141 and melting points on a Kofler stage. Elemental analysis was carried out with a Perkin—Elmer analyzer, type 240. Composition of the reaction mixtures and purity of isolated saccharides was examined by paper chromatography in the solvent system 1-butanol—ethanol—water 5:1:4 (v/v). Compounds were visualized under u.v. light and with anilinium hydrogen phthalate and sodium periodate. Relative mobilities of nitrosaccharides were referred to that of starting aldoses (R_{Glc}, R_{Lac}, *etc.*). Circular dichroism spectra were measured with a Jobin Yvon Dichrograph III (0.5 and 5 mm cells) and u.v. spectra with a Beckman DB-GT equipment (1 and 5 mm cells), in both cases in aqueous solutions bubbled with nitrogen, at a saccharide concentration of 0.4—0.8 mg cm^{-3} and room temperature. 1-Deoxy-1-nitroheptitols (-D-*glycero*-D-gulo-, -D-*glycero*-D-ido-, -D-*glycero*-L-manno-, and -D-*glycero*-L-gluco-) were prepared as described [2, 7].

β-Lactosylnitromethane (I)

A. A solution of lactose (20 g) in dimethyl sulfoxide (80 cm^3) was mixed with methanol (40 cm^3), nitromethane (20 cm^3) and sodium methoxide solution (2.5 g of sodium in 150 cm^3 of methanol), and stirred for 24 h at room temperature. After addition of 1-butanol (100 cm^3) and stirring, the mixture was filtered to collect the crystalline product which, after being washed with cold methanol (2×50 cm^3), was transferred to a mixture of water (100 cm^3), a cation exchanger in the H form (150 g), and crushed solid carbon dioxide (*ca.* 50 g), under stirring. The ion exchanger was filtered off, washed with water (3×100 cm^3) and the filtrate and the washings passed through a column (30×2 cm) of a catex in the H form. The column eluate was concentrated to about one third of its volume (*ca.* 150 cm^3) and heated at 100°C for 30 h. After treatment with activated charcoal (0.5 g) and filtration, the solution was poured on a strongly basic anion exchanger in the OH form (Dowex 1 X-4, 297—149 μm, 150 g) and left to stand under occasional stirring for 1 h. The anex was filtered off and washed with water (1000 cm^3). The filtrate and washings were evaporated to give a portion of the starting lactose (*ca.* 9 g). The washed anex was poured into water (100 cm^3) and crushed solid carbon dioxide (100 g) was added by portions under stirring and heating (20°C) to prevent freezing of the mixture. The anex was finally filtered off, washed with water (3×100 cm^3) and the combined filtrates evaporated under reduced pressure to a sirupy β-lactosylnitromethane (8.4 g, 37%) which was crystallized from methanol—chloroform 3:1 (R_{Lac} 3.01). Recrystallization from methanol—acetone 5:1 and drying (70°C, 1 h) gave product having m.p. 174—175°C and $[\alpha]_D^{20} = +27 \pm 0.5°$ (*c* 2, water).

For $C_{13}H_{23}O_{12}$ calculated: 40.52% C, 6.02% H, 3.64% N; found: 40.41% C, 6.27% H, 3.53% N. Chromatography of the mother liquor showed the presence of the other isomer, α-lactosylnitromethane (R_{Lac} 2.69).

B. The sirupy residue (9 g) obtained after the nitromethane synthesis with lactose (10 g), deionization and evaporation of the filtrate, was fractionated on a column (90×2.5 cm) of

Dowex 1 X-8, 149—74 μm, in the acetate form, eluted with water at a rate of 40 $cm^3 h^{-1}$. Fraction *1* contained lactose (1.8 g, 95—130 cm^3), fraction *2* a mixture of lactose and nonreducing saccharides (2.6 g, 130—160 cm^3), and fraction *3* nonreducing saccharides (R_{Lac} 1.86 and 2.00, 4.4 g, 160—320 cm^3). Fraction *3* was concentrated to one fourth of its volume (*ca.* 40 cm^3), heated at 100°C for 30 h and further processed as described in Part *A* to give β-lactosylnitromethane (3.1 g, 27%) and a portion of the starting lactose (0.9 g).

β-Cellobiosylnitromethane (II)

The procedure *A* for the preparation of β-lactosylnitromethane applied to cellobiose (5 g) afforded β-cellobiosylnitromethane sirup (1.9 g, 34%, R_{Cel} 3.13) which after crystallization from a mixture methanol—acetone 3:1 and drying had m.p. 239—240°C and $[\alpha]_D^{20} = +2.1 \pm 0.2°$ (*c* 2, water).

For $C_{13}H_{23}O_{12}$ found: 40.33% C, 6.21% H, 3.46% N. Traces of α-cellobiosylnitromethane (R_{Cel} 2.65) were present in the mother liquor.

β-Maltosylnitromethane (III)

The procedure *A* carried out with maltose (20 g) gave β-maltosylnitromethane (7.9 g, 35%, R_{Mal} 2.96) containing traces of the α isomer (R_{Mal} 2.64). The β isomer was purified by chromatography on Whatman No. 3 paper (elution for 65 h at room temperature). Its zone on the chromatograms, localized under u.v. light, was eluted with methanol, the eluate evaporated and dried *in vacuo* over P_2O_5 (72 h) to give amorphous β-maltosylnitromethane, $[\alpha]_D^{20} = +109 \pm 0.5°$ (*c* 2, water).

For $C_{13}H_{23}O_{12}$ found: 40.18% C, 6.30% H, 3.48% N.

β-D-Glucopyranosylnitromethane (IV)

D-Glucose (50 g) was dissolved in a mixture of dimethyl sulfoxide (200 cm^3) and methanol (100 cm^3) and treated with nitromethane in the presence of sodium methoxide (100 cm^3 of nitromethane, 12.5 g of sodium in 350 cm^3 of methanol). The reaction mixture was then processed according to the procedure *A* to give crude sirupy β-D-glucopyranosylnitromethane (33 g, 53%, R_{Glc} 3.07) containing low amounts of other three isomeric D-glucosylnitromethanes. Crystallization and recrystallization from methanol gave β-D-glucopyranosylnitromethane, m.p. 175—176°C, $[\alpha]_D^{20} = +9 \pm 0.5°$ (*c* 2, water); Ref. [3] gives m. p. 177—177.5°C and $[\alpha]_D^{22} = +8.2°$ (*c* 3.7, water). Chromatography of the mother liquor on Whatman No. 3 paper (elution for 40 h at room temperature) followed by elution of the zones corresponding to isomeric D-glucosylnitromethanes with methanol, evaporation and crystallization gave α-D-glucopyranosylnitromethane (0.1 g, R_{Glc} 2.84), m.p. 162—164°C, $[\alpha]_D^{22} = +56 \pm 0.5°$ (*c* 1, water); α-D-glucofuranosylnitromethane (0.3 g, R_{Glc} 4.23), m.p. 128°C, $[\alpha]_D^{22} = \pm 0.5°$ (*c* 1, water); and β-D-glucofuranosylnitromethane (0.2 g, R_{Glc} 3.63), sirup having $[\alpha]_D^{22} = -17 \pm 0.5°$ (*c* 1, water). On heating in aqueous solution (100°C, 30 h) all four isolated isomers afford identical mixture of isomeric D-glucosylnitromethanes and D-glucose (chromatographic test).

β-D-Galactopyranosylnitromethane (V)

The procedure described in the case of D-glucose applied to D-galactose (50 g) gave crude crystalline β-D-galactopyranosylnitromethane (41 g, 66%, R_{Gal} 3.19). After recrystallization from methanol the product had m.p. 198—200°C and $[\alpha]_D^{20} = +37 \pm 0.5°$ (*c* 2, water); Ref. [2] gives m.p. 198.5—199.5°C, $[\alpha]_D^{24} = +36.5°$ (*c* 2, water) or Ref. [4] gives m.p. 199.5—200.5°C, $[\alpha]_D^{25} = +36.0°$ (*c* 2.9, water). Crystallization of concentrated mother liquor from methanol—acetone 1 : 1 afforded α-D-galactofuranosylnitromethane (2.5 g, R_{Gal} 4.58) which after recrystallization from methanol had m.p. 161—163°C and $[\alpha]_D^{20} = +2.2 \pm 0.2°$ (*c* 2, water); Ref. [2] gives m.p. 155—157°C, $[\alpha]_D^{24} = -0.5°$ (*c* 2, water). Chromatography of the second mother liquor on Whatman No. 3 paper led to isolation of α-D-galactopyranosylnitromethane (0.2 g, R_{Gal} 2.95), m.p. 158—160°C, $[\alpha]_D^{22} = +149 \pm 0.5°$ (*c* 1, water), and β-D-galactofuranosylnitromethane (0.2 g, R_{Gal} 4.02), sirup having $[\alpha]_D^{22} = -47 \pm 0.5°$ (*c* 1, water); Ref. [2] gives for β-D-galactofuranosylnitromethane $[\alpha]_D^{24} = -55°$ (*c* 1.4, water). On heating in aqueous solution all four isomers afford identical final mixture of D-galactosylnitromethanes and D-galactose.

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Translated by P. Biely