Nitromethane Addition to Aldoses Promoted by Strongly Basic Anion-Exchange Resin in the OH⁻ Form

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1-Deoxy-1-nitroalditols can be readily obtained by one-pot reaction of aldoses with nitromethane in aqueous methanol in the presence of a strongly basic anion-exchange resin in the OH⁻ form and subsequent transformation of the resin into the HCO_3^- form with dry ice. All D-pentoses and six available D-hexoses gave moderate to high conversions (48—91 %) to the nitroaldol products, mostly both epimeric 1-deoxy-1-nitroalditols, in some cases accompanied by tautomeric 2,5- and 2,6-anhydro-1-deoxy-1-nitroalditols. Both types of the strongly basic anion-exchange resins used, R—$CH_2N^+Me_3$ OH⁻ and R—$CH_2N^+Me_2(CH_2CH_2OH)$ OH⁻ showed comparable catalytic efficiency. Examples of preparation of 1-deoxy-1-nitro-L-mannitol and -L-glucitol as well as L-mannose and L-glucose show a practical application of the procedure.

1-Deoxy-1-nitroalditols are useful synthetic intermediates usually obtained by a base-catalyzed addition of nitromethane to an aldose, a modification of the nitroaldol (Henry) reaction [1], being known for 100 years. In spite of that, the nitroaldol reaction is still being improved [2, 3]. For preparation of 1-deoxy-1-nitroalditols, sodium methoxide in methanol or methanol—methyl sulfoxide mixtures have been most often used as base under both homogeneous and heterogeneous conditions of the reaction [4]. Other bases as sodium hydroxide [5, 6] or barium hydroxide [7] in water have also been employed giving comparable yields of 1-deoxy-1-nitroalditols. To obtain the nitroalditols, acidification of the reaction mixture containing 1-deoxyalditol-1-nitronate anions is a next step. This is usually done with a cation-exchange resin that simultaneously removes the base used as catalyst leaving free nitroalditols. Herein, a simple procedure of the nitromethane addition to aldoses promoted by strongly basic anion-exchange resin including acidification of the resin with carbon dioxide affording free 1-deoxy-1-nitroalditols is described. Also ozonolysis of such a resin in the 1-deoxyalditol-1-nitronate form to corresponding aldoses and the resin in the NO_3^- form leaving the aldoses in salt-free solution is shown.

EXPERIMENTAL

Melting points were measured on a Kofler stage. Optical rotations were obtained at 20 °C using a Perkin—Elmer 141 polarimeter. Chromatographic analysis and separations were performed on a column C_1 (90 cm × 0.9 cm) of Dowex 50W (X-8, 37—75 μm, La^{3+} form) by elution with degassed water at the flow rate 18 cm^3 h^{-1} using a method described previously [8]. Solvents were evaporated under diminished pressure at temperatures below 40 °C. D-Glucose, D-galactose, D-xylose, and D-ribose were purchased from Lachema, the other aldoses used were products of the Institute of Chemistry, Slovak Academy of Sciences. Strongly basic anion-exchange resins Dowex 1 and Dowex 2 (both X-8, 75—150 μm, Cl⁻ form, purchased from Aldrich) were washed with water by decantation (5×), conventionally converted into the OH⁻ form, and their exchange capacity was determined by titration of a stirred mixture of 10 cm^3 of the resin and 10 cm^3 of aqueous HCl ($c = 1$ mol dm^{-3}) with aqueous NaOH ($c = 1$ mol dm^{-3}) to phenolphthalein. A Fischer 502 ozone generator was used for the preparation of ozone from gaseous oxygen.

Addition of Nitromethane to Aldoses

a) A solution of L-arabinose (0.2 g; 1.3 mmol) in water (0.4 cm^3) and methanol (4 cm^3) with added Dowex 1 or Dowex 2 (OH⁻ form, 0.8 mmol cm^{-3}, 3—8 cm^3) was stirred at room temperature for 5 min, and after addition of nitromethane (0.8 cm^3; 14 mmol) for

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Table 1. Conversion of L-Arabinose (*I*) to 1-Deoxy-1-nitro-L-mannitol (*II*) and -L-glucitol (*III*) Catalyzed with Strongly Basic Dowex Resins in the OH⁻ Form

Resin	$w(II)$: $w(III)$: $w(I)$			$w(II)$: $w(III)$		x	Conversion %
Dowex 1	14.4	4.4	1	3.3	1	1.9	93
	32.0	6.0	1	5.3	1	2.5	96
	7.7	2.4	1	3.8	1	4.2	87
Dowex 2	4.2	1.3	1	3.2	1	2.5	79
	8.9	1.7	1	5.0	1	3.5	88
	7.9	1.6	1	4.5	1	4.5	87

w_i – Mass fraction of components in the reaction mixture; x – mole fraction of tetraalkylammonio hydroxide groups of resin and *I*.

additional 2.5 h. The liquid phase was removed by filtration and the resin was added to water (20 cm³) and stirred with crushed dry ice (5 g) being maintained in a bath at 20 °C for 10 min. Then the mixture was filtered and washed with water (3 × 5 cm³). The filtrates were concentrated and the residue was analyzed by chromatography on column C_1 (Table 1).

b) A solution of an aldose (0.55 mmol) in water (0.2 cm³) and methanol (2 cm³) with added Dowex 1 (OH⁻, 0.8 mmol cm⁻³, 5 cm³) was stirred at room temperature for 5 min and after addition of nitromethane (0.4 cm³; 7 mmol) for additional 2.5 h. Then crushed dry ice (5 g) was added under stirring and the mixture was maintained in a bath at 20 °C for 10 min. The mixture was filtered and washed with water (3 × 5 cm³). The filtrates were concentrated and the residues were analyzed by chromatography on column C_1 (Table 2).

1-Deoxy-1-nitro-L-mannitol (*II*) and -L-glucitol (*III*)

Dowex 1 (OH⁻, 0.5 mmol cm⁻³, 60 cm³) was added to a solution of L-arabinose (*I*) (2 g; 13 mmol) in water (4 cm³) and methanol (40 cm³) and the mixture was stirred at room temperature for 5 min and after addition of nitromethane (8 cm³) for additional 2.5 h. After the treatment of the reaction mixture with crushed dry ice (30 g) for 10 min at 10—20 °C, the mixture was filtered and washed with water (3 × 50 cm³). The filtrates were concentrated. Crystallization of the residue from methanol afforded the first portion of *II* (0.69 g, 25 %), m.p. = 134—136 °C; Ref. [9] gives m.p. = 133—134 °C. Chromatography of the mother liquor on column C_1 afforded starting *I* (0.2 g), the second portion of *II* (0.86 g, 31 %) and *III* (0.44 g, 16 %), m.p. = 107—109 °C; Ref. [9] gives m.p. = 107—108 °C.

L-Mannose (*IV*) and L-Glucose (*V*)

After the 2.5 h initial stirring of the reaction mixture prepared from 2 g of *I* according to the above procedure for preparation of *II* and *III*, the mixture was filtered. The resin and water (50 cm³) were added to the residue, obtained by evaporation of methanol from the filtrate, and ozone (60 mg min⁻¹) was introduced into the stirred mixture at ambient temperature for 1 h. Then the reaction mixture was flushed with nitrogen for 10 min and treated with crushed dry ice (30 g) at 10 °C for another 10 min. The resin was removed by filtration, washed with water (3 × 30 cm³), and the filtrate was concentrated to the volume of 10 cm³. After addition of phenylhydrazine (1.6 cm³) and ethanol (4 cm³), the mixture was left to stand at room temperature for 24 h. The filtration of the precipitate and washing with water (3 × 3 cm³) afforded L-mannose phenylhydrazone (1.9 g, 50 %), m.p. = 186—187 °C; Ref. [9] gives m.p. = 186—188 °C.

The filtrate after isolation of L-mannose phenylhydrazone was mixed with benzaldehyde (1.2 cm³), pyridine (0.5 cm³), and ethanol (1.7 cm³) and the mixture was heated at 100 °C for 3 h. The cold mixture was filtered, the filtrate was extracted with ethyl acetate (3

Table 2. Conversion of Some Aldoses (A) to Corresponding Epimeric Pairs of 1-Deoxy-1-nitroalditols (NA) and Their Anhydro Forms (ANA) Catalyzed with Dowex 1 Resin in the OH⁻ Form

A	$w(NA + ANA)$: $w(A)$		$w(NA_1)$: $w(NA_2)$: $w(ANA)$			Conversion %
D-Arabinose	7.0	1	4.9	2.1	0	83
D-Ribose	15.4	1		x		91
D-Lyxose	9.5	1	1.8	3.7	4	87
D-Xylose	3.8	1		x		76
D-Allose	5.0	1		x		78
D-Altrose	7.3	1	5.6	1.7	0	84
D-Galactose	2.0	1	0.7	0.8	0.5	59
D-Glucose	1.3	1	0.4	0.3	0.6	48
D-Mannose	1.8	1	0.6	0.9	0.3	56
D-Talose	4.7	1		x		77

w_i – Mass fraction of components in the reaction mixture; NA_1 – 1-deoxy-1-nitroalditol with a lower retention on a column of a strongly acidic cation-exchange resin in the La^{3+} form than its epimer NA_2; x – not assessed because of insufficient separation.

× 10 cm³), and the water layer was decolourized with charcoal (0.1 g) and evaporated. Chromatography of the residue on column C_1 with water elution at the flow rate 10 cm³ h⁻¹ afforded a fraction of V eluted as the first and a fraction of the starting I eluted as the second. Evaporation of the first fraction and crystallization of the residue from methanol afforded V (0.3 g, 13 %), m.p. = 144—146 °C, $[\alpha]$(D, 20 °C, ρ = 20 g dm⁻³, water) = −51.6°; Ref. [9] gives m.p. = 146—147 °C and $[\alpha]$(D, 22 °C, ρ = 26 g dm⁻³, water) = −52.6°.

A similar treatment and work-up of the mixture composed of L-mannose phenylhydrazone (1.9 g), benzaldehyde (1.1 cm³), pyridine (0.4 cm³), ethanol (1.4 cm³), and water (10 cm³) as above, evaporation of the filtrate, and its crystallization from methanol yielded IV (1.1 g, 48 %), m.p. = 129—131 °C, $[\alpha]$(D, 20 °C, ρ = 20 g dm⁻³, water) = −14.2°; Ref. [9] gives m.p. = 128—132 °C and $[\alpha]$(D, 20 °C, ρ = 34 g dm⁻³, water) = −14.5°.

RESULTS AND DISCUSSION

Addition of nitromethane to L-arabinose (I) in a methanol—water mixture in the presence of strongly basic anion-exchange resin of the type I, Dowex 1, in the OH⁻ form resulted in the formation of a mixture of 1-deoxy-1-nitro-L-mannitol (II) and -L-glucitol (III). Three different amounts of the resin in relation to I were used (Table 1) and the highest conversion of I to a mixture of II and III (96 %) was achieved when 2.5 mol of the resin active groups R—CH₂N⁺Me₃ OH⁻ (R = poly(styrenedivinylbenzene) matrix) were used. In this case, the final reaction mixture, after treatment with carbon dioxide in water, contained compounds I, II, and III in the mole ratio 1:5:20.

For a slightly less basic anion-exchange resin of the type II, Dowex 2, possessing functional groups R—CH₂N⁺(CH₂CH₂OH)Me₂ OH⁻, the highest conversion of I to II and III (88 %) was observed at about 3.5 mol of the resin active groups, however, there was not achieved such a high conversion as observed with Dowex 1. In all cases studied, with both Dowex 1 and Dowex 2, nitroalditol II that does not contain any stereochemical strain in its zig-zag conformation was significantly prevailing product of the addition. For both types of the resin investigated as catalysts of the nitromethane addition to I, a further increase of their amounts used for the catalysis resulted in a decreased conversion of I to II and III.

The observation is obvious because of the interaction of both reacting species as weak acids with hydroxide ions localized at the heterogeneous matrix of the resin (respective approximate values of pK_a of aldoses and nitromethane are 12.5 and 10.3); the increased population of the hydroxide centres causes a more distant mutual immobilization of nitromethane and I thus disabling their interaction. Due to a higher pK_a value of 1-deoxy-1-nitroalditols II and III formed ($pK_a \cong 9.0$), the equilibrium of the reaction is shifted in favour of addition products. These were finally released from the anion-exchange resin into ion-free solution by treatment with carbonic acid (pK_{a1} = 6.3) made by addition of dry ice into water.

Similarly as with I, the addition of nitromethane to four D-pentoses and six available D-hexoses catalyzed by a strongly basic anion-exchange resin in the OH⁻ form was investigated (Table 2). For this study, only Dowex 1 that was found to be a more convenient catalyst of the addition of nitromethane to I was used. Except of D-arabinose and D-altrose, where 1-deoxy-1-nitroalditols (NA) were the only products, in all other cases, also the formation of tautomeric 2,5- and 2,6-anhydro-1-deoxy-1-nitroalditols (ANA) was observed and their portion reached in some cases up to 60 %. Similar formation of ANA already in a basic medium has been reported, e.g. for D-ribose [10]. As seen in Table 2, the separation of the products of the nitromethane addition to aldoses by chromatography on a strongly acidic cation-exchange resin in the La³⁺ form [8] was not always sufficient and therefore it did not enable their complete determination. However, at least an estimate of the total conversion of an aldose to the mixture of NA and ANA was possible and this was in the range of 48—91 %.

A special advantage of a strongly basic anion-exchange resin in the OH⁻ form was when nitroalditols prepared under its catalysis were converted into corresponding aldoses. Being in the nitronate form, 1-deoxy-1-nitroalditols I and II were converted by ozonolysis [11] to L-mannose (IV) and L-glucose (V), respectively, and nitrate ions, which were trapped by the resin. To avoid a partial chemisorption of the formed aldoses on an excessive amount of the resin still being partially in the OH⁻ form, a final treatment with carbon dioxide converting the resin into the HCO₃⁻ form was applied which released the aldoses into the solution free of salts.

In conclusion, the presented modification of the Henry reaction offers a simple procedure for preparation of 1-deoxy-1-nitroalditols and, in combination with ozonolysis, also for preparation of aldoses. However, taking into account a relatively low exchange capacity of commercial strongly basic anion-exchange resins (the value of about 1 mmol cm⁻³ for a freshly new resin significantly drops with every recycling of the resin to a limit value of about 0.3 mmol cm⁻³), the procedure requires large quantities of the resin yielding relatively small amounts of products. Therefore, it might be rather convenient for preparation of more valuable, e.g. isotopically labelled 1-deoxy-1-nitroalditols and aldoses.

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