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Zinc–proline catalyzed pathway for the formation of sugars†

Jacob Kofoed, Miguel Machuqueiro, Jean-Louis Reymond* and Tamis Darbre*
Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, CH-3012, Bern, Switzerland. E-mail: tamis.darbre@ioc.unibe.ch; Fax: +41 31 631 80 57; Tel: +41 31 631 43 70

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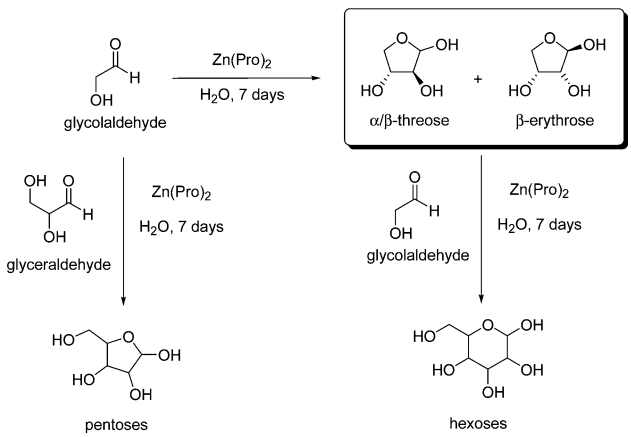
Zn–proline catalyzes the aldolisation of unprotected glycolaldehyde in water to give tetroses and hexoses; threose (33% of the product mixture) was formed with 10% enantiomeric excess of the D-isomer.

The prebiotic formation of sugars has been a subject of several studies and speculations. One prevailing theory accepted today has sugars being formed by a sequence of aldol reactions, starting with formaldehyde (formose reaction). This reaction can be initiated by an alkaline earth catalyst such as calcium hydroxide to give a complex mixture containing straight- and branched-chain C3–C7 sugars.[1–4] Eschenmoser and coworkers have shown that the aldolisation of glycolaldehyde phosphate in 2M NaOH solution gives a mixture of tetrose and hexose derivatives (ratio 1 : 10), due to the lack of aldose–ketose tautomerisation.[5] Pentoses (ribose, arabinose, xylose and lysose) can also be formed under alkaline conditions from formaldehyde and glycoaldehyde, although they rapidly decompose to generate polymeric mixtures. However, pentoses, formed by aldol reaction of glycolaldehyde and formaldehyde, can be stabilized by complexation with borate, a process that could have relevance in the prebiotic synthesis of pentoses.[6] The origin of sugar chirality has only recently been addressed. Amino acids were reported to act as asymmetric catalysts for the conversion of glycolaldehyde to tetroses in aqueous medium. Threose was formed with enatiomeric excess (~10%) in the presence of alanine or isovaline, whereas proline did not act as a catalyst in this context.[7] Proline catalyzed aldolization of propionaldehyde in DMF has been reported to give carbohydrates with 47% ee.[8]

We are interested in developing catalysts for the asymmetrical aldol reaction in aqueous media and we have shown that the $Zn(Pro)_2$ complex as well as $Zn(Arg)_2$ and $Zn(Lys)_2$ are able to catalyze the direct reaction between aldehydes and ketones in water with moderate enantioselectivity.[9] Herein, we report that unprotected glycolaldehyde can be converted to mainly tetroses and hexoses in water using the $Zn(Pro)_2$ complex as catalyst (Scheme 1)



Scheme 1 $Zn(Pro)_2$ catalyzed pathway for the formation of sugars.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b404465g/

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under conditions that are compatible with a prebiotic environment. Zn is an abundant transition metal and it is found in a large number of metalloenzymes including aldolases involved in the metabolism of sugars.[10] Furthermore, chiral amino acids were possibly present in the prebiotic period, either formed on earth or from extra-terrestrial origine.[7,11]

Aqueous glycolaldehyde solution was stirred at room temperature in the presence of a catalytic amount (15 mol%) of $Zn(Pro)_2$ complex (Scheme 1). After 7 days, the water was removed by lyophilization and the reaction mixture was peracetylated and analyzed by gas-chromatography.‡ Commercial sugars were equilibrated and peracetylated, and used as references. The product consisted of tetroses (51%), hexoses (27%) and unidentified compounds (22%). The tetroses consisted of 65% threose and 35% erythrose.[12] The hexose mixture contained mainly glucose, galactose (together 40% of the hexose mixture) and talose (10% of the hexose mixture). Similar results were obtained with zinc complexes of the amino acids arginine or lysine. However, conversion with $Zn(Arg)_2$ was lower than with $Zn(Pro)_2$ with around 50% of starting glycolaldehyde still present in the reaction mixture after 7 days. When glycolaldehyde was stirred in the presence of proline alone, under the same reaction conditions, formation of sugars was not observed and only glycoladehyde could be detected by ^{1}H NMR. Proline, therefore, does not act as a catalyst for the aldol reaction under our reaction conditions.

The product mixture from the $Zn(Pro)_2$ catalyzed reaction was reduced with $NaBH_4$ and peracetylated to produce a less complex mixture of tetrol and hexitol acetates. Chiral GC allowed the separation of the threitol acetate enantiomers. The threitol formed was non-racemic (ee ~ 10%),[13] similar to the enantiomeric excess obtained with isovaline as catalyst.

The cross-aldolization of glycolaldehyde and racemic glyceraldehyde under the same conditions as above, gave a mixture of tetroses and pentoses (Scheme 1).§ The identification of the pentoses was made by comparison of the ^{1}H NMR chemical shifts for anomeric protons of the α-/β-pyranoses of commercial sugars with the chemical shifts of the reaction products. The pentose mixture contained ribose (34%), lyxose (32%), arabinose (21%) and xylose (13%), which were stable under the reaction conditions. The reaction mixture did not turn brown after one week, neither was formation of polymeric material observed.

The excess of threose over erythrose at the C4-level and the preferential formation of glucose, galactose and talose at the C6-level indicate a catalyzed aldol reaction occurring with stereodifferentiation both in the addition of C2 to C2 and the addition of C2 to C4.[14] We postulate formation of a Zn-chelated glycoaldehyde enolate as the nucleophile which can attack the electrophilic carbonyl group of the aldehyde. Commercially available tetroses (threose and erythrose) and hexoses (glucose, galactose, mannose, talose, fructose) remained unchanged upon incubation with $Zn(Pro)_2$ under the conditions of the glycolaldehyde reaction (25 °C, 7 days), showing that the $Zn(Pro)_2$ complex did not catalyze stereoisomerization of different sugars.

In conclusion, the Zn–proline complex catalyzed the aldolisation of glycoaldehyde in aqueous medium, at room temperature and in the absence of strong bases. Threose was the main product and an enantiomeric excess of the natural D-tetrose was observed. The cross aldolisation of glycoaldehyde and glyceraldehyde gave

tetroses and pentoses that were stable under the reaction conditions. The Lewis acid catalyzed formation of sugars in water described here adds a new reaction in the group of transformations that have been cited in the discussion of possible prebiotic routes to sugars. The diastereomeric and enantiomeric selection observed adds support to the possibility that amino acids could have been the source of chirality for the prebiotic sugar synthesis. The fact that a metal coordinated to an amino acid is able to catalyze the synthesis of sugars in water with a catalytic asymmetric effect, suggests also that such systems could have been metalloenzyme precursors. Furthermore, threofuranosyl oligonucleotides have been mentioned as possible RNA analog, that could have been more easily synthesized under prebiotic conditions.[15,16]

Notes and references

‡ *Sugar synthesis*: A solution of glycolaldehyde (60 mg, 1 mmol) and Zn-amino acid complex (0.15 mmol) in H_2O (5 ml) was stirred for 7 days at room temperature. The solvent was removed by lyophilization and the residue was peracetylated and analyzed by gas-chromatography.
§ *Cross-aldolization:* A solution of glycolaldehyde (60 mg, 1 mmol), glyceraldehyde (90 mg, 1 mmol) and Zn-amino acid complex (0.15 mmol) in H_2O (5 mL) was stirred for 7 days at room temperature. The solvent was removed by lyophilization.

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