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# Prebiotic carbohydrate synthesis: zinc–proline catalyzes direct aqueous aldol reactions of α-hydroxy aldehydes and ketones†

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***Received 31st January 2005, Accepted 22nd March 2005***
***First published as an Advance Article on the web 14th April 2005***

Zn–proline catalyzed aldolisation of glycoladehyde gave mainly tetroses whereas in the cross-aldolisation of glycoladehyde and *rac*-glyceraldehyde, pentoses accounted for 60% of the sugars formed with 20% of ribose.

## Introduction

The importance of carbohydrates for living organisms, and especially the prominent role of ribose as building block of ribonucleic acid (RNA), has prompted studies towards possible routes for the synthesis of sugars under prebiotic conditions.[1] The discovery that RNA acts as both the carrier of genetic information and as an RNA autoreplicase indicates the existance of an early "RNA world",[2] where ribozymes could perform vital chemical functions such as phosphorylation,[3] acyl transfer,[4] peptide-bond formation[5] and carbon–carbon bond formation.[6] The early earth was probably rich in organic molecules[7] making it plausible to envision the formation of pentoses and hexoses by condensation of smaller molecules. Recently, glycolaldehyde was discovered in interstellar molecular clouds from which new stars are forming providing circumstantial evidence for the existence of glycolaldehyde on the early earth.[8] Amino acids such as glycine, alanine, glutamic acid, valine and proline have been found in meteorites.[9]

The condensation of formaldehyde (the formose reaction) initited by alkaline earth catalysts leads to a complex mixture of straight- and branched-chain sugars, including tetroses, pentoses and hexoses.[10] Sugars and especially ribose are however unstable under such basic reaction conditions undergoing rapid decomposition.[11,12] The yield of pentoses in the formose reaction has been improved by the addition of lead(II) salts and dihydroxyacetone.[13] Weber showed that *rac*-glyceraldehyde could undergo aldolisation catalyzed by iron(III) hydroxide oxide yielding keto-hexoses that were stable under the reaction conditions.[14] Recently, it has been shown that pentoses, formed by the aldol reaction of glycolaldehyde and formaldehyde, can be stabilized by complexation with borate.[15] Ribose 2,4-diphosphate can be obtained as a major product from the reaction of glycoaldehyde phosphate and formaldehyde.[16] Tetroses are also formed by condensation of glycolaldehyde catalyzed by amino acids.[17]

In Nature such aldol condensations are promoted by two distinct classes of aldolases: Class I aldolases contains an active site lysine involved in the formation of nucleophilic enamine intermediate,[18] or Class II aldolases that contains an active site Zn(II) cofactor facilitating the enolate formation by coordinating to the carbonyl oxygen of the ketone donor (Fig. 1).[18]

Proline and short peptides incorporating *N*-terminal proline residues are capable of catalyzing direct aldol reactions in organic solvents operating *via* an enamine mechanism[19,20,22] (class I aldolase mimics). A few class I mimics operating in water has also been reported.[21] 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 (class II aldolase mimic).[23] We have recently reported that unprotected glycolaldehyde can be converted to mainly tetroses and some hexoses in water using the $Zn(Pro)_2$ complex as catalyst under conditions that are compatible with a prebiotic environment.[24] Zn is an abundant transition metal and it is found in a large number of metalloenzymes including aldolases involved in the metabolism of sugars.[25] Furthermore, chiral amino acids were possibly present in the prebiotic period, either formed on earth or from an extraterrestrial origin.[9,11]

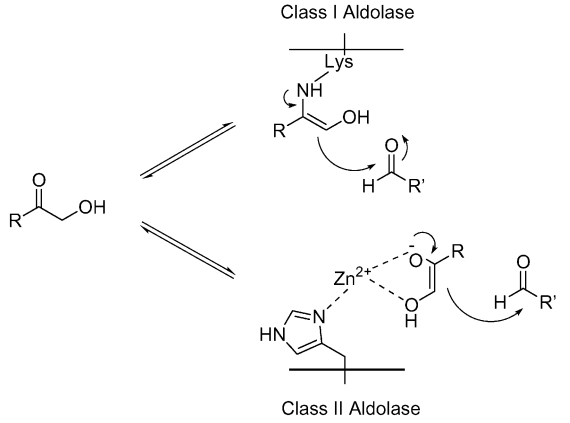



**Fig. 1** The two distinct aldolases.[18]

Herein, we report that in general unprotected α-hydroxy aldehydes and ketones can undergo aldol additions in the presence of $Zn(Pro)_2$ as catalyst in water. Depending on the starting aldehyde, the products obtained included tetroses, pentonse, hexoses, keto-pentoses, keto-hexoses and smaller amounts of higher sugars. For ease of analysis the sugars were also reduced to polyols using $NaBH_4$.[27] The reactions are summarized in Scheme 1.

## Results and discussion

### Synthesis of Zn–proline

$Zn(Pro)_2$ (Fig. 2) is easily synthesized by stirring $Zn(OAc)_2$ (1 eq.), L-proline (2 eq.) and triethylamine (2 eq.) in methanol. The complex precipitates from the methanolic solution and can be easily isolated.

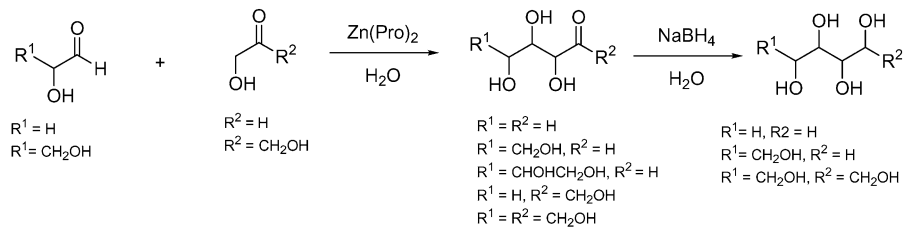
### Zn–proline catalyzed aldolisation of glycoladehyde

Aqueous glycolaldehyde was stirred for 7 d at room temperature in the presence of catalytic $Zn(Pro)_2$ (10 mol%) and the product, obtained after lyophilization, was treated with acetic anhydride.

† Electronic supplementary information (ESI) available: Selected NMR spectra and GC chromatograms. See http://www.rsc.org/suppdata/ob/b5/b501512j/

DOI: 10.1039/b501512j




**Scheme 1** Zn–proline catalyzed aldol reaction to give sugars and their reduction with $NaBH_4$. The products were identified by GC analysis of the peracetates. Further identification was obtained from the alditols by GC analysis of the peracetates.

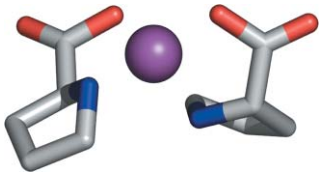


**Fig. 2** X-ray structure of zinc–proline complex.[26]

The crude peracetyled sugar mixture was subjected to GC analysis, reveling two discrete areas corresponding to tetroses and hexoses (Fig. 3). The individual sugars present in the mixture were identified by co-injection with reference peracetylated sugars obtained from commercially available hexoses and treoses.

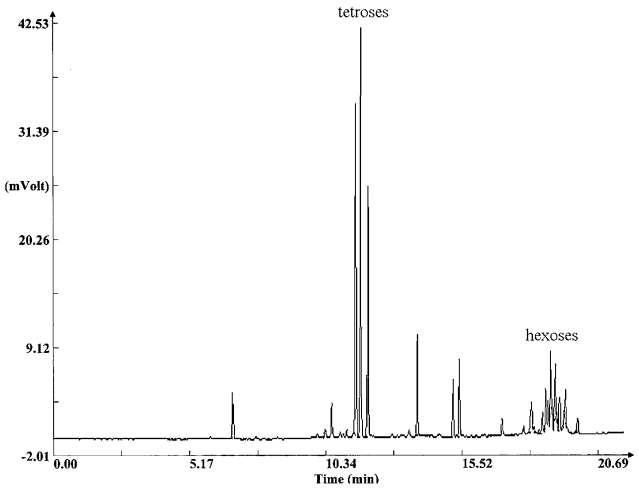



**Fig. 3** Crude GC analysis of peracetylation mixture from the aldolisation of glycolaldehyde.

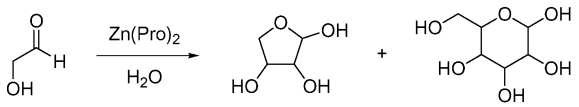
Sodium borohydride reduction of the crude aldolization product followed by peracetylation gave a less complex sugar mixture and allowed the unambiguous identification of the sugars as their alditol peracetylates.[27] Especially, the rare idose could be identified as iditol with the reference compound obtained from $NaBH_4$ reduction of sorbose. Furthermore, the threitol was formed with 10% enantiomeric excess of the D-isomer.[24] The tetroses consisted mainly of threose whereas the minor hexose fraction contained mostly mannose and glucose (Table 1).

When the sugar distribution was analyzed regarding the ratio of the erythrose and threose and the ratio of the combined hexoses formed from erythrose and the combined hexoses formed from threoses, it was found that although threose was the major tetrose present in the mixture after 7 d, the hexoses formed from erytrose (allose, altrose, glucose and mannose) predominated over the threo-hexoses (gulose, idose, galactose and talose) (Fig. 4).[28] We attribute the origin of this stereoselectivity to a faster aldol reaction of the less stable erythrose with glycolaldehyde (Fig. 4).

In order to determine if the mixture obtained was derived from equilibration, commercial hexoses and tetroses were stirred under the reaction conditions. After 7 d, only the initial sugars were obtained and epimerization was not observed indicating that the kinetic products formed from glycolaldehyde did not undergo isomerization.

In an attempt to increase the ratio of hexoses by preventing cyclization of treoses, we synthesized glycolaldehyde phosphate by periodate cleavage of 1-phosphate glycerol (Scheme 2).[29] This substrate was however inert to the reaction conditions.

**Table 1** Tetroses and hexoses obtained by aldolization of glycolaldehyde. The products were identified by GC using two different ways; peracetylation and after reduction and acetylation




| Peracetylated aldoses[f] | Yield from GC (%) | Peracetylated alditols | Yield from GC (%) |
|---|---|---|---|
| Erythrose | 13 | Erythritol[a] | 18 |
| Threose | 38 | Threitol[b] | 33 |
| Allose | 5 | Allitol | 6 |
| Talose | 3 | Talitol[e] | 2 |
| Altrose | 2 | | |
| Galactose | 4 | Galactitol | 4 |
| Glucose | 6 | Sorbitol[c] | 8 |
| Gulose | 5 | | |
| Idose[d] | N/a | Iditol | 2 |
| Mannose | 7 | Mannitol | 8 |
| Unidentified | 19 | Unidentified | 19 |
| Total | 100 | Total | 100 |

[a] Erythritol is a *meso*-compound. [b] Threitol was formed with 10% enantiomeric excess of the D-isomer. [c] Corresponds to the reduced glucose and gulose. [d] Reference sugar was not commercially available. [e] Corresponds to reduced talose and altrose. [f] Aldoses correspond to a α/β anomeric mixture.

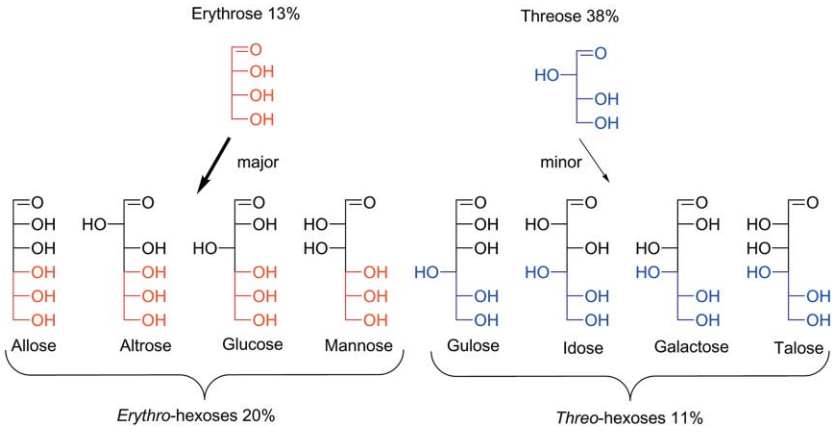
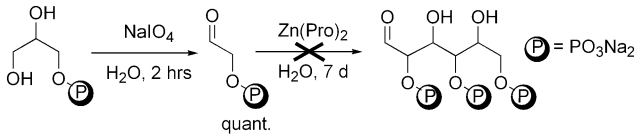



**Fig. 4** The acylic forms of D-aldotetroses and -hexoses as their Fischer projections showing the preferential formation of threose (blue) and *erythro*-hexoses (black and red).




**Scheme 2** Synthesis and aldolisation attempt of phosphate glycolaldehyde.

### Zn–proline catalyzed cross-aldolisation of glycolaldehyde and *rac*-glyceraldehyde

The possible formation of pentoses under our reaction conditions was investigated with the cross-aldolization of glycolaldehyde and *rac*-glyceraldehyde. This reaction is of particular interest because, under conditions described as possibly prebiotic, pentoses proved to be unstable.[13] The latter results raised some questions about the choice of ribose by Nature as the building block of RNA.

Thus, equimolar amounts of glycolaldehyde and *rac*-glyceraldehyde were stirred using the same conditions as above. After 7 d, tetroses (20%), pentoses (60%) and hexoses (20%, complex mixture of aldo- and ketohexoses) were formed. The reaction mixture was also reduced with $NaBH_4$ to give tetrols, pentitols and hexitols. The sugars identified by GC analysis of peracetylated aldols and peracetylated alditols are shown in Table 2. Interestingly, the percentage of tetroses decreased in this experiment, whereas the amount of hexose remained unchanged. *rac*-Glyceraldehyde, therefore, can act as the electrophile for the aldol reaction, whereas the glycolaldehyde enolate is formed preferentially. Thus, condensation between glycolaldehyde and *rac*-glyceraldehyde is the most favorable reaction, yielding pentoses as the major components (Fig. 5).

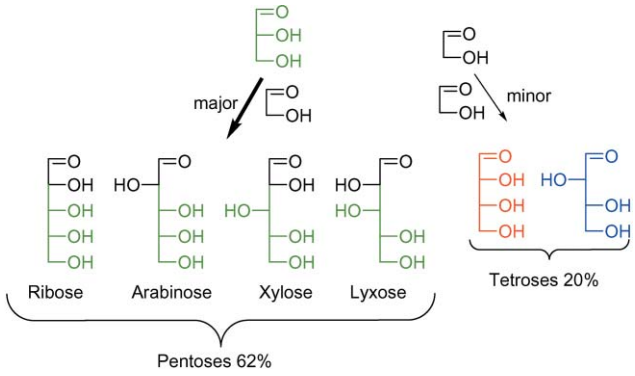
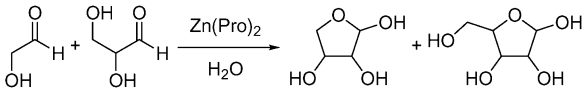



**Fig. 5** The acylic forms of D-aldo-tetroses (red and blue) and pentoses as their Fischer projections showing the preferential formation of pentoses (black and green).

The selectivity towards pentoses is remarkable in a reaction run with equimolar amounts of glycolaldehyde and *rac*-glyceraldehyde. Ribose accounts for 20% of the total product and 30% of the pentoses. Ribose alone was stirred in the presence of Zn–proline for two weeks without epimerization to more stable pentoses.

**Table 2** Tetroses, pentoses and hexoses obtained by cross-aldolization of glycolaldehyde and *rac*-glyceraldehyde. The products were identified by GC[c] after acetylation and after reduction and acetylation and coinjection with prepared references




| Peracetylated aldoses | Yield from GC (%) | Peracetylated alditol | Yield from GC (%) |
|---|---|---|---|
| Erythrose | 7 | Erythritol | 9 |
| Threose | 13 | Threitol | 11 |
| Arabinose | 14 | Arabitol[a] | 34 |
| Lyxose | 21 | | |
| Ribose | 19 | Ribitol | 13 |
| Xylose | 9 | Xylitol | 15 |
| Hexoses[b] | 14 | Hexoses | 12 |
| Unidentified | 3 | Unidentified | 6 |
| Total | 100 | Total | 100 |

[a] Corresponds to reduced arabinose and lyxose. [b] Complex mixture of aldo- and keto-hexoses. Peracetylated aldoses and peracetylated alditols were analyzed by GC. [c] In ref. 24 we reported the following distribution of pentoses based on $^1$H NMR chemical shift of the anomeric protons: arabinose (21%) ribose (34%), lyxose (32%,) and xylose (13%).

The aldolization of glycoaldeahyde seems to be slower than the crossaldolization with only 20% of tetroses formed, and aldolization of *rac*-glyceraldehyde does not take place at a significant rate. Although it is not possible to draw conclusions about Nature's choice of ribose over other sugars, it is a remarkable result indicating that ribose is a viable and stable sugar under aqueous conditions without additional stabilizing procedures. These results shows the same trend, however not as pronounced, as reported by Krishnamurthy *et al.* who found ribose (48%), arabinose (16%), lyxose (25%) and xylose (11%) as their 2,4-biphosphates starting from glycolaldehyde phosphate and glyceraldehyde-2-phosphate.[16b] The isomerisation of *rac*-glyceraldehyde into dihydroxyacetone was not significant, however we did note a singlet at *ca.* 4.3 ppm in the $^1$H NMR spectrum of the crude besides a very complex mixture in the hexose region of the GC spectra. This prompted us to investigate the self-condensation of *rac*-glyceraldehyde which should lead to ketohexoses.

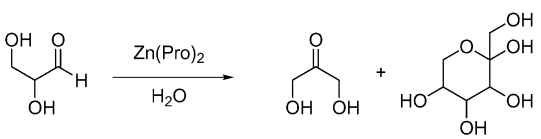
### Zn–proline catalyzed self-condensation of *rac*-glyceraldehyde

When *rac*-glyceraldehyde *alone* was stirred in the presence of Zn(Pro)$_2$,dihydroxyacetone (42%) and keto-hexoses (42%) (Table 3) were observed after one week. Fructose (26%) accounted for the major part of the keto-hexose mixture. Anomeric protons of aldoses were absent in the $^1$H NMR spectrum of the crude mixture (see electronic supplementary information). These results indicate that the *rac*-glyceraldehyde is isomerized into the more stable dihydroxyacetone *via* a zinc-chelated glyceraldehyde enediolate. The isomerisation is apparently much slower than the addition of glycolaldehyde-enolate to *rac*-glyceraldehyde by comparison of the results in Tables 2 and 3. The present results are also in agreement with earlier studies[13] of the iron(III) hydroxide oxide catalyzed condensation of *rac*-glyceraldehyde (sorbose (15.2%), fructose (12.9%), psicose (6.1%) and tagatose (5.6%) were reported).

### Zn–proline catalyzed condensation of glycolaldehyde and dihydroxyacetone

Keto-pentoses were formed from glycolaldehyde and dihydroxyacetone as seen in Table 4. Although the yields are given for the peracetylated alditols obtained by sugar reduction with $NaBH_4$, the crude product of the aldol reaction was analyzed by $^1$H NMR before reduction. The absence of peaks corresponding to the anomeric protons of aldoses indicated the formation of ketoses. Thus, no isomerization of dihydroxyacetone to the more electrophilic *rac*-glyceraldehyde was seen and it should also be noted that the conversion into ketopentoses is much lower than

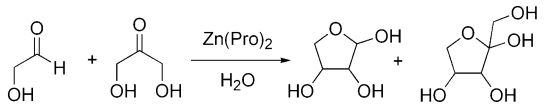
**Table 3** Aldol condensation of *rac*-glyceraldehydes. The products were identified by GC after acetylation with coinjection of prepared references




| Peracetylated ketose | Yield from GC (%)[a] |
|---|---|
| Dihydroxyacetone | 42 |
| Fructose | 26 |
| Sorbose | 13 |
| Tagatose | 3 |
| Unidentified[c] | 16 |
| Total | 100 |

[a] Obtained from peracetyletion of the crude sugar mixture and analysis by GC. [b] Without addition of dihydroxyacetone. [c] Consists most probably of psciose and dendro-ketoses. Psicose was not commercially available at a reasonable price.

**Table 4** Products obtained from aldol reaction between glycolaldehyde and dihydroxyacetone




| Peracetylated alditol (corresponding ketose) | Yield from GC (%)[a] |
|---|---|
| Glycerine (dihydroxyacetone) | 39 |
| Erythritol (erythrose) | 8 |
| Threitol (threose) | 16 |
| Xylitol (xylulose) | 11 |
| Ribitol (ribulose) | 7 |
| Unidentified | 20 |
| Total | 100 |

[a] Obtained from reduction and peracetylation of the crude sugar mixture and analysis by GC of the resulting alditols.

in the case of aldopentoses (Table 2). Consequently, the cross-aldolisation between glycolaldehyde and *rac*-glyceraldehyde (Table 2) predominates over homo-aldolisation to give a remarkably clean reaction considering the many possible products (62% of pentoses).

### Mechanistic considerations

We propose a Lewis acid catalyzed mechanism for the aldol reaction mediated by Zn–proline complex. The steps involved in the proposed mechanism are shown in Fig. 6. Coordination of hydroxyaldehyde to the metal induces formation of the chelating enolate. This is reminiscent of the class II aldolases in Nature that contain a $Zn^{2+}$ cofactor in the active site facilitating the enolate formation. The electrophilic aldehyde reacts with the enolate with or without coordination with zinc.

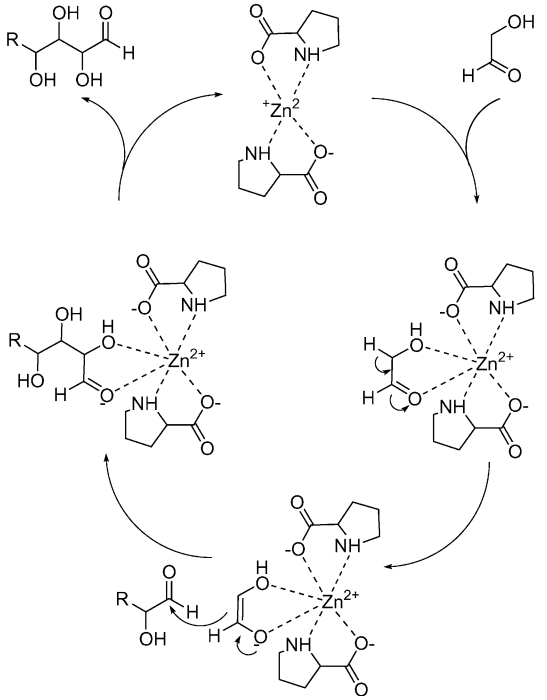


**Fig. 6** Proposed Lewis acid catalyzed mechanism for the aldolisation of glycolaldehyde mediated by Zn–proline complex.

The product distribution obtained by aldolization of glycoladehyde (Table 1) shows a preference for the hexoses formed by reaction of erythrose with glycoladehyde. The yields of individual hexoses are too low to rationalize further for a preferential stereochemistry around the new C2–C3 bond.[29]

In the pentose series, however, ribose and lyxose, the two pentoses with *erythro*-configuration in the new C2–C3 bond, are formed in higher ratio (40%) compared to the arabinose and xylose, the two sugars with threo configuration in the C2–C3 bond (23%). These results are similar to the ones obtained in the studies with glycoladehyde phosphate[17] and can be interpreted by analysis of the possible conformers resulting from the interaction of aldehyde and enolate as shown in Fig. 7. The conformation **A** (and the corresponding enantiomer) leads to ribose and lyxose whereas the less favored conformation **B** (and its enantiomer) gives arabinose and xylose.

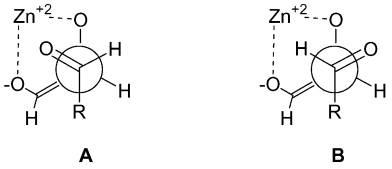



**Fig. 7** Possible interactions of glycoaldehyde enolate and *rac*-glyceraldehyde with **A** giving ribose and (in the enantiomeric form) lyxose and **B** giving arabinose and xylose.

The rate of decomposition of pentoses have been measured at neutral pH and 100 °C. Ribose and lyxose are less stable than xylose and arabinose[14] indicating that the mixture obtained in the aldol reaction does not represent a thermodynamic equilibrium.

## Conclusion

Sugars were formed by aldol reaction of simpler aldehydes in the presence of Zn–proline complex. By studying small subsystems of the formose reaction we were able to identify the reaction of glycoaldehyde and *rac*-glyceraldehyde as the most favorable, giving rise to pentoses (62%) with ribose accounting for *ca.* 30% of the pentoses. The lack of stability of pentoses under several conditions has been evoked as the major problem when considering pentoses as possible prebiotic reagents. Under basic conditions, condensation of formaldehyde yields less than 1% of ribose.[14] Consequently, methods for increasing the yields and stabilizing the formed pentoses were investigated. We have shown that ribose and other pentoses can be formed by Lewis acid catalyzed aldol reactions and that the products are stable in aqueous media and at room temperature. The Zn–amino acid complex required as catalyst could be present in the prebiotic environment. Indeed, we formulated such complexes as class II aldolase precursors able to catalyze carbon–carbon bond formation and maybe promote chirality transfer from amino acid to sugars. Our results leads to think that ribose could have been present in an early stage of evolution, under possible prebiotic conditions, and that further stabilization procedures were not strictly necessary.

## Experimental

NMR spectra and GC chromatograms are found in the supplementary information. Chemicals and solvents were purchased in the best possible quality from commercial suppliers. For thin-layer chromatography (TLC), silica gel plates Merck 60 $F_{254}$ were used and compounds were visualized by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. $H_2SO_4$ (60 mL), and $H_2O$ (940 mL) followed by heating. Flash chromatography was performed using silicagel Merck 60 (particle size 0.040–0.063 mm), Solvents were distilled before use. $^1$H NMR spectra were recorded on Bruker AVANCE300 (300 MHz) or Bruker DRX500 (500 MHz). Chemical shifts are given in ppm referred to solvent residual peak. Coupling constants ($J$) are reported in Hertz (Hz). GC experiments were run on a MACHERY-NAGEL OPTIMA δ 3 column (30 m × 0.25 mm) with He (0.8 ml min$^{-1}$) as carrier gas, makeup gas $N_2$ and $H_2$-flame. The temperature programs were as follows: (A) starting at 180 °C for 5 min (isotermic) then heating at 5 °C min$^{-1}$ to 200 °C; 200 °C for 5 min (isotermic) then heating at 5 °C min$^{-1}$ to 220 °C; 220 °C for 20 min (isotermic) then heating at 5 °C min$^{-1}$ to 350 °C; and (B) starting at 180 °C and heating at 5 °C min$^{-1}$ to 220 °C; 220 °C for 20 min (isotermic) then heating at 10 °C min$^{-1}$ to 350 °C. All sugar mixtures, except for reduced pentoses which were analyzed using method (B), were analyzed using method (A). Data recording was done with the ChromCard Software and processing done with the free CHROMuLAN package (http://chromulan.org).

### Aldolization of glycolaldehyde

A solution of glycolaldehyde (60 mg, 1 mmol) and $Zn(Pro)_2$–complex (29 mg, 0.10 mmol) in $H_2O$ (5 mL) was stirred for 7 d at room temperature. The solvent was removed by lyophilization and the $^1$H NMR spectrum in $D_2O$ was recorded. A portion of the sugar mixture was peracetylated using the general method below and injected on GC. Another portion was reduced using the general method below, and then peracetylated and injected on GC.

### Cross-aldolisation between glycolaldehyde and *rac*-glyceraldehyde

A solution of glycolaldehyde (60 mg, 1 mmol), *rac*-glyceraldehyde (90 mg, 1 mmol) and $Zn(Pro)_2$–complex (29 mg, 0.10 mmol) in $H_2O$ (5 mL) was stirred for 7 d at room temperature. The solvent was removed by lyophilization and the $^1$H NMR spectrum was recorded in $D_2O$. A portion of the sugar mixture was peracetylated using the general method below. Another portion was reduced using the general method below, both samples were analyzed by GC.

### Aldol reaction between glycolaldehyde and dihydroxyacetone

A solution of glycolaldehyde (60 mg, 1 mmol), dihydroxyacetone (90 mg, 1 mmol) and $Zn(Pro)_2$–complex (29 mg, 0.10 mmol) in $H_2O$ (5 mL) was stirred for 7 d at room temperature. The solvent was removed by lyophilization and the $^1$H NMR spectrum was recorded in $D_2O$. The sugar mixture was peracetylated using the general method below and injected on GC.

### Aldol reaction between *rac*-glyceraldehyde and dihydroxyacetone

A solution of *rac*-glyceraldehyde (90 mg, 1 mmol), dihydroxyacetone (90 mg, 1 mmol) and $Zn(Pro)_2$–complex (29 mg, 0.10 mmol) in $H_2O$ (5 mL) was stirred for 7 d at room temperature. The solvent was removed by lyophilization and the $^1$H NMR spectrum was recorded in $D_2O$. The sugar mixture was peracetylated using the general method below and injected on GC.

### Sodium borohydride reduction of sugar mixtures

A solution of a sugar mixture in $H_2O$ (5 mL) was added $NaBH_4$ (*ca.* 100 mg, *ca.* 2.6 mmol) in $H_2O$ (10 mL) and was stirred for 3 h, then, treated with acetic acid and lyophilized.

### Peracetylation of the sugar mixtures

The dry residue was stirred for 24 h in a mixture of acetic acid (2 mL) and pyridine (2 mL) with DMAP (10 mg), then quenched with $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The organic phase was extracted with, respectively, 1 N HCl (60 mL), brine (60 mL) and $H_2O$ (60 mL), dried ($Na_2SO_4$) and evaporated to dryness.

### Tetrol tetraacetates

The tetrol tetraacetates were separated from the hexitol hexaacetates by flash chromatography (hexane–ethyl acetate (2 : 1). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.04–2.08 (m, 12H,

4 × OAc), 4.03 (m, 1H, $CH_2$), 4.16 (m, 1H, $CH_2$), 4.30 (m, 2H, $CH_2$), 5.24 (m, 1H, CH), 5.30 (m, 1H, CH). Anal. chiral GC (240 °C, 106 KPa, 1.35 mL $min^{-1}$): $t_R$ = 90.7 (*meso*-erythritol tetraacetate), $t_R$ = 109.6 (D-threitol tetraacetate), $t_R$ = 113.8 (L-threitol tetraacetate), ee *ca.* 10%. L-Threitol tetraacetate was synthesized as reference for chiral GC and NMR: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.09–2.13 (m, 12H, 4 × OAc), 4.08 (m, 2H, $CH_2$), 4.36 (m, 2H, $CH_2$), 5.35 (m, 2H, CH). Anal. chiral GC (240 °C, 106 KPa, 1,35 mL $min^{-1}$): $t_R$ = 114.7.

## Acknowledgements

This work was supported by the University of Berne, the Otto Mønsted Foundation, the COST D25 program and the Swiss National Science Foundation, the COST program, the Otto Mønsted Fond and the Office Federal Suisse de la Recherche Scientifique.

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