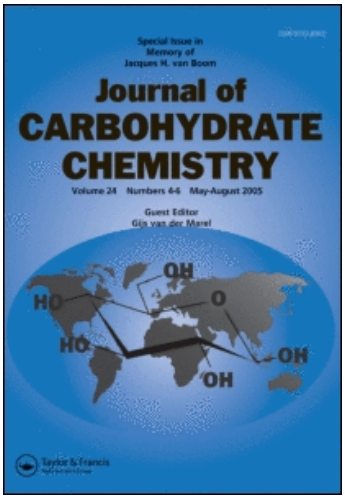

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Stereoselectivity in the Triose Aldol Condensation and the Aldol Condensation Between Glyceraldehyde and Glycolaldehyde

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To cite this Article Morgenlie, Svein(1987) 'Stereoselectivity in the Triose Aldol Condensation and the Aldol Condensation Between Glyceraldehyde and Glycolaldehyde', Journal of Carbohydrate Chemistry, 6: 4, 661 — 671
To link to this Article: DOI: 10.1080/07328308708058895
URL: http://dx.doi.org/10.1080/07328308708058895

J. CARBOHYDRATE CHEMISTRY, 6(4), 661-671 (1987)

STEREOSELECTIVITY IN THE TRIOSE ALDOL CONDENSATION AND THE ALDOL CONDENSATION BETWEEN GLYCERALDEHYDE AND GLYCOLALDEHYDE

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Received May 25, 1987 - Final Form September 23, 1987

ABSTRACT

Hydroxides of various alkali and alkaline earth metals have been investigated as catalysts in the triose aldol condensation and the aldol condensation between glyceraldehyde and glycolaldehyde. The proportions of diastereomers are very similar in the different product mixtures. Mechanistic models, previously suggested for other aldol condensations, have been considered for the reaction, and the observed diastereoselectivity is in accordance with a pericyclic transition state formed from a cis-enediolate-attack on the aldehyde.

INTRODUCTION

The aldolase-catalysed aldol condensation between triose phosphates to give fructose-1,6-diphosphate, and the analogous reaction between D-erythrose-4-phosphate and 1,3-dihydroxy-2-propanone-phosphate, are well-known biological reactions. Whereas these reactions proceed stereospecifically, the base-catalysed reactions carried out in the laboratory with the corresponding non-phosphorylated small sugars give diastereomeric mixtures.[1-5] In older work dealing with this subject, methods of determining the proportions of the diastereomers in the product mixture were limited,

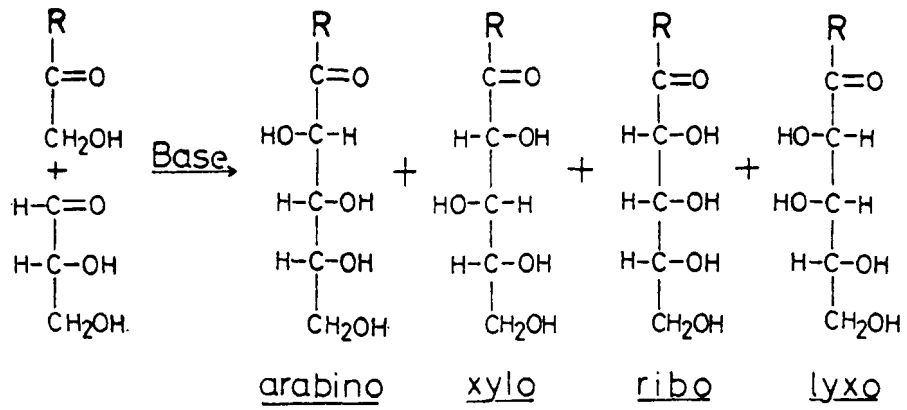
and product identification might be doubtful. Fischer and Baer[1] observed correctly that in the triose aldol condensation, the products formed in major amounts were the arabino- and xylo-2-hexuloses (fructose and sorbose). Previous work in our laboratory[6] has shown that in addition to this primary preference of formation of compounds with threo-configuration at C3-C4, a secondary preference of erythro-configuration at C4-C5 also exists, since the proportions of the products decrease in the order arabino- > xylo- > ribo- > lyxo-2-hexulose with all the catalysts employed.

The aim of the present work has been to compare the diastereoselectivity in the alkali and alkaline earth hydroxide-catalysed aldol condensation between glyceraldehyde and glycolaldehyde with that in the triose aldol condensation, and to see if any of the different mechanistic models which have been discussed[7-10] to explain the stereoselectivity in other aldol condensations, can explain that observed with the small sugars.

RESULTS AND DISCUSSION

A complex product mixture is obtained from the aldol condensation between glyceraldehyde and glycolaldehyde since partial isomerisation of the former to 1,3-dihydroxypropanone occurs. Together with the aldopentoses, 2-hexuloses from triose aldol condensation[6] are present (Scheme 1), and condensation between glycolaldehyde and 1,3-dihydroxypropanone leads to 2-pentuloses.[11] In addition, tetroses are formed from self-condensation of glycolaldehyde[11] and the branched ketohexose dendroketose from two molecules of 1,3-dihydroxypropanone.[12] All these compounds may be analysed by GLC-MS as their O-isopropylidene derivatives.[6,11,13]

In order to reduce the extent of isomerisation of glyceraldehyde, and thus the formation of ketoses in the condensation reaction, an excess of glycolaldehyde is applied in the condensation with glyceraldehyde. The tetroses formed from two molecules of glycolaldehyde give isopropylidene



R=H or CH_2OH

Scheme 1

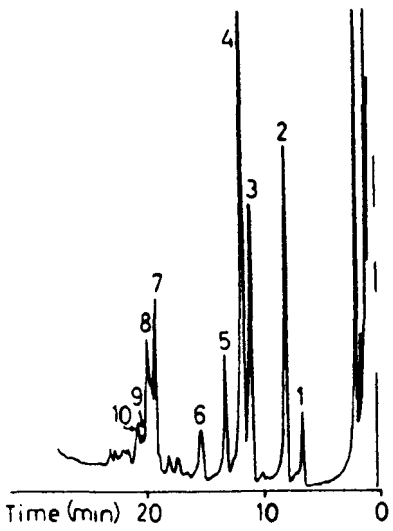


FIG. 1. Gas-chromatogram of the isopropylidene derivatives of the condensation-products from glycolaldehyde and glyceraldehyde with NaOH as catalyst. The derivatives are those of erythro-2-pentulose and 1,5-anhydro--ribofuranose (1), erythrose (2), arabinose (3), threose (4), xylose (5), dendroketose (6), threo-2-pentulose (7), fructose (8), lyxose (9), and sorbose (10).

TABLE 1

Proportions of the Diastereomers formed in the Triose Aldol Condensation and the Condensation between Glycolaldehyde and DL-Glyceraldehyde.

Catalyst	Diastereomeric composition (%)							
	2-Hexuloses				Aldopentoses			
	arabino	xylo	ribo	lyxo	arabino	xylo	ribo	lyxo
LiOH 0.02 M	55	29	11	5	58	29	10	< 3
NaOH 0.02 M	54	34	10	2	60	28	9	< 3
$Ca(OH)_2$ 0.01 M	50	30	14	6	54	28	15	< 3
$Sr(OH)_2$ 0.01 M	57	29	11	3	61	28	8	< 3
$Ba(OH)_2$ 0.01 M	50	33	13	4	65	23	9	< 3

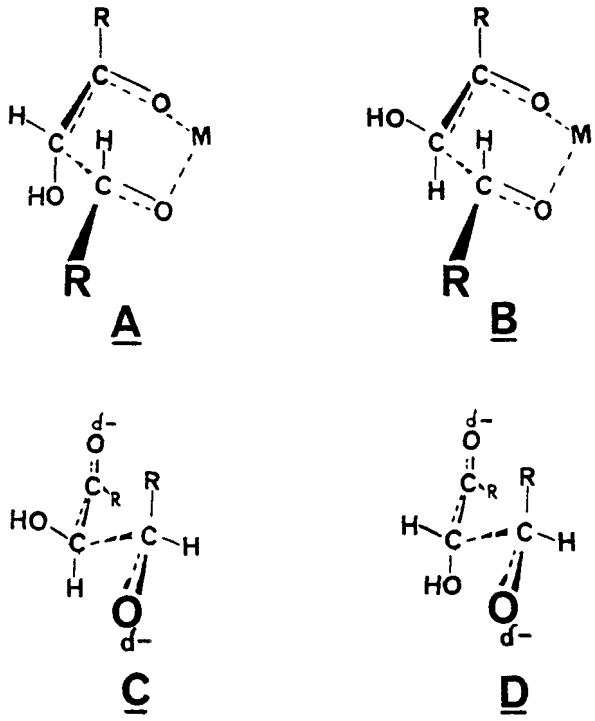


FIG. 2. Models of possible transition-states in condensations of enediolates with aldehydes.

derivatives that are well separated from the aldopentose derivatives in GLC (Fig. 1).

The diastereoselectivity in the formation of aldopentoses from glyceraldehyde and glycolaldehyde is similar to that observed for the 2-hexuloses in the triose aldol condensation (Table 1).

When four different models, previously considered for the transition state in aldol condensations,[10] are applied to the reaction between glycolaldehyde or 1,3-dihydroxypropanone and an aldehyde, they may be illustrated as in Figure 2. Two of the models are pericyclic, one based on attack of a cis-1,2-enediolate (A) and one on a trans-1,2-enediolate attack (B). The two others are extended models from cis- (C) and trans- (D) enediolates respectively.

TABLE 2

1,3-Parallel-, Axial-, and Gauche-Interactions in the Transition States leading to the Different Diastereomers for Models A - D.

Model	Destabilising interactions			
	arabino	xylo	ribo	lyxo
A	-	gauche	axial	axial, gauche
B	1,3-	1,3-	gauche	-
C and D	2 gauche	gauche	1,3-, gauche	1,3-, gauche

The destabilising interactions in the transition states leading to the different diastereomers in the aldol condensation of the small sugars are summarized for the four models (Table 2). The interactions are based upon consideration of general principles of conformational analysis and the observed tendency for alditols to adopt a gauche (synclinal) conformation about a carbon-carbon bond to avoid 1,3-parallel interactions between hydroxyl groups.[14]

Recent investigations with heptitols[15] have shown that 1,3-parallel interactions between carbon and oxygen are not more unfavourable than those between two oxygen atoms, and these interactions have been considered to be of equal magnitude in the present connection. On the basis of the destabilising interactions (Table 2), the order of decrease in stability of the various transition states has been calculated (Table 3). It is seen that only model A, involving a pericyclic transition state from a cis-enediolate, can explain the observed order of diastereomeric preference. The transition states according to this model, leading to the different diastereomers, are shown in Figure 3.

TABLE 3

Expected Order of Decrease in Stability of the Transition States leading to the Different Diastereomers for Models A-D, based on the Destabilising Interactions summarized in Table 2.

Model	Order of decrease in stability
A	arabino > xylo > ribo > lyxo
B	lyxo > ribo > xylo ~ arabino
C and D	xylo > arabino > ribo ~ lyxo

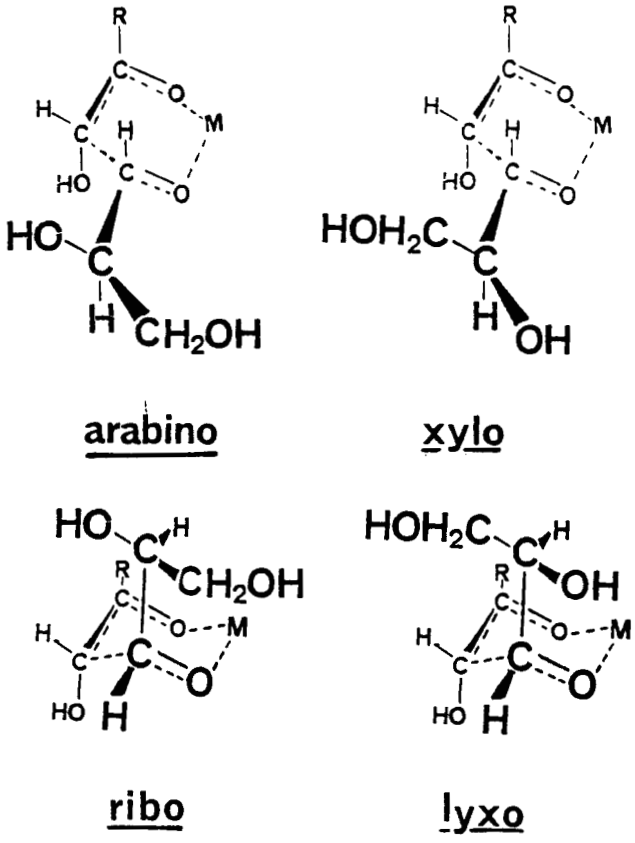


FIG. 3. Transition-states leading to the different diastereomers according to model A. The xylo- and ribo-isomers are shown as L-enantiomers to facilitate visual comparison.

The transition state for the arabino-isomer may have a zigzag planar conformation for the carbon chain from C1 to C5 (C2 to C6 for the hexuloses) without 1,3-parallel interactions. For the xylo-configuration, a gauche orientation of the chain about the C3-C4 bond prevents a 1,3-parallel interaction between OH2 and OH4. In the ribo- and lyxo-transition states, C4 is axially oriented on the six-membered ring. The lyxo-isomer in addition must have a gauche conformation of the carbon chain about C3-C4 to avoid 1,3-parallel interaction between OH4 and C1.

The possibility that the aldol condensation of the small sugars is thermodynamically controlled should not be excluded a priori. Thermodynamic control with stereoselection based on the conformational stability factors of the acyclic products in a non-chelated form is unlikely, since the lyxo- and arabino-isomers both may exist in the most stable zigzag planar conformation without 1,3-parallel interactions between hydroxyl groups. Thermodynamic control with a pericyclic reaction mechanism normally leads to an intermediate with the same geometry as in the transition state B (Fig. 2), since the equatorial position is preferred by the substituents.[10] This would lead to erythro-configuration at C2-C3 in the resulting aldopentoses (C3-C4 in the hexuloses), which also is inconsistent with the observed product composition. In light of the known ability of alkaline earth metal ions to form tridentate complexes with carbohydrates,[16] thermodynamic control with a tridentate complex-stabilised cyclic intermediate is, however, not completely excluded with these ions. An intermediate with configuration at C2 as that in transition state A (Fig. 2) is then possible, having O1, OH2 and O3 complexed with the alkaline earth metal ion. The geometry should not deviate much from that of the transition state A in such a chelate, except for the metal ion, which must occupy a position leading to a boat-like conformation of the six-membered ring.

The mechanistic models discussed in the present work are based on product-like transition states. The stereoselectivity in nucleophilic additions of organometallic and complex metal hydride reagents to carbonyl compounds is often explained from reactant-like transition state models, of which the one most widely accepted is the Felkin-Anh model.[17,18] This model does not predict the diastereoselectivity at C2-C3 (C3-C4 for the 2-hexuloses) in the aldol condensation between the small sugars. Whereas the erythro : threo ratio of about 2 at C3-C4 is in accordance with the Felkin-Anh model, it can not explain the much higher threo-selection at C2-C3 with a threo : erythro-ratio of about 6 in this reaction.

EXPERIMENTAL

General Procedures. Gas liquid chromatography (GLC) was performed on a Perkin-Elmer F 11 gas chromatograph, equipped with a flame ionisation detector. Three glass columns (6 ft x 2 mm i.d.) filled with: a, 3% of OV-225; b, 3% of Dexsil 300; and c, a mixture of 63% of 3% OV-225 and 37% of 3% ECNSS-M on 100/120 Supelcoport were applied. The temperature programme was 4 °/min from 90 to 180 °C for columns a and b, for column c it was 5 °/min from 100 to 200 °C. For GLC-MS, a Varian Aerograph 2400 gas chromatograph was used in combination with a Micromass 12 F mass spectrometer; the ionisation energy was 70 eV, the ion-source temperature 200 °C, and the accelerating voltage 4 kV.

Aldol Condensations. DL-Glyceraldehyde (20 mg) or a mixture of glycolaldehyde (14 mg) and DL-glyceraldehyde (6 mg) in water (4 mL) containing the catalyst (Table 1) was kept at room temperature for 45-60 min. The solutions were then neutralised with Dowex 50 W (H^+) ion- exchange resin, filtered, and concentrated under reduced pressure.

Preparation of O-Isopropylidene Derivatives. The products from the aldol condensations were stirred with

acetone (3 mL) containing 2% (V/V) of concd sulfuric acid for 2 h at room temperature. After neutralisation with solid sodium hydrogencarbonate, the solutions were used immediately for analysis by GLC or GLC-MS as described earlier.[6,11,13] The aldopentoses, except ribose, were analysed with column a, the 2-hexuloses with column b, and ribose as its 1,5-anhydro-2,3-O-isopropylidene derivative (retention time 6 min) with column c, on which it is separated from the derivative of erythro-2-pentulose.

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