Green Chemistry

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ROYAL SOCIETY OF CHEMISTRY

rsc.li/green-chem

View Article Online
DOI: 10.1039/C7GC03077K

Journal Name

ARTICLE

Production of keto-pentoses *via* isomerization of aldo-pentoses catalyzed by phosphates and recovery of products by anionic extraction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Xylulose and ribulose are rare keto-pentoses which are in high demand for synthesis of commodities and fine chemicals. Production of keto-pentoses via isomerization of aldo-pentoses presents a carbon-efficient synthetic method. However, the isomerizations are equilibrium processes with thermodynamically limited yields of the products. In this work we examined isomerization of aldo-pentoses into keto-pentoses in the presence of NaH_2PO_4+Na_2HPO_4 as a soluble catalyst at pH 7.5. A reaction network was proposed based on a product distribution with D-(1-^{13}C)-ribose as a substrate. Additionally, kinetics of the isomerization reactions was addressed. Selectivity for the keto-pentoses dramatically depends on a structure of a substrate. Arabinose and xylose give rise to a number of isomeric pentoses with low selectivities for the target products. Investigation of the reaction kinetics suggests that xylose and arabinose slowly isomerize into xylulose and ribulose, respectively. The latter react further significantly quicker to produce a number of isomers as subsequent products. This causes a complex mixture of products with low selectivity for the keto-pentoses. On the contrary, ribose and lyxose as substrates yield ribulose and xylulose with rather high selectivities of 68-79 % at 20 % conversion. Ribose and lyxose quickly isomerize into ribulose and xylulose, respectively, whereas the subsequent processes are relatively slow. This results in a high selectivity for the keto-pentoses based on ribose and lyxose. Moreover, the isolation of xylulose from the reaction mixture was also studied. Xylulose can be selectively recovered after the isomerization of lyxose using an anionic extraction with *o*-hydroxymethyl phenylboronic acid (HMPBA). After extraction, the aqueous phase containing phosphates and remaining lyxose can be recycled. After four cycles, the yield of xylulose reached 37 % though only 19 % can be achieved under batch conditions. Xylulose can be further recovered from the organic phase by back extraction using an acidified solution. Ribulose can also be extracted as an anionic complex with HMPBA, though ribose is co-extracted in this case and a separation of ribulose from ribose cannot be achieved. Extraction of the keto-pentoses occurs due to formation of β-xylulose-HMPBA and α-ribulose-HMPBA anionic complexes, which molecular structures were established by NMR and MS.

Introduction

Monosaccharides present the majority of available land biomass. For many years monosaccharides have been utilized for food industry and synthesis of chiral fine chemicals.[1] The interest towards chemistry of saccharides has recently increased further due to a necessity of developing a circular economy based on renewable resources. Only seven monosaccharides can be isolated in large quantities from natural sources, namely four hexoses: D-glucose, D-mannose, D-fructose, and D-galactose and three pentoses: D-ribose, D-xylose, and L-arabinose. All other monosaccharides are classified as rare and have to be manufactured synthetically. In this regard isomerization of readily available aldoses presents a carbon efficient synthetic approach that gives rise to valuable C2 ketoses. The isomerization has been thoroughly studied for hexoses, mainly glucose.[2, 3] The isomerization of aldo-pentoses results in formation of ribulose and xylulose, which are in demand as chiral substrates for synthesis of pharmaceuticals and fine chemicals.[4] In addition xylulose and ribulose can be considered as intermediates for synthesis of bio-based bulk chemicals such as furfural.[5, 6]

In general, yields of ketoses upon isomerization of aldoses are thermodynamically limited. Aldo-pentoses exist mainly in stable six-member pyranose forms, whereas keto-pentoses can be stabilized only in less energetically favourable furanose forms.[7] As a result, thermodynamic equilibriums via isomerization of the aldo-pentoses into the keto-pentoses are shifted towards the reagents. Tewari et al. investigated thermodynamics of the isomerization reactions

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C7GC03077K

under discussion,[8] and obtained the dependences of the equilibrium constants on temperature presented in Fig. 1S in the ESI. At 25 °C, the equilibrium yield of xylulose based on xylose is 15 %. At the same temperature, the yields of ribulose are thermodynamically limited to 24 and 7 % starting from ribose and arabinose, respectively.[8]

The isomerization of the aldo-pentoses requires a catalyst and can be performed for example enzymatically with a high selectivity for a desired product.[9-11] Especially the isomerization of xylose into xylulose was minutely examined, and a number of microorganisms was found to be efficient for this transformation.[9, 12-14] It was found out that the addition of borate salts significantly improves the yield of the keto-pentoses due to their *in situ* complexation with the borate anion.[12, 15] Since the formation of these stable complexes is energetically favourable, the yield of ketoses upon addition of borates can be enhanced. Nevertheless tedious downstream procedures are required to separate the products from the reaction media that contain borates in high concentrations. Dehydrogenation of a corresponding polyol presents another possibility to manufacture keto-pentoses by means of microbial synthetic methods.[10, 16] In this case no thermodynamic limitation is present, and a quantitative yield of a ketose can be achieved. Utilization of alternative substrates, for instance glyceraldehyde, pyruvic acid, and serine, provides another opportunity for biocatalytic cascade synthesis of keto-pentoses.[17] Despite great catalytic performance, a high price of enzymes can somewhat limit their applicability.

Chemo-catalytic processes can be an alternative to enzymatic methods for synthesis of keto-pentoses.[2] Typically, chemo-catalysts exhibit higher thermal stability compared to enzymes. High temperatures favour greater reaction rates and consequently higher space-time yields. Moreover a thermodynamic study predicts higher yields of the products at elevated temperatures (Fig. 1S). For example, as high yields of xylulose and ribulose as 38 and 40 %, respectively, were reported for transformations of xylose and ribose in a subcritical ethanol (80 %)-water (20 %) mixture at 180 °C.[18] At the same time, a careful optimization of temperature and a contact time is required because the saccharides exhibit limited thermal stabilities.

Isomerization catalyzed by bases known as Lobry de Bruyn-Alberda van Ekenstein reaction enables transformation of aldoses into ketoses.[1] The reaction was uncovered upon using soluble hydroxides of alkaline and alkaline-earth metals in aqueous medium. However, under these conditions, a great number of by-processes take place leading to low yields of the target products.[19, 20] The side processes can be significantly supressed in pyridine acting both as a solvent and as a base catalyst.[1] Moreover, addition of aluminates[21] or Al_2O_3[22, 23] enables further acceleration of the isomerization rates in pyridine. Despite high efficiency of this approach, utilization of aqueous solvent rather than pyridine would be of great advantage from ecological and economical viewpoints. Furthermore, the isomerization of arabinose into ribulose in the presence of calcined hydrotalcites in aqueous medium has very recently been reported. Under these conditions a 20 % selectivity for ribulose was observed.[24] Moreover, an 18 % xylulose yield at 50 % conversion of xylose was reported using a Mg-Al hydrotalcite as a catalyst and *N,N*-dimethylformamide as a solvent.[25]

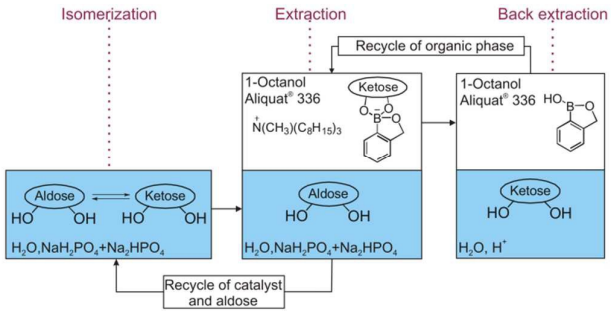

Fig. 1. Scheme of extraction-assisted isomerization of aldoses into ketoses

Utilization of Lewis acids for catalytic transformations of saccharides has recently attracted significant attention. Tin atoms embedded into a matrix of a hydrophobic material exhibited especially high catalytic activity for the aldose-ketose isomerizations among the other tested Lewis acidic catalysts.[26] Holm et al. reported the compositions of equilibrium mixtures of pentoses obtained in the presence of Sn-Beta.[27] The compositions somewhat differ from those predicted by Tewari et al.,[8] though the percentages of the pentoses are in line with their free energies.[7] Most importantly, the structure of the matrix, in which the tin atoms are embedded, appeared to play a major role in isomerization of aldo-pentoses. For example, xylose selectively isomerizes into xylulose with lyxose as a side product in the presence of Sn-Beta zeolite, *i.e.* a hydrophobic defect-free material synthesized in a fluoride medium.[5, 28] Dijkmans et al. proposed another method for synthesis of Sn-containing zeolites via a partial dealumination of BEA zeolites followed by grafting of Sn^{4+} atoms.[29] A catalyst prepared by this way catalyzes formation of lyxose as a main product, whereas xylulose was detected in lower yield.[29, 30] Moreover, Dapsens et al. reported an influence of a catalyst preparation method on the reaction selectivity in a comparative study of Sn-MFI materials prepared by bottom-up and top-down methods.[31] Additionally, we have recently uncovered a high efficiency of tin-organic frameworks for selective epimerization of monosaccharides including aldo-pentoses.[30] In conclusion, Sn-containing materials appeared to be very promising for the isomerization of pentoses, though the structure-selectivity relationships have not been fully understood yet.

In order to overcome the thermodynamic limitations, Vuorinen et al. proposed an alternative two-step method for preparation of the keto-pentoses. In the first step, an aldo-pentose, i.e. arabinose or xylose, was oxidized with copper acetate into a corresponding 1,2-dicarbonyl compound. An aldehyde group of the latter can be selectively reduced over Pd/C catalyst yielding the keto-pentoses. The overall yields of xylulose and ribulose equalled 20 and 32 %, respectively.[32]

Isolation of the ketoses from the reaction mixture presents a major challenge considering extremely low volatility of saccharides and their high polarity. The ketoses can be crystallized after derivatization yielding hydrazons.[33] Alternately the keto-pentoses can be recovered after conversion into isopropylidene acetals followed by vacuum distillation or liquid-liquid extraction.[22] Another type of purification methods is based on a selective transformation of the remaining aldose into an easily removable substance. For

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example, the aldose can be oxidized with bromine into a corresponding aldonic acid; the latter can be removed for example using anion-exchanged resins.[21] Chiang et al. proposed a treatment of the obtained mixture after isomerization xylose-xylulose with microorganisms which selectively consumed xylose leaving pure xylulose.[13] Though the described methods enable manufacture of pure ketoses, a simultaneous recovery of the remaining aldoses is mainly impossible.

This work addresses the challenges of both catalysis and product isolation using an extraction-assisted approach shown in Fig. 1. In the first step the aldose-ketose isomerization proceeds in aqueous medium in the presence of NaH_2PO_4+Na_2HPO_4 as a soluble catalyst (Isomerization in Fig. 1). We have recently shown that this catalyst is efficient for the isomerization of glucose into fructose at a mild pH 7.5.[34] At this pH value, a NaH_2PO_4+Na_2HPO_4 mixture exhibits a buffer capacity. This prevents potential influence of acidic by-products, which typically partly neutralize a base catalyst and thereby impact catalytic activity.[20, 35, 36] Since the yields of the ketoses are thermodynamically limited, a recovery of a ketose along with a reuse of the remaining aldose and the catalyst is crucial. In this work, the isolation of the keto-pentoses was performed using an anionic extraction with *o*-hydroxymethyl phenylboronic acid (HMPBA). In addition to HMPBA, an organic phase contains a tertiary amine with a bulky cation – in this case Aliquat® 336 – dissolved in 1-octanol. Formation of an ionic pair between a bulky amine cation and a bulky HMPBA-ketose complex anion favours transfer of a ketose into the organic phase (Extraction in Fig. 1). Selective extraction of a ketose from a solution containing an aldose-ketose mixture is expected due to higher affinities of ketoses to boronic acids.[37, 38] The aqueous phase after the extraction contains mainly the aldose and the phosphates and can be recycled for the isomerization. The organic phase after the extraction can be treated with an acidified solution to back-extract the ketose (Back extraction in Fig. 1). Thereafter the organic phase can be recycled as well. We have recently shown high efficiency of this approach for the isomerization of glucose into fructose.[34] Moreover, the anionic extraction with phenylboronic acid enables valorization of microbially produced 2,3-butanediol into methyl ethyl ketone.[39] Noteworthy, a similar approach for the extraction-assisted isomerization using anionic complexing with naphthalene-2-boronic acid has been recently proposed by Li et al.[40] They utilized enzymatic catalysis coupled with the *in situ* extraction of the products to synthesize xylulose based on xylose. Herein we focus on soluble phosphates as an alternative inexpensive catalyst to examine the extraction-assisted synthesis of the valuable keto-pentoses via isomerization of aldo-pentoses.

Experimental

Chemicals

D-Xylose (≥ 99.8 %) was purchased from SAFC. D-Arabinose (≥ 99 %) was obtained from Alfa Aesar. D-Ribulose (≥ 85 %) was provided by MP Biomedicals. D-(1-^{13}C)-ribose (> 98 %) was purchased from Cambridge Isotope Laboratories. Amberlyst® 15 in H^+-form was obtained from Fluka Analytical. Sodium dihydrogen phosphate monohydrate (Reag. Ph. Eur.) and 98% sulphuric acid were provided by Merck. D-Lyxose (99 %), 1-octanol (>99 %), Aliquat® 336, and Amberlite® IRA 96 free base were supplied by Sigma Aldrich. NaOH (≥ 98.8 %) from Geyer Chemsolute and chloroform-d from Deutero were used. *Ortho*-hydroxymethyl phenylboronic acid (98 %) and deuterium oxide (99.8 atom. % D) were obtained from ABCR.

All aqueous solutions were prepared in distilled water.

Isomerization

Phosphate buffers were prepared by dropwise addition of 4 M NaOH solution to the solution of 0.5 M NaH_2PO_4 using a Titroline alpha titrator unit (Schott) to pH 7.5. The experiments for investigation of the reaction network were carried out in a 20 mL autoclave equipped with a glass inlet as described previously.[34] Data for kinetic modeling was collected in experiments in glass flasks placed in a thermostated oil bath and equipped with a reflux condenser. Typically, a substrate was dissolved in the phosphate buffer at room temperature to obtain a 10 wt. % solution and charged into a flask. Temperature was measured inside the reaction mixture. The experiments were conducted under agitation on a magnetic stirrer. The samples were periodically taken and analyzed by HPLC. Noteworthy, 15-90 minutes were typically required for thermal equilibration after charging the reaction solution into a flask. Therefore, the experimental points collected in these initial periods were not considered for kinetic modeling.[41] Kinetic modeling was performed using PrestoKinetics software with a power law model for reversible reactions.[42] Estimation of parameters was performed using a simulated annealing algorithm. The 95% confident standard errors for apparent pre-exponential factors (k_0) and activation energies (E_a) were calculated using least squares lines.

Extraction

Aqueous solutions after the catalytic reactions were used to investigate a competitive extraction of aldoses and ketoses. A 10 wt. % solution of lyxose in phosphate buffer was allowed to react at 78 °C for 60 minutes in an oil bath. A 10 wt. % solution of ribose in phosphate buffer was allowed to react at 78 °C for 45 minutes in an oil bath. Thereafter the solutions were cooled down in an ice bath and the extraction experiments were carried out.

Typically, an organic phase contained HMPBA and Aliquat® 336 in equimolar concentrations dissolved in 1-octanol. Prior to the extraction, the organic phase was pretreated by stirring with 0.5 M NaH_2PO_4+Na_2HPO_4 at pH 7.5 for 30 minutes at room temperature. In a typical extraction experiment, 4 mL of an organic phase and 4 mL of an aqueous phase were stirred at 750 rpm for 1 h at room temperature. Thereafter the phases were separated by centrifugation for 1 min at 7000 rpm. After splitting the phases, back-extraction was performed: 4 mL of the organic phase after the extraction were stirred with 4 mL of 0.5 M H_2SO_4 for 30 minutes at room temperature.

The samples for analysis by electrospray ionization mass spectrometry (ESI-MS) were prepared using a typical extraction procedure. After separation of the phases, the organic phase was diluted 1:50 with 1-octanol. The diluted samples were injected into an LCMS-2020 liquid chromatograph mass spectrometer.

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For NMR investigations, typical extraction experiments were performed. An aqueous phase presented a solution after isomerizing 10 wt. % lyxose or ribose in 0.5 M phosphate buffer prepared in D_2O. An organic phase was prepared by dissolution of HMPBA (0.2 M) and Aliquat® 336 (0.2 M) in $CDCl_3$. The organic phase was pretreated prior to the extraction experiment: The organic phase was stirred with 0.5 M phosphate buffer prepared in D_2O (1:1 vol:vol) for 30 minutes at room temperature. After the pretreatment, the phases were separated after centrifugation for 1 min at 7000 rpm. The extraction was performed under stirring at room temperature for 1 h. After completing the extraction and separation of the phases, the organic phase was investigated using NMR. ^{1}H (400 MHz), ^{13}C (101 MHz), and ^{11}B (96 MHz) NMR spectra were recorded on Bruker spectrometers. Chemical shifts are reported in δ (ppm) units using ^{13}C and residual ^{1}H signals from deuterated solvents. CH_3OH (δ 49.5 ppm) was used as an internal reference for ^{13}C NMR spectra recorded in D_2O. The ^{11}B NMR spectra were referenced to Et_2O-BF_3 in $CDCl_3$ as 0. Structures of complexes of xylulose and ribulose with HMPBA were proposed based on the results of COSY, HSQC, DEPT 90, DEPT 135, and APT ^{13}C NMR spectra.

Extraction-assisted isomerization

The isomerization was performed using 10 mL of 10 wt. % lyxose solution in NaH_2PO_4+Na_2HPO_4 at pH 7.5 at 89 °C for 20 minutes. The experiments were conducted in a glass flask as described above. After the isomerization experiment, the reaction mixture was cooled down using an ice bath. A sample of 1 mL was taken for analysis. Xylulose was extracted from the reaction mixture (5 mL) using an organic solution of 0.1 M HMPBA and 0.1 M Aliquat® 336 in 1-octanol (5 mL). After the extraction, a sample of 0.5 mL was taken from the aqueous phase for analysis. The rest of the reaction mixture after the extraction (4 mL) was mixed with 4 mL of 11.8 wt. % lyxose solution in NaH_2PO_4+Na_2HPO_4. The pH of the obtained solution was adjusted to 7.5 according to pH-meter by dropwise adding 4 M NaOH. The prepared solution was used as a feedstock for the next run of the isomerization.

High-performance liquid chromatography (HPLC)

Concentrations of saccharides in aqueous phase in all cases were determined by means of HPLC using a Shimadzu Prominence LC-20 system. Typically the samples after catalytic or extraction experiments were 10-fold diluted with water. Prior to the analysis, the diluted samples were treated with ion-exchanged resins to remove dissolved salts. 10 mL of a solution were first allowed to stir with 200 mg of Amberlyst® 15 in H^+-form at room temperature for 30 minutes. Thereafter the solution was separated by centrifugation and was allowed to stir at room temperature for 60 minutes with 500 mg of Amberlite® IRA 96 free base. After the treatments with the ion-exchanged resins, the solutions were filtered through a polyamide syringe filter (Chromaphil, polyamide, pore size 0.2 µm). The samples were injected into an Accucore Amid-Hilic 0.05M trimethylamine column (Thermo Fischer, 100 mm × 4.6 mm) at 40 °C; the eluent (90 vol. % acetonitrile + 10 vol. % 0.02 trimethylamine in water) was supplied at 1 mL min^{-1} flow rate. Additionally the saccharides were separated on two successively connected Organic Acid Resin columns (CS-Chromatographie, 100 mm × 8.0 mm and 300 mm × 8.0 mm) thermostated at 40 °C and eluted with a CF_3COOH solution (154 µL of in 1L of water) at a 1 mL min^{-1} flow rate. The system was equipped with an RI detector.

Results and discussion

Reaction network and kinetics

The NaH_2PO_4+Na_2HPO_4 catalyst was tested for isomerization of aldo-pentoses of various structures, namely xylose, lyxose, arabinose, and ribose. Table 1 presents data on product distributions at conversion of the substrates of 15-24 %. We previously showed that the isomerization of glucose in the presence of NaH_2PO_4+Na_2HPO_4 yields fructose with selectivity of 90 % at conversion of 20 %.[34] Selectivities for keto-pentoses were clearly lower compared to fructose. Formation of the both keto-pentoses and a C2 epimeric aldose was observed for every substrate. Similar product distributions were reported for the isomerization of the aldo-pentoses in pyridine. Formation of numerous products was explained by relatively high free energies of the keto-pentoses, which brings about an easy epimerization at C3 positions.[22, 23]

A reaction network shown in Scheme 1 can be proposed for isomerization of pentoses. In this case isomerization of an aldose first gives rise to a C2 ketose and an aldose epimeric at C2 position. The obtained ketose undergoes epimerization at the C3 position. Finally, the latter ketose isomerizes into corresponding aldoses as well. For example, isomerization of ribose gives rise to ribulose and arabinose as primary products; the epimerization of ribulose at the C3 positions causes the formation of xylulose; xylose and lyxose are finally formed upon isomerization of xylulose.

At the same time, El Khadem et al. reported that fragmentation-recombination is partly responsible for the formation of monosaccharides in aqueous solution with KOH as a catalyst.[19] The isomerization of glucose into fructose in the presence of NaH_2PO_4+Na_2HPO_4 presents a specific-base-catalyzed reaction in aqueous phase.[34] In this work, the products of fragmentation via retro aldol reaction, i.e. glycolaldehyde, glyceraldehyde, and dihydroxyacetone, were detected in reaction mixtures in minor amounts. Therefore, formation of monosaccharides owing to consecutive retro aldol and aldol reactions cannot be excluded.

Table 1 Results of the isomerization of aldo-pentoses in the presence of NaH_2PO_4+Na_2HPO_4. Reaction conditions: 10 wt. % aqueous solution of a substrate, 78 °C, 750 rpm.

Entry	Substrate	Time, h	Conversion, %	Distribution of pentoses, %						Mass balance, %
				Xylose	Lyxose	Arabinose	Ribose	Xylulose	Ribulose	
1	Xylose	3.6	15	87	4	1	1	6	1	94
2	Lyxose	1.1	24	2	85	0	0	12	1	94
3	Arabinose	3.3	20	0	3	83	7	3	5	93
4	Ribose	0.8	22	0	1	3	75	5	15	96

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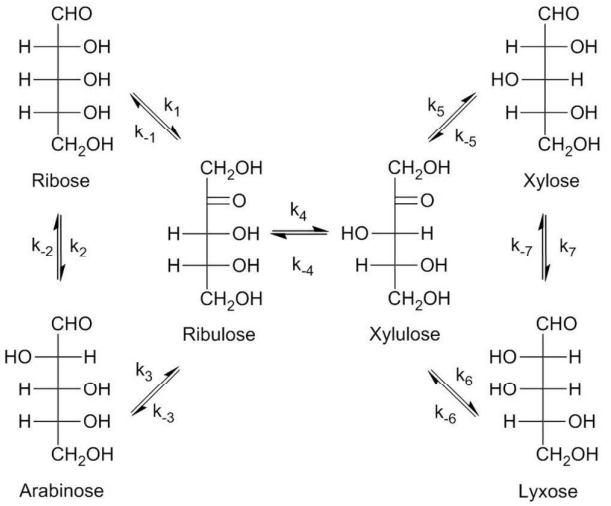
If the formation of monosaccharides takes place according to the reaction network presented in Scheme 1, the sequence of carbon atoms in the skeletons remains unchanged. However, if the mechanism of successive retro aldol and aldol, i.e. fragmentation-recombination, significantly contributes to the formation of the products, a change of the sequence of carbon atoms can be expected.[43] Two examples of the consecutive retro aldol and aldol reactions leading to a rearrangement of a carbon chain are shown in Scheme 1S. We investigated the isomerization of D-(1-^{13}C)-ribose as a substrate to uncover the isomerization mechanism. Fig. 2 presents the results of this investigation. A ^{13}C NMR spectrum before reaction exhibits four intensive signals at 101.6, 96.9, 94.5, and 94.2 ppm, corresponding to the first atoms of β-D-ribofuranose, α-D-ribofuranose, β-D-ribopyranose, and α-D-ribopyranose, respectively. After the reaction, a number of other ^{13}C NMR resonance signals appeared in the spectrum of the reaction mixture. The most intensive of them correspond to the first labeled atoms of D-(1-^{13}C)-ribulose (at 67.0, 63.4, and 63.2 ppm) and D-(1-^{13}C)-xylulose (at 66.6, 63.7, and 63.1 ppm) that are present in solution in various tautomeric forms. Moreover, a signal at 97.4 ppm can be assigned to D-(1-^{13}C)-arabinose. However, a few strong resonance signals (peaks NN 1, 7, 8, and 9 in Fig. 2) correspond to the labeled atoms of the saccharides in the positions C5 and C2 (Table 1S), which indicates an isotopic scrambling to some extend upon the isomerization. Additionally, the fragmentation of pentoses would give rise to C_2 and C_3 building blocks which recombine to yield C_4, C_5, and C_6 saccharides.[44] The reaction mixtures after the isomerization in the presence of NaH_2PO_4+Na_2HPO_4 were treated with $NaBH_4$ to yield corresponding polyols and derivatized with acetic anhydride after evaporation of water in vacuum. The acetylated polyols were analyzed by GC as reported previously by Hausoul et al.[45] This analysis indicated formation of nearly exclusively C_5-polyols (results are not shown), proving formation of C_4 and C_6 saccharides in negligible amounts.



Scheme 1. Reaction network for the isomerization of pentoses in the presence of NaH_2PO_4+Na_2HPO_4.

Based on these results, we can conclude that the reaction network shown in Scheme 1 indeed displays the main reaction pathways for the formation of isomeric pentoses in the presence of NaH_2PO_4+Na_2HPO_4, though the fragmentation-recombination pathway also contributes a minor share to the overall process.

Interestingly, the reaction rates of the isomerization and the selectivities for the ketoses considerably depend on the structure of the substrate (Table 1). For example, rather promising results were obtained for the isomerizations of ribose into ribulose and lyxose into xylulose. Further investigations were focused on studying the kinetics of the isomerization processes in order to obtain a better insight into the reaction pathways.

Kinetic modeling was performed using a power law model. We previously showed that the glucose isomerization in the presence of NaH_2PO_4+Na_2HPO_4 is a specific-base-catalyzed reaction.[34]

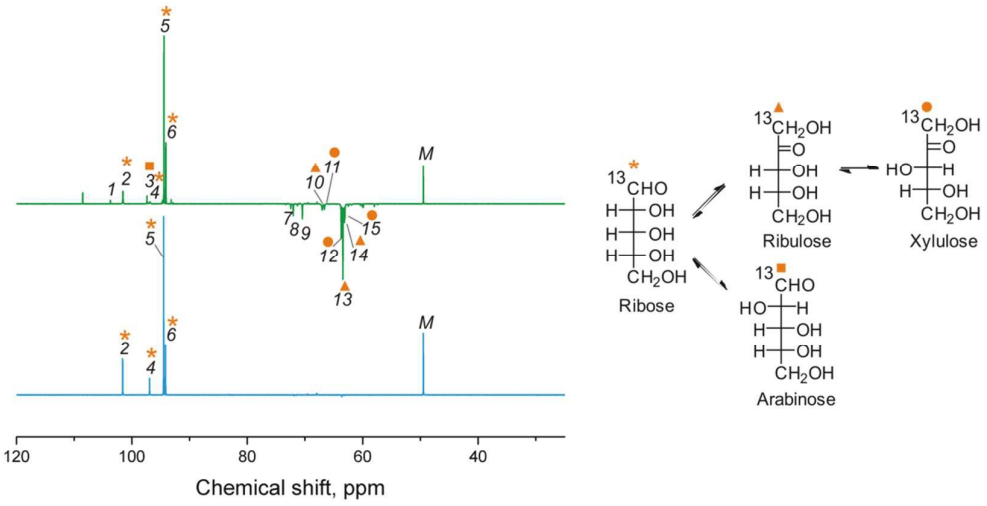


Fig. 2. ^{13}C NMR spectra of D-(1-^{13}C)-ribose as a substrate (bottom) and the reaction mixture after the reaction (top) in the presence of NaH_2PO_4+Na_2HPO_4. *M* denotes a resonance signal of methanol used as an internal standard. A full list of the resonance signals with their assignments is provided in Table 1S.

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Consequently, the reaction rate depends on the pH value, i.e. on the concentration of the OH^- ions in solution. Since NaH_2PO_4+Na_2HPO_4 exhibits the properties of a buffer at pH 7.5, the pH value of the reaction mixture remains constant during the course of the reactions. As a result, the apparent rate constants k determined in this work present lumped parameters including the intrinsic rate constants and the catalyst concentration. The isomerization exhibited a first-order reaction with respect to a substrate (Fig. 2S). The reaction network presented in Scheme 1 was supplemented with the pathways to by-products (Scheme 2S) to improve the fittings. Noteworthy, 15-90 minutes were typically required for thermal equilibration of the solution after charging a reaction mixture into a flask. The points corresponding to these initial periods of time were not considered for the modelling. Mass balances for the isomerization reactions were typically better than 90 %.

The defined kinetic parameters described the behaviour of the reaction system rather good (Fig. 3 and Figures 3S-6S), although slight deviations at some experimental data were observed. Table 2 summarizes the determined kinetic parameters. The obtained pre-exponential factors are of the same order of magnitude as previously reported for isomerization of glucose in the presence of a base catalyst sodium aluminate.[46] The activation energies for the isomerization reactions are in the range of 100-150 kJ mol^{-1} (Table 2). These values are in line with the previously reported activation energy for isomerization of arabinose catalyzed by a CoMnAlMg mixed oxide as a solid base.[24] Additionally, the obtained values of kinetic constants were verified addressing the thermodynamics of the isomerization reactions.[8, 47] Equilibrium constants for different steps of the process were estimated as ratios of the rate constants for forward and backward reactions. The calculated values are in good agreement with the literature data (Table 3S). In addition, the reaction network presents two cycles of reversible reactions, including isomerizations of ribose-arabinose-ribulose and lyxose-xylose-xylulose (Scheme 1). Due to the reversibility, the Gibbs energy of these cycles equals zero and the values of the overall equilibrium constants equal one. Based on this, accuracy of the determined reaction constants was estimated. In most cases a relative error of the rate constant is in range of 5-15% (Table 4S). Most importantly, the parity plot shown in Figure 7S confirms the choice of a suitable kinetic model for this reaction.

Table 2. Apparent pre-exponential factors (k_0) and activation energies (E_a) ± standard errors obtained for the isomerization of pentoses in the presence of NaH_2PO_4+Na_2HPO_4.

Entry	Reaction	ln k_0	E_a, kJ mol^{-1}
1	Ribose $\xrightarrow{k_1}$ Ribulose	31.5 ± 1.1	118 ± 3
2	Ribulose $\xrightarrow{k_{-1}}$ Ribose	31.4 ± 0.9	117 ± 2
3	Ribose $\xrightarrow{k_2}$ Arabinose	34.2 ± 1.0	138 ± 3
4	Arabinose $\xrightarrow{k_{-2}}$ Ribose	26.2 ± 0.9	116 ± 3
5	Arabinose $\xrightarrow{k_3}$ Ribulose	35.9 ± 1.1	138 ± 3
6	Ribulose $\xrightarrow{k_{-3}}$ Arabinose	27.9 ± 1.0	111 ± 3
7	Ribulose $\xrightarrow{k_4}$ Xylulose	27.9 ± 0.8	107 ± 2
8	Xylulose $\xrightarrow{k_{-4}}$ Ribulose	30.5 ± 1.0	116 ± 3
9	Xylulose $\xrightarrow{k_5}$ Xylose	33.4 ± 1.0	127 ± 3
10	Xylose $\xrightarrow{k_{-5}}$ Xylulose	38.0 ± 1.1	143 ± 3
11	Xylulose $\xrightarrow{k_6}$ Lyxose	35.9 ± 0.9	129 ± 3
12	Lyxose $\xrightarrow{k_{-6}}$ Xylulose	36.0 ± 1.1	133 ± 3
13	Xylose $\xrightarrow{k_7}$ Lyxose	35.6 ± 1.1	146 ± 3
14	Lyxose $\xrightarrow{k_{-7}}$ Xylose	35.0 ± 1.2	143 ± 3

Values of kinetic constants for isomerization of aldoses into corresponding ketoses decrease in a row: ribose > lyxose > xylose > arabinose. According to the Arrhenius law, a kinetic constant represents a superposition of a pre-exponential factor and activation energy. For monomolecular reactions, a pre-exponential factor is determined by a frequency of a bond vibration as well as by geometry of a substrate and a transition state. The results shown in Table 2 suggest that the pre-exponential factors significantly depend on the substrate nature (Entries 1, 5, 10, and 12, Table 2). It has to be taken into account that all the substrates are present in aqueous solutions as mixtures of four cyclic isomers, namely as α-furanoside, α-pyranoside, β-furanoside, and β-pyranoside (Fig 8S). Geometry of each of cyclic isomers is quite complex; therefore, interpretation of the obtained pre-exponential factors requires further investigations which are out of scope of this study. However, different values of the obtained activation energy can be explained in terms of relative free energy of the substrates. A term "relative free energy" was coined by Angyal to evaluate energy differences of monosaccharides in pyranose conformation.[7] Relative free energy can be estimated by adding the values of non-bonded interactions occurring in each conformer plus the value of the anomeric effect. For example, interaction between an axial hydrogen atom and an axial oxygen atom is 0.45 kcal mol^{-1}, between two axial oxygen atoms is 1.5 kcal mol^{-1}, etc. Further details on calculation of relative free energy are provided in reference [7]. Low relative free energies correspond to more thermodynamically stable molecules. Though this estimation is quite simple, it enables rather accurate predicting a ratio of α-to-β anomers and a predominant C1 or 1C pyranose conformation.[7] Comparison of relative free energies explains differences in activation energy of isomerization of aldo-pentoses (Table 2) and glucose (125 kJ mol^{-1}, as determined previously[34]) in the presence of the phosphates. All these substrates are mainly present as pyranoses in aqueous solutions (Fig 8S, Table 5S). According to Angyal, an average relative free energy decreases as follows: ribose (2.6 kcal mol^{-1}) > glucose (2.2 kcal mol^{-1}) > arabinose (2.05 kcal mol^{-1}) ≈ lyxose (2.0 kcal mol^{-1}) > xylose (1.7 kcal mol^{-1}).[7] This indicates ribose and xylose as the least and most thermodynamically stable molecules, respectively. This correlates rather well with the obtained values of activation energy: ribose-to-ribulose (119 kJ mol^{-1}) < glucose-to-fructose (125 kJ mol^{-1}) < arabinose-to-ribulose (138 kJ mol^{-1}) ≈ lyxose-to-xylulose (133 kJ mol^{-1}) < xylose-to-xylulose (143 kJ mol^{-1}) (Fig. 9S).

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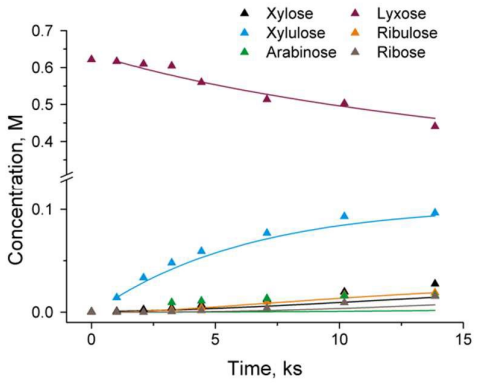
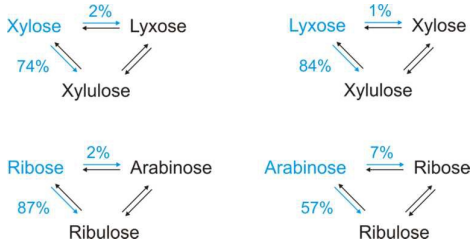


Fig. 3. Model (solid line) and experimental data (markers) of lyxose isomerization in the presence of NaH_2PO_4+Na_2HPO_4 at 70 °C. Results of kinetic modeling for other substrates and temperatures are provided in the ESI.

With the kinetic model in hand, a further insight into the reaction progress can be performed. According to the reaction network (Scheme 1), an aldose substrate can isomerize either into a ketose or into an epimeric aldose. Differential selectivity can be used to identify a contribution of each pathway into an overall consumption of a substrate. By definition, differential selectivity is the ratio of the rate of desired product formation to the total rate of the substrate consumption.[36] Integral selectivity can depend on the substrate conversion, whereas a differential selectivity cannot. Further details on calculation of differential selectivities in this work are provided in the ESI. Scheme 2 demonstrates that the isomerization of a substrate into a 2-ketose in the presence of NaH_2PO_4+Na_2HPO_4 significantly predominates over the epimerization for all the tested aldo-pentoses.

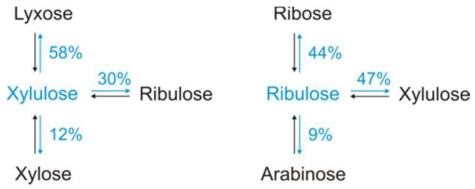


Scheme 2. Differential selectivities for an isomeric keto-pentose and an epimeric aldo-pentose in the presence of NaH_2PO_4+Na_2HPO_4 at 78 °C.

Differential selectivity can also be used to elucidate the pathways for consumption of the keto-pentoses. They can interconvert into one of corresponding aldo-pentoses or undergo an epimerization at C3 position to yield an isomeric ketose (Scheme 3). The rate of xylulose conversion into lyxose is significantly greater than into xylose. Similarly, the rate of ribose formation based on ribulose dramatically exceeds the rate of arabinose formation. *Ca.* 30-50 % of primarily formed keto-pentoses are converted into an isomeric ketose by undergoing an epimerization at C3 position.

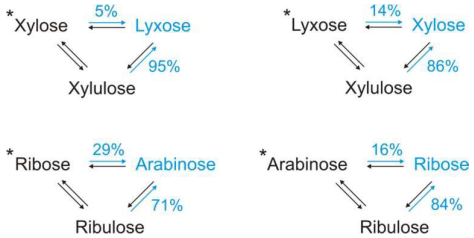
According to Scheme 2, the aldo-pentoses isomerize mostly into the keto-pentoses, whereas only minor shares of aldoses undergo direct epimerization. Nevertheless, the epimeric aldo-pentoses were present in significant amounts especially as products of isomerization of xylose and arabinose (Table 1). A comparison of the formation rates of aldoses based on ketoses and epimeric aldoses explains these observations (Scheme 4, details on rate estimations are provided in the ESI). The epimeric aldoses are formed predominantly due to isomerization of ketoses, whereas only a minor part of aldoses is formed due to the direct epimerization. Noteworthy, the rates of epimerizations and ketose-to-aldose isomerizations clearly depend on conversion of an aldose. However, already at very low conversions of 2-6 %, the isomerization of ketoses becomes a major pathway yielding epimeric aldoses (results not shown).

The results of kinetic modeling can be summarized as follows. Ribose and lyxose isomerize quickly to yield mainly the corresponding ketoses, namely ribulose and xylulose, respectively (Table 6S). The latter are relatively stable under the reaction conditions, since their isomerization into by-products is slower or at least of comparable rate than the rates of their formation and the



Scheme 3. Differential selectivities for various isomers during the conversion of keto-pentoses in the presence of NaH_2PO_4+Na_2HPO_4 at 78 °C.

backward reaction yielding the substrates (Scheme 3). The quick formation of the product and the slow subsequent reactions enable high selectivity for the ketoses based on ribose and lyxose. Xylose and arabinose also yield the ketoses (xylulose and ribulose, respectively) as the primary products (Scheme 2). However, these reactions are rather slow compared to the subsequent transformations of the ketoses (Table 4S, Scheme 3). As a result, the ketoses quickly undergo further isomerization processes and do not accumulate in the reaction mixtures when using xylose and arabinose as substrates.



Scheme 4. Percentage of an epimeric aldo-pentose formed via direct epimerization of an aldo-pentose and isomerization of a ketose in the presence of NaH_2PO_4+Na_2HPO_4 at 78 °C at 10 % conversion of a substrate. An asterisk indicates a substrate.

A positive effect of high temperature on the maximal yield of the ketoses based on ribose and lyxose is of practical importance (Fig. 10S). According to the results of kinetic modeling, a temperature increase from 50 to 100 °C leads to the improvement of maximum yield of ribulose from 16 to 21 % and of xylulose from 15 to 18 %. This can be explained by somewhat higher activation energies of the isomerization of aldoses into ketoses, i.e. ribose-ribulose and

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lyxose-xylulose, compared to the C3 epimerization of ribulose-xylulose. In addition, dependences of the equilibrium constants on temperature also predict improvement of the yields of ketoses at high temperature (Fig. 1S).[8]

Extraction of keto-pentoses

Anionic extraction using a boronic acid can be utilized for selective recovery of ketoses from a solution containing a mixture of an aldose and a ketose. The selective separation can be achieved due to higher complexation constants of ketose-boronate complexes than aldose-boronate complexes. HMPBA (Fig. 1) demonstrates greater complexation constants with saccharides than phenylboronic acid due to formation of an intrinsic ester bond.[37, 48] HMPBA was shown to be efficient for selective recovery of fructose from a fructose-glucose mixture[34] and therefore was tested in this work for extraction of keto-pentoses.

Reaction mixtures obtained after isomerization of lyxose or ribose in the presence of NaH_2PO_4+Na_2HPO_4 were utilized for investigating the anionic extraction of xylulose or ribulose, respectively. These reaction mixtures contained rest of a substrate, and a corresponding ketose; additionally a C3 epimeric keto-pentose and other pentoses in minor amounts were present in the solutions (Table 7S). In order to optimize the extraction conditions, the concentration of HMPBA in the organic phase was varied. First, the recovery of xylulose from the lyxose-xylulose mixture with some minor amounts of ribulose was considered (Entries 1-6, Table 3). Lowering concentration of HMPBA in the organic phase results in somewhat diminishing amount of the extracted xylulose, though selectivity for the extracted xylulose rises and reaches its maximum of 80 % at the HMPBA:xylulose molar ratio of 1.4. Under these conditions, 71 % of xylulose was extracted from the solution (Entry 4, Table 3). Interestingly, selectivity of extraction somewhat decreased when using sub-equimolar amounts of HMPBA with respect to xylulose (Entries 5 and 6, Table 3). Next, the isolation of ribulose from a ribulose-ribose mixture (Entries 7-12, Table 3) was examined. Ribulose can be indeed isolated from the mixture, though its separation from ribose was not achieved at any concentration of HMPBA. The highest selectivity for ribulose separation of 54 % was achieved at 46 % of ribulose recovery (Entry 10, Table 3). Apparently, the differences in complexation constants of ribulose-ribose are not as considerable as for glucose-fructose and lyxose-xylulose. Indeed, outstandingly stable complexes of ribose with borate anions are well known. Their stability is superior to the stability of complexes with other aldo-pentoses, since only ribose can form a complex at C2 and C3 with a borate anion in *trans*-position towards both the -CH_2OH and the -OH rests on the furanose ring.[49]

The structural formulae of the xylulose-HMPBA and ribulose-HMPBA complexes were determined. The ESI-MS traces exhibited a characteristic peak of m/z 265 in negative mode (Fig. 11S). This suggests a 1:1 ketose-to-HMPBA molar ratio upon the complexation. ^{13}C and ^{1}H NMR studies suggest the extraction of the xylulose and ribulose as the most abundant tautomers, i.e. β-xylulose and α-ribulose. Comparing ^{13}C NMR spectra of pure saccharides and complexed saccharides provides information on the molecular structure of complexes (Fig. 12S). Typically, ^{13}C resonances of the atoms involved in the cyclic borate ester undergo

Table 3. Results of anionic extraction of saccharides with HMPBA. Extraction conditions: 4 mL of an aqueous phase containing 0.5 M NaH_2PO_4 + Na_2HPO_4 and saccharides; 4 mL of an organic phase containing equimolar amounts of HMPBA and Aliquat® 336 in 1-octanol under stirring at 750 rpm for 1 h at room temperature

Entry	Initial concentration of saccharides, M			[HMPBA], M	Ratio HMPBA-to-ketose, mol:mol [a]	Extracted saccharides, % [b]			Selectivity of extraction, % [b]		
Separation of lyxose-xylulose											
	$[Xylulose]_0$	$[Lyxose]_0$	$[Ribulose]_0$		HMPBA: xylulose	Xylulose	Lyxose	Ribulose	Xylulose	Lyxose	Ribulose
1	0.073	0.45	0.009	0.4	5.5	90	16	87	45	48	3
2	0.073	0.45	0.009	0.3	4.1	89	14	81	47	45	6
3	0.073	0.45	0.009	0.2	2.7	87	6	65	64	28	6
4	0.073	0.45	0.009	0.1	1.4	71	1	52	80	8	8
5	0.073	0.45	0.009	0.075	1.0	65	2	37	77	12	6
6	0.073	0.45	0.009	0.05	0.7	51	2	25	72	13	5
Separation of ribose-ribulose											
	$[Ribulose]_0$	$[Ribose]_0$	$[Xylulose]_0$		HMPBA: ribulose	Ribulose	Ribose	Xylulose	Ribulose	Ribose	Xylulose
7	0.087	0.43	0.014	0.4	4.9	83	24	94	39	54	7
8	0.087	0.43	0.014	0.3	3.7	76	17	86	43	48	8
9	0.087	0.43	0.014	0.2	2.4	68	12	86	47	41	10
10	0.087	0.43	0.014	0.1	1.2	46	6	65	54	33	12
11	0.087	0.43	0.014	0.075	0.9	41	9	62	40	47	11
12	0.087	0.43	0.014	0.05	0.6	26	4	42	43	39	12

[a] molar ratio of HMPBA-to-xylulose for entries 1-6 and HMPBA-to-ribulose for entries 7-12, respectively; [b] details on calculation of share of extracted saccharides and selectivity of extraction are provided in ESI.

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downfield shift compared to the pure saccharide. Chemical shifts of carbon atoms not involved in complexation do not vary dramatically for pure saccharides and complexes.[49] The ^{13}C resonance signals of the β-xylulose-HMPBA and α-ribulose-HMPBA complexes significantly varied only in the shifts of the C3 atoms (Table 8S). However, the quaternary C2 atoms were not registered due to low intensity in spectrum. This result implies the structures of complexes shown in Fig. 4.

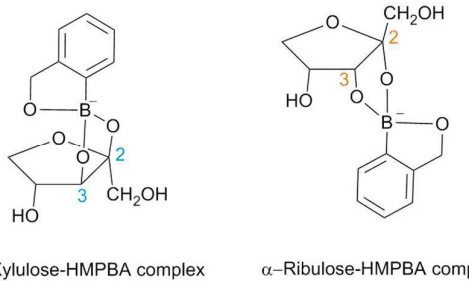

Fig. 4. Structural formulae of the anionic complexes xylulose-HMPBA and ribulose-HMPBA.

We implemented the extraction-assisted isomerizations of lyxose into xylulose (Fig. 1) using a phosphate buffer NaH_2PO_4+Na_2HPO_4 at pH 7.5 as a catalyst. The isomerization was performed at 89 °C for 20 minutes. Under these conditions, conversion of lyxose was in the range of 16-22 %, and high selectivity for xylulose of ca. 70 % was observed (Table 9S). After the isomerization, xylulose was isolated from the reaction mixture using the anionic extraction with 0.1 M HMPBA, as these conditions favor selective extraction of xylulose (Table 3). About 50 % of xylulose was extracted from the reaction mixture with a rather high selectivity of ca. 90 %. The aqueous phase obtained after the extraction was reused for the next run of the isomerization and the extraction. Since the pH decreased to 7.1 during the extraction, the pH of the aqueous phase was adjusted to 7.5 prior to the next isomerization run by adding NaOH solution. Additionally, a concentrated solution of lyxose was added to keep the initial substrate concentration of *ca.* 10 wt. %. The results of the extraction-assisted experiments are shown in Fig. 5 and Table 9S. The yield of xylulose under batch conditions does not exceed 19 % due to thermodynamic limitations and the consecutive reactions. Isolation of xylulose using the anionic extraction enables an equilibrium shift towards the product. A doubled yield of xylulose was obtained after four runs (Fig. 5). In addition, the proposed method allows recovery of xylulose by means of a rather selective extraction of the product. Xylulose can be isolated from the organic phase by back extraction with 0.5 M H_2SO_4 according to the previously described procedure.[34] About 80-90 % of xylulose can be recovered upon the back extraction. Apparently, highly reactive xylulose and ribulose cannot be stored in an acidic solution and a further work-up, such as a neutralization or treatment with ion-exchange resins followed by lyophilization, is required. In addition, the products have to be stored under low temperature to avoid further reactions.

Conclusions

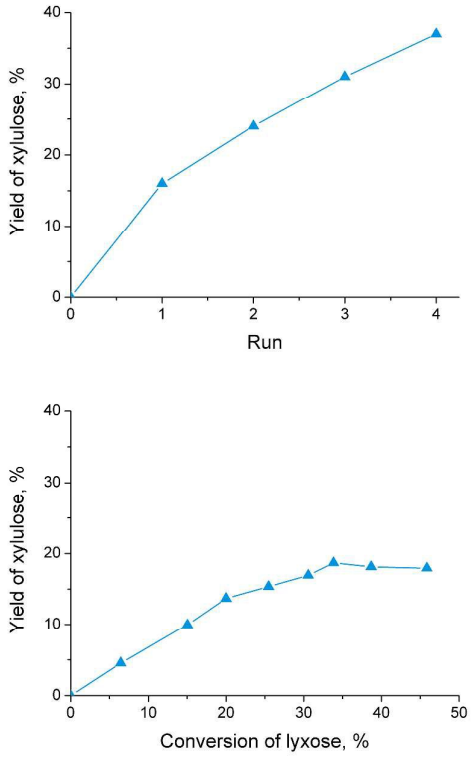

Fig. 5. Yield of xylulose obtained by the extraction-assisted isomerization of lyxose (top) or the isomerization of lyxose under batch conditions (bottom) at 89 °C using 10 wt. % lyxose as a substrate and NaH_2PO_4+Na_2HPO_4 as a catalyst.

A method to produce rare keto-pentoses based on aldo-pentoses is proposed in this study. NaH_2PO_4+Na_2HPO_4 can be used for the isomerization as a simple soluble base catalyst. Four tested aldo-pentoses demonstrated different reactivities and selectivities for the target products. Isomerization of lyxose and ribose exhibits the greatest selectivities for xylulose and ribulose, respectively. Examination of the reaction network and the kinetics enabled insight into the reaction pathways. A possibility to recover a ketose from a solution containing an aldose and a ketose using an anionic extraction with HMPBA was examined. Xylulose can be selectively extracted from the mixture with lyxose, whereas the aldose and the phosphate catalyst remain in the aqueous medium. This enables recovery of the product and utilizing the rest of the substrate for the isomerization. Unfortunately, ribulose cannot be recovered in the same way from a mixture of ribulose-ribose owing to similar affinities of ribose and ribulose to HMPBA.

The proposed method can be expected to be of relevance for synthesis of xylulose as a highly demanded and nevertheless a very expensive keto-pentose. Though lyxose is not as readily available as other aldo-pentoses, its price is significantly lower than the price of xylulose. The promising results of selective catalytic synthesis of ribulose based on ribose in the presence of NaH_2PO_4+Na_2HPO_4 can be utilized provided that an efficient method to separate ribulose is uncovered. Our current studies are focused on this point along with the improvement of the environmental impact of this approach. This includes diminishing the utilization of organic solvents as well as acids/bases as auxiliaries.

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Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

We thank Prof. Dr. Regina Palkovits for the valuable discussions. We thank Noah Avraham and Simon Petring for the HPLC and ESI-MS analysis. The work is funded by the Excellence Initiative of the German federal and state governments.

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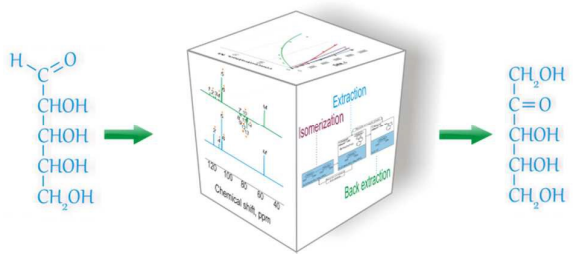
DOI: 10.1039/C7GC03077K



The article considers catalytic isomerization of aldo-pentoses into keto-pentoses combined with a product recovery by anionic extraction