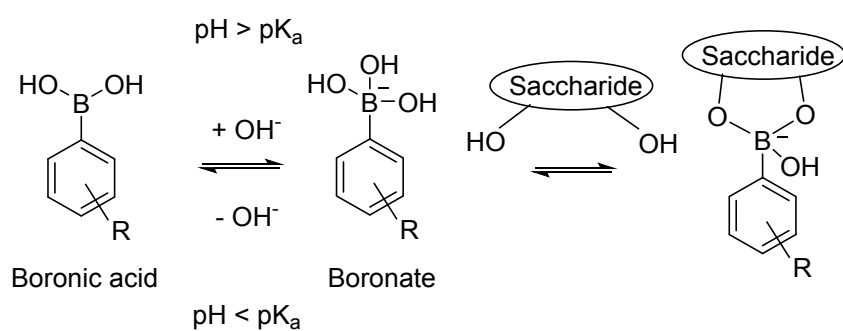


Fructose production via extraction-assisted isomerization of glucose catalyzed by phosphates

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Scheme 1S. Interconversion of boronic acids and boronates upon pH changes and complexation of a saccharide with a boronate anion.

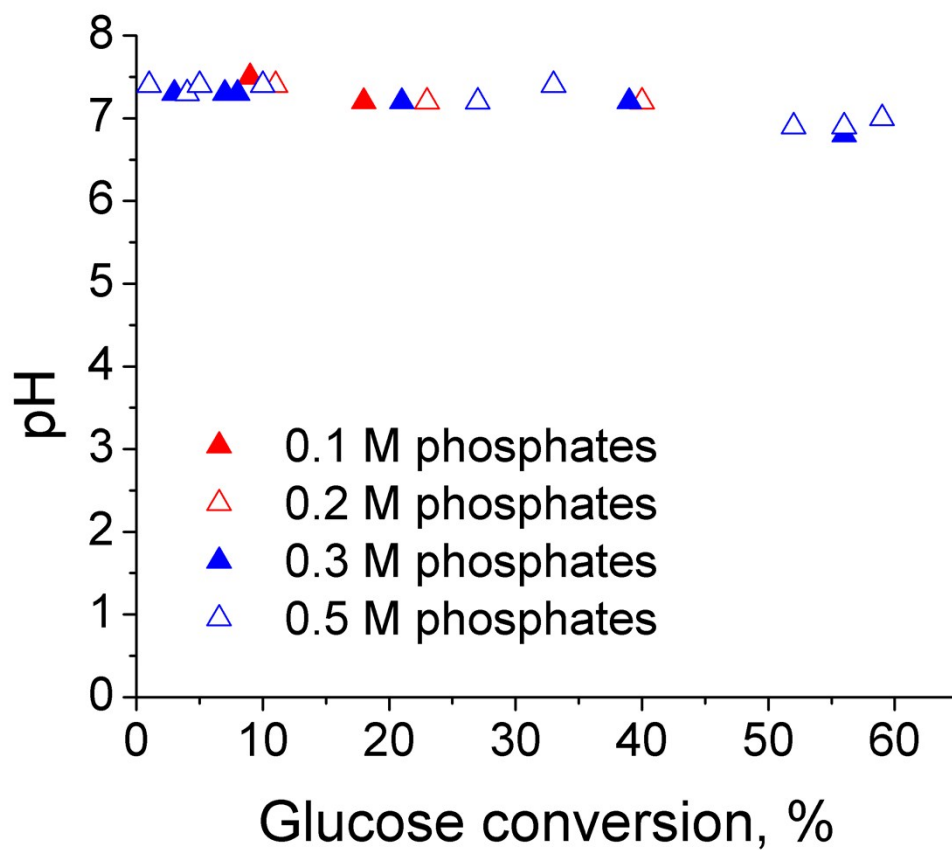


Figure 1S. pH of the reaction mixture obtained after isomerization of glucose in the presence of $\text{NaH}_2\text{PO}_4 + \text{Na}_2\text{HPO}_4$ with pH_0 7.5 at different concentrations of the catalyst. Reaction conditions: 10wt.% aqueous glucose solution, 110°C, 750 rpm.

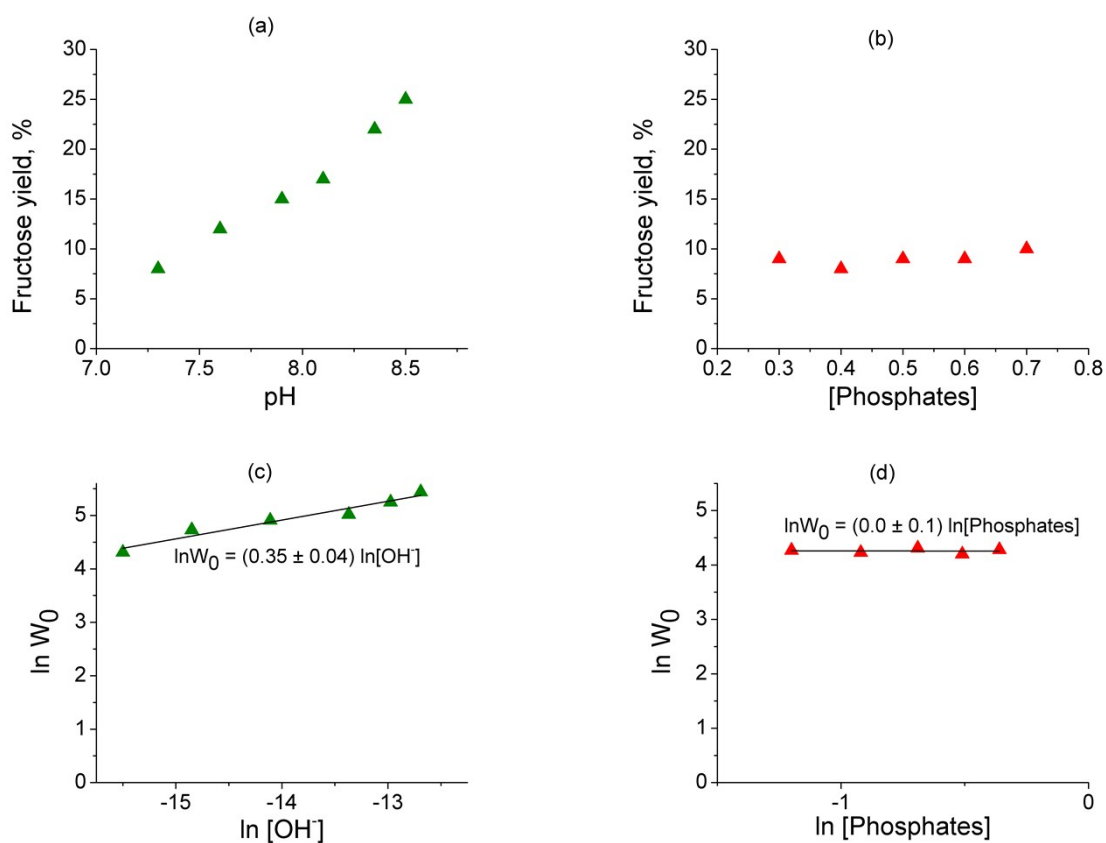
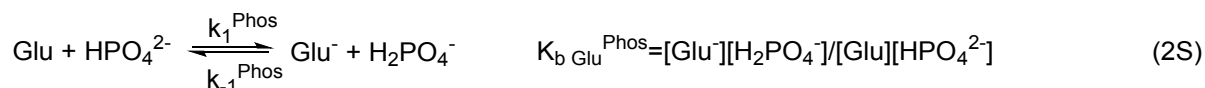
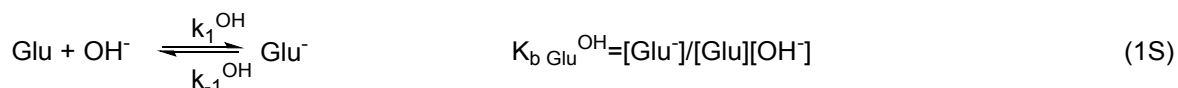


Figure 2S. Dependency of fructose yield or initial reaction rate on concentration of OH⁻ and phosphates. Reaction conditions: 10wt.% aqueous glucose solution, 110°C, 750 rpm, 20 min. Catalysts for (a) and (c): 0.7M NaH₂PO₄+Na₂HPO₄ with a respective pH₀. Catalysts for (b) and (d): NaH₂PO₄+Na₂HPO₄ with a corresponding concentration of phosphates and pH₀ 7.5.

According to our results, the isomerization in the presence of $\text{NaH}_2\text{PO}_4 + \text{Na}_2\text{HPO}_4$ takes place via a proton abstraction leading to formation of an enediol anion. In our opinion, both HPO_4^{2-} and OH^- can serve as bases at the first step of the mechanism (Scheme 1 in the manuscript). According to ^{13}C NMR studies of de Wit et al., deprotonation of glucose (step 1) readily occurs in aqueous alkaline solutions, giving Glu^- in quasi-equilibrium concentration.¹



However, it is difficult to reveal real active basic species which are responsible for ionization of glucose molecule since percentage of HPO_4^{2-} and H_2PO_4^- species depends on concentration of OH^- ions:



As a result, concentration of $[\text{Glu}^-]$ can be expressed as

$$[\text{Glu}^-] = K_{\text{b Glu}}^{\text{OH}} [\text{Glu}][\text{OH}^-] \quad (4\text{S})$$

no matter which basic species lead to the ionisation.

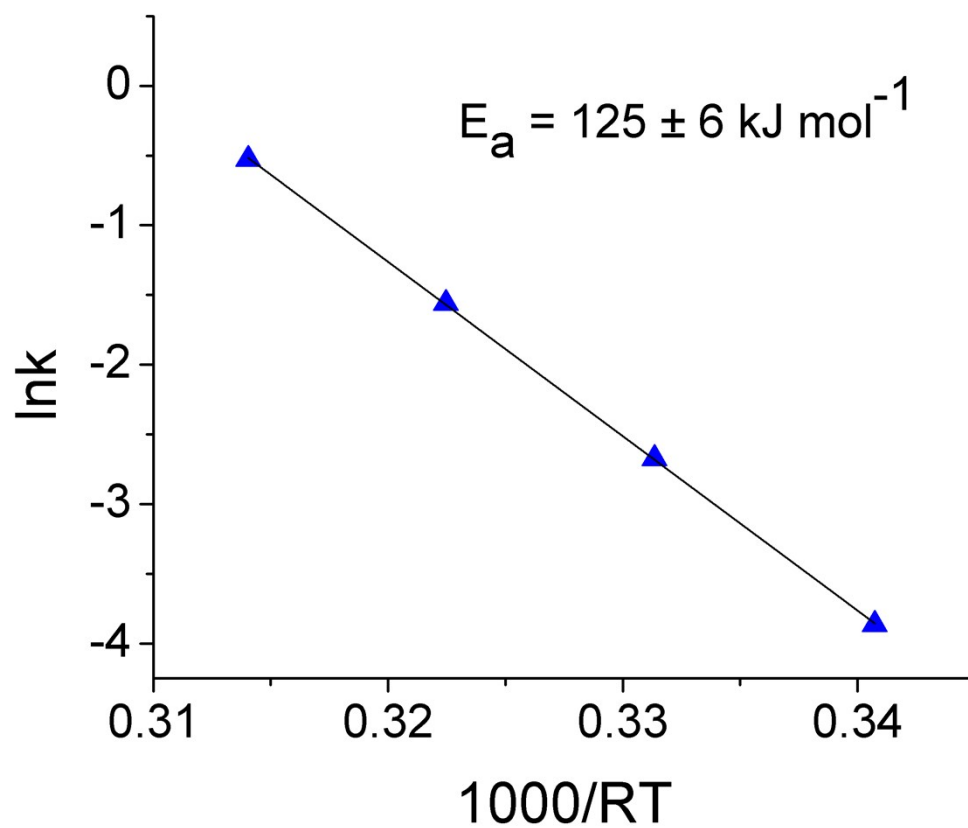


Figure 3S. Arrhenius plot for the isomerization. Reaction conditions: 10wt.% aqueous glucose solution, 0.5M $\text{NaH}_2\text{PO}_4 + \text{Na}_2\text{HPO}_4$, 80-110°C, 750 rpm.

Table 1S. Extraction of fructose and glucose using various boronic acids. Extraction conditions: 4 mL of 0.5M $\text{NaH}_2\text{PO}_4 + \text{Na}_2\text{HPO}_4$ containing fructose and glucose (aqueous phase); 4 mL of 0.04 M boronic acid, 0.04 M Aliquat® 336, octanol-1, (organic phase), stirring at 750 rpm for 1 h at room temperature.

Entry	Boronic acid	[Fructose] ₀ , wt.%	[Glucose] ₀ , wt.%	Extracted fructose, %	Extracted glucose, %	Selectivity for fructose extraction, %
1	PBA	0.3	-	10	-	-
2	PBA	0.3	0.7	9	0	100
3	HMPBA	0.3	-	26	-	-
4	HMPBA	0.3	0.7	25	1	96
5	NPBA	0.3	-	1	-	-
6	NPBA	0.3	0.7	1	0	100

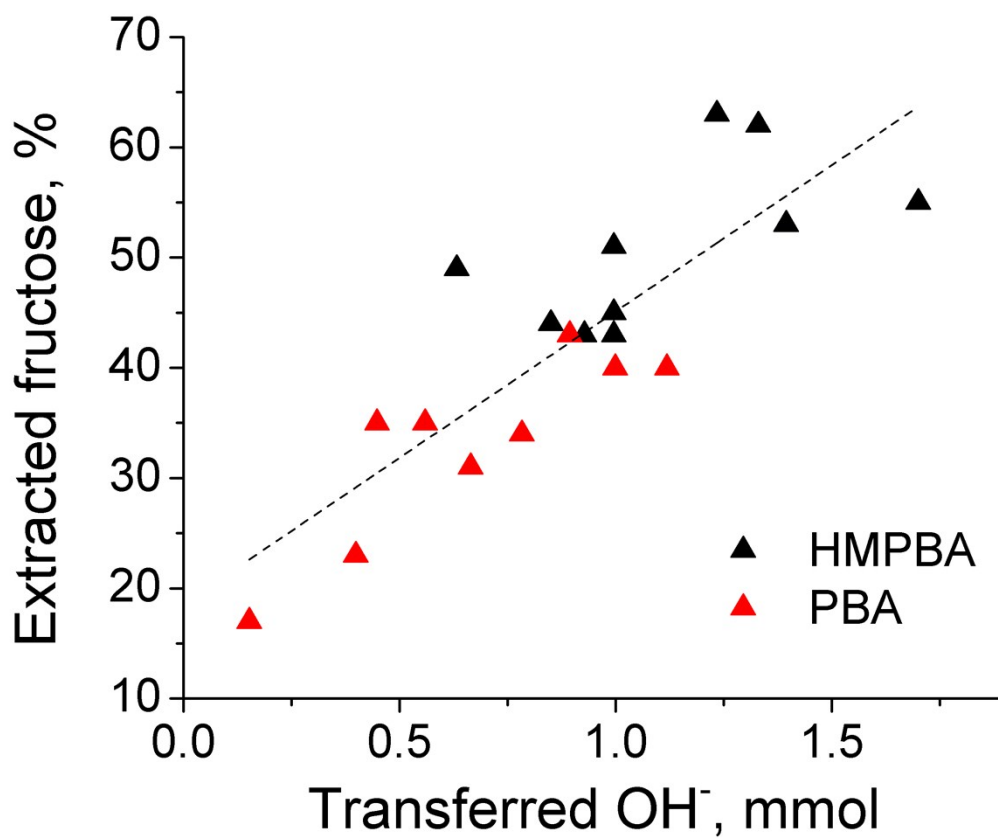


Figure 4S. Extraction of fructose depending on amount of OH⁻ anions transferred from the aqueous to the organic phase.

Table 2S. Recycling of the organic phases for extraction of saccharides. Extraction conditions: 4 mL of 0.5M NaH₂PO₄+Na₂HPO₄ containing fructose and glucose (aqueous phase); 4 mL of 0.4 M boronic acid, 0.4 M Aliquat® 336, octanol-1 (organic phase), stirring at 750 rpm for 1 h at room temperature. Back-extraction conditions: aqueous phase (4 mL of 0.25M H₂SO₄) and organic phase (obtained after the 1st extraction) were stirred at 750 rpm for 1 h at room temperature. The organic phase after back-extraction was used directly for the 2nd extraction without pretreatment of the organic phase.

Enrtry	Boronic acid	Content of monosaccharides in aqueous phase, mmol		1 st extraction		Back-extraction		2 nd extraction	
				Amount of extracted saccharides, mmol		Amount of back-extracted saccharides, mmol		Amount of extracted saccharides, mmol	
		Fructose	Glucose	Fructose	Glucose	Fructose	Glucose	Fructose	Glucose
1	HMPBA	0.67	1.56	0.31	0.09	0.25	0.08	0.30	0.08
2	PBA	0.67	1.56	0.21	0.05	0.19	0.04	0.2	0.02

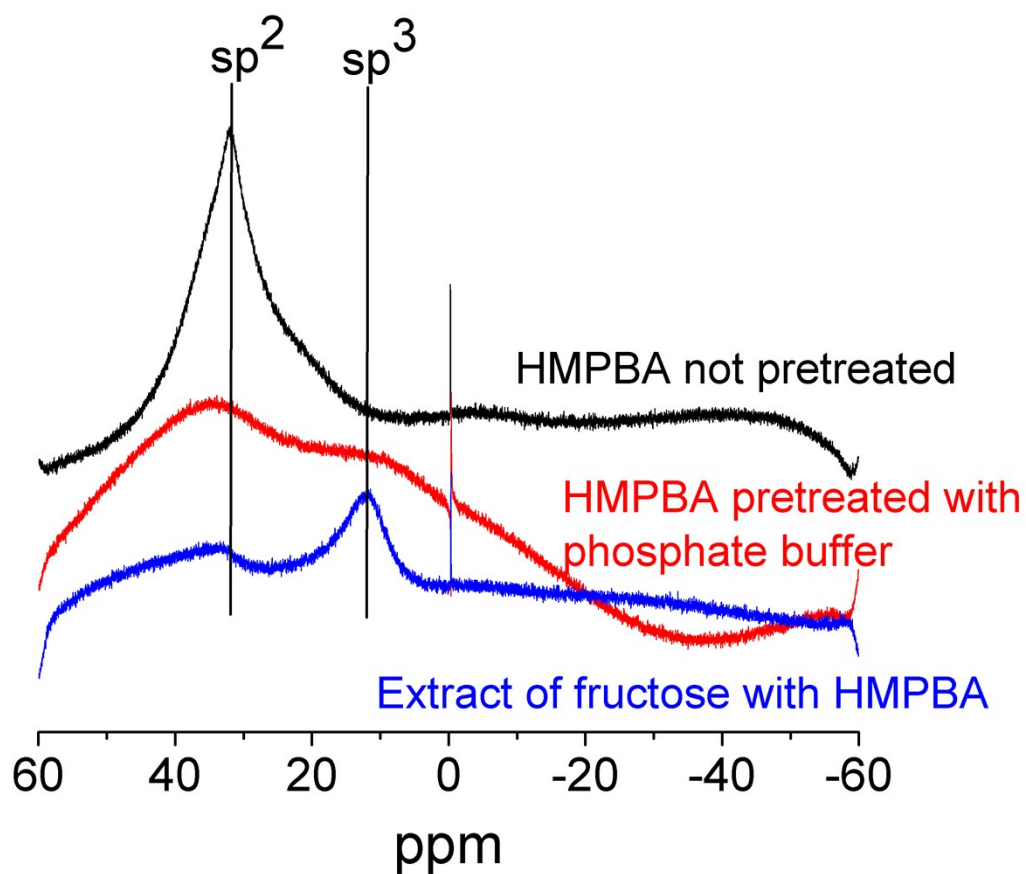


Figure 5S. ^{11}B NMR spectra of HMPBA in C_6D_6 before and after pretreatment with phosphate buffer and a spectrum of the organic phase obtained after extraction of fructose with HMPBA.

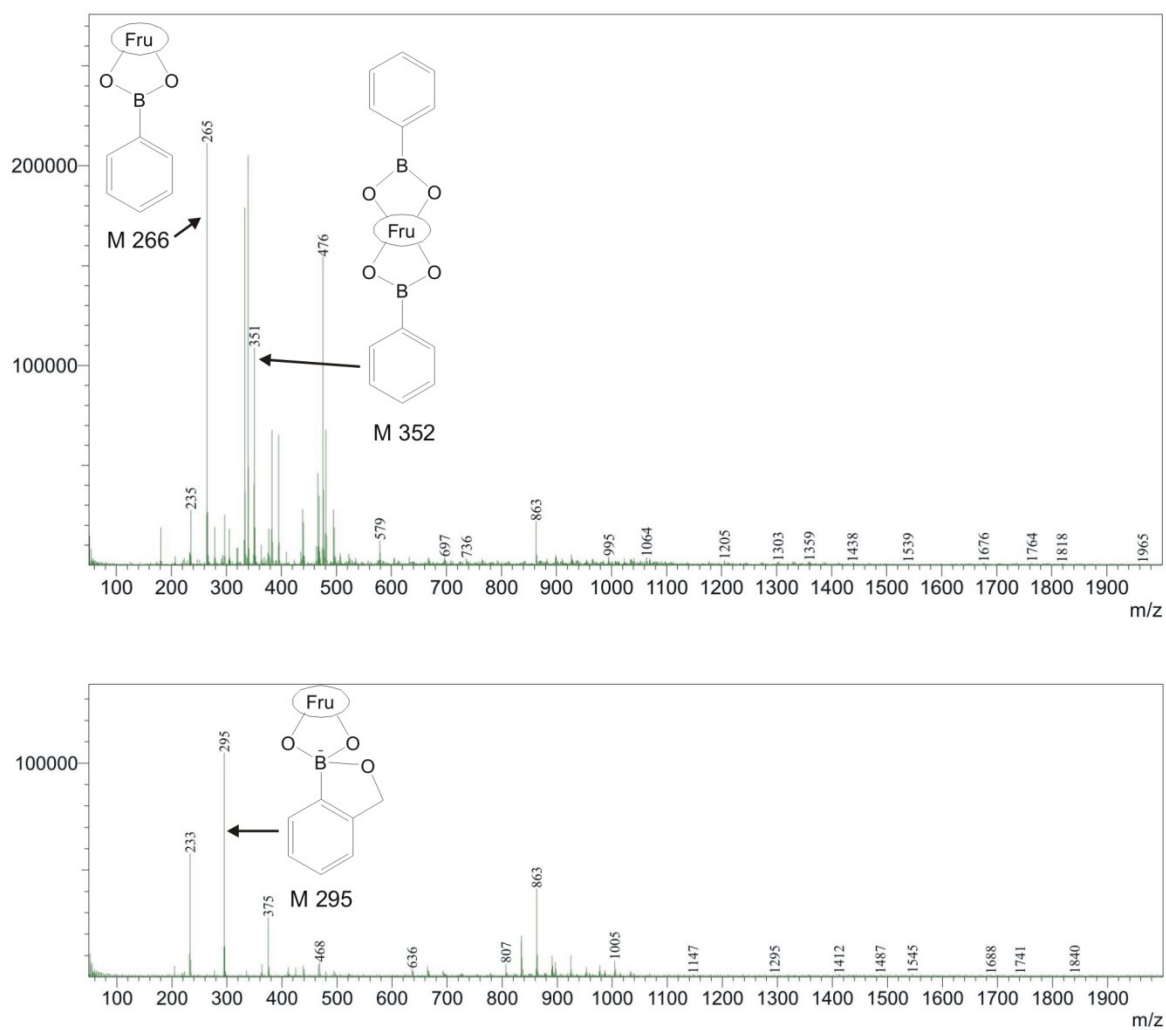


Figure 6S. Mass spectra of the organic phases obtained after extraction of fructose with PBA (up) and HMPBA (down).

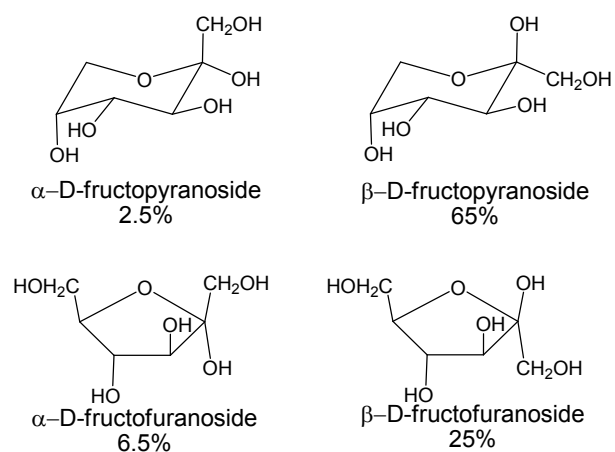


Figure 7S. Structures and percentage of cyclic fructosides present in aqueous solution.²

Table 3S. Percentage of cyclic forms for model disaccharides²

Disaccharide	α P ^a	β P ^b	α F ^c	β F ^d
Lactulose	0	61.5	7.6	29.3
Palatinose	0	0	28.6	71.4
Sucrose	0	0	0	100
Turanose	<4	39	20	41

^a α P denotes α -pyranoside

^b β P denotes β -pyranoside

^c α F denotes α -furanoside

^d β F denotes β -furanoside

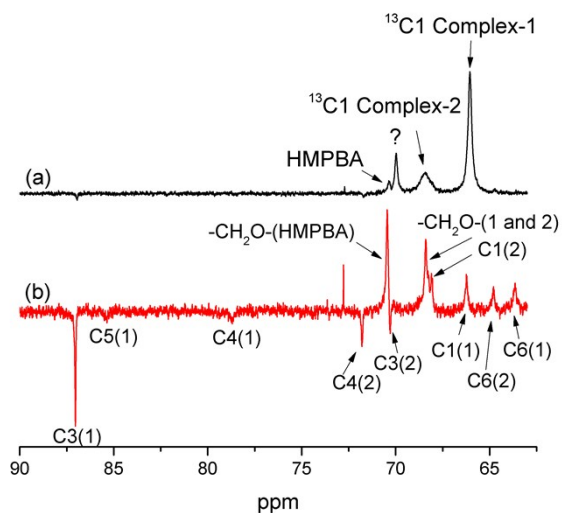


Figure 8S. ^{13}C APT NMR spectra of an organic phase obtained by extraction with HMPBA in C_6D_6 ; aqueous phase is a phosphate buffer prepared using D_2O containing (a) D-fructose-1- ^{13}C ; (b) D-fructose; the resonances are provided for Complex-1 (1) and Complex-2 (2).

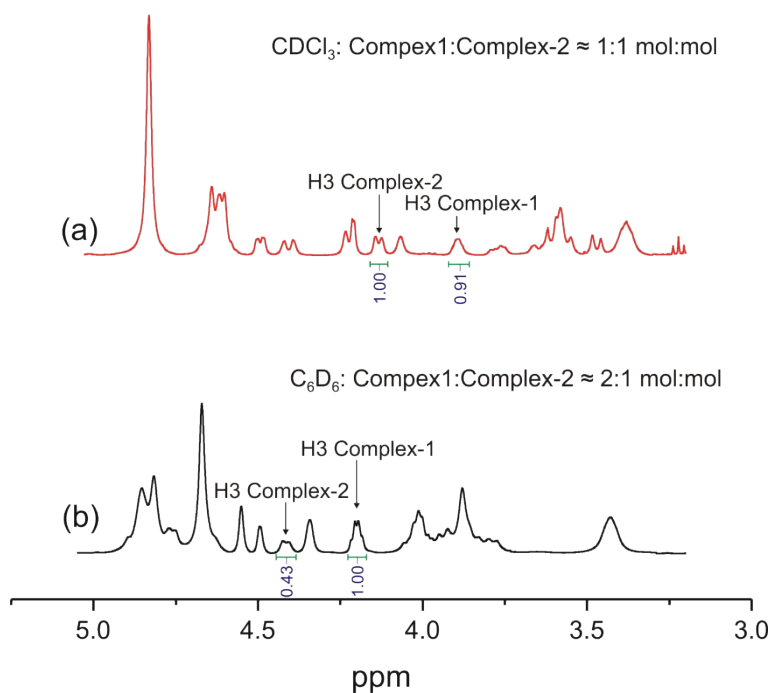


Figure 9S. ^1H NMR spectra of organic phases obtained after extraction of fructose with HMPBA in (a) CDCl_3 , (b) C_6D_6 .

NMR data

Aliquat® 336: ^1H NMR (400 MHz, C_6D_6) δ 3.58 (s, 3H, N- CH_3), 3.30-3.45 (m, 6H, N- CH_2 -), 1.61 (s, 6H) 1.23-1.43 (m, 38H, $-(\text{CH}_2)_n\text{-CH}_3$), 0.83-1.00 (m, 9H, $-(\text{CH}_2)_n\text{-CH}_3$). ^1H NMR (400 MHz, CDCl_3) δ 3.10-3.24 (m, 6H, N- CH_2 -), 3.03 (s, 3H, N- CH_3), 1.36-1.52 (m, 6H), 0.92-1.20 (s, 38H, $-(\text{CH}_2)_n\text{-CH}_3$), 0.54-0.68 (m, 9H, $-(\text{CH}_2)_n\text{-CH}_3$). ^{13}C NMR (101 MHz, C_6D_6) δ 128.1, 127.82, 127.6, 61.9, 60.9, 49.5, 33.7, 32.2, 32.1, 30.1, 30.0, 29.8, 29.73, 29.6, 29.6, 29.5, 26.7, 26.7, 23.0, 23.0, 22.9, 22.5, 14.2, 14.2. ^{13}C NMR (101 MHz, CDCl_3) δ 77.8, 77.5, 77.2, 62.1, 61.4, 48.8, 32.8, 31.8, 31.7, 31.5, 29.5, 29.3, 29.3, 29.1, 29.1, 29.0, 28.9, 26.2, 25.9, 22.5, 22.5, 22.5, 22.3, 14.0, 13.9.

HMPBA+Aliquat® 336: ^1H NMR (400 MHz, C_6D_6) δ 8.59 (d, 1H, $J = 7.19$ Hz) 7.30 (t, 1H, $J = 7.24$ Hz), 7.22 (t, 1H, $J = 7.40$ Hz), 7.00 (d, 1H, $J = 7.52$ Hz), 4.90 (s, 2H), 3.17-3.35 (m, Aliquat® 336), 1.55 (s, Aliquat® 336), 1.13-1.37 (m, Aliquat® 336), 0.82-0.95 (m, Aliquat® 336). ^1H NMR (400 MHz, CDCl_3) δ 8.10 (d, 1H, $J = 7.45$ Hz) 7.33-7.41 (m, 1H), 7.20-7.29 (m, 2H), 4.98 (s, 2H), 3.52-3.42 (m, Aliquat® 336), 3.19 (s, Aliquat® 336), 1.56-1.58 (m, Aliquat® 336), 1.08-1.35 (m, Aliquat® 336), 0.74-0.90 (m, Aliquat® 336). ^{13}C NMR (101 MHz, C_6D_6) δ 154.0, 132.7, 130.6, 130.3, 127.8, 127.6, 127.020, 120.7, 70.5, 62.2, 61.3, 49.1, 33.3, 32.2, 32.0, 29.9, 29.8, 29.7, 29.5, 29.5, 29.4, 26.5, 26.4, 22.9, 22.4, 14.2. ^{13}C NMR (101 MHz, CDCl_3) δ 153.0, 131.3, 130.1, 129.8, 126.3, 120.5, 120.1, 77.2, 76.8, 76.5, 70.6, 70.0, 64.6, 61.8, 61.0, 48.3, 32.1, 31.2, 31.0, 28.8, 28.8, 28.6, 28.5, 28.5, 28.4, 25.7, 25.3, 22.0, 21.9, 21.7, 13.5, 13.4.

^{11}B NMR (96 MHz, C_6D_6 , no pretreatment) δ 32.0.

Fructose+HMPBA+Aliquat® 336: ^1H NMR (400 MHz, C_6D_6) δ 7.10-7.37 (m), 7.0 (d, $J = 7.4$ Hz), 4.93-5.18 (m, 5H, Ph- $\text{CH}_2\text{-O-Complex-1}$, Ph- $\text{CH}_2\text{-O-Complex-2}$, and H-4-Complex-2), 4.88-4.93 (m, 3H, HMPBA and H $^{\alpha}$ -6-Complex-2), 4.77 (s, 1H, H-5-Complex-1), 4.71 (s, 1H, H-5-Complex-2), 4.63 (d, 1H, $J = 6.45$ Hz, H-3-Complex-2), 4.56 (s, 1H, H-4-Complex-1), 4.36-4.45 (m, 1H, H-3-Complex-1), 3.91-4.31 (m, 7H, H $^{\alpha,\beta}$ -1-Complex-1, H $^{\alpha,\beta}$ -6-Complex-1, H $^{\beta}$ -6-Complex-2, H $^{\alpha,\beta}$ -1-Complex-2), 3.16 (s, Aliquat® 336), 2.82-3.03 (m, Aliquat® 336), 1.15-1.54 (m, Aliquat® 336), 0.83-1.03 (m, Aliquat® 336).

^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, $J = 5.97$, 4.4H), 7.49-7.56 (m, 0.9H), 7.29-7.43 (m, 2.1H), 7.18-7.28 (m, 5.7 H), 7.05-7.18 (m, 10.6 H), 6.88-6.97 (m, 7.7H), 6.78-6.88 (m, 3.6H), 4.83 (s, 10.5 H, Ph- $\text{CH}_2\text{-O}$ -HMPBA), 4.55-4.72 (m, 7.2 H, Ph- $\text{CH}_2\text{-O}$ – Complexes 1 and 2), 4.49 (dd, $J = 7.1$, 2.0 Hz, 1H, H-4-Complex-2), 4.41 (d, $J = 10.6$, 1H, H^α -6-Complex-2), 4.23 (s, 1H, H-5-Complex-1), 4.21 (d, 1H, H-5-Complex-2), 4.13 (d, $J = 7.6$, 1H, H-3-Complex-2), 4.07 (s, 1H, H-4-Complex-1), 3.84-3.92 (m, 1H, H-3-Complex-1), 3.72-3.81 (m, 1H, H^α -6-Complex-1), 3.66 (s, 1H, H^β -6-Complex-1), 3.55-3.61 (m, 4H, $\text{H}^{\alpha,\beta}$ -1-Complex-1, H^β -1-Complex-2, H^α -6-Complex-2), 3.47 (d, $J = 10.2$, 1H, H^β -1-Complex-2), 3.31-3.43 (m, Aliquat[®] 336), 3.18 (s, Aliquat[®] 336), 2.91-3.06 (m, Aliquat[®] 336), 2.86 (s, Aliquat[®] 336).

^{13}C NMR (101 MHz, C_6D_6) 133.0, 130.7, 130.3, 128.2, 127.1, 120.7, 86.9 (C-3-Complex-1), 85.3 (C-5-Complex-1), 78.5 (C-4-Complex-1), 74.4 (C-5-Complex-2), 71.7 (C-4-Complex-2), 70.6 (Ph- $\text{CH}_2\text{-O}$ -HMPBA), 70.0 (C-3-Complex-2), 68.2 (C-1-Complex-2), 68.0 (Ph- $\text{CH}_2\text{-O}$ –Complexes 1 and 2), 65.9 (C-1-Complex-1), 64.7 (C-6-Complex-2), 63.5 (C-6-Complex-1), 62.2, 61.3, 49.3, 33.4, 32.3, 32.1, 30.0, 29.8, 29.6, 29.5, 23.0, 22.5, 14.3, 14.2.

^{13}C NMR (101 MHz, CDCl_3) δ 131.3, 129.8, 126.4, 125.5, 125.1, 125.5, 120.4, 119.77, 86.4 (C-3-Complex-1), 84.6 (C-5-Complex-1), 77.2, 77.1 (C-4-Complex-1), 73.7 (C-5-Complex-2), 71.0 (C-4-Complex-2), 70.0 (Ph- $\text{CH}_2\text{-O}$ -HMPBA), 69.5 (C-3-Complex-2), 67.5 (Ph- $\text{CH}_2\text{-O}$ –Complexes 1 and 2), 67.1 (C-1-Complex-2), 65.2 (C-1-Complex-1), 63.5 (C-6-Complex-2), 62.3 (C-6-Complex-1), 48.3, 32.2, 31.4, 31.2, 31.1, 29.1, 29.0, 29.0, 28.9, 28.8, 28.7, 28.6, 28.6, 28.5, 25.7, 25.44, 22.2, 22.1, 21.9, 21.7, 13.6, 13.6, 13.5.

^{11}B NMR (96 MHz, C_6D_6) δ 33.0, 12.1.

Table 4S. Results of extraction-assisted isomerization of glucose into fructose. Reaction conditions of the 1st experiment: isomerization over 0.5M NaH₂PO₄+Na₂HPO₄, 110 °C, 70 min, 750 rpm; extraction was repeated twice at room temperature for 1 h, 750 rpm using 0.4 M HMPBA, 0.4 M Aliquat® 336 in octanol-1 as organic phase, reaction mixture after the isomerization was used as aqueous phase. The conditions of the 2nd experiment were like that of the 1st experiment, but concentrations of HMPBA were 0.2 and 0.09 M for the first and the second extractions, respectively.

Run	Isomerization					Extraction					Fructose yield, %
	[Glu] ₀ , ^a M	[Fru] ₀ , ^a M	[Glu] _{fin} , ^b M	[Fru] _{fin} , ^b M	Glucose conversion, %	[Glu] _{extr} , ^c M	[Fru] _{extr} , ^c M	Extracted Glu, %	Extracted Fru, %	Selectivity for Fru extraction, %	
The 1 st experiment											
1	0.56	0	0.47	0.09	16	0.4	0.03	14	72	50	16
2	0.5	0.01	0.43	0.08	24	0.37	0.02	13	75	52	24
3	0.49	0.01	0.39	0.09	33	0.35	0.03	10	69	62	31
4	0.47	0.02	0.38	0.09	39	0.34	0.02	11	72	60	34
5	0.46	0.01	0.37	0.10	43	0.32	0.03	15	68	54	39
6	0.47	0.02	0.37	0.09	46	0.33	0.03	13	70	58	40
7	0.47	0.01	0.39	0.09	47	0.34	0.03	12	67	55	42
8	0.49	0.01	0.39	0.09	49	0.35	0.03	10	70	62	43
9	0.48	0.01	0.39	0.09	51	0.34	0.03	13	68	55	45
The 2 nd experiment											
1	0.53	0	0.45	0.08	15	0.44	0.04	4	55	67	15
2	0.51	0.02	0.41	0.10	30	0.4	0.06	4	44	80	27
3	0.48	0.03	0.43	0.08	34	0.38	0.05	5	51	60	34
4	0.48	0.03	0.38	0.12	42	0.38	0.07	2	40	87	41
5	0.47	0.04	0.37	0.11	49	0.35	0.07	5	39	67	45
6	0.46	0.04	0.38	0.11	52	0.36	0.06	6	40	71	47
7	0.49	0.03	0.37	0.11	57	0.36	0.07	4	41	80	49
8	0.46	0.04	0.36	0.10	60	0.35	0.06	4	41	80	50
9	0.49	0.03	0.38	0.10	62	0.38	0.06	5	40	86	51

^a[Glu]₀ and [Fru]₀ are concentrations of glucose and fructose in the reaction mixture prior to isomerization

^b[Glu]_{fin} and [Fru]_{fin} are concentrations of glucose and fructose in the reaction mixture after isomerization

^c[Glu]_{extr} and [Fru]_{extr} are concentrations of glucose and fructose in aqueous phase after extraction

Calculation of conversion, selectivity, and yield for the reaction-assisted isomerization

Glucose conversion was calculated as follows

$$\text{Glucose conversion} = \frac{\sum_i ([\text{Glu}]_{0,i} - [\text{Glu}]_{\text{fin},i})}{\sum_i ([\text{Glu}]_{0,i} - [\text{Glu}]_{\text{extr},i-1})} \quad (5S)$$

Fructose yield was calculated for the total amount of formed fructose according to the formula:

$$\text{Fructose yield} = \frac{\sum_i ([\text{Fru}]_{\text{fin},i} - [\text{Fru}]_{0,i})}{\sum_i ([\text{Glu}]_{0,i} - [\text{Glu}]_{\text{extr},i-1})} \quad (6S)$$

Used for Equations 5S and 6S parameter i denotes a number of run, whereas $[\text{Glu}]_0$, $[\text{Fru}]_0$, $[\text{Glu}]_{\text{fin}}$, $[\text{Fru}]_{\text{fin}}$, $[\text{Glu}]_{\text{extr}}$, and $[\text{Fru}]_{\text{extr}}$ denote concentrations of glucose and fructose provided in Table 4S.

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