ESI for

Preferential Formation of Specific Hexose and Heptose in Formose Reaction under Microwave Irradiation

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Formose reaction under MW irradiation using various catalysts

To compare the activities of catalysts, we conducted formose reaction by irradiating an aqueous solution of formaldehyde (1.0 mol kg^{-1}, 5 mL) with MW at 2.45 GHz with a Biotage Initiator+ microwave synthesizer using various catalysts. The conditions and results are summarized in Table S1. The concentration of catalyst was fixed at 200 mmol kg^{-1} unless otherwise specified. If the catalyst was not dissolved completely, the concentration was reported assuming complete dissolution. The concentrations of $Ca(OH)_2$ and $Ba(OH)_2 \cdot 8H_2O$ were reduced to 50 mmol kg^{-1}. The set temperature was fixed at 150 °C. The reaction time was determined depending on the activity of catalyst. In this study, the reaction time was adjusted close to the yellowing point, at which the yield of sugars is maximum. The conversions were evaluated with

$$\text{conversion (\%)} = \frac{[\text{HCHO}]_0 - [\text{HCHO}]}{[\text{HCHO}]_0} \times 100 \tag{S1}$$

where $[\text{HCHO}]_0$ and $[\text{HCHO}]$ are the initial and final concentrations of formaldehyde determined by the acetylacetone method.[S1] When hydroxides of alkali and alkali earth metals were used, the conversions were relatively high. In particular, $Ca(OH)_2$ and $Ba(OH)_2 \cdot 8H_2O$ showed a higher conversion even at a lower concentration (50 mmol kg^{-1}). When some organic bases (e.g., DABCO and *N*-methylpiperidine) were used as catalyst, formose reaction also proceeded efficiently. Using the data in the table, the apparent activities of catalysts (A_{cat}) were roughly estimated as

$$A_{\text{cat}} = \frac{\text{conversion} / 100}{t C_{\text{cat}}} \tag{S2}$$

where t is the reaction time and C_{cat} is the catalyst concentration. As it can be seen in Fig. S1, hydroxides of alkali and alkali earth metals showed higher activities. DABCO and *N*-

methylpiperidine also exhibited higher activities.

Formose reaction by heating with an oil bath

In separate experiments, formose reaction was carried out by heating with an oil bath thermostated at 150, 100 and 60 °C to elucidate the effect of heat source. Figure S10A compares the time–conversion plots obtained at different temperatures. When formose reaction was carried out by heating with an oil bath thermostated at 150 °C, the conversion reached a quantitative one in ca. 1.5 min, which was slightly slower than that under MW irradiation (Fig. S2A). Using a 2 – 5 mL vial with an oil bath, the temperature of reaction mixture (5 mL) increased to ca. 90 °C in 1.5 min, and then increased gradually to 150 °C in the following 10 min (Fig. S3B). These observations indicate that MW irradiation was more effective than oil bath heating, resulting in faster formose reaction under MW irradiation. When an oil bath thermostated at 100 °C was used, the conversion increased to 40% in 10 min and then leveled off. At this set temperature, the heat source was critical for the conversion of formose reaction. At 60 °C, the conversion leveled off at ca. 20% after 120 min. These data were practically the same as those for formose reaction under MW irradiation at a set temperature of 60 °C. These products were treated with ion-exchange resins and also characterized by HPLC, as it can be seen in Fig. S10B. This figure shows the HPLC charts for the products of formose reaction by heating with an oil bath were practically the same as those for the products of formose reaction under MW irradiation. These observations indicate that high temperature (> ca. 100 °C) and short time are critical for the selectivity of formose reaction, but the type of heat source (MW or an oil bath) is not important.

Reference

S1 Y. Y. Maruo, J. Nakamura and M. Uchiyama, *Talanta*, 2008, **74**, 1141-1147.

Table S1 Conditions and results for formose reactions using various catalysts.[a]

catalyst	reaction time / min	conversion / %	A_{app} / M^{-1} s^{-1}	appearance of reaction mixture
$Ca(OH)_2$ [b]	3	71	7.9×10^{-2}	clear
$Ba(OH)_2 \bullet 8H_2O$ [b]	5	53	3.5×10^{-2}	clear
NaOH	5	62	1.0×10^{-2}	clear
$LiOH \bullet H_2O$	5	56	9.3×10^{-3}	clear
KOH	5	47	7.8×10^{-3}	clear
$Mg(OH)_2$	45	92	1.7×10^{-3}	yellow
$BaCO_3$	60	25	3.5×10^{-4}	clear
Ag_2O	60	25	3.5×10^{-4}	clear
Al_2O_3	60	13	1.8×10^{-4}	clear
DABCO [c]	5	57	9.5×10^{-3}	pale yellow
N-methylpiperidine	15	81	4.5×10^{-3}	pale yellow
2-(dimethyl)aminoethanol	30	97	2.7×10^{-3}	brown
N,*N*,*N′*,*N′*-tetraethylethylenediamine	30	88	2.4×10^{-3}	pale yellow
triethylamine	30	66	1.8×10^{-3}	pale yellow
2-picoline	60	33	4.6×10^{-4}	clear
imidazole	60	14	1.9×10^{-4}	clear
3-picoline	60	12	1.7×10^{-4}	clear
pyridine	60	4	5.6×10^{-5}	clear

[a] Using a 1.0 mol kg^{-1} HCHO aqueous solution and 200 mmol kg^{-1} catalyst at 150 °C.

[b] 50 mmol kg^{-1}.

[c] 1,4-diazabicyclo[2.2.2]octane.

Table S2 The total energies evaluated by DFT calculations for the isomers of trioses, tetroses and pentoses.

isomer	total energy / Hartree
C3-1	–343.69151754
C3-2	–343.7006881
C4-1RR	–458.25812444
C4-1RS	–458.26284904
C4-2	–458.26386122
C4-b2	–458.25762146
C5-1RRR	–572.8273971
C5-1RRS	–572.82488934
C5-1RSR	–572.83214616
C5-1RSS	–572.82637109
C5-2RR	–572.83624749
C5-2RS	–572.83430921
C5-3RR	–572.83740546
C5-3RS	–572.8259223
C5-1b2RR	–572.82373432
C5-1b2RS	–572.82471953
C5-1b3	–572.81450331
C5-2b3	–572.83143388

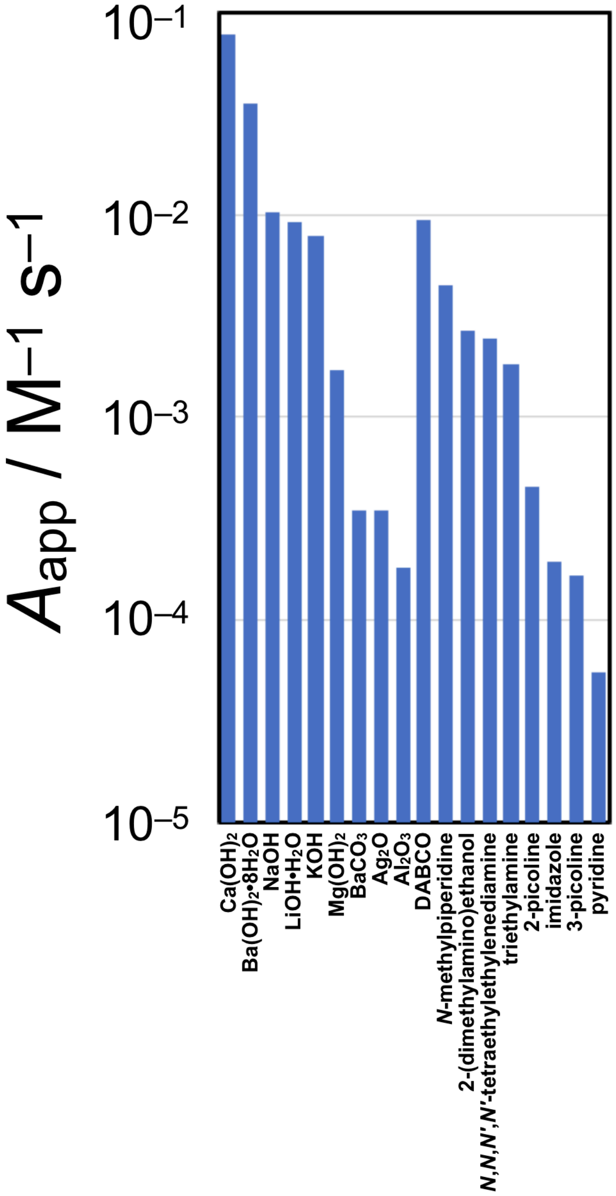


Fig. S1 Apparent activities (A_{app}) for formose reaction under MW irradiation using 1.0 mol kg^{-1} formaldehyde and various catalysts at a set temperature of 150 °C.

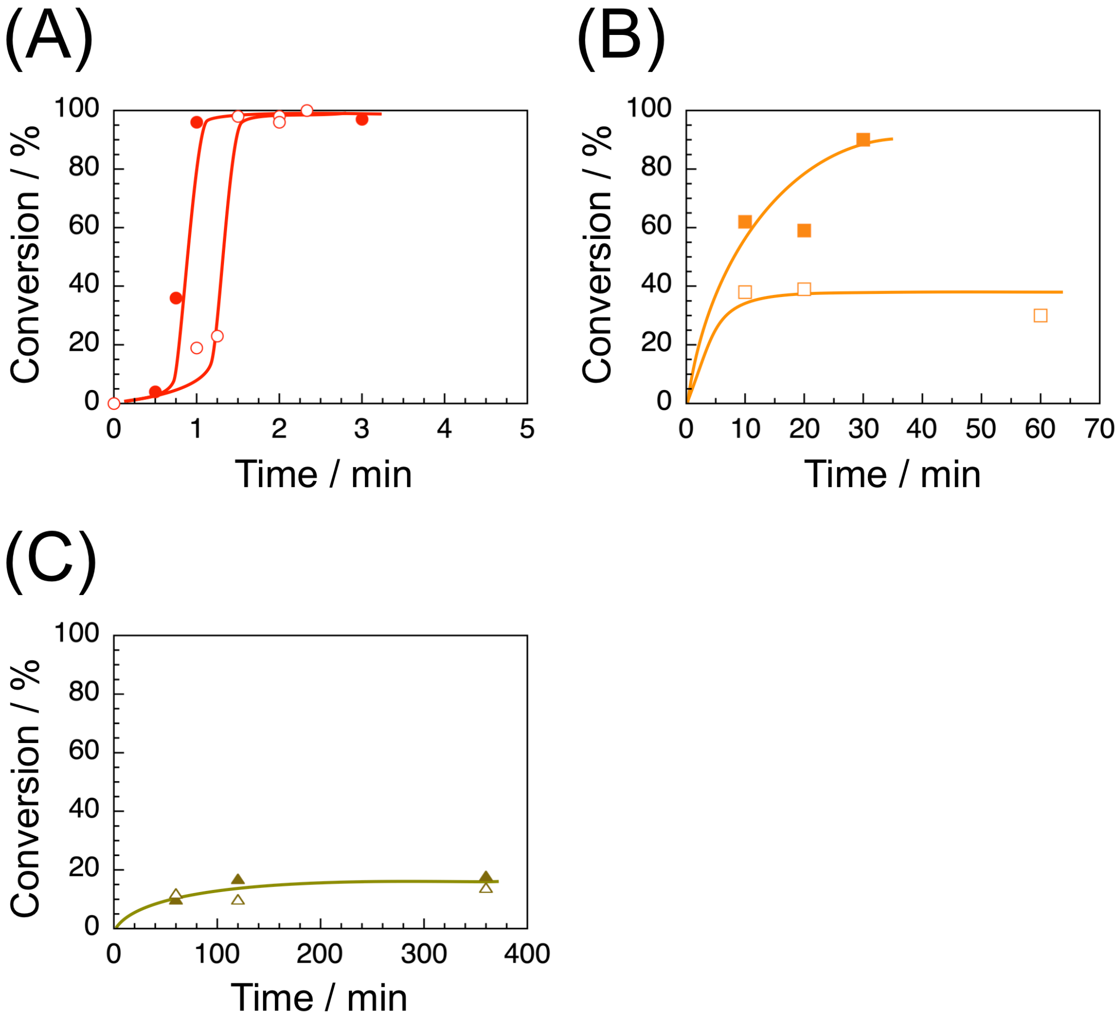


Fig. S2 Time–conversion plots for formose reaction carried out using 1.0 mol kg^{-1} formaldehyde and 55 mmol kg^{-1} $Ca(OH)_2$ under MW irradiation (closed symbol) and by heating with an oil bath (open symbol) at (A) 150, (B) 100 and (C) 60 °C.

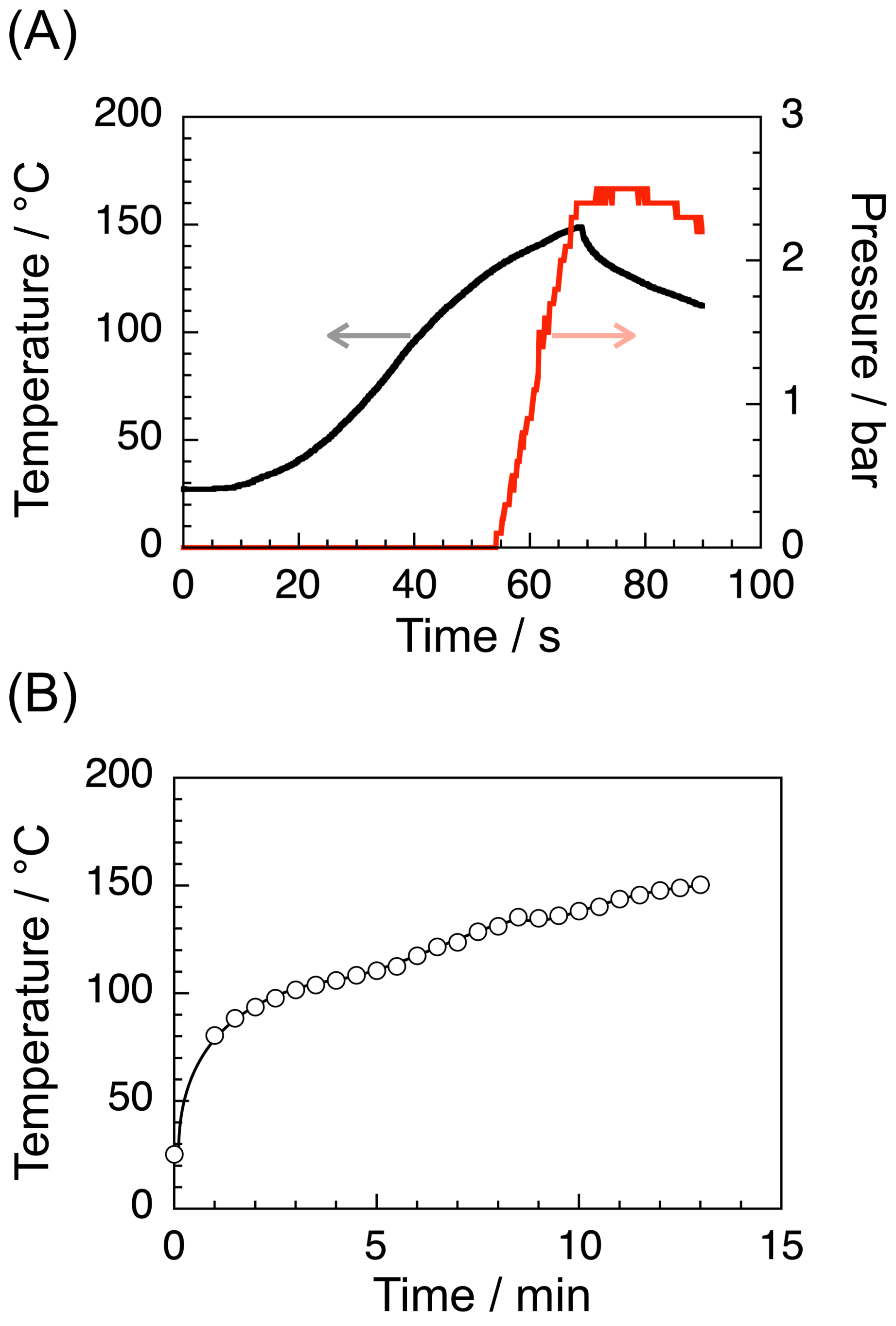


Fig. S3 (A) The time evolutions of temperature and pressure of the reaction mixture (5 mL) using a 2 – 5 mL vial under MW irradiation at a set temperature of 150 °C for 1 min and (B) the time evolution of temperature of the reaction mixture (5 mL) using a 2 – 5 mL vial by heating with an oil bath thermostated at 150 °C.

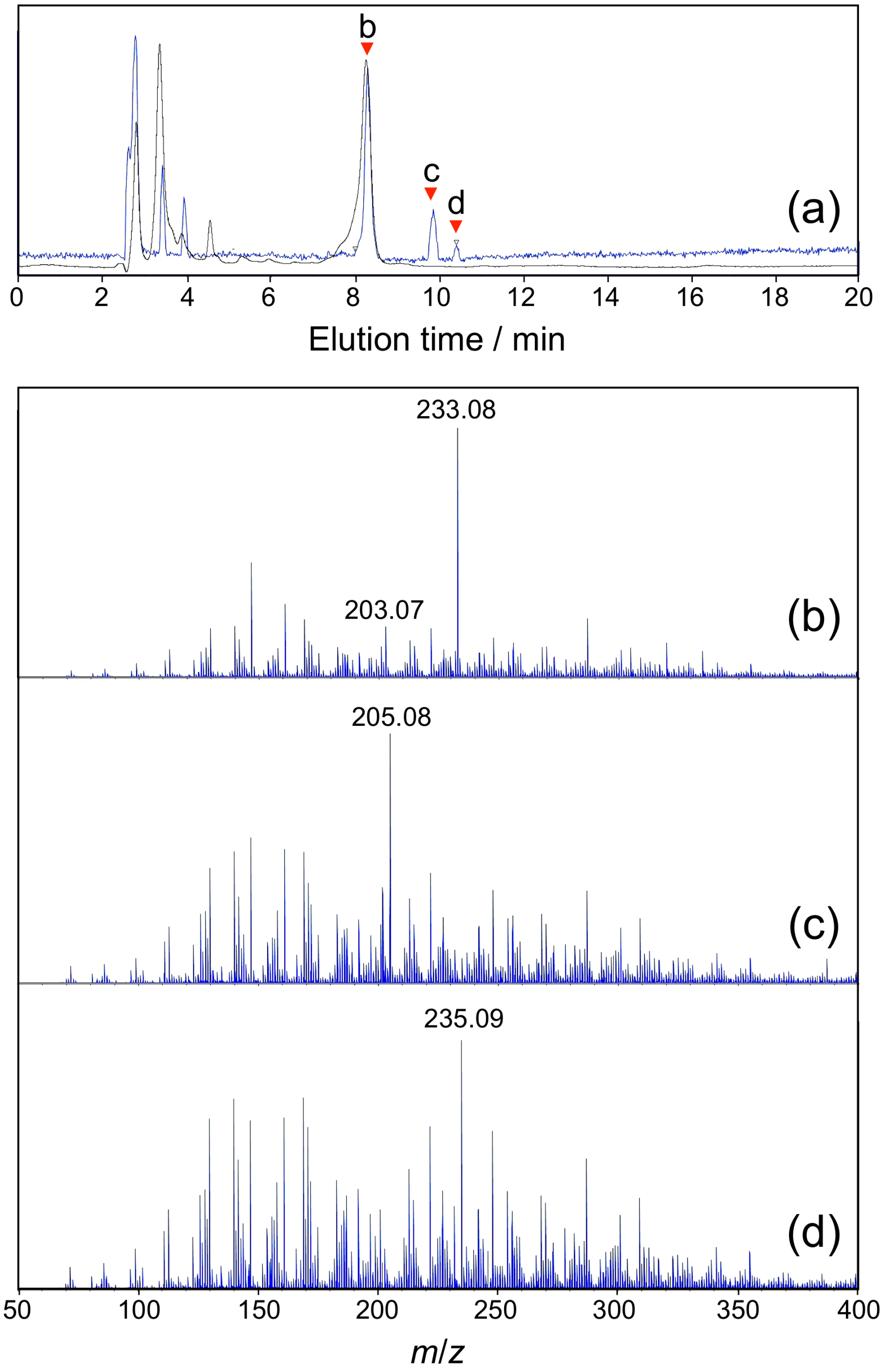


Fig. S4 LS-MS data for the product obtained by formose reaction under MW irradiation using 1.0 mol kg^{-1} formaldehyde and 55 mmol kg^{-1} Ca(OH)$_2$ at a set temperature of 150 °C for 45 s. (a) The LS chart. The MS data for (b) the signal b, (c) the signal c and (d) the signal d in the LC chart.

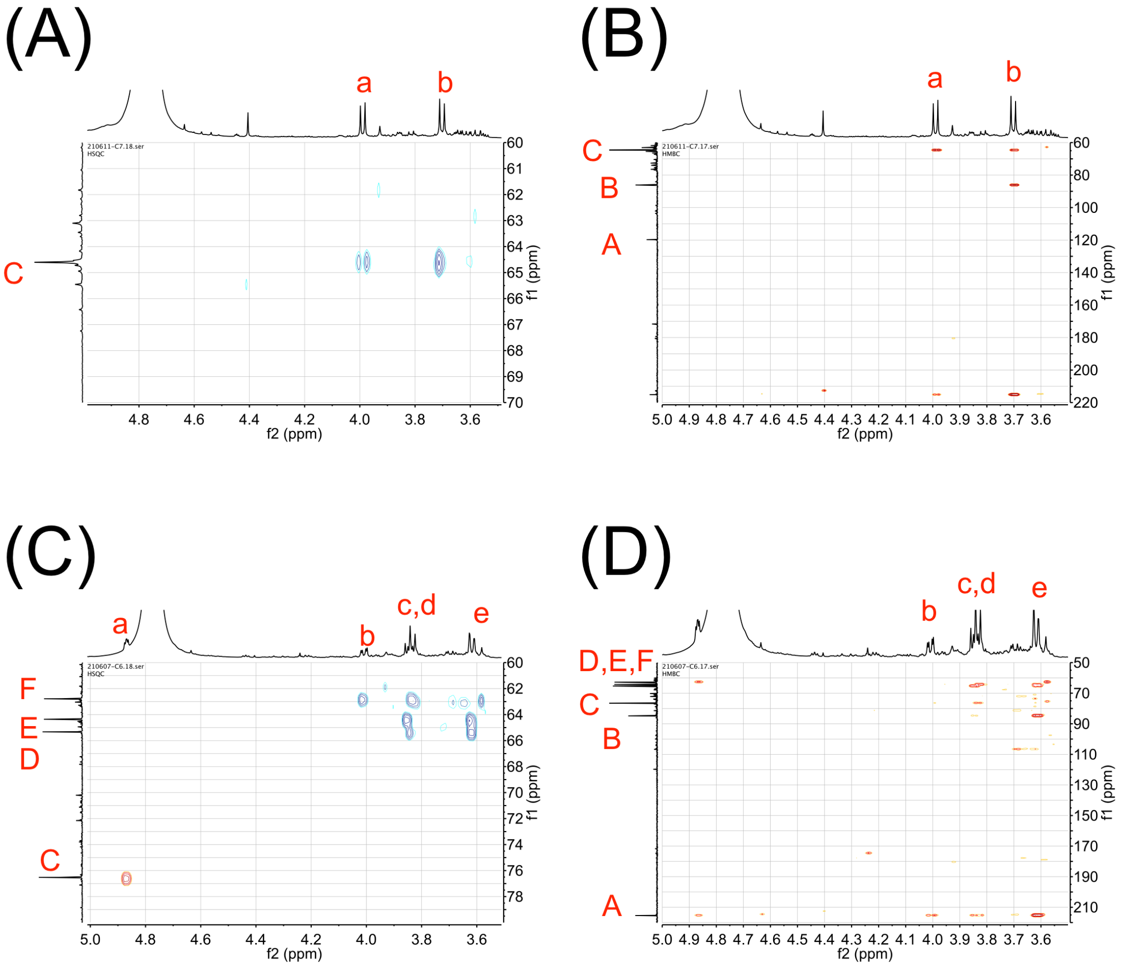
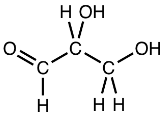
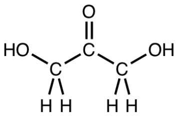


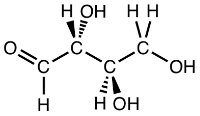
Fig. S5 Two-dimensional NMR spectra for C7* and C6* (D_2O). (A) HSQC and (B) HMBC for **C7***, (C) HSQC and (D) HMBC for **C6***.

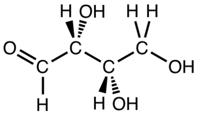
C3


C3-1


C3-2

C4


C4-1RR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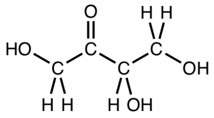
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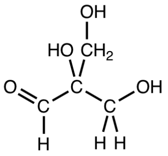
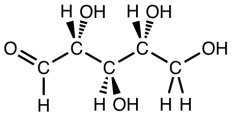

C4-2

C5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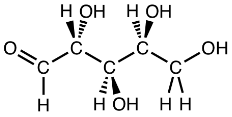
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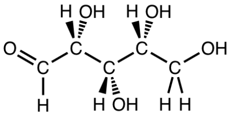
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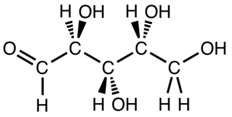
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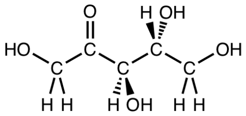
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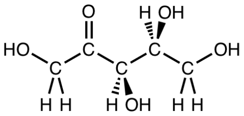
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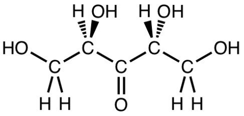
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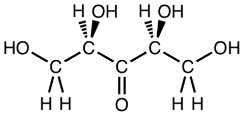
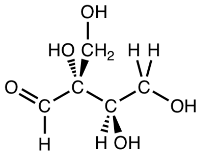
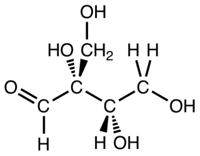

C5-3RS


C5-1b2RR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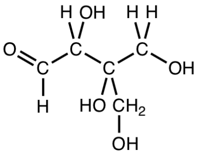
C5-1b3

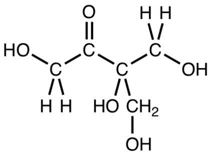
C5-2b3

Fig. S6 Chemical structures of the isomers of trioses, tetroses and pentoses.

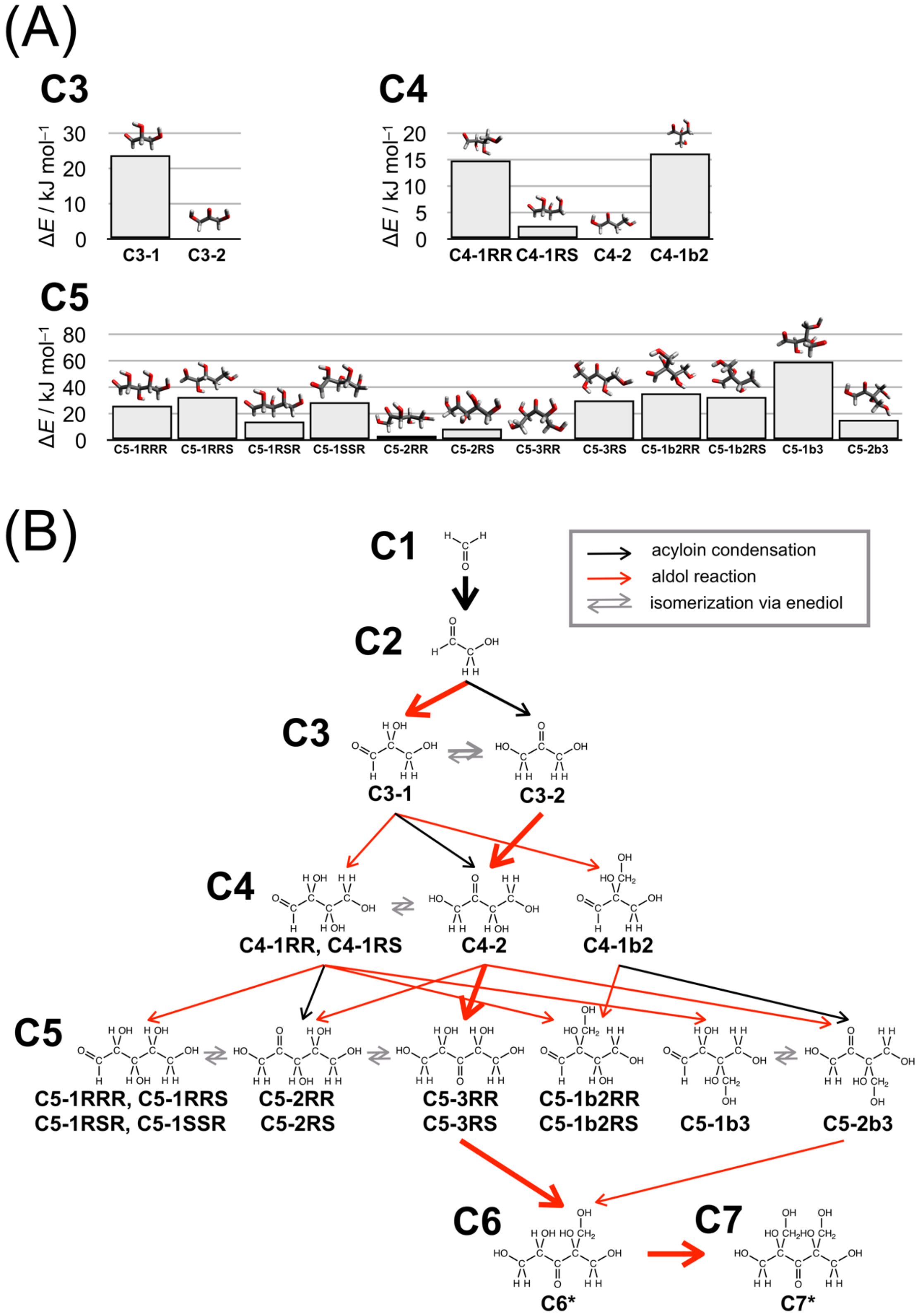

Fig. S7 (A) The differences in total energies (Δ*E*) for the isomers of trioses, tetroses and pentoses. (B) A plausible reaction pathway (indicated by thick arrows) for the preferential formation of **C6*** and **C7*** in the formose reaction under MW irradiation.

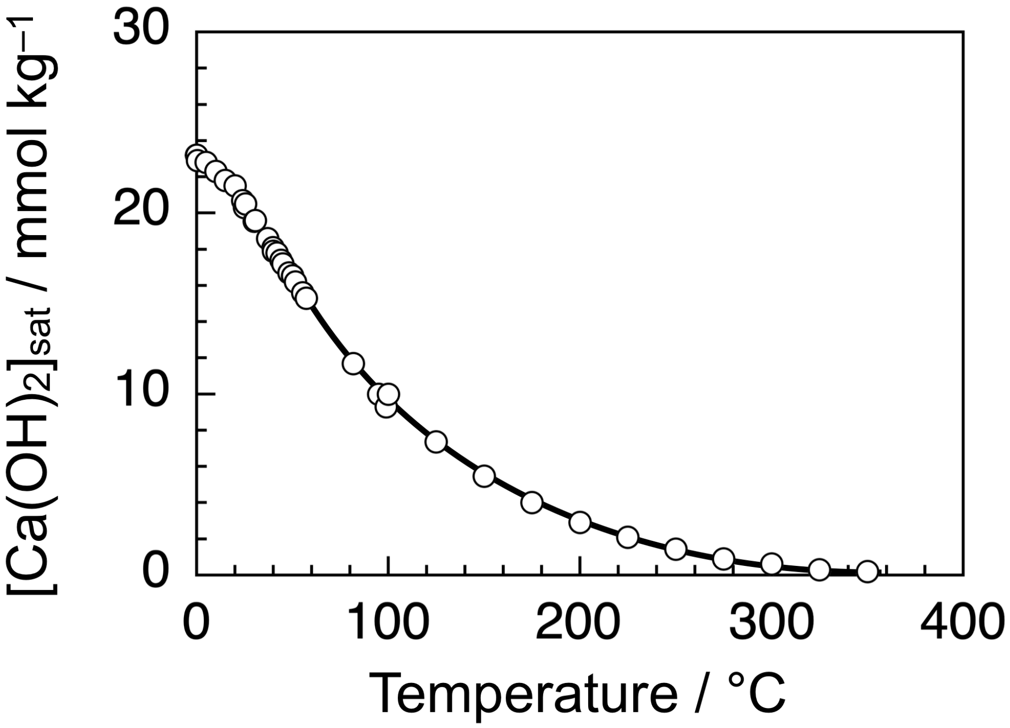

Fig. S8 The saturation concentration of $Ca(OH)_2$ ($[Ca(OH)_2]_{sat}$) in water at varying temperatures.

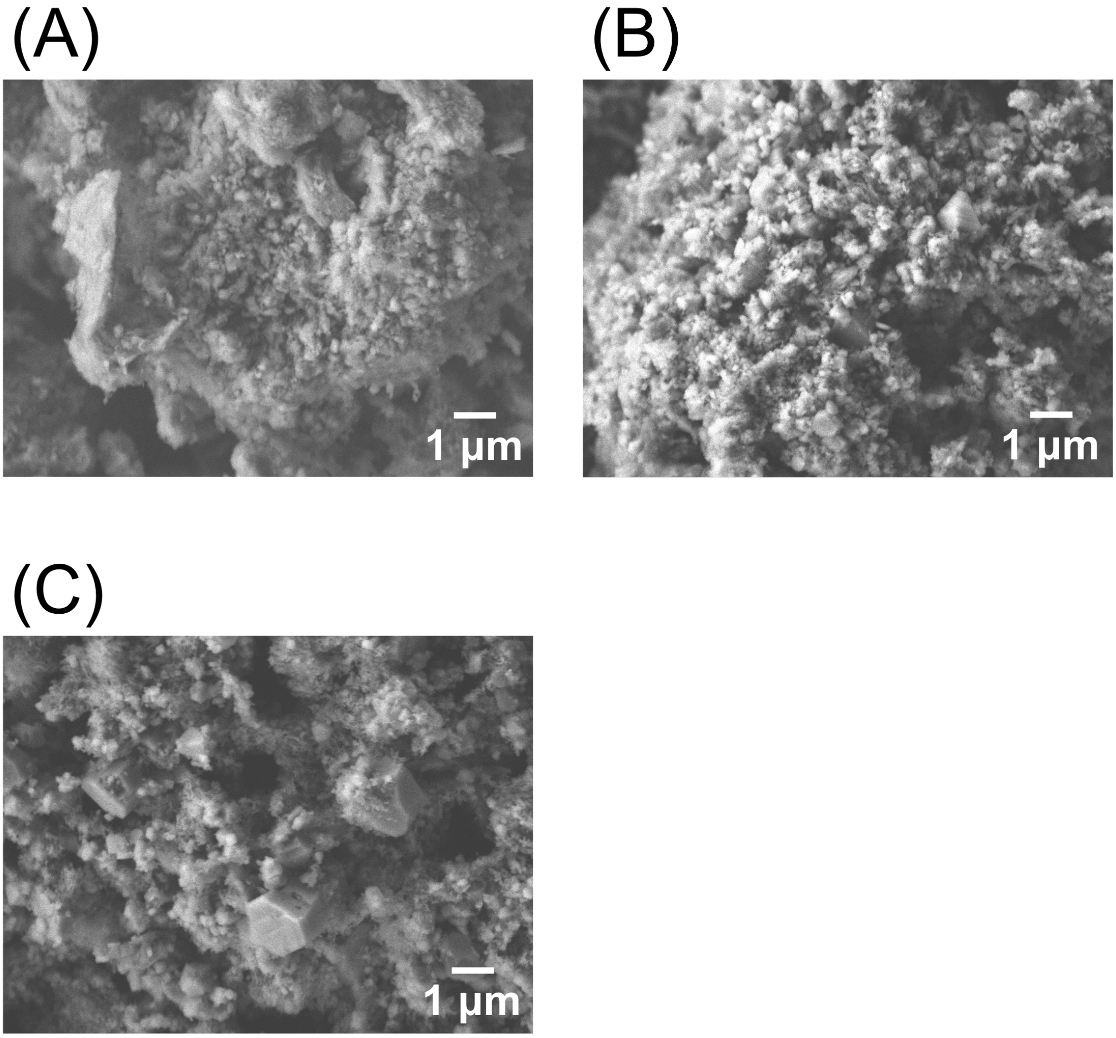

Fig. S9 SEM images for $Ca(OH)_2$ crystallites. (A) $Ca(OH)_2$ sample just received from the provider. (B) $Ca(OH)_2$ sample recovered by centrifugation of a mixture with water. (C) $Ca(OH)_2$ sample recovered by centrifugation of a mixture with water after MW irradiation at 150 °C for 1 min.

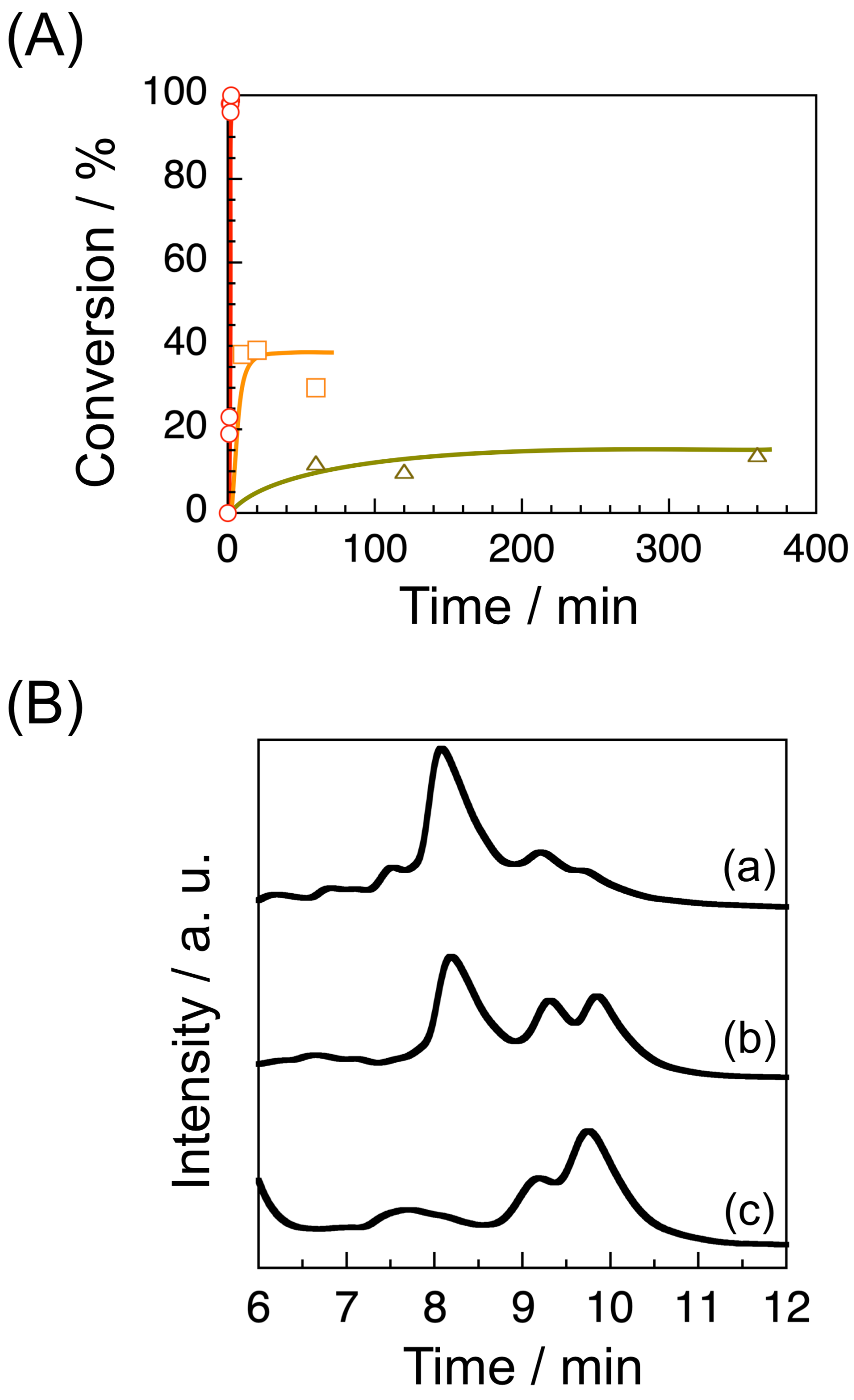

Fig. S10 Formose reaction by heating with an oil bath. (A) Time–conversion plots for formose reaction carried out using 1.0 mol kg^{-1} formaldehyde and 55 mmol kg^{-1} $Ca(OH)_2$ by heating with an oil bath thermostated at 150 (red circle), 100 (orange square) and 60 °C (dark yellow triangle). (B) HPLC charts for the products of formose reaction carried out using 1.0 mol kg^{-1} formaldehyde and 55 mmol kg^{-1} $Ca(OH)_2$ by heating with an oil bath thermostated at (a) 150, (b) 100 and (c) 60 °C for 2.33, 20 and 360 min, respectively.