Supplementary Materials for

Selective Formose Reaction under Microwave Irradiation

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Methods

Materials

An aqueous solution of formaldehyde (36 wt %), barium carbonate ($BaCO_3$), and *N*,*N*,*N*′,*N*′-tetraethylethylenediamine were purchased from Sigma-Aldrich (St. Louis, MO). Calcium hydroxide ($Ca(OH)_2$), silver(I) oxide (Ag_2O), alumina (Al_2O_3), imidazole, pyridine, and acetylacetone were purchased from FUJIFILM Wako Pure Chemical Corp. (Osaka, Japan). Barium hydroxide octahydrate ($Ba(OH)_2•8H_2O$), sodium hydroxide (NaOH), potassium hydroxide (KOH), triethylamine, 2-picoline, 3-picoline, acetic acid, and ammonium acetate were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Lithium oxide monohydrate ($LiOH•H_2O$), 2-(dimethylamino)ethanol, and acetonitrile for HPLC were purchased from Kishida Chemical Co., Ltd. (Osaka, Japan). Magnesium hydroxide ($Mg(OH)_2$), 1,4-diazabicyclo[2.2.2]octane (DABCO), and *N*-methylpiperidine were purchased from Kanto Chemical Co. Inc. (Tokyo, Japan). Amberlite® IR-120 H and IRA-910 Cl were purchased from Sigma-Aldrich (St. Louis, MO). Amberlite® IRA-910 Cl was used after exchanging Cl^- ions to OH^- ions (Amberlite® IRA-910 OH) by washing with 1.0 M NaOH. For TLC, Merck precoated TLC plates (silica gel 60 F254) were used. Water was purified with a Millipore Milli-Q system. Other reagents were used without further purification.

Measurements

The UV-visible absorption spectra were recorded on a HITACHI U-4100 spectrometer. ^{1}H NMR spectra were measured on a JNM ECS400 or ECA500 spectrometer using D_2O as solvent at 30 °C. Chemical shifts were referenced to acetonitrile signal (δ = 2.08 ppm). ^{1}H NMR, ^{13}C NMR,

HSQC, and HMBC spectra were recorded on a Bruker AVANCE700 spectrometer using D_2O as a solvent at 25 °C. Acetonitrile was used as an internal standard, and chemical shifts were referenced to the signal due to the methyl carbon of acetonitrile (δ = 1.47 ppm). HPLC measurements for the formose samples were carried out on a Jasco LC-200 Plus system equipped with a Jasco PU-2080 pump and an RI-2031 detector. A Shodex Asahipak 5NH 2P-50 4E column was used, and a mixed solvent of acetonitrile and water (3/1, v/v) was used as eluent with a flow rate of 0.6 mL min^{-1} and the preset temperature of column oven was 40 °C. LC-MS measurements were performed on a Bruker Daltonics micrOTOF-QIII compact connected with a Shimadzu Prominence UFLC system. In the LC system, Shimadzu LC-20AD pumps and a Shodex 5NH2P-50 4E column were equipped, and a mixed solvent of acetonitrile and water (3/1, v/v) containing 0.1 vol% formic acid was used as an eluent at a flow rate of 0.6 mL min^{-1}. ESI-MS data were recorded in a positive mode on a Thermo Fisher Scientific LTQ-Orbitrap-XL, controlled by the XCARIBUR 2.1 software package. The condition of ionization was set to the following parameters; ion spray voltage at 3.5 kV, ion spray temperature at 100 °C, and ion transfer tube temperature at 275 °C. Mixed solvent of methanol and water (1/1, v/v) was used as solvent. Internal calibration of ESI-MS was carried out using the monoisotopic peaks of sodium adducted ion of diethylphthalate (*m*/*z* 314.1410), protonated ion of di-2-ethylhexylphthalate (*m*/*z* 391.2843), and sodium adducted ion of di-2-ethylhexyl-phthalate (*m*/*z* 413.2662). SEM images were obtained on a JEOL JSM-7600F scanning electron microscope. $Ca(OH)_2$ crystallites were directly mounted on a conductive tape. The morphology of $Ca(OH)_2$ crystallites was scanned at an accelerating voltage of 5.0 kV with the LEI mode.

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 $Ba(OH)_2•8H_2O$ 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 determined at predetermined reaction times by the acetylacetone method[31]. When hydroxides of alkali and alkali earth metals were used, the conversions were relatively high. In particular, $Ca(OH)_2$ and $Ba(OH)_2•8H_2O$ 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

$$A_{cat} = \frac{\text{conversion} / 100}{tC_{cat}} \quad (1)$$

where t is the reaction time and C_{cat} is the catalyst concentration. As can be seen in Figure S2, 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 S7A 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 (Figure S3A). 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 (Figure S4B). 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 can be seen in Figure S7B. 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.

S1 Maruo, Y. Y., Nakamura, J. & Uchiyama, M. Development of formaldehyde sensing element using porous glass impregnated with beta-diketone. *Talanta* **74**, 1141-1147,

doi:10.1016/j.talanta.2007.08.017 (2008).

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

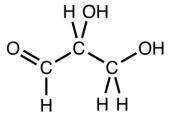
catalyst	reaction time / min	conversion / %	A_{app} / M^{-1} s^{-1}	the appearance of reaction mixture
$Ca(OH)_2$ [b]	3	71	7.9×10^{-2}	clear
$Ba(OH)_2 \cdot 8H_2O$ [b]	5	53	3.5×10^{-2}	clear
NaOH	5	62	1.0×10^{-2}	clear
$LiOH \cdot H_2O$	5	56	9.3×10^{-3}	clear
KOH	5	47	7.8×10^{-3}	clear
$Mg(OH)_2$	45	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.

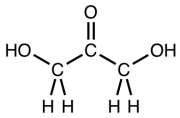
Table S2 | The total energies evaluated by DFT calculations for the isomers of trioses, tetroses, and pentoses.

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

C3

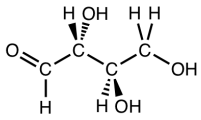


C3-1

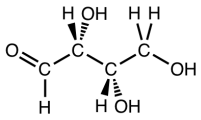


C3-2

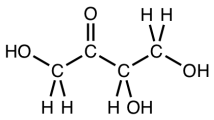
C4



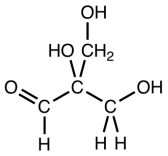
C4-1RR



C4-1RS

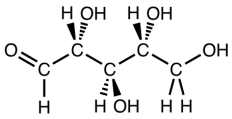


C4-1b2

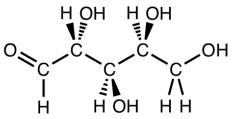


C4-2

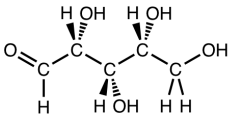
C5



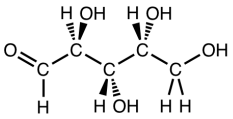
C5-1RRR



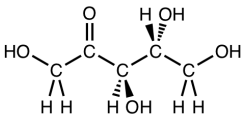
C5-1RRS



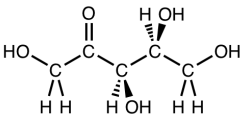
C5-1RSR



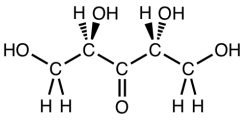
C5-1SSR



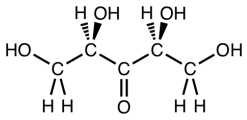
C5-2RR



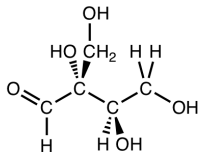
C5-2RS



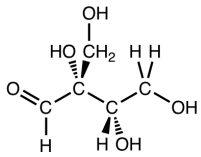
C5-3RR



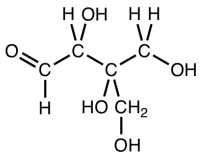
C5-3RS



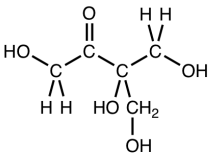
C5-1b2RR



C5-1b2RS



C5-1b3



C5-2b3

Scheme S1 | Chemical structures of the isomers of trioses, tetroses, and pentoses.

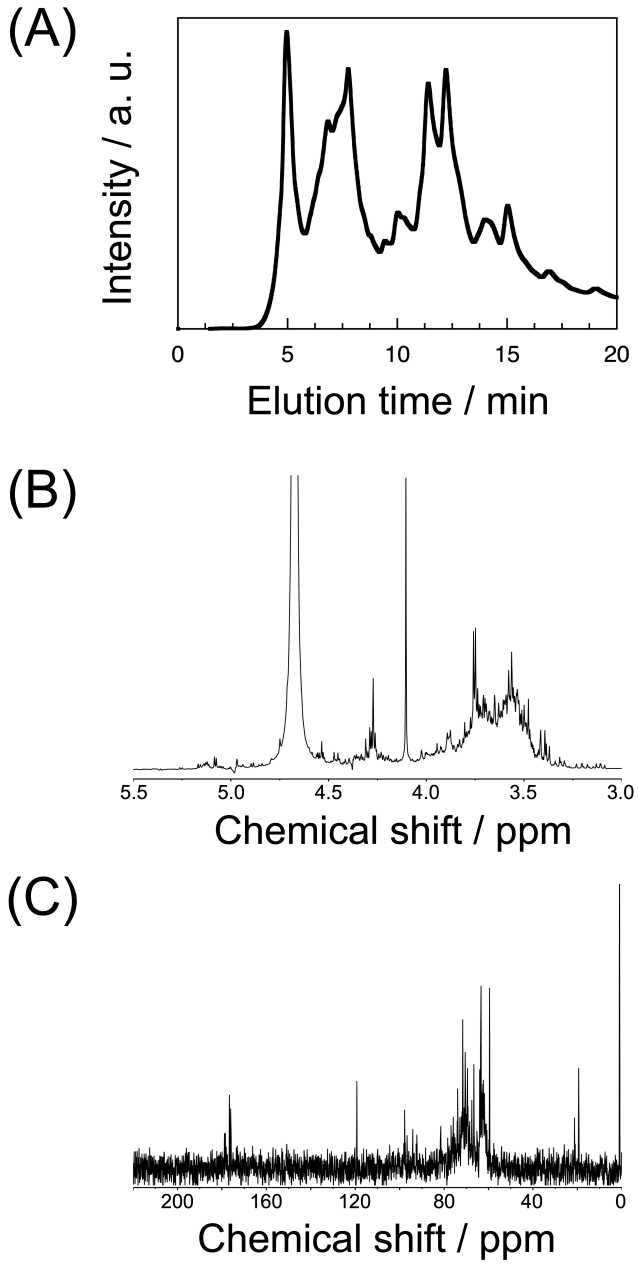


Figure S1 | Typical examples of data for conventional formose reaction carried out using 200 mM formaldehyde, 20 mM $Ca(OH)^2$, and 6.9 mM glyceraldehyde (a cocatalyst) at 60 °C for 30 min. (A) An HPLC chart recorded on a Jasco LC-200 Plus system equipped with a Shodex Asahipak 5NH 2P-50 4E column, a Jasco PU-2080 pump, and an RI-2031 detector, using a mixed solvent of acetonitrile and water (3/1, v/v) as eluent with a flow rate of 0.6 mL min^{-1} at 40 °C. (B) ^{1}H NMR and (C) ^{13}C NMR spectra for the product treated ion-exchange resins (Amberlite® IR-120 H and IRA-910 OH).

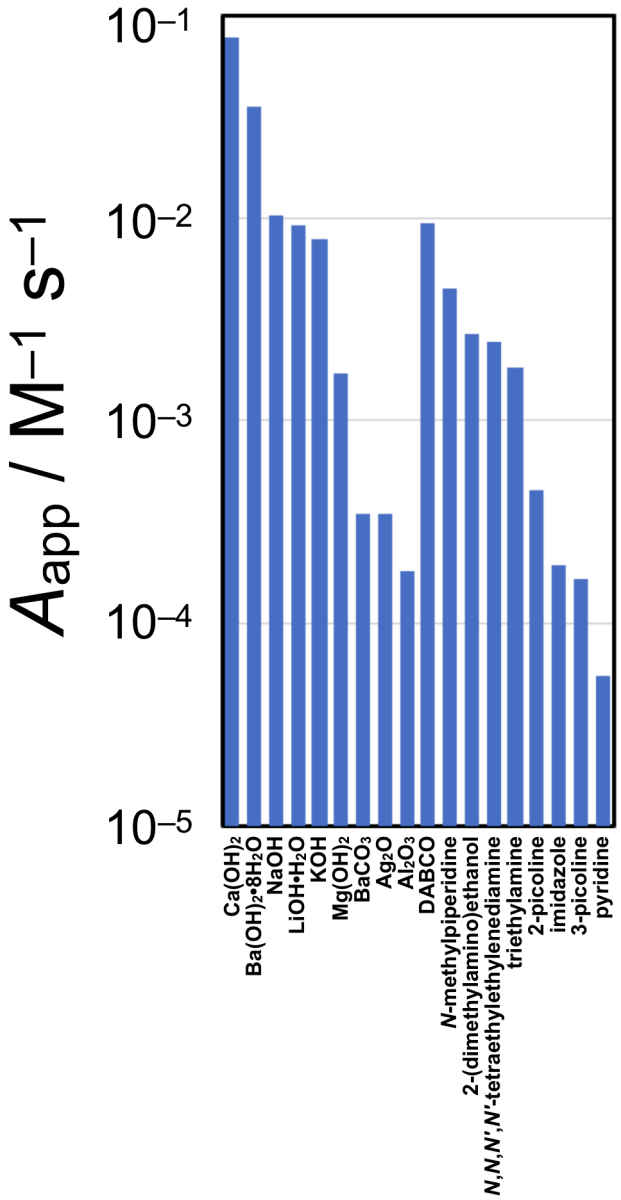


Figure S2 | Apparent activities (A_{app}) for formose reaction under MW irradiation using 1.0 mol kg^{-1} formaldehyde and various catalysts at a set temperature of 150 °C.

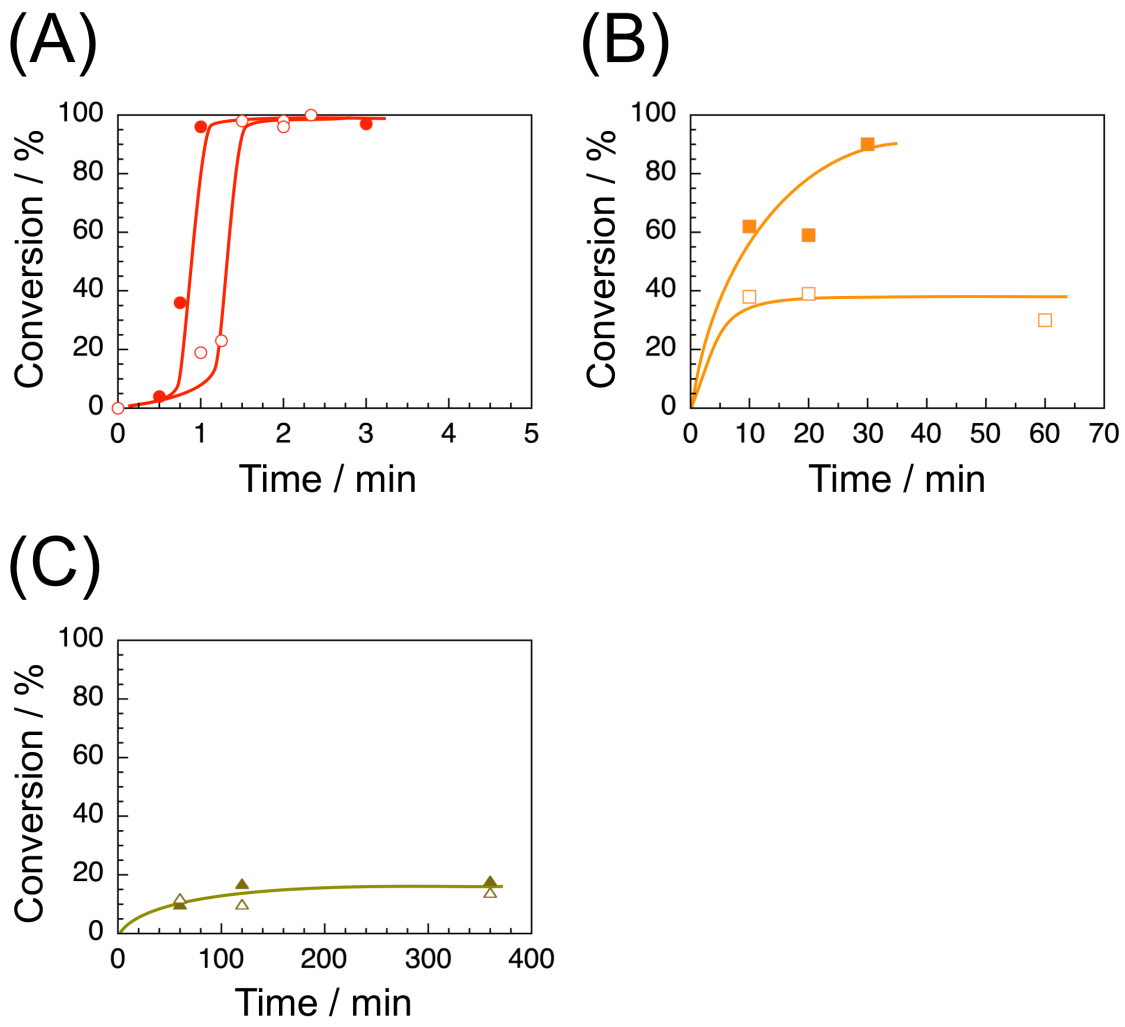


Figure S3 | Time–conversion plots for formose reaction carried out using 1.0 mol kg^{-1} formaldehyde and 55 mmol kg^{-1} $Ca(OH)_2$ under MW irradiation (closed symbol) and by heating with an oil bath (open symbol) at (A) 150, (B) 100, and (C) 60 °C.

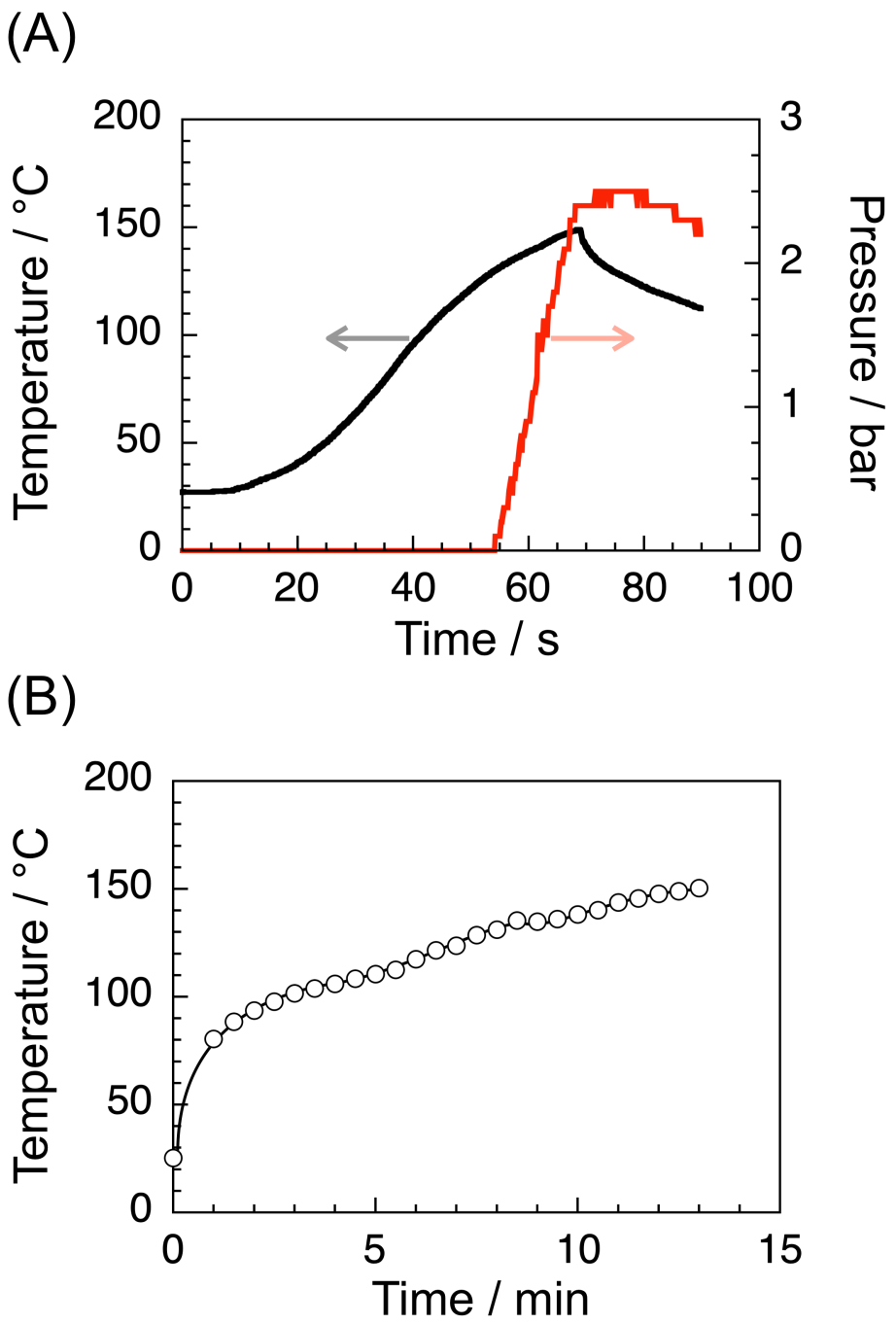


Figure S4 | (A) The time evolutions of temperature and pressure of the reaction mixture (5 mL) using a 2 – 5 mL vial under MW irradiation at a set temperature of 150 °C for 1 min and (B) the time evolution of temperature of the reaction mixture (5 mL) using a 2 – 5 mL vial by heating with an oil bath thermostated at 150 °C.

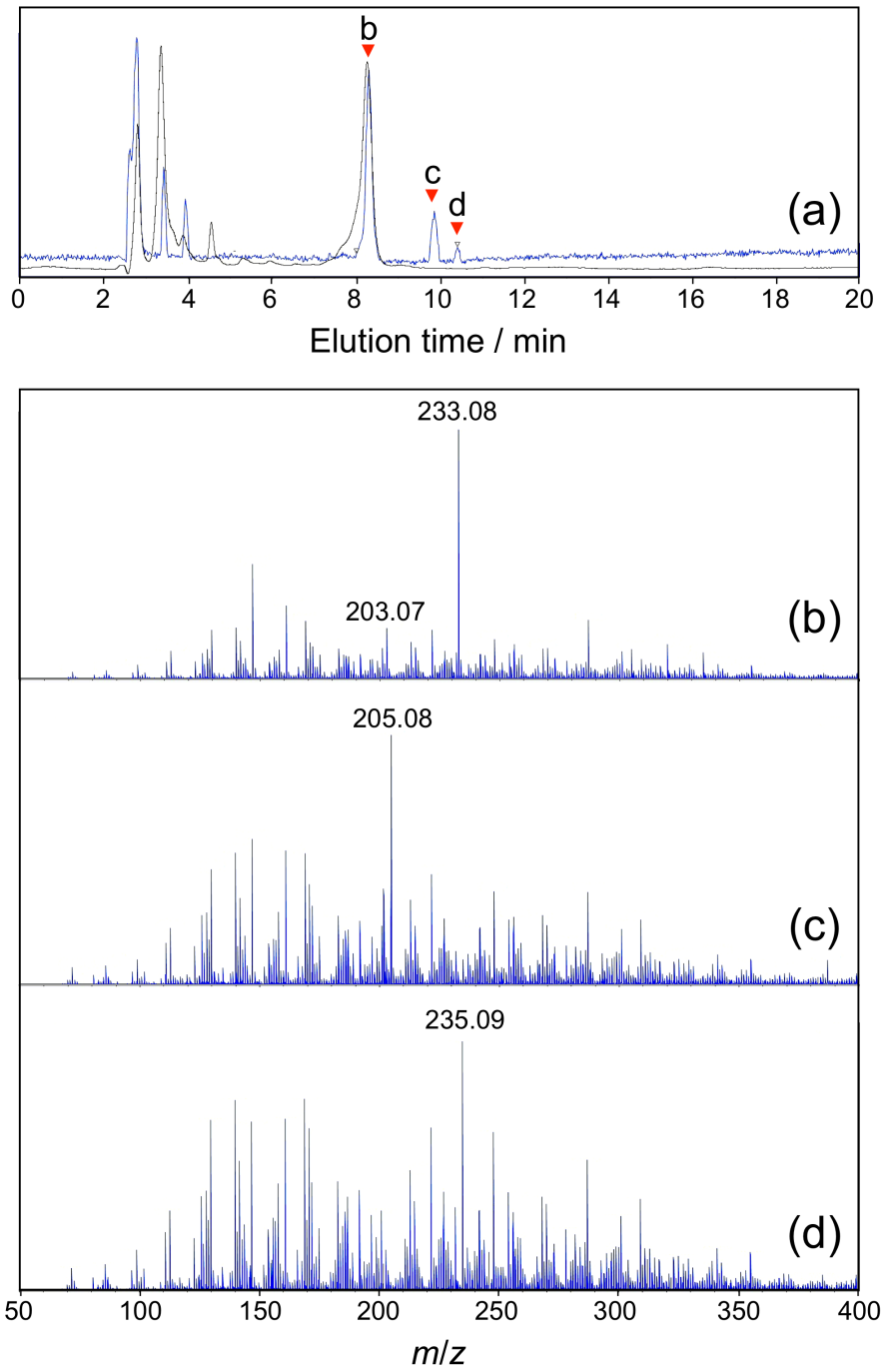


Figure S5 | LS-MS data for the product obtained by formose reaction under MW irradiation using 1.0 mol kg^{-1} formaldehyde and 55 mmol kg^{-1} $Ca(OH)_2$ at a set temperature of 150 °C for 45 s. (a) The LS chart. The MS data for (b) the signal b, (c) the signal c, and (d) the signal d in the LC chart.

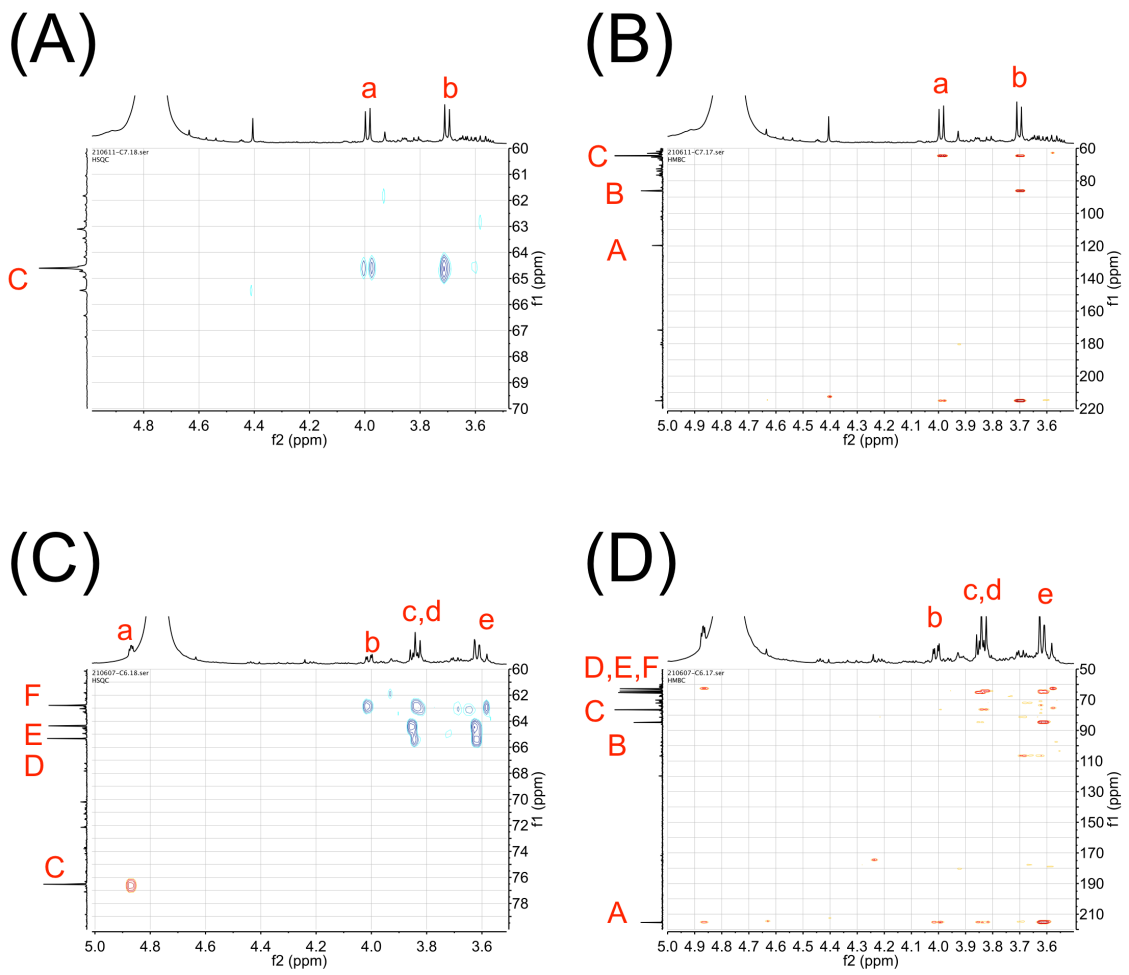


Figure S6 | Two dimensional NMR spectra for **C7*** and **C6*** (D_2O). (A) HSQC and (B) HMBC for **C7***, and (C) HSQC and (D) HMBC for **C6***.

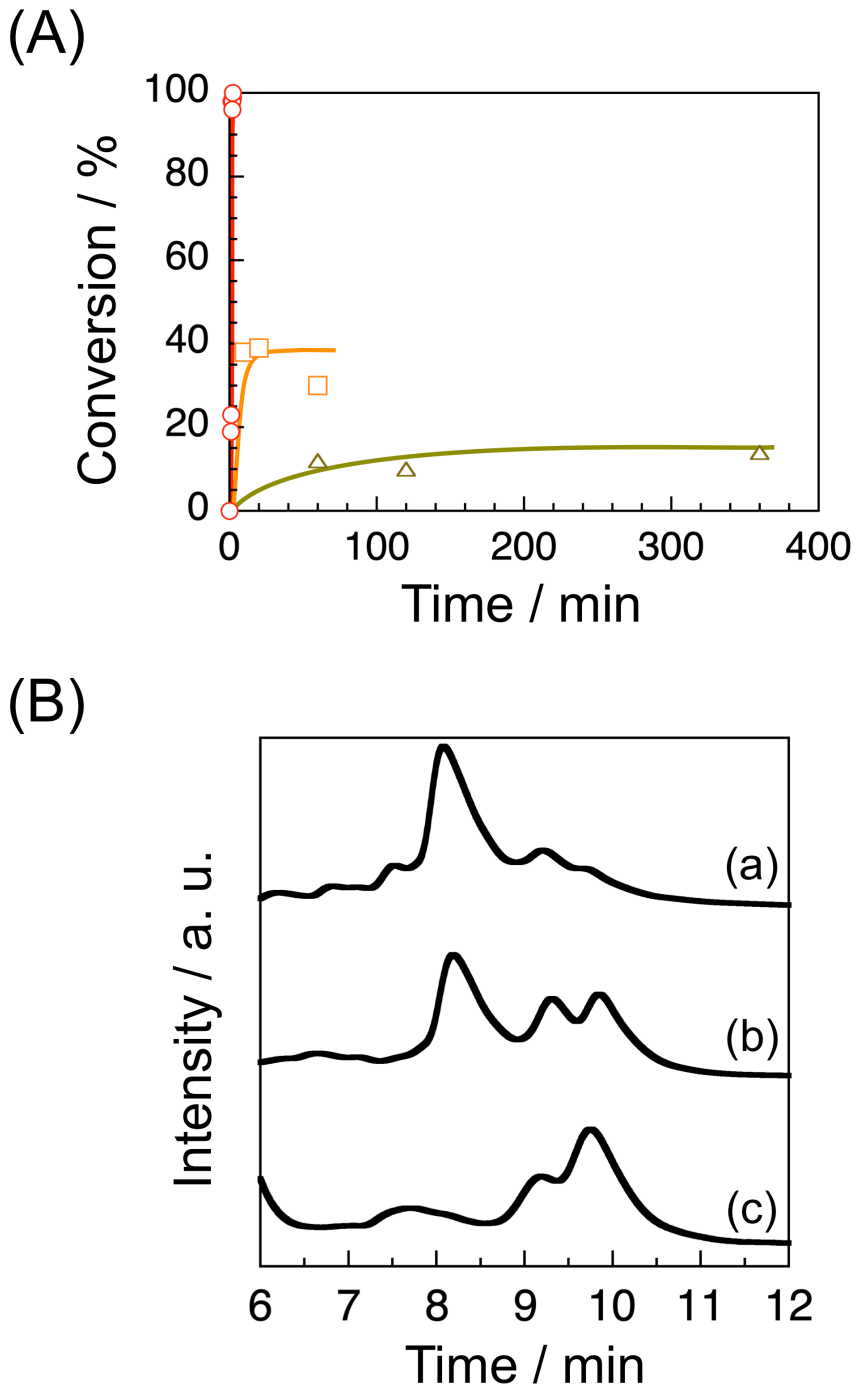


Figure S7 | Formose reaction by heating with an oil bath. (A) Time–conversion plots for formose reaction carried out using 1.0 mol kg^{-1} formaldehyde and 55 mmol kg^{-1} $Ca(OH)_2$ by heating with an oil bath thermostated at 150 (red circle), 100 (orange square), and 60 °C (dark yellow triangle). (B) 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.

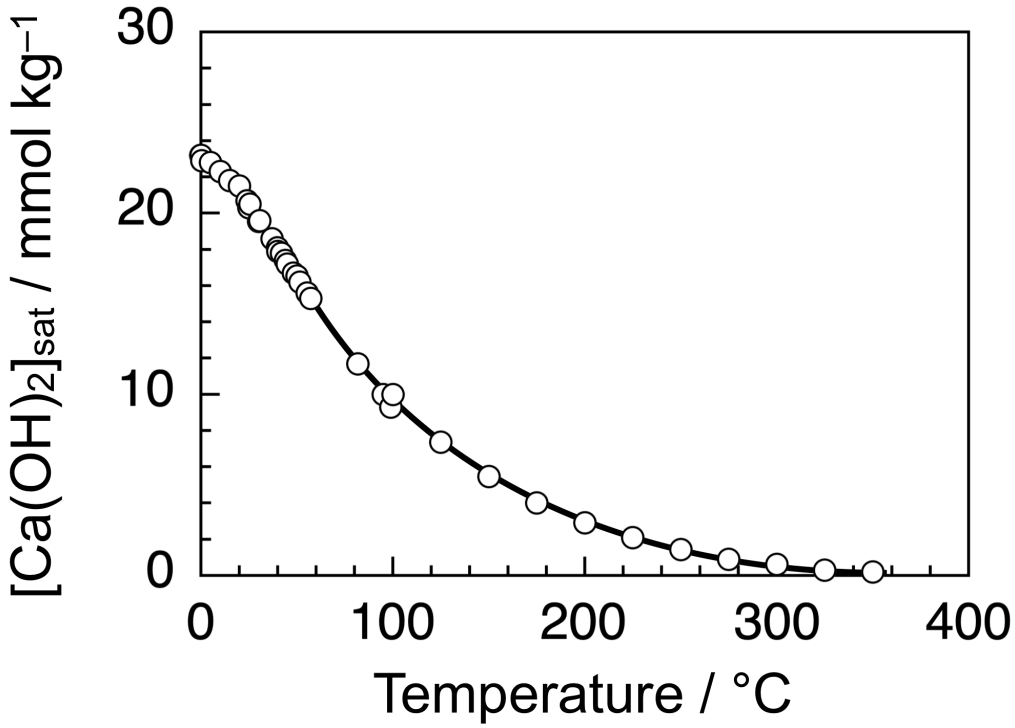


Figure S8 | The saturation concentration of $Ca(OH)_2$ ($[Ca(OH)_2]_{sat}$) in water at varying temperatures.

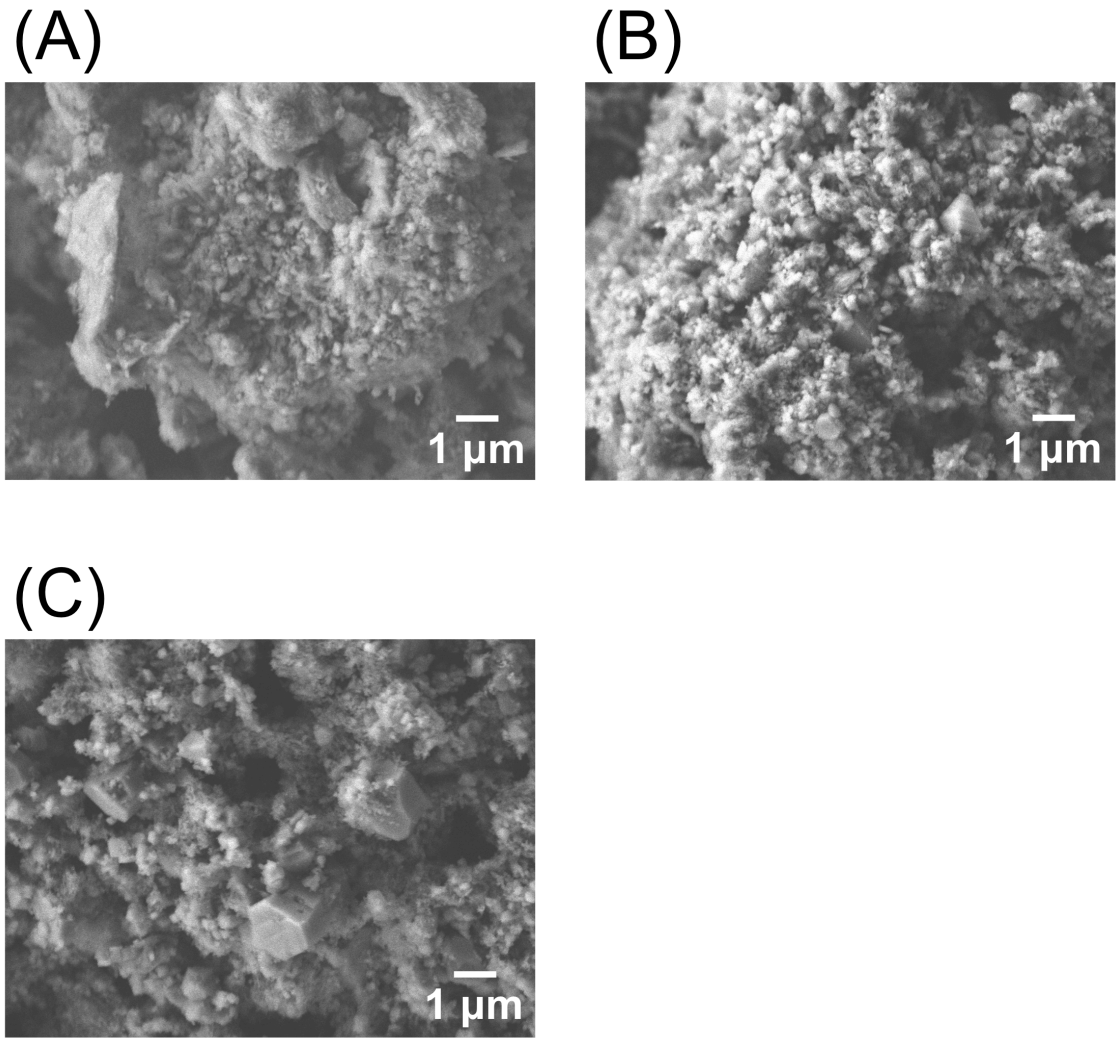


Figure S9 | SEM images for $Ca(OH)_2$ crystallites. (A) $Ca(OH)_2$ sample just received from the provider. (B) $Ca(OH)_2$ sample recovered by centrifugation of a mixture with water. (C) $Ca(OH)_2$ sample recovered by centrifugation of a mixture with water after MW irradiation at 150 °C for 1 min.