

PLANETARY SCIENCES

Synthesis of ^{13}C -enriched amino acids with ^{13}C -depleted insoluble organic matter in a formose-type reaction in the early solar system

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Solvent-soluble organic matter (SOM) in meteorites, which includes life's building molecules, is suspected to originate from the cold region of the early solar system, on the basis of ^{13}C enrichment in the molecules. Here, we demonstrate that the isotopic characteristics are reproducible in amino acid synthesis associated with a formose-type reaction in a heated aqueous solution. Both thermochemically driven formose-type reaction and photochemically driven formose-type reaction likely occurred in asteroids and ice-dust grains in the early solar system. Thus, the present results suggest that the formation of ^{13}C -enriched SOM was not specific to the cold outer protosolar disk or the molecular cloud but occurred more widely in the early solar system.

INTRODUCTION

Carbonaceous meteorites contain various types of organic matter, including refractory macromolecules and life's building molecules, such as amino acids, nucleobases, and sugars (1–3). This matter is crucial for understanding the astrochemical reactions of the early solar system. Furthermore, they are important for understanding chemical evolution in the origin of life, as a portion of these molecules were accreted to the prebiotic Earth.

The origin of primitive organic matter has not yet been identified, although it has been investigated extensively since its discovery in meteorites. Stable isotope ratios have been used as evidence to constrain the source and formation processes of planetary materials. Carbon in polar solvent-soluble organic matter (SOM), such as amino acids, nucleobases, aldehydes, sugar acids, and sugars, are all enriched in ^{13}C relative to the terrestrial carbon standard (2–9). For example, the $\delta^{13}\text{C}$ values of glycine and alanine in the Murchison meteorite exhibit highly positive values ranging from +13 to +41‰ (per mil) and from +27 to +52‰, respectively (4–6). Nucleobases and sugars also range from +38 to +45‰ and from –1 to +43‰, respectively (2, 3). Furthermore, ^{13}C enrichment was reported for cometary glycine (10). The origin and specific processes of enrichment in ^{13}C have not yet been identified, but they are suspected to have originated from the cold outer regions of the protosolar disk or the cold molecular cloud (5, 6, 11, 12).

Insoluble organic matter (IOM), which represents the major carbon pool in carbonaceous meteorites, is depleted in ^{13}C relative to the terrestrial standard, as represented by negative $\delta^{13}\text{C}$ values ranging from –34 to –17‰ for unheated Renazzo-like (CR) and Mighei-like (CM) carbonaceous chondrites (13). This depletion is also found in refractory organic macromolecules in interplanetary dust particles and cometary materials (14, 15). The origin of the distinct difference in $^{13}\text{C}/^{12}\text{C}$ between coexistent SOM and IOM is unknown, but it may assist in understanding the origin and formation processes of organic compounds in the primitive solar system.

Conflicting models for the origin of IOM and SOM have been proposed in previous studies. Some models propose that the origins of coexistent IOM and SOM are entirely different (16, 17); this is supported by the large differences in $^{13}\text{C}/^{12}\text{C}$. Other models propose specific relations in their origins, such as the formation of SOM by IOM alteration (18, 19) and simultaneous formation in the series of a reaction (20, 21). Cody *et al.* (20) first proposed that formaldehyde polymerization may be responsible for the formation of IOM and cometary refractory organic solids. Similarities in the compositions of amino acids, sugars, and N-cyclic compounds in the products of formaldehyde polymerization with ammonia to those in primitive meteorites support this model as a major synthetic route of meteorite organics (3, 21–23). Formaldehyde polymerization is referred to as the formose reaction, which forms various sugars and yields caramel-like compounds in the final product (24). Although isotope fractionation in this reaction has been poorly constrained, we hypothesize that the kinetic isotope effect (KIE) in competing elemental reactions within the formose-type reaction potentially generates the large differences in $^{13}\text{C}/^{12}\text{C}$ between products.

RESULTS AND DISCUSSION

Isotope fractionation in ammonia-involved formose-type reactions

In this section, we report on ^{13}C enrichment in amino acids and ^{13}C depletion in synthetic IOM, simultaneously produced by a series of reactions in an ammonia-involved formose-type reaction (AFR) containing formaldehyde ($\delta^{13}\text{C} = -42.6\text{‰}$), glycolaldehyde ($\delta^{13}\text{C} = -16.7\text{‰}$), and ammonia and reacted at 80°C for up to 90 days (Fig. 1). This temperature is reasonable for parent body reactions, as suggested by several previous studies (25, 26), and similar reactions would have occurred in the early stages of aqueous processes in carbonaceous asteroids. The effect of minerals was not considered to simplify reactions, thus avoiding catalytic and adsorption effects. The isotope differences between amino acids and IOM produced in the reaction are up to 47.8‰ (Fig. 2 and table S1). This difference is consistent with or close to the enrichment observed in primitive carbonaceous meteorites: 31 to 58‰ in the Murchison meteorite, 48 to 56‰ in EET92042, 29‰ in ALH 83100, 57 to 62‰ in GRA95229, and 59 to 63‰ in QUE99177 (5, 6, 13, 27).

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As the formose reaction is a rapid polymerization of aldehydes, preferential consumption of ^{12}C aldehydes by a KIE is expected, and this leaves a limited amount of ^{13}C -enriched aldehydes in the residue. In this study, formaldehyde was rapidly consumed, decreasing to less than 0.2% after 0.5 days of the reaction (Fig. 2A). Some of the initial formaldehyde would have been used to form hexamethylenetetramine (HMT) rapidly (28). This reaction is reversible, and thus, the following formose-type reaction consumed HMT via formaldehyde (28). The AFR forms large soluble molecules from small aldehydes and ammonia in the products, which further react to form larger insoluble matter (28). Thus, in the products of the present study, most of the carbon was present as large soluble molecules. The yields of glycine, alanine, and β -alanine increased after the substantial aldehyde consumption (Fig. 2A), thereby indicating that amino acids were formed using ^{13}C -enriched formaldehyde because of the KIE (Fig. 3A). We thus concluded that KIE during the AFR



Fig. 1. AFR experiments and their products. Simple heating of formaldehyde, glycolaldehyde, and ammonia with calcium hydroxide formed amino acids, amines, carboxylic acids, and synthetic IOM. Photo credit for the scanning electron microscopy (SEM) image: Yoshinari Iwasa, Tohoku University. Photo credit for the synthetic IOM and SOM: Yoshihiro Furukawa, Tohoku University.

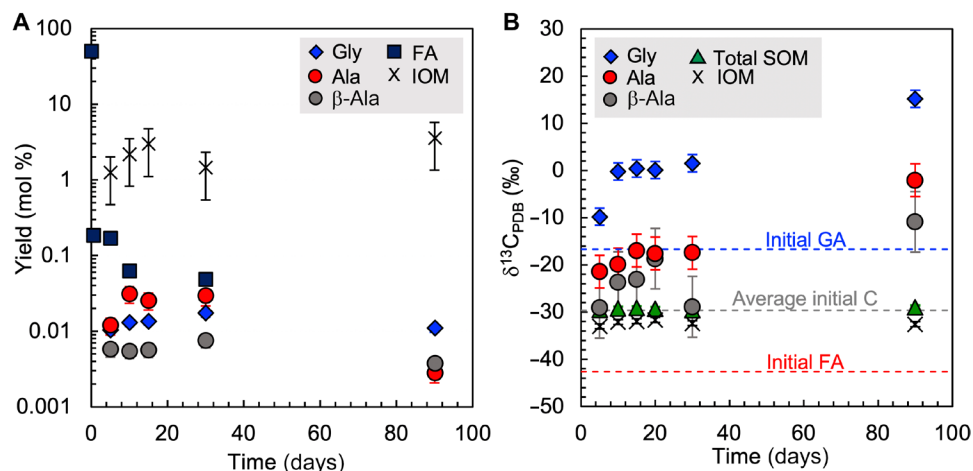


Fig. 2. Yields and $\delta^{13}\text{C}$ values. (A) Yields of amino acids and synthetic IOM. Yields are shown on the basis of molar amounts of carbon in products and total starting materials. Initial carbon-based formaldehyde (FA) content is 50%, and glycolaldehyde (GA) content is 50%. (B) Value of $\delta^{13}\text{C}$ for amino acids, synthetic IOM, and bulk SOM. Blue, red, and gray dashed lines indicate initial $\delta^{13}\text{C}$ values of GA, FA, and average carbon in the starting materials, respectively. The experimental reproducibility of $\delta^{13}\text{C}$ values in glycine (Gly), alanine (Ala), β -alanine (β -Ala), total SOM, and synthetic IOM are ± 1.8 , ± 3.5 , ± 6.4 , ± 0.4 , and $\pm 0.5\%$, respectively (1σ , $n = 3$).

was the major factor that produced the large isotope discrimination among products of the AFR. Moreover, the ^{13}C enrichment in the residue of a successive reaction via KIE was proposed in a previous study to explain the decrease in the $\delta^{13}\text{C}$ value with an increasing carbon number of low-molecular weight hydrocarbons and carboxylic acids in carbonaceous meteorites (29).

At temperatures less than 80°C , IOM was not formed within 5 days, whereas at higher temperatures, the yields of IOM increase with temperature and the $\delta^{13}\text{C}$ values become closer to the bulk carbon isotope composition of the starting aldehydes (fig. S1). This characteristic is consistent with the gradual formation of IOM through the addition of kinetically fractionated, lighter to heavier carbon atoms in AFR.

Five free amino acids were formed, including glycine, alanine, β -alanine, α -aminobutyric acid, and β -aminoisobutyric acid (fig. S2). The amounts of contaminated glycine, alanine, and β -alanine during the experiments and in the starting material were ≤ 0.1 , ≤ 0.2 , and $\leq 0.3\%$ of the product (at 80°C for 5 days), respectively. Thus, the effect of contamination on the yields and $\delta^{13}\text{C}$ values of amino acids was negligible. The $\delta^{13}\text{C}$ values of the contaminant amino acids were most likely negative, given that they are biogenic (30). The yields of detected amino acids increased with the reaction temperature (fig. S1A). β -Alanine became the most abundant detected amino acid at the highest temperature. This was also reported by Kebukawa *et al.*, (21) and is consistent with the amino acid compositions in aqueously altered carbonaceous chondrites (31).

Previous studies have suggested that amino acids are formed from aldehydes and ammonia through reductive amination coupled with the oxidation of aldehydes (32). The presence of sugar acids, which represent an oxidized form of sugar, in meteorites and the formation of carboxylic acids in the present study (Fig. 4) are consistent with the aldehyde oxidation in the AFR (7). The higher $\delta^{13}\text{C}$ values of glycine (the C2 amino acid) than alanine and β -alanine (the C3 amino acids) found in the experiments support the formation of glycine from a high- $\delta^{13}\text{C}$ glycolaldehyde (C2 aldehyde; $\delta^{13}\text{C} = -16.7\%$) and that of alanine and β -alanine from both high- $\delta^{13}\text{C}$ glycolaldehyde (C2 aldehyde) and low- $\delta^{13}\text{C}$ formaldehyde

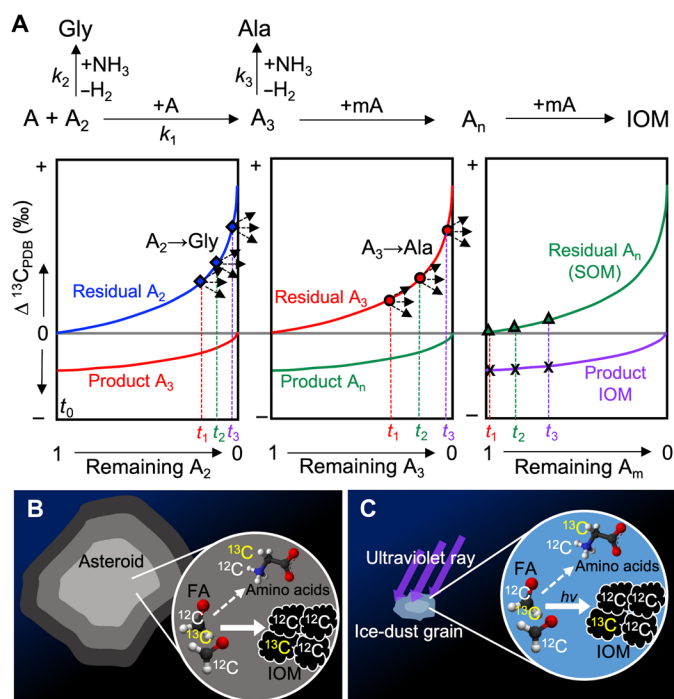


Fig. 3. Schematic model of kinetic isotope fractionation in an AFR. (A) Isotope fractionation in the laboratory experiment. A, A_2 , A_3 , mA, and A_n represent formaldehyde, glycolaldehyde, glyceraldehyde, many formaldehyde, and soluble large aldehyde molecules, respectively; k_1 , k_2 , and k_3 represent the rate constants of the respective reaction. The initial $\delta^{13}C$ values of A and A_2 are shown as the same value in this figure but were different in the experiments. The rate constant of an elemental reaction in the formose reaction (k_1) was significantly higher than the rate constants of amino acid formation (k_2 and k_3). Black dashed arrows represent potential isotope fractionation associated with amino acid formation from aldehydes. For simplification, the initial isotope ratios of A and A_2 should be the same. The variables t_1 to t_3 represent the time of amino acid formation from the corresponding aldehyde. (B) Isotope fractionation in carbonaceous asteroids in the early solar system. (C) Isotope fractionation in ice-dust grains in the early solar system.

(C1 aldehyde; $\delta^{13}C = -42.6\%$; Fig. 2B). The difference in the $\delta^{13}C$ values between amino acids in meteorites can provide information for relevant synthetic routes (6). The $\delta^{13}C$ values of AFR products can be used to estimate these synthetic routes if the initial $\delta^{13}C$ values of formaldehyde and glycolaldehyde in asteroids and comets are known.

Aldehyde is a major substrate used to produce amino acids with Strecker-cyanohydrin synthesis, as suggested in many previous studies on meteoritic amino acids (1, 6, 33, 34). HCN, another source material of Strecker-cyanohydrin synthesis, is found in meteorites and comets (34–36). Strecker synthesis itself does not produce ^{13}C enrichment in the product amino acids (6); however, ^{13}C enrichment in amino acids might have been possible if the Strecker-cyanohydrin process occurred with AFR, given that the reaction rate of the Strecker-cyanohydrin process is far lower than that of aldehyde polymerization (i.e., formose-type reaction).

IOM contains both labile aliphatic carbon and refractory aromatic carbon (37). The former is more enriched in ^{13}C , whereas the latter is depleted in ^{13}C (38, 39). This difference in $^{13}C/^{12}C$ has been frequently explained by the contributions of isotopically distinct carbon sources between aliphatic and aromatic carbons (38, 39). However,

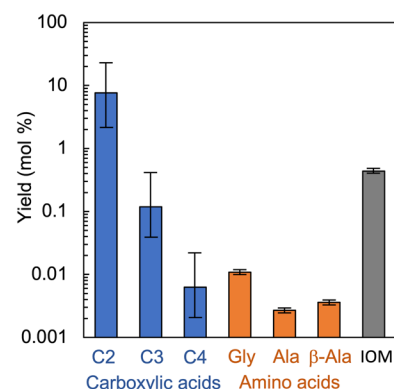


Fig. 4. Carbon-based yields of carboxylic acids, amino acids, and synthetic IOM in the experimental product of 80°C heating for 90 days. A larger signal of formic acid was detected in the gas chromatography–mass spectrometry (GC/MS) analysis, but the yield was unquantified.

the difference in the $\delta^{13}C$ value of IOM could be explained by the KIE during the aromatization of carbonaceous matter (i.e., lighter aliphatic carbons in the carbonaceous matter are preferentially consumed to form aromatic carbon; Fig. 3A).

Carbon isotope fractionation in the early solar system

The conditions of the present experiments are closer to aqueous processes in carbonaceous asteroids than to the interstellar medium (Fig. 3B). Aldehydes are present in aqueously altered carbonaceous meteorites, and those abundances decrease with an increasing aqueous alteration level (8). This suggests that aldehydes were present before aqueous processes and that AFR produced IOM and ^{13}C -enriched small-molecular weight organics in asteroids. Carboxylic acid is one of the most abundant classes of soluble organic compounds in meteorites and its concentration is more than one order of magnitude higher than that of amino acids in the Murchison meteorite (1). Formic acid, acetic acid, propanoic acid, and butyric acid were formed in the present experiment (Fig. 4). In general, the total amount of carboxylic acids is one order of magnitude higher than that of amino acids. The concentration of total amines in the Murchison meteorite is smaller than the total concentration of amino acids, but they are of the same orders of magnitude (1). This relationship is also observed in the total yields of amines in the present experiment, which were approximately half those of the amino acids (fig. S2). Furthermore, a small amount of calcium carbonate was formed in the experiment. Carbonate is the secondary carbon pool after organic compounds in carbonaceous meteorites; for example, 0.09 weight % in the Murchison meteorite (26). The similarity in the compositions of soluble organic compounds and carbonate, as well as the isotope characteristics of amino acids and IOM between meteorites and the AFR products, indicates the substantial contribution of the AFR in the meteorite's organic synthesis.

Organic macromolecules found in Comet 81/Wild 2 particles and the Tagish Lake meteorite (the latter of which is considered to contain cold molecular cloud materials or outer protosolar disk materials) indicate that IOM formation also occurred before the accretion of asteroids (15, 40). Both formaldehyde and ammonia are contained in cometary ice (36). A photochemical formose reaction has been deemed possible (41), but isotope fractionation of $^{13}C/^{12}C$ in this type of reaction has not been investigated. Photolysis of an interstellar

ice analog containing methanol, ammonia, water, and carbon monoxide forms HMT as a major product via formaldehyde (42). This suggests that a substantial amount of methanol is converted into formaldehyde in this reaction. Similar photochemical reactions also form amino acids, sugars, nucleobases, and complex insoluble organic molecules (43–46). The $\delta^{13}\text{C}$ values of refractory organic globules found in samples of Comet 81P/Wild2 ($\delta^{13}\text{C} = -35 \pm 3\%$) (15), in some interplanetary dust particles (mean $\delta^{13}\text{C}$ values of clustered and individual interplanetary dust particles are -45 and -30% , respectively) (14), and the Tagish Lake meteorite ($\delta^{13}\text{C} = -77$ to $+16\%$, generally below -9%) (40) all had similar values to primitive meteorites. The ^{13}C -enriched glycine ($\delta^{13}\text{C} = +29 \pm 6\%$) was detected from the comet-exposed foil of the Stardust mission that collected samples from Comet 81/Wild2, although it was not clear whether the detected glycine was completely pristine (10). The similar isotope gap between the present experimental products (up to 47.8%) and the gap between the cometary glycine and cometary organic-globules ($\sim 64\%$) suggest the presence of similar KIE associated with AFR in the cold protosolar disk or cold molecular cloud (Fig. 4C).

Several models have been proposed for the potential mechanism of carbon isotope fractionation in the early solar system, including the gas-phase ion-molecular reaction, isotope-selective photodissociation, and the Fischer-Tropsch-type (FTT) reaction (12, 47–49). Formations of ^{13}C -enriched and ^{13}C -depleted organics have been proposed for a cold molecular cloud of <10 K, resulting from the selective removal of ^{13}C in CO through a gas-phase ion-molecular reaction (49). In contrast, the isotope-selective photodissociation of CO enriches ^{13}C in the gas phase (47). This reaction is also expected to occur in cold regions of molecular clouds. On the basis of these proposed fractionations in the cold region of the early solar system, the linkage between meteoritic ^{13}C -enriched SOM and the cold region of the early solar system has been widely proposed (5, 6, 12). However, these models do not explain ^{12}C enrichment in IOM and ^{13}C enrichment in SOM. Furthermore, these models are contradictory regarding the absence of a positive correlation between ^{13}C enrichment and D and ^{15}N enrichments in organic compounds in primitive solar system materials (i.e., primitive meteorites, interplanetary dust particles, and cometary materials) (14, 15, 40). The D and ^{15}N enrichments are characteristic signatures indicating the origin of organic compounds in cold regions (50–52). The formation of SOM and IOM in AFR presented in this study is substantially different from these cold-specific models but is consistent with the absence of the positive correlation between ^{13}C enrichment and D and ^{15}N enrichments and with the formation of ^{13}C -enriched SOM and ^{13}C -depleted refractory organics found in meteorites and comets.

The FTT reaction was also proposed as a model to explain carbon isotope fractionation found in meteorites (53). In the experimental simulations of the FTT reaction, ^{13}C -depleted long hydrocarbons and ^{13}C -enriched CO_2 were formed as a simulation of ^{13}C -depleted IOM and ^{13}C -enriched carbonate in meteorites. However, the produced aliphatic hydrocarbons were different from mostly aromatic IOM carbon (37). Furthermore, the isotope effect that is systematic of unreacted heavy CO and the produced light hydrocarbons from the FTT reaction is opposite to that of the light CO and heavy hydrocarbons found in the Murchison meteorite (29, 53). Meanwhile, the FTT mechanism has been proposed to explain the preponderance of ^{13}C -depleted straight-chain amino acids (i.e., n - ω -amino acids) in thermally altered carbonaceous meteorites because of the similarity in the ^{13}C -depleted characteristics of aliphatic hydrocarbons in FTT products (54).

The $\delta^{13}\text{C}$ values of IOM produced in the present AFR experiment are close to the average value of the original aldehydes. This suggests that the $\delta^{13}\text{C}$ values of IOM in meteorites, comets, and interplanetary dust particles (i.e., $^{12}\text{C}/^{13}\text{C} = \sim 90$) (13–15) represent that of the bulk original polar organic compounds, including aldehydes and reactive organic compounds such as HCN and alcohols. The $^{12}\text{C}/^{13}\text{C}$ values of IOM are consistent with the homogeneous value of early solar materials, that is, $^{12}\text{C}/^{13}\text{C} = 90 \pm 10$ for the solar system and $^{12}\text{C}/^{13}\text{C} = 85 \pm 20$ for cold outer regions (55). This suggests that the ^{13}C enrichment in polar small-molecular weight organic molecules does not have a direct relationship with the outer protosolar materials and cold molecular clouds; instead, it was probably formed more commonly by KIE in the early solar system where thermochemical or photochemical reactions occurred with volatiles, including formaldehyde and ammonia.

MATERIALS AND METHODS

Heating experiments

Heating experiments of aldehydes solution were conducted in an electric furnace with a polytetrafluoroethylene (PTFE) bottle containing 120 mg of paraformaldehyde ($\geq 95\%$; Serva), 120 mg of glycolaldehyde dimer (Merck), 30 mg of calcium hydroxide (Wako), 0.1 ml of 28% NH_3 aq (28% NH_3 in double-distilled water, PTFE grade; Sigma-Aldrich), and 2 ml of pure water (purified with a Milli-Q Integral MT, total organic carbon: <5 parts per million, 18.2 megohm-cm). The PTFE bottle was used to avoid contamination of Na, Al, Si, and B from a glass tube because the chemical erosion rate of glass by a highly alkaline heated solution is generally high; moreover, it is known that borate ion significantly affect the formose reaction (56, 57). The PTFE bottle was washed with purified water, methanol [grade 5000 for pesticide residue and polychlorinated biphenyl (PCB) analysis; Wako], and hexane (grade 5000 for pesticide residue and PCB analysis; Wako) before use. The amounts of contaminated glycine, alanine, and β -alanine in the starting material were <0.125 , <0.2 , and $<0.3\%$ of the product (at 80°C for 5 days), respectively. Furthermore, the amounts of contaminated glycine, alanine, and β -alanine during the course of the experiment were <0.05 , 0.2 , and 0.3% of the product (at 80°C for 5 days), respectively. The product was centrifuged to separate SOM and synthetic IOM fractions. The synthetic IOM fraction was treated with an aqueous solution of HCl, rinsed with water, methanol, and hexane, and dried in a vacuum.

At most, 0.5 to 3% of carbon in the aldehydes was converted to IOM within 90 days (Fig. 2A). The $\delta^{13}\text{C}$ values of bulk IOM were slightly lower than the average $\delta^{13}\text{C}$ value of formaldehyde and glycolaldehyde in the starting material ($\delta^{13}\text{C} = -29.7\%$) but increased slightly from -33.0 to -31.6% during incubation (Fig. 2B). In contrast, the $\delta^{13}\text{C}$ values of bulk SOM (i.e., the supernatant of the reaction products, $\delta^{13}\text{C} = -29.6$ to -29.0%) were slightly higher than the average $\delta^{13}\text{C}$ value of the starting aldehydes (Fig. 2B). This isotopically balanced discrimination in $^{13}\text{C}/^{12}\text{C}$ among the starting aldehydes, SOM, and IOM indicates no leakage of carbon from the system during the experiments.

Product analyses

The synthetic IOM and an aliquot of the SOM were analyzed with an elemental analyzer isotope ratio mass spectrometer (EA-irMS; Flash 2000 connected to DELTA V; Thermo Fisher Scientific). The reproducibility of this analysis was $\pm 0.06\%$ (1σ , $n = 6$). Amino

acids and amines were collected from an aliquot of the SOM. A part of this fraction was analyzed by ultrahigh-performance liquid chromatography–tandem mass spectrometry (Shimadzu LCMS-8040) with a reversed-phase column [Waters CORTECS; 2.1-mm inner diameter (ID), 100 mm long, 1.7- μm particles] and eluents (ammonium formate buffer and acetonitrile) as described elsewhere (58).

Another part of this fraction was purified with a cation exchange resin (AG50-X8; Bio-Rad). Then, the cation fraction was analyzed by gas chromatography–combustion–isotope ratio mass spectrometry (GC-c-irMS) with Agilent DB-5 column (30 m, 0.25-mm ID, 25- μm -thick film) for the compound-specific carbon isotopic composition of amino acids as described in (59). The reproductivity of this analysis was $\pm 1.4\%$ (1σ) (60).

Carboxylic acids were analyzed with a gas chromatograph mass spectrometer (Agilent 5977B) with an Agilent DB-FATWAX UI column (30 m, 0.25-mm ID, 25- μm -thick film). Sample injection was conducted using the solid-phase microextraction technique (polyethylene glycol phase coating). The oven temperature was initially kept at 35°C for 6 min, ramped up to 135°C at 25°C/min and then to 185°C at 1.5°C/min, and left for 10 min at 185°C.

Formaldehyde was analyzed with an ultraviolet-visible spectrophotometer (Agilent 8453) after derivatization with 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (AHMT). A total of 2 ml of diluted supernatant of the sample was added to 2 ml of a 5 M KOH solution and 2 ml of 34.5 mM AHMT in 0.5 M HCl solution. This mixture was vortexed and left at ambient temperature ($\sim 20^\circ\text{C}$) for 20 min. Then, 2 ml of 32.6 mM KIO_4 in 0.2 M KOH solution was added to the sample solution. This mixture solution was vortexed, left for ~ 1 min, and analyzed with the ultraviolet-visible spectrophotometer at 550 nm.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at <http://advances.sciencemag.org/cgi/content/full/7/18/eabd3575/DC1>

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