

Catalysis at the Origin of Life

Ruvan de Graaf,¹ Victor Sojo^{2, *}, and Reuben Hudson^{1, *}

AUTHOR ADDRESS: ¹ College of the Atlantic, Bar Harbor, Maine, USA, 04609 ² Institute for Comparative Genomics & Richard Gilder Graduate School, American Museum of Natural History, 79th Street at Central Park West, New York, NY 10024-5192, USA.

KEYWORDS: *Origin of Life, Catalysis, Metabolism*

ABSTRACT: The construction of hypothetical environments to produce organic molecules such as metabolic intermediates or amino acids is the subject of ongoing research into the emergence of life. Experiments specifically focused on an anabolic approach typically rely on a mineral catalyst to facilitate the supply of organics that may have produced prebiotic building blocks for life. Alternatively to a true catalytic system, a mineral could be sacrificially oxidized in the production of organics, necessitating the emergent 'life' to turn to virgin materials for each iteration of metabolic processes. The aim of this perspective is to view the current 'metabolism-first' literature through the lens of materials chemistry to evaluate the need for higher catalytic activity and materials analyses. While many elegant studies have detailed the production of chemical building blocks under geologically plausible and biologically relevant conditions, none appear to do so with sub-stoichiometric amounts of metals or minerals. Moving toward sub-stoichiometric metals with rigorous materials analyses could finally demonstrate the viability of an elusive cornerstone of the 'metabolism-first' hypotheses: catalysis. We emphasize that future work should aim to demonstrate decreased catalyst loading, increased productivity, and/or rigorous materials analyses for evidence of true catalysis.

Various 'metabolism first' theories¹ for the origin of life hold that 'the first stage of the origin of life began with the onset of a primitive nonenzymatic version of metabolism, initially catalyzed by naturally occurring minerals and metal ions'.² In the traditional history of the field, this has been contrasted with the "replication-first" view of life's emergence, in which RNA and DNA—or some predecessor—are thought to have appeared early on and ushered the emergence of living beings through increasingly faithful replication.¹

The distinction between the two views is still under active discussion in the field,³⁻⁵ and some consider the purported differences between the two to be blurring.⁶ Replication-first theories on the origin of life also make extensive use of catalysis⁷⁻⁸ and therefore are equally concerned about the use of relevant metals. Over the past few years, several exciting demonstrations of anabolic origins have been made to produce small organic molecules from simple building blocks under geologically plausible conditions. Typically, these reports discuss the possibility of minerals acting as catalysts, while leaving 'catalytic' demonstrations unattended. Molar equivalents of the possible catalysts typically far exceed the starting material and products, resulting in turnover numbers (TON) far below 1. TONs are the average number of times any individual metal center would need to facilitate a reaction; calculated as [products]/[metal].

Herein, we review work that could be traditionally classed under the 'metabolism-first' umbrella, with a critical eye toward demonstrations of true catalysis. We suggest that reactive minerals displaying TONs far less than 1 (most reported examples) cannot presently be considered catalysts, while TONs close to 1 (a few examples) might be considered truly catalytic provided that rigorous materials analyses demonstrate little-to-no significant change to the mineral (none reported). Of course, TONs greater than 1 could be considered catalytic regardless of material analyses, but we have found no examples of this in the literature.

In doing this, we cast no aspersions on the field, but instead emphasize that future work should aim to demonstrate decreased catalyst loading, increased productivity, and/or include rigorous materials analyses in support of true catalysis. Furthermore, we aim to highlight the discrepancy of the use of the term 'catalysis' in the origin of life field. Without any demonstrations of actual 'catalysts' facilitating production of small organic molecules, we are left with 'reactive minerals' or 'reactive metals' which may be sacrificially oxidizing during the process of carbon fixation, requiring emergent life to constantly move toward virgin minerals/metals. This would be inconsistent with a strict "metabolism first", "anabolic", "autotrophic", or "bottom-up" view, and so we anticipate that shining a light on this issue would aid in advancing the field. Life that relies on the sacrificial, stoichiometric oxidation of minerals to enable

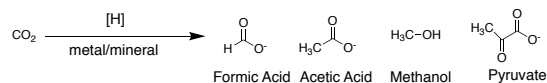
endergonic metabolic pathways does exist today (chemolithoheterotrophs).⁹ However, heterotrophic pathways¹⁰ speak in favor of a 'replication-first' origin of life.¹¹ Therefore, future research in support of a more autotrophic 'metabolism-first' emergence must produce compelling and unequivocal examples of catalysis.

Production of Organic Molecules

Potential demonstrations of geologically plausible early metabolism seek to identify a source of abiotically reduced organic molecules that would act as building blocks for complex metabolic processes to emerge and maintain themselves. Enzymes currently fulfill the role of catalysts and are crucial as their specificity accelerates reactions necessary for metabolism. Due to this specificity, modern evolutionary pressures tend to direct enzymes to reinforce and reuse existing chemical processes. Therefore, prebiotic analogues using similar chemistry may have catalyzed the first metabolic pathways.¹² By extrapolation, prebiotic forms of metabolism may have involved metals such as iron, nickel or molybdenum, arranged in minerals whose structures are seen analogously in contemporary metabolisms. These minerals would thus have served the role of proto enzymes in an abiotic environment. One such process would have involved the fixation of carbon dioxide through chemotrophic pathways, as geological and biological records show a later emergence of photosynthetic life,¹³ ruling out phototrophic pathways. Some studies within this general view of life's origin have probed the potential emergence of metabolic pathways starting with CO₂ as the carbon source, while others have investigated processes further downstream in the production of larger organic molecules. In all cases, a metal catalyst is proposed in the varying types of reactions to produce complex organics.¹⁴⁻¹⁶

CO₂ Reduction (formate, acetate, methanol, pyruvate)

Several iron-based minerals have been used in the production of reduced organics with CO₂ as a source of available carbon. Schemes 1 and 2 outline several studies that have used various batch and flow conditions to fix CO₂ into organic molecules. Under pressurized batch conditions, iron nanoparticles mediated the reduction of CO₂ with H₂ to formic acid and acetic acid.¹⁷ Fe powder in water¹⁸ (without another reductant) likewise facilitates this transformation, as does a variety of iron-based minerals¹⁹ (greigite, awaruite, magnetite; with H₂) to generate several additional reduction products (including methanol, acetate and pyruvate. A variety of other metal sulfides (Fe₃S₄, Ni₃S₂, FeS₂, CuS, MoS, and CoS) can also reduce CO₂ with H₂S as the reductant.²⁰⁻²¹ Similarly, with H₂S as a reductant (as well as sulfur source), CO₂ can be fixed into a variety of thiols, dimethyl sulfide, and other organics, facilitated by FeS.²²⁻²³



Feng, 2009, [H] = H₂; metal = Fe; products = formate, acetate; max TON = 0.0144

Moran, 2018, [H] = only Fe; metal = Fe; products = formate, acetate; methanol, pyruvate; max TON = 0.0097

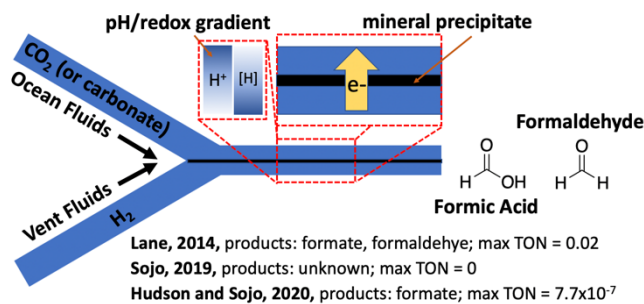
Leeuw, 2015, [H] = H₂S; mineral = Fe₃S₄; products = formate, acetate; methanol, pyruvate; max TON = 0.062

Jing, 2019, [H] = H₂S; mineral = Ni₃S₂, FeS₂, CuS, MoS, and CoS; products = formate; max TON = 0.772

Moran and Martin, 2019, [H] = H₂; mineral = Fe₃S₄, Fe₃O₄, Ni₃Fe; products = formate, acetate, methanol, pyruvate; max TON = 0.20

Scheme 1. Batch reactions for CO₂ fixation under geologically plausible conditions

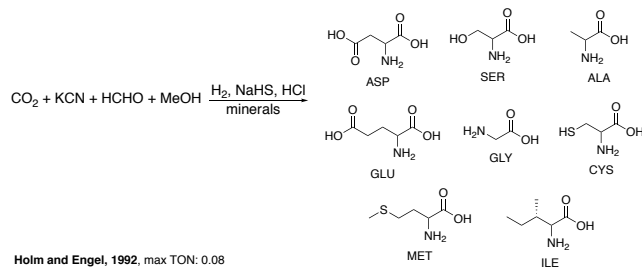
Rather than batch conditions, some studies have attempted to harness the pH and redox gradients of hydrothermal systems in order to facilitate CO₂ reduction across a mineral precipitate. These laboratory-scale disequilibrium systems were designed to mimic the pH/redox gradient dynamics that present-day living cells share in common with hydrothermal vents by generating *in situ* Fe(Ni)S precipitates as mineral barrier between simulated vent and ocean analogues to create a redox gradient.²⁴⁻²⁵ The alkaline vent efflux can be pressurized with H₂ where the mineral facilitates the reduction of CO₂ to formaldehyde or formate.²⁶



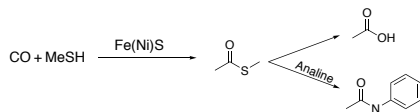
Scheme 2. Disequilibrium flow reactions for CO₂ fixation under geologically plausible conditions

Alternative C₁ precursors (formate, formaldehyde, CO, CS₂, MeSH, MeOH, KCN)

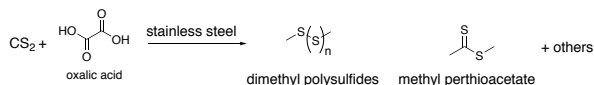
Rather than using CO₂ as a carbon source, a variety of other C₁ feedstocks have been used toward the production of larger organic molecules. Starting from CO₂, formaldehyde, methanol and KCN as carbon sources, along with H₂ as a reductant and in the presence of NH₄Cl, pyrite, pyrrhotite, magnetite, or illite facilitated the production of a variety of amino acids.²⁷ With formic acid as a C₁ precursor, pyruvate could be produced at high pressures and elevated temperatures.²⁸ With CO and CH₃SH as carbon sources, Fe(Ni)S mediated the production of acetic acid (and other organics).²⁹ While the stainless steel reactor itself has been proposed as the facilitator of CS₂ (as a C₁ precursor) conversion toward the generation of a variety of aliphatic and straight-chain polysulfides.³⁰



Holm and Engel, 1992, max TON: 0.08



Wächtershäuser, 1997, max TON: 0.15



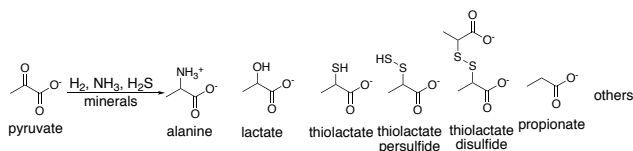
Simoneit, 2005, max TON: 8.4×10^{-4}

Scheme 3. Production of organics from C_1 carbon feedstocks other than CO_2

Pyruvate to larger organics (sugars, amino acids, etc.)

While many of the CO_2 fixation demonstrations have generated pyruvate as one of several products, pyruvate used instead as a starting material showcases its key as a metabolic intermediate.

A variety of different minerals can facilitate the production of alanine, lactate, thiolactate, thiolactate persulfide, thiolactate disulfide, propionate and other products under batch conditions with NH_3 , H_2 , H_2S .³¹ The product distribution was greatly influenced by the mineral and the temperature. The production of alanine and lactate has also been demonstrated under disequilibrium flow conditions meant to more closely resemble the dynamics of both a hydrothermal systems and a present-day cell.³²⁻³³ Starting from a combination of both pyruvate and glyoxylate, Fe^{2+} facilitates the production of an even broader suite of metabolites: 9 of the 11 Krebs cycle intermediates.³⁴ Similarly, iron has been proposed to accelerate the formation/interconversion of sugars, pyruvate, and precursors to various nucleic and amino acids.³⁵



Copley, 2013 (batch conditions) products: alanine, lactate, thiolactate, thiolactate persulfide, thiolactate disulfide, propionate and others, max TON: 0.028

Barge, 2019 (flow conditions) products: alanine, lactate, max TON: 0.043

Scheme 4. Batch and flow conditions for the mineral facilitated conversion of pyruvate into various metabolites

Superstoichiometric ‘catalysts’

The metabolism-first theory for the origin of life is predicated on catalysis and the majority of literature shows strong evidence toward the facilitation of early metabolic processes. Although this is promising in the origin-of-life field, there is only minor evidence to support true catalysis at these metal centers. Not all studies in the field make

claims of catalysis, but in order to support a viable hypothesis for abiogenesis, catalytic mechanisms must eventually be demonstrated. In this section, we calculate the turnover numbers for each report—not to put into question the results of any specific study, but to make a case for how the field collectively can evolve. Indeed, by this metric, our own use of Fe(Ni)S to facilitate the reduction of CO_2 to formate²⁶ may represent the least ‘catalytic’ example cited. Herein, we suggest that turnover numbers far greater than 1 can be considered catalytic because each metal center must then act multiple times. Meanwhile, turnover numbers far below 1 cannot be considered catalytic because only a small percentage of the available metal centers are involved, and nothing could preclude sacrificial reactivity on the part of the metal. Turnover numbers near 1 could potentially be considered catalytic—if rigorous material analysis confirms that the metals or minerals remain mostly unchanged after the reaction.

The generation of simple carboxylic acids used 5 mmol iron nanoparticles in the production of 0.051 mmol formic acid and 0.021 mmol acetic acid, for a TON of 0.0144.¹⁷ When native iron (1 mmol) facilitated the production of acetate (0.0016 mmol), pyruvate (0.00011 mmol),¹⁸ methanol (0.00075) and formate (0.00721 mmol), the TON equated to 0.0097; without an external reducing agent, this study did not seek to support a catalytic mechanism, as the generation of organics was known to accompany the sacrificial oxidation of iron. With the addition of hydrogen gas as an external reducing agent under similar conditions (with a variety of Fe- or Ni-based minerals), the TON still remains below 1.³⁶ Similarly, the use of greigite as a mineral facilitator (33.8 mmol), but with sulfide as a reductant likewise led to low TONs (maximum: 0.062); with the amount of reduced organics (1.3 mmol formate; 0.35 mmol methanol; 0.49 mmol pyruvate) only totaling 2.1 mmol.²⁰

While the hydrothermal-vent disequilibrium systems may offer a compelling homology with present day cells, the TONs showcased in these studies lag far behind the batch systems described above. In a flow-through reactor using a FeS mineral facilitator, the molar equivalents of FeS (2 mmol) far outnumbered those of the reported formic acid (0.04 mmol) and formaldehyde (0.00008 mmol).²⁴ Our early microfluidic laminar-flow device may at best have produced trace amounts of an unidentified reduction product.²⁵ While our later analogous system with pressure-driven pumps (CO_2 on the ‘ocean’ side and H_2 on the ‘vent’ side) did produce formate, albeit with the paltry TON of 0.00008.²⁶

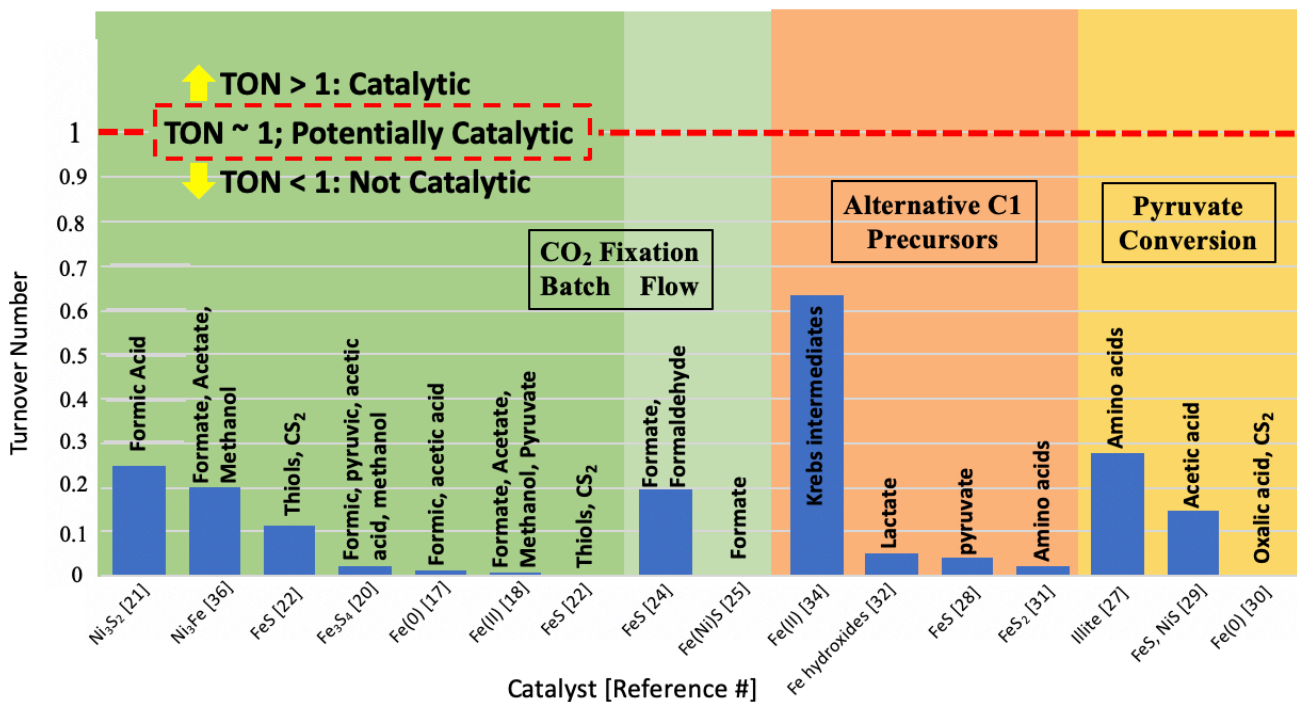


Figure 1. Turnover numbers for various metals/minerals all below the ‘catalytic’ threshold. The data are clustered by reaction type, with products listed above the bar for each reaction.

Characterization of metal/mineral facilitators

Rigorous material analyses typically accompany reports of heterogeneous catalysts for applications in synthetic chemistry.³⁷⁻⁴⁰ Even when TONs range in the 7 figures, it is important to verify that catalysts are able to not only turn over billions of times in a single reaction, but also be isolated with little change in composition so they can be reused for additional reaction cycles. Iron, often used in origin-of-life contexts for its geological and biological relevance, is generally not considered to be particularly catalytically active, but can nevertheless offer TONs in the millions for various reduction reactions.⁴¹⁻⁴⁶ These high TONs for synthetic reactions highlight how low the threshold for ‘catalysis’ is in much of origin-of-life research. In the context of ‘metabolism-first’ scenarios for a potential origin of life, where the field has not yet demonstrated a metal or mineral capable of turning over even a single time (let alone billions of times), characterization should be all the more important. Regardless of before/after mineral characterizations, if a TON is much greater than 1, then the mineral must by definition be catalytic, since it must engage in multiple consecutive reaction cycles. If the TON is considerably below one, then it is hard, albeit not necessarily impossible, to make a case for catalysis. However, if the TON is on the order of ~1, then the likelihood of a catalytic mechanism becomes greater, but rigorous materials analyses must confirm little to no degradation of the metal or mineral. For example, if Fe⁰ is used as a possible catalyst, offering a TON of 0.4, but TEM, XRD or XPS suggest that ~40% of the iron is oxidized after the reaction, then sacrificial metal oxidation seems more

likely than catalysis. The lower the TON, the finer the resolution of characterization required to make a case for catalysis; if a TON of 0.01 is reported, the characterization techniques should be able to confirm that less than ~1% of the ‘catalyst’ has degraded after the reaction (a tall order for most characterization techniques). Table 1 summarizes the characterization techniques used for the various ‘metabolism first’ reports detailed above. Since none of the reports offer TONs above 1, the simplest case to make for ‘catalysis’, we must turn instead to characterization of the higher performing metals/minerals.

Table 1. Turnover Numbers and characterization of mineral and metals for prebiotically relevant reactions

Reaction (reactor type, facilitator)	Max. TON	Characterization
CO ₂ fixation (batch, Fe) ¹⁷	0.0144	XRD before/after
CO ₂ fixation (batch, Fe) ¹⁸	0.0097	--
CO ₂ fixation (batch, Fe ₃ S ₄) ²⁰	0.07	--
CO ₂ fixation (batch, Ni ₃ S ₂) ²¹	0.24	XRD before/after
CO ₂ fixation (batch, Ni ₃ Fe) ³⁶	0.2	XRD before/after
CO ₂ fixation (batch, FeS) ²²	0.12	XRD before/after
CO ₂ fixation (flow, FeS) ²⁴	0.02	XRD, SEM/EDX, TEM (all after)

CO ₂ fixation (flow, Fe(Ni)S) ²⁵	0	Visible microscopy
CO ₂ fixation (flow, Fe(Ni)S) ²⁶	0.00008	Visible microscopy
C ₁ → amino acids (batch, ilite) ²⁷	0.28	--
Formate → pyruvate (batch, FeS) ²⁸	0.044	--
CO & MeSH → acetate (batch, Fe(Ni)S) ²⁹	0.1	--
CS ₂ → alkyl sulfides (batch, stainless steel) ³⁰	0.0008	--
Pyruvate → alanine, lactate & more (batch) ³¹	0.0204	XRD, ICP, BET (all before)
Pyruvate → alanine & lactate (flow, iron hydroxyhydroxides) ³²	0.05	XRD, colorimetry, BET
Pyruvate & Glyoxylate → Krebs intermediates (batch, Fe ²⁺) ³⁴	0.63	--

Only a few reports offer TONs close enough to 1 that we may reasonably detect the amount of catalyst degradation that would have resulted from some sort of sacrificial oxidation. The Ni₃S₂-mediated production of formate from CO₂ afforded a TON of 0.24.²¹ The XRD analysis of the Ni₃S₂ after catalysis indicated the growth of new peaks, suggesting potential breakdown of the mineral. The production of Krebs cycle intermediates from pyruvate and glyoxylate offered a TON of 0.63,³⁴ although because this reaction was facilitated by homogeneous Fe²⁺, the suite of available characterization techniques is limited (XPS, TEM, XRD cannot be used), but EPR could potentially differentiate between ferrous and ferric iron to give a sense of whether the involved metal centers were ‘catalytic’ or simply ‘reactive’. The production of peptides from a variety of C₁ feedstocks facilitated by various minerals resulted in TONs of 0.28,²⁷ but characterization was not reported for the minerals, so little can be assumed about the durability of the material. Most other studies outlined here offer TONs on the order of 0.1 to 0.0001, which would require a very high bar of materials characterization in order to suggest that the small amount of produced organics did not result from simultaneous degradation of the involved metal/mineral.

Next Steps—Making a Case for Catalysis

In order to less ambiguously make a case for true catalysis, future studies should demonstrate TONs above 1 (ideally by orders of magnitude) to suggest that metals or minerals can facilitate multiple reaction cycles. Reduced mineral/metal loading and/or higher yields could push TONs above the minimal threshold of 1. Alternatively, if higher production rates cannot be achieved in a single reaction (for example, because the reaction conditions keep the yields low), the catalysts could be isolated and recycled for subsequent reactions to increase the aggregate TON. For example, the production of formate from the H₂S reduction of CO₂ offered

a TON of 0.24, but the catalyst characterization (XRD) implied some degree of mineral degradation.²¹ However, to bolster their claims of catalysis, they were able to reuse the mineral for 5 consecutive reactions, with little loss in activity from run to run, thereby effectively increasing their aggregate TON by ~fivefold (0.24 x 5 = 1.2; just above the threshold of catalysis). In some cases where complex organics are present, a higher TON could be assumed if we could be sure of reaction pathways. For example, in the Fe²⁺-mediated production of Krebs cycle intermediates from pyruvate and glyoxylate, the presence of malate could have arisen from oxidative decarbonylation of hydroxy ketoglutarate, which itself would have arisen from an aldol condensation of glyoxylate and pyruvate.³⁴ Therefore, the presence of a molecule of malate would suggest two separate reactions. So, if the reaction pathways were known, TON calculations could be adjusted to count the presence of complex organics as resulting from a sequence of multiple individual reactions. The TON of 0.63 for this study could therefore represent the lowest-case scenario, where each product (even complex ones) result from the single action of a metal center facilitator. On the other hand, not all reactions in this network require metal facilitation, so in that sense the calculated TON could be an overestimate (because reactions that did not require facilitation count toward the activity of the metal center). By detailing specific reaction pathways and which reactions were likely to result from metal facilitation, we could better calculate where the presence of complex products could reasonably represent the action of multiple metal centers (or a single metal center multiple times).

Conclusions

Our analysis of potentially ‘catalytic’ vs. simply reactive (stoichiometrically sacrificial) minerals is not meant as a pedantic diatribe on word choice. Indeed, several of the studies included above strictly avoided this language either because they never meant the metals/minerals to be catalytic in the first place or because the case for catalysis was not easy to prove. Instead, our analysis is meant to highlight a discrepancy in the language we use to describe the possible rise of ‘metabolism first’, and the experimentation carried out in support of this theory. An autotrophic ‘metabolism-first’ emergence of life would rely on catalytic metals or minerals unless the emergent life could secure virgin materials—and even this would need to be considered heterotrophic, at least in terms of metal usage. Increased turnover numbers (through better yields or lower metal loading) coupled with rigorous materials analyses could finally offer evidence for true catalysis in a geologically plausible and biologically relevant scenario, and thus strengthen the plausibility of such an autotrophic ‘metabolism-first’ emergence of life.

Author Information

Corresponding Authors

Reuben Hudson, College of the Atlantic, 105 Eden Street, Bar Harbor, Maine, 04609, USA.

Email: rudson@coa.edu

Victor Sojo, Institute for Comparative Genomics & Richard Gilder Graduate School, American Museum of Natural History, 79th Street at Central Park West, New York, NY 10024-5192, USA

Email: vsojo@amnh.org

Acknowledgements

RdG was supported by a summer fellowship through an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant number P20GM103423.

RHH & VS acknowledge support from the Maine Space Grant Consortium (EP-21-06, EP-23-01, SG-19-14, SG-20-19). VS acknowledges support from the Gerstner Family Foundation.

References

1. Lilley, D. M. J.; Sutherland, J., The chemical origins of life and its early evolution: an introduction. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* **2011**, *366* (1580), 2853-2856.
2. Muchowska, K. B.; Varma, S. J.; Moran, J., Nonenzymatic Metabolic Reactions and Life's Origins. *Chem. Rev.* **2020**, *120* (15), 7708-7744.
3. Pross, A., Causation and the origin of life. Metabolism or replication first? *Orig. Life Evol. Biosph.* **2004**, *34* (3), 307-321.
4. Vasas, V.; Szathmáry, E.; Santos, M., Lack of evolvability in self-sustaining autocatalytic networks constrains metabolism-first scenarios for the origin of life. *Proc. Natl. Acad. Sci.* **2010**, *107* (4), 1470-1475.
5. Saladino, R.; Botta, G.; Pino, S.; Costanzo, G.; Di Mauro, E., Genetics first or metabolism first? The formamide clue. *Chem. Soc. Rev.* **2012**, *41* (16), 5526-5565.
6. Preiner, M.; Asche, S.; Becker, S.; Betts, H. C.; Boniface, A.; Camprubi, E.; Chandru, K.; Erastova, V.; Garg, S. G.; Khawaja, N., The future of origin of life research: bridging decades-old divisions. *Life* **2020**, *10* (3), 20.
7. Pace, N. R.; Marsh, T. L., RNA catalysis and the origin of life. *Orig. Life Evol. Biosph.* **1985**, *16* (2), 97-116.
8. Scott, W. G.; Szöke, A.; Blaustein, J.; O'Rourke, S. M.; Robertson, M. P., RNA catalysis, thermodynamics and the origin of life. *Life* **2014**, *4* (2), 131-141.
9. Callbeck, C. M.; Pelzer, C.; Lavik, G.; Ferdelman, T. G.; Graf, J. S.; Vekeman, B.; Schunck, H.; Littmann, S.; Fuchs, B. M.; Hach, P. F.; Kalvelage, T.; Schmitz, R. A.; Kuypers, M. M. M.; Drake, H. L., *Arcobacter peruenis* sp. nov., a Chemolithoheterotroph Isolated from Sulfide- and Organic-Rich Coastal Waters off Peru. *Appl. Environ. Microbiol.* **2019**, *85* (24), e01344-19.
10. Schönheit, P.; Buckel, W.; Martin, W. F., On the origin of heterotrophy. *Trends Microbiol.* **2016**, *24* (1), 12-25.
11. Lazcano, A., Alexandr I. Oparin and the origin of life: a historical reassessment of the heterotrophic theory. *J. Mol. Evol.* **2016**, *83* (5), 214-222.
12. Shapiro, R., A simpler origin for life. *Scientific American* **2007**, *296* (6), 46-53.
13. Weiss, M. C.; Sousa, F. L.; Mrnjavac, N.; Neukirchen, S.; Roettger, M.; Nelson-Sathi, S.; Martin, W. F., The physiology and habitat of the last universal common ancestor. *Nature microbiology* **2016**, *1* (9), 1-8.
14. Li, Y.; Kitadai, N.; Nakamura, R., Chemical diversity of metal sulfide minerals and its implications for the origin of life. *Life* **2018**, *8* (4), 46.
15. Belmonte, L.; Mansy, S. S., Metal catalysts and the origin of life. *Elements* **2016**, *12* (6), 413-418.
16. Camprubi, E.; Jordan, S. F.; Vasiliadou, R.; Lane, N., Iron catalysis at the origin of life. *IUBMB life* **2017**, *69* (6), 373-381.
17. He, C.; Tian, G.; Liu, Z.; Feng, S., A mild hydrothermal route to fix carbon dioxide to simple carboxylic acids. *Org. Lett.* **2010**, *12* (4), 649-651.
18. Varma, S. J.; Muchowska, K. B.; Chatelain, P.; Moran, J., Native iron reduces CO₂ to intermediates and end-products of the acetyl-CoA pathway. *Nat. Ecol. Evol.* **2018**, *2* (6), 1019-1024.
19. Preiner, M.; Igarashi, K.; Muchowska, K. B.; Yu, M.; Varma, S. J.; Kleinermanns, K.; Nobu, M. K.; Kamagata, Y.; Tüysüz, H.; Moran, J., A hydrogen-dependent geochemical analogue of primordial carbon and energy metabolism. *Nat. Ecol. Evol.* **2020**, *4* (4), 534-542.
20. Roldan, A.; Hollingsworth, N.; Roffey, A.; Islam, H.-U.; Goodall, J.; Catlow, C.; Darr, J.; Bras, W.; Sankar, G.; Holt, K.; Hogarth, G.; de Leeuw, N., Bio-inspired CO₂ conversion by iron sulfide catalysts under sustainable conditions. *Chem. Commun.* **2015**, *51* (35), 7501-7504.
21. He, R.; Hu, B.; Zhong, H.; Jin, F.; Fan, J.; Hu, Y. H.; Jing, Z., Reduction of CO₂ with H₂S in a simulated deep-sea hydrothermal vent system. *Chem. Commun.* **2019**, *55* (8), 1056-1059.
22. Heinen, W.; Lauwers, A. M., Organic sulfur compounds resulting from the interaction of iron sulfide, hydrogen sulfide and carbon dioxide in an anaerobic aqueous environment. *Orig. Life Evol. Biosph.* **1996**, *26* (2), 131-150.
23. Heinen, W.; Lauwers, A., The iron-sulfur world and the origins of life: abiotic thiol synthesis from metallic iron, H₂S and CO₂; a comparison of the thiol generating FeS/HCl (H₂S)/CO₂-system and its Fe-0/H₂S/CO₂-counterpart. *Proc. Kon. Ned. Akad. v. Wetensch.* **1997**, *100* (1-2), 11-25.
24. Herschy, B.; Whicher, A.; Camprubi, E.; Watson, C.; Dartnell, L.; Ward, J.; Evans, J. R.; Lane, N., An origin-of-life reactor to simulate alkaline hydrothermal vents. *J. Mol. Evol.* **2014**, *79* (5-6), 213-227.
25. Sojo, V.; Ohno, A.; McGlynn, S. E.; Yamada, Y.; Nakamura, R., Microfluidic reactors for carbon fixation under ambient-pressure alkaline-hydrothermal-vent conditions. *Life* **2019**, *9* (1), 16.
26. Hudson, R.; de Graaf, R.; Rodin, M. S.; Ohno, A.; Lane, N.; McGlynn, S. E.; Yamada, Y. M.; Nakamura, R.; Barge, L. M.; Braun, D., CO₂ reduction driven by a pH gradient. *Proc. Natl. Acad. Sci.* **2020**, *117* (37), 22873-22879.

27. Hennet, R.-C.; Holm, N.; Engel, M., Abiotic synthesis of amino acids under hydrothermal conditions and the origin of life: a perpetual phenomenon? *Naturwissenschaften* **1992**, *79* (8), 361-365.
28. Cody, G. D.; Boctor, N. Z.; Filley, T. R.; Hazen, R. M.; Scott, J. H.; Sharma, A.; Yoder, H. S., Primordial Carbonylated Iron-Sulfur Compounds and the Synthesis of Pyruvate. *Science* **2000**, *289* (5483), 1337-1340.
29. Huber, C.; Wächtershäuser, G., Activated Acetic Acid by Carbon Fixation on (Fe,Ni)S Under Primordial Conditions. *Science* **1997**, *276* (5310), 245-247.
30. Rushdi, A. I.; Simoneit, B. R. T., Abiotic Synthesis of Organic Compounds from Carbon Disulfide Under Hydrothermal Conditions. *Astrobiology* **2005**, *5* (6), 749-769.
31. Novikov, Y.; Copley, S. D., Reactivity landscape of pyruvate under simulated hydrothermal vent conditions. *Proc. Natl. Acad. Sci.* **2013**, *110* (33), 13283-13288.
32. Barge, L. M.; Flores, E.; Baum, M. M.; VanderVelde, D. G.; Russell, M. J., Redox and pH gradients drive amino acid synthesis in iron oxyhydroxide mineral systems. *Proc. Natl. Acad. Sci.* **2019**, *116* (11), 4828-4833.
33. Barge, L.; Flores, E.; VanderVelde, D.; Weber, J.; Baum, M.; Castonguay, A., Effects of geochemical and environmental parameters on abiotic organic chemistry driven by iron hydroxide minerals. *J. Geophys. Res.* **2020**, *125* (11), e2020JE006423.
34. Muchowska, K. B.; Varma, S. J.; Moran, J., Synthesis and breakdown of universal metabolic precursors promoted by iron. *Nature* **2019**, *569* (7754), 104-107.
35. Keller, M. A.; Turchyn, A. V.; Ralser, M., Non-enzymatic glycolysis and pentose phosphate pathway-like reactions in a plausible Archean ocean. *Mol. Syst. Biol.* **2014**, *10* (4), 725.
36. Preiner, M.; Igarashi, K.; Muchowska, K. B.; Yu, M.; Varma, S. J.; Kleinermaans, K.; Nobu, M. K.; Kamagata, Y.; Tüysüz, H.; Moran, J.; Martin, W. F., A hydrogen-dependent geochemical analogue of primordial carbon and energy metabolism. *Nat. Ecol. Evol.* **2020**, *4* (4), 534-542.
37. Weckhuysen, B. M., Preface: recent advances in the in-situ characterization of heterogeneous catalysts. *Chem. Soc. Rev.* **2010**, *39* (12), 4557-4559.
38. Bentrup, U., Combining in situ characterization methods in one set-up: looking with more eyes into the intricate chemistry of the synthesis and working of heterogeneous catalysts. *Chem. Soc. Rev.* **2010**, *39* (12), 4718-4730.
39. Meirer, F.; Weckhuysen, B. M., Spatial and temporal exploration of heterogeneous catalysts with synchrotron radiation. *Nat. Rev. Mater.* **2018**, *3* (9), 324-340.
40. Hudson, R.; Zhang, H. R.; LoTemplio, A.; Benedetto, G.; Hamasaka, G.; Yamada, Y. M. A.; Katz, J. L.; Uozumi, Y., Poly(meta-phenylene oxides) for the design of a tunable, efficient, and reusable catalytic platform. *Chem. Commun.* **2018**, *54* (23), 2878-2881.
41. Hudson, R.; Rivière, A.; Cirtiu, C. M.; Luska, K. L.; Moores, A., Iron-iron oxide core-shell nanoparticles are active and magnetically recyclable olefin and alkyne hydrogenation catalysts in protic and aqueous media. *Chem. Commun.* **2012**, *48* (27), 3360-3362.
42. Hudson, R.; Hamasaka, G.; Osako, T.; Yamada, Y. M. A.; Li, C.-J.; Uozumi, Y.; Moores, A., Highly efficient iron(0) nanoparticle-catalyzed hydrogenation in water in flow. *Green Chem.* **2013**, *15* (8), 2141-2148.
43. Sonnenberg, J. F.; Coombs, N.; Dube, P. A.; Morris, R. H., Iron Nanoparticles Catalyzing the Asymmetric Transfer Hydrogenation of Ketones. *J. Am. Chem. Soc.* **2012**, *134* (13), 5893-5899.
44. Rangheard, C.; de Julián Fernández, C.; Phua, P.-H.; Hoorn, J.; Lefort, L.; de Vries, J. G., At the frontier between heterogeneous and homogeneous catalysis: hydrogenation of olefins and alkynes with soluble iron nanoparticles. *Dalton Trans.* **2010**, *39* (36), 8464-8471.
45. Phua, P.-H.; Lefort, L.; Boogers, J. A. F.; Tristany, M.; de Vries, J. G., Soluble iron nanoparticles as cheap and environmentally benign alkene and alkyne hydrogenation catalysts. *Chem. Commun.* **2009**, (25), 3747-3749.
46. Wei, D.; Darcel, C., Iron Catalysis in Reduction and Hydrometalation Reactions. *Chem. Rev.* **2019**, *119* (4), 2550-2610.

