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Assessment of Stoichiometric Autocatalysis across Element Groups

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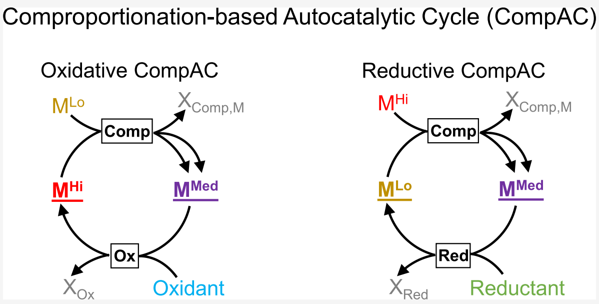
Comproportionation-based Autocatalytic Cycle (CompAC)

ABSTRACT: Autocatalysis has been proposed to play critical roles during abiogenesis. These proposals are at odds with a limited number of known examples of abiotic (and, in particular, inorganic) autocatalytic systems that might reasonably function in a prebiotic environment. In this study, we broadly assess the occurrence of stoichiometries that can support autocatalytic chemical systems through comproportionation. If the product of a comproportionation reaction can be coupled with an auxiliary oxidation or reduction pathway that furnishes a reactant, then a **Comp**roportionation-based **A**utocatalytic **C**ycle (CompAC) can exist. Using this strategy, we surveyed the literature published in the past two centuries for reactions that can be organized into CompACs that consume some chemical species as food to synthesize more autocatalysts. 226 CompACs and 44 Broad-sense CompACs were documented, and we found that each of the 18 groups, lanthanoid series, and actinoid series in the periodic table has at least two CompACs. Our findings demonstrate that stoichiometric relationships underpinning abiotic autocatalysis could broadly exist across a range of geochemical and cosmochemical conditions, some of which are substantially different from the modern Earth. Meanwhile, the observation of some autocatalytic systems requires effective spatial or temporal separation between the food chemicals while allowing comproportionation and auxiliary reactions to proceed, which may explain why naturally occurring autocatalytic systems are not frequently observed. The collated CompACs and the conditions in which they might plausibly support complex, "life-like" chemical dynamics can directly aid an expansive assessment of life's origins and provide a compendium of alternative hypotheses concerning false-positive biosignatures.

1. INTRODUCTION

Autocatalysis is usually defined as the phenomenon where the product of a single- or multi-step reaction also catalyzes that same reaction[1] and is a shared feature of all living organisms. Reproduction is by definition a form of autocatalysis, and there are numerous examples of autocatalytic relationships that underpin metabolic processes,[2,3] all of which are regulated by highly specialized organic polymers, e.g., proteins. Considering the similarity of dynamic behaviors afforded by biotic and abiotic autocatalytic systems, multiple studies have suggested that abiotic autocatalysis played critical roles prior to the establishment of life's characteristic sequence-specific, polymer-regulated autocatalysis.[4−21]

Attributes typically associated with living organisms, such as multistability, competition, mutualism, predation, priority effects, gradual complexification, and adaptive responses to selection, can readily emerge from interacting abiotic autocatalytic reaction systems that do not involve macromolecules.[8,12,13,19,22−25] The Belousov-Zhabotinsky reaction is a classic example of an autocatalytic reaction network generated from the aqueous combination of a few simple organic and inorganic reagents that yields bistability and chemical oscillations.[26] Epstein and Huskey demonstrated in 1989 an apparent bistability in the formose reaction, a well-known example of autocatalysis relying on the simple feedstock molecule formaldehyde, and is a reaction often cited as a source of ribose being implicated in a variety of reported prebiotic nucleotide syntheses.[27,28] The Grzybowski group in 2010 harnessed the pH oscillations of the autocatalytic formaldehyde-sulfite-gluconolactone reaction to induce temporal and spatial periodic transitions between fatty acid vesicles and micelles.[29] The Whitesides group in 2016 engineered an autocatalytic reaction network capable of bistability and oscillatory behavior based on simple α-aminothioesters, disulfides, electron-deficient olefins, and the auto-amplification of cysteamine.[30] A recent study in 2022 by Muñuzuri and Pérez-Mercader demonstrated that a number of these behaviors become apparent in systems with as few as three unique molecular compounds, provided there are both Hopf and Turing instabilities present.[31]

It seems likely that examples of primitive "life-like" autocatalytic systems that can be generated from only small-molecule reactions will become increasingly more common, at

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least in the laboratory setting, but the question still remains: how probable are abiotic autocatalytic networks, especially in the context of natural environmental settings like those of early Earth? The unique capabilities of autocatalysis make a compelling case for assessing their generic pervasiveness, but searching for autocatalytic systems is an inherently difficult problem,[32] even though some researchers have attempted to use algorithms based on simple chemical principles to identify and design abiotic autocatalytic cycles.[33−35] It has been shown that recognizing autocatalysis in chemical reaction networks is an NP-complete problem.[36] If no autocatalytic system is detected in a given reaction network, it is also correspondingly difficult to ascertain whether some reactions are capable of forming an autocatalytic system by the inclusion of a few more reactions or the provision of new reagents. This analytical opacity presents a specific challenge toward assessing the roles and pervasiveness of autocatalysis during life's origins or within any naturally occurring (abiotic) systems of sufficient or even mild analytical complexity.

The pervasiveness of prebiotic autocatalysis remains an open debate even after decades of study, in part because not many functional examples of abiotic, especially inorganic autocatalytic systems have been identified.[37,38] Further compounding the problem is the fact that some autocatalytic reaction networks may require spatial or temporal separation of components in order to operate, and recognition of these unique situations may easily elude analytical scrutiny. In comparison, biochemistry is replete with autocatalytic systems that afford vital metabolic functions via enzymatically constructed substrates and reaction pathways that are themselves regulated by the autocatalytic production of co-occurring catalytic polymers.[14] As a result, some researchers have suggested that abiotic autocatalytic reaction networks, lacking the custodianship of Darwinian natural selection, must be comparatively few and far between, and are therefore sparse in the chemical probability space.[39,40]

Assessing whether abiotic autocatalysis is (i) truly rare or (ii) is in some ways limited to, or more pronounced in, chemical compounds of a given composition or class, would greatly aid in the development of new experimental designs for prebiotic autocatalytic protocols in the laboratory, as well as in the estimation of the emergence of autocatalysis in yet-to-be determined exoplanetary or otherwise exotic astrochemical environments. The search for plausible prebiotic autocatalytic systems has been generally centered on carbon-mediated cycles because biological autocatalysis largely relies on organic substrates mediated by linear polymers, e.g., proteins and nucleic acids. No reason has been unequivocally enunciated, however, to ignore wholesale other elements and inorganic compounds that might have scaffolded life's origins terrestrially or elsewhere in the cosmos.[41] For example, complex functions, though seemingly requiring diverse and highly evolved catalytic polymers, may be partially, albeit imperfectly, undertaken by inorganic catalysts (e.g., metal ions) and interactions between simple autocatalytic cycles.[8,9,12,13,22,23,42,43] It is also possible that other pathways to alternative, non-Terran examples of life-like systems can arise under laboratory or exoplanetary/astrochemical conditions that largely deviate from terrestrial environments.[44−46]

Herein, we focus on a specific type of reaction—comproportionation—to outline one possible strategy for enumerating chemical reaction networks with autocatalytic motifs across the periodic table. Comproportionation (alternatively referred to as con-, sym-, or synproportionation) is typically defined as when two chemical species containing the same element with different oxidation numbers react to yield a product species with the same intermediate oxidation state[47,48] (Figure 1a). Comproportionation reactions are a potentially interesting basis for assessing autocatalysis because they combine two general attributes of cellular biochemical systems: (i) reactions driven by electrochemical potentials (redox reactions) to yield reduced or oxidized product(s) and (ii) stoichiometric (potentially autocatalytic) amplification of those products. A stoichiometric autocatalytic cycle can be formed by coupling a comproportionation process with either an auxiliary oxidation (Figure 1b) or reduction pathway (Figure 1c) to form a loop that amplifies the intermediate-oxidation-state species and either the most oxidized- or reduced-state species, respectively. Such an autocatalytic cycle herein is termed a **Comp**roportionation-based **A**utocatalytic **C**ycle (CompAC).

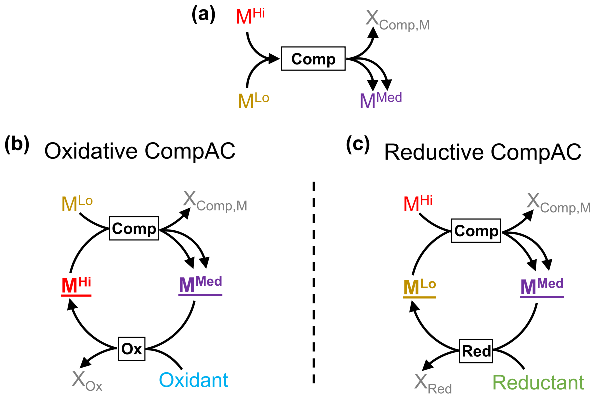

Figure 1. Conceptualization of Comproportionation-based Autocatalytic Cycles (CompACs). (a) For an element/compound M that can take three or more oxidation states (Lo = lowest oxidation state, Med = intermediate oxidation state, Hi = highest oxidation state), comproportionation between oxidized M^{Hi} and reduced M^{Lo} produces two intermediate-state M^{Med} plus any associated waste products ($X_{Comp,M}$). Note that for some comproportionation reactions, the stoichiometry may be different; for example, one M^{Hi} may comproportionate with two M^{Lo} while consuming an additional food species F_{Comp}: $M^{Hi} + 2M^{Lo} + F_{Comp} \rightarrow 3M^{Med} + X_{Comp,M}$. (b) An oxidative auxiliary process utilizes an oxidant to oxidize an M^{Med} to an M^{Hi}; the result is an oxidative CompAC. (c) A reductive auxiliary process utilizes a reductant to reduce an M^{Med} to an M^{Lo}; the result is a reductive CompAC. Autocatalysts reside on the cycles and are underlined; intermediate-state, the most oxidized, and the most reduced M's are highlighted purple, red, and gold, respectively; oxidant and reductant foods of the auxiliary processes are highlighted blue and green, respectively; waste products are highlighted gray.

We developed a specific search strategy for CompACs and used this strategy to document 226 CompACs across 46 elements from the literature published during the past two centuries. Each of the 18 groups, lanthanoid series, and actinoid series in the periodic table have the potential for multiple CompACs. We also documented 44 prospective abiotic autocatalytic cycles that do not necessarily involve redox reactions but can be interpreted as Broad-sense CompACs, if an infrequent definition of "comproportionation" that only considers stoichiometry is applied.[47−50] A full explanation of Broad-sense CompACs will be given in Section 3. We demonstrate that autocatalysis is likely a broadly existing

Table 1. Representative Examples of Comproportionation-Based Autocatalytic Cycles (CompACs)[a]

group or series	count of CompACs	representative CompAC	references
group 1	8	$NaH + \mathbf{HCl} \rightarrow NaCl + \mathbf{H_2}$ $2\,CuCl + \mathbf{H_2} \rightarrow 2\,Cu + \mathbf{2\,HCl}$	[53,54]
group 2	2	$\mathbf{Ca} + CaF_2 \rightarrow \mathbf{2\,CaF}$ $\mathbf{3\,CaF} + Sc \rightarrow \mathbf{3\,Ca} + ScF_3$	[55,56]
lanthanoid	3	$\mathbf{2\,EuCl_3} + Eu \rightarrow \mathbf{3\,EuCl_2}$ $\mathbf{2\,EuCl_2} + Cl_2 \rightarrow \mathbf{2\,EuCl_3}$	[57,58]
actinoid	5	$ThO_2 + \mathbf{Th} \rightarrow \mathbf{2\,ThO}$ $\mathbf{ThO} + Si \rightarrow \mathbf{Th} + SiO$	[59,60]
group 3	2	$\mathbf{2\,YF_3} + Y \rightarrow \mathbf{3\,YF_2}$ $\mathbf{YF_2} + CaF \rightarrow \mathbf{YF_3} + Ca$	[56,61]
group 4	4	$TiBr_2 + \mathbf{TiBr_4} \rightarrow \mathbf{2\,TiBr_3}$ $\mathbf{2\,TiBr_3} + 2\,HBr \rightarrow \mathbf{2\,TiBr_4} + H_2$	[62,63]
group 5	18	$\mathbf{2\,VCl_3} + V \rightarrow \mathbf{3\,VCl_2}$ $\mathbf{2\,VCl_2} + 2\,HCl \rightarrow \mathbf{2\,VCl_3} + H_2$	[64]
group 6	11	$\mathbf{Cr_2O_7^{2-}} + 6\,Cr^{2+} + 14\,H^+ \rightarrow \mathbf{8\,Cr^{3+}} + 7\,H_2O$ $\mathbf{2\,Cr^{3+}} + 3\,MnO_2 + 2\,H_2O \rightarrow \mathbf{2\,HCrO_4^-} + 3\,Mn^{2+} + 2\,H^+$ $\mathbf{2\,HCrO_4^-} \rightarrow \mathbf{Cr_2O_7^{2-}} + H_2O$	[65−68]
group 7	21	$2\,MnO_4^- + \mathbf{3\,Mn^{2+}} + 2\,H_2O \rightarrow \mathbf{5\,MnO_2} + 4\,H^+$ $\mathbf{MnO_2} + 2\,Fe^{2+} + 4\,H^+ \rightarrow \mathbf{Mn^{2+}} + 2\,Fe^{3+} + 2\,H_2O$	[69,70]
group 8	5	$Fe + \mathbf{2\,Fe^{3+}} \rightarrow \mathbf{3\,Fe^{2+}}$ $\mathbf{2\,Fe^{2+}} + Cl_2 \rightarrow \mathbf{2\,Fe^{3+}} + 2\,Cl^-$	[71−73]
group 9	6	$\mathbf{Co_3O_4} + Co \rightarrow \mathbf{4\,CoO}$ $\mathbf{6\,CoO} + O_2 \rightarrow \mathbf{2\,Co_3O_4}$	[54,74,75]
group 10	7	$NiS_2 + \mathbf{Ni_3S_2} \rightarrow \mathbf{4\,NiS}$ $\mathbf{3\,NiS} + H_2 \rightarrow \mathbf{Ni_3S_2} + H_2S$	[76,77]
group 11	9	$Cu + \mathbf{Cu^{2+}} \rightarrow \mathbf{2\,Cu^+}$ $\mathbf{Cu^+} + Fe^{3+} \rightarrow \mathbf{Cu^{2+}} + Fe^{2+}$	[78−80]
group 12	7	$\mathbf{Hg} + Hg^{2+} \rightarrow \mathbf{Hg_2^{2+}}$ $\mathbf{Hg_2^{2+}} + 2\,Fe^{2+} \rightarrow \mathbf{2\,Hg} + 2\,Fe^{3+}$	[52,81]
group 13	14	$2\,B_2O_3 + \mathbf{2\,B} \rightarrow \mathbf{3\,B_2O_2}$ $\mathbf{B_2O_2} + 2\,H_2 \rightarrow \mathbf{2\,B} + 2\,H_2O$	[82−84]
group 14	22	$C + \mathbf{CO_2} \rightarrow \mathbf{2\,CO}$ $\mathbf{5\,CO} + I_2O_5 \rightarrow I_2 + \mathbf{5\,CO_2}$	[64,85]
group 15	25	$\mathbf{HNO_2} + HNO_3 \rightarrow \mathbf{2\,NO_2} + H_2O$ $\mathbf{2\,NO_2} + Cu + 2\,H^+ \rightarrow \mathbf{2\,HNO_2} + Cu^{2+}$	[86,87]
group 16	32	$\mathbf{SO_2} + 2\,H_2S \rightarrow \mathbf{3\,S} + 2\,H_2O$ $\mathbf{S} + O_2 \rightarrow \mathbf{SO_2}$	[88−90]
group 17	21	$\mathbf{HCl} + HOCl \rightarrow \mathbf{Cl_2} + H_2O$ $\mathbf{Cl_2} + H_2 \rightarrow \mathbf{2\,HCl}$	[88,91]
group 18	4	$\mathbf{XeF_4} + Xe \rightarrow \mathbf{2\,XeF_2}$ $\mathbf{XeF_2} + F_2 \rightarrow \mathbf{XeF_4}$	[54,92,93]

[a] The arrows in this table do not mean that the reactions are irreversible but are intended to indicate the autocatalytic direction. Autocatalysts are shown in bold. For the extended list of CompACs, please refer to Table S1 and Supporting Information 4. Comproportionation reactions are shown by the upper equations, while the auxiliary oxidation or reduction reactions are shown by the lower equations.

phenomenon, as it can be manifested by multiple sets of reaction rules under a wide variety of conditions and through the coordination of relatively small numbers of reactions between simple chemical species. Reconceptualizing the parameter space of environmental conditions under which autocatalytic dynamics are more easily observable may enable researchers to access ACs under a broader array of laboratory conditions.

2. METHODS

Following the formalism of CompACs described above (Figure 1), we collated comproportionation reactions on an element-by-element basis from literature and databases, including primary literature that reported experimentally confirmed reactions as well as secondary literature such as reviews, textbooks, handbooks of chemical reactions and substances, and the Reaxys database (www.reaxys.com). Specifically, all candidate reactions retrieved from the Reaxys database were cross-checked with primary literature sources. Auxiliary reaction pathways that lead from the intermediate-oxidation-state product of comproportionation to one of the reactants of comproportionation were similarly collected and collated. Although all of these reactions are known to occur, only a very limited number of combinations of them, such as the Belousov-Zhabotinsky reaction,[26] the chlorite-iodide reaction,[51] and the formation of colloidal mercury in a Hg^{2+}–Fe^{2+} system,[52] have been explicitly reported as cases of autocatalysis. This search strategy for CompACs brings the advantage of providing a simple and generalized framework for identifying stoichiometric autocatalytic motifs across different elements, according to current knowledge, without explicit reference to terrestrial prebiotic plausibility. A detailed description of how CompACs were sought and identified can be found in Supporting Information 3.

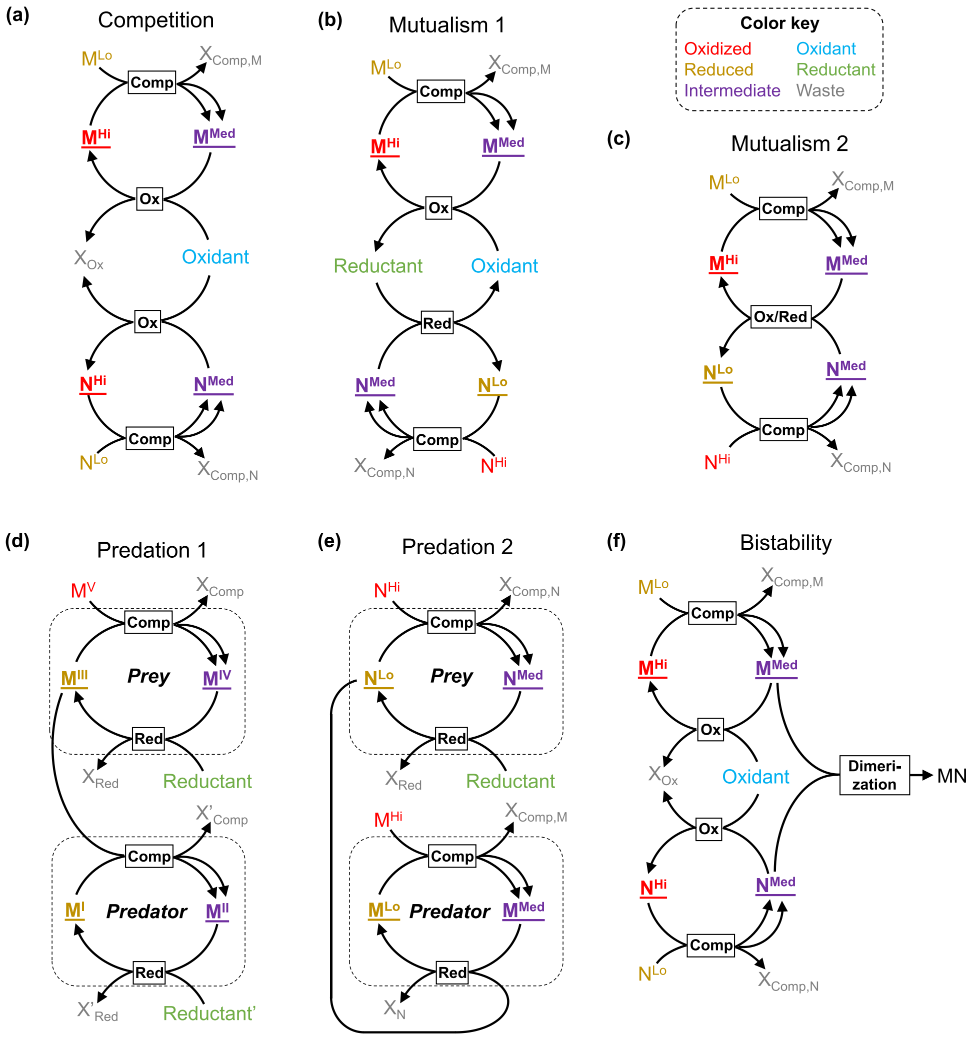

Figure 2. Possible mechanisms of ecological interactions between abiotic CompACs. Abiotic CompACs can be coupled through an array of chemical reaction types. Depending on how a pair of CompACs are coupled, the relationship between CompACs can be interpreted as different ecological interactions. Note that these examples are not the only mechanisms for these ecological interactions among abiotic autocatalytic systems. Autocatalysts are underlined; intermediate-state, the most oxidized, and the most reduced M/N's are highlighted purple, red, and gold, respectively; oxidant and reductant foods of the auxiliary processes are highlighted blue and green, respectively; waste products are highlighted gray. (a) If two oxidative CompACs consume the same oxidant as food for their auxiliary processes, then the CompACs compete for a shared food species. (b) An oxidative CompAC and a reductive CompAC can be mutualistic if the auxiliary process of the oxidative CompAC (M^{Hi}–M^{Med}) and the auxiliary process of the reductive CompAC (N^{Lo}–N^{Med}) recycle the shared oxidant-reductant pair. (c) An oxidative CompAC and a reductive CompAC can also be mutualistic if the auxiliary process of one happens to also be the auxiliary process of the other. (d) A predator CompAC (M^{I}–M^{II}) can prey on another CompAC (M^{III}–M^{IV}), if the autocatalyst of the latter (M^{III}) is consumed as food by the comproportionation process of the former ($M^{I} + M^{III} \rightarrow 2M^{II} + X'_{Comp}$). (e) A predator CompAC (M^{Med}–M^{Lo}) can also prey on another CompAC (N^{Lo}–N^{Med}), if the autocatalyst of the latter (N^{Lo}) is consumed as food by the auxiliary process of the former ($M^{Med} + N^{Lo} \rightarrow M^{Lo} + X_N$). (f) If the autocatalysts (M^{Med} and N^{Med}) of different CompACs (M^{Hi}–M^{Med} and N^{Hi}–N^{Med}) dimerize to form a new chemical species (MN), then these two CompACs may form a bistable system wherein either the M-dominated or N-dominated state is locally stable.

3. RESULTS

We documented 226 CompACs across the periodic table, and most of them do not involve organic molecules (Table 1, Table S1, Supporting Information 4). At least two CompACs are documented for each of the 18 groups, lanthanoid series, and actinoid series in the periodic table. Of these, most CompACs are composed of two reactions, and only eight CompACs consist of four or more reactions.

In addition, the use of the term "comproportionation" in published literature is sometimes not necessarily associated with redox reactions following the pattern shown in Figure 1a but only emphasizes a specific stoichiometric relationship.[47,48] For example, $O_2SCl_2 + O_2SF_2 \rightarrow 2O_2SFCl$ is sometimes referred to as a comproportionation reaction because different species react to produce another species with stoichiometric excess,[49,50] while the oxidation numbers of the involved atoms remain unchanged. In this regard, we also formalize a "Broad-sense CompAC" by combining this broader definition of a comproportionation reaction with an auxiliary process. For example, $O_2SCl_2 + \mathbf{O_2SF_2} \rightarrow \mathbf{2O_2SFCl}$ can be combined with $\mathbf{O_2SFCl} + KSO_2F \rightarrow \mathbf{O_2SF_2} + KCl + SO_2$,[94] to form a Broad-sense CompAC (autocatalysts are shown in bold). Consequently, we documented 44 Broad-sense CompACs (Table S2) that are stoichiometrically capable of autocatalysis. Again, most Broad-sense CompACs consist of two reactions, and no Broad-sense CompAC consists of four or more reactions. In

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addition, some other classic examples of abiotic autocatalysis, such as the formose reaction,[5,95] pyrite oxidation in an aqueous environment,[96] and the oxidation of oxalic acid by permanganate,[97−99] may also be enumerated as Broad-sense CompACs. The last example is also a CompAC since the elementary steps can be grouped such that MnC_2O_4 and MnO_4^- comproportionate to Mn^{3+} instead of Mn^{2+}. Taken together, CompACs do not reflect an isolated or particularly specialized attribute of elements of any particular group.

CompACs are documented by only considering stoichiometry and oxidation numbers without explicitly considering the thermodynamics of their constituent reactions. Thermodynamic considerations bring to attention two potential complications concerning the empirical observation of CompACs. First, for a reversible reaction pathway which is a part of a CompAC, its rate constant(s) in the autocatalytic direction may be much smaller than that of the reverse direction under a given set of environmental conditions, such that the autocatalytic process could be very slow or the steady-state concentrations of autocatalysts could be very small. Nevertheless, in principle, it is possible to make autocatalysis more prominent by making environmental conditions more extreme, e.g., high temperatures, or far from equilibrium, e.g., high concentrations of food with low initial concentrations of autocatalysts in a continuous-flow stirred tank reactor. Second, the comproportionation and auxiliary processes of a CompAC may require very different environmental conditions to be thermodynamically feasible, making it challenging to actualize such a CompAC in a well-mixed reactor. Nevertheless, there are spatial and temporal mechanisms capable of organizing reactions requiring different conditions into activated CompACs (see Section 4.2).

4. DISCUSSION

Based on experimentally confirmed chemical reactions compiled from almost two centuries of literature, we documented empirically testable CompACs in all groups, the lanthanoid series, and the actinoid series in the periodic table. Broad-sense CompACs can contain large numbers of reactions, such as the formose reaction. However, we focus on CompACs consisting of just a few (mostly two and no more than five; see Table S1: Serial 146) reactions in this study, because experimentally testing these small CompACs and coupling multiples of them together to form a more complex, ecosystem-like network, setting aside the possibility of side reactions, ought to be more straightforward than testing large autocatalytic cycles. These findings suggest that, although computationally searching for autocatalysis in any given reaction network is a highly challenging task, there may exist generic chemical circumstances or attributes that are correlated with a potential for autocatalytic behavior.

The composition of many of these CompACs (Table 1; Tables S1−S2) seems only tangentially relevant to living organisms. Some CompACs center around the chemical elements that are absent or very rare in most organisms (e.g., Th and Hg);[100,101] some are unlikely to occur under ambient terrestrial pressure or temperature conditions; and some produce chemicals that are deleterious or lethal to most living organisms. They are nevertheless potentially relevant for exploring the origins of life and the distribution of complex chemical dynamics in various astrochemical and exoplanetary locales. First, the conditions under which life originated could be dramatically different from what living organisms are dealing with today, and extraterrestrial life, if it exists, could be very different from life as we know it. The coupling of CompACs to organic chemistry in a variety of different environmental contexts could encompass a subset of reactions suitable for the sustenance of alternative life-like chemical systems. Secondly, abiotic CompACs might have played critical roles during life's emergence but were subsequently lost from living organisms later, becoming the "missing links", analogous to how construction scaffolds are removed after houses are built.[41,102] Third, even if some CompACs are completely irrelevant to life, either as we know it or in a form yet to be known, they may nevertheless generate secondary or tertiary chemical effects that may be misinterpreted as false positive biosignatures.[103] Any and all of these conditions may be leveraged to engineer life-like chemical systems with useful chemosynthetic and information-processing properties.

4.1. Emergent Patterns from Interactions between CompACs.

Being based on redox reactions, different CompACs may be coupled to form complexes of autocatalytic networks[13] (Figure 2). For example, the auxiliary processes of two oxidative CompACs may consume the same oxidant, making these CompACs compete for food (Figure 2a). The auxiliary process of an oxidative CompAC and that of a reductive CompAC may recycle a shared oxidant-reductant pair, making these CompACs mutualistic (Figure 2b). Mutualism is also possible if the auxiliary process of an oxidative CompAC and that of a reductive CompAC happen to be the same reaction (Figure 2c). The comproportionation or auxiliary process of a CompAC may consume an autocatalyst of another CompAC as food, synonymizing these CompACs to a predator−prey relationship[22,23] (Figure 2d,e). Bistability and the priority effect are also possible if autocatalysts of different CompACs dimerize to form a new chemical species[104] (Figure 2f).

In contrast to autocatalytic cycles observed in biochemistry that may involve dozens of reaction steps and/or biomacromolecules (e.g., the Calvin cycle and DNA replication), CompACs are much simpler since they usually consist of only two or three reactions. Such simplicity could be important for a primitive, life-like autocatalytic system to emerge and persist. An autocatalytic cycle with fewer reaction steps tends to have a higher "carrying capacity",[13] and it is arguably easier to find naturally occurring or laboratory-generated conditions that allow every reaction in a smaller autocatalytic cycle to occur.

4.2. Separation between Food Species Facilitates the Observation of Autocatalytic Dynamics.

Although we have detailed many small-reaction-number CompACs, real chemical reaction systems are rarely this simple. Real systems, even those under controlled laboratory conditions, should be expected to be "messy", with multiple side reactions and alternative pathways. For this reason, the theoretical existence of a CompAC does not necessarily mean that it will be easily observable nor that it will generate complex dynamics between and among species in a chemical system. There are systemic constraints that are known to facilitate complicated autocatalytic dynamics within representative examples of the described reaction sets. For example, the Belousov-Zhabotinsky reaction can exhibit bursting and chaotic oscillations in a continuous-flow stirred tank reactor but not in a closed one.[26]

Although the acceleration of a reaction over time is neither sufficient nor necessary for autocatalysis, it is usually the phenomenon that is most easily measured in experimental protocols. Another method of observing autocatalysis is to check whether a tiny amount of candidate autocatalysts can be used as a "seed" to trigger a reaction system that produces much more autocatalysts.[12] A CompAC is more likely to exhibit reaction acceleration or seed-dependence when direct reactions between the complementary reductive and oxidative food of the comproportionation and auxiliary steps are suppressed. Based on the CompACs we documented, there are generally three ways to suppress the direct reaction between oxidative food and reductive food: kinetic, spatial, and temporal separations.

The dissolution of copper in nitric acid[86,87,105] shows an example of **kinetic separation** in an autocatalytic system (Figure 3). Upon addition of a piece of copper metal to a nitric acid solution, the dissolution of copper is slow at the beginning, which is a consequence of the fact that the rate of heterogeneous reaction between Cu and HNO_3 is low (Figure 3a). As the dissolution reaction continues, NO_2 is slowly formed by the reaction between HNO_3, H^+, and electrons from Cu. Once NO_2 is formed, it activates a new reaction pathway that is much faster than the direct reaction between the Cu metal and nitric acid (Figure 3b):

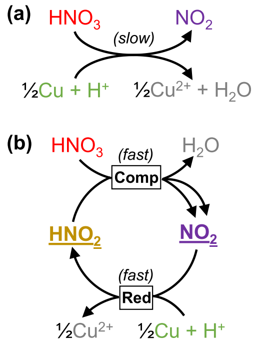

Figure 3. Autocatalytic dissolution of copper in nitric acid and kinetic separation between food species. (a) Direct reaction between HNO_3, Cu, and H^+ is slow, which "kinetically separates" the food species HNO_3, Cu, and H^+. (b) Autocatalytic dissolution of copper consists of two fast reactions: the comproportionation between HNO_3 and HNO_2, which yields NO_2, and the reduction of NO_2 by Cu and H^+, which produces HNO_2.

$$\mathbf{NO_2} + 1/2\mathrm{Cu} + \mathrm{H}^+ \rightarrow \mathbf{HNO_2} + 1/2\mathrm{Cu}^{2+}$$

$$\mathbf{HNO_2} + \mathrm{HNO_3} \rightarrow \mathbf{2NO_2} + \mathrm{H_2O}$$

Here, NO_2 and HNO_2 catalyze the formation of themselves through these two fast reactions, and this pathway is thus autocatalytic. Now consider another metal Z in the mixture that directly and quickly reacts with nitric acid; even if Z can be dissolved through the autocatalysis of NO_2 and HNO_2, the autocatalytic dynamics may be obscured. In this case, slowing the reaction between the oxidative food, HNO_3, and the reductive food, metal and H^+, is important for observing autocatalytic dynamics; the food species are kinetically separated as a consequence of the dramatic differences between the rate constants involved. Another classic example of kinetic separation is the formose reaction, because the direct dimerization between formaldehydes is dramatically slower (perhaps not even possible except through a radical mechanism) than the autocatalytic pathway formed by ketose-aldose isomerizations, aldol, and retro-aldol reactions.[5]

Spatial separation can also limit the interaction between oxidative food and reductive food. For example, consider the comproportionation direction of the Boudouard reaction, possible under high temperatures:[54,64]

$$\mathrm{CO_2(g) + C(s) \rightarrow 2CO(g)}$$

This reaction and the oxidation of CO by I_2O_5 under room temperature[64] can form a CompAC:

$$\mathbf{CO_2}\mathrm{(g) + C(s)} \rightarrow \mathbf{2CO}\mathrm{(g)}$$

$$\mathbf{5CO}\mathrm{(g) + I_2O_5(s)} \rightarrow \mathbf{5CO_2}\mathrm{(g) + I_2(s/g)}$$

where the autocatalysts CO_2 and CO consume C and I_2O_5 as food, generating I_2 as waste. This CompAC could be difficult to observe, however, in the case where one simply mixes the food species C and I_2O_5 together in a heated reactor. This is because I_2O_5 will directly decompose to I_2 and O_2[54] and/or react with C[106] at temperatures much lower than the desired temperature of CO_2 + C → 2CO; thus, the autocatalytic dynamics may be obscured.

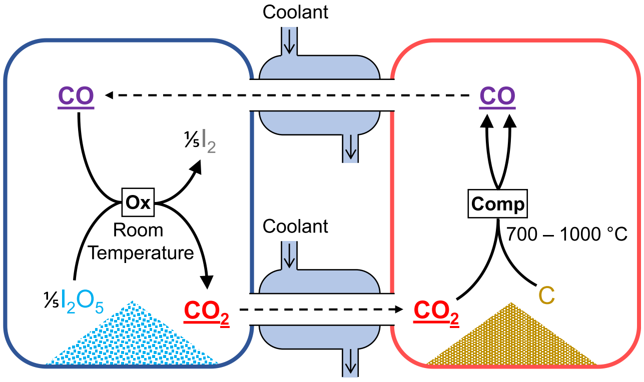

Figure 4. Autocatalytic amplification of CO and CO_2 based on spatial separation between food species. Two reactors are connected by tunnels with cooling jackets; the right reactor is heated up to 700−1000 °C, while the left reactor is at room temperature.[64] In the right reactor, CO_2 is heated and comproportionates with C to produce more CO; then the hot CO moves to the left reactor while being cooled down to room temperature. In the left reactor, CO is oxidized to CO_2 by reacting with I_2O_5, then this room-temperature CO_2 moves to the right reactor. To initiate the autocatalytic cycle, at least a small amount of CO_2 or CO needs to be added as a "seed".

One way to facilitate the observation of this CompAC is to place I_2O_5 and C, which are solids, in two reactors connected by two tunnels only allowing the diffusion of gaseous molecules; the temperature of the reactor with I_2O_5 is low while that of the reactor with C is high, with the tunnels surrounded by cooling jackets (Figure 4). Carried out in this way, the I_2O_5 and C will be spatially separated and cannot directly react with each other[4] while each resides in a reactor with appropriate reaction conditions. To initiate the conversion of I_2O_5 and C into CO_2 and CO, a small amount of CO_2 or CO gas needs to be introduced to a reactor or tunnel as a "seed". With CO_2 as the seed, C will first react with CO_2 to produce more CO by CO_2 + C → 2CO in the hot reactor. The hot CO gas will then move mainly through the upper tunnel and be cooled down, eventually making contact with I_2O_5 in the other reactor and reacting to regenerate CO_2 by 5CO + I_2O_5 → 5CO_2 + I_2. Then, the low-temperature CO_2 will move mainly through the lower tunnel to enter the hot

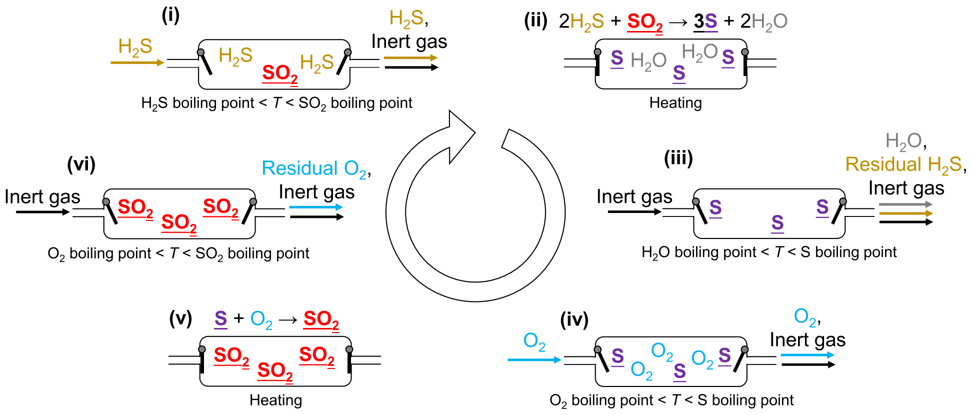

Figure 5. Autocatalytic amplification of SO_2 and S based on temporal separation between food species. In a periodically open-closed reactor with some liquid SO_2 present at the beginning, the input of food species H_2S and O_2 is temporally separated such that the direct reaction between them is impossible but the autocatalytic amplification of SO_2 and S is still afforded. (i) The reactor is open, receiving H_2S at a temperature between the boiling points of H_2S and SO_2. (ii) The reactor is closed; the comproportionation between H_2S and SO_2 produces S and H_2O. (iii) The reactor is open, releasing H_2O and residual H_2S at a temperature between the boiling points of H_2O and S. (iv) The reactor is open, receiving O_2 at a temperature between the boiling points of O_2 and S. (v) The reactor is closed; S is oxidized to SO_2 by O_2, completing the autocatalytic cycle. (vi) The reactor is open, releasing residual O_2 at a temperature between the boiling points of O_2 and SO_2. Boiling points: $O_2 < H_2S < SO_2 < H_2O < S$.

reactor. As this process continues, more and more CO_2 and CO will be synthesized within the connected reactors by autocatalysis.

Compared to kinetic separation, spatial separation is able to not only inhibit direct and rapid reactions between food species but also organize reactions that require very different conditions into an autocatalytic cycle. In abiotic environments, spatial separation may occur in multiple forms.[107−110] For example, if an autocatalytic cycle needs food from hydrothermal vents and the atmosphere, the food species can be separated by the body of water above the vents; if the food species are from different minerals, they can be separated by geographical barriers, such as mountains and rivers, or by simple spacing between different rocks or ores.

If the physicochemical conditions are insufficient to afford effective kinetic or spatial separation, then **temporal separation** between food species may also be factored. For example, consider the CompAC:

$$2H_2S + \mathbf{SO_2} \rightarrow \mathbf{3S} + 2H_2O$$

$$\mathbf{S} + O_2 \rightarrow \mathbf{SO_2}$$

where the autocatalysts SO_2 and S consume H_2S and O_2, generating H_2O as a waste product. Given that the reaction volume is seeded by a small amount of liquid SO_2 blanketed by an inert gas (e.g., N_2) and the volume periodically receives and releases gaseous molecules in the following pattern (Figure 5), autocatalysis can be achieved:

(i) H_2S is received at a temperature between the boiling points of H_2S and SO_2;
(ii) the reaction volume is closed at a temperature high enough to allow for $2H_2S + SO_2 \rightarrow 3S + 2H_2O$;
(iii) gases are released at a temperature between the boiling points of H_2O and S;
(iv) O_2 is received at a temperature between the boiling points of O_2 and S;
(v) the reaction volume is closed at a temperature high enough to allow for $S + O_2 \rightarrow SO_2$;
(vi) gases are released at a temperature between the boiling points of O_2 and SO_2, and then starting over at step (i).

Under these periodically changing environmental conditions, wherein the food species H_2S and O_2 are provided at different, non-overlapping time intervals (i.e., temporally separated), the observation of autocatalytic amplification of SO_2 and S is expected. In a natural environment, temporal separation may appear in multiple forms, such as intermittent raining, tidal cycles, geyser eruptions, a diurnal cycle, secondary weathering, or runoff patterns that lead to chemical oscillations.

As a basis for comparison, each of these three types of separation is utilized in essential ways by living organisms. For example, CO_2, ATP, NADPH, and H_2O are kinetically separated during the Calvin cycle because they do not directly react to produce monosaccharides, and activating the Calvin cycle requires monosaccharide phosphates as autocatalysts. Intracellular compartments (e.g., the nucleus or the mitochondria in eukaryotes) or macromolecular centralization of multifaceted processes (e.g., ribosomal subunit interactions) can provide a microscopic structural basis for spatial separation.[111,112] Temporal separation can be mediated by vegetative growth and reproductive growth. One underexplored implication for prebiotic chemistry is that a stoichiometric capability for abiotic autocatalysis may be relatively common across elements, but circumstances facilitating effective separation of key food species and reactions may be a more substantial bottleneck to actualizing autocatalytic dynamics under most cosmochemical and geochemical conditions.

4.3. Implications for Biosignature Interpretation.

One of the most challenging aspects of assessing the existence of life beyond Earth is the possibility that chemical conditions on remotely sensed bodies may generate complex variations that resemble biotic influences.[113] Autocatalytic cycles in general and key reactions that compose CompACs in particular may present significant challenges to biosignature characterization under conditions of pressure, temperature, and energy input that exoplanets can facilitate. The collated list of CompACs can serve as a useful compendium for alternative chemical systems to be compared to remote sensing data in the event that anomalous compositions or redox disequilibria are detected.[103]

Another question relevant to both biosignature characterization and evolutionary biology is the extent to which bioessential inorganic cofactors are utilized as a result of selection among many possible options or whether they are more likely to be imprinted upon biology through a broader planetary or physicochemical context.[114] Recent studies of reconstructed ancestral metal cofactor binding sites have provided reasonable cause for scrutinizing facile assumptions that link biological utilization to general environmental abundance.[115] Responsive chemical dynamics afforded by autocatalysis are potentially impactful to biochemistry, whether incorporated within the cell or mediated through external interactions. One intriguing possibility is that the same basic properties of the redox-active class of metal cofactors (e.g., iron, copper, manganese, molybdenum, etc.)[116] that can support complex comproportionation-driven chemical dynamics are, in parallel, coincident with their propensity for biological utilization. In this view, organic chemistry may open novel possibilities for chemical separation (kinetic, temporal, or spatial) that lack geochemical counterparts. To better assess which chemical species played more critical roles during the origins or early evolution of life, theoretical analyses based on principles of chemistry and empirical data obtained by geochemical studies can be leveraged. For example, one may test whether an element with more oxidation states and a Frost diagram where the curve is generally more concave up[117] is more likely to underlie complex dynamics based on CompACs, and then test these attributes against the probability of biological uptake.

5. CONCLUSIONS

Life utilizes three separation mechanisms (kinetic, spatial, and temporal) to modulate aspects of cellular homeostasis and facilitate contingent responses to stimuli. Examples provided by a small number of well-studied abiotic autocatalytic systems, such as the formose reaction and the Belousov-Zhabotinsky reaction, showed that only under conditions of effective separation can chemical disequilibria be leveraged to generate suitably "life-like" compositional variations. Based on an analysis of the presence of comproportionation reactions across element groups reported in the literature, we demonstrate that abiotic autocatalytic reaction systems underpinned by comproportionation (i.e., CompACs) are more frequent than previously thought; importantly, the presence of CompACs is not restricted to a specific part of the periodic table. CompACs with the potential to interact are probably a general phenomenon rather than a collection of special cases.

The collated CompAC reaction sets establish a starting point for a more systematic assessment of the conditions under which complicated dynamics afforded by autocatalysis can occur in geochemical or cosmochemical settings that are relevant to the search for life in the universe. Such a systematic assessment may be necessary for pushing forward our understanding of abiogenesis, for disentangling false positive biosignatures from *bona fide* ones, and for circumscribing conditions suitable for the organization of complex chemical systems in general.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c07041.

Extended lists of CompACs and Broad-sense CompACs, and detailed descriptions of tools and methods used to document these ACs (PDF)

An interactive version of the lists (PDF)

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■ ABBREVIATION

CompAC comproportionation-based autocatalytic cycle

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