Title: What Wilhelm Ostwald meant by "Autokatalyse" and its significance to origins-of-life research

Subtitle: Facilitating the search for chemical pathways underlying abiogenesis by reviving Ostwald's thought that reactants may also be autocatalysts

Authors

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Abstract

A closer look at Wilhelm Ostwald's articles that originally proposed the concept of autocatalysis reveals that he accepted reactants, not just products, as potential autocatalysts. Therefore, that a process is catalyzed by some of its products, which is the common definition of autocatalysis, is only a proper subset of what Ostwald meant by "Autokatalyse". As a result, it is necessary to reconsider the definition of autocatalysis, which is especially important for origins-of-life research because autocatalysis provides an abiotic mechanism that yields reproduction-like dynamics. Here, we translate and briefly review the two key publications on autocatalysis by Ostwald to revive his understanding of autocatalysis, and we introduce the concepts of recessive and expansive autocatalysis. Then we discuss the twofold significance of such a revival: first, facilitating the search for candidate processes underlying the origins of life, and second, updating our view of autocatalysis in complex reaction networks and metabolism.

Keywords

28   Autocatalysis, Wilhelm Ostwald, Origins of life, Metabolism, Chemical Reaction Networks

1. Introduction

Wilhelm Ostwald's article *Ueber Autokatalyse* (1890) [1] formally proposed the concept of autocatalysis, although actual examples of autocatalysis had been reported even earlier, such as the formose reaction [2] and the oxidation of oxalate by permanganate [3]. Autocatalysis especially attracts researchers interested in the origins of life because it provides an abiotic way to achieve self-replication and growth, key features of life [4–6].

The most commonly stated definition of autocatalysis is that a reaction, which can be single-step or multi-step, is catalyzed by one of its products [7]. Despite the importance of autocatalysis in origins-of-life research, a closer look at the literature reveals that this definition is inconsistent with how autocatalysis is described in some publications, especially some early-20th-century ones (see p. 49) [8]. There are two possible resolutions of this discrepancy: that a process is catalyzed by some of its products is the only correct definition of autocatalysis and any deviation from this definition is flawed, or that the common definition somehow misinterprets autocatalysis. To determine which is the case, we thought it helpful to investigate exactly what Ostwald meant by "Autokatalyse".

2. Ostwald's "Autokatalyse"

Ueber Autokatalyse contains no statement that can be interpreted as a direct definition of "Autokatalyse" (Supporting Information 1). Nevertheless, we can still infer Ostwald's definition of "Autokatalyse" from the first paragraph, where he stated his motivation for proposing the concept:

"Bei Gelegenheit früherer Arbeiten über Oxydations- und Reductionsvorgänge bei Gegenwart »katalylischer« Stoffe hatte sich mir die Frage entgegengestellt, ob ein Stoff, welcher einer langsam verlaufenden Reaction unterliegt, auf sich selbst katalytisch einwirken könne, wenn er im übrigen die zur katalytischen Wirksamkeit erforderlichen Eigenschaften besitzt."

"*On the occasion of earlier work on oxidation and reduction processes in the presence of 'catalytic' substances, the question arose in my mind whether a substance, which is subject to a slow reaction, can have a catalytic effect on itself if it also possesses the properties necessary for catalytic activity.*"

57 It is clear Ostwald wanted to define "Autokatalyse" as a phenomenon where "*a substance, which*

58 *is subject to a slow reaction, can have a catalytic effect on itself if it also possesses the*

59 *properties necessary for catalytic activity.*" But what did Ostwald mean with "*unterliegt*" or "*is*

60 *subject to*"? Can this "*substance*" be either a reactant or a product of the reaction, or must the

61 "*substance*" be a reactant, or must it be a product?

62 In the following paragraphs of the same text, Ostwald described an example of "Autokatalyse"

63 that can be summarized as follows: since γ-valerolactone is more stable than γ-hydroxyvaleric

64 acid, aqueous solutions of γ-hydroxyvaleric acid are gradually transformed to those of γ-

65 valerolactone by losing water:

66 $$\text{γ-hydroxyvaleric acid} \rightarrow \text{γ-valerolactone} + H_2O \ (1)$$
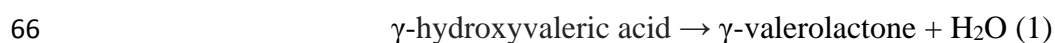
67 This reaction can be catalyzed by an acid:

68 $$\text{γ-hydroxyvaleric acid} \rightarrow \text{γ-valerolactone} + H_2O, \text{ catalyzed by } H^+ \ (2)$$
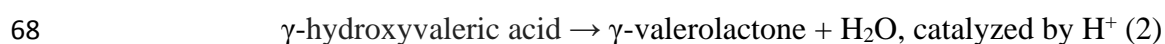
69 And because γ-hydroxyvaleric acid can dissociate to γ-hydroxyvalerate and H^+:

70 $$\text{γ-hydroxyvaleric acid} \rightarrow \text{γ-hydroxyvalerate} + H^+ \ (3)$$

71 γ-hydroxyvaleric acid itself can generate a catalyst for the reaction (3).

72 Therefore, somehow to our surprise, in the earliest paper where "Autokatalyse" was introduced,

73 the example of "Autokatalyse" does *not* match today's commonly seen definition: it is the

74 reactant, not the product, that acts as a catalyst.

75 Did Ostwald think that autocatalysis only applies when a reactant acts as a catalyst, excluding

76 other possibilities? The answer is no. In a later, more influential article, *Über Katalyse* (1901) [9],

77 he presented an example where a product of a reaction catalyzes the reaction (Supporting

78 Information 2). In this article, Ostwald stated:

79 "*Ich will von den hier vorhandenen Möglichkeiten der Autokatalyse nur den Fall erwähnen, dass*

80 *durch die Reaktion selbst ein Beschleuniger entsteht.*"

81 "*Of the possibilities of autocatalysis available here, I will mention only the case where an*

82 *accelerator is created by the reaction itself.*"

83 Note that Ostwald used "*possibilities of autocatalysis*" or "*Möglichkeiten der Autokatalyse*",

84 implying that the example that he mentioned in the sentence is a proper subset of all cases of

85   "Autokatalyse." He proceeded to mention that when metals are dissolved in nitric acid, the

86   product nitrous acid also acts as a catalyst in the dissolution reaction. Now it is known that the

87   dissolution of copper can occur following the mechanism:

88 $$H^+ + e^- \rightarrow H \ (4)$$

89 $$H + HNO_3 \rightarrow H_2O + NO_2 \ (5)$$

90 $$NO_2 + e^- \rightarrow NO_2^- \ (6)$$

91 $$H^+ + NO_2^- \rightarrow HNO_2 \ (7)$$

92 $$HNO_2 + HNO_3 \rightarrow H_2O + 2\ NO_2 \ (8)$$

93   The reactions (6), (7) and (8) can form a net reaction:

94 $$e^- + H^+ + HNO_3 \rightarrow NO_2 + H_2O, \text{ catalyzed by } NO_2 \ (9)$$

95   where NO_2 catalyzes the production of itself. Similarly, NO_2^- and HNO_2 also catalyze the

96   production of themselves. As a result, we may say that NO_2, NO_2^-, and HNO_2 "propagate" by

97   consuming "food" corresponding to e^- (provided by copper), H^+, and HNO_3, while producing

98   H_2O as "waste." This example matches the common definition of autocatalysis: a product of a

99   process catalyzes that process.

100   After a careful analysis of the excerpts quoted above, we may confidently claim that Ostwald's

101   concept of "Autokatalyse" covers not only the common definition of autocatalysis but also the

102   cases where a *reactant* of a process catalyzes the process.

103   The reason that most modern researchers have focused on cases where a product of a process

104   catalyzes the process is probably because Ostwald himself specifically emphasized such a case in

105   his influential article *Über Katalyse* (1901). Additionally, some early-20th-century researchers

106   applied the concept of autocatalysis to biological research (Supporting Information 3) without

107   considering the example in *Ueber Autokatalyse* (1890). Finally, IUPAC also adopted the

108   common definition while missing the nuance just described [7].

109   **3. Updated definitions of "Autokatalyse" and its subcategories**

110   From here onwards we will use autocatalysis as defined by Ostwald. In this sense we reinforce

111   that autocatalysis applies to a reaction (e.g., oxidation of oxalate by permanganate) or multiple

112   reactions (e.g., the Calvin cycle) that can be written as a net reaction equation where reactants

113 and products are non-overlapping sets with at least one reactant or product that has a catalytic
114 effect on the process represented by that equation.

115 Within this broad definition of autocatalysis, we can recognize two subcategories. If it is a
116 reactant that provides a catalytic effect, we say that the process is *recessively* autocatalytic
117 because the reactant promotes the consumption of itself. If it is a product that provides a catalytic
118 effect, we say that the process is *expansively* autocatalytic because the product facilitates the
119 production of itself. Some early-20th-century researchers (e.g., Sir William Maddock Bayliss)
120 used "positive autocatalysis" and "negative autocatalysis" to refer to what we call expansive and
121 recessive autocatalysis, respectively (see p. 49) [8]. However, since "negative autocatalysis" has
122 also been used to refer to different concepts (e.g., autoinhibition and exponential decay, see
123 Supporting Information 3), we adopt new terms to avoid ambiguity.

124 In the context of expansive and recessive autocatalysis, net reactions with multiple reaction steps
125 merit special attention. Multi-step reactions have intermediates which are both products of some
126 steps and reactants of others; therefore, intermediates may also be autocatalysts. For example,
127 one of the proposed mechanisms of the Soai reaction states that a reaction intermediate, the Zn–
128 hemiacetalate, catalyzes the formation of itself, making the Soai reaction expansively
129 autocatalytic [10–12]. In this case, the intermediate is a product of the process that it catalyzes,
130 which is covered by IUPAC's definition of autocatalysis [7]. However, intermediates may also be
131 recessive autocatalysts. For example, a process that a trypsinogen undergoes after it is secreted
132 can be seen as a two-step reaction. In the first step, a trysinogen is cleaved to make an active
133 trypsin, and this step is expansively autocatalytic if it is catalyzed by an existing trypsin. In the
134 second step, a trypsin is cleaved into shorter peptides, and this step is recessively autocatalytic if
135 it is catalyzed by another trypsin. The intermediate trypsin, as a product in the first step, reactant
136 in the second step, and possible catalyst for both steps, may undergo expansive and recessive
137 autocatalysis. Nevertheless, it should be noted that a step can be catalyzed by other proteases
138 (e.g., enterokinase), making the step no longer autocatalytic.

4. The significance of Ostwald's "Autokatalyse" to origins-of-life research

140 One may wonder why Ostwald's understanding of "Autokatalyse" should be seriously
141 considered, especially after much successful research used the common definition that is also
142 adopted by the IUPAC [7]. Our goal in clarifying the concept of autocatalysis is to show that the

143   underlying distinction between expansive and recessive autocatalysis can provide new insights

144   for future origins-of-life research.

145   If we consider reversible processes, then it is obvious that any expansively autocatalytic process

146   also has a conjugate recessively autocatalytic process. For example, a reversible reaction

147    $$M + F \rightleftharpoons 2\,M \quad (10)$$

148   can be rewritten as

149    $$F \rightleftharpoons M, \text{ catalyzed by } M \quad (11)$$

150   then the forward reaction

151    $$F \rightarrow M, \text{ catalyzed by } M \quad (12)$$

152   is expansively autocatalytic, while the reverse reaction

153    $$M \rightarrow F, \text{ catalyzed by } M \quad (13)$$

154   is recessively autocatalytic.

155   In principle, every chemical reaction is reversible, and "irreversible reactions" are those where

156   the forward reaction rate constant is much higher than the reverse one. Therefore, we may claim

157   that any autocatalytic process has two directions: expansive and recessive. This claim enlarges

158   the range of candidate processes that underlie abiogenesis. This is because some recessively

159   autocatalytic processes, which were easily ignored under the scope of the common definition of

160   autocatalysis, might be able to run in the reverse direction in environments extremely different

161   from those known today (e.g., the prebiotic Earth or other planets). For example, the Krebs cycle

162   together with an oxaloacetate-to-acetyl-CoA pathway in the PEP-pyruvate-oxaloacetate node

163   (Fig. 1A) is recessively autocatalytic in our framework. Nevertheless, researchers have shown

164   that this process can run in the reverse direction (Fig. 1B), being expansively autocatalytic, as a

165   plausible prebiotic process synthesizing multiple important metabolites [13].

166   A more complicated situation would be one where an autocatalytic process is both expansive and

167   recessive along the same direction. For example, for a reversible reaction

168    $$P + 2\,Q \rightleftharpoons 2\,P + Q \quad (14)$$

169   we can rewrite its forward reaction as

$$Q \rightarrow P, \text{ catalyzed by both P and Q (15)}$$

which would make it expansively autocatalytic for P and recessively autocatalytic for Q. This example demonstrates that to fully grasp the potential for autocatalysis (both expansive and recessive) in a chemical process, the stoichiometry of each chemical species involved should be considered. Otherwise, some autocatalysts may be missed, especially if they are too simple and/or too abundant such that they are treated as backgrounds rather than entities with propagation potential that may underlie nonlinear dynamics in metabolism.

The simple example of the reaction (14) may seem contrived, yet it is not difficult to find processes with similar properties in complex reaction networks. For example, if we combine the Krebs cycle, the oxaloacetate-to-acetyl-CoA pathway, and oxidative phosphorylation, the resulting process can in theory also be expansively autocatalytic (Fig. 1C). The Krebs cycle must run in an environment with water (Fig. 1C,E), yet oxidative phosphorylation produces more water by consuming NADH and $FADH_2$ that are generated by the Krebs cycle and the oxaloacetate-to-acetyl-CoA pathway (Fig. 1C,F). Therefore, the process consisting of the Krebs cycle, the oxaloacetate-to-acetyl-CoA pathway, and oxidative phosphorylation can be recessively autocatalytic for the carboxylic acids involved in the Krebs cycle and expansively autocatalytic for H_2O (Fig. 1C–F). In other words, the entire metabolic process shown in Fig. 1C may be seen not only as a process where organic molecules are consumed by recessive autocatalysis, but also as one where H_2O "propagates" by expansive autocatalysis. Could H_2O be a *de facto* autocatalyst prebiotically? Was the prototype of central metabolism an abiotic or even inorganic process that was expansively autocatalytic for H_2O? Is it possible that Earth's enrichment in H_2O is partially because H_2O can self-maintain by expansive autocatalysis? Could other metabolic modules, besides the ones shown in Fig. 1, also have abiotic or even inorganic precursors where very simple chemicals acted as autocatalysts? For example, could a precursor of the electron transport chain be formed by coupling the expansive autocatalysis of HNO_2, which was described in Ostwald's *Über Katalyse* (1901), with pyrite oxidation by Fe^{3+} (Supporting Information 4)? These questions may inspire new insights into the origins, regulation, and evolution of metabolism and life.

Fig. 1 also shows that in a complex reaction network, i) whether a process is autocatalytic, ii) whether an autocatalytic process is expansive, and iii) which chemical species are autocatalysts

largely depend on which reactions are involved. This triggers several questions concerning network autocatalysis, a process gaining momentum in studies of abiogenesis [4–6, 13]. For example, what are the criteria for determining which reactions should be included in a reaction network that can be written as a net reaction? How can autocatalytic processes be detected in a reaction network? Under what conditions can a reaction network be described as a collection of interacting autocatalytic processes? How could these autocatalytic processes emerge in simple environments? What are the possible relationships between autocatalytic processes (e.g., separate, coupled, nested)? Can such relationships be mapped to evolutionary and ecological features?

In summary, a careful analysis of Ostwald's historical use of "Autokatalyse" can help resolve fuzziness and ambiguities around the concept of autocatalysis, and provides new insights into the logic of complex reaction networks, metabolism and the origins of life.

Acknowledgements

Conflict of interest

The authors declare that there is no conflict of interest.

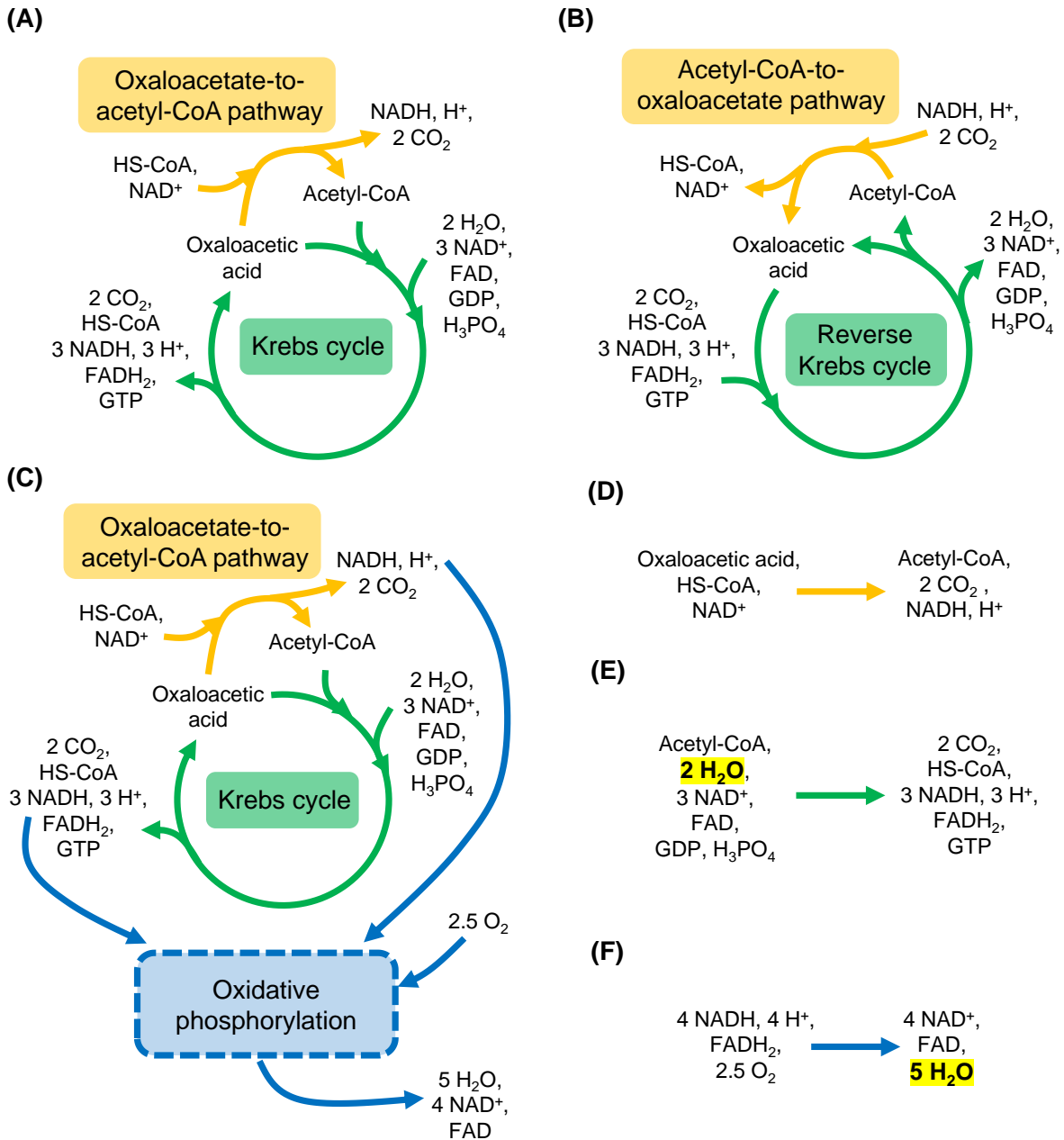## References

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(A)

Oxaloacetate-to-acetyl-CoA pathway

NADH, H$^+$, 2 CO_2

HS-CoA, NAD$^+$

Acetyl-CoA

Oxaloacetic acid

2 H_2O, 3 NAD$^+$, FAD, GDP, H_3PO_4

2 CO_2, HS-CoA 3 NADH, 3 H$^+$, FADH$_2$, GTP

Krebs cycle

(B)

Acetyl-CoA-to-oxaloacetate pathway

NADH, H$^+$, 2 CO_2

HS-CoA, NAD$^+$

Acetyl-CoA

Oxaloacetic acid

2 H_2O, 3 NAD$^+$, FAD, GDP, H_3PO_4

2 CO_2, HS-CoA 3 NADH, 3 H$^+$, FADH$_2$, GTP

Reverse Krebs cycle

(C)

Oxaloacetate-to-acetyl-CoA pathway

NADH, H$^+$, 2 CO_2

HS-CoA, NAD$^+$

Acetyl-CoA

Oxaloacetic acid

2 H_2O, 3 NAD$^+$, FAD, GDP, H_3PO_4

2 CO_2, HS-CoA 3 NADH, 3 H$^+$, FADH$_2$, GTP

Krebs cycle

2.5 O_2

Oxidative phosphorylation

5 H_2O, 4 NAD$^+$, FAD

(D)

Oxaloacetic acid, HS-CoA, NAD$^+$ → Acetyl-CoA, 2 CO_2 , NADH, H$^+$

(E)

Acetyl-CoA, **2 H_2O**, 3 NAD$^+$, FAD, GDP, H_3PO_4 → 2 CO_2, HS-CoA, 3 NADH, 3 H$^+$, FADH$_2$, GTP

(F)

4 NADH, 4 H$^+$, FADH$_2$, 2.5 O_2 → 4 NAD$^+$, FAD, **5 H_2O**

259

260 **Fig. 1. The Krebs cycle, an oxaloacetate-to-acetyl-CoA pathway in the PEP-pyruvate-**

261 **oxaloacetate node, and oxidative phosphorylation form a metabolic process that can be**

262 **recessively autocatalytic for carboxylic acids and expansively autocatalytic for H$_2$O.**

263 Simplified depictions of the Krebs cycle, a pathway from oxaloacetic acid to acetyl-CoA in the

264 PEP-pyruvate-oxaloacetate node, and oxidative phosphorylation emphasize the key nodes

265 linking the three modules; ATP production, ATP hydrolysis, several intermediary steps, reagents

266 and products are omitted. The oxaloacetate-to-acetyl-CoA pathway may be regulated by PEP

carboxykinase, pyruvate kinase, and pyruvate dehydrogenase complex. **(A)** The Krebs cycle and the oxaloacetate-to-acetyl-CoA pathway form a recessively autocatalytic process for carboxylic acids and acetyl-CoA. **(B)** The reverse Krebs cycle and the acetyl-CoA-to-oxaloacetate pathway form an expansively autocatalytic process for carboxylic acids and acetyl-CoA. **(C)** The Krebs cycle, the oxaloacetate-to-acetyl-CoA pathway, and oxidative phosphorylation form a process that is expansively autocatalytic for H_2O and recessively autocatalytic for carboxylic acids and acetyl-CoA. **(D)** The net reaction of the oxaloacetate-to-acetyl-CoA pathway. **(E)** The net reaction of the Krebs cycle. **(F)** The net reaction of oxidative phosphorylation. Note that the Krebs cycle consumes 2 units of H_2O while oxidative phosphorylation produces 5 units of H_2O, making H_2O an expansive autocatalyst for the whole system.

278   **Supporting Information for:**

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282   Ostwald's thought that reactants may also be autocatalysts

283

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292

293   This file contains four appendices:

294   **Supporting Information 1. The German text and English translation of *Ueber Autokatalyse***

295   **Supporting Information 2. The German text excerpted from *Über Katalyse* and its English**

296   **translation**

297   **Supporting Information 3. Excerpts from the literature to show ambiguities around the**

298   **concept of autocatalysis**

299   **Supporting Information 4. A hypothetical inorganic electron transport chain consisting of**

300   **expansively autocatalytic motifs**

301

302 **Supporting Information 1. The German text and English translation of *Ueber Autokatalyse***

303 The original German text was obtained from

304 https://babel.hathitrust.org/cgi/pt?id=mdp.39015064505723&view=1up&seq=723;

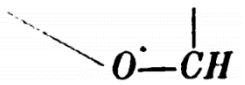305 https://archive.org/details/bub_gb_2dszAAAAMAAJ/page/189/mode/2up .

306 **Ueber Autokatalyse**

307 Bei Gelegenheit früherer Arbeiten über Oxydations- und Reductionsvorgänge bei Gegenwart

308 »katalylischer« Stoffe hatte sich mir die Frage entgegengestellt, ob ein Stoff, welcher einer

309 langsam verlaufenden Reaction unterliegt, auf sich selbst katalytisch einwirken könne, wenn er

310 im übrigen die zur katalytischen Wirksamkeit erforderlichen Eigenschaften besitzt. Die allzu

311 verwickelte Beschaffenheit der damals untersuchten Vorgänge gestattete mir nicht, die Frage

312 befriedigend zu beantworten.

313 Während einer auf meine Veranlassung von Dr. Paul Henry ausgeführten Untersuchung über die

314 Gesetze, welchen die Umwandlung der γ-Oxysäuren in Lactone unterliegt, ergab sich eine

315 Gelegenheit, diese für die Theorie der chemischen Vorgänge wesentliche Frage in

316 entscheidender Weise, und zwar bejahend zu beantworten. Die Thatsachen, auf welche sich diese

317 Entscheidung stützt, sind folgende.

318 Das aus der Lävulinsäure durch Reduction mit Natriumamalgam zu erhaltende Valerolacton[1]

$$CH^3-CH-CH^2-CH^2$$

319 $O\!-\!CH$ ist eine weit stabilere Verbindung, als die entsprechende γ-

320 Oxyvaleriansäure $CH^3\,CH\,(CH)\,CH^2\!-\!CH^2\!-\!CO\,OH$[2]. Dementsprechend verwandeln

321 sich wässerige Lösungen der Säure, (die man aus dem gut krystallisirenden Silbersalz durch

322 Zersetzen mit verdünnter Salzsäure bei 0° rein erhält) unter Wasserverlust allmählich in solche

323 des Lactons. Es war vorauszusehen, dass dieser Vorgang wie viele andere durch die Gegenwart

324 fremder Säuren »katalytisch« beschleunigt werden würde. Dies trifft nun in der That zu; in

---

[1] There seems to be an error in the molecular structure, as the original graph does not show a valerolactone, unless the rules of depicting a molecular structure was different from today. In the English translation, we will use the correct molecular structure.

[2] There seems to be a typo in the expression of γ-hydroxyvaleric acid, because CH₃CH(CH)CH₂-CH₂-COOH is 4-hexenoic acid; γ-hydroxyvaleric acid should be CH₃CH(OH)CH₂-CH₂-COOH. This typo is fixed in the English translation.

325 salzsäurehaltiger Lösung geht die Bildung des Lactons (welche man durch Titriren der

326 Flüssigkeit mit verdünntem Barytwasser leicht verfolgen kann) weit schneller vor sich, als für

327 sich.

328 Da hier wie in allen früher untersuchten Fällen die zugesetzten Säuren ihre beschleunigende

329 Wirkung nach Massgabe ihrer Affinitätscoefficienten, d. h. ihres Gehaltes an activem oder

330 elektrolytisch dissociirtem Wasserstoff ausüben, so gab es für die Thatsache, dass die wässerige

331 Lösung der Säure freiwillig in das Lacton übergeht, zwei Erklärungen. Entweder die γ-

332 Oxyvaleriansäure katalysirt sich selbst vermöge des in ihrer Lösung vorhandenen Antheils

333 elektrolytisch dissociirter Molekeln, speciell des Wasserstoffs, oder es ist unabhängig von dem

334 dissociirten Antheil die Säure als ein unbeständiger Stoff anzusehen, welcher auch ohne die

335 Gegenwart katalysirender Säurewasserstoffatome der allmählichen Umwandlung unter

336 Wasserverlust unterliegt.

337 Die Alternative liess sich auf folgende Weise zur Entscheidung bringen. Setzt man zu der

338 Lösung der Säure eine gewisse Menge ihres Natriumsalzes, so geht der Dissociationszustand

339 derselben stark zurück. Denn sei a die Anzahl der Säurejonen, h die der Wasserstoffjonen, so

340 findet nach den Gesetzen der Massenwirkung Gleichgewicht statt, wenn das Product ah einen

341 bestimmten Werth, etwa c angenommen hat. Wird nun durch Zusatz eines Salzes, welches

342 dasselbe Jon a enthält, die Menge dieses Jons vermehrt, so wird, da immer die Gleichung $ah = c$

343 bestehen muss, die Grösse h entsprechend abnehmen, d. h. die Dissociation der Säure geht

344 zurück. In unserem Falle ist der Rückgang ein bedeutender, da der dissociirte Antheil der Säure

345 nicht gross ist.

346 Wenn also die freiwillige Umsetzung der Säure in Lakton aus der Beschaffenheit derselben

347 heraus, und nicht infolge des katalytischen Einflusses der vorhandenen Wasserstoffjonen erfolgt,

348 so müsste der Zusatz eines Salzes dieser Säure den Vorgang nicht wesentlich beeinflussen. Im

349 anderen Falle aber müsste, da durch diesen Zusatz die Wasserstoffjonen fast zum Verschwinden

350 gebracht werden, die Selbstzersetzung der Säure fast völlig aufhören. Der Versuch hat im

351 zweiten Sinne entschieden: bei Gegenwart des Neutralsalzes behält die γ-Oxyvaleriansäure ihren

352 Säuretiter tagelang fast unverändert bei und lässt nur einen äusserst langsamen Uebergang in das

353 Lacton erkennen.

354 Umgekehrt geht der Uebergang bei Gegenwart von Salzsäure, wie schon erwähnt wurde, mit

355 grosser Schnelligkeit vor sich. Da in diesem Falle durch die Salzsäure eine grosse Anzahl von

356 Wasserstoffjonen in die Lösung gebracht wird, so wird in dem constanten Product $a\dot{h} = c$ wegen

357 des starken Anwachsens von h der Factor a sehr klein werden müssen, d. h. auch bei Gegenwart

358 von Salzsäure geht die Dissociation der Oxysäure sehr stark zurück. Da trotzdem die

359 Umwandlung in das Lacton sehr schnell erfolgt, so ist daraus zu schliessen, dass der *nicht*

360 *dissociirte* Antheil der Säure derjenige ist, welcher die Umbildung zu Lacton erleidet.

361 Es wirken also in der reinen Lösung der Säure die Wasserstoffjonen, welche aus dem dissociirten

362 Antheil stammen, katalytisch auf den nicht dissociirten ein. Aus diesem Ergebniss lässt sich ein

363 weiterer beachtenswerther Schluss ziehen. Da es sich hier um die Betheiligung zweier Factoren

364 handelt, welche beide mit der Menge der noch nicht in das Lacton umgewandelten Säure

365 veränderlich sind, so muss der Vorgang durch eine Reactionsgleichung von der Gestalt, wie sie

366 für die Wechselwirkung *zweier verschiedener Stoffe* gilt, darstellbar sein und nicht den Gesetzen

367 solcher Vorgänge folgen, bei denen nur ein einziger Stoff eine Aenderung seiner Menge erfährt.

368 In der That wurden wir auf die Bedeutung der vorbeschriebenen Erscheinungen aufmerksam, als

369 Dr. Henry vergeblich seine Versuche über die Selbstzersetzung der Säure ohne fremde Zusätze

370 durch die Reactionsgleichung erster Ordnung darzustellen versuchte. Die Reactionsgleichung

371 zweiter Ordnung erwies sich dagegen im Einklang mit den Ergebnissen der Beobachtungen.

372 Die Einzelheiten dieser Untersuchungen, welche von Dr. P. Henry mit bemerkenswerther

373 Ausdauer und Geschicklichkeit durchgeführt wurden, werden in der Zeitschrift für physikalische

374 Chemie zum Abdruck gelangen.

375

376

377 English translation:

378 **About Autocatalysis**

379 On the occasion of earlier work on oxidation and reduction processes in the presence of

380 "catalytic" substances, the question arose in my mind whether a substance, which is subject to a

381 slow reaction, can have a catalytic effect on itself if it also possesses the properties necessary for

382 catalytic activity. The all-too-complicated nature of the processes investigated at that time did

383 not allow me to answer the question satisfactorily.

384 During an investigation carried out at my instigation by Dr. Paul Henry on the laws governing

385 the conversion of γ-hydroxy acids into lactones, an opportunity arose to answer this question,

386 which is essential for the theory of chemical processes, in a decisive and indeed affirmative

387 manner. The facts on which this decision is based are as follows.
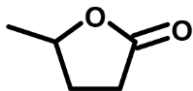
388 The valerolactone obtained from levulinic acid by reduction with sodium

389 amalgam is a much more stable compound than the corresponding γ-hydroxyvaleric acid

390 $CH_3CH(OH)CH_2\text{-}CH_2\text{-}COOH$. Accordingly, aqueous solutions of the acid (which is obtained in

391 pure form from the well-crystallizing silver salt by decomposition with dilute hydrochloric acid

392 at 0 degrees Celsius) are gradually transformed into those of the lactone by loss of water. It was

393 to be expected that this process, like many others, would be "catalytically" accelerated by the

394 presence of other acids. This is indeed true; in a solution containing hydrochloric acid, the

395 formation of the lactone (which can be easily tracked by titrating the liquid with diluted barium

396 hydroxide) proceeds much faster than it does by itself.

397 Since here, as in all previously investigated cases, the added acids exert their accelerating effect

398 according to their affinity coefficients, i.e. their content of active or electrolytically dissociated

399 hydrogen, there were two explanations for the fact that the aqueous solution of the acid passes

400 freely into the lactone. Either the γ-hydroxyvaleric acid catalyzes itself by virtue of the

401 proportion of electrolytically dissociated molecules, especially hydrogen, present in its solution,

402 or, independently of the dissociated proportion, the acid is to be regarded as an unstable

403 substance which, even without the presence of catalyzing acid hydrogen atoms, undergoes

404 gradual transformation with loss of water.

405 The alternative could be decided in the following way. If a certain amount of its sodium salt is

406 added to the solution of the acid, the dissociation state of the acid decreases strongly. If a is the

407 number of acid anions, h the number of hydrogen ions, then equilibrium takes place according to

408 the laws of mass action, when the product ah has assumed a certain value, for example c. If the

409 quantity of this anion is increased by the addition of a salt which contains the same anion, then,

410 since the equation $ah = c$ must always hold, the quantity h will decrease accordingly, i.e. the

411 dissociation of the acid will decrease. In our case, the decrease is significant, since the

412 dissociated portion of the acid is not large.

413 If, therefore, the voluntary conversion of the acid into lactone is due to the nature of the acid and

414 not to the catalytic influence of the hydrogen ions present, then the addition of a salt of this acid

415 would not have to influence the process significantly. In the other case, however, since by this

416 addition the hydrogen ions are almost made to disappear, the self-decomposition of the acid

417 would have to cease almost completely. The experiment supported the second case: in the

418 presence of the neutral salt, the γ-hydroxyvaleric acid retains its acid titer almost unchanged for

419 days and shows only an extremely slow transition to the lactone.

420 Conversely, in the presence of hydrochloric acid, as already mentioned, the transition proceeds

421 with great rapidity. Since in this case a large number of hydrogens are brought into the solution

422 by the hydrochloric acid, the factor a must become very small in the constant product $a\dot{h} = c$

423 because of the strong increase in h, i.e. even in the presence of hydrochloric acid the dissociation

424 of the hydroxy acid is very strongly reduced. Since, despite this, the transformation into lactone

425 takes place very quickly, it can be concluded that the *non-dissociated* portion of the acid is the

426 one which undergoes the transformation into lactone.

427 Thus, in the pure solution of the hydroxy acid, the hydrogen ions, which originate from the

428 dissociated portion, have a catalytic effect on the non-dissociated portion. From this result

429 another noteworthy conclusion can be drawn. Since we are dealing here with the participation of

430 two factors, both of which are variable with the quantity of the hydroxy acid not yet converted

431 into the lactone, the process must be representable by a reaction equation of the form that applies

432 to the interaction *of two different substances*, and not follow the laws of such processes in which

433 only one substance undergoes a change in its quantity. In fact, we became aware of the

434 significance of the phenomena described above when Dr. Henry tried in vain to represent his

435 experiments on the self-decomposition of acid without foreign additives by the first-order

436 reaction equation. The second-order reaction equation, on the other hand, proved to be in

437 agreement with the results of the observations.

438 The details of these investigations, which were carried out by Dr. P. Henry with remarkable

439 perseverance and skill, will be printed in the *Zeitschrift für physikalische Chemie*.

440

Supporting Information 2. The German text excerpted from *Über Katalyse* and its English translation

The original German text was obtained from https://doi.org/10.1002/bbpc.19010077203 .

Über Katalyse

… Einen verwickelteren Fall katalytischer Erscheinungen bilden solche Vorgänge, wo die an der Reaktion beteiligten Stoffe selbst noch ausserdem katalytisch wirken. Ich will von den hier vorhandenen Möglichkeiten der Autokatalyse nur den Fall erwähnen, dass durch die Reaktion selbst ein Beschleuniger entsteht. Dies tritt beispielsweise bei einer der bekanntesten Reaktionen, der Auflösung der Metalle in Salpetersäure, ein. Die hierbei entstehende salpetrige Säure beschleunigt in hohem Grade die Geschwindigkeit der Einwirkung der Salpetersäure, und dadurch kommt folgende Erscheinung zu stande.

Wird das Metall in die reine Säure gebracht, so beginnt die Reaktion äusserst langsam. In dem Maasse, wie sie fortschreitet, wird sie schneller, und schliesslich stürmisch. Ist diese Periode vorüber, so verlangsamt sich der Prozess und endet mit einer gegen Null konvergierenden Geschwindigkeit.

Dieses steht in auffallendem Widerspruche mit dem gewöhnlichen Verlauf der Reaktionen, die mit der grössten Geschwindigkeit beginnen und wegen des allmählichen Verbrauches der wirkenden Stoffe immer langsamer werden.

Hier drängen sich die physiologischen Analogieen unwiderstehlich auf; es ist eine typische Fiebererscheinung. Und noch eine andere wichtige physiologische Thatsache lässt sich auf gleichem Wege illustrieren: die Gewöhnung und das Gedächtnis. Ich habe hier zwei Proben derselben Salpetersäure, die nur dadurch verschieden sind, dass ich in der einen vorher ein Stückchen Kupfer aufgelöst habe. Ich bringe zwei gleiche Kupferbleche in die beiden Säuren, die in demselben Wassergefäss stehen, damit sie die gleiche Temperatur haben. Alsbald sehen Sie, dass die Säure, welche schon einmal Kupfer gelöst hatte, sich an diese Arbeit "gewöhnt" hat und sie sehr geschickt und geschwind auszuführen beginnt, während die ungeübte Säure mit dem Kupfer nichts anzufangen weiss und ihre Wirkung so träge und ungeschickt ausführt, dass wir sie nicht abwarten können. Dass es sich um eine Katalyse durch salpetrige Säure handelt, wird

469 ersichtlich, wenn ich etwas Natriumnitrit zur trägen Säure füge: alsbald wird auch hier das

470 Kupfer angegriffen und aufgelöst. …

471

472

473 English translation:

474 **About Catalysis**

475 … A more complicated case of catalytic phenomena are those processes where the substances

476 that are involved in the reaction themselves also have a catalytic effect. Of the possibilities of

477 autocatalysis available here, I will mention only the case where an accelerator is created by the

478 reaction itself. This occurs, for example, in one of the best-known reactions, the dissolution of

479 metals in nitric acid. The nitrous acid formed here greatly accelerates the speed of action of the

480 nitric acid, and this gives rise to the following phenomenon.

481 If the metal is brought into the pure acid, the reaction starts extremely slowly. As it progresses, it

482 becomes faster, and finally stormy. When this period is over, the process slows down and ends

483 with a speed converging towards zero.

484 This is in striking contradiction with the usual course of reactions, which begin with the greatest

485 speed and become slower and slower because of the gradual consumption of the active

486 substances.

487 Here the physiological analogies irresistibly impose themselves; it is a typical symptom of fever.

488 And another important physiological fact can be illustrated in the same way: habituation and

489 memory. I have here two samples of the same nitric acid, which differ only in that I have

490 previously dissolved a piece of copper in one of them. I put two identical copper sheets in the

491 two acids, which are in the same water vessel, so that they have the same temperature.

492 Immediately you see that the acid, which had already dissolved copper once, has "got used" to

493 this work and begins to perform it very skillfully and swiftly, while the untrained acid does not

494 know what to do with the copper and performs its action so sluggishly and clumsily that we

495 cannot wait for it. That this is an example of catalysis by nitrous acid becomes apparent when I

496 add some sodium nitrite to the sluggish acid: immediately the copper is corroded and

497 dissolved. …

Supporting Information 3. Excerpts from the literature to show ambiguities around the concept of autocatalysis

As shown in the main text, Supporting Information 1, and Supporting Information 2, Ostwald accepted reactants, not just products, as potential autocatalysts. This idea was adopted by multiple scholars living in the early 20th century. For example, Sir William Maddock Bayliss, a prestigious physiologist who co-discovered hormones with Ernest Henry Starling, wrote in his book *The Nature of Enzyme Action* (1908) (see p. 49) [1]:

"*Phenomena of a similar kind are known in pure chemistry and are called by Ostwald 'autocatalysis'. When an ester is acted on by water the hydrolysis is at first very slow, but as acid is set free the reaction is rapidly accelerated as the acid concentration increases. This is positive autocatalysis. Other cases are known where the catalyst disappears during the reaction, as in the transformation of oxyacids*[3] *into their respective lactones, with disappearance of the hydrion which was acting as catalyst. Such a condition is negative autocatalysis.*"

Here, Bayliss made it very clear that there are two types of autocatalysis: that a reaction produces substances that catalyze the reaction, which is positive autocatalysis, and that a reaction consumes substances that catalyze the reaction, which is negative autocatalysis. If this understanding had been widely spread since then, our paper would have been unnecessary.

However, Bayliss was not the only biologist who published work concerning autocatalysis in the year 1908. For example, Frederick Frost Blackman, a famous plant physiologist who proposed the law of limiting factors, wrote in *The Manifestations of the Principles of Chemical Mechanics in the Living Plant* (1908) [2]:

"*In the Chemical Section they call this class of phenomenon 'autocatalysis,' and a number of cases of it are known. In these a chemical reaction gives rise to some substance which happens to catalyze the particular reaction itself, so that it goes on and on with ever-increasing velocity. Thus, we said that free acid was a catalyst to the hydrolysis of cane-sugar; suppose now that free acid were one of the products of the hydrolysis of sugar, then the catalyst would continually increase in amount in the test tube, and the reaction would go faster and faster.*"

---

[3] What was called "oxyacids" by Bayliss is called "hydroxy acids" today.

Thorburn Brailsford Robertson, a famous biochemist, wrote in *On the Normal Rate of Growth of an Individual, and its Biochemical Significance* (1908) [3]:

"*Hence, in the first unit of time after the beginning of cell-division a mass m of nuclear material is formed, in the second a mass 2 m, in the third a mass 4 m and so on; thus the velocity of the synthesis increases with lapse of time and with the mass of nuclear material already formed. This is a characteristic of that class of reactions known as autocatalytic, in which one of the products of the reaction, or, in this case, one of the constituents of the nucleus, accelerates the reaction.*"

It is obvious that both Blackman and Robertson exclusively focused on the cases where a reaction is catalyzed by some of its products and equated those to autocatalysis, ignoring the content in Ostwald's *Ueber Autokatalyse* (1890) [4].

Concerning the usage of "negative autocatalysis", there were even more ambiguities. Bayliss's "negative autocatalysis" emphasized that autocatalysts are consumed as reactants, which makes the process negative. However, some researchers did not understand "negative" from this angle. For them, "negative autocatalysis" is synonymous with exponential decay. For example, Cinquin and Demongeot wrote in *Positive and Negative Feedback: Striking a Balance Between Necessary Antagonists* (2002) [5]:

"*For example, if a protein whose concentration corresponds to x_i exerts a positive but saturable effect on its own synthesis (positive autocatalysis), and undergoes exponential decay (negative autocatalysis) ...*"

For yet other authors, "negative autocatalysis" means that a reaction produces some chemical species that inhibit the reaction. For example, Moré et al. wrote in *Photodimerization of Crystalline 9-Anthracenecarboxylic Acid: A Nontopotactic Autocatalytic Transformation* (2010) [6]:

"*The negative sign of the dimensionality can be explained by a negative autocatalytic step within the reaction, also termed as autoinhibition.*"

These two examples show that the same term (i.e., negative autocatalysis) was used to refer to different concepts.

On the other hand, Bayliss's concepts of "positive autocatalysis" and "negative autocatalysis" were also used by some researchers, although they used "autocatalysis" and "reverse autocatalysis" to refer to these concepts, respectively [7, 8]. This is likely because "autocatalysis" and "reverse autocatalysis" are, with this usage, compatible with the IUPAC's definition of autocatalysis [9].

As a result, to avoid ambiguities around "autocatalysis", "negative autocatalysis" and "reverse autocatalysis", we decided to use "autocatalysis" as defined by Ostwald, "expansive autocatalysis" to refer to catalysis by a product, and "recessive autocatalysis" to refer to catalysis by a reactant.
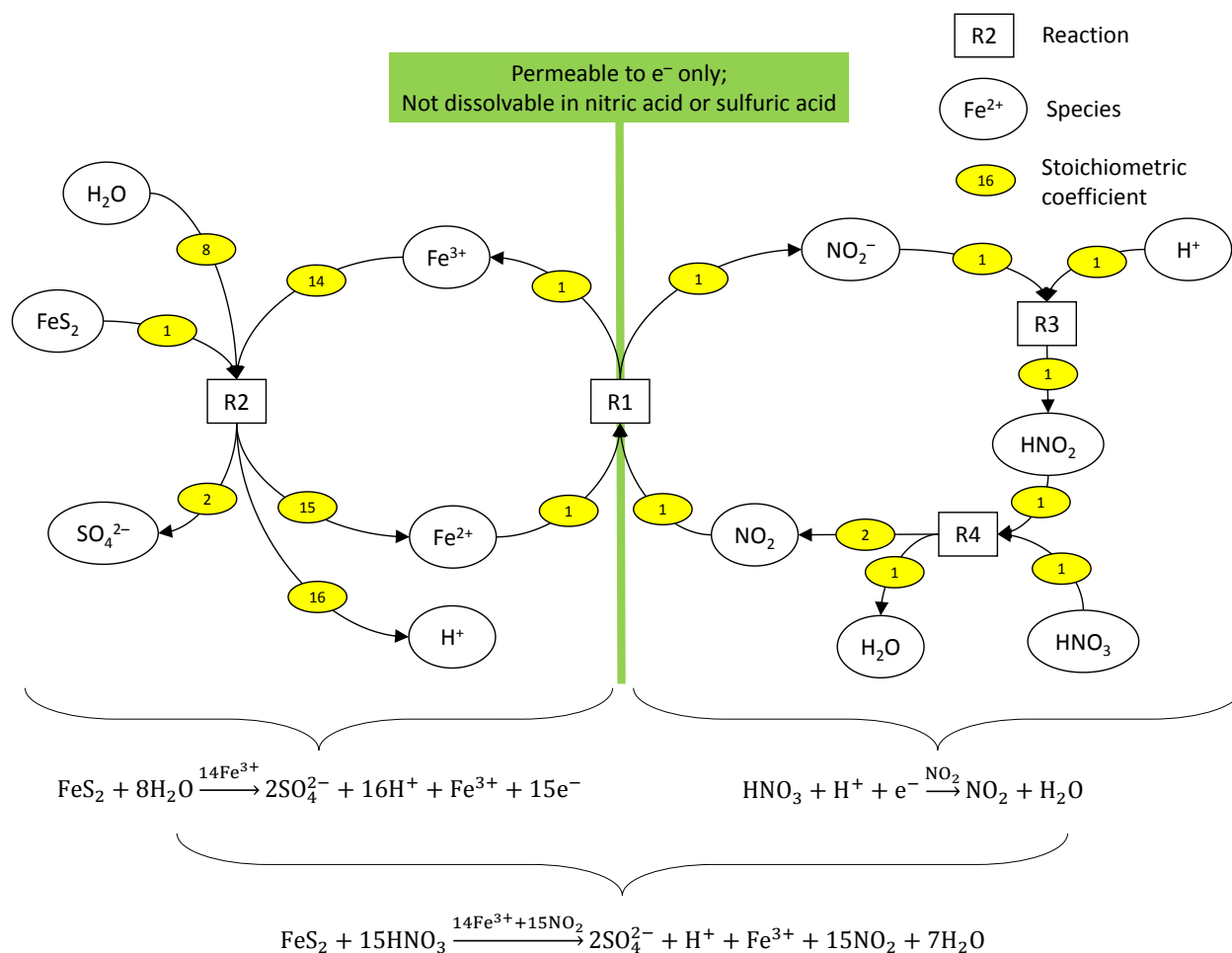
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Supporting Information 4. A hypothetical inorganic electron transport chain consisting of expansively autocatalytic motifs

An electron transport chain (ETC) is a sequence of molecules that transport electrons from reductants to oxidants while gradually consuming the energy stored in electrons to create a proton gradient on two sides of a barrier, such as the inner membrane of mitochondria. The ETC is extremely important for metabolism because it is how cells and organelles generate the proton gradient that drives ATP synthases.

If we focus on the key functions of an ETC and temporarily forget about the chemical identities of ETC components, then it is not difficult to posit an ETC performed by much simpler chemical species.

$$FeS_2 + 8H_2O \xrightarrow{14Fe^{3+}} 2SO_4^{2-} + 16H^+ + Fe^{3+} + 15e^-$$

$$HNO_3 + H^+ + e^- \xrightarrow{NO_2} NO_2 + H_2O$$

$$FeS_2 + 15HNO_3 \xrightarrow{14Fe^{3+}+15NO_2} 2SO_4^{2-} + H^+ + Fe^{3+} + 15NO_2 + 7H_2O$$

Fig. S1. A hypothetical inorganic electron transport chain consisting of expansively autocatalytic motifs. The green bar depicts a barrier (which could be formed by metal oxides for

example) that is permeable only to electrons and does not dissolve in nitric acid or sulfuric acid. The left compartment has an abundant FeS_2 supply while the right compartment constantly replenishes HNO_3. In this scenario, it is possible to have a Fe^{2+}/Fe^{3+}-catalyzed expansively autocatalytic cycle in the left compartment and a $NO_2/NO_2^-/HNO_2$-catalyzed expansively autocatalytic cycle in the right compartment. These two expansively autocatalytic cycles may thus form an ETC that transfers electrons from FeS_2 to HNO_3 while producing an excess of H^+ in the left compartment (i.e., a proton gradient between the left and right compartments is generated).

Fig. S1 shows a hypothetical inorganic ETC that transfers electrons from FeS_2 to HNO_3 while resulting in an excess of H^+ in the compartment where FeS_2 is oxidized if the compartment where HNO_3 is reduced has a high-enough pH. This is similar to the mitochondrial ETC, where electrons are transferred from NADH and $FADH_2$ to O_2, resulting in an excess of H^+ in the intermembrane space. However, there are three key differences between the hypothetical ETC in Fig. S1 and the mitochondrial ETC. First and foremost, the hypothetical ETC is completely inorganic, while the mitochondrial ETC is formed by a series of complex organic molecules. Second, the hypothetical ETC is formed by two autocatalytic cycles, while the mitochondrial ETC is formed by multiple redox cycles that are not autocatalytic; for example, the mitochondrial ETC transfers electrons from NADH to cytochrome c while recycling Q by the reactions $NADH + H^+ + \mathbf{Q} + 4H^+_{in} \rightarrow NAD^+ + \mathbf{QH_2} + 4H^+_{out}$ and $\mathbf{QH_2} + 2$ cytochrome c $(Fe^{III}) + 2 H^+_{in} \rightarrow \mathbf{Q} + 2$ cytochrome c $(Fe^{II}) + 4 H^+_{out}$. Third, the proton gradient potentially formed by the hypothetical ETC does not require transferring H^+ from one side to the other, while the mitochondrial ETC creates a proton gradient by transferring H^+ from the matrix to the intermembrane space.

For the origins of life, an ETC formed by inorganic expansively autocatalytic cycles could be important for several reasons. First, it does not require complex molecules, so it was more likely to arise spontaneously. Second, it could provide a gradient to drive other processes, acting as an energy source. Third, expansive autocatalysis could make it easier for the process to persist given the loss of components in permeable compartments. Finally, it could be a prototype or "template" for later, more complex ETCs to evolve upon. This is because prebiotic natural

627   selection could have favored more efficient and regulated ETCs by gradually updating the

628   components of the inorganic ETC and/or adding new components.