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

2 **life research**

3 **Subtitle:** Facilitating the search for chemical pathways underlying abiogenesis by reviving

4 Ostwald's thought that reactants may also be autocatalysts

5

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14

15 **Abstract**

16 A closer look at Wilhelm Ostwald's articles that originally proposed the concept of autocatalysis

17 reveals that he accepted reactants, not just products, as potential autocatalysts. Therefore, that a

18 process is catalyzed by some of its products, which is the common definition of autocatalysis, is

19 only a proper subset of what Ostwald meant by "Autokatalyse". As a result, it is necessary to

20 reconsider the definition of autocatalysis, which is especially important for origins-of-life

21 research because autocatalysis provides an abiotic mechanism that yields reproduction-like

22 dynamics. Here, we translate and briefly review the two key publications on autocatalysis by

23 Ostwald to revive his understanding of autocatalysis. Then we discuss the significance of such a

24 revival from two aspects: first, facilitating the search for candidate processes underlying the

25 origins of life, and second, updating our view of autocatalysis in metabolism.

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 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 correct, 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" according to 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.*"

It is clear Ostwald wanted to define "Autokatalyse" as a phenomenon where "*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." But what did Ostwald mean with "*unterliegt*" or "*is subject to*"? Can this "*substance*" be either a reactant or a product of the reaction, or must the "*substance*" be a reactant, or must it be a product?

In the following paragraphs of the same text, Ostwald described an example of "Autokatalyse", which can be summarized as follows: since γ-valerolactone is more stable than γ-hydroxyvaleric acid, aqueous solutions of γ-hydroxyvaleric acid are gradually transformed to those of γ-valerolactone by losing water:

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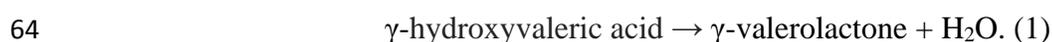
This reaction can be catalyzed by an acid:

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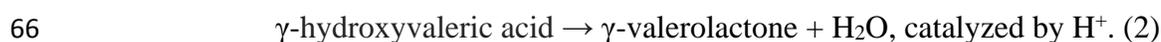
And because γ-hydroxyvaleric acid can dissociate to γ-hydroxyvalerate and H^+:

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

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

Therefore, somehow to our surprise, in the earliest paper where "Autokatalyse" was introduced, the example of "Autokatalyse" does *not* match today's commonly seen definition: it is the reactant, not the product, that acts as a catalyst.

Did Ostwald think that autocatalysis only applies when a reactant acts as a catalyst, excluding other possibilities? The answer is no. In a later, more influential article, *Über Katalyse* (1901) [9], he presented an example where a product of a reaction catalyzes the reaction (Supporting Information 2). In this article, Ostwald stated:

"*Ich will von den hier vorhandenen Möglichkeiten der Autokatalyse nur den Fall erwähnen, dass durch die Reaktion selbst ein Beschleuniger entsteht.*"

"*Of the possibilities of autocatalysis available here, I will mention only the case where an accelerator is created by the reaction itself.*"

Note that Ostwald used "*possibilities of autocatalysis*" or "*Möglichkeiten der Autokatalyse*", implying that the example that he mentioned in the sentence is a proper subset of all cases of "Autokatalyse." He proceeded to mention that when metals are dissolved in nitric acid, the

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

85   dissolution of copper can occur following the mechanism:

86 $$H^+ + e^- \rightarrow H, (4)$$

87 $$H + HNO_3 \rightarrow H_2O + NO_2, (5)$$

88 $$NO_2 + e^- \rightarrow NO_2^-, (6)$$

89 $$H^+ + NO_2^- \rightarrow HNO_2, (7)$$

90 $$HNO_2 + HNO_3 \rightarrow H_2O + 2\,NO_2. (8)$$

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

92 $$e^- + H^+ + HNO_3 \rightarrow NO_2 + H_2O, \text{ catalyzed by } NO_2, (9)$$

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

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

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

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

97   process catalyzes that process.

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

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

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

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

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

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

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

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

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

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

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

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

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

111 and products are non-overlapping sets with at least one reactant or product that has a catalytic

112 effect on the process represented by that equation.

113 Within this broad definition of autocatalysis, we can recognize two subcategories. If it is a

114 reactant that provides a catalytic effect, we say that the process is recessively autocatalytic

115 because the reactant promotes the consumption of itself. If it is a product that provides a catalytic

116 effect, we say that the process is expansively autocatalytic because the product facilitates the

117 production of itself. Some early-20th-century researchers (e.g., Sir William Maddock Bayliss)

118 used "positive autocatalysis" and "negative autocatalysis" to refer to what we call expansive and

119 recessive autocatalysis, respectively (see p. 49) [8]. However, since "negative autocatalysis" has

120 also been used to refer to different concepts (e.g., autoinhibition and exponential decay, see

121 Supporting Information 3), we adopt new terms to avoid ambiguity.

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

123 One may wonder why Ostwald's understanding of "Autokatalyse" should be seriously

124 considered, especially after much successful research used the common definition that is also

125 adopted by the IUPAC [7]. Our goal in clarifying the concept of autocatalysis is to show that the

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

127 for future origins-of-life research.

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

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

130 $$M + F \leftrightarrow 2\,M \quad (10)$$

131 can be rewritten as

132 $$F \leftrightarrow M, \text{ catalyzed by M}, \quad (11)$$

133 then the forward reaction

134 $$F \rightarrow M, \text{ catalyzed by M} \quad (12)$$

135 is expansively autocatalytic, while the reverse reaction

136 $$M \rightarrow F, \text{ catalyzed by M} \quad (13)$$

137 is recessively autocatalytic.

138   In principle, every chemical reaction is reversible, and "irreversible reactions" are the cases

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

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

141   enlarges the range of candidate processes that underlie abiogenesis. This is because some

142   recessively autocatalytic processes, which were easily ignored under the scope of the common

143   definition of autocatalysis, might be able to run in the reverse direction in environments

144   extremely different from those known today (e.g., the prebiotic Earth or other planets). For

145   example, the Krebs cycle together with an oxaloacetate-to-acetyl-CoA pathway in the PEP-

146   pyruvate-oxaloacetate node (Fig. 1A) is recessively autocatalytic in our framework. But

147   researchers have shown that this process can run in the reverse direction (Fig. 1B), being

148   expansively autocatalytic, as a prebiotic process synthesizing multiple important organic

149   molecules [10].

(A)

Oxaloacetate-to-acetyl-CoA pathway

NADH, H$^+$, 2 CO$_2$

HS-CoA, NAD$^+$

Acetyl-CoA

Oxaloacetic acid

2 H$_2$O, 3 NAD$^+$, FAD, GDP, H$_3$PO$_4$

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$_2$O, 3 NAD$^+$, FAD, GDP, H$_3$PO$_4$

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$_2$O, 3 NAD$^+$, FAD, GDP, H$_3$PO$_4$

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

Krebs cycle

2.5 O$_2$

Oxidative phosphorylation

5 H$_2$O, 4 NAD$^+$, FAD

(D)

Oxaloacetic acid, HS-CoA, NAD$^+$ → Acetyl-CoA, 2 CO$_2$, NADH, H$^+$

(E)

Acetyl-CoA, **2 H$_2$O**, 3 NAD$^+$, FAD, GDP, H$_3$PO$_4$ → 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$_2$O**

150

Fig. 1. The Krebs cycle, an oxaloacetate-to-acetyl-CoA pathway in the PEP-pyruvate-oxaloacetate node, and oxidative phosphorylation form a metabolic process that can be recessively autocatalytic for carboxylic acids and expansively autocatalytic for H$_2$O.
Simplified depictions of the Krebs cycle, a pathway from oxaloacetic acid to acetyl-CoA in the PEP-pyruvate-oxaloacetate node, and oxidative phosphorylation emphasize the key nodes linking the three modules; ATP production, ATP hydrolysis, several intermediary steps, reagents 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.

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

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

$$P + 2\,Q \leftrightarrow 2\,P + Q, \text{(14)}$$

we can rewrite its forward reaction as

$$Q \rightarrow P, \text{ catalyzed by both P and Q, (15)}$$
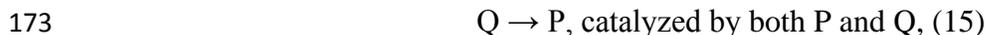
which would make it expansively autocatalytic for P and recessively autocatalytic for Q. This

example suggests that to fully understand an autocatalytic process, the stoichiometry of every

chemical species involved should be carefully assessed to infer the subcategory of autocatalysis.

Otherwise, some autocatalysts may easily be ignored, 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 some nonlinear dynamics in metabolism.

Although this last specific example seems contrived, in Fig. 1A we have partially covered a real-

world example with such a property – the Krebs cycle combined the oxaloacetate-to-acetyl-CoA

pathway. If we further combine this process with oxidative phosphorylation, the resulting

process can in theory also be expansively autocatalytic (Fig. 1C). The Krebs cycle must run in an

environment where some water is present (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

187   cycle, the oxaloacetate-to-acetyl-CoA pathway, and oxidative phosphorylation can be recessively

188   autocatalytic for the carboxylic acids involved in the Krebs cycle and expansively autocatalytic

189   for H_2O (Fig. 1C–F). In other words, the entire metabolic process shown in Fig. 1C may be seen

190   as not only a process where organic molecules are consumed by recessive autocatalysis, but also

191   one where H_2O "propagates" by expansive autocatalysis. Could H_2O be a *de facto* autocatalyst

192   prebiotically? Was the prototype of central metabolism an abiotic or even inorganic process that

193   was expansively autocatalytic for H_2O? Is it possible that Earth's enrichment in H_2O is partially

194   because H_2O can self-maintain by expansive autocatalysis? Could other metabolic modules,

195   besides the ones shown in Fig. 1, also have abiotic or even inorganic precursors where simple

196   chemical species acted as autocatalysts? For example, could a precursor of the electron transport

197   chain be formed by coupling the expansive autocatalysis of HNO_2, which was described in

198   Ostwald's *Über Katalyse* (1901), with pyrite oxidation by Fe^{3+} (Supporting Information 4)?

199   These questions may inspire new insights into the origins and regulation of metabolism and life.

200   Fig. 1 also shows that in a complex reaction network, i) whether a process is autocatalytic, ii)

201   whether an autocatalytic process is expansive, and iii) which chemical species are autocatalysts

202   largely depend on which reactions are involved. This triggers several questions concerning

203   network autocatalysis. For example, what are the criteria for determining which reactions should

204   be included in a reaction network that can be written as a net reaction? How can autocatalytic

205   processes be detected in a reaction network? Under what conditions can a reaction network be

206   described as a collection of interacting autocatalytic processes? How could these autocatalytic

207   processes emerge from simple environments? What are the possible relationships between

208   autocatalytic processes (e.g., separate, coupled, nested)? Can such relationships be mapped to

209   evolutionary and ecological features?

210   In summary, a careful analysis of Ostwald's historical use of "Autokatalyse" can help resolve

211   fuzziness and ambiguities around the concept, and may provide new insights into the logic of

212   autocatalysis potentially overlooked with the use of the common definition.

213

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Conflict of interest

The authors declare that there is no conflict of interest.

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15

16 This file contains four appendices:

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

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

19 **translation**

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

21 **concept of autocatalysis**

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

23 **expansively autocatalytic motifs**

24

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

26 The original German text was obtained from

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

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

29 **Ueber Autokatalyse**

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

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

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

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

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

35 befriedigend zu beantworten.

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

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

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

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

40 Entscheidung stützt, sind folgende.

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

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

42 ist eine weit stabilere Verbindung, als die entsprechende γ-

43 Oxyvaleriansäure $CH^3 CH (CH) CH^2-CH^2-CO OH$[2]. Dementsprechend verwandeln

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

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

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

47 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 $CH_3CH(CH)CH_2$-CH_2-COOH is 4-hexenoic acid; γ-hydroxyvaleric acid should be $CH_3CH(OH)CH_2$-CH_2-COOH. This typo is fixed in the English translation.

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

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

50 sich.

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

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

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

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

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

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

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

58 Gegenwart katalysirender Säurewasserstoffatome der allmählichen Umwandlung unter

59 Wasserverlust unterliegt.

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

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

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

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

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

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

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

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

68 nicht gross ist.

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

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

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

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

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

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

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

76 Lacton erkennen.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

93 durch die Reactionsgleichung erster Ordnung darzustellen versuchte. Die Reactionsgleichung

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

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

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

97 Chemie zum Abdruck gelangen.

98

99

100 English translation:

101 **About Autocatalysis**

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

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

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

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

106 not allow me to answer the question satisfactorily.

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

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

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

110 manner. The facts on which this decision is based are as follows.

111 The valerolactone obtained from levulinic acid by reduction with sodium

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

113 $CH_3CH(OH)CH_2$-CH_2-COOH. Accordingly, aqueous solutions of the acid (which is obtained in

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

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

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

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

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

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

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

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

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

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

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

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

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

127 gradual transformation with loss of water.

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

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

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

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

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

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

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

135 dissociated portion of the acid is not large.

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

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

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

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

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

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

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

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

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

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

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

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

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

149 one which undergoes the transformation into lactone.

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

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

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

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

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

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

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

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

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

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

160 agreement with the results of the observations.

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

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

163

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

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

193 Kupfer angegriffen und aufgelöst. …

194

195

196 English translation:

197 **About Catalysis**

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

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

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

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

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

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

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

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

206 with a speed converging towards zero.

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

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

209 substances.

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

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

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

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

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

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

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

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

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

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

220 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.

248 Thorburn Brailsford Robertson, a famous biochemist, wrote in *On the Normal Rate of Growth of*

249 *an Individual, and its Biochemical Significance* (1908) [3]:

250 "*Hence, in the first unit of time after the beginning of cell-division a mass m of nuclear material*

251 *is formed, in the second a mass 2 m, in the third a mass 4 m and so on; thus the velocity of the*

252 *synthesis increases with lapse of time and with the mass of nuclear material already formed. This*

253 *is a characteristic of that class of reactions known as autocatalytic, in which one of the products*

254 *of the reaction, or, in this case, one of the constituents of the nucleus, accelerates the reaction.*"

255 It is obvious that both Blackman and Robertson exclusively focused on the cases where a

256 reaction is catalyzed by some of its products and equated those to autocatalysis, ignoring the

257 content in Ostwald's *Ueber Autokatalyse* (1890) [4].

258 Concerning the usage of "negative autocatalysis", there were even more ambiguities. Bayliss's

259 "negative autocatalysis" emphasized that autocatalysts are consumed as reactants, which makes

260 the process negative. However, some researchers did not understand "negative" from this angle.

261 For them, "negative autocatalysis" is synonymous with exponential decay. For example, Cinquin

262 and Demongeot wrote in *Positive and Negative Feedback: Striking a Balance Between*

263 *Necessary Antagonists* (2002) [5]:

264 "*For example, if a protein whose concentration corresponds to x_i exerts a positive but saturable*

265 *effect on its own synthesis (positive autocatalysis), and undergoes exponential decay (negative*

266 *autocatalysis) …*"

267 For yet other authors, "negative autocatalysis" means that a reaction produces some chemical

268 species that inhibit the reaction. For example, Moré et al. wrote in *Photodimerization of*

269 *Crystalline 9-Anthracenecarboxylic Acid: A Nontopotactic Autocatalytic Transformation* (2010)

270 [6]:

271 "*The negative sign of the dimensionality can be explained by a negative autocatalytic step within*

272 *the reaction, also termed as autoinhibition.*"

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

274 different concepts.

275 On the other hand, Bayliss's concepts of "positive autocatalysis" and "negative autocatalysis"

276 were also used by some researchers, although they used "autocatalysis" and "reverse

277 autocatalysis" to refer to these concepts, respectively [7, 8]. This is likely because "autocatalysis"

278 and "reverse autocatalysis" are, with this usage, compatible with the IUPAC's definition of

279 autocatalysis [9].

280 As a result, to avoid ambiguities around "autocatalysis", "negative autocatalysis" and "reverse

281 autocatalysis", we decided to use "autocatalysis" as defined by Ostwald, "expansive

282 autocatalysis" to refer to catalysis by a product, and "recessive autocatalysis" to refer to catalysis

283 by a reactant.

284

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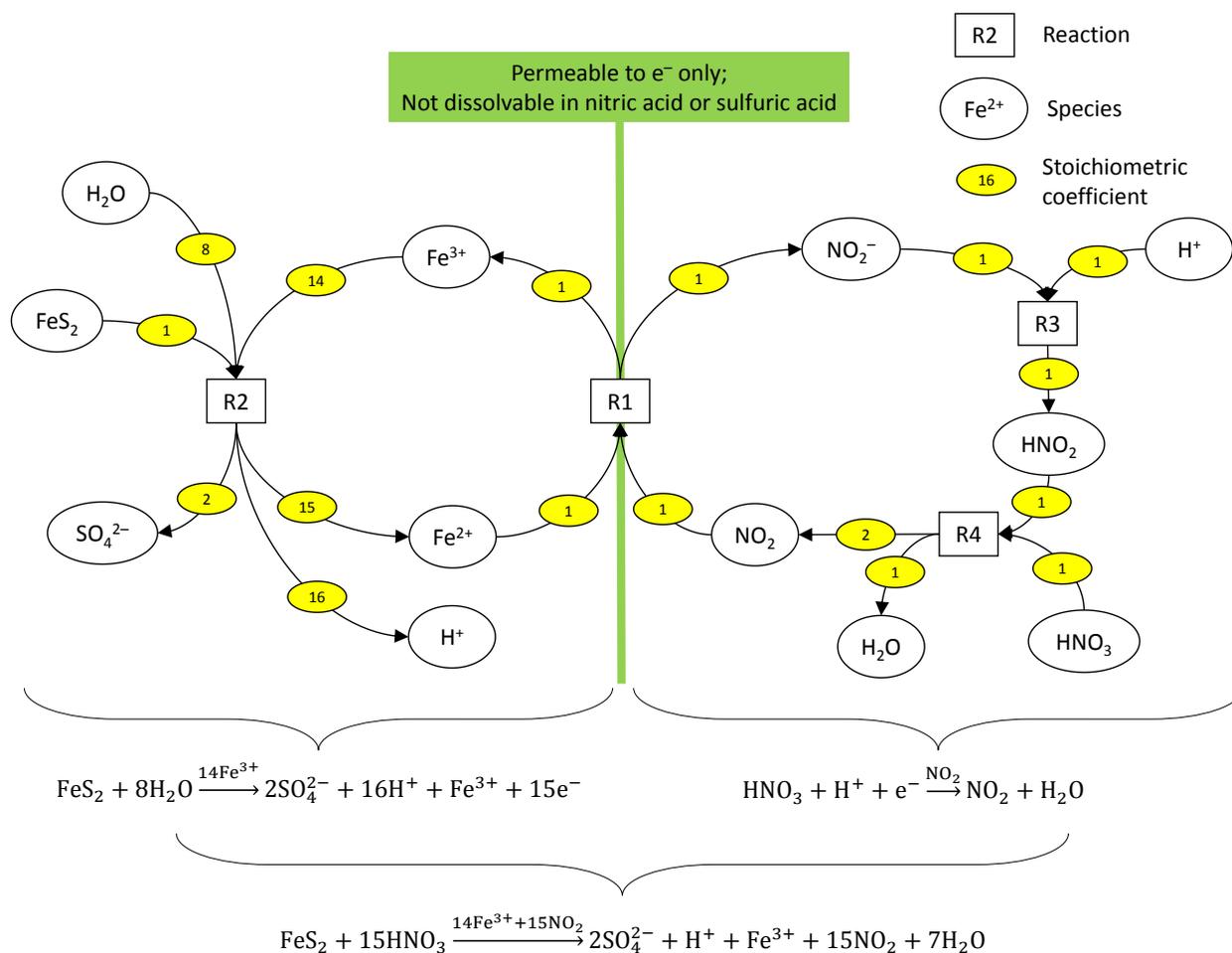299   Autocatalytic Transformation. J. Phys. Chem. C, 114, 4142–8.

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306

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

308 **expansively autocatalytic motifs**

309 An electron transport chain (ETC) is a sequence of molecules that transport electrons from

310 reductants to oxidants while gradually consuming the energy stored in electrons to create a

311 proton gradient on two sides of a barrier, such as the inner membrane of mitochondria. The ETC

312 is extremely important for metabolism because it is how cells and organelles generate the proton

313 gradient that drives ATP synthases.

314 If we focus on the key functions of an ETC and temporarily forget about the chemical identities

315 of ETC components, then it is not difficult to posit an ETC performed by much simpler chemical

316 species.

317

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

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

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

318 **Fig. S1. A hypothetical inorganic electron transport chain consisting of expansively**

319 **autocatalytic motifs.** The green bar depicts a barrier (which could be formed by metal oxides for

320   example) that is permeable only to electrons and does not dissolve in nitric acid or sulfuric acid.

321   The left compartment has an abundant FeS_2 supply while the right compartment constantly

322   replenishes HNO_3. In this scenario, it is possible to have a Fe^{2+}/Fe^{3+}-catalyzed expansively

323   autocatalytic cycle in the left compartment and a $NO_2/NO_2^-/HNO_2$-catalyzed expansively

324   autocatalytic cycle in the right compartment. These two expansively autocatalytic cycles may

325   thus form an ETC that transfers electrons from FeS_2 to HNO_3 while producing an excess of H^+ in

326   the left compartment (i.e., a proton gradient between the left and right compartments is

327   generated).

328

329   Fig. S1 shows a hypothetical inorganic ETC that transfers electrons from FeS_2 to HNO_3 while

330   resulting in an excess of H^+ in the compartment where FeS_2 is oxidized if the compartment

331   where HNO_3 is reduced has a high-enough pH. This is similar to the mitochondrial ETC, where

332   electrons are transferred from NADH and $FADH_2$ to O_2, resulting in an excess of H^+ in the

333   intermembrane space. However, there are three key differences between the hypothetical ETC in

334   Fig. S1 and the mitochondrial ETC. First and foremost, the hypothetical ETC is completely

335   inorganic, while the mitochondrial ETC is formed by a series of complex organic molecules.

336   Second, the hypothetical ETC is formed by two autocatalytic cycles, while the mitochondrial

337   ETC is formed by multiple redox cycles that are not autocatalytic; for example, the

338   mitochondrial ETC transfers electrons from NADH to cytochrome *c* while recycling Q by the

339   reactions $NADH + H^+ + \mathbf{Q} + 4H^+_{in} \rightarrow NAD^+ + \mathbf{QH_2} + 4H^+_{out}$ and $\mathbf{QH_2} + 2$ cytochrome *c* (Fe^{III}) +

340    $2 H^+_{in} \rightarrow \mathbf{Q} + 2$ cytochrome *c* (Fe^{II}) $+ 4 H^+_{out}$. Third, the proton gradient potentially formed by

341   the hypothetical ETC does not require transferring H^+ from one side to the other, while the

342   mitochondrial ETC creates a proton gradient by transferring H^+ from the matrix to the

343   intermembrane space.

344   For the origins of life, an ETC formed by inorganic expansively autocatalytic cycles could be

345   important for several reasons. First, it does not require complex molecules, so it was more likely

346   to arise spontaneously. Second, it could provide a gradient to drive other processes, acting as an

347   energy source. Third, expansive autocatalysis could make it easier for the process to persist given

348   the loss of components in permeable compartments. Finally, it could be a prototype or

349   "template" for later, more complex ETCs to evolve upon. This is because prebiotic natural

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

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

352