Systems Chemistry

DOI: 10.1002/anie.200804565

# An Examination of the Role of Autocatalytic Cycles in the Chemistry of Proposed Primordial Reactions**

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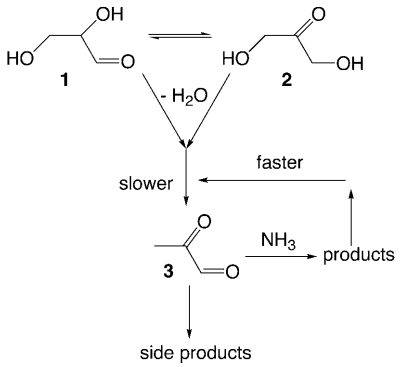
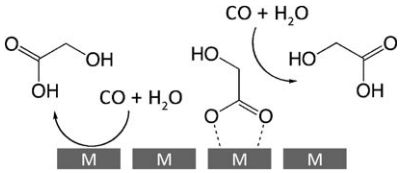
The search for chemical processes that might lead to self-organization under potentially prebiotic conditions has not yet yielded a compelling set of experimental clues for how life on earth could have emerged from chemical matter.[1,2] Autocatalytic cycles figure prominently in most discussions of the chemical origin of life. When such cycles involve small organic molecules, their role has traditionally been envisioned as a means of stocking the "prebiotic broth" with starting materials for the subsequent building of more complex biomolecules. Another school of thought proposes that simple autocatalytic cycles might themselves be responsible for a primitive metabolic system that might have preceded the development of informational polymers such as enzymes.[3,4] For example, models based on the chemistry of thioesters,[5] peptides,[6] and sugars[7] have been proposed as precursors to the RNA world. In a recent reworking of a chemoautotrophic origin of life model, "autocatalytic feedback" through ligand-accelerated catalysis has been proposed as a means of reproduction for the so-called "pioneer organism".[3b]

Herein, assumptions explicit and implicit in proposals for the importance of autocatalytic reaction networks in prebiotic chemistry prior to the development of enzymes are examined. As noted by Orgel,[2] a key point is to ascertain whether such cycles could persist over time—and therefore potentially play a meaningful role in the emergence of self-organization. An evaluation must be made not only of general chemical plausibility but also of the efficiency and the specificity of proposed pre-metabolic cycles in a defined environment. This work clarifies an important difference between autocatalytic and autoinductive behavior, and demonstrates that only truly autocatalytic cycles exhibit the critical properties that endow persistence to a proposed prebiotic reaction cycle. This work also helps to delineate the experimental challenges that such models must meet and may guide the search for realistic model chemistry.

Autoinductive reaction cycles have been invoked in two recent models for prebiotic chemistry shown in Scheme 1 and Scheme 2, the "sugar model" introduced by Weber[7b] and Wächtershäuser's "pioneer organism model".[3b] While the goal of this work is not a critical assessment of the chemical plausibility of either model, these two cases help to illustrate features of such cycles that are general, regardless of the particular chemistry invoked. Weber suggests that the rate of formation of pyruvaldehyde from glyceraldehyde is enhanced by an unspecified product of the triose–ammonia reaction (Scheme 1). Wächtershäuser proposes that a reaction product could bind as a ligand to a catalytic metal center and increase the catalytic activity for a rate-determining step in a pre-enzymatic metabolic pathway. However, neither model outlines the details of the mechanism through which these networks might lead to a system that could self-replicate, self-organize, convey heritable properties, and evolve.




***Scheme 1.*** "Sugar model" proposed in Ref. [7b].




***Scheme 2.*** Ligand-accelerated catalysis as described in Ref. [3b].

The generally accepted experimental signatures of an autocatalytic process include: a) observation of an enhancement in reaction rate with one or more reaction products added to the reaction vessel, and b) observation of a temporal product concentration profile that exhibits a sigmoidal shape. More precisely, an autocatalytic reaction is defined as a system in which a reaction product serves as a catalyst for its own production. This definition associates an autocatalytic reaction with the process of self-replication, which is essential to the origin of life. In this respect autocatalysis must be distinguished from autoinduction, where a reaction product or side product accelerates the rate of a kinetically meaningful step of a reaction sequence without directly producing more of itself. Autoinductive processes may exhibit kinetic signatures similar to autocatalytic processes.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804565.

A quantitative clarification of the critical difference between autoinduction and autocatalysis is provided by consideration of the reaction networks presented in Scheme 3. Each case outlined in this Scheme describes the net reaction stoichiometry of **A** + **B** → **C**. The simple catalytic reaction of Case i (Scheme 3a) is supplemented in each of the further cases by inclusion of a second cycle involving a type of enhanced rate process.

Case ii (Scheme 3b) shows the simple catalytic reaction coupled to a second cycle in which an interaction between product **C** and substrate **B** gives an activated substrate **B′** that reacts with the same catalytic intermediate **int** to form **C** at a faster rate than in the simple catalytic cycle. This product-enhanced network is autoinductive and is reminiscent of the "sugar model" proposed by Weber (Scheme 1).[7b]

Case iii (Scheme 3c) couples the simple catalytic cycle to a second cycle in which the reaction product **C** interacts with the original catalyst (rather than with substrate) to produce an improved catalyst (**cat′**) in the second cycle involving a new catalytic intermediate **int1**. This network has the features of "ligand-accelerated catalysis" outlined by Wächtershäuser (Scheme 2).[3b]

Case iv (Scheme 3d) illustrates the case of a truly autocatalytic reaction network. In this case product **C** becomes a catalyst in a new cycle for its own production. Once product **C** is present, the autocatalytic route can proceed independently of **cat**, the original catalyst for the simple network.

In addition to the reactions shown in Scheme 3, another feature is considered critically important for evaluating the plausibility of prebiotic networks, that of degradation processes. First, there is the possibility that the desired product **C** may react further, essentially irreversibly, to form either desired or undesired products [Eq. (1)]; second, there is the possibility that the catalyst **cat** in the primary catalytic cycle may undergo irreversible degradation to form an inactive species **X** over time [Eq. (2)]. Each of these features represents a challenge to the robustness of the reaction network for maintaining a viable concentration of the desired product **C** over time.

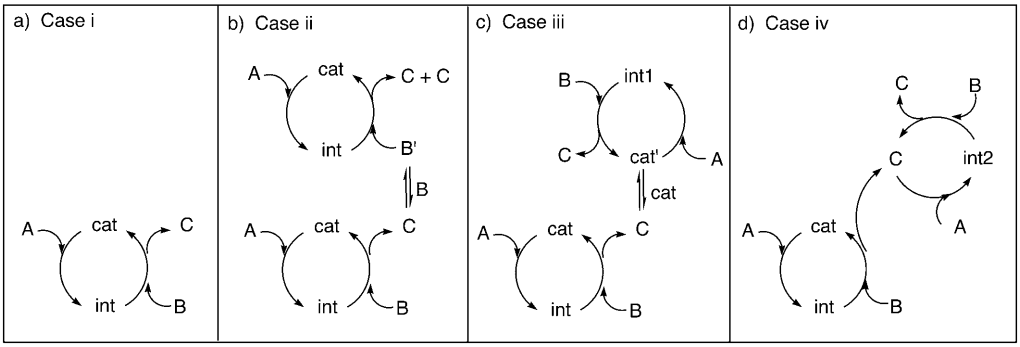
$$\mathbf{C} \xrightarrow{k_d} \mathbf{D} \quad (1)$$

$$\mathbf{cat} \xrightarrow{k_x} \mathbf{X} \quad (2)$$

The behavior of the reaction networks shown in Scheme 3 may be compared by carrying out reaction simulations,[8] by employing appropriate kinetic parameters for each of the cases in Scheme 3. The parameters chosen for the simulations presented here (see the Supporting Information) describe a general cycle in which a rapid equilibration of intermediate **int** results from the strong interaction between **A** and **cat** (saturation kinetics) followed by rate-limiting reaction of **int** with substrate **B**, as in Michaelis–Menten kinetics. The overall reaction is strongly driven to **C** such that high conversions of **A** and **B** may be obtained.

For the two autoinductive cases (Scheme 3b and c), product-forming rate constants $k_2'$ and $k_2''$ were chosen that are ten-fold greater than $k_2$, the rate constant for the simple catalytic network of Scheme 3a, to simulate rate enhancement owing to product participation. The rate constant for the autocatalytic network of Scheme 3d is chosen to be identical to that for the simple catalytic pathway and thus ten-fold smaller than those for the autoinductive pathways. The rate constants for the degradation processes of Equations (1) and (2) that were employed in simulations of all four cases were chosen to simulate slow degradation of product and catalyst, as compared to the rate of the main reaction cycles. Units for the rate constants are chosen arbitrarily to give conditions of rapid pre-equilibrium binding relative to slow product formation rates. Therefore the time axis in plots showing concentration profiles obtained from these simulations may be considered as having arbitrary units. The reaction stoichiometry **A** + **B** → **C** applies to all of the cases shown in Scheme 3, and therefore rate constants chosen for simulations of these networks must obey relationships set by the equilibrium condition, in keeping with the principle of microscopic reversibility, even when reactions are carried out far from equilibrium[9] (see the Supporting Information). Values for the kinetic parameters are not chosen to evaluate the specific chemical plausibility of prebiotic proposals, but simply to provide a plausible comparison of the features of autoinductive and autocatalytic pathways. As noted in the discussion of the simulation results, a wide range of values of kinetic parameters may yield comparable results.

The simulation results in Figure 1 consider the four cases described above under conditions such as would be found in a stagnant pool containing finite concentrations of substrates **A**, **B**, and catalyst **cat**. In this scenario, the pool functions as a




***Scheme 3.*** Reaction networks for the net reaction **A** + **B** → **C**. a) Case i: simple catalytic cycle; b) Case ii: simple catalytic cycle plus product-enhanced cycle; c) Case iii: simple catalytic cycle plus ligand-accelerated cycle; d) Case iv: simple catalytic cycle plus autocatalytic cycle.

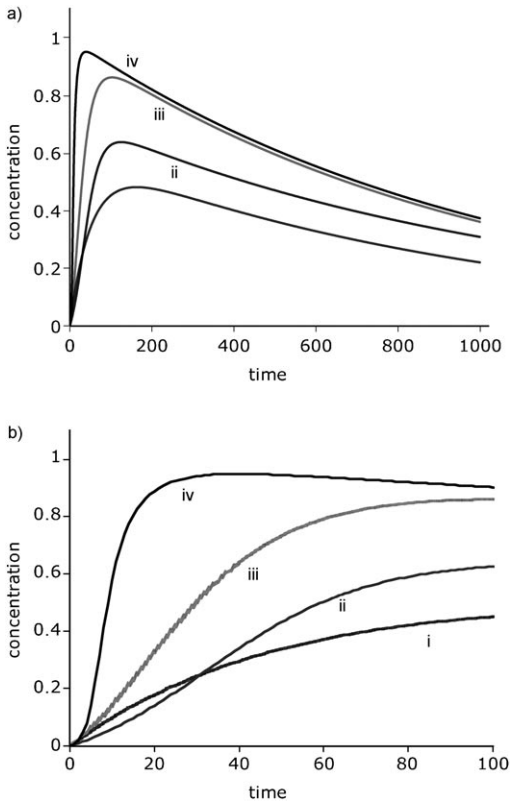



***Figure 1.*** Concentration of product **C** as a function of time in reaction simulations of the four cases in Scheme 3, coupled with the degradation processes of Equations (1) and (2) under conditions of a batch reactor. $[\mathbf{A}]_0 = 1$ M; $[\mathbf{B}]_0 = 1.2$ M. a) extended reaction times; b) early reaction times highlighting maximum in [**C**].

batch reactor where no mass flow is permitted in or out of the system. Figure 1a follows the reaction to longer reaction times as erosion of **C** becomes significant, while Figure 1b highlights the reaction profile at short reaction times where the yield of product **C** is maximized.

Figure 1 shows that Cases ii and iii, the autoinductive product-enhanced and ligand-accelerated networks, both show significant improvement of rate and maximum yield of product **C** compared to the simple catalytic Case i. This enhancement is rationalized by the rate constants $k_2'$ and $k_2''$ for product formation being ten-fold greater for these product-enhanced pathways compared to $k_2$ for the simple catalytic pathway. The autocatalytic pathway of Case iv shows an even greater rate enhancement, with rapid and almost quantitative formation of **C**, even though its rate constant is an order of magnitude lower than those for the autoinductive routes of Cases ii and iii. This feature outcome highlights the hallmark of a true autocatalytic reaction: each turnover increases the concentration of catalyst within the cycle, with a concomitant increase in rate and yield, even for modest values of the rate constant.

Both the autoinductive (Cases ii and iii) and the truly autocatalytic (Case iv) reactions exhibit sigmoidal profiles at early reaction times (Figure 1b). It is clear, however, that neither the simple catalytic cycle nor any of the product-enhanced processes can sustain a concentration of product **C** in a stagnant pool with finite resources in the face of persistent degradation processes (Figure 1a). Application of different values for the kinetic parameters can alter the time frame over which this degradation occurs but cannot alter the final outcome.

A second scenario of potential prebiotic relevance is one in which the stagnant pool is replaced with an open system where nutrients are continually supplied at a low concentration level to a pool containing the catalyst.[10] Simulations based on this scenario were carried out for the four cases presented in Scheme 3, again including the catalyst and product degradation terms of Equations (1) and (2). The results are presented in Figure 2.

At very early reaction times under these conditions, there is little distinction between the four different reaction networks. For the catalytic cycle of Case i and the two product-enhanced cycles (Cases ii and iii), net production of **C** reaches a peak and then decays, even though the supply of substrates **A** and **B** remains constant. By contrast, the significant advantage of the true autocatalytic pathway compared to the autoinductive reactions of Cases ii and iii is highlighted under these open mass flow conditions. Case iv shows accelerated production of **C** over time, even coupled with

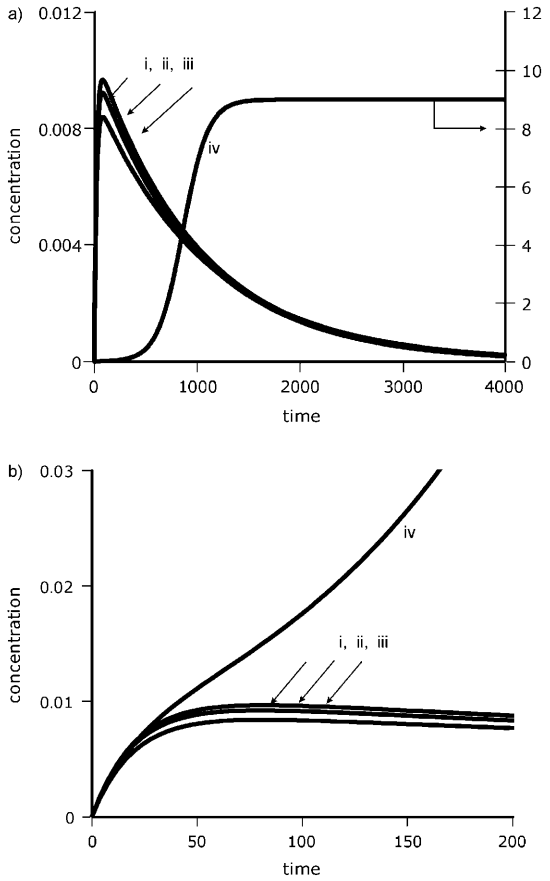



***Figure 2.*** Concentration of product **C** as a function of time in reaction simulations of the four cases in Scheme 3, coupled with the degradation processes of Equations (1) and (2) under conditions of a constant input of nutrients to a pool containing the catalyst **cat**. $[\mathbf{A}] = [\mathbf{B}] = 0.1$ M (fixed). a) extended reaction times; note the change in scale for the autocatalytic concentration profile for Case iv; b) early reaction times.

catalyst and product degradation pathways. With a constant input of nutrients, this system eventually reaches a steady-state where the continual autocatalytic production of **C** is balanced by its consumption in side reactions; under the conditions of this simulation, this sustained production provides a steady-state concentration of **C** that is nearly three orders of magnitude greater than the maximum amount of **C** achievable by the autoinductive pathways—even though the rate constant for this pathway is an order of magnitude smaller.

Notably, the trends shown in Figure 2 for autocatalytic versus autoinductive reaction pathways are general, and are not dependent on the magnitude of the rate constants chosen for the simulations. Neither of the autoinductive pathways of Cases ii or iii can ultimately persist, even given a much slower catalyst degradation pathway, as for Case iii (illustrated in the Supporting Information) using a value of the catalyst degradation rate constant one million times less than that used in the simulation shown in Figure 2. By the same token, stronger catalyst stability constants do not permit persistence, as for Case iii (illustrated in the Supporting Information) with a million-fold increase in the catalyst-ligand binding constant.

The results of the reaction simulations presented above highlight a number of concepts important for consideration of reaction networks proposed to rationalize the chemical origin of life, concepts that are general to the nature of the network and are independent of the specific chemical reactions proposed in such networks. In a stagnant pool where nutrients are not replenished, autoinductive cycles may enhance the rate of production of product **C** as well as increase its maximum concentration, provided the kinetically meaningful rate constant for the autoinductive cycle is greater than that for the base catalytic cycle. More significant rate amplification is possible for true autocatalysis under these conditions, even when more modest rate constants are exhibited by the autocatalytic cycle. However, the influence of degradation processes is especially profound under such conditions where further nutrients are not supplied to the pool. In this case the advantage in rate and yield offered by any and all of the enhanced networks disappears. Producing more of product **C** at a faster rate does not prevent its decomposition process from being egalitarian: ultimately the concentration profile converges for all the networks of Scheme 2 as **C** decays (see Figure 1 a). This suggests that the question of robustness of proposed prebiotic chemical reactions must take environmental conditions into account: product enhanced reactions that proceed at higher rates to give higher yields may not be highly beneficial in closed systems with an inexorable decay of product or catalyst.

This result has implications for the experimental results of the "sugar model" proposed by Weber; in that case, a reaction product appeared to act autoinductively to increase the rate of production of pyruvaldehyde, which eventually underwent degradation. Any biosynthetic advantage claimed for autoinductive pyruvaldehyde production is not supported by these results. For example, an improved catalyst for the simple catalytic cycle of Case i could play a similar evolutionary role in the absence of any autoinductive effect. An argument for the prebiotic significance of a reaction is made neither more nor less compelling by proposing an autoinductive rate enhancement.

Degradation reactions are also important in the second scenario treated here, where a constant supply of nutrients is available to the catalyst pool. Under these conditions, however, the simulations highlight an important distinguishing feature of true autocatalysis. While both the product enhanced and ligand-accelerated autoinductive cycles can increase rate in the presence of product, each cycle is also intrinsically linked to maintaining a viable concentration of **cat**. Loss of **cat** through a degradation process proves fatal to both the product-enhanced and the ligand-accelerated cases as well as to the case of the simple cycle. Even though the supply of nutrients remains constant, an inexorable decay of **cat** prevents these cycles from persisting.[11] This conclusion is general regardless of the chemical nature of the species **cat** (or **cat′**).

Comparison of the results for these cycles with that for the true autocatalytic pathway of Case iv (Scheme 3) reveals the key feature that distinguishes the latter: since the product **C** acts as a catalyst to produce more of itself, its cycle rapidly becomes independent of the original catalytic cycle and thus can withstand degradation of its original catalyst. This pathway may persist over time as long as conditions are such that the rate of autocatalytic production of **C** equals or surpasses the net rate of consumption of **C**. This is in fact the situation revealed by the sigmoidal plot for the autocatalytic case in Figure 2 b. A nonzero concentration of **C** is assured as the system ultimately achieves a steady state in net production of **C** through the autocatalytic cycle. By contrast, the autoinductive cycles of Cases ii and iii (Scheme 3) cannot continue to operate in the absence of **cat**, even if the concentration of product **C** is high.

Confusion between product-enhanced rate (as illustrated by Cases ii and iii) and the true self-replication of autocatalysis is common in the literature and may arise from the similar kinetic features of the two types of processes. For example, Yoon and Mirkin[12] recently asserted that sigmoidal product formation curves are significant in an acyl transfer reaction using a zinc(II)-based supramolecular catalyst system because they are "reminiscent" of autocatalytic and self-replicating systems, such as those reported by Rebek and co-workers.[13] However, on closer examination, the sigmoidal profiles observed in that case may be attributed to an in situ catalyst activation process similar to Case iii, and is not related either to self-replication or to PCR-type amplification.

The nonpersistence inherent in autoinductive reaction networks is important for discussing the model for the pioneer organism developed by Wächtershäuser.[3b] The increasing product (ligand) concentration is described as a form of "autocatalytic feedback" that is claimed to make the system more and more independent from its environment. The results presented here demonstrate that because such ligand-accelerated processes remain intrinsically bound to the fate of the primary catalyst, they remain dependent on the robustness of the original catalyst. If the ligand can help to protect the catalyst, this may improve the evolutionary chances of such a model, but this must be treated as a separate mechanistic feature.

Most recently Wächtershäuser has proposed a refinement of his model that combines ligand feedback with autocatalytic cycles such as the reductive citric acid cycle or a simpler protometabolic variant thereof;[14] however, no experimental results have been reported, and synthesis of the aminoacylnucleotide conjugates, which would appear to be an essential feature of the proposal, has not been described.

Interesting additional complexity arising from truly autocatalytic reactions may be found in a reciprocal model where two complementary templates cooperate, each to enhance the formation of the other. Unlike many current models relevant to the question of the origin of life, this cross-catalytic case has experimental verification in the work of Kassianidis and Philp,[15] with Diels–Alder reactions that serve as parallels with nucleic acid replication and represent pioneering work in the emerging area of "systems chemistry"[16]

An important distinction between autoinductive processes and true autocatalysis has been clarified here, and is revealed to be essential to the ability of a catalytic network to persist in the face of disruptions that challenge the activity and selectivity of the reaction network. The implicit assumption that product-accelerated activity is a hallmark for reactions leading to self-organization, and that product-enhanced activity with plausible prebiotic substrates endows such reactions with the potential to develop directly into modern biosynthesis, has been examined. A link between autoinductive processes that deliver the simple imperative "make product faster" and the complex processes of replication that might achieve self-organization and evolution, is not supported by experimental results. Further experimental evidence for truly autocatalytic reactions and reaction networks of potential prebiotic significance is therefore of great interest.

Received: September 16, 2008
Revised: October 22, 2008
Published online: December 3, 2008

**Keywords:** autocatalysis · autoinduction · ligand acceleration · prebiotic chemistry · systems chemistry

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