

# DID REFLEXIVE CATALYSTS DRIVE CHEMICAL EVOLUTION?

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**Abstract.** High-energy starting materials and energy sources on the primitive earth would have generated abundant and varied organic molecules of small or medium size. It is questionable, however, whether ordinary chemical evolution could have produced information-carrying polymers. The end point might have been a fixed steady state if some form of autocatalysis had not intervened. Autocatalytic synthesis is possible for small molecules as illustrated by the formose reaction, in which glycolaldehyde condenses with formaldehyde to form sugars, and resulting tetroses may cleave into two molecules of glycolaldehyde. This and other 'reflexive catalysts', some functioning in molecular aggregates, may have energized chemical evolution and carried it to a level at which RNA or an RNA analog could replicate itself.

Probably nobody studying the origin of life now believes that the present DNA/RNA/protein system was the original form of life. A more modest theory postulates a molecule of RNA which acted both as an enzyme and as a template for its own replication. Even this poses obstacles to a spontaneous origin from the primitive environment, summarized by Joyce (1989), requiring for example abundant and diverse 'catalytic materials' (Eigen and Schuster, 1978).

Lederberg (1960), Spach (1984), and others have suggested that nucleic acids were preceded by a simpler type of template polymer, but Joyce concedes that ordered replication of any linear polymer seems unlikely without controlling enzymes. And difficulties arise even earlier in chemical evolution. Unstable starting materials like HCN and H<sub>2</sub>CO would have led nowhere until they could be used promptly. As they condensed to larger molecules such as sugars, random combination would have formed many isomers, precluding the emergence of a few dominant species among the products (Shapiro, 1988).

Starting from small molecules such as amino acids, many spontaneous reactions would be possible, but products would be limited by probability. Always in an approximate steady state, such a system would eventually reach a state in which new molecules were so rare that evolution would cease. In the view of some authors, this end point would occur before macromolecules were numerous (Hulett, 1969; Brooks and Shaw, 1978; Keosian, 1978) and without producing the abundance of uniform monomers needed for a regular polymer (Shapiro, 1984).

A steady state, however, is not an equilibrium. The 'primitive soup' was certainly a system of high potential, ready to evolve further given the right catalysts. The importance of catalysis has always been recognized in discussions of chemical evolution (e.g., speculations by Cairns-Smith, 1966, 1982; studies up to 1985

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summarized by Ferris, 1985), but interest has centered on clays and other minerals. It does not appear that mineral catalysts could evolve in parallel with organic compounds; as a fixed part of the environment, they might determine the final state, but that end point would still be approached asymptotically and perhaps early.

Very little attention has been paid to small organic catalysts, whose activity is known mainly from complex biochemical systems. So simple a molecule as ethanol is an effective catalyst by itself under some conditions (Langenbeck, 1950). In an ordinary catalytic role, however, even organic catalysts would become merely part of the final steady state.

A self-reproducing system like RNA would clearly break out of the steady state, but a transitional system is needed before RNA or an RNA-analog could plausibly arise (Joyce, 1989). Melvin Calvin (1956, 1969) suggested that the chemical environment may have been ordered by what Joyce terms 'non-instructed processes'. That account postulates the early intervention of autocatalysis. This might occur not as direct autocatalytic synthesis, but as a reflexive catalytic cycle. Calvin pointed out that iron-porphyrin can catalyze oxidations, and that oxidation is required in the condensation of  $\delta$ -laevulinic acid to protoporphyrin. Of the newly synthesized protoporphyrin, some would acquire iron atoms to make more iron-porphyrin molecules, which in turn would catalyze more synthesis of protoporphyrin in a branching chain reaction.

The term reflexive catalysis encompasses a variety of phenomena, many hypothetical, all tending to generate products at an exponential rate (Allen, 1957). In Calvin's porphyrin example a catalyst facilitates a step in its own synthesis, and subsequent steps then proceed spontaneously, if slowly. This would seem to be the most effective form of reflexive catalysis because, if the catalyst is readily restored or reactivated, it can repeatedly catalyze not only a necessary step in its own synthesis, but other similar reactions. But this may not be the most probable form of reflexive catalysis.

Another general example is a reaction that has two identical molecules on one side of the equation. This constitutes a branch-point at which the yield of subsequent products is doubled. In the formose reaction, the only documented example of simple autocatalytic synthesis, glycolaldehyde condenses readily with formaldehyde to yield trioses and higher sugars, and the tetroses may cleave to two molecules of glycolaldehyde, doubling the number of condensation centers in each cycle (Mizuno & Weiss, 1974; Joyce, 1989).

Other examples of this form of autocatalysis have been proposed. Redox dismutation yields two identical molecules or radicals at the intermediate oxidation level (King, 1980) and might enable an autocatalytic process. Saygin (1981) studied the phosphorylation of ADP by carbamyl phosphate catalyzed by  $\text{Ca}^{2+}$  or  $\text{Ba}^{2+}$  and pointed out that if this were preceded by a disproportionation of ATP and AMP the amount of ATP would double in each cycle as long as AMP and carbamyl phosphate were supplied. Saygin did not specify a complete reaction system.

In more complicated examples of reflexive catalysis two catalysts might each facilitate the other's critical synthetic step. This is analogous to the replication of DNA if that could occur without other organic catalysts and, at a higher complexity, to the replicating 'hypercycle' (Eigen and Schuster, 1978). Conceptually, it would be appropriate to apply the term to a membrane molecule that physically maintained the integrity of droplets in which it was synthesized. Finally, every organism is a grand example of reflexive catalysis in which each constituent facilitates reproduction of the whole system and hence of itself.

Calvin stated that the porphyrin system would generate the catalyst at an exponential rate, but he may not have appreciated the extent of the transformation it could have initiated. At that moment and for an important interval, instead of nearly constant reaction rates and asymptotic concentration changes, at least one reaction would increase. Not only would synthesis of the catalyst and its immediate precursors accelerate; so too would synthesis of all by-products. At first this cluster of reactions would be unique, but they might start a branching chain reaction of wider scope which can be explained as follows:

As long as organic compounds are on the increase, the opportunities for catalytic interactions also increase and hence the probability of reflexive catalysis. For this reason alone the probability of emergence of a reflexive catalyst is greater at time B than at an earlier time, A. If a reflexive catalyst occurred at time A, it would generate new products and increase still more the likelihood of catalytic interactions at time B. The first reflexive catalyst, or branching chain reaction, would increase its catalyst and any by-products exponentially, and if one of the by-products gave rise to a second reflexive catalyst, this would constitute a secondary branching, compounding the autocatalytic process.

*With each added reflexive catalyst, new molecules would be possible and evolution as a whole, instead of drifting toward stagnation, would be reactivated.*

The first reflexive catalyst, conceivably iron-porphyrin catalyzing an oxidation, would probably reproduce as a simple cycle; i.e., dependent on only one reflexive catalyst. Later cycles, and even the first, might all be more complicated. A second reflexive catalyst, effecting, say, a transphosphorylation required in its synthesis, might also employ iron-porphyrin to catalyze a required oxidation step. Eventually, a complicated web of metabolism might be possible. The most advanced reactions would require molecular aggregates somewhat like Oparin's coacervates (Oparin, 1938).

Known instances of autocatalytic organic synthesis other than of the biopolymers are restricted to the formose reaction (Decker and Speidel, 1972; Mizuno and Weiss, 1974), and this may have sufficed to start the branching chain reaction. Other autocatalytic syntheses may be unknown only because few attempts have been made to discover them; if inefficient, their presence would not be easily detected, though they could still be important in evolution. Common laboratory methods generally allow only batch reactions which quickly go to completion or equilibrium, giving little opportunity for unanticipated autocatalytic side reactions to emerge. In contrast,

a nearly steady-state system fueled by high-energy starting compounds and permitting a long residence time would be exquisitely sensitive to autocatalysis. The difference is like that between simple and compound interest. If the reflexive catalyst were a one-percent by-product increasing at a relative rate of 1.01, the amount of catalyst would be one percent when the reaction ended. But if the products of the first run were recycled with fresh reagents, the reflexive catalyst would become more significant. In a steady-state system resembling the primitive ocean, a relative rate of 1.01 would allow the autocatalytic reaction eventually to dominate.

At least two experimental approaches are better designed to reveal reflexive catalysis than familiar laboratory procedures. One is to take any simple organic compound with known catalytic activity, *however feeble*, and search for a synthesis in which the catalyst could facilitate an important step followed by spontaneous completion. Reaction cycles that double at a branch-point should be subjected to varying conditions that might make them autocatalytic like the formose reaction. This method would detect only simple cycles, which may have been exceptional in chemical evolution.

A less rational approach that casts a wider net would employ a steady state reaction mixture with high chemical potential and multiple products, monitored for any change in product concentrations. Since a reflexive catalyst might begin as a single, improbable molecule and increase slowly, a long time would doubtless be needed; but high concentrations would speed the process. One set of such experiments was conducted unsuccessfully for a 2-year period with relatively crude methods (Allen, 1965).

What molecules could thus have driven chemical evolution? Aside from glycolaldehyde in the formose reaction, the most specific proposal is ATP in the system studied by Saygin (1981), but ATP is already a complex molecule. Redox cycles and the porphyrin system of Calvin have not been tried. The more advanced catalysts would include some of the simpler catalysts and cofactors known in contemporary biochemistry. For example, thiamine and pyridoxal are effective catalysts in their own right (Metzler *et al.*, 1954; Breslow, 1958). Those with no activity by themselves may have started as members of a mutually catalytic network, perhaps functioning in molecular aggregates or droplets. Known catalysts may be only a small residue of those that once existed. Just as proteins appear to have taken over the functions of primitive RNA catalysts, so RNA catalysts may have taken over the functions of more primitive reflexive catalysts. Simple catalysts now remaining may have proved the most difficult to incorporate into, or replace with, RNA or protein. Primary development of purines and pyrimidines in a system of reflexive catalysts would have laid the synthetic foundation for subsequent production of RNA.

The possibility of autocatalytic reproduction by simple molecules thus presents, if not the required transitional system preceding the RNA-analog, at least a mechanism to keep chemical evolution going from an early stage when it might otherwise have slowed or ceased. When self-replicating macromolecules did arise, they may have used not only a ready supply of chemical building blocks, but also an established, self-reproducing system of organic catalysts.

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