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AUTOCATALYSIS AND ALL THAT[·]

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> "The search for the chemistry of life's origin is a search for potentially primordial autocatalytic *cycles*." (Eschenmoser, 2007a)

Autocatalysis is an immensely popular concept and a term which is frequently encountered in origin of life literature. Much of this interest and the activity related to it lies in the realm of theory and computation, particularly with reference to complex systems and the origins of homochirality. Some controversial aspects of the latter subject have recently been discussed by Blackmond (2009). However, autocatalysis is both real and important. It is encountered in such familiar phenomena as the maintenance of a flame or the occurrence of an explosion. We are, in fact, surrounded by examples of autocatalysis in everyday life. However, the subject has been the focus of an unusual degree of interest in the area of origin of life research.

Autocatalytic copying of template information has been explored with polynucleotides, several kinds of polynucleotide analogues and even with polypeptides, at various information levels and with varying degrees of success. For all these cases the role of molecular complex formation under the directing influence of hydrogen-bonding and other forms of weak (non-covalent) interactions is familiar and understood. Even small-molecule autocatalytic replicators, such as those studied by Rebek and colleagues, work on the basis of the same principles and contain a binding region which operates as a template (Tjivikua *et al.*, 1990; Wintner and Rebek, 1996 and references therein). These phenomena have been modeled experimentally. In contrast, another - largely hypothetical - example of autocatalysis has seen something of a resurgence of interest recently.

[·] Dedicated to Professor Dr. Albert Eschenmoser, on the occasion of his 85th birthday.

While the general phenomenon of catalysis by small molecules is a familiar phenomenon in organic chemistry, there appear to be only a few examples known of autocatalytic reactions involving small molecules of possible *prebiotic* interest. Complex systems such as the Belousov-Zhabotinsky reaction (Noyes, 1990) are therefore not considered here, although it is frequently mentioned as an example of self-organizing autocatalysis of relevance to origins of life (see, for example, Lazcano, 2010). An example of a very simple autocatalytic reaction with interesting morphological properties of potential prebiological relevance has been based on the formation of fatty acid micelles. The micelles were generated via the hydrolysis of a fatty acid ester and catalysis of the reaction was shown to result from the uptake of ester into the micelles (Bachmann *et al.*, 1992). Weber has also inferred autocatalysis in the reaction of triose sugars with ammonia (Weber, 2007).

The most well-known example of an autocatalytic reaction of possible prebiotic interest, however, is the familiar formose reaction. First described by Butlerow (1861), the mechanism of this base-catalyzed autocatalytic condensation of formaldehyde was clarified by Breslow (1959). A series of publications by Weiss, Socha and co-workers (Socha *et al.*, 1980 and references therein) examined a number of aspects of the reaction. However, a claim that the occurrence of the formose reaction depends on the presence of impurities (presumably traces of carbohydrate) was reinvestigated by Schwartz and de Graaf (1993), who concluded that this view was not correct. The autocatalytic reaction does not require strongly basic conditions and is catalyzed by a number of minerals (Gable and Ponnamperuma, 1967; Reid and Orgel, 1967; Cairns-Smith et al. 1972; Schwartz and de Graaf, 1993). However, this exponentially expanding reaction system is always destructive if allowed to continue.

The initial supply of formaldehyde is consumed and converted to a highly complex mixture of products. Perhaps fortunately for biology, the formose reaction is an exceptional example of autocatalysis, since *all* products of the reaction system can interact with the starting material to contribute to its ultimate destruction. The reaction is frequently described as a possible prebiotic source of carbohydrate, but due to the usual results obtained, this would not seem to be a valid suggestion.

Successful approaches to carbohydrate synthesis from formaldehyde have *avoided* the autocatalytic reaction itself by the use of conditions which suppress it, as in the first such demonstration by Eschenmoser and colleagues, which utilized glycolaldehyde phosphate as a starting material. In the presence of formaldehyde and under basic conditions, aldopentose diphosphates were preferentially synthesized, including 33% of ribose-diphosphate (Müller *et al.*, 1990). Recent examples of synthetic strategies which also avoid autocatalysis include the application of high concentrations of borate (Ricardo *et al.*, 2004), of silicate (Lambert *et al.*, 2010) and possibly also the earlier use of magnesium and lead hydroxides as catalysts (Zubay, 1998).

A rather different proposal concerning the possible occurrence of autocatalysis by small molecules seems first to have been muted more than fifty years ago. The concept described as “reflexive catalysis” appears, at first glance, to be fairly simple (Allen, 1957; Calvin 1969). In outline, it involves the idea that the product of a synthetic reaction chain might exert a catalytic influence on an earlier reaction in the chain and thereby catalyze its own formation.

The suggestion is that the reaction chain producing the catalyst would consequently “out-compete” other reaction chains. The concept therefore implicitly infers the emergence of exponential growth. Such an idea is appealing, but we may ask how common such effects actually are. The short answer seems to be that they are not encountered very frequently. Even in the realm of template-directed autocatalysis, using carefully designed systems, exponential growth is difficult to achieve (Kiedrowski, 1993).

The idea of autocatalysis via a metabolic cycle is a rejuvenated version of reflexive catalysis. In a review entitled “The implausibility of Metabolic Cycles on the Prebiotic Earth” Leslie Orgel - with characteristic succinctness - remarked: “Lack of specificity rather than inadequate efficiency may be the predominant barrier to the existence of complex autocatalytic cycles of almost any kind.” (Orgel, posthumous, 2008). Nevertheless, the subject of autocatalytic networks seems not to have lost its appeal. What apparently was a first version of the idea can be found in Ycas (1955) and has been revived once more by Shapiro (2006). It is not clear what, if any, evidence exists which would underpin such a process. Experimental modeling of ideas by the sometimes tedious route of the careful synthesis of candidate compounds and the directed testing of specific molecular interactions, as has been employed with remarkable success by Albert Eschenmoser (see 2007a and 2007b for some general discussion of principles) has produced spectacular results (for example, Bolli *et al.*, 1997). In contrast, vague invocations of the importance of self-organizing networks have thus far offered little in the way of directions for future research. It is probably no accident that biology makes no use of small molecule autocatalysis, but of specific interactions driven by several kinds of weak bonding. This phenomenon includes, of course, the binding sites and activities of enzymes.

REFERENCES

G. Allen, *American Naturalist*, 1957, **91**, 65.

P. A. Bachmann, P. L. Luisi, and J. Lang, *Nature*, 1992, **357**, 57.

D. G. Blackmond, *Angew. Chem. Int. Ed.*, 2009, **48**, 2648.

M. Bolli, R. Micura, and A. Eschenmoser, *Chemistry & Biology*, 1997, **4**, 309.

R. Breslow, *Tetrahedron Lett.*, 1959, **21**, 22.

A. Butlerow, *Justus Liebigs Ann. Chem.*, 1861, **120**, 295.

G. Cairns-Smith, P. Ingram, and G. L. Walker, *J. Theoret. Biol.*, 1972, **35**, 601.

M. Calvin, '*Chemical Evolution Towards the Origin of Living Systems on the Earth and Elsewhere*', Oxford University Press, London, 1969, Chapter 7.

A. Eschenmoser, *Chemistry & Biodiversity*, 2007a, **4**, 554.

A. Eschenmoser, *Tetrahedron*, 2007, **63**, 12821.

N. W. Gable and C. Ponnamperuma, *Nature*, 1967, **216**, 453.

G. Kiedrowski, 'Bioorganic Chemistry Frontiers Vol. 3', Springer-Verlag, Berlin Heidelberg, 1993, pp. 113-146.

A. Lazcano, *Origins Life Evol. BioSph*., 2010, **40**, 161.

J. B. Lambert, S. A. Gurusamy-Thangavelu, and K. Ma, *Science*, 2010, **327**, 984.

D. Müller, S. Pitsch, A. Kittaka, E. Wagner, C. E. Wintner, and A. Eschemoser, *Helv. Chim. Acta*, 1990, **73**, 1410.

R. M. Noyes, *J. Phys. Chem*., 1990, **94**, 4404.

L. E. Orgel, *PLoS Biol.*, 2008, **6**(1), e18.

C. Reid and L. E. Orgel, *Synthesis of Sugars in Potentially Prebiotic Conditions. Nature*, 1967, **216**, 455.

A. Ricardo, M. A. Carrigan, A. N. Olcott, and S. A. Benner, *Science*, 2004, **303**, 196.

A. W. Schwartz, *Chem. & Biodiversity*, 2007, **4**, 656.

A. W. Schwartz and R. M. de Graaf, *J. Mol. Evol.*, 1993, **36**, 10l.

R. Shapiro, *Quart. Rev. Biol.*, 2006, **81**, 105.

R. F. Socha, A. H. Weiss, and M. M. Sakharov, *React. Kinet. Catal. Lett.*, 1980, **14**, 119 and references therein.

T. Tjivikua, P. Ballester, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1990, **112**, 1249.

A. L. Weber, *Origins Life Evol. BioSph*., 2007, **37**, 105.

E. A. Wintner and J. Rebek, Jr., *Acta Chem. Scan.*, 1996, **50**, 469.

M. čas, *PNAS*, 1955, **41**, 714.

G. Zubay, *Origins Life Evol. BioSph.*, 1998, **28**, 13.