Towards synthetic self-replication

Constructing chemical systems capable of replicating themselves is an intermediate goal in the reductionist agenda. There is now a little progress to report.

If the properties of living things reflect only the properties of their molecular components, which appears to be the case, it is not sufficient merely to say so, however well founded the evidence for the assertion may be. At some stage, it is also necessary to demonstrate that it is possible to start with a suitable molecular mixture and to follow the replication of some molecular entity in (so to speak) the test-tube. The ideal, of course, would be to reconstruct the circumstances in which the first living things emerged, but that goal is a long way off, if only because so little is known of the original circumstances. But, meanwhile, may there not be simpler systems that demonstrate self-replication?

Indeed, it seems that there are. One of them, just described in print, is nothing less than a scheme for constructing synthetic micelles from polar molecules of sodium octanoate, filling them with the alcohol 1-octanol and using permanganate as an oxidizing agent to form the polar acid. According to Bachmann, Walde, Luisi and Lang (the first three from the ETH at Zurich , the last from the CNRS Institut Charles Sadron at Strasbourg), the micelles multiply in number as the reaction produces more membrane material (*J. Am. Chem. Soc.***113**, 8204; 1991). The only snag, as the system is set up, is that the micelles become progressively smaller as the reaction proceeds, hardly a fundamental difficulty.

The other approach to self-replication to have been tried seems inevitably to involve molecules capable of forming hydrogen-bonded complexes suggestive in many ways of the behaviour of nucleic acid molecules. Last year, Tjivikua, Ballester and Rebek from the Massachusetts Institute of Technology described a simple chemical reaction between an amino-adenosine and an aromatic ester whose product proved to be a catalyst of the coupling. Moreover, these molecules through hydrogen bonding proved to form dimers which, to the eye of the beholder (or at least the authors) have some of the characteristics of real nucleic acid polymers (*J. Am. Chem. Soc.* **112**, 1,249; 1990). The two molecules of each dimer are presumed to be held together head to toe.

The objectives of both exercises is the simulation of life, or at least of some aspects of it, but readers will not fail to be struck by the diffidence with which this ambition is suggested. Thus Tjivikua *et al.* drop a hint of what they are driving at with the statement, made delphic by the tense of the verb, that "[t]he ability of nucleic acids to act as templates for self-replication has been unique". At the end they are a little more explicit; they say that their system can, "at best", be regarded as "a primitive sign of life", and continue with the speculation that systems may be designed that will synthesize peptide molecules on a nucleic acid backbone which, they say, would "provide models for events that occurred some time ago".

In reality, those working in this intriguing field have no obligation to be arch about their work, especially when the results are as interesting as these. The autocatalytic character of the reaction is, of course, crucial. People who mix together hydrogen and chlorine will produce as much HCl as they wish. In the origin of real life, pathways of chemical synthesis involving auto-catalytic steps are likely to be preferred, while it has been found in the past six years or so that some RNA molecules have retained this property, presumed primitive but still useful for the functioning of some cellular machinery.

On this occasion, the reasons why the process is auto-catalytic become apparent. By dissociation, the dimers become a template on which the reactants can conveniently assemble. Each of the two reactants takes up, by hydrogen bonding, the position it would have in a dimer, whereupon the condensation that is the crux of the reaction is easily accomplished. At the very least, this will suggest useful pointers to those who brood about the properties of small RNA molecules involved in editing, splicing and auto-catalysis generally. That in itself is a good reason for not being arch. Indeed, there is much in the belief that the most immediate benefit of attempts to replicate the origin of life will be the understanding it brings of the more complicated processes in real cells.

The tricks that Bachmann *et al.* play with micelles are necessarily more complicated. The self-replication of molecules from a mixture of reactants becomes significant as a pointer to how life may have begun only when it has been shown that the process catalyses itself. But micelles are physical structures of molecules held together by forces of longer range than hydrogen bonding, and whose stability is sensitively determined by the medium in which they are immersed.

The working definition of self-replication is necessarily roundabout. Bachmann *et al.* say that the process must involve the multiplication of geometrically closed structures as a consequence of chemical reactions taking place within themselves. They adopt, in short, the principle that one of the essential features of all living things, from cells to mammals, is that they are separated by a well-defined boundary from the medium in which they live, and that their offspring are produced from within themselves as other geometrically closed structures (which may be eggs, not necessarily parental replicas).

For what it is worth, the single-layered micelle system made of sodium octanoate (in which the polar acid group is on the outside of the artificial membrane and immersed in water) is one of several. There are other systems consisting of reversed micelles, formed in organic solvents in which the polar acid groups are on the inside, containing water. This obviously simplifies the process of using more complicated reactions to generate micellar material; one of the systems described uses naturally occurring lipases as a means of controlling the production of octanoate (by the hydrolysis of the glycerol ester).

The results are suggestive, but not compelling, although for a simple reason. As the chemical reactions proceed, the number of micelles in suspension (measured optically) does increase much as the chemical reactions suggest they should. The difficulty, of course, is that each system is fated to have a limited life. In the reverse micelle systems (with the polar groups on the inside), the process must stop when the initial stock of microinjected material has been used up. And the same is bound to happen with the ordinary micelles in which the raw material for new membranes is internally packaged.

Even so, the next steps should be clear. The simple one-layer system cannot allow for the transport of raw materials from the exterior to the interior, which is what happens in real life. For that to happen, all the reactants must be soluble on both sides, which argues for a double layer (as in real life). But it should not be too difficult to construct such a system.

What will that mean? Nothing decisive, of course. Merely that another step in the origin of life has been shown to be feasible. But even reductionists often overlook the propaganda value of these demonstrations. Vitalism, after all, would still be rampant if Wohler had never synthesised urea.

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