Capturing Chemical Evolution in a Jar

A system of self-replicating molecules can now spin off a faster-multiplying "mutant" form

"IT'S ALIVE!" SCREAMED COLIN CLIVE, PLAYing the maniacal doctor in the 1931 film *Frankenstein*, when his monstrous patchwork of once-dead human anatomy first twitched with life. Julius Rebek, Jr., an organic chemist at the Massachusetts Institute of Technology, hasn't let out a eureka scream just yet. But he expects to see the day when his chemical brews might deserve one.

"My goal is to generate something that approaches what most people would call living," Rebek says calmly. At more cautious moments, he portrays his research team's aim as an attempt to "model evolution on the molecular level." In the past few years, he and his co-workers have captured the attention of origin-of-life researchers by developing a clever chemical system of molecules that, like DNA and RNA, can replicate. And on page 848 of this issue, Rebek and MIT colleagues Jong-In Hong, Qing Feng, and Vincent Rotello report adding to their system an additional feature of biological molecules: the ability to "mutate" into a form somewhat more efficient at replicating than the original.

Rebek doesn't shy from using such biological terms to describe his chemical creations. But some origin-of-life researchers downplay the parallels. While praising Rebek's contribution as "a very important initiative" in the broader effort to understand the chemical origins of life, nucleic acid chemist Albert Eschenmoser of the Swiss Federal Institute of Technology (ETH) in Zurich warns, "there should be no oversell of a dramatic concept like the synthesis of life." Chemical approaches like Rebek's may help uncover phenomena—such as the appearance of self-replicating populations of molecules—relevant to the molecular drama from which biology presumably emerged, he says, but only far more complex systems could be anything more than a metaphor for life.

But Rebek thinks that even a chemical brew quite different from the molecules of life as we know it can qualify as a new form of life if it exhibits behaviors such as replication, mutation, and evolution. Gerald Joyce, a molecular biologist and origin-of-life experimentalist at the Research Institute of Scripps Clinic in La Jolla who has been developing his own model evolutionary systems based on RNA molecules, endorses this unorthodox view of biology. "It is quite likely that life will be made in the laboratory by the end of the decade," he predicts with enthusiasm, and he bets that will be in Rebek's lab.

Even by those broader standards of life, though, Rebek has a long way to go. It was just 2 years ago that he and colleagues at MIT and the University of Pittsburgh reported in the *Journal of the American Chemical Society* that they had devised a two-component synthetic molecule that replicates itself. In a solvent, the two components—an imide ester and an adenine-containing amine—pair to form j-shaped products. These then replicate by serving as templates on which new ester-amine pairs line up, guided by hydrogen bonds similar to those that keep double strands of DNA together. The templates also catalyze the covalent union of the ester-amine pairs to form "offspring" molecules identical to their parents.

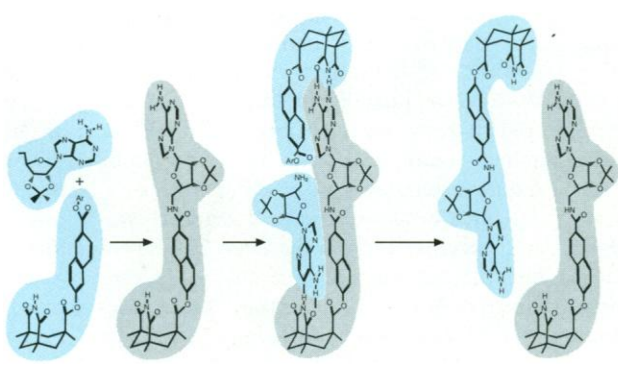
That was the first time anyone had demonstrated replication in a system of synthetic molecules, though Günter von Kiedrowski of the University of Göttingen and Leslie Orgel of the Salk Institute for Biological Studies had done so in simple systems of modified biochemicals. Indeed, Rebek's strategy still sets him apart from most other origin-of-life researchers, who examine the kinds of chemistry that might ultimately have led to the biochemical machinery of living cells.

Rebek argues that his strategy frees him of many of the chemical constraints facing researchers who work with elaborate biomolecules. A case in point: His success at modifying the system to overcome a limitation of the original ester-amine system. The problem, says Joyce, was its inability to generate variation—the raw material of evolution. Because each template turned out identical descendants, selection pressures would be unable to put different molecules at greater or lesser reproductive advantage. As a result, the system had no way of evolving chemically.

Now the MIT chemists have modified their self-replicating system so that it can generate diversity and even appear to take a simple "evolutionary" step. Their system now includes several different amine components that differ only in a single chemical side group, giving rise to a small family of mixed-and-matched ester-amine structures, which replicate with somewhat different efficiencies. The MIT team also modified some amine components to make them sensitive to an environmental stimulus—ultraviolet radiation. As they report in this issue, ultraviolet exposure of the sensitive amines yields what Rebek calls a "mutated" template that replicates faster than its unexposed version.

But a one-shot mutation won't open the way to evolution. And some other origin-of-life researchers wonder if Rebek's system can be taken much further. "The main thing missing in Rebek's system," says Joyce, "is information." DNA strands carry information encoded in the myriad possible sequences of its chemical building blocks, which are analogous to bits in a computer code. At the moment, Rebek's templates can embody only a few bits at most. And the researchers say that until Rebek endows his replicators with the ability to store and pass on far more information, perhaps by giving them a many-part structure like that of DNA chains, they will have little or no evolutionary potential. "The holy grail is to combine informational content with replication," says Orgel, who suspects DNA-like molecules are a better bet for reaching that goal.

Still, he praises Rebek's work for providing "the opportunity to develop a new sort of organic chemistry in which ideas like replication and mutation will play a role." Rebek, for his part, is determined to bolster the parallels between his system and life's molecular machinery. In papers submitted for publication, he and his co-workers describe a new synthetic replicator that can swap components with the original molecule, yielding hybrid descendants. One hybrid, Rebek claims, replicates faster than either parent; the other hybrid can't replicate at all. "It's sterile, like a mule," he says. Or maybe it's just behaving like a relatively unreactive chemical. ■ IVAN AMATO



Self-made molecules. *Two components link to form a unit that serves as a template for its own replication.*

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