Closing the Gap Between Proteins and DNA

A relatively simple molecule that makes copies of itself may hint at how the molecular precursors to life behaved on early Earth

ONE OF THE GREAT MYSTERIES surrounding the origin of life is the question of how nucleic acids and proteins arose concurrently. Nowadays protein enzymes perform the chemical work of making and replicating nucleic acids, but it's the nucleic acids that carry the genetic information needed for making enzymes and all other proteins. So which came first?

The discovery of catalytic RNA, which won last year's Nobel Prize in Chemistry for Yale University's Sidney Altman and Thomas Cech of the University of Colorado, has led many origin-of-life researchers to suppose that an RNA-like molecule came first because it could be both self-replicating and have the catalytic activity necessary to synthesize itself and maybe proteins, too. But exactly how primitive nucleic acids would have catalyzed protein synthesis remains to be definitively answered.

However, the recent laboratory creation of a synthetic self-replicating molecule by chemists Julius Rebek, Tjama Tjivikua, and Pablo Ballester of the Massachusetts Institute of Technology could offer new insights into this issue, say researchers who study the origins of life. The molecule, which is sort of a cross between a nucleic acid and a protein, may help bridge the gap between the two types of biological molecules by suggesting how a nucleic acid–like molecule might have facilitated the formation of amide bonds, which join amino acids in proteins. "It's an exciting beginning," says Gerald Joyce, a biochemist at Scripps Research Institute in La Jolla, California.

The molecule designed by Rebek and colleagues consists of two chemicals—amino adenosine and an ester—linked together. When this compound, which goes by the abbreviation AATE (for aminoadenosine triacid ester), is put into a chloroform solution with the unlinked ester and amino adenosine building blocks, it acts as a template to make copies of itself.

AATE can do this, Rebek explains, because the ester end is "sticky" and will latch onto a passing amino adenosine; similarly, an ester in the solution will attach itself to the amine end of the AATE (see figure). Once the AATE molecule has grabbed both an ester and an amine, the two molecules come close enough to bond, forming a second AATE molecule just like the first. In the last step, thermal motions shake the pair of AATE molecules apart, leaving each to act as a template to make still more copies. The reaction occurs about 100 times faster with the template than without, Rebek says.

The general technique to make such a self-replicating system, Rebek says, is to find a molecule that is self-complementary and then "break it down the middle" into two molecules. Those two will then naturally join to form a template, and with a little luck the template will work to catalyze a reaction, making more copies of itself.

But more than luck went into making the AATE molecule. It was designed and redesigned over a couple of years, Rebek says. "The first ones worked too well," he says. His first template molecule "folded shut on itself like a jackknife." The two ends were so attracted to each other that they stuck together and would not come apart. As a result the molecule could not pick up the two building block molecules from solution.

The MIT workers fixed that problem, but their next attempt ran into a second difficulty: Once the template formed a copy of itself, the two molecules would not separate. Finally, 2 years ago, Rebek designed a bulge into the template so that the original and its copy would not fit together quite so perfectly, and this version worked.

It took more than a year to do control experiments and iron out various details before publication, but having done it once should make designing other self-replicating systems simpler, Rebek says. "I think it's going to be easy to find other such systems."

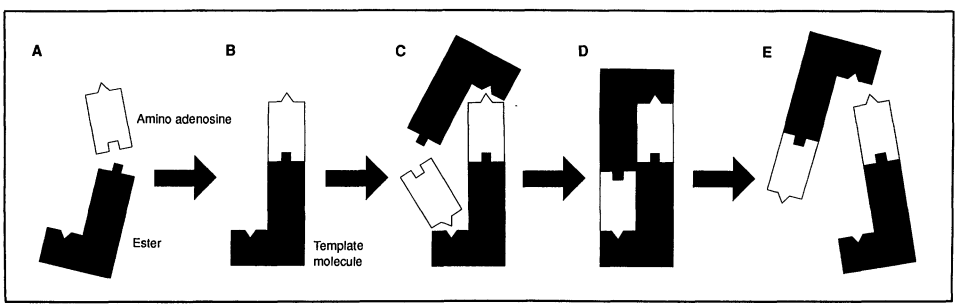
Rebek did not set out, he says, to duplicate how life on earth began. Indeed, since the self-replication system works in an organic solvent instead of water, it isn't even close to conditions on primitive Earth. Nonetheless, origin-of-life researchers are excited about the Rebek group's molecule because of its unusual hybrid nature.

Two other researchers, Günter von Kiedrowski of the University of Göttingen in West Germany and Leslie Orgel of the Salk Institute in San Diego, had previously shown that molecules can replicate without the aid of enzymes, but both investigators used abbreviated nucleic acids. In Orgel's work, for instance, a nucleic acid molecule containing only four bases, guanine alternating with cytosine (GCGC), catalyzed the joining of two GC molecules.

In contrast, Rebek's AATE system, although having some DNA-like features, also includes a typical protein characteristic. It is DNA-like because the AATE template grabs hold of the ester and adenosine with hydrogen bonds—the same kind of weak bond that joins the two complementary strands in the DNA double helix. But the amine and the adenosine are joined to each other with an amide bond—the type of bond that links amino acids in proteins. The system "uses base pairing to make amide bonds," says Rebek, who suggests it may offer some insight into how life on Earth began.

In future work, Rebek hopes to develop larger, more complex template molecules that produce chains from simple building blocks joined by amide bonds. Eventually it might be possible to "diverge" the structure to consist of a DNA-like template and a protein-like product.

Such an expanded system would mark a big improvement over existing ones, Joyce says. Rebek's, von Kiedrowski's, and Orgel's self-replicating systems all have the same shortcoming: a lack of choice. The building block molecules pair up the same way with or without a template; the template just speeds things up. A system with two or more molecules that can line up in different ways but that are arranged in one specific pattern by a template would be a major breakthrough, Joyce adds. ■ **ROBERT POOL**



John Ryan

Simple self-replication. *The ester and the amino adenosine join naturally to form a template, which then catalyzes the formation of more of the same molecule.*