

## PERSPECTIVES: ORIGIN OF LIFE

## A Simpler Nucleic Acid

Leslie Orgel

The nucleic acids, DNA and RNA, are the genetic material that cells and viruses use to produce faithful copies of themselves. The physical properties and chemical reactions of DNA and RNA, therefore, have come under intense scrutiny.

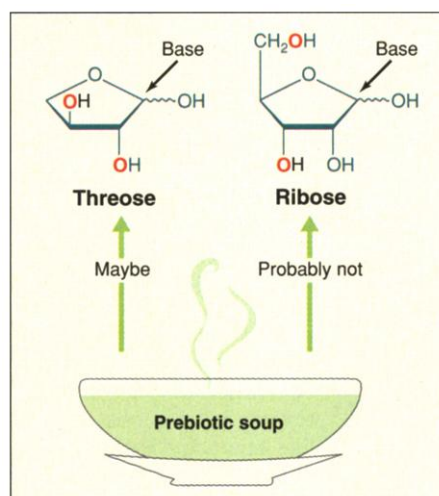
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Yet, very few experimental programs have explored in a systematic way the chemistry of DNA and RNA analogs with a modified backbone that, at least in principle, might be alternative genetic material for Earth's earliest organisms. Identification of nucleic acid analogs that could have been synthesized under the chemical (prebiotic) conditions on Earth that preceded the appearance of the earliest life forms may shed light on the origin of life. To this end, Eschenmoser and his co-workers (1) report on page 1347 of this issue the synthesis of an RNA analog that, in principle, could be an alternative genetic material for primitive life forms.

Only two classes of nucleic acid polymer have been studied in detail as suitable alternatives to RNA and DNA. Nielson's group has worked on peptide nucleic acids that have backbones related to those of proteins (2, 3). Eschenmoser and co-workers have systematically synthesized and studied the properties of nucleic-acid analogs in which the ribose phosphate backbone of RNA is replaced by a backbone constructed from a different sugar, such as a hexose (4). Earlier results from this group included a number of surprises. They discovered unexpectedly that the ribopyranose nucleotides—isoforms of the standard nucleotides in which the usual five-carbon sugar rings are replaced by six-carbon sugar rings—assemble into polymers called pyranosyl RNAs (pRNAs) that pair up in double helices. Although of interest to structural chemists, it is not clear whether these pRNAs could have been a source of genetic material in early life forms. Pairs of complementary pRNAs form double helices that are structurally very different from those formed by DNA and RNA. Consequently, pRNAs and RNAs are not able to form duplexes with each other, which would preclude exchange of information between these two molecules, sug-

gesting that pRNAs are unlikely to have been the genetic material that preceded RNA. The same problem arises for many of the other nucleic acid analogs synthesized by the Eschenmoser group (4, 5).

It has been supposed that for a nucleic acid analog to pair with RNA it must, like RNA, have a backbone with at least a six-atom repeat; a shorter backbone presumably would not stretch far enough to bind RNA properly. The Eschenmoser group has shown, however, that this first impression is incorrect. They realized that, by orienting the



**Soup on the primitive Earth.** The synthesis of threose-based nucleic acid (TNA) and RNA under the chemical conditions on primitive Earth. The solid arrows indicate the positions in the threose and ribose sugars that are substituted by bases in TNA and RNA. The red oxygen atoms indicate that the positions must be linked by phosphodiester bonds. Three carbon atoms separate the red oxygens in ribose, but only two carbon atoms separate the red oxygens in threose.

various bonds in the five-atom repeat backbone of a nucleic acid analog to give a maximally stretched conformation, it was possible to match the geometry of the analog to that of RNA. They confirmed this with a polymer of  $\alpha$ -lyxopyranosyl nucleotides (5).

This seemingly obscure detail of polynucleotide chemistry turns out to have important implications for prebiotic chemistry. Tetrose sugars with their four-carbon ring structure could be more readily synthesized in a prebiotic world than the pentose sugars of DNA and RNA because they can be assembled directly from two identical two-carbon fragments—for example, from

two glyceraldehyde molecules. Pentose sugars are assembled in a more complicated way by combining two- and three-carbon fragments and would have been formed in complex mixtures along with tetroses and hexoses. Nucleotides containing a tetrose sugar have not been considered likely components of an early genetic polymer because they cannot be joined together by phosphate groups to give a backbone with a six-atom repeat. However, the discovery that a six-atom repeat is not an essential feature of early genetic material led to the realization that one of the tetrose sugars, threose, might form the basis for polymers with a five-atom repeat and a stereochemistry compatible with that of RNA.

As they report in their new paper, Eschenmoser and co-workers (1) have now synthesized a substantial number of these polymers, which are called (L)- $\alpha$ -threofuranosyl oligonucleotides or TNAs. They are composed of bases linked to a threose sugar-phosphate backbone, with phosphodiester bonds connecting the nucleotides. The investigators discovered that pairs of complementary TNAs do indeed form stable Watson-Crick double helices and, perhaps more importantly, that TNAs form stable double helices with complementary RNAs and DNAs.

It is hard to understand how  $\beta$ -nucleotides, the monomeric components of RNA, could have formed de novo under the prebiotic conditions on the primitive Earth. Consequently, many recent discussions of chemical evolution have emphasized the potential importance of informational polymers that are simpler than RNA (6). Here "simpler" does not refer to structural simplicity but rather to simplicity of synthesis under prebiotic conditions. In this sense, threose nucleic acids are certainly simpler than RNA. Their unexpected ability to mimic RNA in a Watson-Crick double helix suggests that they might possibly have been the precursors of RNA. Whether or not this turns out to be the case, these new results invite attempts to identify even simpler RNA analogs.

Eschenmoser and his colleagues (1) emphasize that a great variety of base-pairing polymers could exist—in some, the sugar component of the RNA backbone could be replaced by a nitrogen-containing analog, and in others, the standard bases could be replaced by nonstandard bases or the method of attachment of bases to the backbone might be unconventional. Their exploration of the potential prebiotic members of this large combinatorial library is a major undertaking. (The authors speculate further about the general implications of their experimental programs in note 26 of their paper).

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The discovery of a plausible precursor for RNA raises an issue that has been previously considered in the context of peptide nucleic acids (6, 7). How is it possible to change genetic material in midstream? How could a primitive organism that, for example, used TNA as its genetic material switch to RNA? There are two extreme possibilities. In one version, the catastrophist scenario, a TNA-based primitive organism synthesized oligoribonucleotides for a purpose other than replication—perhaps to inhibit TNA synthesis in a competing organism. Then RNA replication evolved independently of TNA replication and ultimately took over as the means by which cells reproduce themselves. According to this scenario, there never were heteropolymers containing both TNA and RNA components, and no useful genetic information was ever transferred from TNA to RNA.

In the alternative gradualist scenario, ribonucleotides were at first substituted a

few at a time and at random in TNA sequences. The proportion of RNA components increased over time from almost zero to 100%. The information present originally in the TNA sequence was, at least in part, preserved in the final RNA sequence. This attractive theory suffers from one major drawback. Introduction of a substantial number of ribonucleotides at random might not prevent replication of TNA, but it would almost certainly destroy the catalytic function of any particular TNA sequence and thus would render evolved TNA sequences useless when rewritten accurately as RNA. This flaw may not be fatal. The power of natural selection is easily underestimated, and it is possible that selection could find a “continuous” pathway from TNA to RNA in which the catalytic function of TNA was maintained.

It would be premature to conclude (and, indeed, Eschenmoser does not

claim) that TNA was a precursor of RNA on the primitive Earth. Nevertheless, the existence of a polymer that is significantly “simpler” than RNA, that resembles RNA more closely than do peptide nucleic acids, and that forms stable heteroduplexes with RNA is encouraging to those who believe that RNA was preceded by one or more simpler genetic materials. It should also allow speculations of the type presented here to be subjected to the test of experiment.

#### References

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critical point for the phase transition. The dependence of the position of the critical point on the concentration of particles is especially low, and the simulations suggest that the connectivity in the two phases is quite distinct. One phase resembles a dense network

of polymerlike strands that span the sample, whereas the less concentrated phase looks like a dilute polydisperse polymer solution. In contrast, the traditional “liquid-gas” transition is characterized by two phases that only differ in concentration, not topologies. Experimental observation of the unusual behavior is problematic because of the long relaxation times associated with extended objects.

The reason for the unusual behavior of these systems is the strong anisotropy associated with dipolar forces.

We know from experience with compass needles that dipoles have a strong preference for lining up head to tail. In colloidal suspensions, this property leads to the formation of long polymerlike self-assembled chains of particles (6), which interfere with the normal liquid-gas transition. This occurs because the chain formation tends to saturate the dipolar attractions, leading to a crude type of screening.

Thlusty and Safran demonstrate, theoretically, that a transition is restored when the “dipolar polymers” are considered as the fundamental units. Much like real polymers (7), the dipolar chains have “defects,” that is, free ends and Y-shaped branching points (see the figure). All defects are favorable from

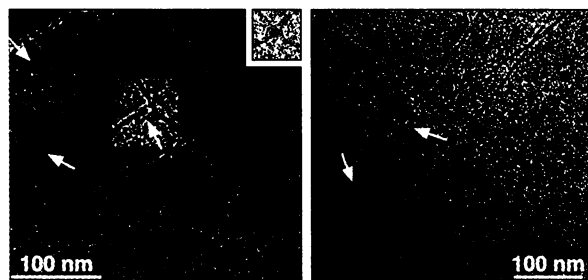
## PERSPECTIVES: PHASE TRANSITIONS

# Y's and Ends

Philip Pincus

Coexisting phases of matter are ubiquitous all around us. For example, we are all familiar with the simultaneous presence of water and steam in a tea kettle or of ice and water in the polar regions of Earth. Multiphase systems do not have to consist of a single molecular species; for example, oil and water coexist but do not mix. In all these cases, depending on external constraints such as temperature, pressure, or magnetic field, the two phases may be induced to undergo a phase transition to a single homogeneous phase. In a multicomponent system, this is a more or less intimate mixture of the components. One example for such a mixture is milk, which is a dispersion of small solid particles (milk solids) suspended in water.

The phase transition between the homogeneous phase and the two coexisting phases occurs at the thermodynamic “critical point.” The transition is generally the result of a competition between entropy, which favors the homogeneous phase because of the strong disorder inherent in mixing, and short-range attractive forces (“like attracts like”) between similar objects, which favor phase separation. Attractive dispersion forces between milk solids lead to phase separation (creaming) in precisely this manner.



**Vital defects.** (Left) Swollen end caps (arrows) of threadlike micelles imaged in a vitrified solution. (Inset) Four-micelle junction. (Right) Lower magnification image showing a sparse network of micelles. Arrows mark threefold (Y) junctions with 120° angles between micelles. Y junctions and ends play an important role in phase separations.

On page 1328 of this issue, Thlusty and Safran (1) bring the understanding of a particularly complex type of phase separation to a new level. They consider colloidal particles suspended in a solvent. This is similar to milk, but the matter is complicated by the fact that the particles have either magnetic or electric dipole moments. Such suspensions are called ferrofluids or electrorheological fluids, respectively. They respond strongly to externally applied fields (2), and this is the basis for their diverse technological applications as clutches, in ink-jet printing, as seals, and so forth. However, the mechanism by which phase separation occurs in these systems has remained obscure both theoretically and experimentally (3, 4). Recent simulations (5) suggest an unusual

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