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## Comment

A “warm formamide” scenario for the origins of life might  
not be so hot

## Comment on “Formamide and the origin of life”

by E. Di Mauro et al.

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In this review, Saladino et al. present an intriguing hypothesis surrounding the role of formamide in the origins of life on Earth, backed by experimental results supporting each step from formamide to RNA polymers [1]. The overall premise is that, from formamide and inorganic phosphate, RNA molecules over 100 nucleotides in length can be produced. In addition, many carboxylic acids likely relevant to prebiotic metabolism, are formed along the way. Thus, from a rather simple organic molecule that has been observed in outer space (formamide), you can generate many of the compounds necessary for the origins of life. However, because high temperatures (160 °C) are required for the formamide reactions, it remains unclear where the “warm formamide” scenario could have occurred.

Low-temperature, aqueous hydrogen cyanide-based prebiotic chemistry that *we know actually happened* has been shown to produce many of the molecules invoked in the formamide hypothesis: amino acids, carboxylic acids, sugar acids, and nucleobases have all been found in meteorites recovered on Earth [*cf.* [2–4]], providing a plausible route for their synthesis and delivery. In contrast, a large portion of the formamide hypothesis is based on relatively high-temperature reactions. A plausible milieu for high-temperature reactions with concentrated formamide is yet to be described, and is critical for this hypothesis to be validated. Hydrothermal vents are attractive heat sources, and the higher boiling point of formamide has been invoked as a mechanism to concentrate it from an aqueous solution. Unless the water can actually evaporate, however, there would be no net enrichment. For example, in the context of a deep-sea vent, any water “removed” by heating would be quickly replaced.

Some of the individual reactions underpinning the present hypothesis [1] have been met with skepticism because they go against conventional wisdom. To name a few of the surprising results: the observation that nucleosides can be converted to cyclic phosphates when heated in the presence of minerals and inorganic phosphate [5]; that 3′–5′ cGMP and cAMP nucleotides polymerize rapidly into RNA oligomers, even in the absence of monovalent counterions [6]; and that end-to-end ligation reactions between RNA oligomers occur in essentially pure water, without requiring any activating groups or counterions [7,8]. Because the polymerization reactions are simply transesterification reactions, that they readily occur in the absence of cations makes one wonder why nearly all ribozyme-catalyzed transesterification reactions are metal-ion dependent; similarly, that the end-to-end ligation reactions do not require activation runs

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1 counter to the observation that all protein-catalyzed ligation and polymerization reactions of RNA and DNA require 1  
2 activated substrates. Detailed mechanistic studies of the reported reactions are warranted and could provide important 2  
3 insights for understanding the chemistry behind the origins of life. 3

4 Because the authors have produced many of the experimental results supporting their hypothesis, they could 4  
5 demonstrate the validity of their hypothesis by converting formamide into ~ 100 nucleotide RNA oligomers, using 5  
6 the products of one reaction as the reactants for the next reaction, under specific conditions plausible on the pre-biotic 6  
7 Earth. Such a demonstration would represent a milestone for our understanding of the origins of life. 7  
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