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Physics of Life Reviews 9 (2012) 105–106

PHYSICS of LIFE reviews

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Comment

Thermodynamics, formamide, and the origin of life
Comment on "Formamide and the origin of life" by R. Saladino et al.

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Received 26 December 2011; accepted 9 January 2012

Available online 11 January 2012

Communicated by M. Frank-Kamenetskii

"There is something rather than nothing because something is more stable", wrote Victor Stenger about the universe [1]. The same applies to the origin of life; but what sort of something, and where? Thermodynamics and life itself are the surest guides. Thermodynamics, because life is more stable than non-life only under certain far-from-equilibrium conditions. Life, because the best explanation for the appearance of appropriate catalysts, whether enzymes or ribozymes, is selection, as noted by de Duve [2]. Catalysts can be selected only if they fit into protometabolism, predicting congruence between prebiotic conditions and biochemical pathways.

Research on the origin of life has been marred by deep historical rifts. Genes first or metabolism first? Panspermia or terrestrial origins? Autotrophic origins in vents or heterotrophic origins in soup? Much fine experimental work has been done, but the gaps between laboratory chemistry, geological environments, and real biochemistry in living cells are still great. Closing those gaps is the task at hand, and we might be surprisingly close. All free-living cells combine six properties – carbon capture, energy transduction, heredity, metabolism, compartmentalisation and excretion. It is doubtful whether any of these traits is much use in isolation: life originated in a thermodynamic system capable of focusing abiotic equivalents of all six living processes. To my knowledge, the only system capable of doing that is a specific type of submarine hydrothermal vent, occupied by hot alkaline solutions rich in H_2, accompanied by minor bisulfide and ammonia. This kind of system is maintained in disequilibrium by spontaneously precipitated inorganic osmotic barriers containing catalytic Fe($\gg$ Ni $\gg$ Mo)S minerals separating the alkaline solution from the ambient CO_2-bearing mildly acidic ocean. The juxtaposition of fluids on either side of these barriers imposes steep redox, proton and thermal gradients. These natural electrochemical reactors have been postulated as the ideal incubators of life by Russell and colleagues for two decades [3,4]; and the discovery of a modern analogue at Lost City, just over a decade ago, provided powerful support [5,6]. Remarkably, thermodynamic calculations under mild alkaline hydrothermal conditions indicate that the synthesis of all cellular materials, including amino acids, bases, sugars and lipids, is exergonic from H_2 and CO_2 between 50 °C and 125 °C [7].

What has been missing from this scenario is extensive experimental work. Russell himself has built a hydrothermal reactor and is exploring the geochemical origins of biochemistry [8,9]; and others, notably Braun and colleagues in Munich, have made headway on the origins of replication via thermal cycling [10]. But a detailed chemical simulation of autotrophic origins under warm alkaline conditions is missing. The next best thing, an impressive body of experimental work, is reported in this issue of *Physics of Life Reviews* by Di Mauro and colleagues in Rome [11].

DOI of original article: 10.1016/j.plrev.2011.12.002.
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1571-0645/$ – see front matter
doi:10.1016/j.plrev.2012.01.005

Di Mauro has worked on the chemistry of the 1-carbon amide formamide (H_2NCOH) for a decade. He has tended to interpret his work in terms of the abundance of precursors such as cyanide and water throughout the universe. Of course, the fact that complex organics are found in meteorites and that formamide is seen in the interstellar medium does not mean that life began in, or was seeded from, space. It tells us only that organic syntheses (but not living cells) are thermodynamically favoured in a certain range of conditions. Formamide can also be formed from formate and ammonia [11]. As formate [6] and ammonia [12,13] are both are known to occur in alkaline hydrothermal solutions, and as water activity is extremely low within the inorganic barriers [9], formamide generated there could potentially reach the effective concentrations required for the chemistry demonstrated by Di Mauro and colleagues. In this issue, they show that all four nucleic bases can be synthesised from formamide, catalysed by a practically indiscriminate range of minerals. The formation of nucleosides is more problematic, but purine acyclonucleosides are formed from formamide; and nucleosides are phosphorylated by phosphate minerals to cyclic nucleotides. Remarkably, under admittedly sensitive conditions, cyclic nucleotides are reported to spontaneously polymerise into short oligomers, which end-join to form longer RNA chains in water [11].

Formamide also reacts to form various carboxylic acids, notably glyoxylate, fumarate, malate, oxaloacetate and pyruvate, albeit each catalysed by different minerals [11]. Thus protometabolism and nucleotide chemistry are potentially linked through the C-1 moiety formamide. Equally pleasing, most of this chemistry works best under warm (80–160 °C), alkaline (pH 9–10) conditions [11]. None of this is to say that life began as formamide chemistry in vents; I would personally favour other pathways reflecting the C1 chemistry of methanogens and acetogens, as postulated by Martin and colleagues [14]. But Di Mauro's work, showing richly relevant organic chemistry under alkaline hydrothermal conditions, beginning with a C1 moiety, is an important step forward. How such chemistry might be driven by other facets of alkaline vents, notably proton and redox gradients [15], is a mouth-watering question for the future.

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