The Future of Prebiotic Chemistry

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Two recent papers reporting advances in our understanding of how a protometabolism may have developed in a prebiotic world add new meaning to the theme “First Reactions” and highlight the challenges facing synthetic organic chemists attempting to retrodict the origins of life.

(along with Beatrice Gerland) the breakthrough 2009 Nature paper demonstrating a prebiotically plausible route to activated pyrimidine ribonucleotides, thus solving a longstanding conundrum of the “RNA World” hypothesis. That work comprised Powner’s PhD studies with Sutherland, who, largely inspired by Eschenmoser and unusually for this field, has from the start dedicated his career to synthetic prebiotic chemistry. Powner seems set to do the same.

The “vestiges of an earlier reactivity” point to α-phosphorylation instead of terminal phosphorylation in the glycolytic and other protometabolic pathways.

The 2016 Powner work tackles the problem of how metabolism could have evolved from reactions of simple organic molecules prior to the emergence of complex enzymatic processes. The focus is on glycolysis with an emphasis directed toward the synthesis of phosphoenol pyruvate (1): a high-energy, versatile, and ubiquitous molecule in modern metabolism (1 in Scheme 1). Nailing down a plausible nonenzymatic synthetic route to this key intermediate would be an important step in unwinding protometabolic pathways.

Starting with glyceraldehyde 3, Powner builds on Krishnamurthy et al.’s report of regioselective phosphorylation with amidotriphosphate using magnesium by showing that the same outcome can be achieved with
phosphate buffer at neutral pH to produce glyceraldehyde-2-phosphate (3-2P). The authors then show that a variety of prebiotically relevant oxidation systems can produce the desired compound 1 as well as 2-phosphoglyceric acid (4-2P).

Powner’s thinking works its way backward from enzymes such as the highly evolved TIM (triose phosphate isomerase), known from Jeremy Knowles’s elegant work as a nearly “perfect” catalyst,7 to what Powner calls the “vestiges of an earlier reactivity” based on α-phosphorylation instead of terminal phosphorylation. At first glance, access to the downstream intermediates in the glycolysis pathway is problematic in nonenzymatic metabolism. The first intermediate after C6 metabolites is glyceraldehyde-3-phosphate (3-3P), which isomerizes to the more thermodynamically stable dihydroxyacetone phosphate (21-P) with an equilibrium ratio of 20:1. In a prebiotic world where TIM does not exist to accelerate rates to the point of diffusion control, a buildup of 21-P would lead to deleterious pathways. Lacking exquisite enzymatic control, the prebiotic world may have chosen the detour via the 2-phosphate to phosphoenol pyruvate in coordinating the first steps toward the biosynthesis of amino acids, sugars, nucleic acids, and lipids.

One of the great mysteries of prebiotic chemistry is picturing how disparate chemical systems that each may explain one small part of the complexities that lead to life could possibly fit in with the rest. For this reason it is valuable to consider this work through the lens of other feats in prebiotic synthesis. Specifically, the 2015 Sutherland work3 develops a geochemical scenario based on what he calls a “cyanosulfidic” chemical homologation theme that can provide the building blocks for the three key subsystems of informational, compartment-forming, and metabolic molecules. Scheme 2 summarizes his grand symphony in four movements8 that leads with startling efficiency to the building blocks of RNA, proteins, and lipids, relying on hydrogen cyanide as the sole carbon and nitrogen source.

This grand symphony in four movements (summarized in Scheme 2) leads with startling efficiency to the building blocks of RNA, proteins, and lipids, relying on hydrogen cyanide as the sole carbon and nitrogen source.

Reductive homologation of HCN (movement a) provides the C2 and C3 sugars needed for subsequent ribonucleotide assembly as well as precursors to amino acids Gly, Ala, Ser, and Thr. Reductive homologation of the products of glyceraldehyde isomerization and reduction leads to lipid precursors as well as amino acids Val and Leu (movement b). Cu(I) catalyzed cross-coupling followed by reductive homologation gives precursors of Pro and Arg (movement c), while Cu(II) driven oxidative cross-coupling leads to precursors of Gln, Glu, Asn, and Asp (movement d).

This simple scenario culminates inexorably in the very set of molecules used by modern biology. Sutherland counters potential criticism of the lack of feasibility of a simultaneous “one-pot” system by describing, convincingly, how different components may be delivered at different times and places via pools and streams, rainfall, and evaporite basins.9 Not only does this description implicate our set of proteinogenic amino acids as preordained for life, it also overcomes perceived incompatibilities between the key subsystems and suggests that they could have developed together rather than sequentially.

Both Powner and Sutherland are quick to concede that the picture emerging from these studies must still be painted with “broad brushstrokes”,3 but the recent advances that...
have been made in our understanding of how the prebiotic world may have facilitated the origin of life are compelling. Parallel efforts focused more narrowly on stereochemical considerations of biomolecules have also advanced significantly,\textsuperscript{10} prompting a Chemistry World quote that we may now be “spoilt for choice”\textsuperscript{11} in models of how biological homochirality evolved. Perhaps the inevitability of the emergence of life from a protometabolism as described in the ongoing work of organic chemists like Powner and Sutherland will become apparent soon enough.

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(5) While ribose and nucleotides have been separately synthesized, no prebiotically plausible means of constructing ribonucleotides by coupling the two had been demonstrated. The work in ref 4 circumvented this problem by reacting 2-aminooxazole with glyceraldehyde to produce riboaminooxazoline, which was converted in a further step to the activated ribonucleotide.
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(8) The physicists and astronomers participating in the Simons Foundation sponsored Simons Collaboration on the Origins of Life (SCOL) refer to the full version of Scheme 2 presented in ref 3 as “the revenge of the chemists” figure.
(9) Although Sutherland calls this a “flow chemistry” scenario, I believe a phrase such as “sequential connected compartmentalization” is more apt, in order to avoid a potentially misleading analogy to modern pharmaceutical flow processes. Indeed, if modern process terms are to be invoked, this scenario is closer to “semi-batch” operation than to typical flow systems.
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