A Storm in a Primordial Teacup

Anthony Futerman, reply by James Tour

In response to "Much Ado about Nothing" (Vol. 6, No. 4).

To the editors:

In a recent review, James Tour wrote that Eddy Jiménez et al., in a study on the chemical origins of life, made "bold claims" about the significance of their work.[1] Tour claimed that their experimental approach is "unconscionable" and stated that "rather than leading to any sort of chemical model, the research serves only to underscore how this particular approach is unlikely to yield any clues about how life emerged." Is Tour correct, or is he "out of his mind" such that "his great learning is driving him insane"?[2]

First, a recap of the Jiménez et al. paper and claims therein. The study centers around the chemical origins of life and, in particular, the so-called RNA-world hypothesis, which suggests that life on earth began with simple RNA molecules that were able to replicate. But what about DNA? Although biochemists do not normally consider that DNA was present alongside RNA in prebiotic scenarios, Jiménez et al. resurrect the hypothesis that RNA and DNA might have emerged together at the origin of life. In a series of experiments constructed around the use of the potential prebiotic phosphorylating agent diamidophosphate (DAP), the authors show that chimeras of DNA and RNA, termed "RDNA," can be generated under appropriate conditions. They then propose that such heterogenous mixtures may have led to the simultaneous appearance of both RNA and DNA in the prebiotic world.

As such, and as a chemistry paper *per se*, the study is well performed and indeed shows that DAP can stimulate deoxynucleosides to oligomerize to form DNA. Tour does not take exception to the chemistry; rather he is scathing about the ramifications of this study for understanding the origin of life. He picks up on five areas he believes are shortcomings that, furthermore, epitomize many studies on the origin of life:

1. The inability of the study to explain the prebiotic source of homochiral precursors such as 2′-deoxyribonucleoside.
2. The high concentrations used in the laboratory studies—that is to say "how might starting materials become available in sufficiently high yields and undiluted by the oceans."
3. The use of a specific precursor, namely DAP, which according to Tour "has become so ubiquitous in origins of life (OOL) research that it is now simply accepted as being prebiotically relevant."
4. The lack of explanation for how the desired reactions managed to occur without competing compounds, which in this case are other nucleophiles.
5. The inability to dispose of unwanted and undesirable chemical products—here, a deleterious 2′, 5′-linkage.

Are Tour's claims valid, or is he on the verge of insanity?

If Tour is insane, then I will offer to join him at the asylum check-in. I find exactly the same assumptions at play in my own area of research, namely lipids, and in the potential roles that lipids may have played in the origin of life and in the formation of the first protocell. To illustrate the similarities with the issues raised by Tour, I will briefly consider a study published in 2019 by Luping Liu et al., from the laboratory of Neal Devaraj, entitled "Enzyme-Free Synthesis of Natural Phospholipids in Water."[3] The claims made by Devaraj et al. might actually be stronger than those made by Jiménez, inasmuch as Devaraj states, "This high-yielding non-enzymatic synthesis of natural phospholipids in water … sheds light on the origin and evolution of cellular membranes." All five of the issues raised by Tour can be seen in this study:

1. The authors do not consider chirality.
2. The study uses high concentrations of precursors, in the millimolar range, without ever discussing how such high concentrations could have been generated prebiotically.
3. The study also uses a specific precursor, in this case an acyl thioester, suggested to be "obtained using prebiotically relevant condensing agents such as dicyandiamid."
4. Competing compounds are barely considered.
5. The authors essentially ignore the effect of unwanted chemical reactions that might produce

> products that would interfere with the required reaction.

Modern cells contain a wide variety of lipids, most of which contain two hydrophobic tails, or acyl chains.[4] The authors' approach is to take a lipid precursor with one tail—a lysophospholipid—and test whether they can chemically add another tail without using enzymes. They compare the ability of some of these lysophospholipids to undergo the addition of another acyl tail, that is, the transacylation reaction required to generate a di-acyl phospholipid. Using high concentrations of one particular species of lysophospholipid, namely lysophosphatidylcholine, and a high concentration of an activated acyl chain, namely an acyl thioester, in the kind of alkaline conditions that may have mimicked conditions in pools and lakes on early earth, the authors obtained laudably high yields of >70% of phosphatidylcholine.

But it is the "Results and Discussion" section that gives away the game. I can do no better than quote the authors, who state,

> We further attempted to obtain various diacylphospholipids such as phosphatidylethanolamine, phosphatidylserine and phosphatidylglycerol by oleoylating the corresponding lysophospholipids; however, the reactivity of [the] acylation reagent is insufficient for these lysolipids and no considerable yields of the desired diacylphospholipids were achieved.

In other words, the conditions selected for the enzyme-free synthesis of phospholipids only works with one specific lysolipid precursor. But it gets worse. While the authors did not consider the presumably deleterious role of side-products that would have accumulated during the reactions, the addition of other lipids, such as sodium dodecyl sulfate, almost completely inhibited the acylation reaction even using the one lipid precursor that had worked previously—i.e., lysophosphatidylcholine—such that the yield dropped to less than 10%. Presumably, the inclusion of other lipids or chemical side-products would similarly inhibit the transacylation reaction. Rather than "Enzyme-Free Synthesis of Natural Phospholipids in Water," a more accurate title for the study might have been "Enzyme-Free Synthesis of One Specific Natural Phospholipid in Water under Very Controlled Conditions, Using Pure Precursors, without Taking into Account Chain Length or the Effect of Lipid Mixtures or Side-Products." It is a less catchy title than the original, but a far more accurate description of the data presented in the study.

Just as the Jiménez et al. paper seems to be much ado about nothing, I would argue, agreeing with Tour, that many similar articles about the origin of life do not actually explain anything. Admittedly, careful choice of conditions, whether realistic or not for prebiotic scenarios, demonstrates that certain reactions and pathways might conceivably occur. But when considering the kind of issues raised by Tour, and raised herein, it might be more realistic, and humble, to tone down widely publicized claims that researchers understand the chemical reactions and pathways that result in the emergence of life. Perhaps a more tempered outlook might mirror that of the great British astronomer Sir Fred Hoyle, who, when comparing the complexity of living systems to the complexity of the universe, asked, "Isn't it even more ridiculous to suppose that the vastly more complicated systems of biology had been obtained by throwing chemicals at random into a wildly chaotic astronomical stewpot?"[5]

Anthony Futerman

James Tour *replies*:

Anthony Futerman's letter, which critiques the Devaraj group's work entitled "Enzyme-Free Synthesis of Natural Phospholipids in Water," is just another report in a litany of reports that could be written about the syntheses purported to be relevant to the origins of life. These syntheses simply do not work to do anything other than to show how these molecules *did not* form at the dawn of chemistry. OOL research is a field in crisis. It condemns itself as soon as a bit of chemical critique is applied to its outlandish claims. The proposals of the OOL researchers are so utterly simple to refute. I hope that more scientists come gunning for their exposure. I am glad to welcome Futerman to the posse.

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James Tour is a synthetic organic chemist at Rice University.

1. Eddy Jiménez, Clémentine Gibard, and Ramanarayanan Krishnamurthy, "Prebiotic Phosphorylation and Concomitant Oligomerization of Deoxynucleosides to Form DNA," Angewandte Chemie International Edition 60, no. 19 (2021): 2, doi:10.1002/ange.202015910.
2. Adapted from the Bible, Acts 26:24.
3. Luping Liu et al., "Enzyme-Free Synthesis of Natural Phospholipids in Water," Nature Chemistry 12 (2020): 1,029–34, doi:10.1038/s41557-020-00559-0.
4. Tamir Dingjan and Anthony Futerman, "The Fine-Tuning of Cell Membrane Lipid Bilayers Accentuates Their Composi-

tional Complexity," BioEssays 43, no. 5 (2021), doi:10.1002/bies.202100021.
5. Sir Fred Hoyle, "The Universe: Past and Present Reflections," Engineering and Science (November 1982): 12.

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