This is a letter to a friend, John West, in reference to a talk that I delivered in January 2019.

May 11, 2019

Dear John,

Thank you for reaching out to me for clarity regarding my talk in Dallas on January 19, 2019, entitled “The Mystery of the Origin of Life,” and posted March 18, 2019 on YouTube by the Discovery Institute.
https://www.youtube.com/watch?v=zU7Lww-sBPg&t=8s
I still have not read what anyone has said about the talk in Dallas. I do not read blogs, nor do I write for them. But you tell me that it has caused quite a stir, especially regarding my comments about Professor Szostak’s *Nature* article. Let me clean up one issue with an apology since my word “lying” was inappropriate and I should not have used that term. For that, I am not making an excuse. I am without excuse.

Someone named Peter wrote an email to me discussing some blog posts that made reference to my overly severe word, and I gave him permission to post the following. I heard from a friend, Joshua, which it was posted because Joshua wanted to be sure that I wrote it. The best that I can tell by a cursory reading, my letter of apology was faithfully reproduced by Peter for posting. I reproduce that letter here as well:

> Dear Peter, thank you for writing to me. That was a strong word ("lying") which I regret saying. I have already apologized to Jack Szostak by phone, and he very graciously accepted the apology. If given a chance, I would likewise apologize to any of those cited in that talk to whom I said such a thing. My behavior was inappropriate.
>
> Like many things that I do and say in life, there are elements upon which I have regrets and wish that I had done differently. My life is filled with those occasions. In fact, I can literally claim almost daily I do something or say something which I wish I had not. Those closest to me get the brunt of it, but thankfully they have also been gracious in forgiving me. And for that I am thankful.
>
> "O wretched man that I am! Who shall deliver me from the body of this death? I thank God through Jesus Christ our Lord." Romans 7:24-25a.
>
> I do not read or write on blogs-- or almost never. So if you wish, you may post this on Peaceful Science, though my words were far from peaceful, to my shame.
>
> God bless,
> James Tour

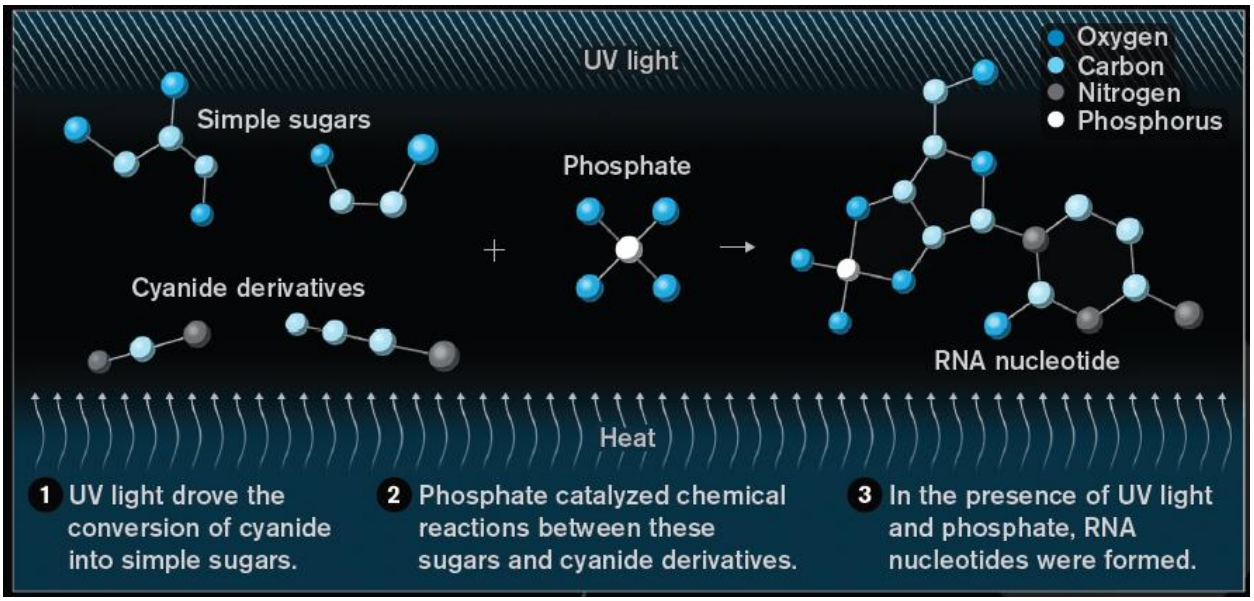
Joshua said that an apology should be as public as the offense. I do not disagree, but how can one go back and make an apology that is going to get thousands of YouTube views since (a) I did not post that video myself and (b) I do not Twitter post so I have no followers. Hopefully this will suffice since it is now an open posting.

Regarding Jack Szostak's article in *Nature*, https://www.nature.com/articles/d41586-018-05098-w, I think it displays to the world a simplicity that is unfounded, and it gives the reader a sense that we are much closer to finding a solution to life's origin than we really are. Indeed, I specifically said in the talk that one day we might figure out the chemistry for origin of life (OOL), but that day is far from today. We are nowhere close. Szostak feels we are not far from cracking this problem. I differ strongly, and I think the synthetic chemist can be the most skeptical because we know what molecules do and do not do in an abiological environment.

This letter is not a personal attack on Professors Jack Szostak and John Sutherland. I have found Jack Szostak to be a fine man during our conversations, and I have never met Professor Sutherland. Neither man has ever meant me ill. This merely shows my different scientific opinion regarding their published articles with respect to the relevancy of their work to address OOL questions, and what has been portrayed by those articles.

The superb work by Professor Sutherland shows the enormous intellectual prowess of some of the top synthetic chemists in the world, restricting themselves to the reagents that might be found on a prebiotic earth, and yet cleverly making some key intermediates and then finally to a racemic nucleotide. That intellectual effort is something that a mindless prebiotic earth would be lacking. Sutherland and his team should be commended for first rate synthetic work. I wish I were as good a synthetic chemist as is John Sutherland.

Here is the first point regarding Szostak's article, albeit the lesser issue. As listed, the sugars do not look like sugars. One needs to have the double bond shown to one of the oxygen atoms or they are not sugars. Shown are a diol and a triol. Even Jack, when he and I spoke on the phone, conceded that point. And he blamed the error on a staff artist from *Scientific American*, and the mistake was transcribed when the article was used by *Nature*. I have written several times for the News and Views section of *Nature* and *Nature* series journals. It is an honor to be so asked. But we are asked as authors to show care to ensure accuracy. And the galley proofs are returned to us for our careful check and documented approval. I reproduce that figure here below:

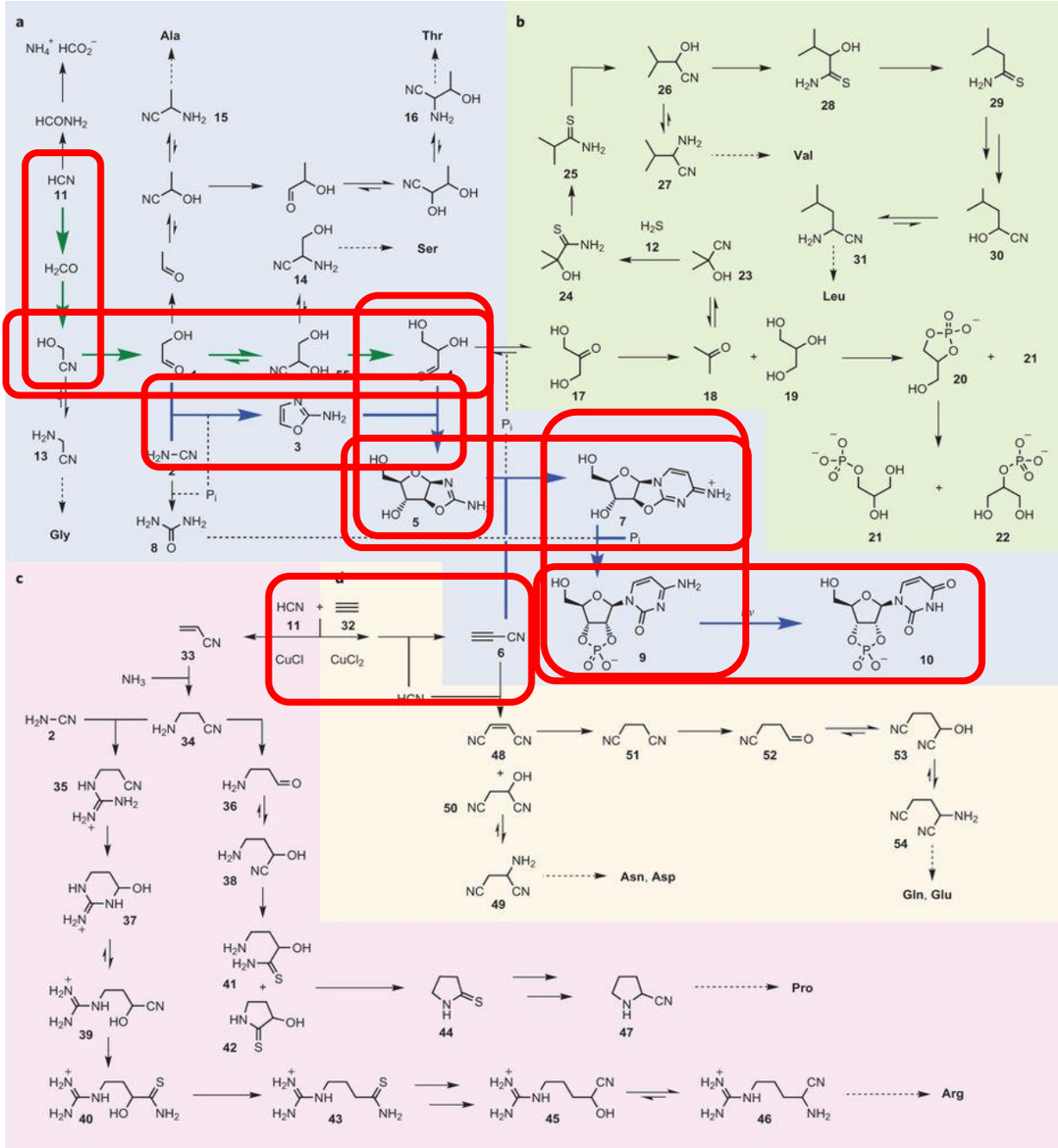


https://www.nature.com/articles/d41586-018-05098-w

If one argues that the hydrogens can be left out and the multiple bonds need not be shown, that is simply incorrect. Without the addition of a double bond to the oxygen, then all remaining valance sites are presumed saturated with hydrogens. Likewise, under a standard where one is free to disregard both hydrogen atoms and the pi bonds, the "Cyanide derivatives" would be diaminomethane and 1-aminopropane. But if one argues that he/she could add as many hydrogen atoms as they like without showing the pi bonds, then the latter of the two "Cyanide derivatives" could be cyanoethene (acrylonitrile) or cyanoethyne. The former could be H_2N-C=NH or HN=C=NH or H_2N-CN (all hydrogen atoms shown immediately tell us that the last of these three listed here is cyanonitrene). Therefore, we cannot have it both ways. Either we fill in the hydrogen atoms or we show the pi bonds. But we cannot omit both. Moreover, the convention is that all heteroatoms should bear the hydrogen atoms. Only carbon can be devoid of hydrogen in the convention. But that is only to fill the valance states. So one needs to see the pi bonds if we are omitting the hydrogen atoms. Therefore, as drawn, the organic starting materials are glycerol (1,2,3-propanetriol or glycerin), ethylene glycol (1,2-ethanediol), diaminomethane (methanediamine), and 1-aminopropane. The latter two are troubling in light of the text which mentions iron cyanide. Iron(III) cyanide complexes are extremely stable; there is little free cyanide expected to be in the solution, so maybe Szostak is speaking of something else.

But all of the above is minor compared to Szostak's showing that in a single step, heat and light can make a compound that resembles a dehydrated nucleotide (though it is not a nucleotide since it is devoid of any stereochemistry) from "simple sugars" and "cyanide derivatives." A professor of psychiatry from a Canadian university even wrote to me last week saying that I was wrong in my Dallas lecture since Sutherland has shown that those simple compounds can lead to the nucleotides, and accusing me of

not being familiar with a 2012 paper by Sutherland. Little did he know that I had extensively studied Sutherland's work and critiqued it in 2016: http://inference-review.com/article/animadversions-of-a-synthetic-chemist.
And that poor psychiatrist had been misled by Szostak to believe that all this chemistry is worked out and simply heat and light can work this magic. How misled even professors can become from these writings in *Nature*. The academy is led astray. The major issue is that heat and light cannot afford that conversion from ethylene glycol, glycerol, or the sugar products derived thereupon after their oxidation to the aldehydes. To present that heat and UV light can act on these compounds (even if we are to use these 2 and 3 carbon simple sugars rather than glycerol and ethylene glycol, and to use any simple cyanide derivative) to afford anything like the listed "RNA nucleotide" (albeit not a nucleotide since it shows no stereochemistry) is incorrect and misleading. There are so many steps involved in such a transformation. But to a biologists, like Szostak, explaining to the non-expert, he feels the details are not essential for him to point out. But the details *are everything*! Stereochemistry is essential. And the reaction details are essential. Just look at the number of steps that Sutherland maps out in his article on "Common origins of RNA…" as he proceeds to the dehydrated RNA nucleotide listed as **10**; the same one that Szostak inaccurately captured in his drawing.
https://www.nature.com/articles/nchem.2202/figures/1

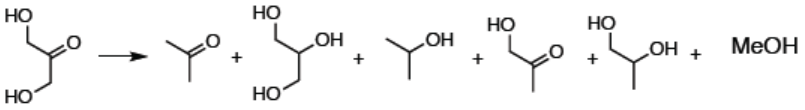


I have highlighted for you what Sutherland, one of the greatest synthetic chemists that the world has ever enjoyed, had to do to afford the dehydrated “RNA nucleotide” that Szostak lists in his figure (albeit devoid of stereochemistry in the Szostak article). It took Sutherland 10-12 steps, with multiple more reagents—that is a hard synthesis! And Szostak showed it in just one step with a few simple reagents. That is misleading of Szostak, and I am sure that the professor of psychiatry is not the only one confused by all this—the poor fellow. Sutherland shows the proper relative stereochemistry (although it is racemic in Sutherland’s case, he draws a single enantiomer). And all that was

reduced, by Szostak, to a mere “UV light and heat”. Szostak writes, “in the presence of UV light and phosphate, nucleotides were formed.” I find that disingenuous and it betrays the depth of the exacting chemistry involved. Just even that simple little formation of the cyanoethyne (**6**, and improperly reproduce in the Szostak article) requires the generation of ethyne by addition of water to calcium carbide and bubbling that through HCN and copper(II) chloride. Try that in a puddle somewhere. Try to keep cyanoethyne from decomposing in the presence of his favorite 254 nm UV light source which seems to be abundant in his prebiotic earth. And that is just the simple compound en route to the desired product. A detailed protocol was required by Sutherland, using advanced labs and the best tools and hundreds of years of chemical literature to aid him. So much chemistry is done, which shows the complexity. Yet to a biologist or a psychiatrist, it is as if: Oh well, it was done in the lab, so it is tantamount to accomplishing it on a prebiotic earth. No way! I work with students all the time. This chemistry is exacting and painful in a lab, and even with the experimental protocols in hand, it would be hard for anyone-- only well-experienced PhD synthetic chemistry students can reproduce this work. And what if they did not have the protocols in hand? It would be much harder. And what if they did not have the best labs? It would be much harder. And what if they had to do it in a cave or an outdoor puddle of water? It would be much harder. And what if they could not characterize after each step? It would be much harder. And what if they had to carry on the intermediates that they made into the next step, rather than just identifying them as a blip in an HPLC, in a mixture of many other compounds with different but related constitution, and others with the same constitution but a different stereochemistry at one or more sites? It would be much much harder! The people most likely to disagree with me, or to insufficiently appreciate what I am talking about, are the untrained. The synthetic chemist know precisely what I mean. But in OOL experiments, if they identify the intermediate as a blip in an HPLC, that can be good enough. Now, rather than using their grossly impure compound as they made, the OOL researcher can either purchase as much of that intermediate as they wish, in pure form(!), or make it using all advanced synthetic methods and separation tools (like Prep-HPLC) and characterization tools. And why do they do it that way, where <u>each step</u> becomes relay-synthesis-like, and not doing the direct synthesis from start to finish, as a prebiotic earth would have to do it? Because the OOL researcher has to! They cannot do it from start to finish using the same material. Not when it involves this many steps to make a dehydrated RNA nucleotide. And what do they write as their excuse for using modern synthetic methods and purchasing purer intermediates to complete their syntheses? They just did it “to simplify the handling procedures.” That is what they write in their experimental sections.
https://www.nature.com/articles/nchem.2202/figures/1
But somehow a mindless prebiotic earth, without a laboratory, without a fine chemicals vender, without chemical literature, without glassware, without characterization methods, could work it out.

I have so far only scratched the surface. Let's look more carefully at the protocols by Sutherland, upon which Szostak blissfully pins his hopes, as do all who read the oversimplified Szostak article that was prepared for readers of *Nature*.

*Formation of glycerol **19** and acetone **18** from dihydroxyacetone **17** by photoredox chemistry*



17 **18** **19** **56** **57** **58** **59**

Dihydroxyacetone (8.0 mg, 0.089 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (45 mg, 0.288 mmol) were dissolved in H_2O/D_2O (85:15, 8 mL) and the resultant solution degassed for 15 min. $NaSH.xH_2O$ (60 mg, assume 60% NaSH, 0.642 mmol) was added and the solution turned yellow. When NaSH was dissolved completely, the pH was adjusted to 7 using degassed NaOH/HCl. The solution was then transferred to a quartz tube containing CuCN (4.5 mg, 0.050 mmol) and immediately sealed, whereupon a black precipitate formed. The tube was placed in a Rayonet reactor and then irradiated for 6 h. After this time an aliquot (0.6 mL) was removed and examined by ^{1}H-NMR spectroscopy after the addition of a known amount of calcium formate ($Ca(HCO_2)_2$) to serve as internal standard for quantitative ^{1}H-NMR spectroscopy. Yields were calculated referring integrals to the internal standard singlet at 8.3 ppm. Glycerol **19** was obtained in 34% yield together with acetone **18** in 29% yield. The by-products were hydroxyacetone **57** (10%), 1,2-propandiol **58** (4%), isopropanol **56** (20%) and, through concurrent Norrish type I photochemistry, methanol **59** (3%). Spiking with authentic standards showed their identity. The mixture contained also traces of thioacetate and acetic acid that we proved to be contaminants of NaSH (data not shown). The remaining mixture was evaporated to dryness without heating and the crude residue was dissolved in H_2O/D_2O (9:1, 1 mL). The mixture was centrifuged and the supernatant was then analysed by ^{1}H-NMR spectroscopy. After evaporation the percentage composition of glycerol **19** in the mixture increased to 60% (Figure S2).

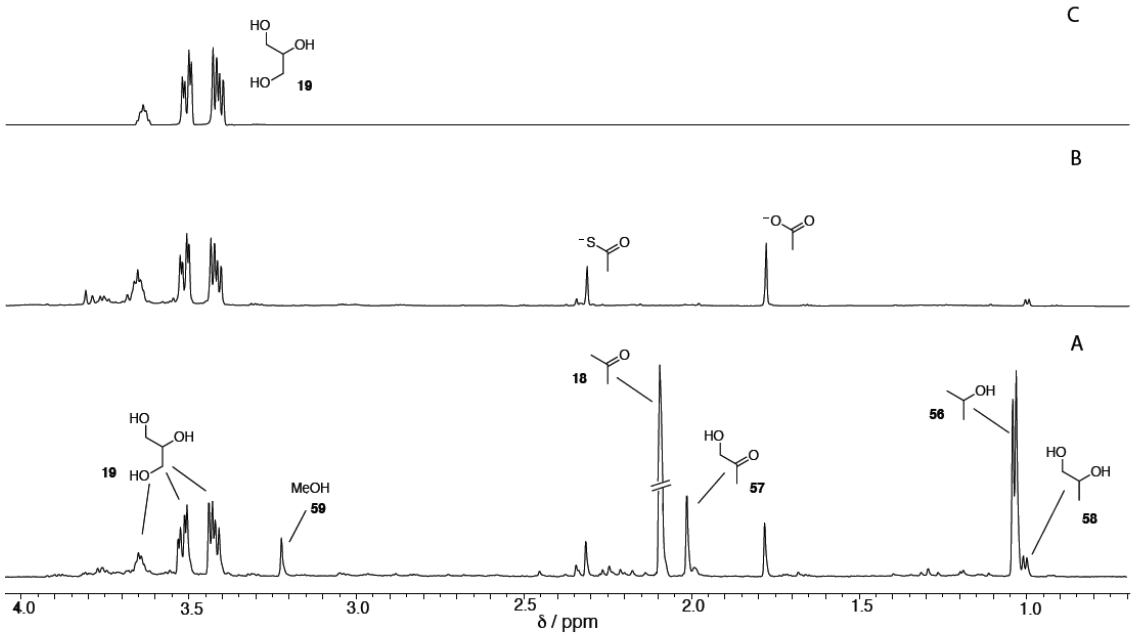
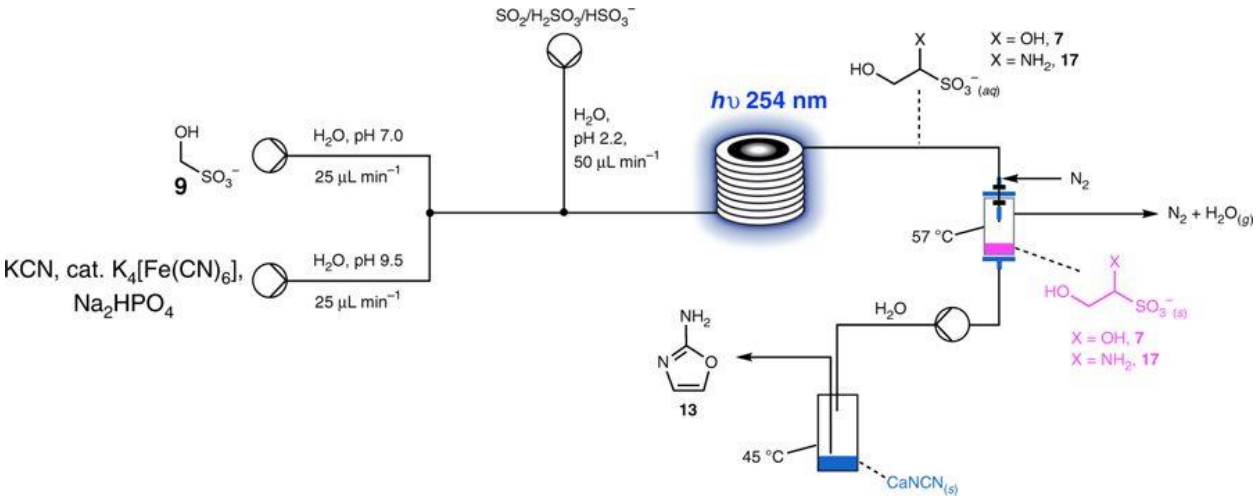


Figure S2. ^{1}H-NMR analysis (H_2O/D_2O, 9:1) of the conversion of dihydroxyacetone **17** into acetone **18** and glycerol **19**. A – spectrum of a sample from the photochemical reaction after 6 h; B – spectrum of the same sample after evaporation to dryness and redissolution in H_2O/D_2O (9:1, 1 mL); C – spectrum of a reference sample of glycerol.

https://media.nature.com/original/nature-assets/nchem/journal/v7/n4/extref/nchem.2202-s1.pdf

Compare Fig. S2A (as-prepared) to Fig. S2C (as purchased). Mixtures abound! Do the researchers proceed with these mixtures? Not generally. The desired compound's presence is good enough, regardless of the accompanying impurities that could easily interfere or actually prevent the next reaction from taking place. Now they purchase the pure intermediate. And if it cannot be purchased, they make it using modern synthetic methods, "to simplify the handling procedures."

This is not to say that Sutherland has not realized the problems associated with this multistep approach to building intermediates. He does discuss it in his 2015 "Common origins…" paper, and more recently in his 2018 paper on "Mimicking the surface and prebiotic chemistry…" DOI: 10.1038/s41467-018-04147-2 So to address this, he tries to make these compounds in a one-pot (simulating one puddle or steam flow, I suppose) approach.



The above is a set-up to "mimic" prebiotic earth conditions. Selective and precisely timed sequential additions are instituted, with pure compounds feeding into each step (or at least there were impurities that did not interrupt the desired chemistry), and selective 254 nm UV irradiation for the precise time, at the precise place in the sequence, sometimes at room temperature, sometimes at 45°C, sometimes at 57°C, sometimes at pH 7.0, sometimes at pH 9.5, sometimes at pH 2.2—that's a sophisticated puddle! This sort of thing would have to happen over and over again, across many many "puddles," just to build these simple intermediates. And then those puddles would have to find each other, at the right time, and before decomposition that results from prolonged exposure to the high energy light of 254 nm. Let us look at what is involved this experiment, done in an advanced laboratory, not merely a cave or a puddle:

Flow chemistry procedure starting from HMSA 9

In one vessel, Na_2SO_3 (302 mg, 2.40 mmol) and formaldehyde (37%, 180 μL, 2.40 mmol) were dissolved in degassed H_2O (15 mL), and the pH adjusted to 7.0 with degassed HCl/NaOH. The volume was made up to 20 mL with degassed H_2O and kept under N_2 atmosphere (solution A). In a second vessel, KCN (182 mg, 2.80 mmol), NaH_2PO_4 (240 mg, 2.00 mmol) and $K_4[Fe(CN)_6].3H_2O$ (167 mg, 0.400 mmol) were dissolved in degassed H_2O (15 mL) and the pH adjusted to 9.5 with degassed HCl/NaOH. The volume was made up to 20 mL with degassed H_2O and kept under N_2 atmosphere (solution B). A third vessel was charged with Na_2SO_3 (328 mg, 2.60 mmol) and degassed H_2O (15 mL), and the pH adjusted to 2.2 with degassed HCl/NaOH. The volume was made up to 20 mL with degassed H_2O and kept under N_2 atmosphere (solution C). Solutions A and B were pumped at a rate of 25 μL min^{-1} each and merged via a T-piece. The resulting reaction stream was then merged via another T-piece with solution C, pumped at 50 μL min^{-1}, and passed through the photochemical reactor at 25 °C (overall flow rate 100 μL min^{-1}, 10 mL

> reactor coil (100 min total irradiation time), and a backpressure regulator was fitted at the output and adjusted so a pressure of ~2 bar was maintained) [the output was checked at the desired time points via the addition of $NaSH.XH_2O$ (1–2 mg), doping with D_2O and acquiring solvent suppression ^1H NMR spectra]. The solution was then pumped into an in-line solvent-switch system[46] heated at 57 °C with an influx of N_2 set at a pressure such that the output was concentrated to dryness. After 100 min of collection, the input was ceased and degassed H_2O (typically 0.5–1 mL) was either pumped or syringed into the solvent switch. The chamber was agitated gently to facilitate dissolution of the solids, and the solution was then pumped into an Eppendorf containing CaNCN (90%, 71 mg, 0.797 mmol) and a stirrer bar. The Eppendorf was sealed and the suspension was stirred and heated at 45 °C for the desired time, after which the reaction was allowed to cool to room temperature and sediment for several hours. An aliquot of the clear solution was then dissolved in D_2O and examined by ^1H NMR spectroscopy. DOI: 10.1038/s41467-018-04147-2

Indeed, Sutherland, a superb chemist, ostensibly uses prebiotic conditions—but are they really prebiotic conditions? How disingenuous for Szostak to write "in the presence of UV light and phosphate, RNA nucleotides were formed." Does Szostak himself appreciate the exactness required to conduct these syntheses? Likely not. Most biologists don't. And they transmit their blissfulness to others. This oversimplification is very easily transmitted such that even professors are confused on these matters, like the confused professor of psychiatry that wrote to me.

We are nowhere close to cracking the OOL problem, as I said in my lecture. And if someone suggests otherwise—I think they are incorrect. I am not just saying OOL is a hard problem. I am saying we are nowhere close to solving it because we are neglecting the fundamentals that need to be addressed—like the fundamentals that I addressed in my Dallas lecture. And even with all the great work by Sutherland, and the citations by Szostak, we are nowhere close to a solution.

As for the suggestion that Szostak's article in *Nature* was primary literature: that was incorrect. Though it was published in the best of journals and therefore garners enormous influence in the scientific community, it was secondary. I concede with apology. The primary literature on the racemic dehydrated RNA nucleotide synthesis is addressed here. I hope this helps to clarify things.

God bless,

Jim Tour, www.jmtour.com