

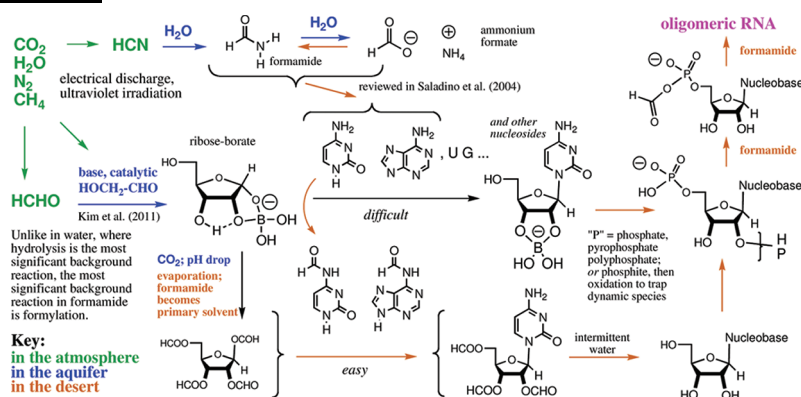
Asphalt, Water, and the Prebiotic Synthesis of Ribose, Ribonucleosides, and RNA

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RECEIVED ON DECEMBER 31, 2011

CONSPECTUS



RNA has been called a “prebiotic chemist’s nightmare” because of its combination of large size, carbohydrate building blocks, bonds that are thermodynamically unstable in water, and overall intrinsic instability. However, a discontinuous synthesis model is well-supported by experimental work that might produce RNA from atmospheric CO_2 , H_2O , and N_2 . For example, electrical discharge in such atmospheres gives formaldehyde (HCHO) in large amounts and glycolaldehyde (HOCH_2CHO) in small amounts. When rained into alkaline aquifers generated by serpentinizing rocks, these substances were undoubtedly converted to carbohydrates including ribose. Likewise, atmospherically generated HCN was undoubtedly converted in these aquifers to formamide and ammonium formate, precursors for RNA nucleobases. Finally, high reduction potentials maintained by mantle-derived rocks and minerals would allow phosphite to be present in equilibrium with phosphate, mobilizing otherwise insoluble phosphorus for the prebiotic synthesis of phosphite and phosphate esters after oxidation.

So why does the community not view this discontinuous synthesis model as compelling evidence for the RNA-first hypothesis for the origin of life? In part, the model is deficient because no experiments have joined together those steps without human intervention. Further, many steps in the model have problems. Some are successful only if reactive compounds are presented in a specific order in large amounts. Failing controlled addition, the result produces complex mixtures that are inauspicious precursors for biology, a situation described as the “asphalt problem”. Many bonds in RNA are thermodynamically unstable with respect to hydrolysis in water, creating a “water problem”. Finally, some bonds in RNA appear to be “impossible” to form under any conditions considered plausible for early Earth.

To get a community-acceptable “RNA first” model for the origin of life, the discontinuous synthesis model must be developed. In particular, the model must be refined so that it yields oligomeric RNA from CO_2 , H_2O , and N_2 without human intervention. This Account describes our efforts in this direction.

Our hypothesis centers on a geological model that synthesizes RNA in a prebiotic intermountain dry valley (not in a marine environment). This valley receives high pH run-off from a watershed rich in serpentinizing olivines and eroding borate minerals. The runoff contains borate-stabilized carbohydrates, formamide, and ammonium formate. As atmospheric CO_2 dissolves in the subaerial aquifer, the pH of the aquifer is lowered. In the desert valley, evaporation of water, a solvent with a nucleophilic “background reactivity”, leaves behind formamide, a solvent with an electrophilic “background reactivity”. As a result, nucleobases, formylated nucleobases, and formylated carbohydrates, including formylated ribose, can form. Well-known chemistry transforms these structures into nucleosides, nucleotides, and partially formylated oligomeric RNA.

The Paradox at the Center of the Bio-origins Problem

At the center of the problem of bio-origins lies a contrast between observations made routinely in two fields. In chemistry, when free energy is applied to organic matter *without* Darwinian evolution, the matter devolves to become more and more “asphaltic”, as the atoms in the mixture are rearranged to give ever more molecular species (Figure 1).^{1–3} Even nonchemists know of this observation, perhaps from having left cooking unattended in a kitchen. In the resulting “asphaltization”, what was life comes to display fewer and fewer characteristics of life.

Biologists routinely observe the opposite. In the *bio*-sphere, when free energy is provided to organic matter that *does* have access to Darwinian evolution, that matter does *not* become asphaltic. Instead, “life finds a way” to exploit available raw materials, including atoms and energy, to create more of itself and, over time, better of itself. This observation is made across the Earth, from its poles to the equator, from high in the atmosphere to the deepest oceans, and in humidities that cover all but the very driest.

The contrast between these commonplace observations in chemistry versus commonplace observations in biology embodies the paradox that lies at the center of the bio-origins puzzle. Regardless of the organic materials or the kinds of energy present early on Earth, chemists expect that a natural devolution took them *away* from biology toward asphalt. To escape this asphaltic fate, this devolution must have transited a chemical system that was, somehow, able to sustain Darwinian evolution. Otherwise, the carbon on Earth would have ended up looking like the carbon in the Murchison meteorite (or the La Brea tar pits without the fossils).⁴

Thus, our goal in bio-origins is to identify a chemical system “in transit” from CO₂, H₂O, N₂, and other species that were present on Earth⁵ that gained Darwinian capabilities just in time to prevent this fate. Subsequent events in the terran biosphere (the origins of translation, modern cells, and consciousness, for example) are qualitatively different. Whatever problems they may have presented must have been easier to solve, because their solution was assisted by Darwinian evolution.

We Appear to Be Stuck with RNA as the Biopolymer That First Supported Life on Earth

In 1962, Alex Rich proposed that RNA, as a single molecule, might be able to support both genetics (by being copied) and phenotype (by having catalytic activity).⁶ Since then, many

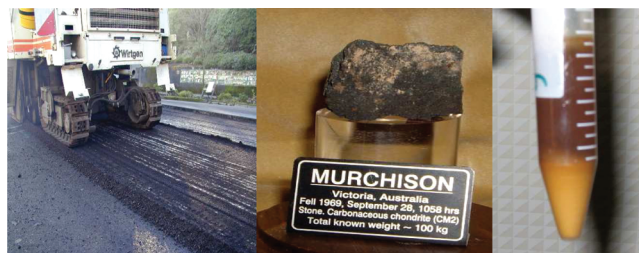


FIGURE 1. Some examples of asphaltization: (a) asphalt itself; (b) the Murchison meteorite; (c) products of the formose process left incubating too long.

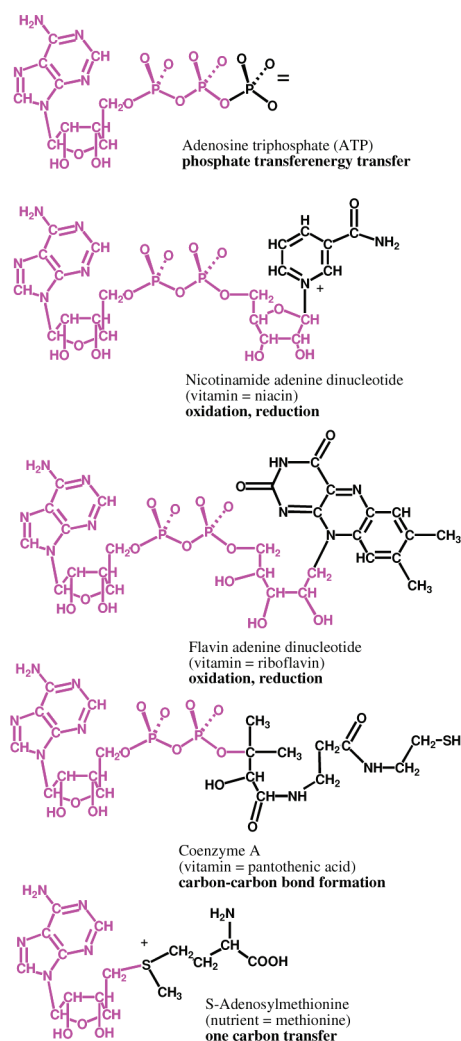


FIGURE 2. Structures of “RNA cofactors”, universal in terran metabolism, whose RNA components (magenta) offer no useful reactivity. These may be vestiges of a time when RNA was the only encoded component of biological catalysis.

have suggested that “RNA first” would avoid the improbability of having multiple biopolymers emerge spontaneously (e.g., DNA and proteins) that must interact to support these two aspects of biology individually.

Many details of the modern terran biosphere make this proposal attractive. For example, the structures and reactivities of “universal” RNA cofactors (Figure 2) argue that modern protein-catalyzed metabolism is a “palimpsest” written over a metabolism that originated when RNA was the only genetically encoded component of biocatalysis.⁷ RNA in the ribosome makes proteins,⁸ and the antiquity of this process is supported by paleogenetic experiments that resurrect components of 3 billion year old translation systems in the laboratory.⁹ Experiments with alternative DNA¹⁰ show that nucleic acids are better catalysts if they carry functional groups reminiscent of functional groups added post-transcriptionally to modern catalytic RNA.

While none of this directly compels an “RNA first” model for the origin of life, other factors (almost) do. In particular, catalysis and genetics place contradicting demands on a single molecular system. For example, catalytic molecules *should* fold, to surround a transition state. Genetic molecules *should not* fold, to allow them to template the synthesis of their complements. Catalytic molecules should have *many* building blocks, to create functional power. Genetic molecules should have *few* building blocks, to ensure high fidelity.

RNA appears to be quite unusual among polymeric systems in its ability to strike a balance between the contradicting needs of catalysis and genetics. Indeed, studies in our laboratories¹¹ and elsewhere seeking to replace the ribose-phosphate backbone in RNA by alternative backbones that might be more “prebiotic” have shown only how special RNA is in this regard.

These facts drive a strategic decision needed in any research program: what *not* to pursue. Considering everything, including (a) the roles of RNA deep within terran metabolism, (b) the catalytic potential of RNA, (c) the ability of RNA to meet the contradicting demands of genotype and phenotype, (d) the lack of substantive models behind “metabolism first” notions,¹² and (e) recent experiments showing how mineral–organic interactions might help make RNA,¹³ we decided that we were “stuck” with RNA as the first genetic biopolymer. So constrained, we are forced to solve the prebiotic problems that RNA presents.

Are the Problems of RNA Prebiotic Synthesis Not Already Solved?

Actually, a “discontinuous synthesis model” already exists that describes how oligomeric RNA might have been formed abiologically on Earth. The atmosphere on early Earth undoubtedly contained CO₂, H₂O, N₂, and some reduced hydrocarbons (e.g., CH₄). Thus, it undoubtedly suffered electrical discharge and ultraviolet irradiation to generate

formaldehyde (HCHO) and hydrogen cyanide (HCN).¹⁴ There is little doubt that igneous rocks on Earth's early surface included serpentinizing olivines that generated reducing power and alkaline environments (pH 10–11) that were subsequently neutralized by atmospheric CO₂.¹⁵ There is little doubt that after they “rained” into these aquifers, HCHO and HCN became (respectively) carbohydrates and formamide. Further, the literature reports examples where, upon heating or drying, formamide gives nucleobases,¹⁶ ribonucleosides are formed from nucleobases and carbohydrates,¹⁷ and ribonucleoside phosphates are formed from ribonucleosides and phosphate, polyphosphates, or phosphite.¹⁸

The literature also contains many reports of the formation of oligomeric RNA from ribonucleotides.¹⁹ Indeed, clay-catalyzed processes are reported to generate RNA up to 50 nucleotides in length.²⁰ Finally, oligomeric RNA molecules have been found to catalyze the synthesis of more RNA.²¹

Who could ask for more? Each step, from CO₂, H₂O, and N₂ to oligomeric RNA that might grasp Darwinian evolution before asphaltization has been illustrated by at least one working example.

So Why Is the “Discontinuous Synthesis Model” Not Compelling “Proof” for the RNA-First Hypothesis to the Bio-origins Community?

Leaving aside the elusiveness of “proof” for any interesting model in science, many in the bio-origins community do not accept the discontinuous synthesis model because it offers only disconnected steps that do not proceed from beginning to end without human intervention. Further, various steps have problems:

- The “asphalt problem”. Some steps in the discontinuous synthesis model are successful only if reactive compounds are presented in a specific order in large amounts. Failing controlled addition, the result is asphalt.
- The “water problem”. Many bonds in RNA are thermodynamically unstable with respect to hydrolysis in water. Thus, even if these are made in water, they will fall apart. Indeed, examples of RNA molecules that catalyze the template-directed synthesis of RNA²¹ are not accepted as a “final proof” of the RNA-first hypothesis in part because they work at high concentrations of Mg²⁺, which in turn catalyzes hydrolysis of product RNA.
- The “impossible bond problem”. Many bonds in RNA appear to be intrinsically challenging to form.

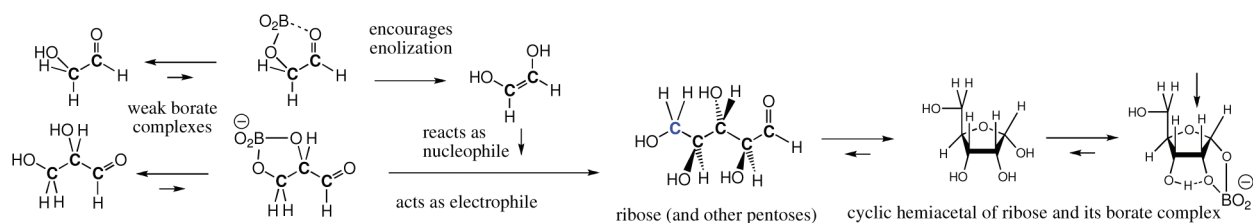


FIGURE 3. Influence of borate on the reaction of glycolaldehyde and glyceraldehyde.

How the Community Evaluates Efforts To Improve the Discontinuous Synthesis Model

If we accept RNA as our goal, the evident next step requires us to convert the discontinuous synthesis model into a community-acceptable model for the prebiotic synthesis of RNA. To illustrate what needs to be done to effect this conversion, consider two recent contributions to the formal model, and how they were criticized in the community.

Borate Minerals Address the “Asphalt Problem” When Forming Carbohydrates from Formaldehyde. One recent contribution from our laboratory¹³ tackled the “asphalt problem” associated with the formose process, which creates mixtures of carbohydrates from HCHO via incubation with calcium hydroxide at pH 10–11 and 60–80 °C. This environment was almost certainly present on early Earth from serpentinizing olivine.¹⁵

Electrical discharge almost certainly generated HCHO continuously in the early terran atmosphere.¹⁴ Because the HCHO carbon atom is intrinsically electrophilic (and therefore not prone to bond to the carbon atom from another HCHO), HCHO should have accumulated in primitive oceans and lakes, perhaps to millimolar concentrations.²² Only the Cannizzaro reaction, which converts two HCHO molecules to one molecule of formate (HCOOH) and one molecule of methanol (CH_3OH), unproductively prevents higher concentrations.

Detailed studies of the formose process showed that small amounts of glycolaldehyde, also made via electrical discharge through moist CO_2 atmospheres,²³ support catalytic reactions that “fix” large amounts of HCHO. New analytical techniques,²⁴ isotopic labeling, and kinetic studies gave a rule-based model for this process.¹³

These studies make inescapable the conclusion that formose carbohydrates were made on early Earth, given the near certainty that the Earth’s atmosphere delivered large amounts of HCHO and significant amounts of glycolaldehyde to the surface and that surface contained serpentinizing rocks. Indeed, it is difficult to imagine scenarios where formose carbohydrates were *not* made on early Earth. We must therefore think about their fate in aquifers that contained them.

In alkaline environments arising from serpentinizing olivines, absent human intervention, these carbohydrates are destined to form asphalt.²⁵ However, beneath a CO_2 -containing atmosphere, the pH of those aquifers would have dropped to neutrality.¹⁵ If the formose carbohydrates could have survived to this point and if they then gained access to amine-containing organic molecules, formose carbohydrates would have formed amino acids.²⁶ Given strongly dehydrating conditions, they may have even combined with nucleobases to form nucleosides,¹⁷ nucleoside phosphates,¹⁸ and RNA.¹⁹

However, for the bio-origins community to consider such optimistic scenarios, an “asphalt” problem needed to be addressed. The strongly alkaline conditions required to make carbohydrates under the formose process also cause the destruction of any compounds containing carbonyl ($\text{C}=\text{O}$) groups capable of “enolization”.^{24,25} Many formose carbohydrates have such $\text{C}=\text{O}$ groups. Thus, without human intervention on a prebiotic Earth, the classical formose process could not have yielded sufficient amounts of five-carbon carbohydrates (like ribose) to support nucleoside formation.

Thus, we looked for ways that useful carbohydrates (ribose and other pentoses), almost certainly *made* on a prebiotic Earth, might have also *accumulated*. Our experiments began by considering other minerals in alkaline aquifers surrounding serpentinizing rocks. In particular, igneous rocks often contain borate minerals.¹³ These are easily weathered to create borate-rich alkaline washes. Death Valley is a modern example of an intermountain valley whose chemistry is dominated by these processes; its soda lakes have highly concentrated borate in a desert environment conducive to dehydration reactions.

Borate binds to 1,2-diol units in organic molecules (Figure 3). This is especially true when its two hydroxyl groups are presented on a ring in a *cis*-conformation pre-organized to bind borate. Many carbohydrates do this in their cyclic hemiacetal forms. The borate complex of ribose is especially stable because of a network of hydrogen

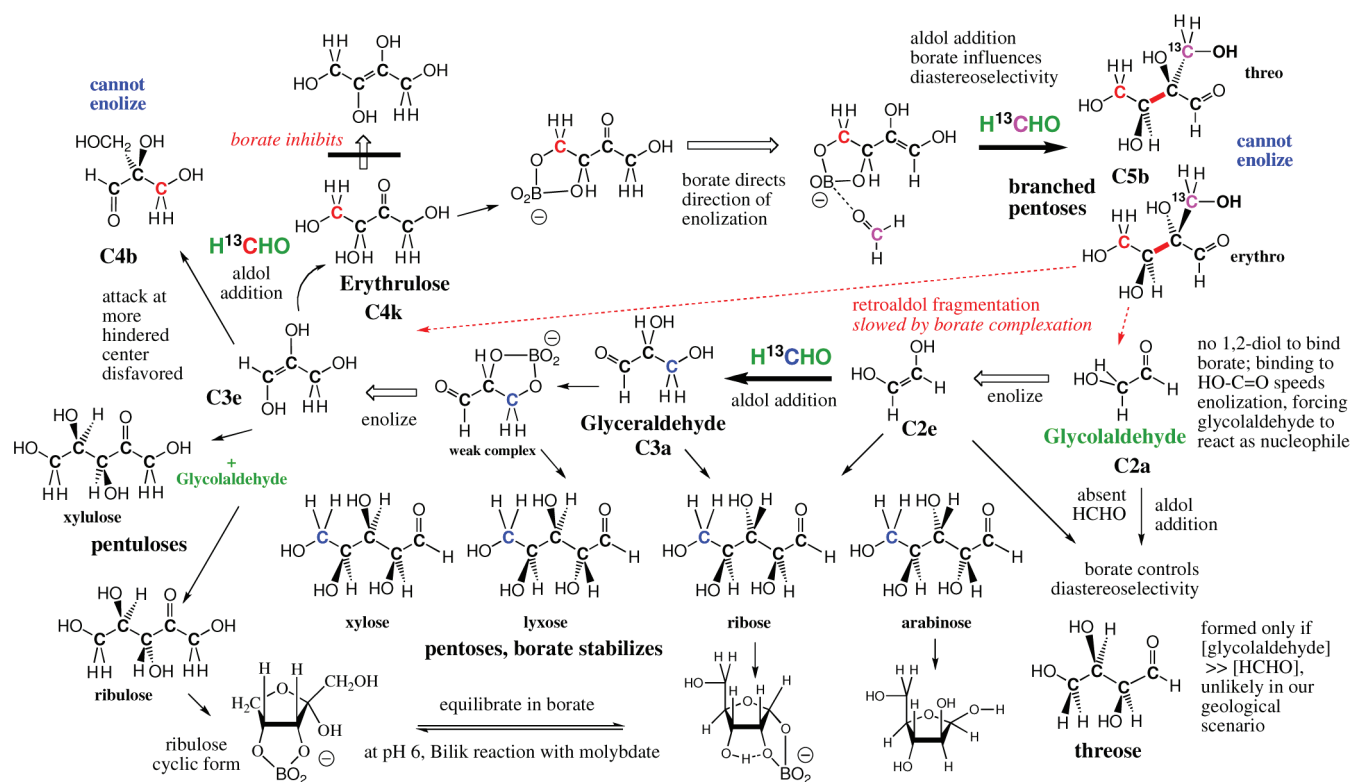


FIGURE 4. The borate-moderated formose process and the production of pentoses. Compounds originating in the atmosphere are **green**. C-13 labels are shown strategically. Features shown include the following: (a) Borate binds to 1,2-dihydroxy units; weak borate complexes with glyceraldehyde and erythrose modulate their reactivity. Strong complexes to ribose and ribulose in their cyclic forms drive their accumulation. (b) Borate enhances the enolization of glycolaldehyde. (c) Borate coordination to the erythrose diol drives enolization to the right and induces HCHO to add to the *more* hindered nucleophilic center to give branched pentoses. (d) The branched pentoses suffer retroaldol fission (red arrows) to generate more **C2a** and **C3e**, which fix more HCHO in a cycle. (f) The Bilik reaction²⁸ supports equilibration among various carbohydrates, as does reversible enolization. Thus, the borate-moderated formose manages the “asphalt problem” without human intervention and generates large amounts of **C5b**.

bonding permitted by its stereochemistry (Figure 3). If equilibration is possible, ribose and two pentuloses (ribulose and xylulose) accumulate as the predominant pentoses from a mixture.

But can pentoses be formed in the presence of borate under conditions where borate would stabilize them once they are formed? Our work showed that they could.²⁷ Glycolaldehyde (**C2a**) does not have a 1,2-diol unit but binds borate with its hydroxy-ketone unit; this increases its rate of enolization and encourages glycolaldehyde to enter aldol reactions as a nucleophile.

Glyceraldehyde (**C3a**) has a 1,2-diol unit but is not pre-organized by a ring to bind tightly to borate. This makes the borate/glyceraldehyde complex too weak to allow glyceraldehyde to accumulate. However, borate's transient binding slows base-catalyzed enolization of glyceraldehyde, and encourages glyceraldehyde to enter an aldol reaction as an electrophile.

Thus, when glycolaldehyde and HCHO are mixed under alkaline conditions in the presence of borate, pentoses (ribose,

arabinose, xylose, and lyxose) are formed (Figure 4). This indicates that glycolaldehyde reacts first as its enediol with HCHO to give glyceraldehyde, which borate constrains to react as an electrophile to give these pentoses. Had the enediol of glyceraldehyde reacted with glycolaldehyde as an electrophile, the product would have been ribulose and xylulose.

Thus, borate moderation of the formose process manages its “asphalt problem”, allowing useful carbohydrates to be made *and* to accumulate in a single pot without human intervention. However, borate complexation also prevents the pentoses formed from enolizing as the *next* step to fix *more* HCHO. Thus, borate appears to limit the amount of pentoses that might have accumulated on Earth to the amount of glycolaldehyde formed in the atmosphere. This would seem to generate too little ribose to support nucleoside synthesis and would waste the large amounts of HCHO expected to rain from prebiotic atmospheres into serpentinizing rocks.

Fortunately, borate acts to mitigate this limitation. For example, weak coordination by borate to the 3,4-diol unit of

erythrose directs its enolization toward C-1 (Figure 4). Further, this coordination also directs the addition of HCHO to the more hindered carbon of the enediol, leading to a pair of diastereomeric branched pentoses (**C5b**) (Figure 4). These branched pentoses, not observed without borate, form cyclic hemiacetals that presented two preorganized hydroxyl units to bind borate. Their borate complexes are strong and accumulate.

However, should borate depart, the branched pentoses immediately suffer retroaldol fission to give glycolaldehyde **C2a** and glyceraldehyde enediol **C3e**. While these could react with each other to form pentuloses, in the presence of HCHO, they fix still more HCHO, establishing a catalytic cycle.^{13,29}

This analysis of the formose process delivers an important conclusion: Five-carbon carbohydrates accumulate in borate-moderated formose processes *because they are the first species formed by one-carbon addition reactions that can form cyclic hemiacetals that present cis-diols preorganized for borate complexation*. In contrast, glycolaldehyde, glyceraldehyde, and erythrose do *not* accumulate because they do not present diols preorganized for borate complexation. Thus, given serpentinizing rocks weathering with igneous borates, a CO₂ atmosphere, and rain containing abundant prebiotic HCHO and catalytic glycolaldehyde, these results force the conclusion that branched carbohydrates, ribulose, xylulose, and pentoses (including ribose), almost certainly formed on early Earth and accumulated as their borate complexes. Indeed, it is hard to imagine scenarios for early Earth where they did *not* accumulate.³⁰

Sutherland Objected to Borate-Moderated Formose Processes As Relevant Prebiotic Routes to RNA³¹. Sutherland and his co-workers did not object to these conclusions. However, they noted (correctly) that the ribose formed in borate-moderated formose processes does not already have a nucleobase attached.³¹ Attaching a nucleobase to ribose was, they argued, an “insurmountable problem”, because coupling of an unactivated ribose and a pyrimidine is thermodynamically disfavored in water.

This is an example of the “water problem”, here with respect to the ribose–pyrimidine C–N bond, which Sutherland suggested was an “impossible bond” to form.³² To solve the “water problem” with respect to this bond, Sutherland et al.³¹ developed a previously adumbrated route to cytidine,³³ where the “impossible” ribose–pyrimidine bond is made *before* the ribose synthesis is complete. Unfortunately, this route relied on the timed delivery of large amounts of prebiotic aminooxazole, glycolaldehyde, and glyceraldehyde.³¹

Notwithstanding its merits, Sutherland's approach is discounted by many in the bio-origins community. It is perhaps

easy to see why. In their attempt to avoid the “water problem” for the glycosidic bond, Sutherland et al. drive themselves back into the “asphalt problem”. Their alternative synthesis requires human addition (at the right times) of high concentrations of two carbohydrates, glycolaldehyde and glyceraldehyde. These carbohydrates are too reactive to accumulate prebiotically, even with borate.

Reviewing Sutherland's proposed route, Shapiro noted that it resembled a golfer, having played an 18 hole course, claiming that he had shown that the golf ball could have, through some combination of wind, rain, heating, cooling, dehydration, and ultraviolet irradiation played itself around the course without the golfer's presence.³⁴

Perhaps recognizing this, Sutherland and his co-workers wrote “Although the issue of temporally separated supplies of glycolaldehyde and glyceraldehyde remains a problem, a number of situations could have arisen that would result in the conditions of heating and progressive dehydration followed by cooling, rehydration and ultraviolet irradiation. Comparative assessment of these models is beyond the scope of this work.”³¹ In Shapiro's view, the need for “temporally separated supplies of glycolaldehyde and glyceraldehyde” is more than “a problem ... beyond the scope” of this work. It is a fatal flaw.

In addition, Sutherland's concern about of the “water problem” in contesting the prebiotic relevancy of the borate-moderated formose process raises an interesting logical conundrum. While it is certainly true that the “water problem” applies to bonds holding nucleobases to carbohydrates, many *other* bonds in RNA are *also* thermodynamically unstable in water. These include the bonds holding the amino groups to adenine, guanine, and cytosine (all suffer deamination in water) and the phosphodiester links that hold the RNA backbone together. The “water problem” must be solved for *all* of these. It is conceivable that if a solution is found for the “water problem” for these other bonds, it might solve the problem for the glycosidic bonds.

Needed: A Continuous Synthesis Model for Prebiotic RNA

At the very least, a continuous synthesis model must deliver RNA from CO₂, H₂O, and N₂, without human intervention, in steps having plausible geological context. Further, no step may involve introducing materials with “temporal precision”. The process must do all of the following:

1. Create bonds attaching nucleobases to ribose from borate-moderated formose processes.
2. Introduce phosphorus, recognizing the insolubility of phosphates in many geological settings.

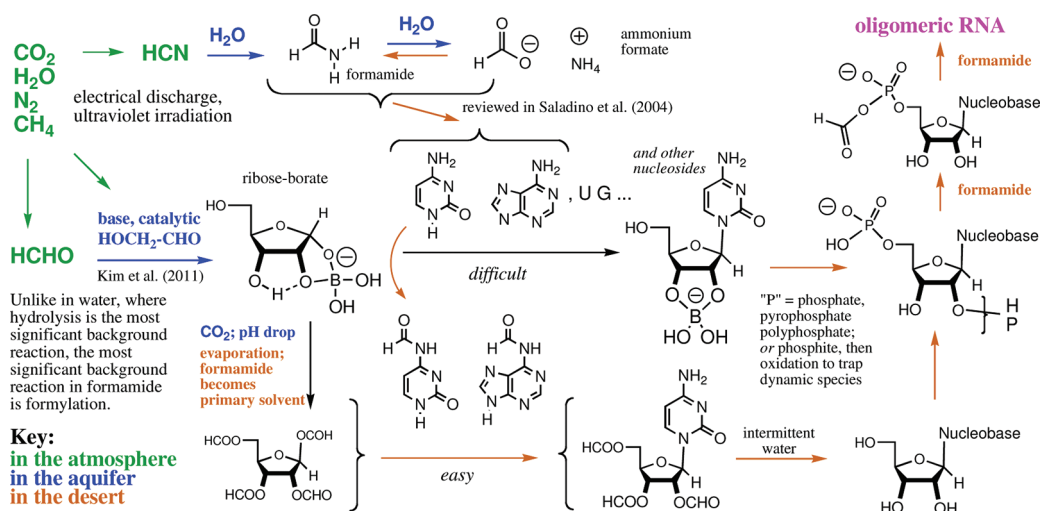


FIGURE 5. A continuous synthesis model for RNA in an intermountain desert valley supplied by a watershed having serpentinizing olivines and eroding tourmalines. (a) HCHO, HOCH₂-CHO, and HCN are formed in CO₂-H₂O atmosphere by lightning and UV.^{14,22} (b) These species are rained into serpentinizing aquifers containing borate, giving formamide, ammonium formate, and carbohydrates (including borate-stabilized ribose).¹³ (c) Atmospheric CO₂ lowers the pH to ~6.¹⁵ (d) Borate releases ribose below pH ≈ 7, and mild molybdate-catalyzed Bilik reactions produce stereospecific carbohydrate rearrangements.^{13,28} (e) Adding nucleobases to a ribose whose 1-position is activated (e.g., as an ester with a carboxylic, phosphorus, or phosphoric acid) is a robust reaction. (f) With 2-esterified ribose, the stereochemistry of the ribonucleoside is the desired β. (g) Desert dehydration makes formamide the solvent and a precursor for nucleobases, makes boron a better electrophile (and leaving group), creates phosphorylating agents from phosphate, and drives formation of phosphite esters; various phosphorus-containing species are collectively represented as "P". (h) Oligomerization in formamide generates N-formylated nucleobase derivatives. (i) Formate esters are easily hydrolyzed in intermittent water, as are N-formylated nucleobases (half-life ~1 month at 80 °C, pH 6); partially protected oligomeric RNA is deprotected after it is delivered to water.

3. Generating oligomeric RNA without undoing the formation of water-sensitive bonds.

The availability of borate-stabilized carbohydrates that escape asphaltization, if only transiently, helps. More help comes from the developing appreciation that formamide, the hydrolysis product of HCN, is a more useful prebiotic reagent than HCN itself.¹⁶ Adenine, guanine, cytosine, and uracil can be formed from formamide, ammonium formate (its hydrolysis product), and HCHO. The aromaticity of the nucleobases allows them to escape asphaltization (at least transiently).

Our favored model is associated with a specific geology:

1. The environment where oligomeric RNA is synthesized is hypothesized to be a subaerial intermountain desert valley.³⁵
2. Temperatures in the valley range from -20 to 60 °C, with higher temperatures intermittently achieved by geothermal activity.
3. The valley collects runoff from a watershed containing serpentinizing olivines and igneous tourmalines, which collect atmospheric HCHO and HCN.
4. The runoff begins as borate-rich aquifers having pH values of 10–11. These contain borate-stabilized carbohydrates, formamide, and ammonium formate,

representing the inventory of the atmospheric HCHO and HCN that was rained into the watershed.

5. The pH in the valley is buffered by atmospheric CO₂ to 6¹⁵ but is intermittently raised as alkaline solutions are reintroduced.
6. The redox potential is ca. -150 mV, maintained by serpentinizing olivines and mantle minerals, allowing phosphate to be in equilibrium with phosphite, avoiding the intrinsic insolubility of phosphate,³⁶ and allowing oligomeric phosphites and phosphates to oligomerize on mineral surfaces, including those of phosphite, phosphate, arsenite, arsenate, and vanadate minerals.
7. The environment frequently suffers evaporation to the point of dehydration, followed by rehydration. A modern analog of this environment is the Sierra Nevada–Death Valley system, differing first because the modern atmosphere, poor in CO₂, allows the valley today to remain alkaline. Further, in any modern valley, any microbial community showered with formate uses formate dehydrogenase to generate reducing power and CO₂. In our prebiotic valley, compounds accumulate (or not) depending only on their chemical reactivities.

This means that liquids other than water were available as solvents in this prebiotic valley. This includes organic

liquids like formamide, which boils at ~ 210 °C, freezes at ~ 0 °C (and below this if it contains some water), and displays a hydrophobic effect (oil and formamide do not mix). Thus, in our prebiotic intermountain environment, formamide must have been left behind upon evaporation. Daniel Hutter in our laboratory showed that at equilibrium, the amount of water in formamide at 42 °C ranges from 8% to 41% as the relative humidity above it rises from 11% to 98%.

One consequence of moving from water to formamide is the transition from an environment having a nucleophilic “background reactivity” to one having an electrophilic “background reactivity”. In water, every phosphate bond, every glycosidic bond, and every heterocyclic amino group can be lost through hydrolysis. In formamide, none of them are.

In formamide, instead of electrophilic solutes being attacked by the nucleophilic oxygen of water, nucleophilic solutes are attacked by the electrophilic carbon of formamide. Some of these reactions are shown in Figure 5. The electrophilic background of formamide allows nucleobases to form and to be formylated. Formamide allows carbohydrates to be derivatized by electrophiles, including phosphate and phosphite, but also by formamide itself. In particular, ribose is converted to its O-formylated derivatives.

This manages directly the objection by Sutherland with respect to the “impossible” glycosidic bond. Although borate–ribose might react directly with nucleobases to give nucleosides in dehydrating conditions, formylated ribose certainly does, with its 1-formyl leaving group and a 2'-O carbonyl group that gives the desired β stereochemistry.

Formamide also may permit formation of oligomeric RNA. For historical reasons, work with template-directed and clay-catalyzed polymerization has focused on pyrophosphate, methylimidazole, and methyladenine as leaving groups. The first is unavoidable in dehydrating environments containing phosphate. The last is a conceivable (although unknown) product of prebiotic transformations of formamide.

However, formamide in an electrophilic “background reactivity” offers an alternative leaving group: formate. Indeed, mixed anhydrides between phosphate and formate are expected as the inevitable products of the reactivity of these species in formamide.

Last, geological environments are rarely static. In our model, the environmental fluctuations work to our advantage. The pH of the valley floor is expected to oscillate from conditions where borate–ribose is stable to those where the complex dissociates. The pH at which the borate–ribose complex dissociates also allows molybdate to create linear

carbohydrates from branched carbohydrates, all under mild conditions that do not generate asphalt.^{13,28} The ratio of formamide to water in the liquid phase also oscillates in an intermountain desert. A high ratio is needed for formamide to react as a precursor for nucleobases, be formed from ammonium formate, and serve as a solvent to manage the “water problem”.

Unsolved Problems

If our hypothesis is correct, oligomeric RNA was formed continuously in intermountain dry valleys on prebiotic Earth. Its carbon, nitrogen, and oxygen atoms originated in HCHO, HCN, and H₂O. Its phosphorus atoms originated from a phosphate–phosphite baths. A few classes of mineral species, including borate, silica–alumina clays, and molybdate, and the replacement of a solvent (water) having a nucleophilic “background reactivity” by a solvent (formamide) having an electrophilic “background reactivity”, all provided control over asphaltization. Together, these features make RNA appear to be a natural outcome of chemistry of prebiotic Earth.

Two issues are not resolved by the model. First, we have not addressed the “chirality problem”. Here, the challenge arises as we attempt to select from among a large number of possible approaches for chiral enrichment, ranging from the interaction of organic species with chiral minerals (e.g., quartz) to the resolution at the time of oligomerization.

Last, current experiments suggest that RNA molecules that catalyze the degradation of RNA are more likely to emerge from a library of random RNA molecules than RNA molecules that catalyze the template-directed synthesis of RNA, especially given cofactors (e.g., Mg²⁺). This could, of course, be a serious (and possibly fatal) flaw to the RNA-first hypothesis for bio-origins. However, this question can be explored independent of any model for prebiotic chemistry.³⁷

Note Added after ASAP Publication. This paper was published on the Web on March 28, 2012. A reference was omitted showing that the late Robert Shapiro's critical views of prebiotic chemistry in general also applied to the 2009 model of Powner et al. That reference has been added as ref 38. The corrected version was reposted on June 11, 2012.

BIOGRAPHICAL INFORMATION

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FOOTNOTES

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The authors declare no competing financial interest.

Dedicated to the memory of Robert Shapiro.

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