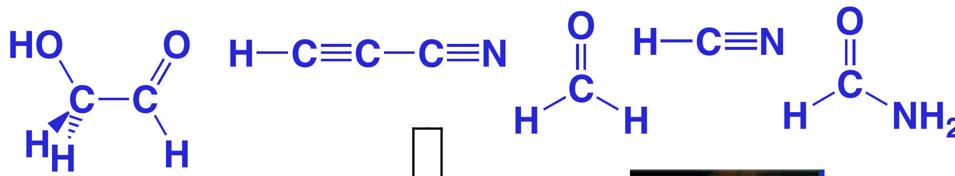
Work on Origins at the FfAME

The Westheimer Institute for Science and Technology

the foundation for applied molecular evolution

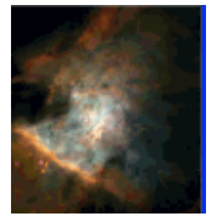
Prebiotic Chemistry



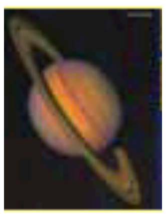
interstellar organics

Ricardo *et al*. (2004) *Science* **303**, 196

forward in time



A path to the simplest first life



understand better the possibilities

an independent genesis?

Explore Solar System

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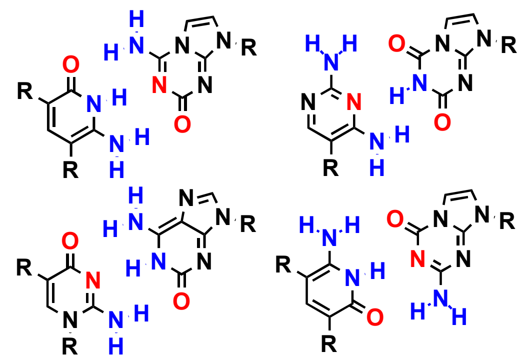
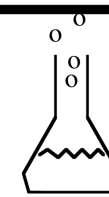
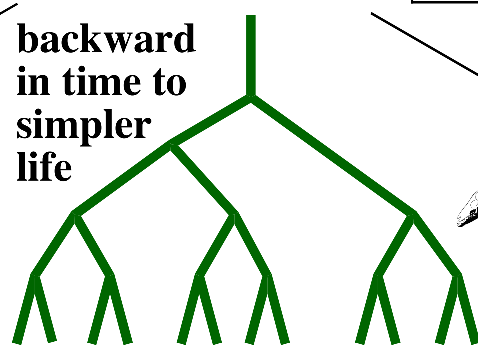
Construct alternatives in the lab



Synthetic biology



backward in time to simpler life



Eucarya Archaea Bacteria

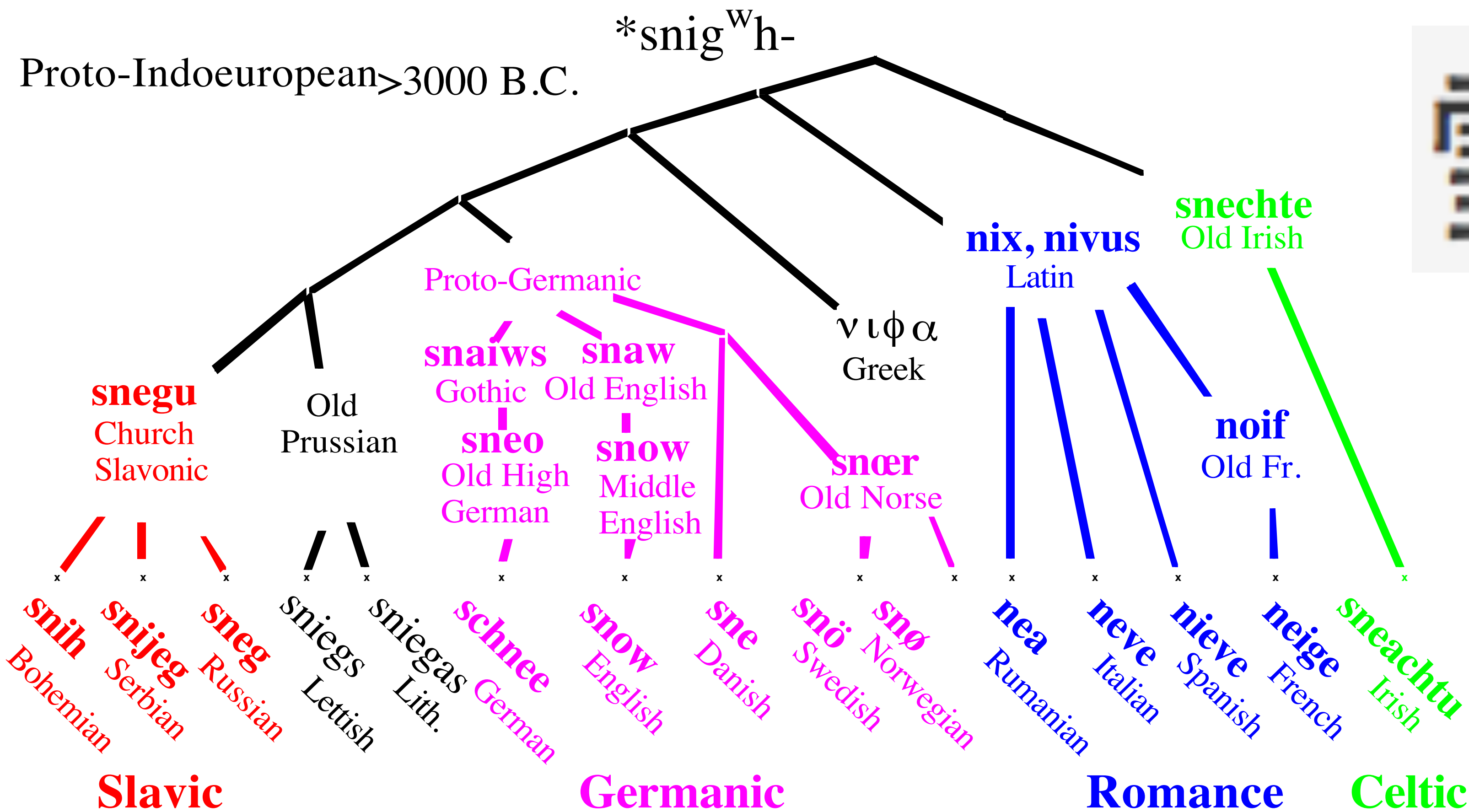
infer ancestral life forms; resurrect for laboratory study

Paleogenetics

Benner *et al*. (2007) *Adv. Enzymol. Mol. Biol. Protein Evol*. **75**, 1-132

Going back in time

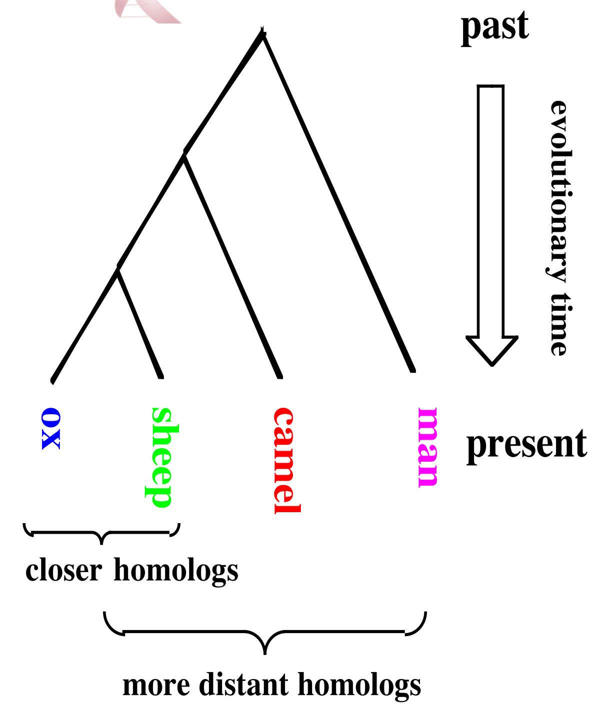
Infer ancestral forms from descendent forms

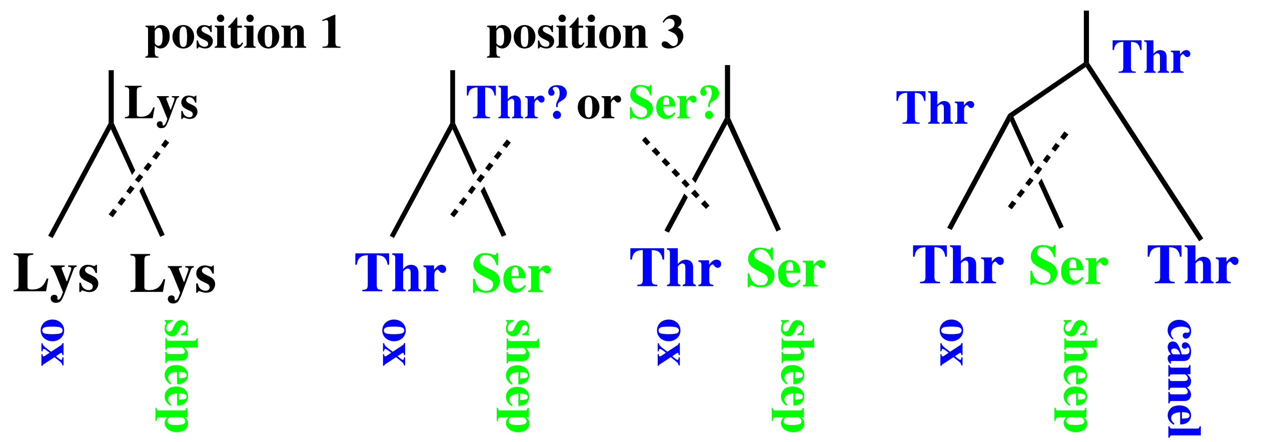


Reconstruction says something about the Proto-Indoeuropeans

They lived where it snowed. No gold. But dogs (*kwón-), horses (*ékwo-), sheep (*^{H3}éwi-), ox (*g^{w}ów-), pigs (*su^{H}-), grain (*yewo), vehicles (*wogho-) with wheels (*k^{w}ek^{w}lo-); Count to 100 (*kmtóm)

Amino acids in protein sequences are like the letters in words





1 reconstruction no mutation

both reconstructions require one mutation

add outgroup; best reconstruction clear

```
                   10        20
              .    |    .    |
ox       KETAAAKFERQHMDSSTSAA
         || ||||||||||||||| |
sheep    KESAAAKFERQHMDSSTSSA
camel    SETAAEKFERQHMDSYSSSS
Ancestor KERAAAKFERQHMDSSTSSA
```

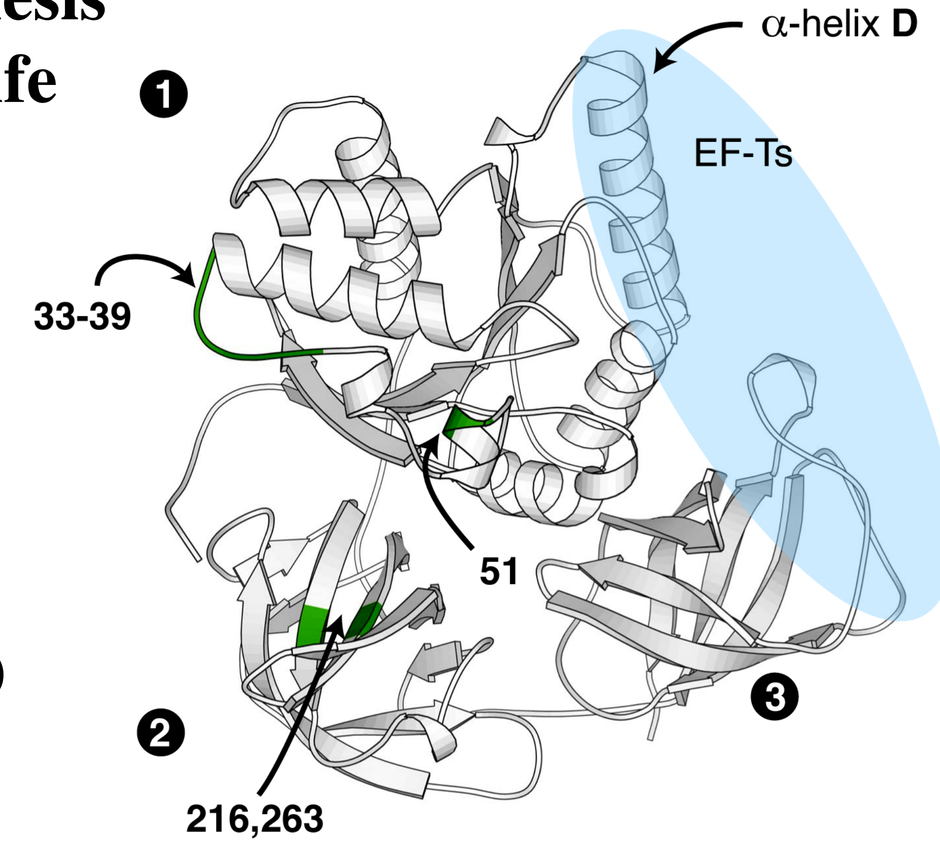
Paleogenetics:

Use recombinant DNA technology, to bring ancient proteins back to life for study

Resurrect ancient life forms

Use biotechnology to make ancient genes and proteins

- **Elongation factor (EF) presents amino acids to ribosomes for protein synthesis**
- **EF homologous in all terran life**
- **Sequences of 3 billion year old ancestral EF inferred from descendent sequences**
- **Ancient EF resurrected**

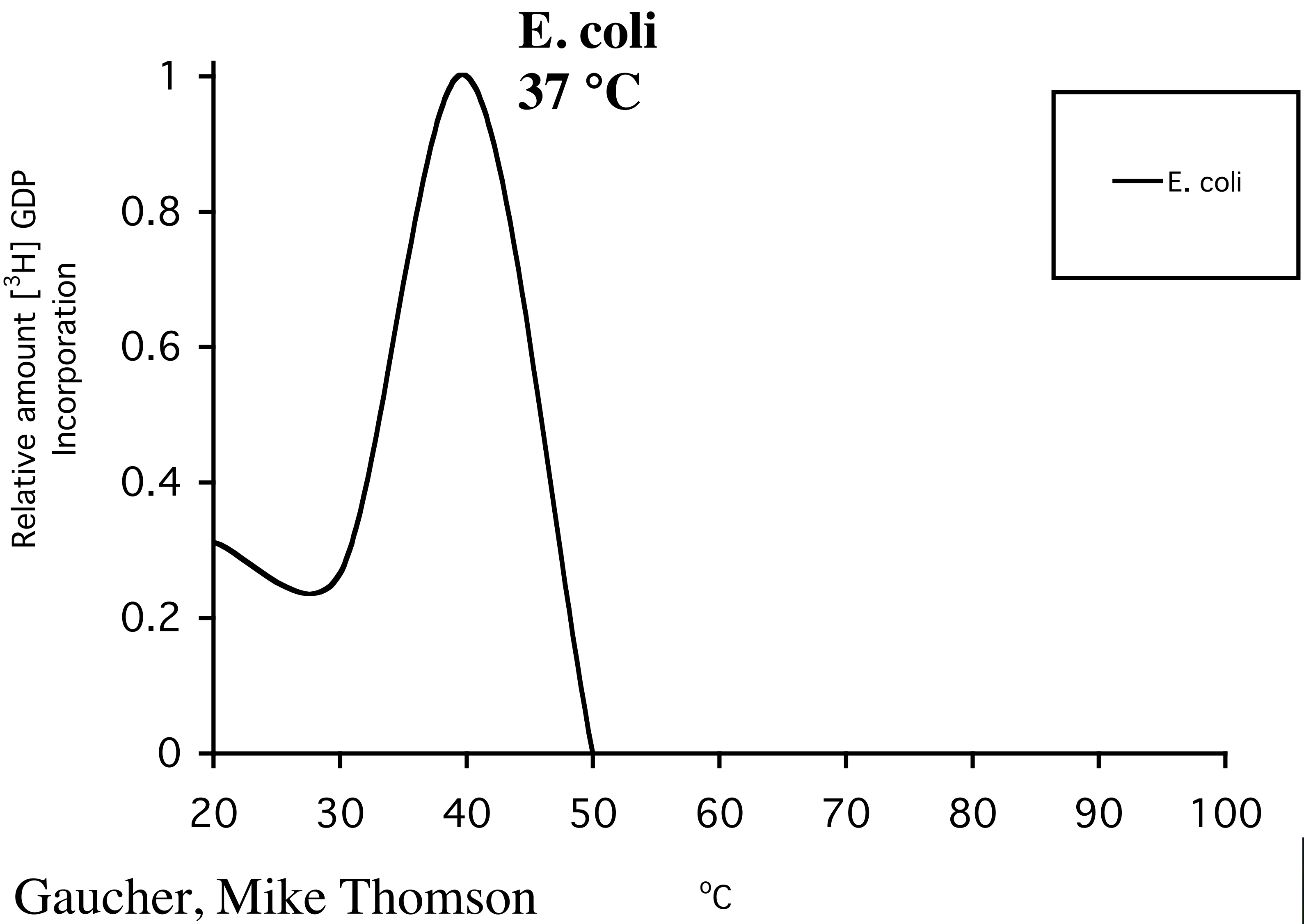


Elongation Factor

Gaucher, E. A., Thomson, J. M., Burgan, M. F., Benner, S. A. (2003) Inferring paleoenvironments based on resurrected ancestral proteins.

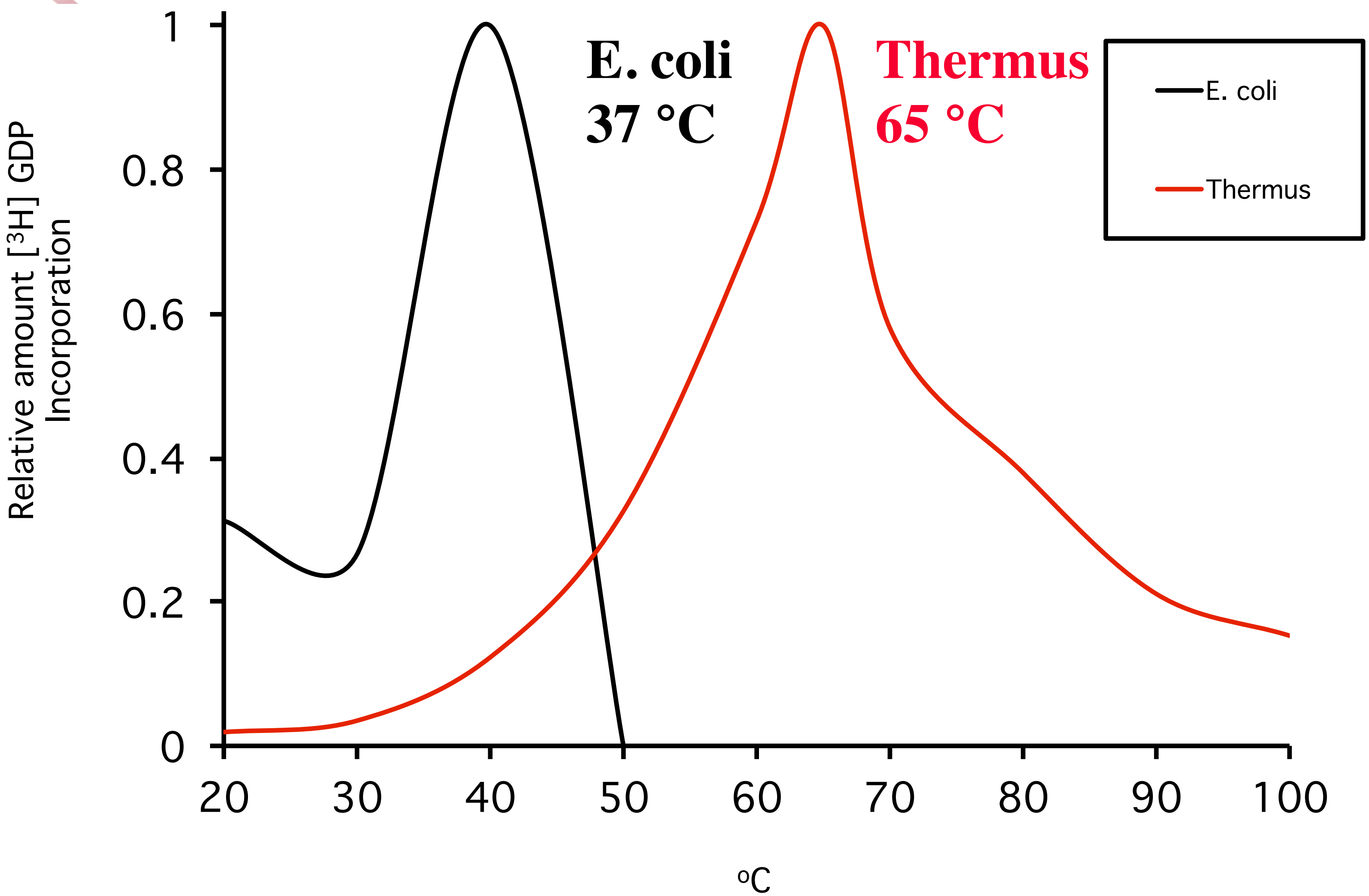
Nature **425**, 285-288

Elongation factors maximally active at surrounding temperature



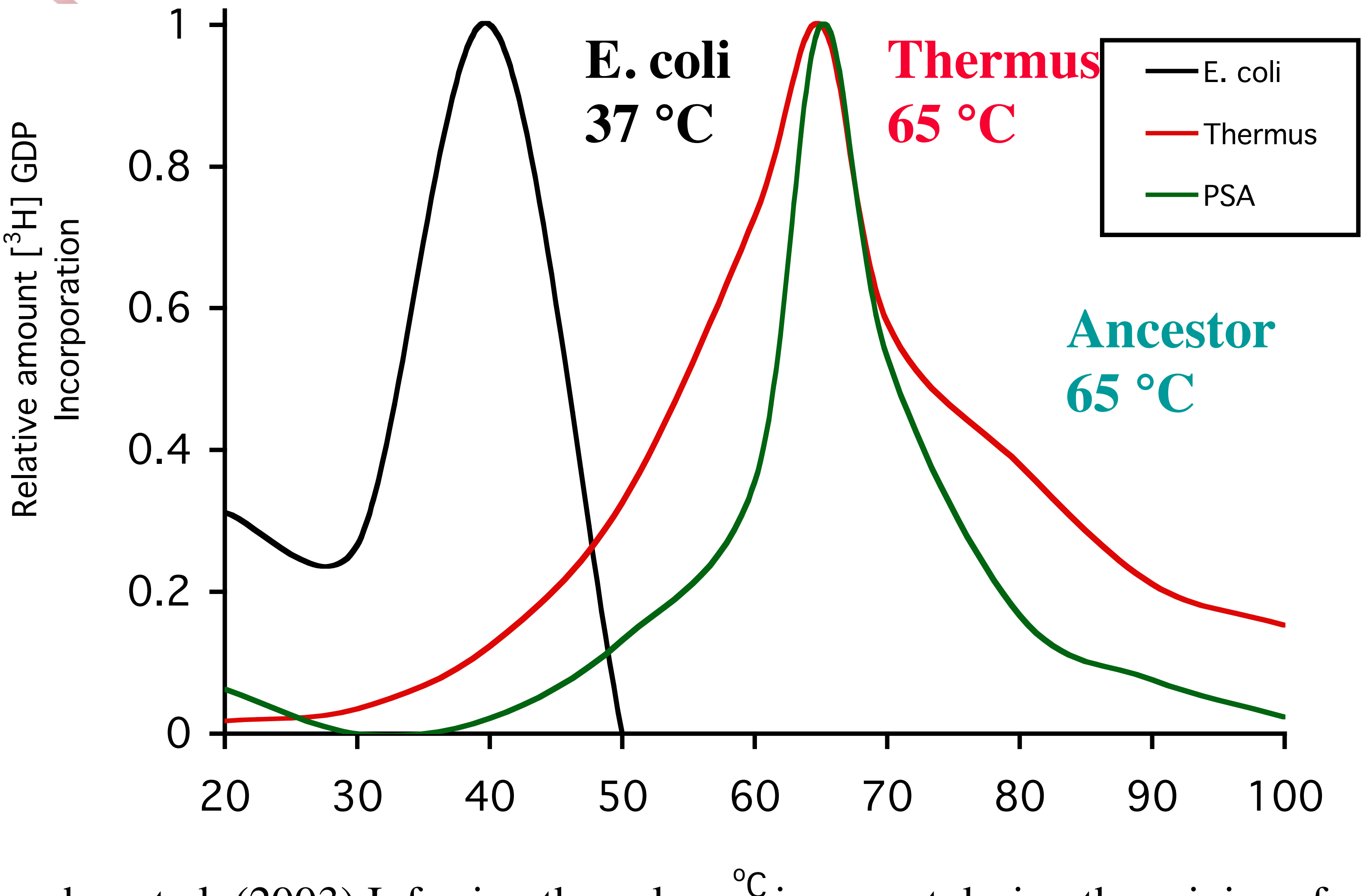
Eric Gaucher, Mike Thomson

Elongation factors maximally active at ambient temperature



At what temperature does the resurrected 3 billion year old Elongation Factor work best?

Ancestral elongation factor most active at 65°C

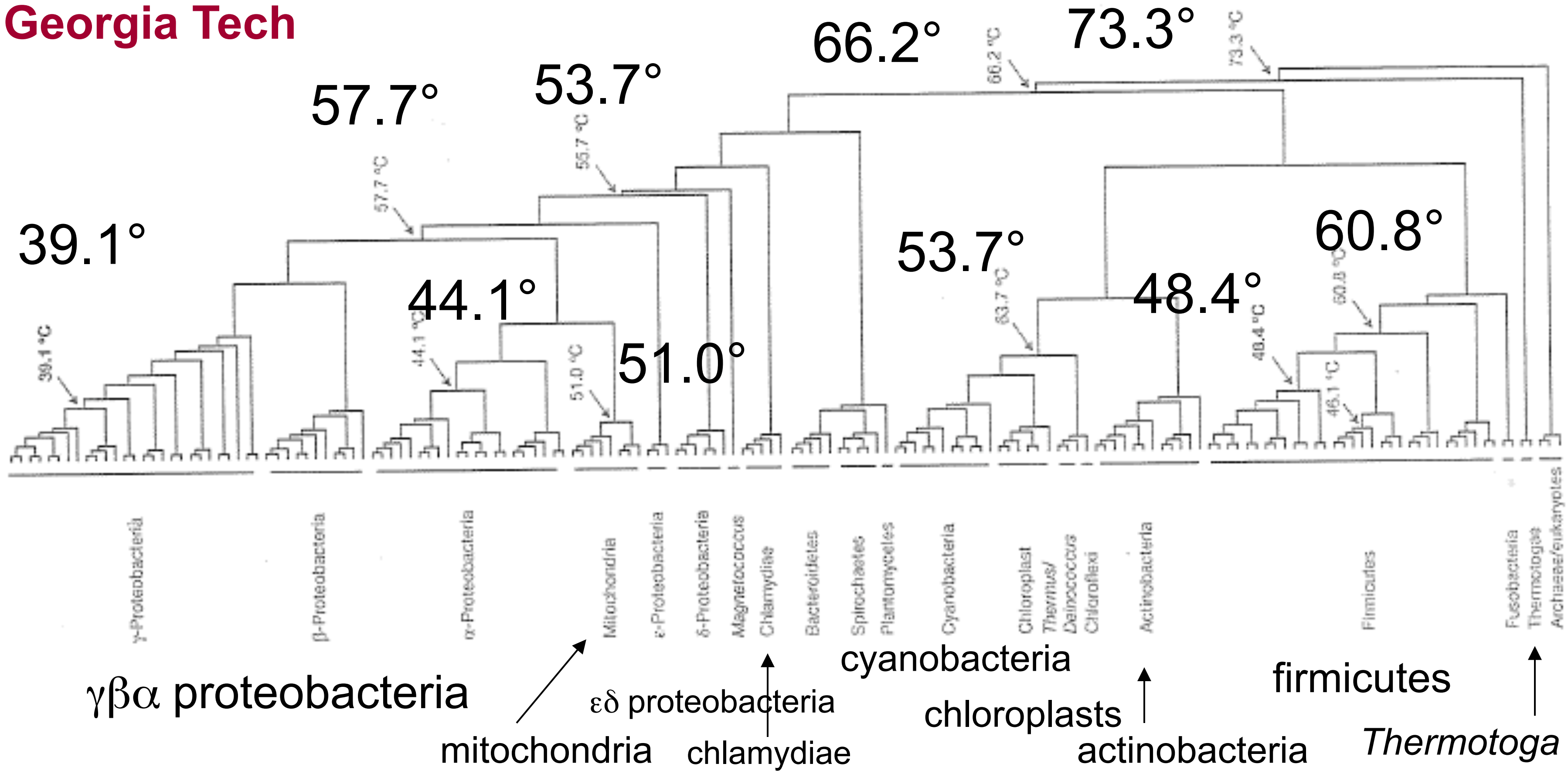


Gaucher et al. (2003) Inferring the paleoenvironment during the origins of bacteria based on resurrected ancestral proteins. *Nature* **425**, 285-288

Begley (2004) *Wall Street Journal*, B1 (April 30)

Temperature history of elongation factors for eubacterial ribosomes

Eric A. Gaucher
Georgia Tech



The ancient RNA-based machine to make proteins

Westheimer Institute

the foundation for applied molecular evolution

FAME

Bioinformatics to analyze the *entire* genome database

Gonnet, G. H., Benner, S. A (1992). Exhaustive matching of the protein sequence database. *Science* **256**, 1443

Gaston Gonnet

A proposed metabolism for last RNA world organism, guy who invented the ribosome

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 7054–7058, September 1989
Evolution

Modern metabolism as a palimpsest of the RNA world

STEVEN A. BENNER*, ANDREW D. ELLINGTON†, AND ANDREAS TAUER

*Laboratory for Organic Chemistry, Eidgenössische Technische Hochschule, CH-8092 Zurich, Switzerland; and †Department of Molecular Biology, Massachusetts General Hospital, Boston, MA 02114

Communicated by F. H. Westheimer, May 15, 1989

ABSTRACT An approach is developed for constructing models of ancient organisms using data from metabolic pathways, genetic organization, chemical structure, and enzymatic reaction mechanisms found in contemporary organisms. This approach is illustrated by a partial reconstruction of a model for the "breakthrough organism," the last organism to use RNA as the sole genetically encoded biological catalyst. As reconstructed here, this organism had a complex metabolism that included dehydrogenations, transmethylations, carbon-carbon bond-forming reactions, and an energy metabolism based on phosphate esters. Furthermore, the breakthrough organism probably used DNA to store genetic information, biosynthesized porphyrins, and used terpenes as its major lipid component. This model differs significantly from prevailing models based primarily on genetic data.

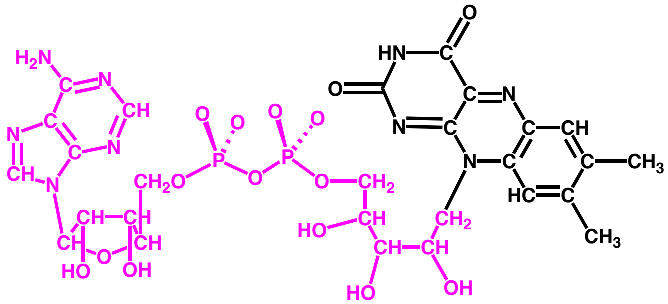
origin of translation, and other events that occurred in the RNA world.

If several descendants of an ancient organism can be inspected, a rule of "parsimony" can be used to model the biochemistry of the ancestral organism by extrapolation from the biochemistry of the descendant organisms. The most parsimonious model is one that explains the diversity in the modern descendants by a minimum number of independent evolutionary events. For the progenote, three independent lineages of descendants are known (archaebacteria, eubacteria, and eukaryotes). Thus, a biochemical trait present in all three can be assigned to the progenote. The assignment is strongest when (*i*) the trait is found in several representative organisms from each of the three kingdoms; (*ii*) assignments of homology in various branches of the progenotic pedigree are supported by high information content (preferably se-

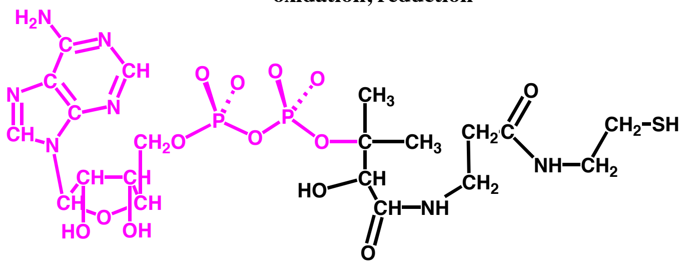
Lots of RNA
Maybe RNA supported *first* Darwinian system

The farther back in time, the more RNA

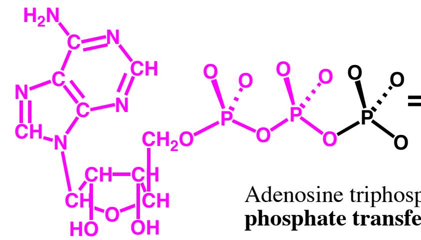
Harold White, Cornelius Visser, Richard Kellogg



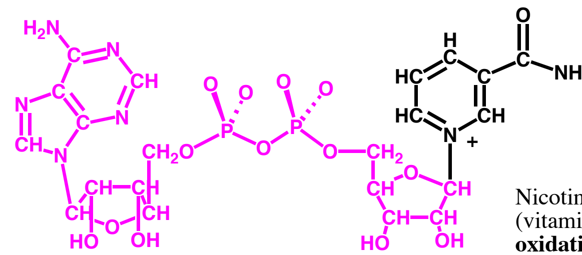
Flavin adenine dinucleotde
(vitamin = riboflavin)
oxidation, reduction



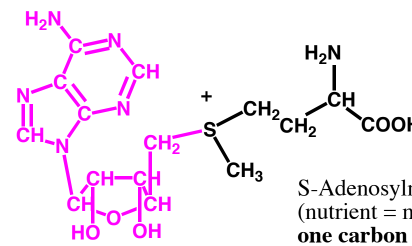
Coenzyme A
(vitamin = pantothenic acid)
carbon-carbon bond formation



Adenosine triphosphate (ATP)
phosphate transferenergy transfer



Nicotinamide adenine dinucleotde
(vitamin = niacin)
oxidation, reduction



S-Adenosylmethionine
(nutrient = methionine)
one carbon transfer

RNA World? Where RNA did *both* genetics *and* catalysis.

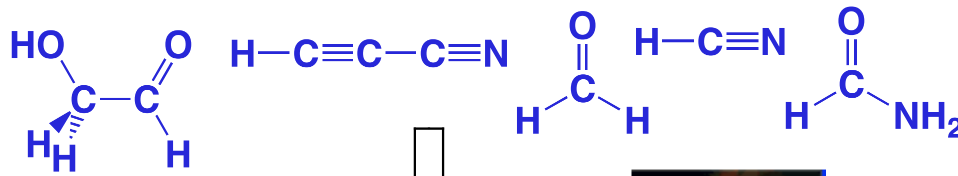
- **The RNA world had a rich metabolism based on RNA cofactors**
- **B12 and possibly chlorophyll emerged in the RNA world**
- **The RNA world invented terpenes**

But this is not at the *origin* of chemical Darwinianism

Alternative: Forward in time

the foundation for applied molecular evolution

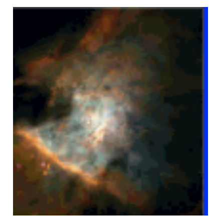
Prebiotic Chemistry



interstellar organics

Ricardo *et al*. (2004) *Science* **303**, 196

forward in time



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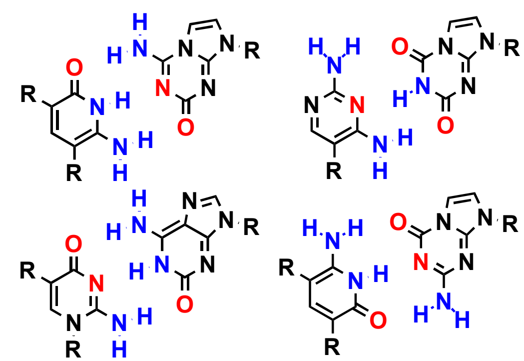

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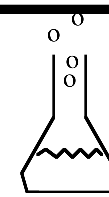

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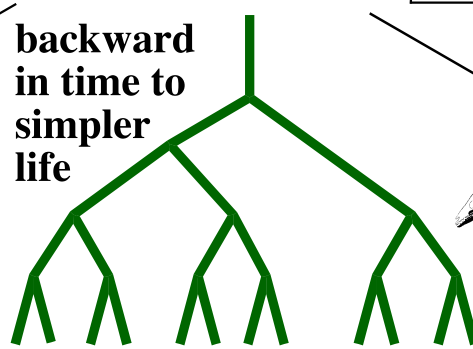

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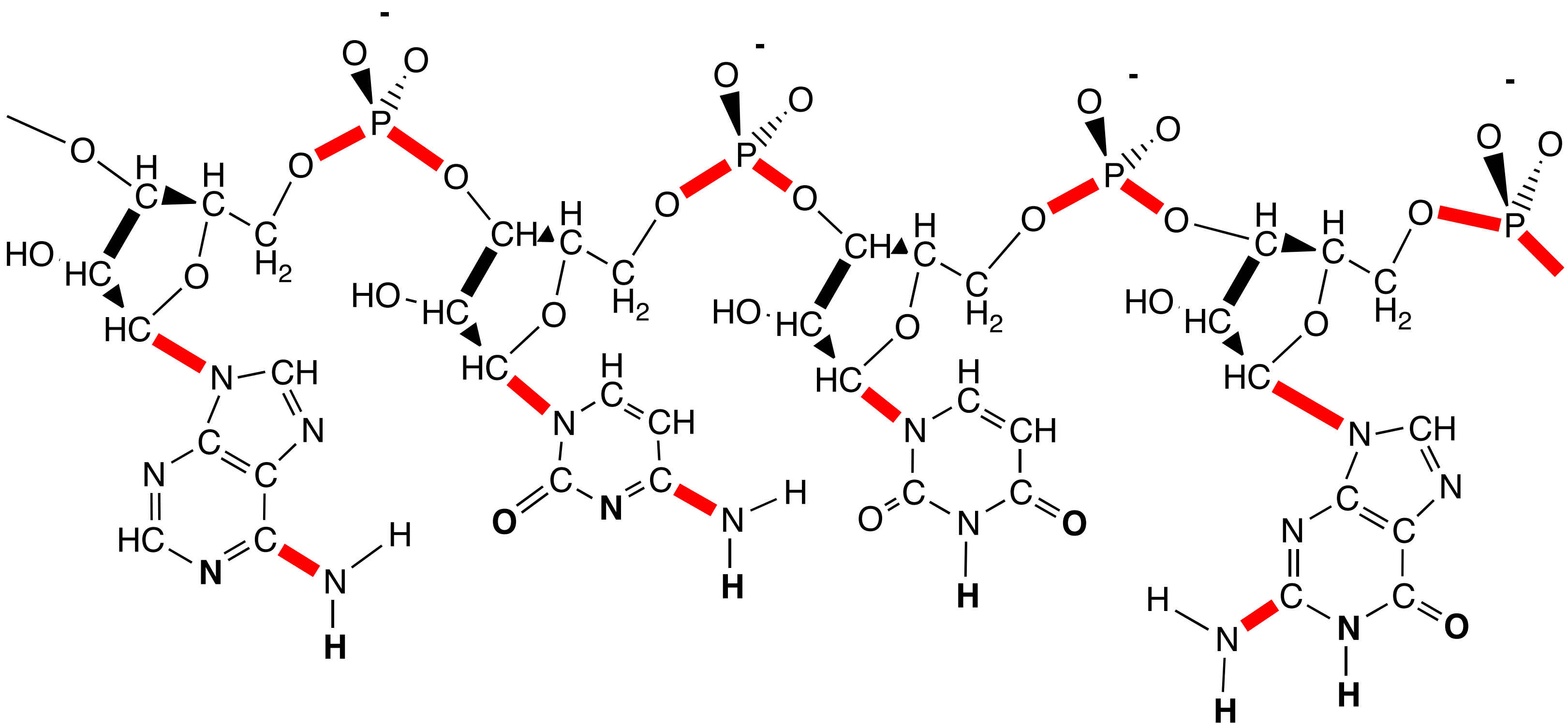
Problems in RNA-first model

1. **The water paradox**
2. **The tar paradox**

Half of the bonds in RNA are unstable in water (you do repair)

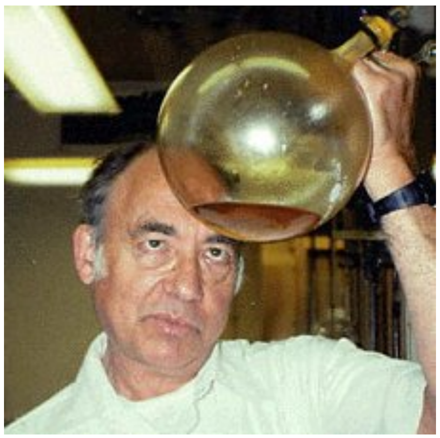


Paradox: Water necessary for life

Corrosive water destroys biopolymers also necessary for life

The Tar Paradox

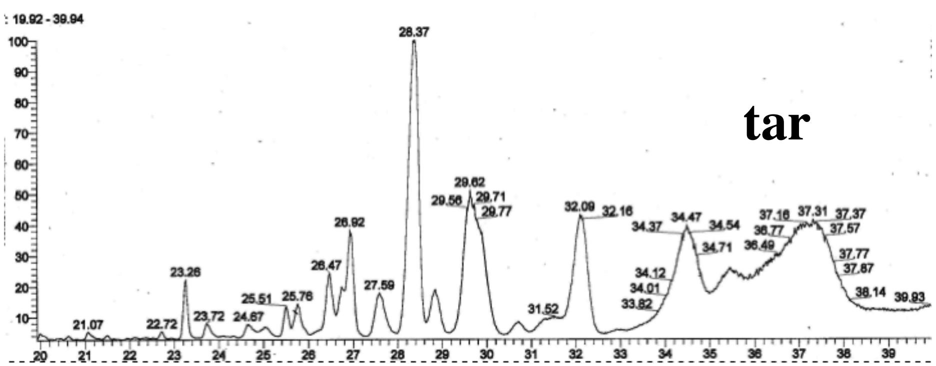
What organic systems do if given energy, *versus*
What organic systems do if given energy *and* Darwinian evolution



Stanley Miller

Energy + organic matter becomes tar

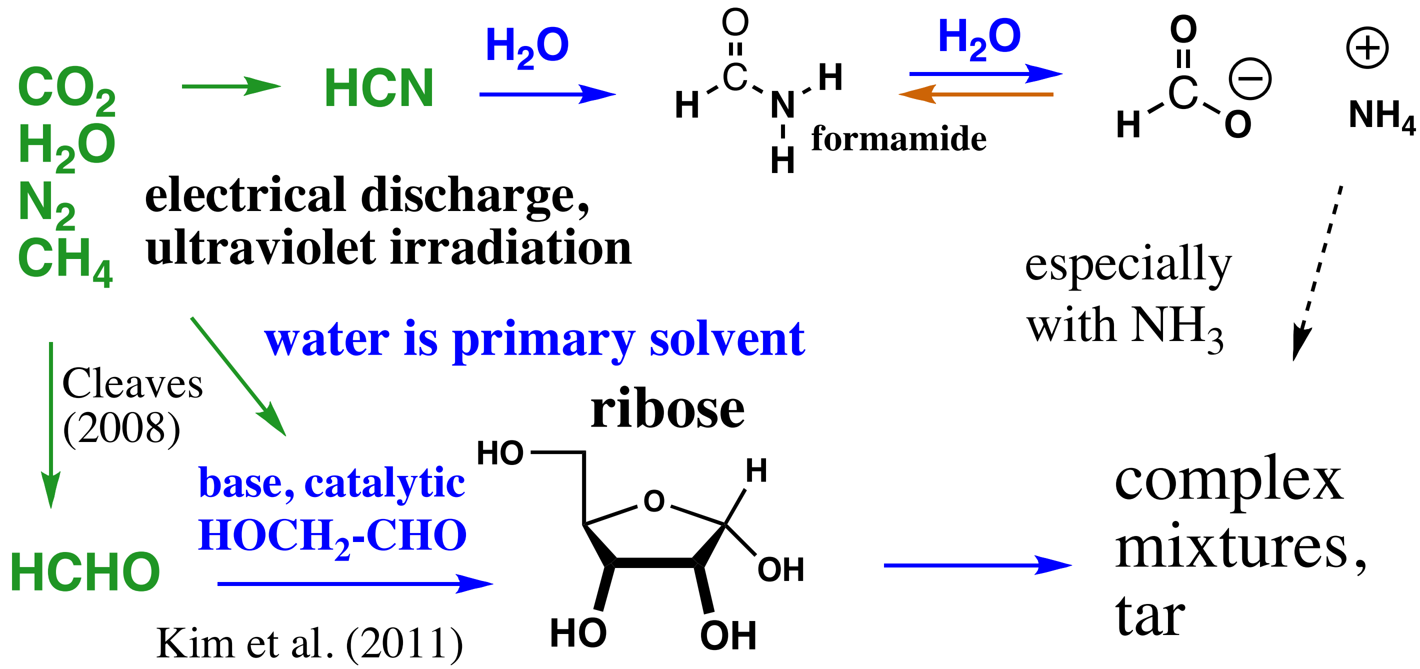
On Earth, given liquid water, Darwinian evolution exploits any chemical disequilibrium to give the chemical order called life

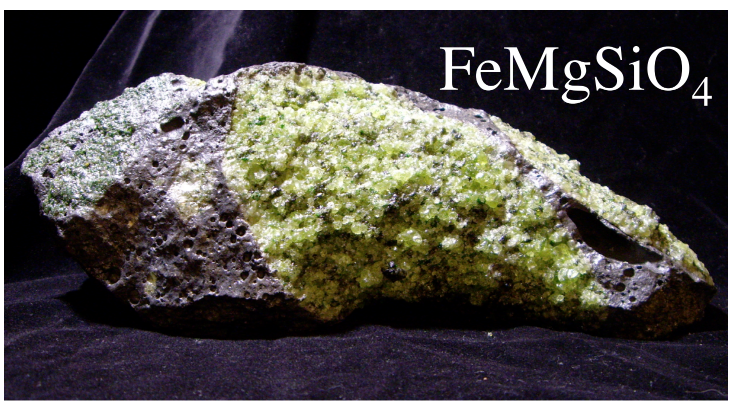


On prebiotic Earth, any assemblages of organic matter, as they devolve to tar, must discover a way to leap into Darwinianism

Discontinuous RNA Synthesis Model

Provides the leap from tar to Darwin





Atmospheric chemistry is robust
Aqueous erosion of olivines generates the high pH (~ 11) needed to get compounds with a C=O unit to react.

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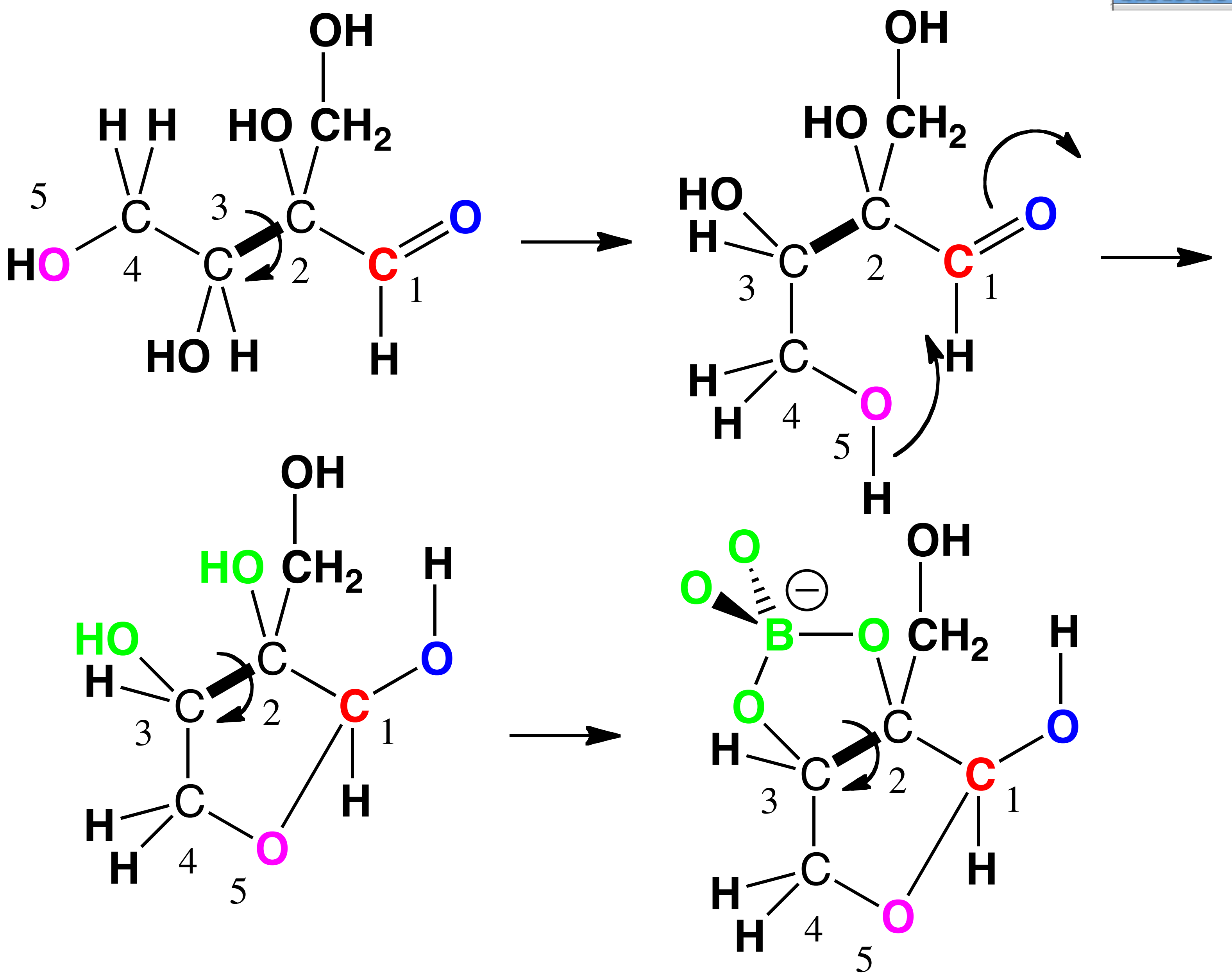
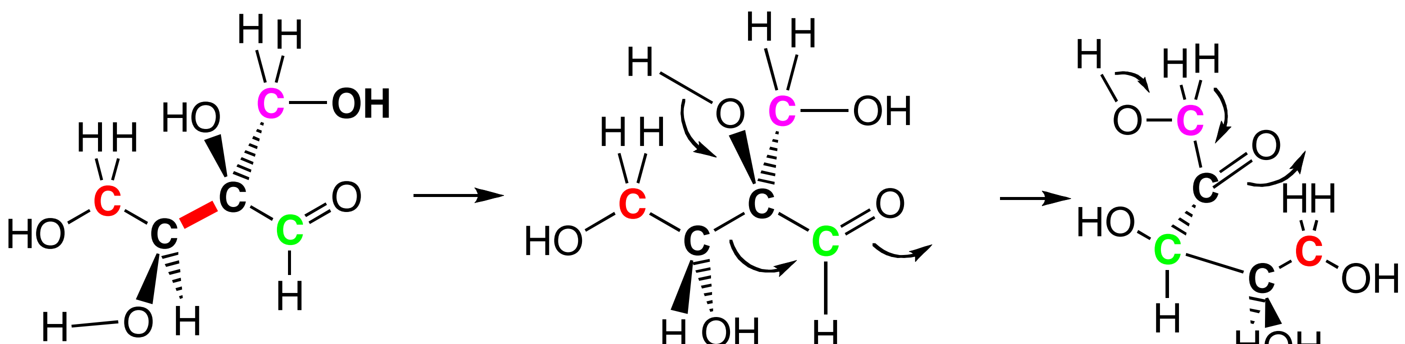
Avoid tar in borate complex

the foundation for applied molecular evolution

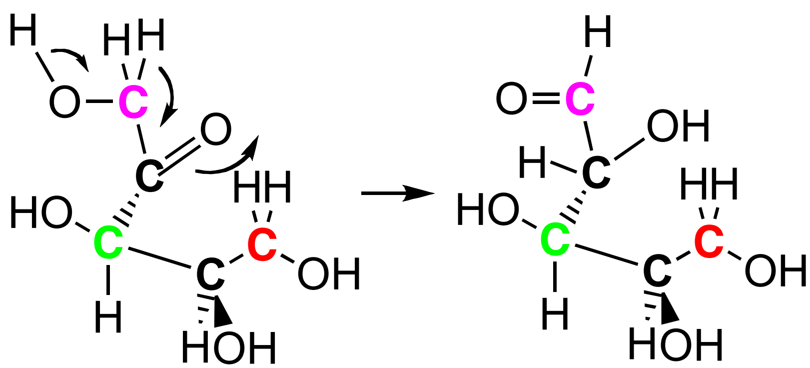


Mo (VI) funnels all C-5 carbons into ribose



C5b

25 °C
One pot
pH 7
stereospecific



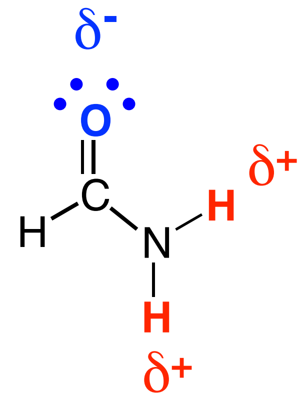
ribulose ribose

Pentoses are the kinetic products in alkaline borate, the first species able to form cyclic hemiacetals and bind borate. The kinetic products are fixed by lowering pH, and then interconverted by molybdate to give other pentoses.

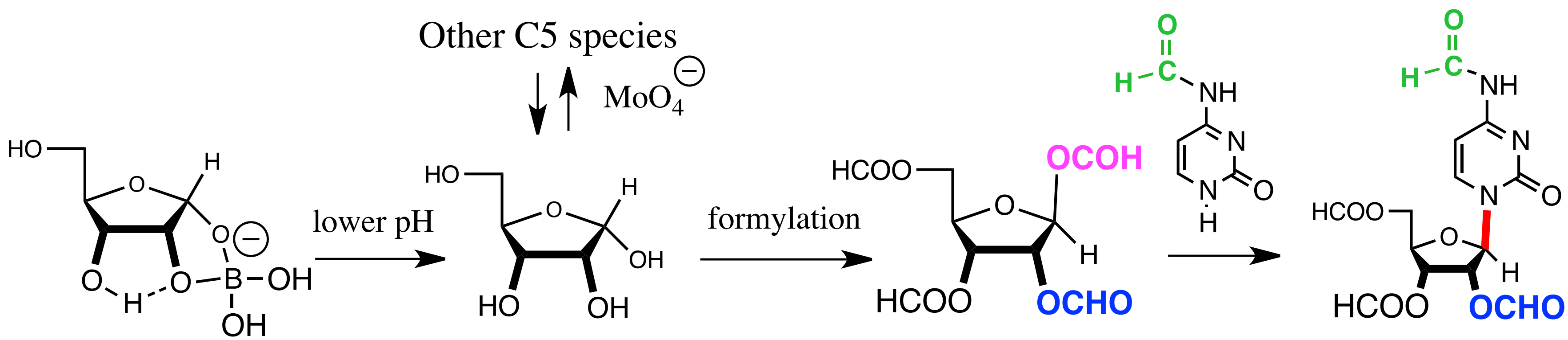
Water then becomes a problem

Need to move from a nucleophilic solvent (water) to an electrophilic solvent

Formamide: An electrophilic solvent.
Does not *hydrolyze* things; it formylates them

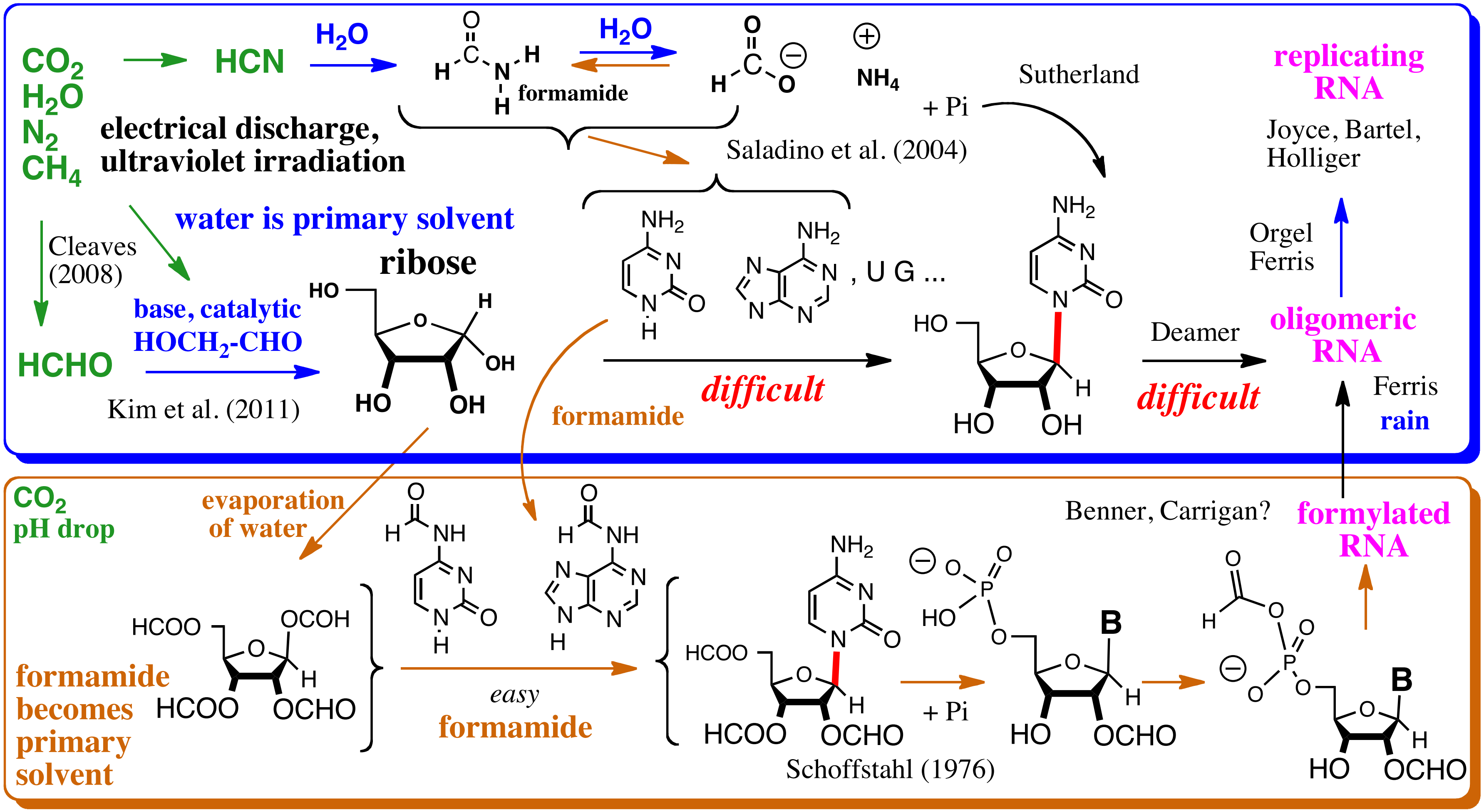


formamide



Formamide (bp 220 °C) is enriched as water leaves.
Formamide is an excellent solvent.
Formamide is a precursor for nucleobases (better than HCN)
Saladino, Hud, etc.

Formamide helps solve the water paradox



Key: in the atmosphere — in the aquifer; Nucleophilic Context — in the desert; Electrophilic Context

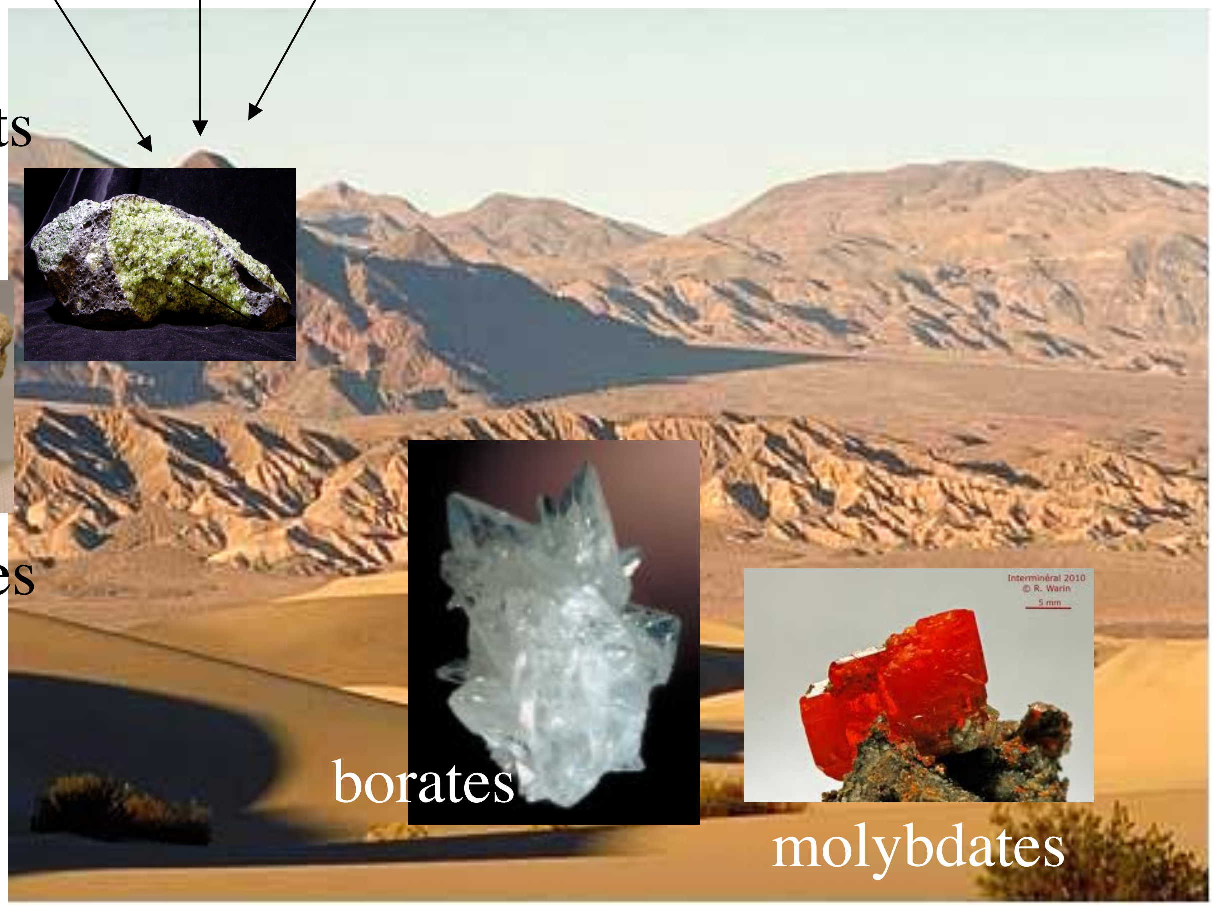
Semi-continuous Synthesis Model Locale

$$CO_2 + N_2 + H_2O$$

Rift valley
Maruyama

HCHO HCN H_2O Glycolaldehyde, formamide

peridots



tourmalines

Some Problems with the Discontinuous RNA Synthesis Model

Some geologists will not give us borate on prebiotic Earth

Bob Hazen, Ed Grew. Not enough crustal processing early on to concentrate the borate in the lithosphere

What about concentration in the hydrosphere

Many geologists will not give us Mo^{6+} on prebiotic Earth

Molybdate is too oxidized

Steve Mojzsis points out that in subduction zones, oxidized minerals are the natural consequence of atom stoichiometry, regardless of the overall redox potential of the atmosphere

Multidisciplinary interactions between Earth scientists and organic chemists.

Q. What minerals do you need?

A. What minerals will you give us?

Other problems with the Discontinuous Synthesis Model

The Kirschvink Objection

Models for planetary formation suggest that the inventory of water on early Earth did not leave *any* dry land before continental drift

Kevin Costner in Waterworld

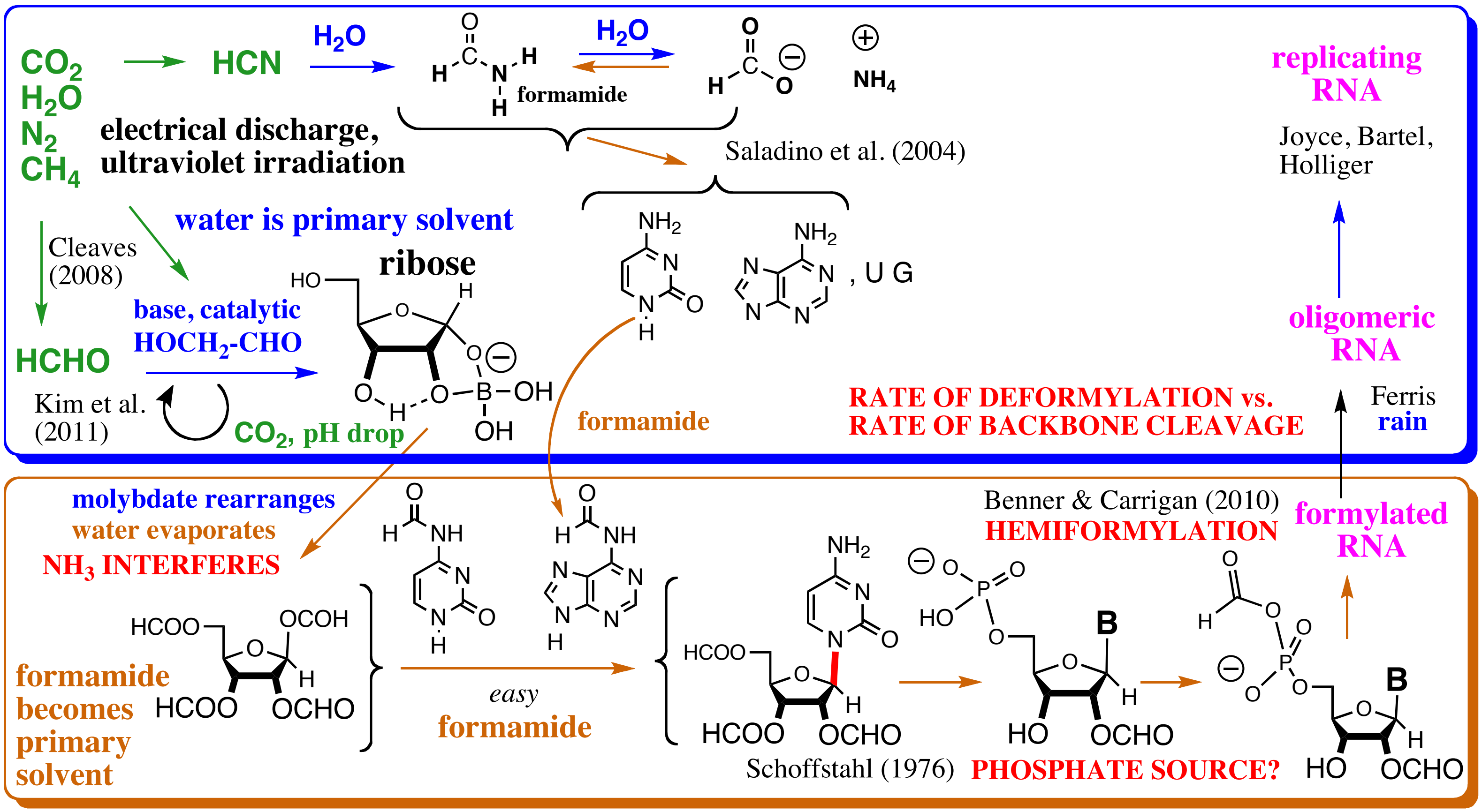
The Kirschvink Solution

Move it all to Mars, where water was never as abundant as on Earth. *Maybe even borate-moderated RNA synthesis now*

We are all Martians ?

The discontinuous RNA synthesis model with formamide, today

GEOLOGICAL CONTEXT DIFFICULT TO SIMULATE IN LAB



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Benner, S. A. Kim, H.J. (2012) Asphalt, water, and the prebiotic synthesis of ribose, ribonucleosides, and RNA. *Accounts Chem. Res.* **45**, 2025–2034

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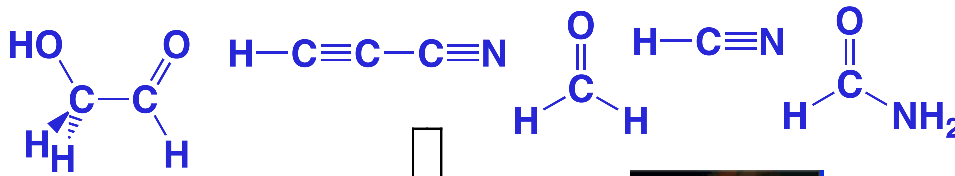
RNA, going back, going forward

the foundation for applied molecular evolution

FAME

Prebiotic Chemistry



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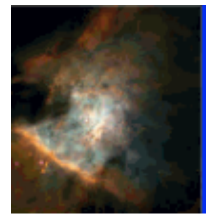

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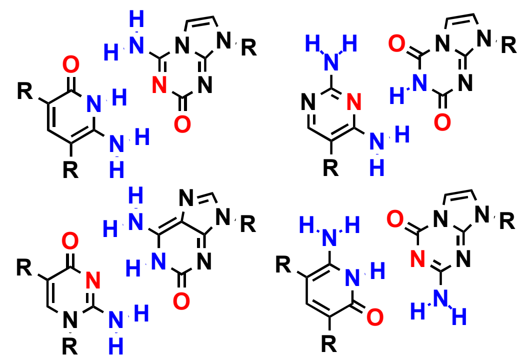

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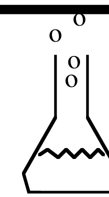

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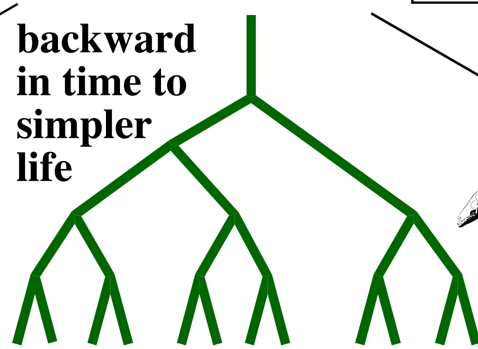

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