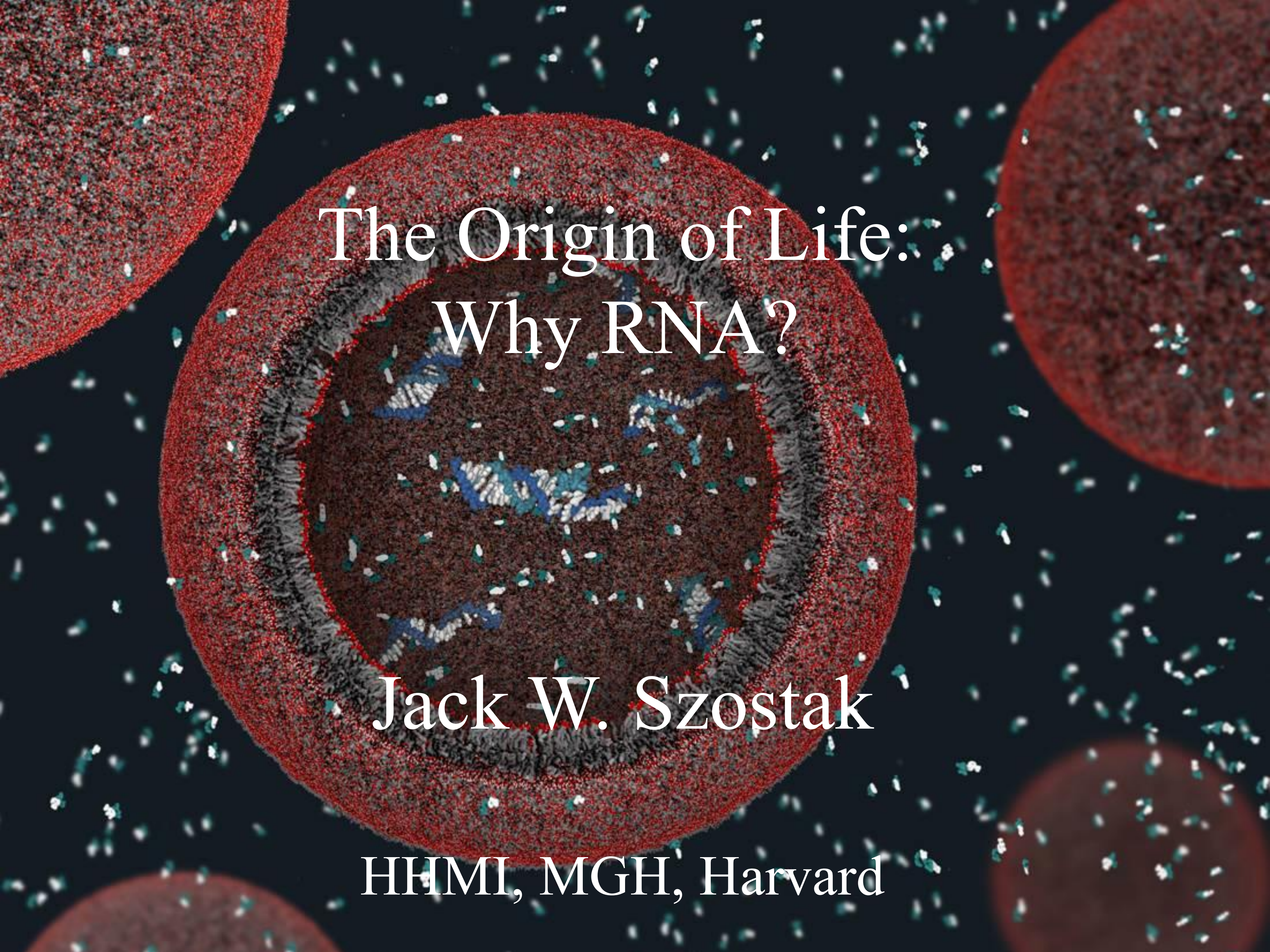


The Origin of Life: Why RNA?

Jack W. Szostak

HHMI, MGH, Harvard

Timeline of the Origin of Life

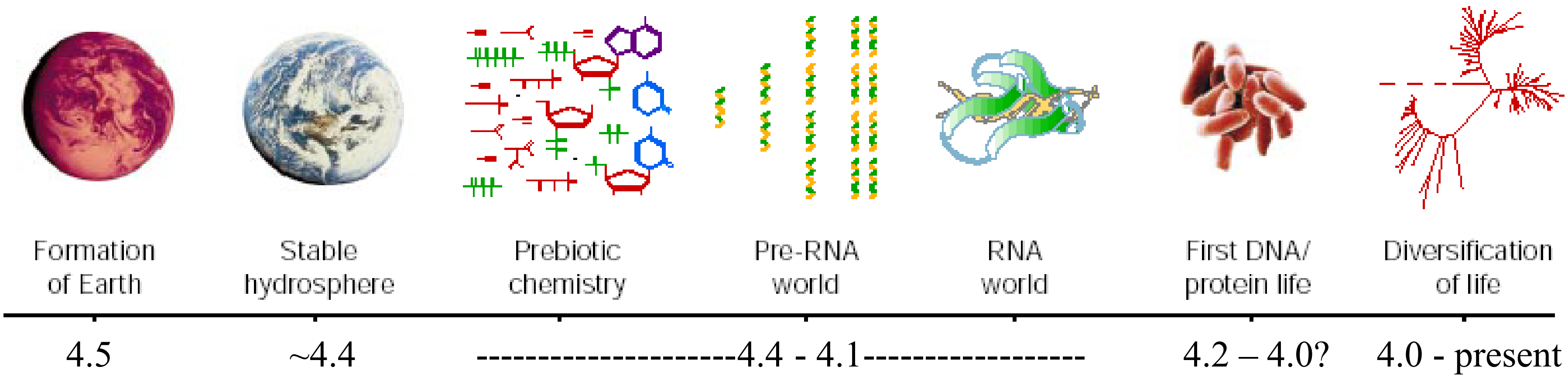
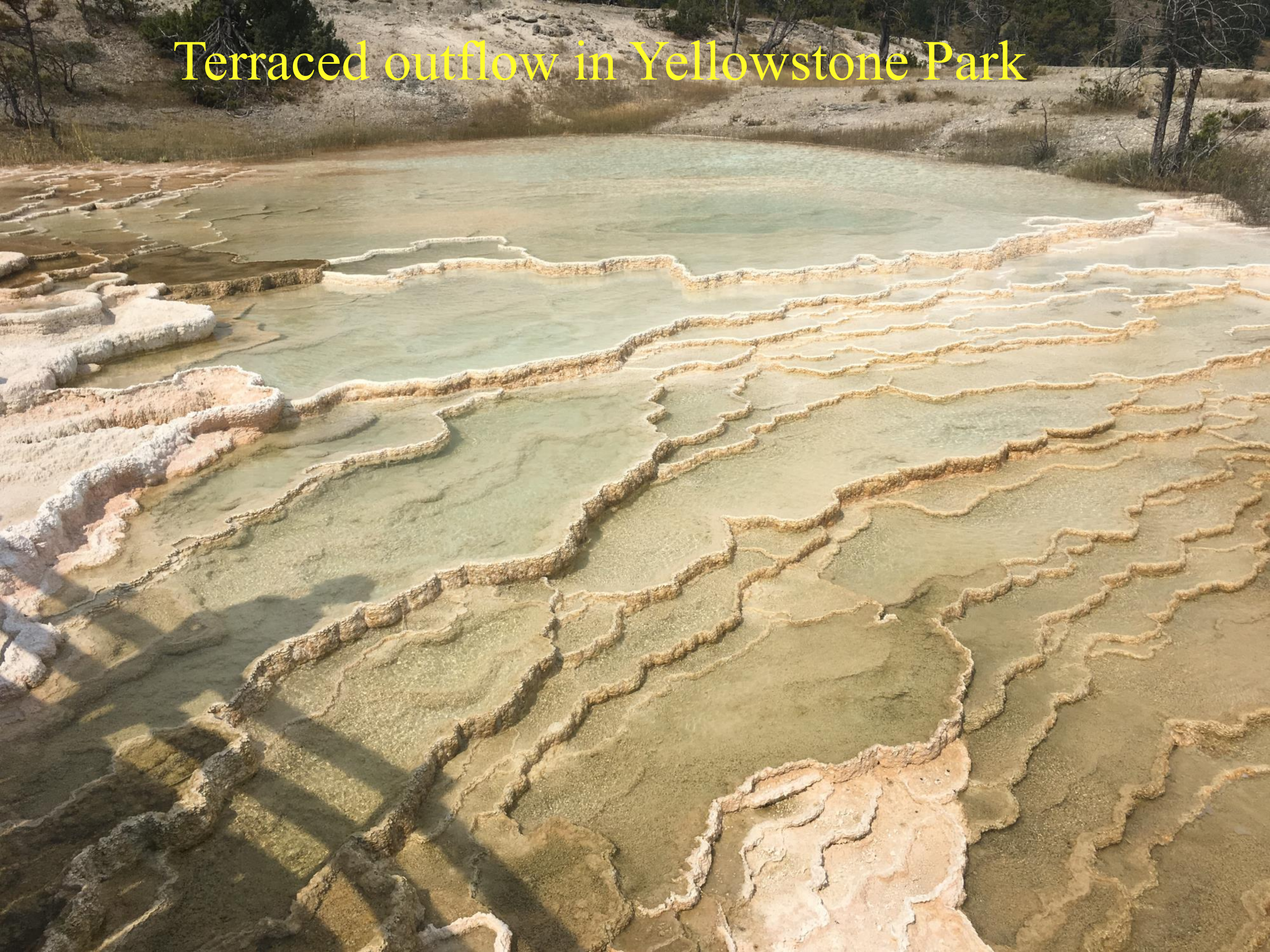


Figure 1 Timeline of events pertaining to the early history of life on Earth, with approximate dates in billions of years before the present.

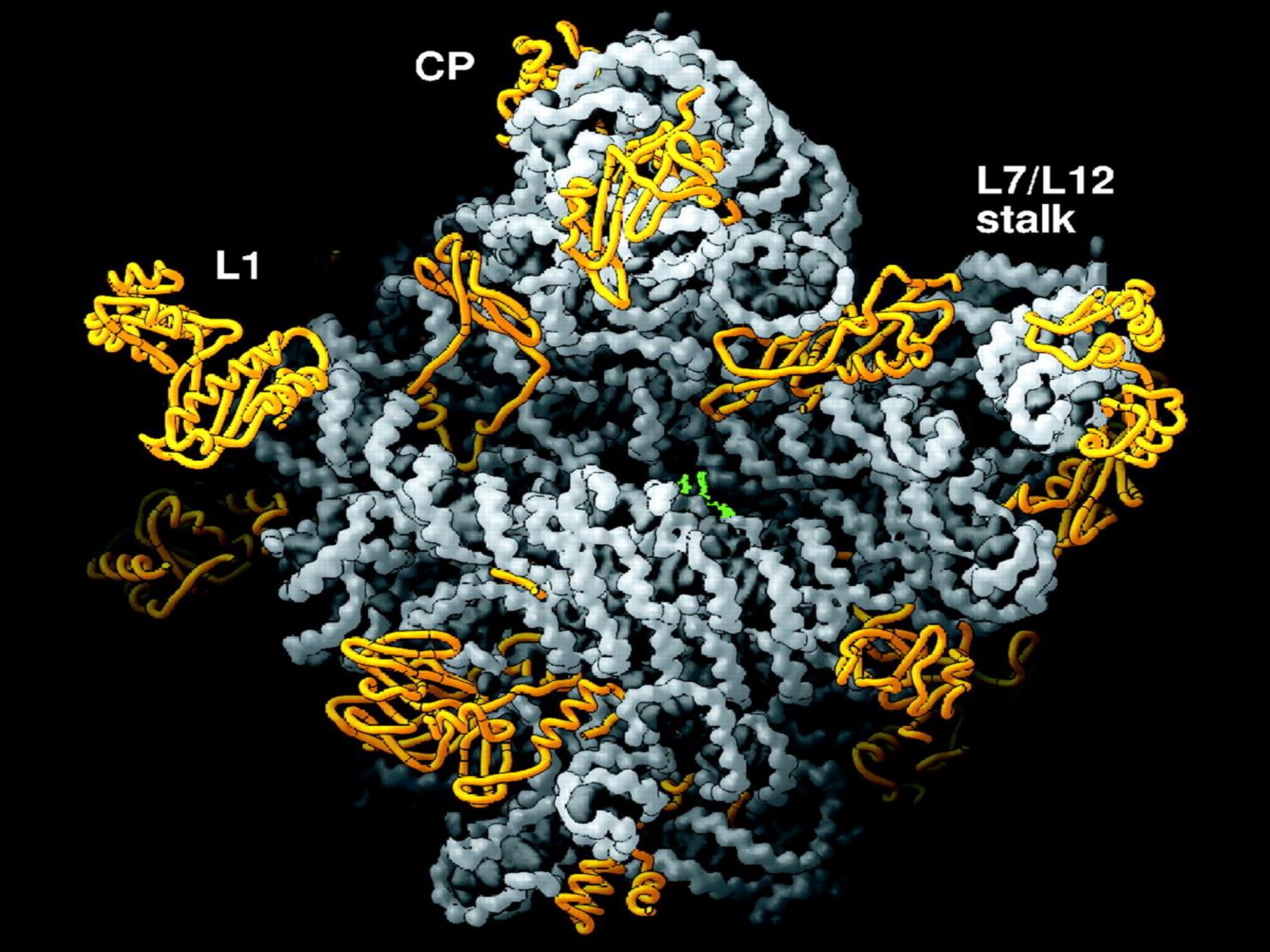
Modified from a figure from G.F. Joyce, 2002, Nature 418: 214-221


Harvard grad students on field trip to Yellowstone
MERRELL

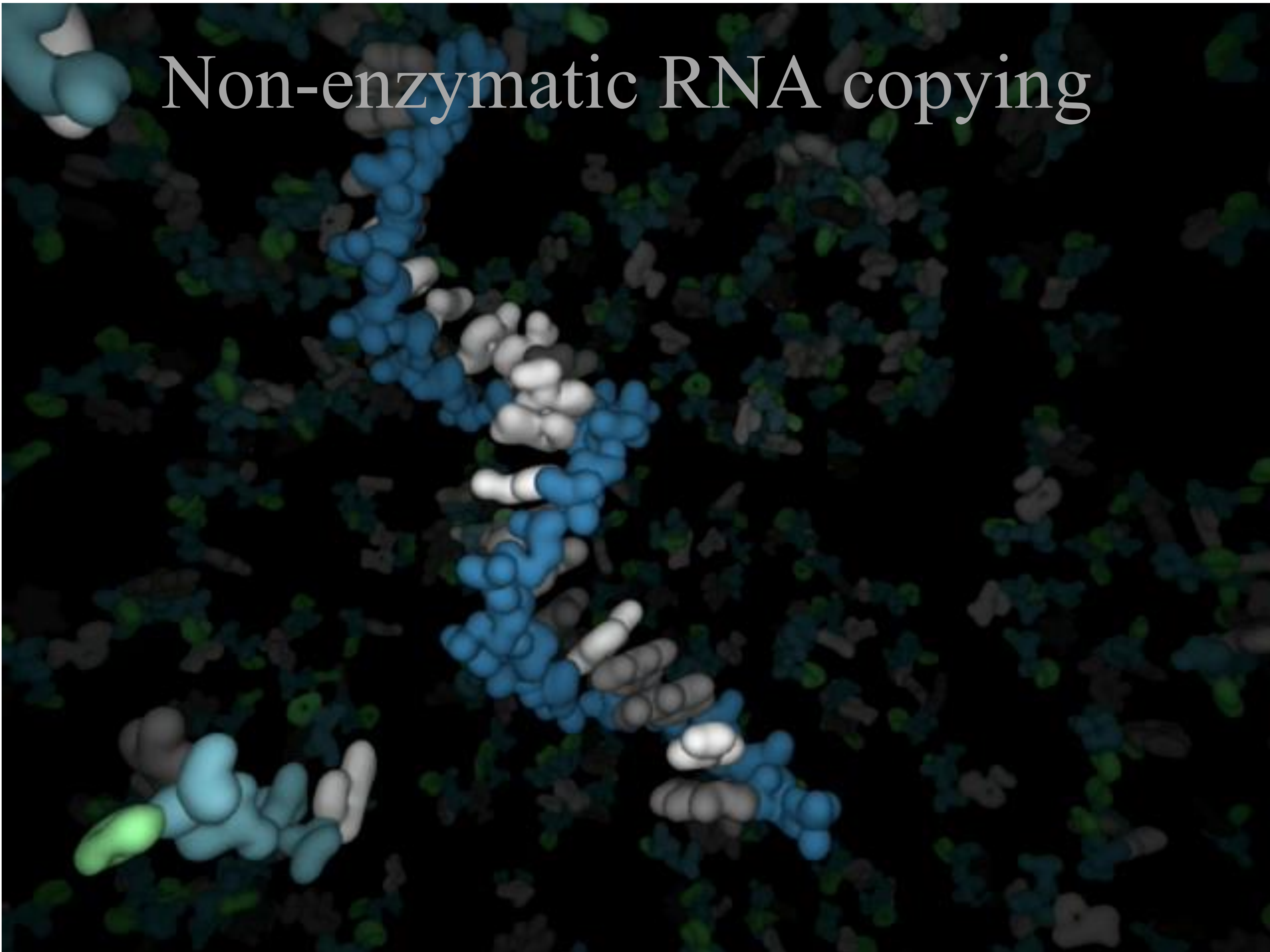

Mini-geyser in Yellowstone Park


Terraced outflow in Yellowstone Park

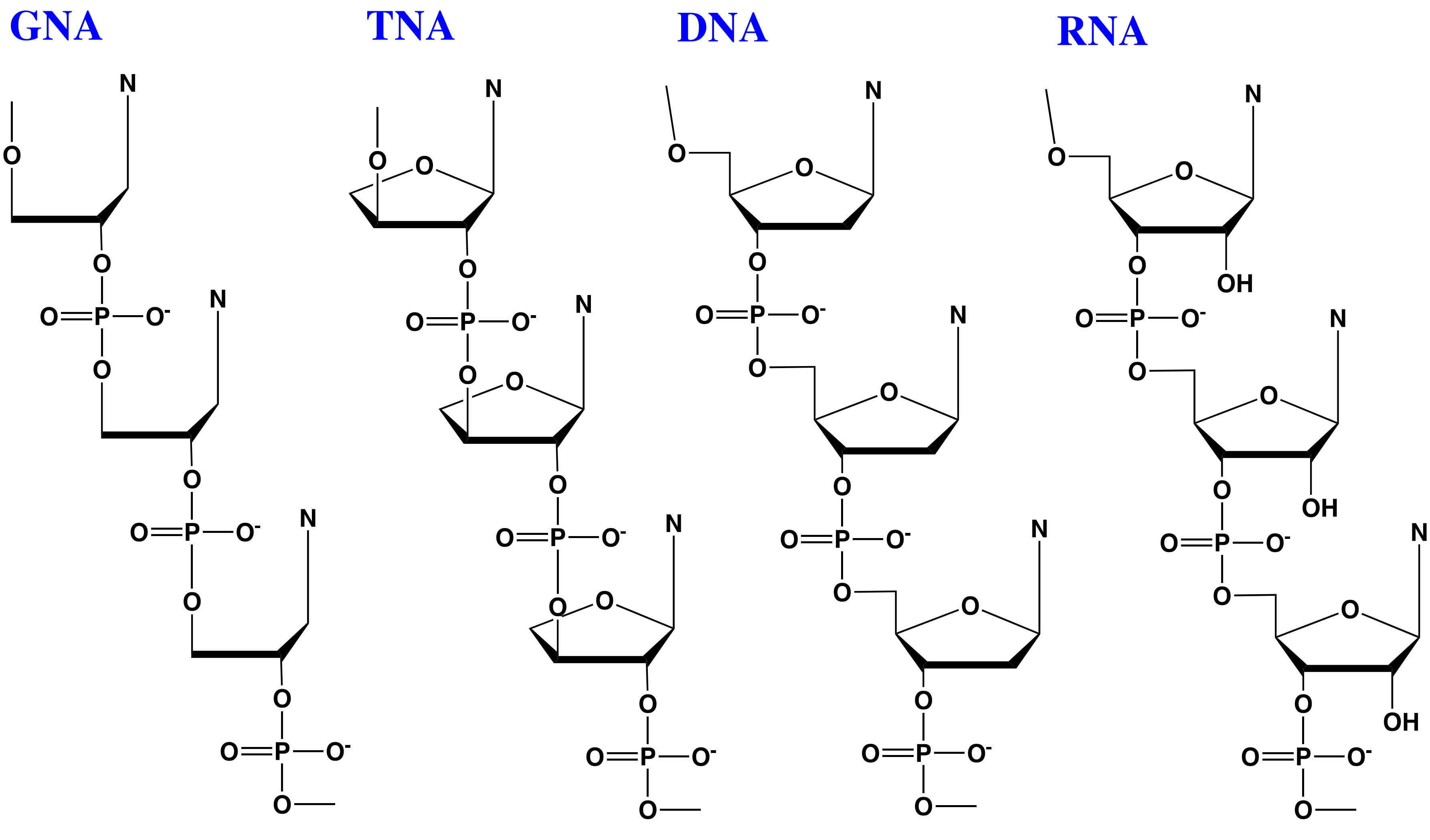
Dales Gorge, Karijini National Park, Pilbara WA


CP
L7/L12
stalk
L1

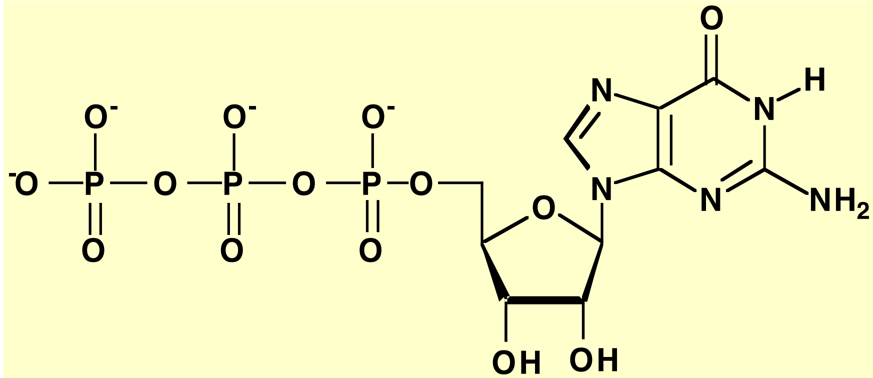
Non-enzymatic RNA copying



A few possible genetic polymers

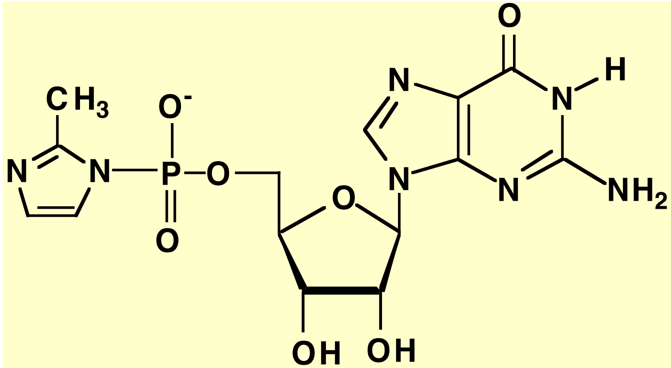


Nucleoside triphosphates



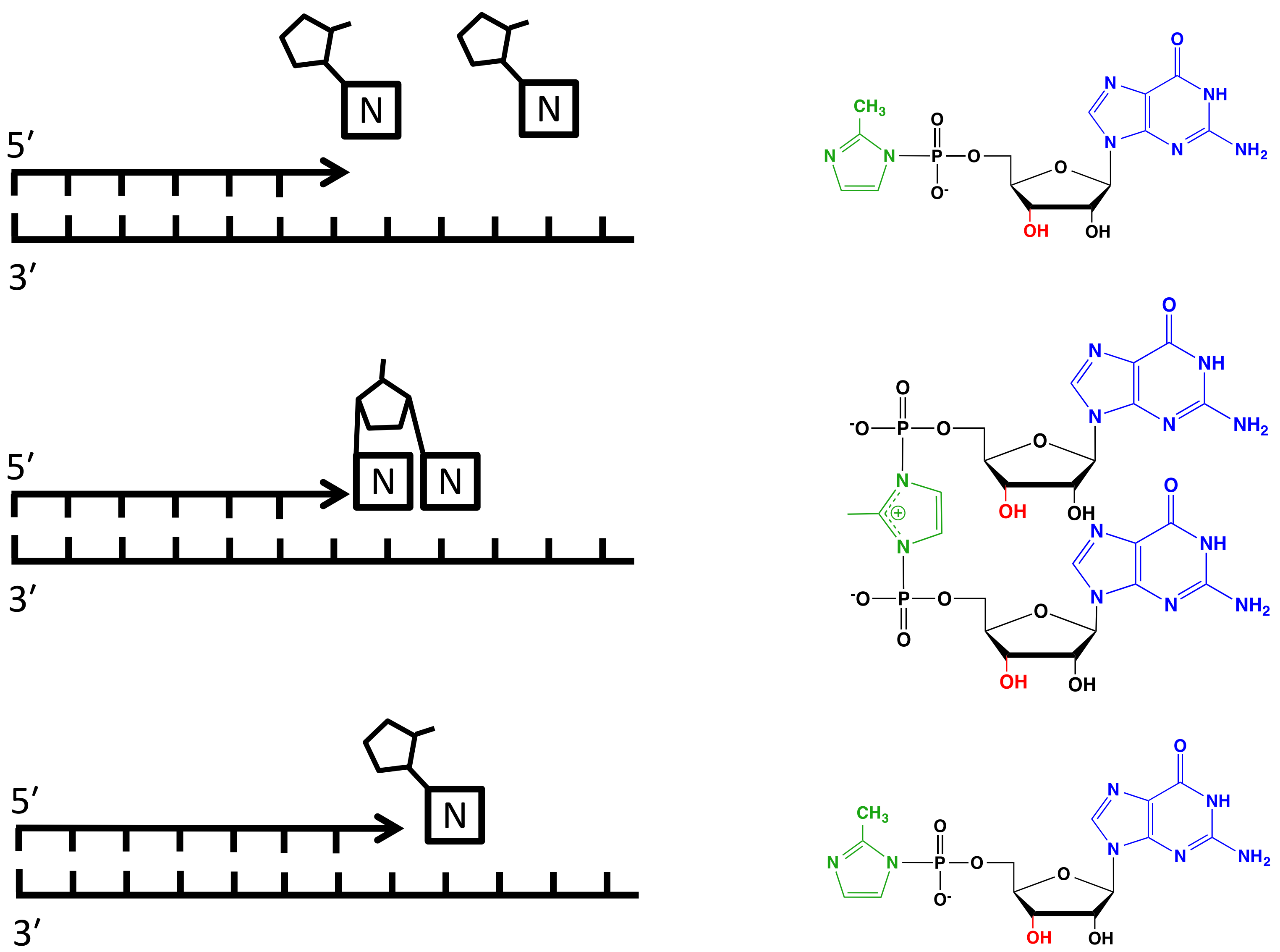
'Modern' substrates
Very polar
Low chemical reactivity

Nucleoside phosphorimidazolides



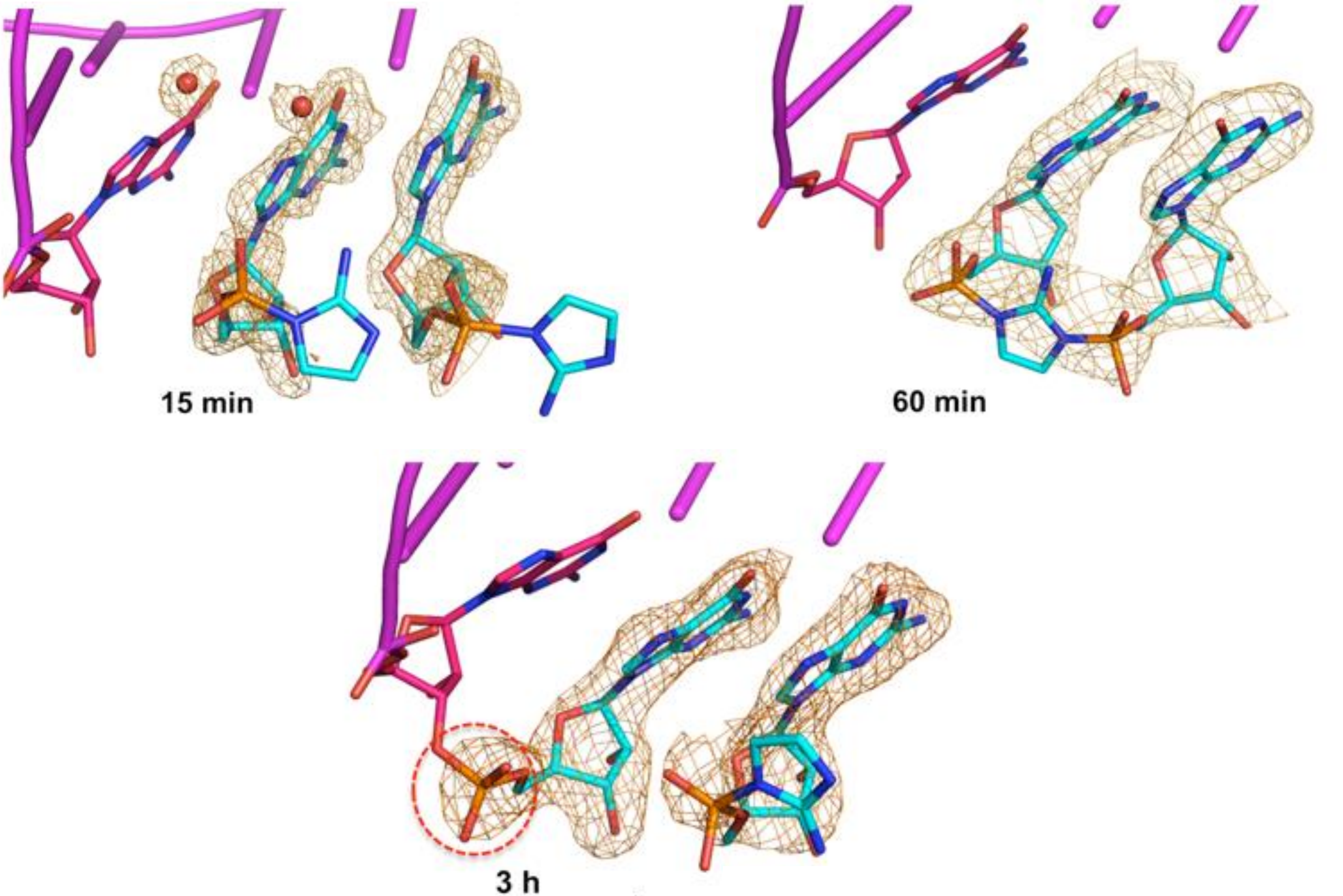
Prebiotic model substrates
Less polar, more permeable
High chemical reactivity

Mechanism of primer extension



Walton T, Szostak JW. *J. Am. Chem. Soc.*, 2016, *138* (36), 11996–12002

2-aminoimidazolium intermediate forms and reacts with primer in the crystal

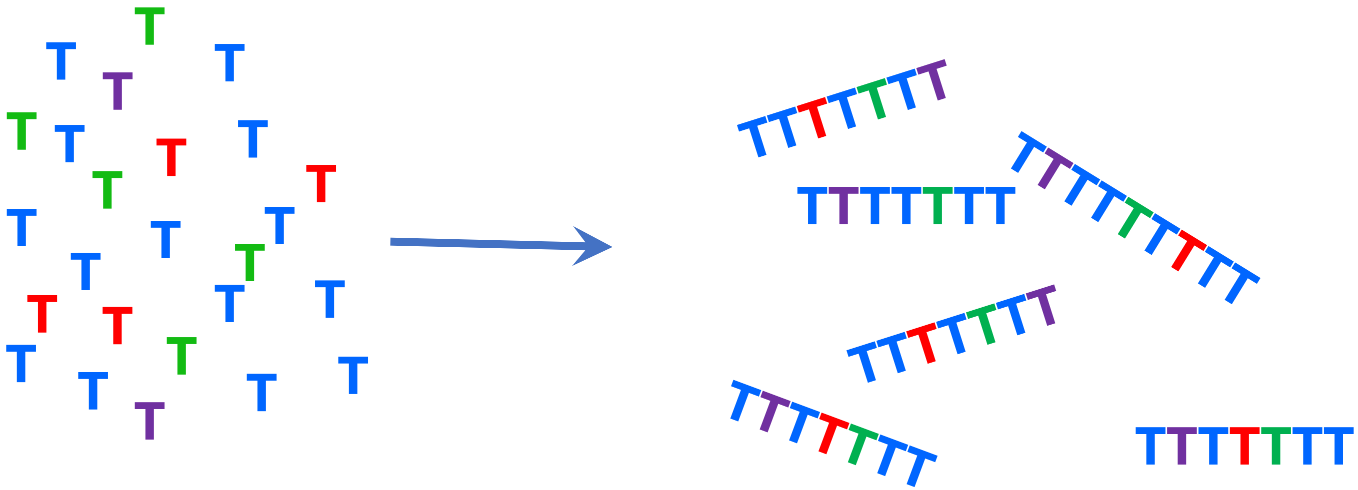


“The Molecular Biologist’s Dream…”

Once upon a time there was a prebiotic pool
full of ß-D-nucleotides….

Joyce and Orgel, CSH, The RNA World, 1993

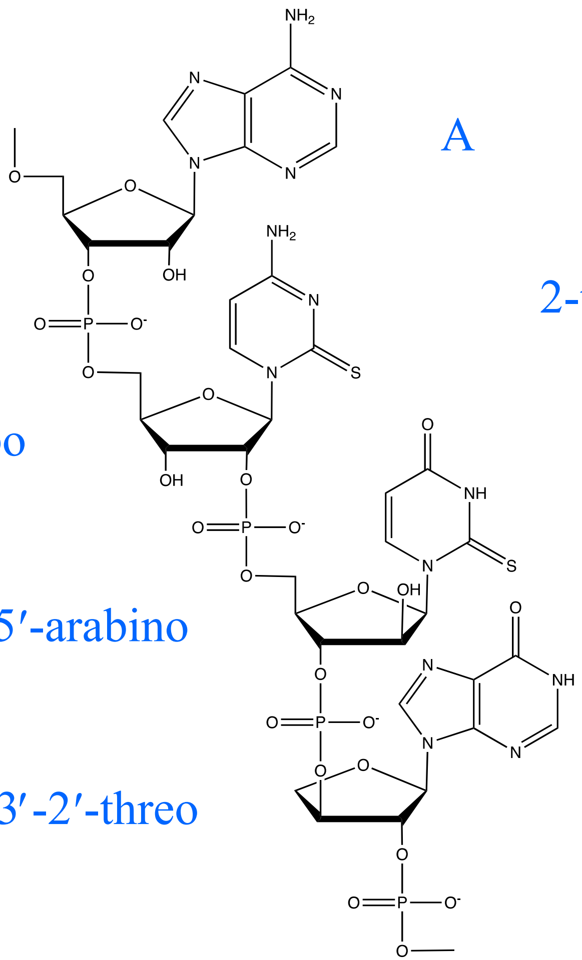
Messy Mixtures yield Messy Oligos



Blue: ribo-nucleotides
Red: arabino-nucleotides
Green: threo-nucleotides
Purple: deoxy-nucleotides

SC Kim et al., *J. Am. Chem. Soc.*, 2020, *142*, 2317

How Messy could Primitive RNA be?



A

3′-5′-ribo

2-thio-C

2′-5′-ribo

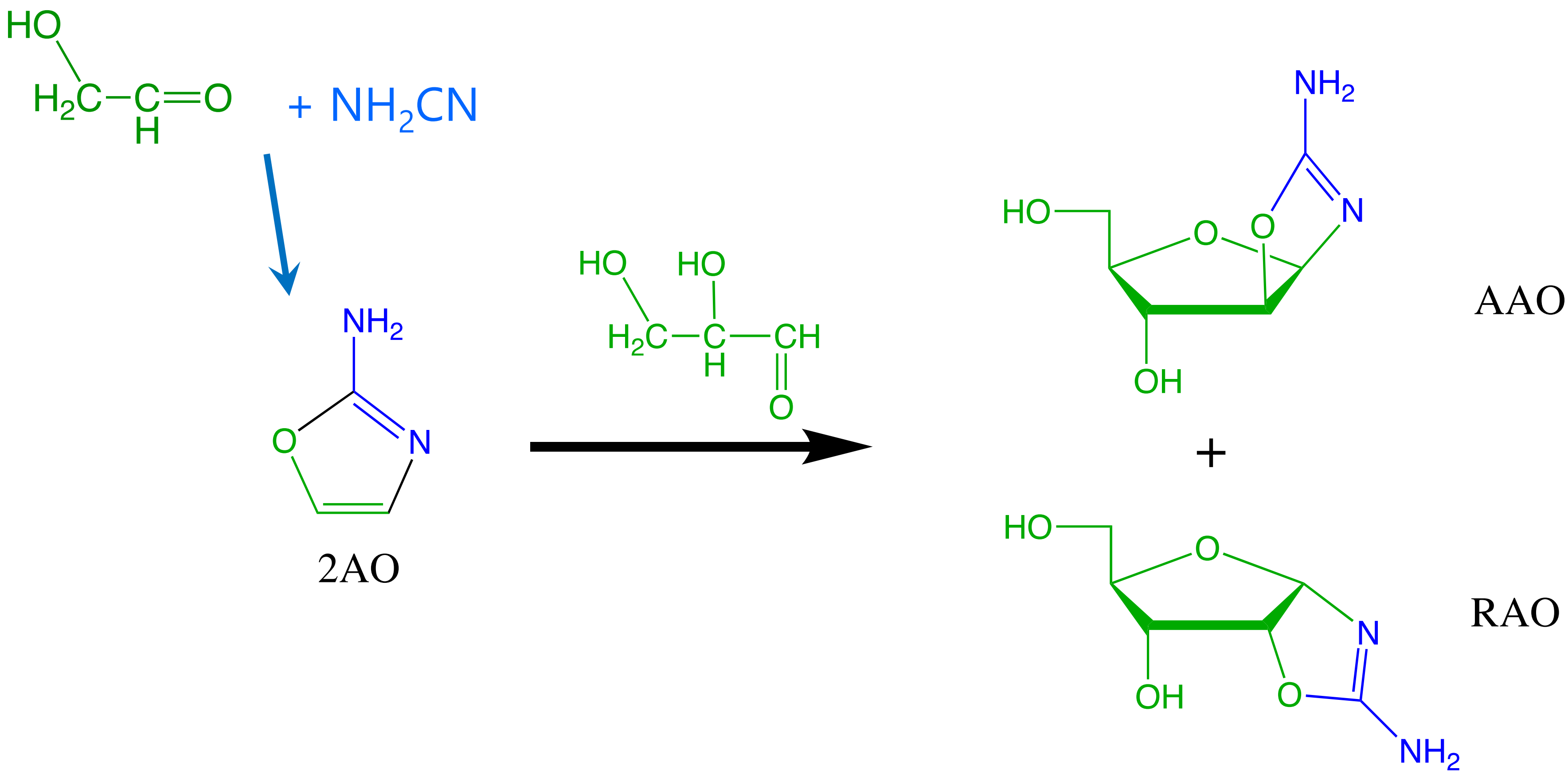
2-thio-U

3′-5′-arabino

inosine

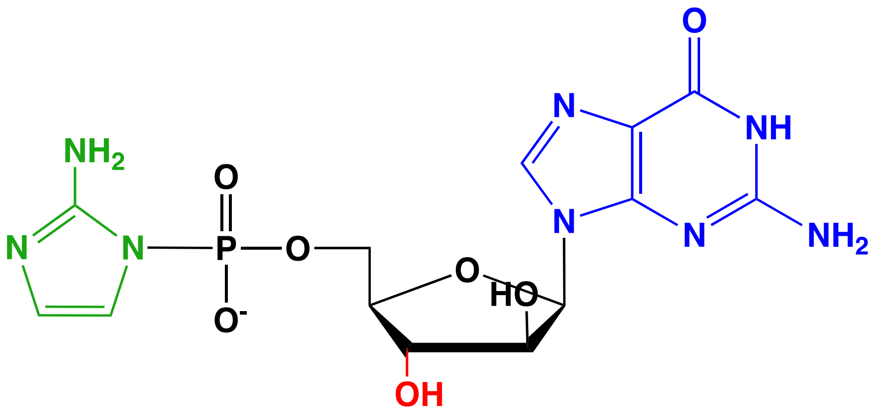
3′-2′-threo

Ribo- and Arabino-nucleotides are built from two sugars

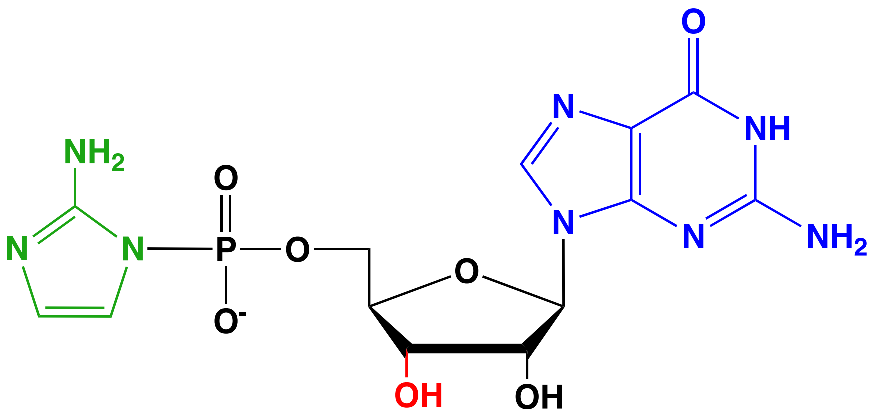


Islam et al., Chem. Eur. J. 2013, 19: 4586-95

Arabino- *vs.* Ribo-Nucleotides

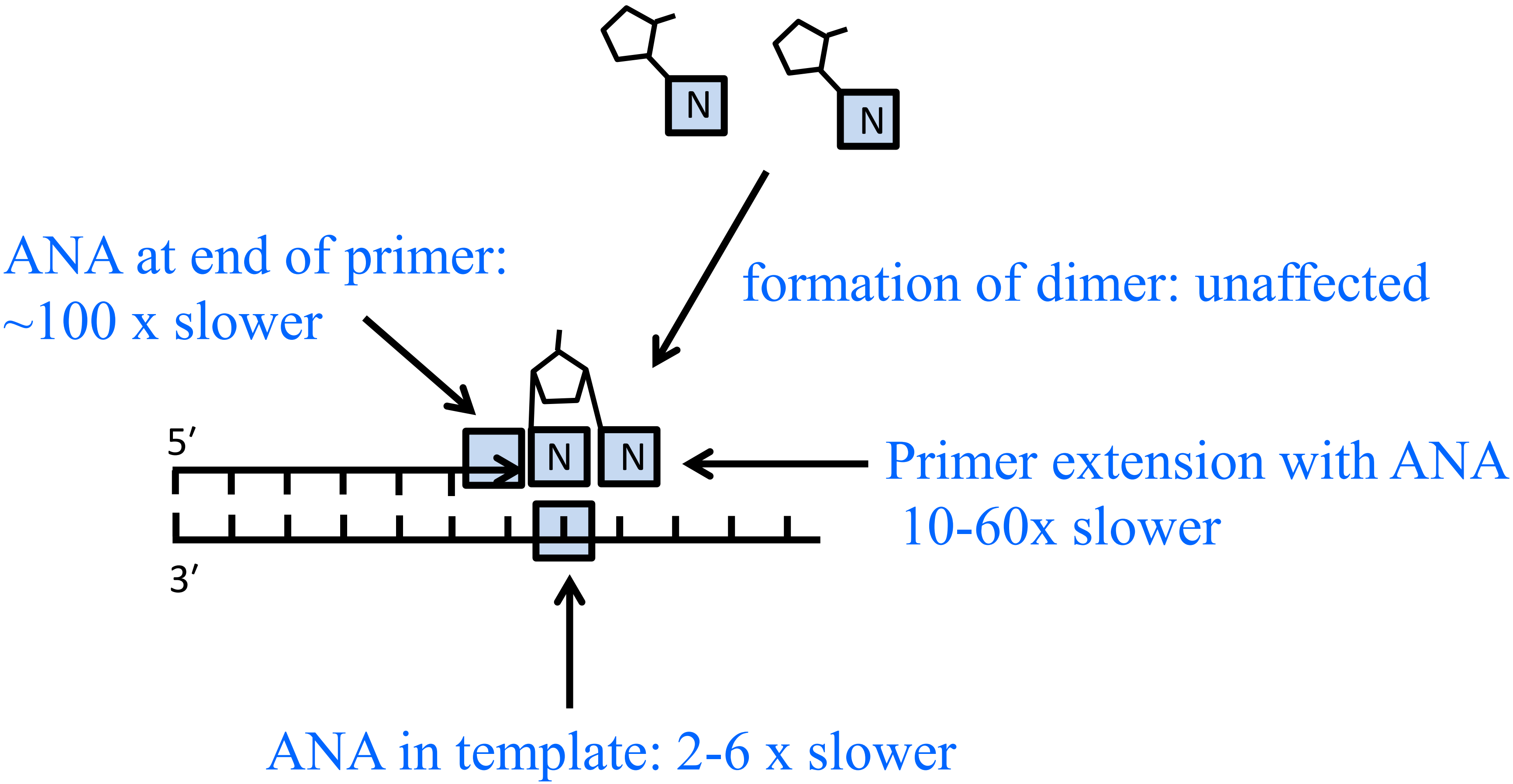


ANA



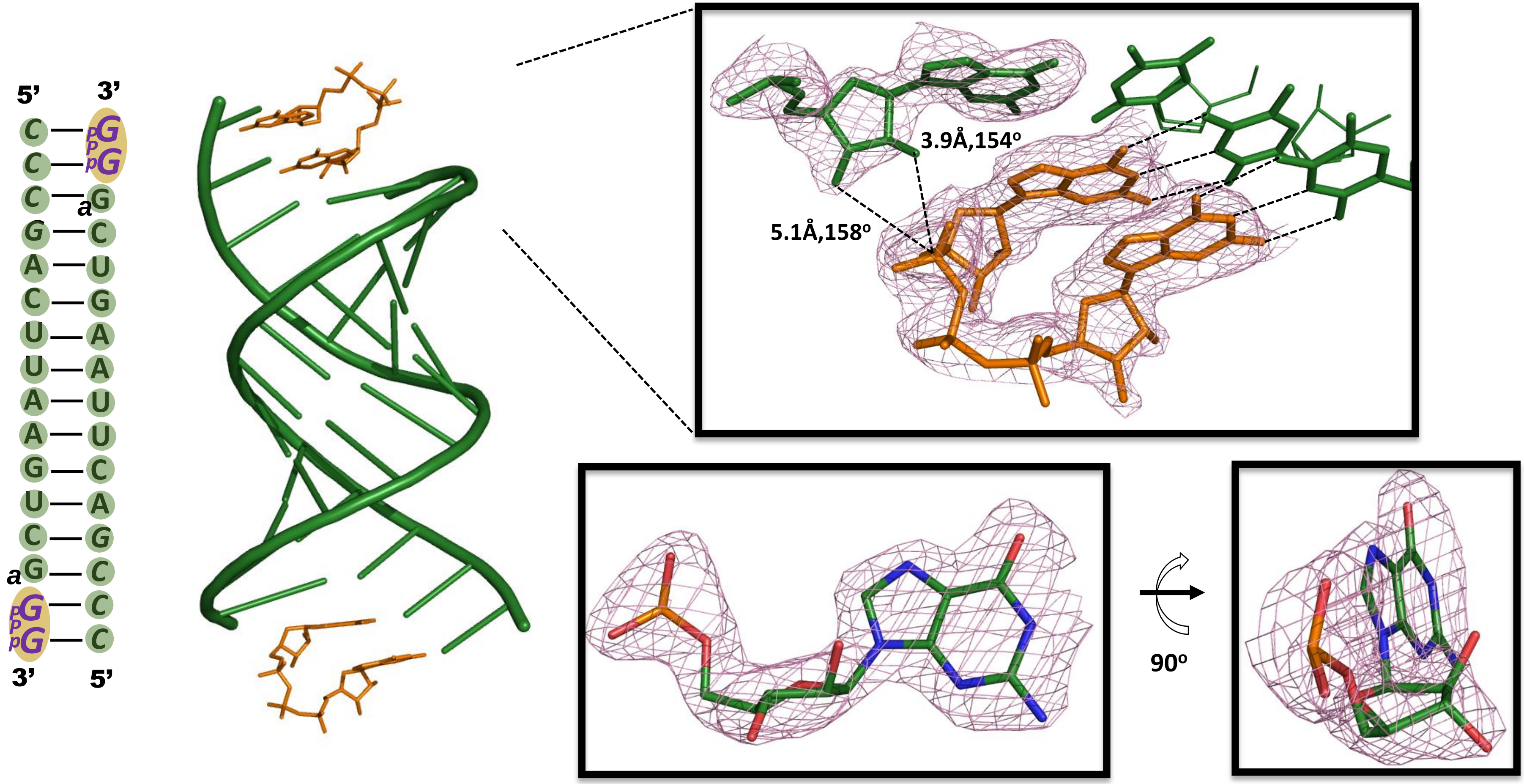
RNA

Primer extension with ANA



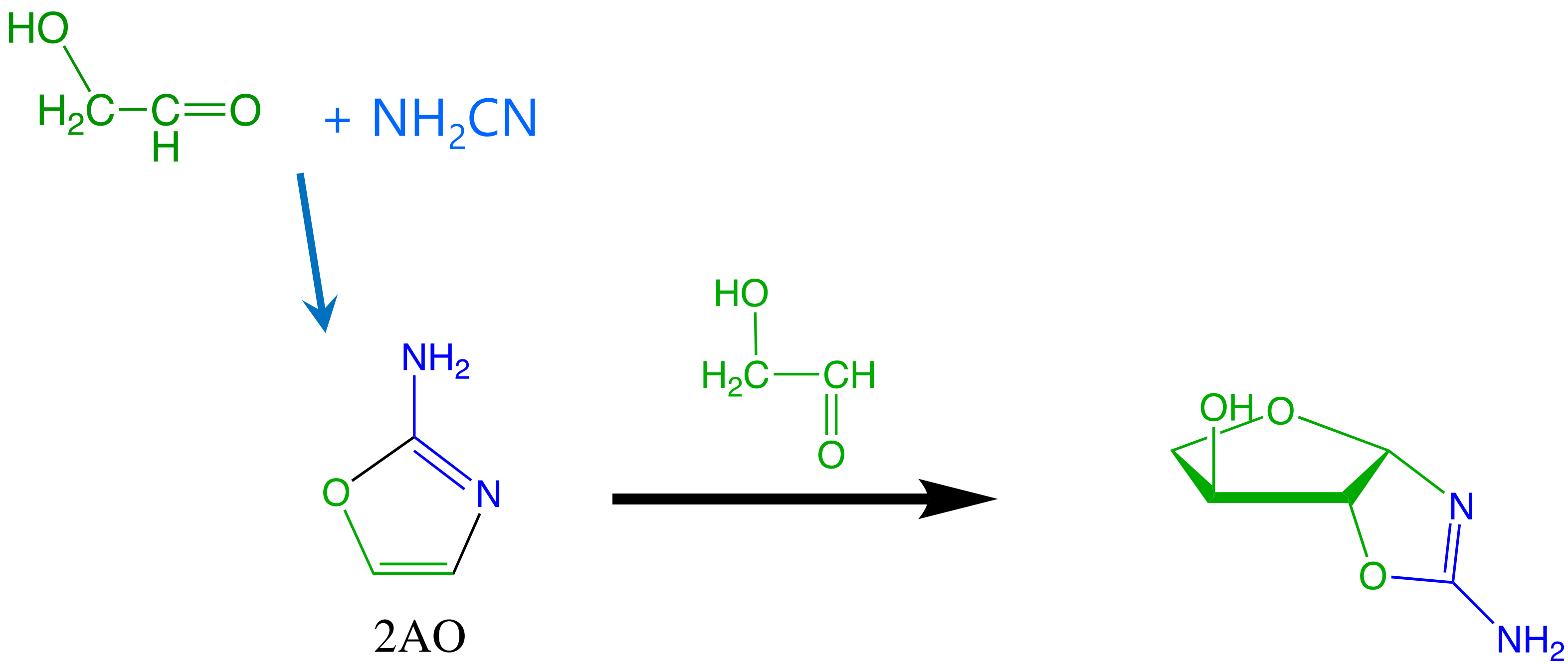
Kim et al., *J. Am. Chem. Soc.*, 2020, *142*: 2317–2326

crystal structures show why primer extension from an arabino-terminated primer is very slow



SC Kim et al., *J. Am. Chem. Soc.*, 2020, *142*, 2317

Threo-nucleotides: easier to make?

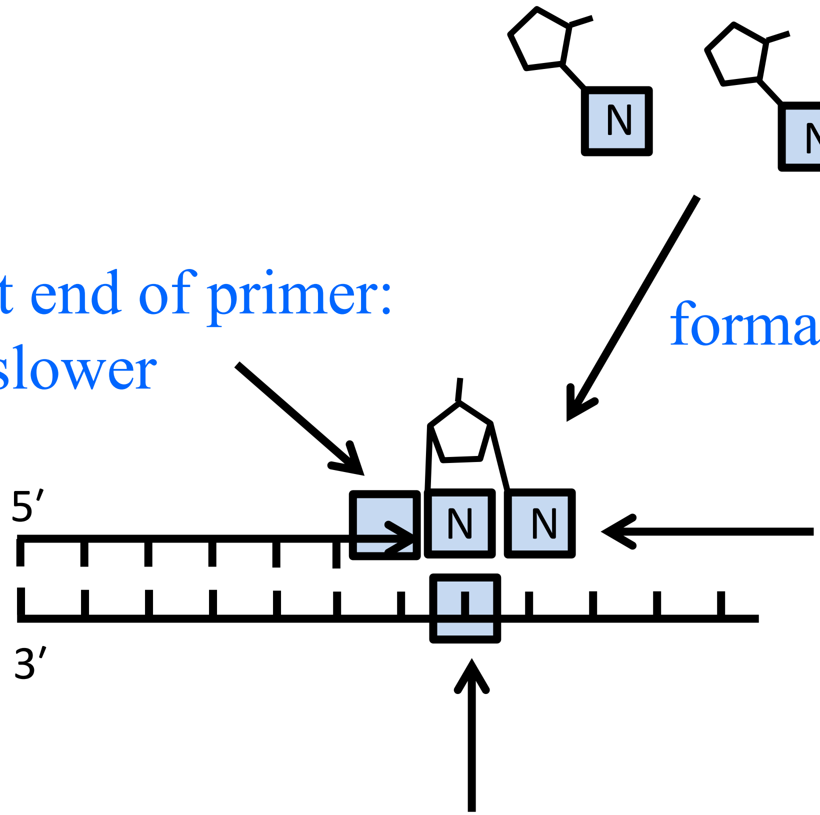


2AO

TAO

Islam et al., Chem. Eur. J. 2013, 19: 4586-95

Primer extension with TNA



TNA at end of primer: ~10 x slower

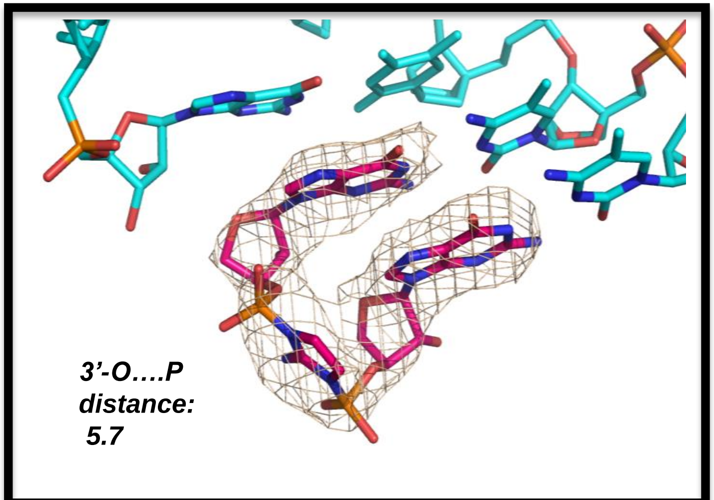
formation of dimer: 4-5 x slower

primer extension with TNA: 4-100x slower

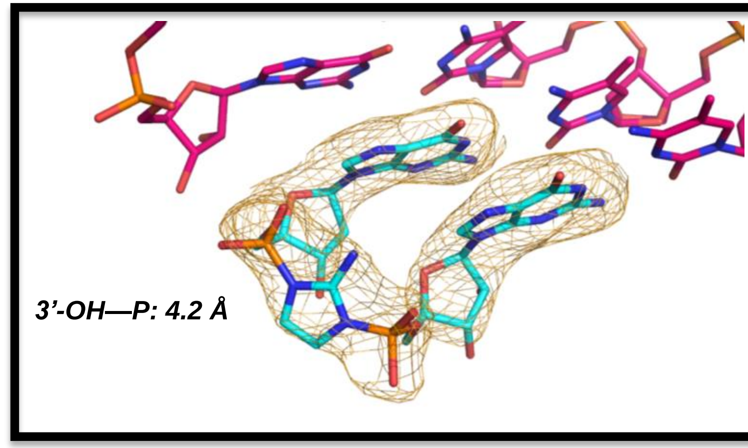
TNA in template: only 2 x slower

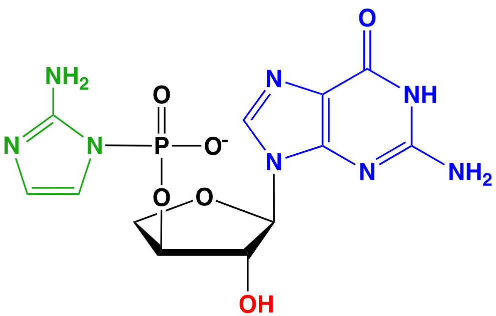
Zhang et al., *Nuc. Acids Res.*, 2020, *49*: 646–656

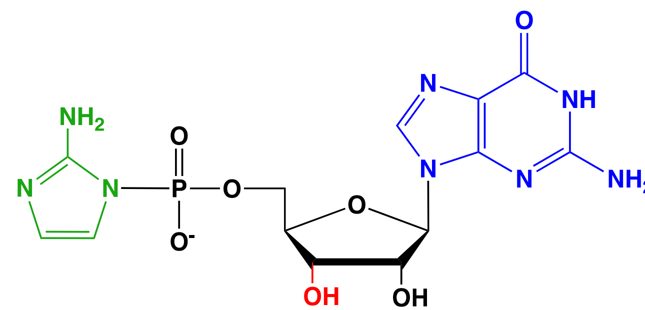
Crystal structures show why Primer Extension with TNA monomers is slow



VS



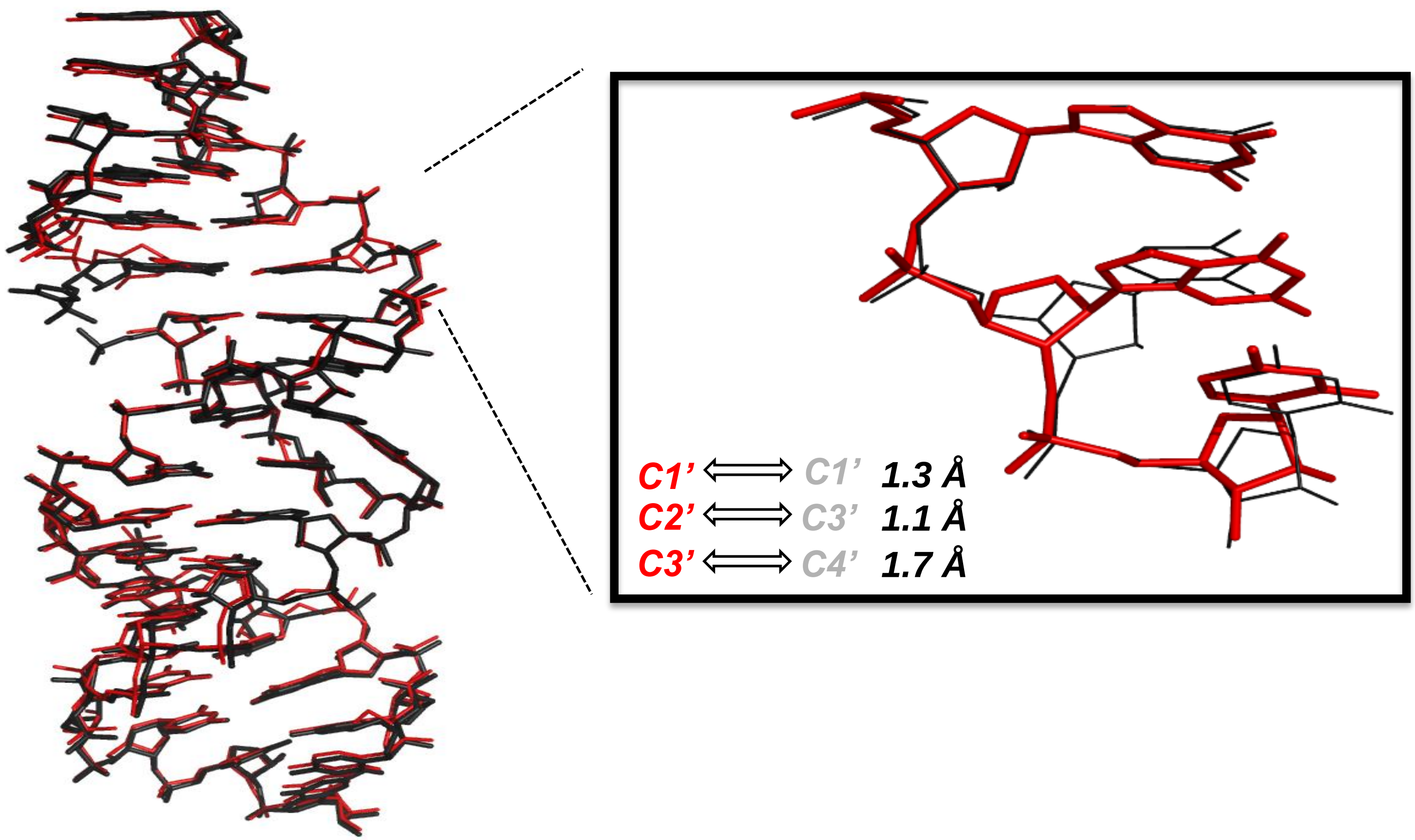




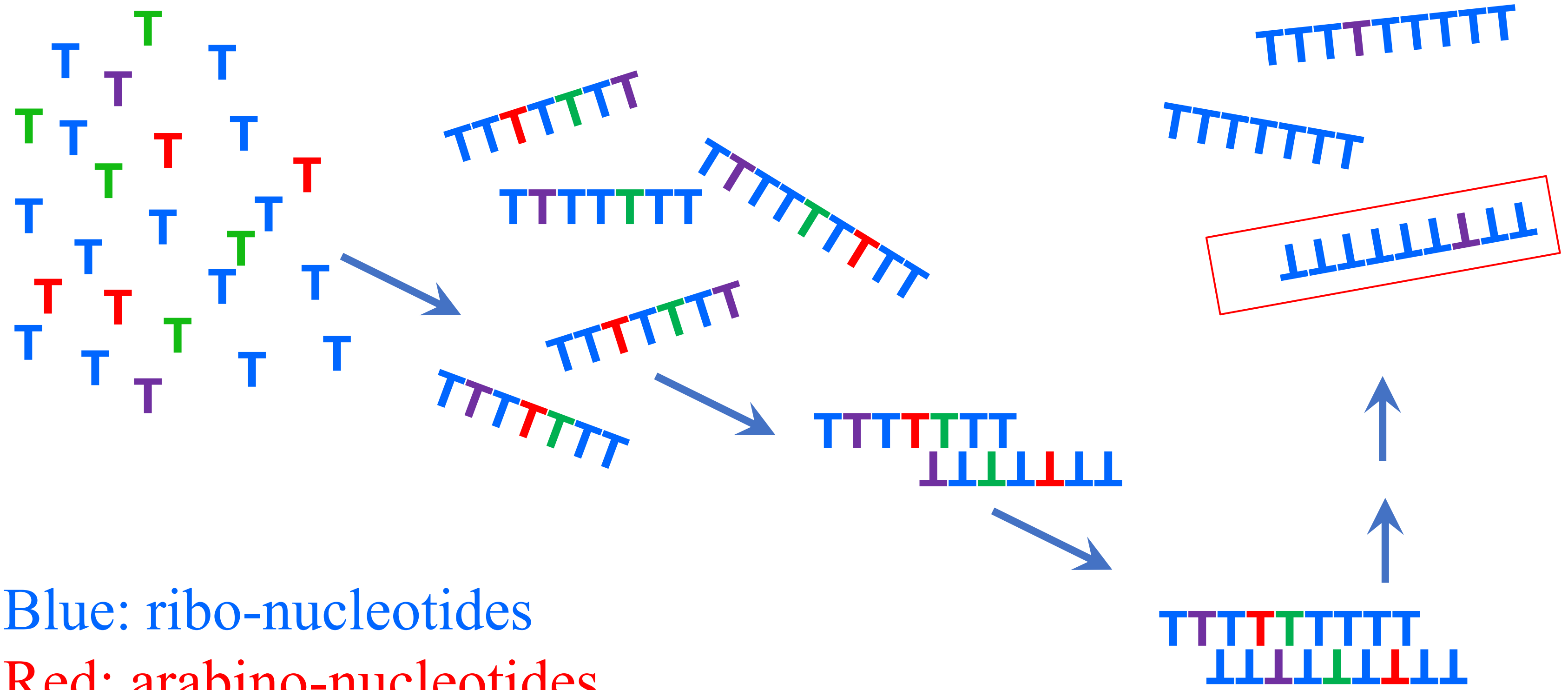
TNA

RNA

Crystal structure shows that a TNA residue causes only a minor perturbation of template structure



From Messy Mixtures to (almost) Modern RNA



Blue: ribo-nucleotides

Red: arabino-nucleotides

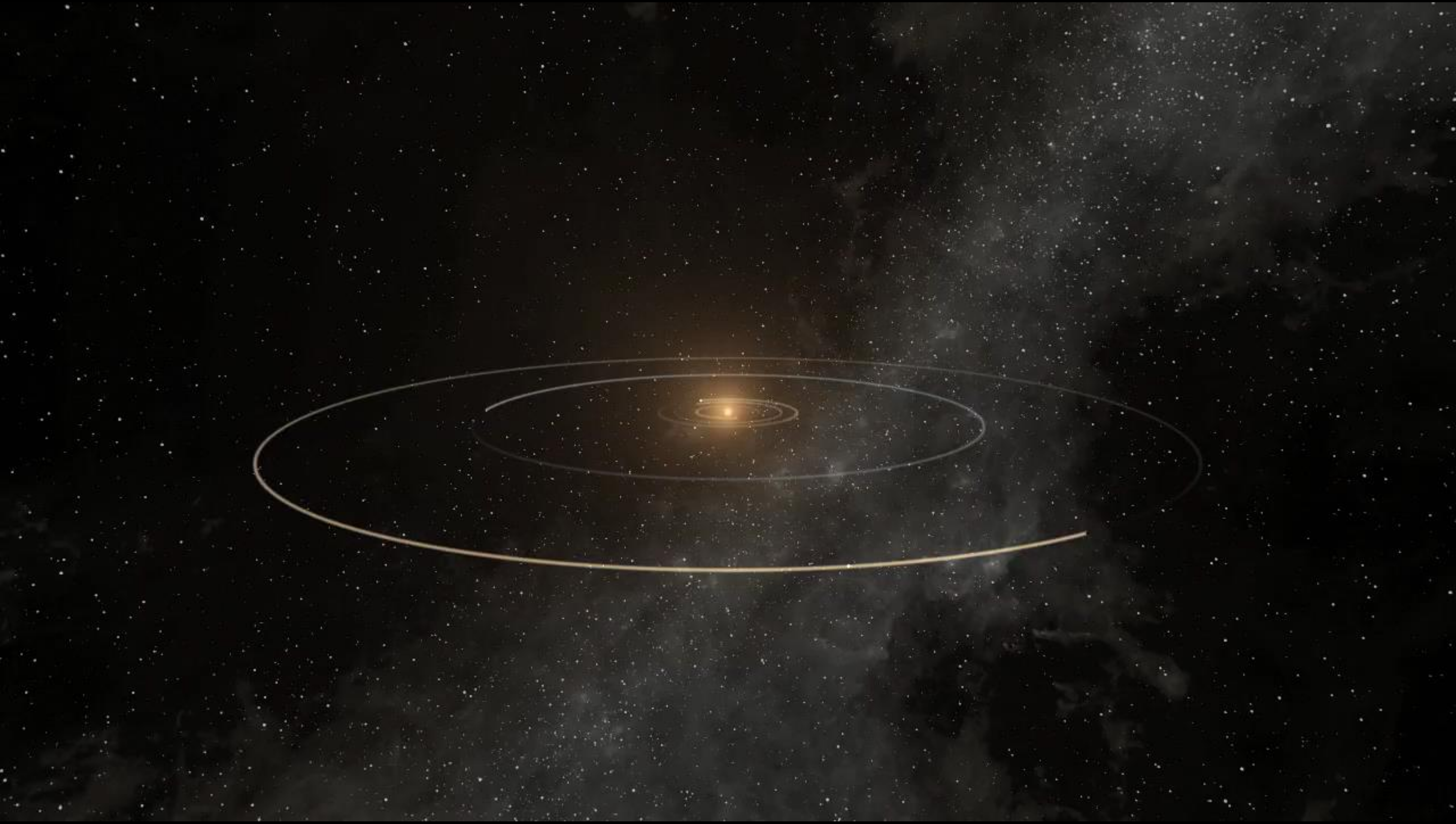
Green: threo-nucleotides

Purple: deoxy-nucleotides

The Origin of Life: easy or hard?

Life: All the same, or really diverse?

Kepler-62



Credit: NASA 2013

Current and Recent Grad Students

Xiwen Jia

Dian Ding

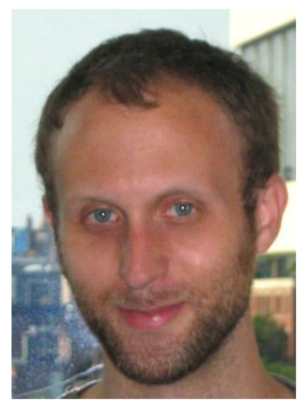
Stephanie Zhang

Constantin Giurgiu

Lydia Pazienza

Aleks Radakovic

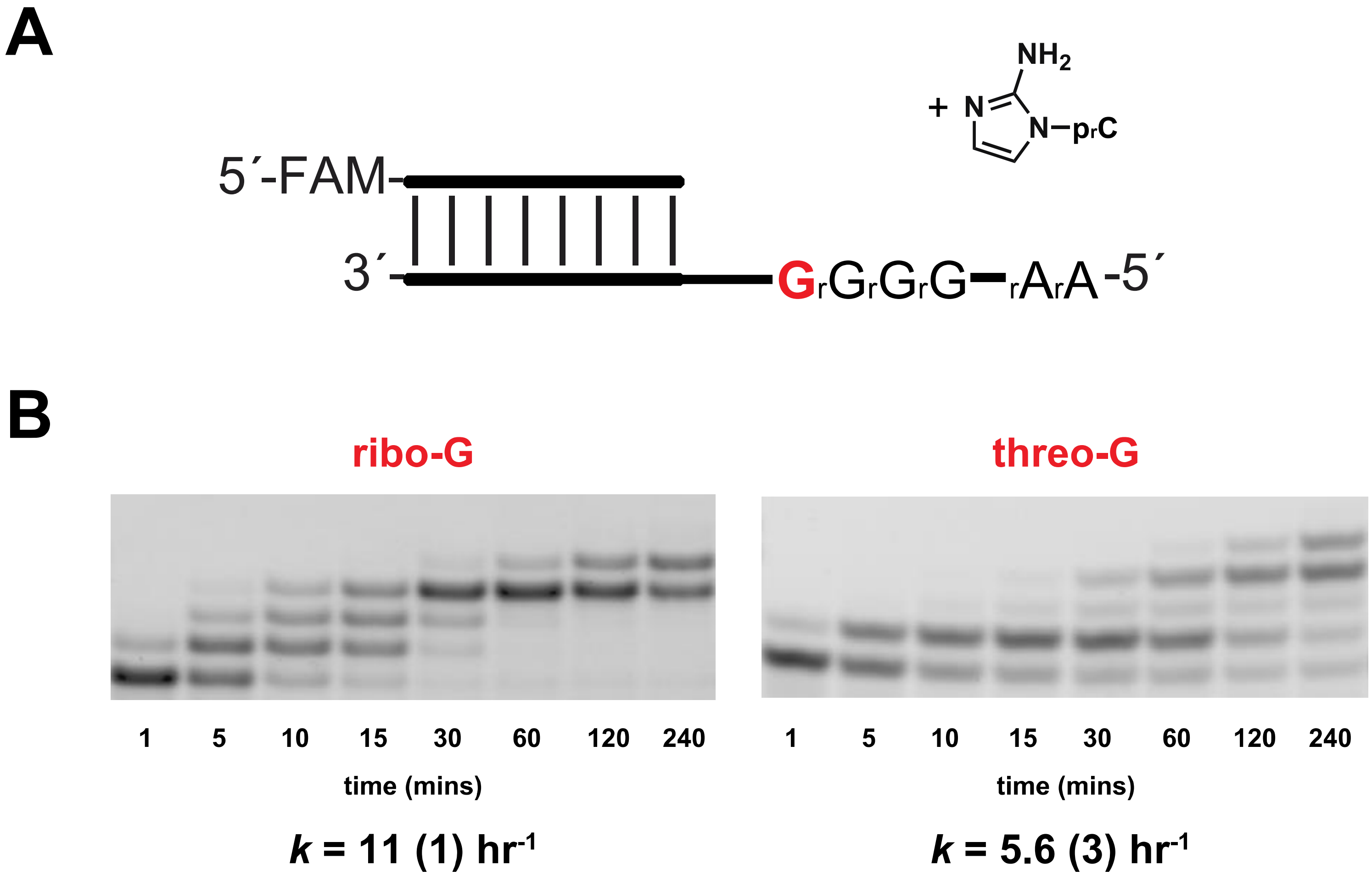
Chris Kim



Travis Walton

James Tam

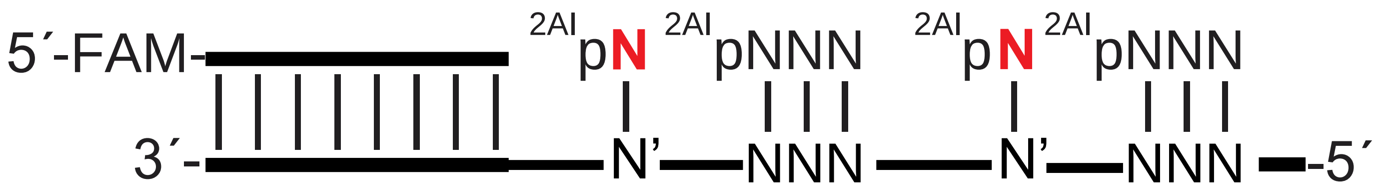
But threo-nucleotides in the template are not too bad



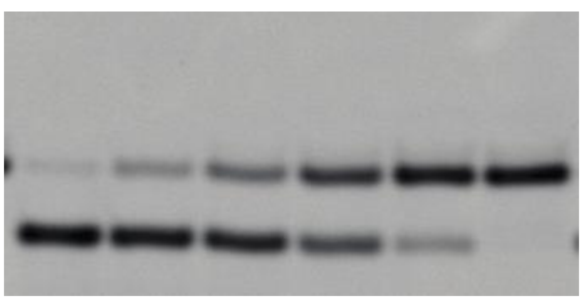
All RNA template

RNA template with single TNA residue

Primer Extension with ara-G is Slow



ribo-G

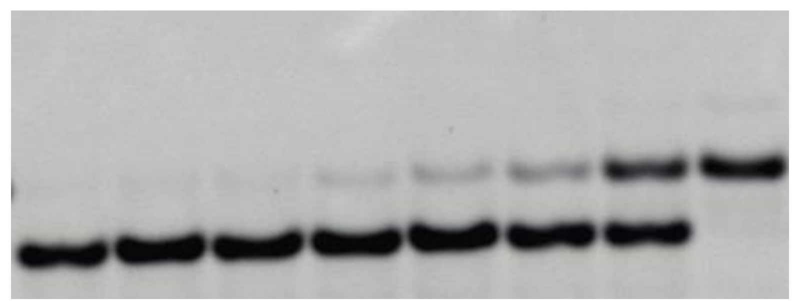


0.5 1 3 5 10 30

time (mins)

k = 11(1) hr^{-1}

ara-G



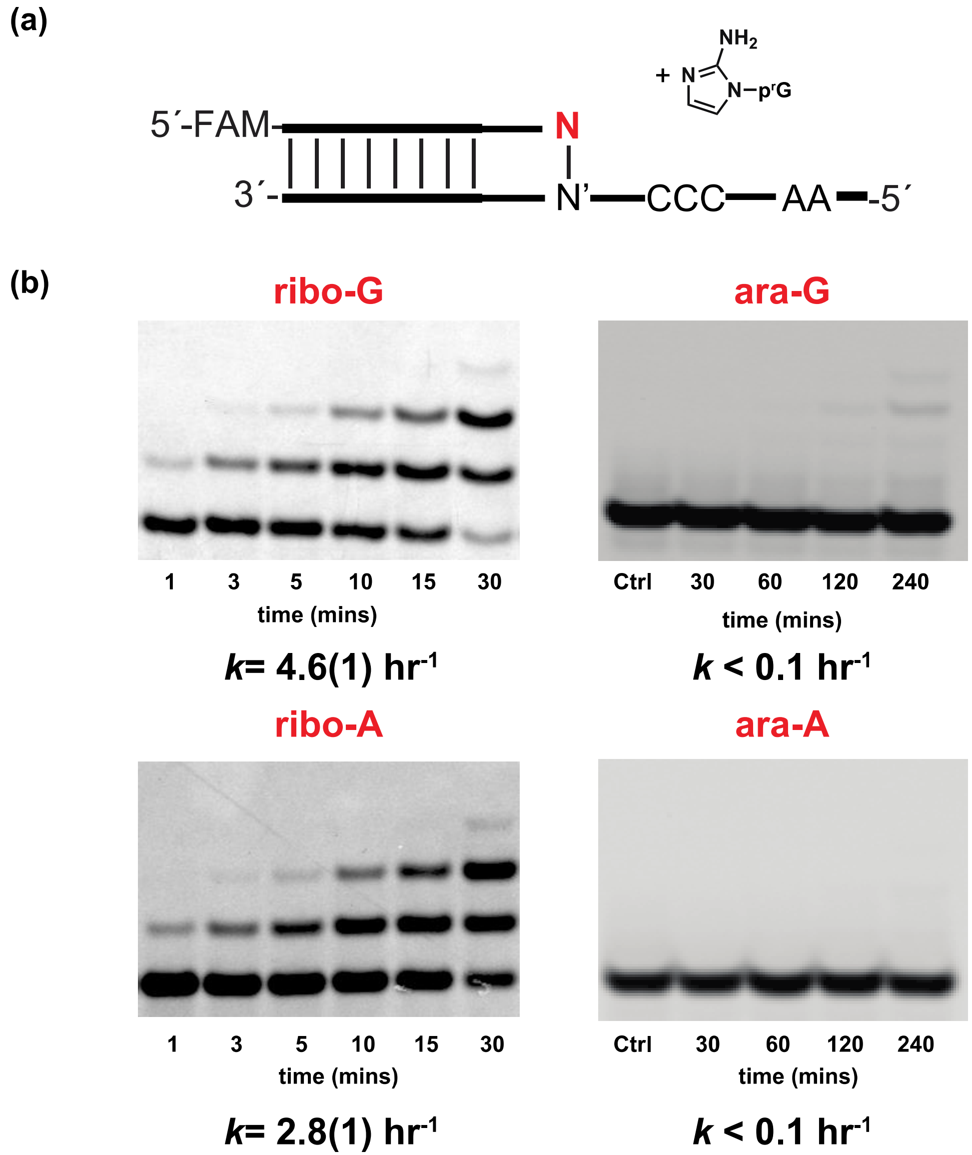
Ctrl 0.5 1 3 5 10 30 1440

time (mins)

k = 0.88(4) hr^{-1}

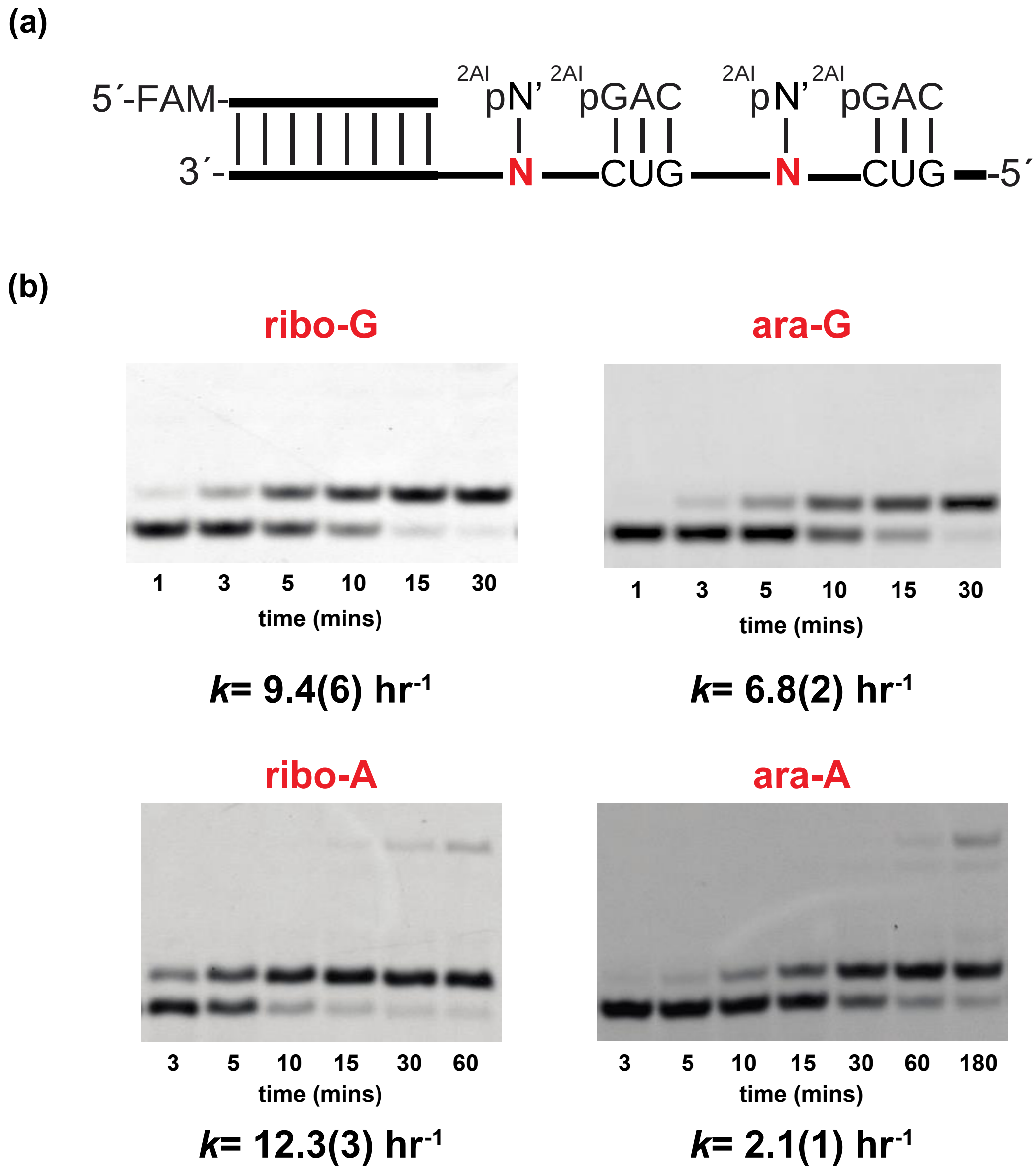
SC Kim et al., *J. Am. Chem. Soc.*, 2020, *142*, 2317

Extension of a Primer ending in ara-G or ara-A is very slow



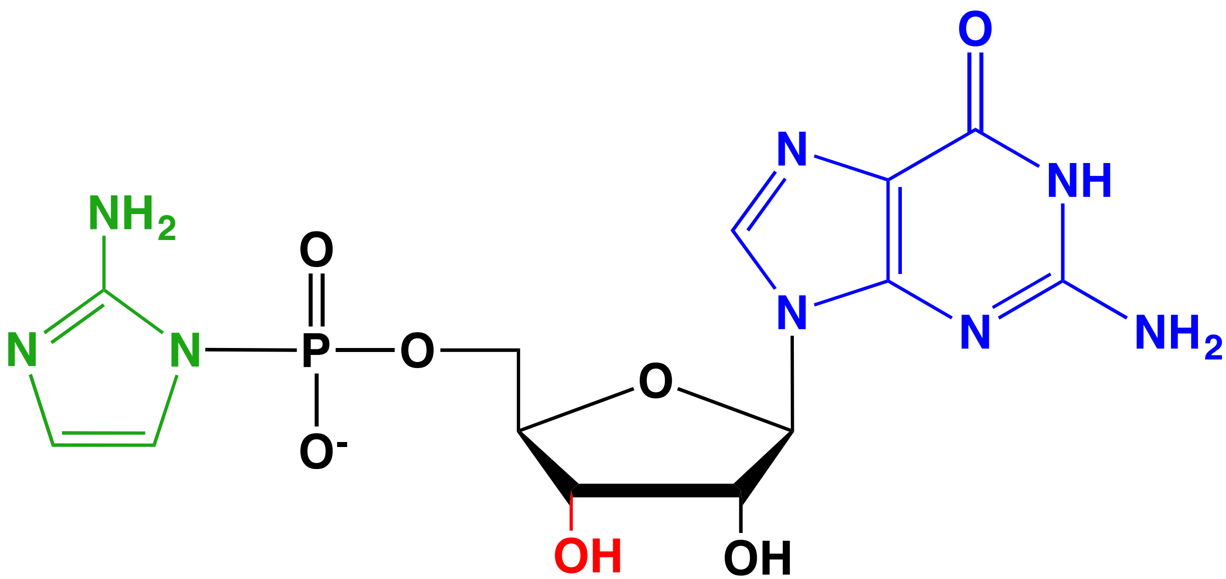
SC Kim et al., *J. Am. Chem. Soc.*, 2020, *142*, 2317

But, arabino nucleotides in the template are not too bad



SC Kim et al., *J. Am. Chem. Soc.*, 2020, *142*, 2317

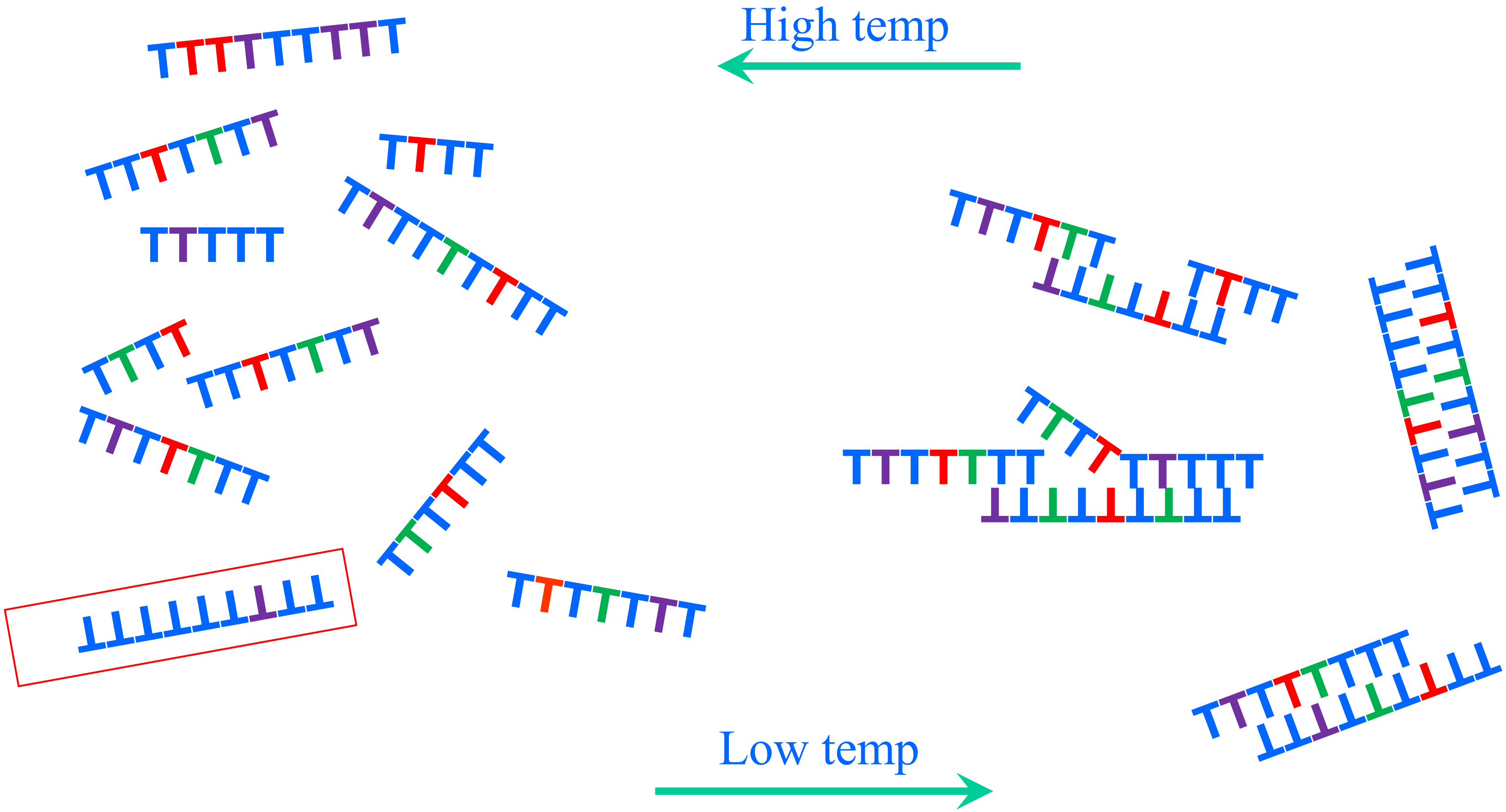
New leaving group for activated monomers: 2-aminoimidazole



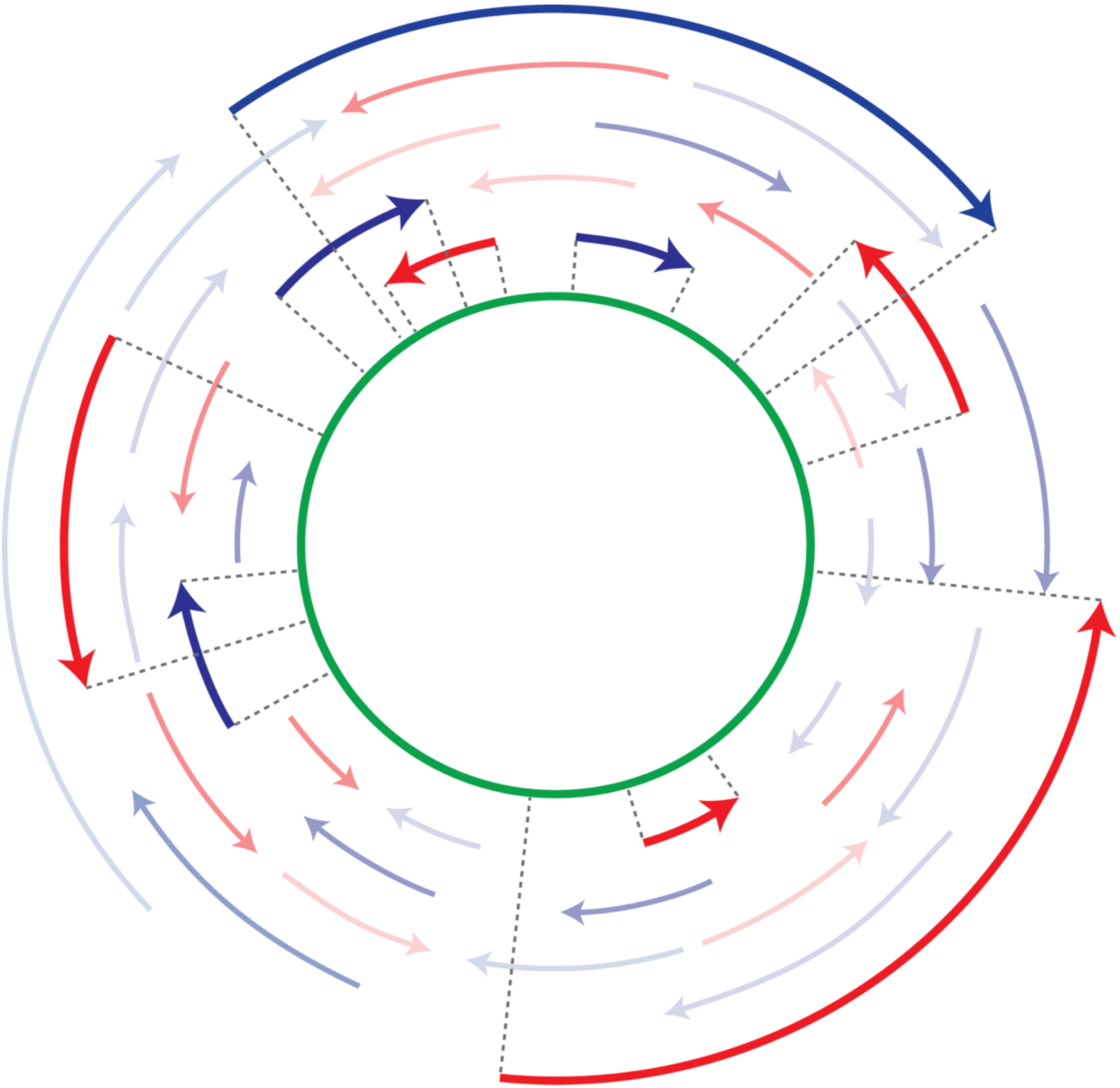
- higher pKa
- imidazolium intermediate is more stable

Li Li et al., *J. Am. Chem. Soc.*, 2017, *139*, 1810

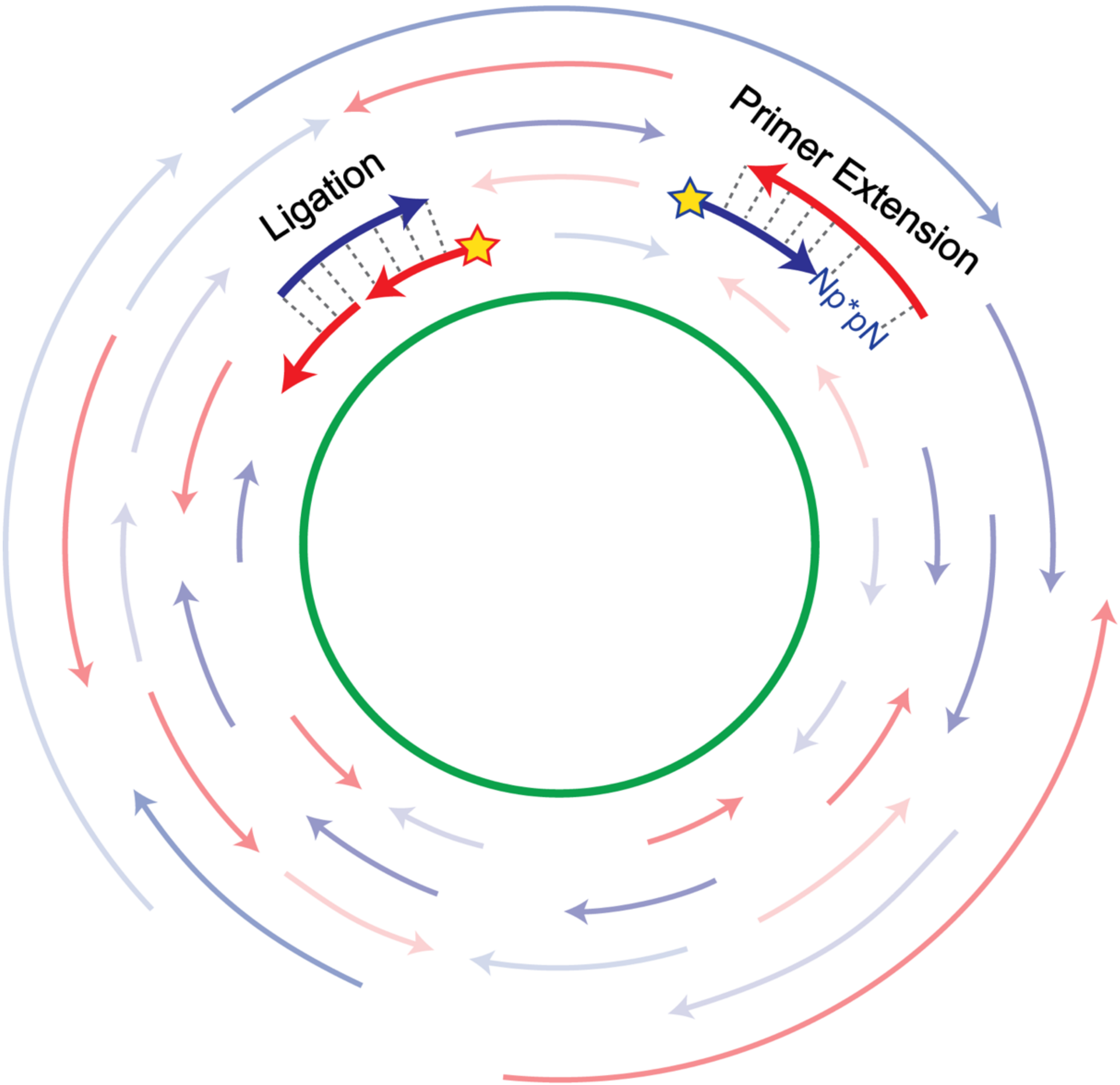
Thermal fluctuations shuffle annealed configurations



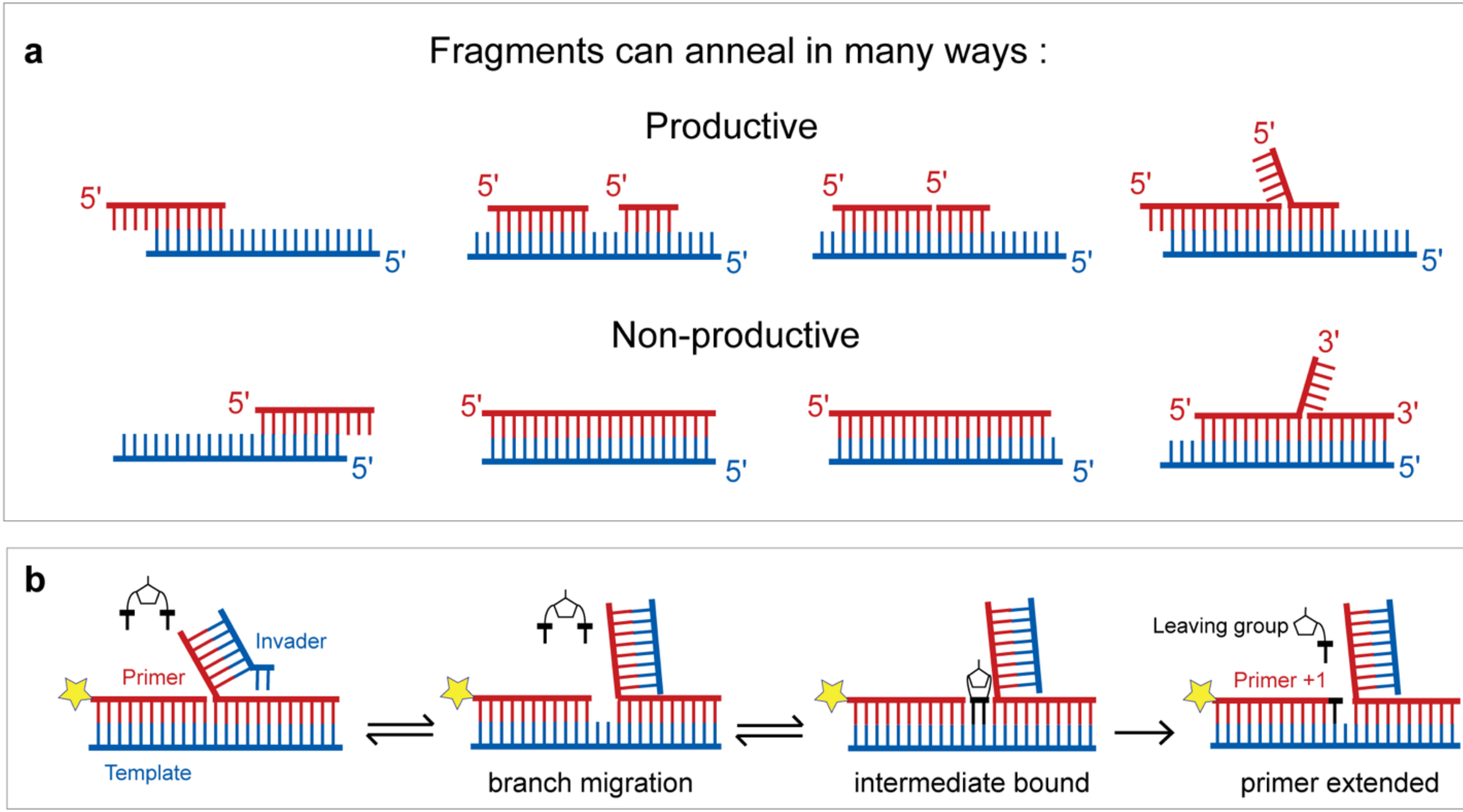
The virtual circular genome model



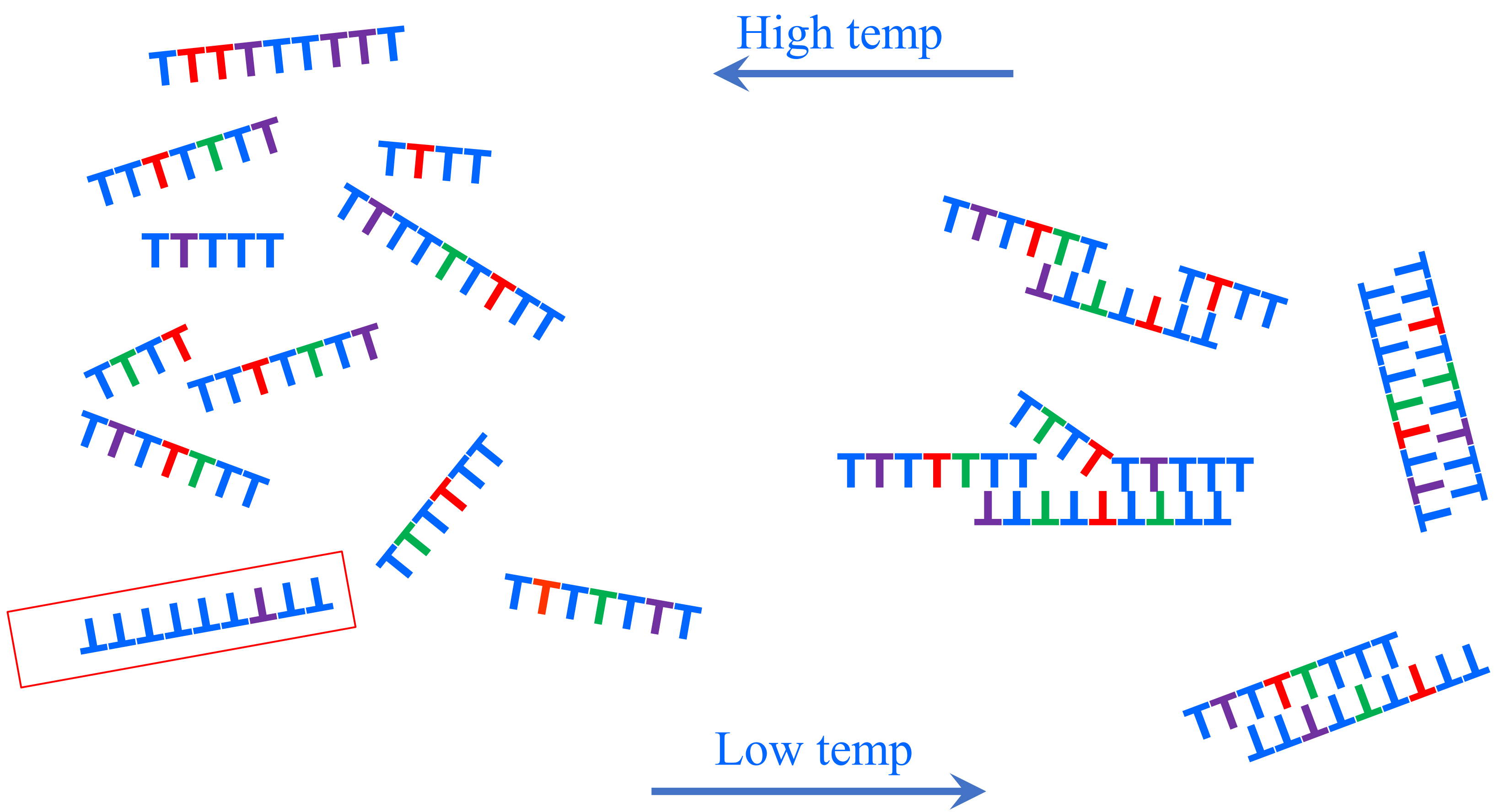
Fragments can grow by primer extension or ligation



Fragments can anneal in many ways:



Thermal fluctuations shuffle annealed configurations



Origin of ATP?