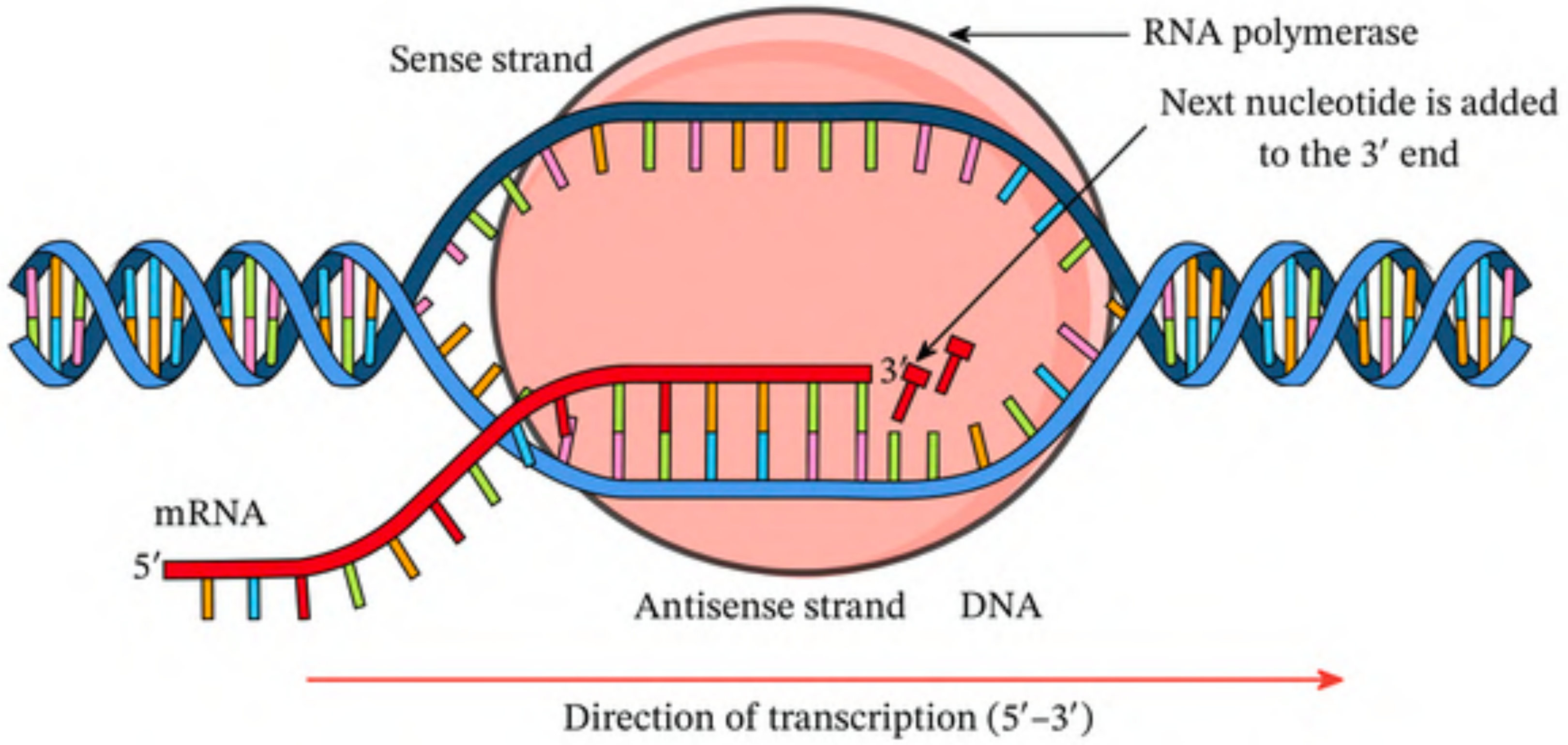
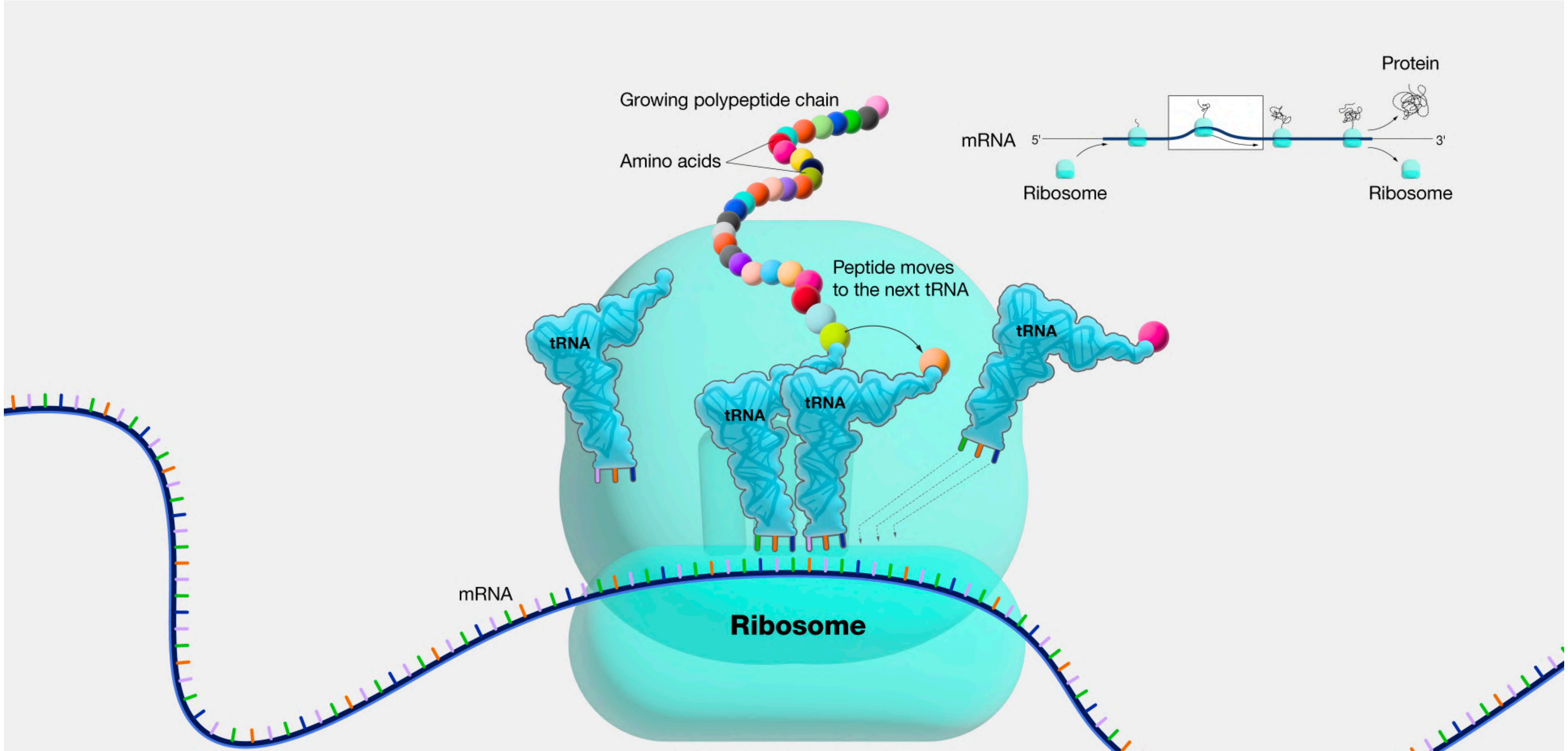
Amino acid–assisted RNA oligomerization

from 2',3'-cyclic ribonucleotides

The Central Dogma of Biology

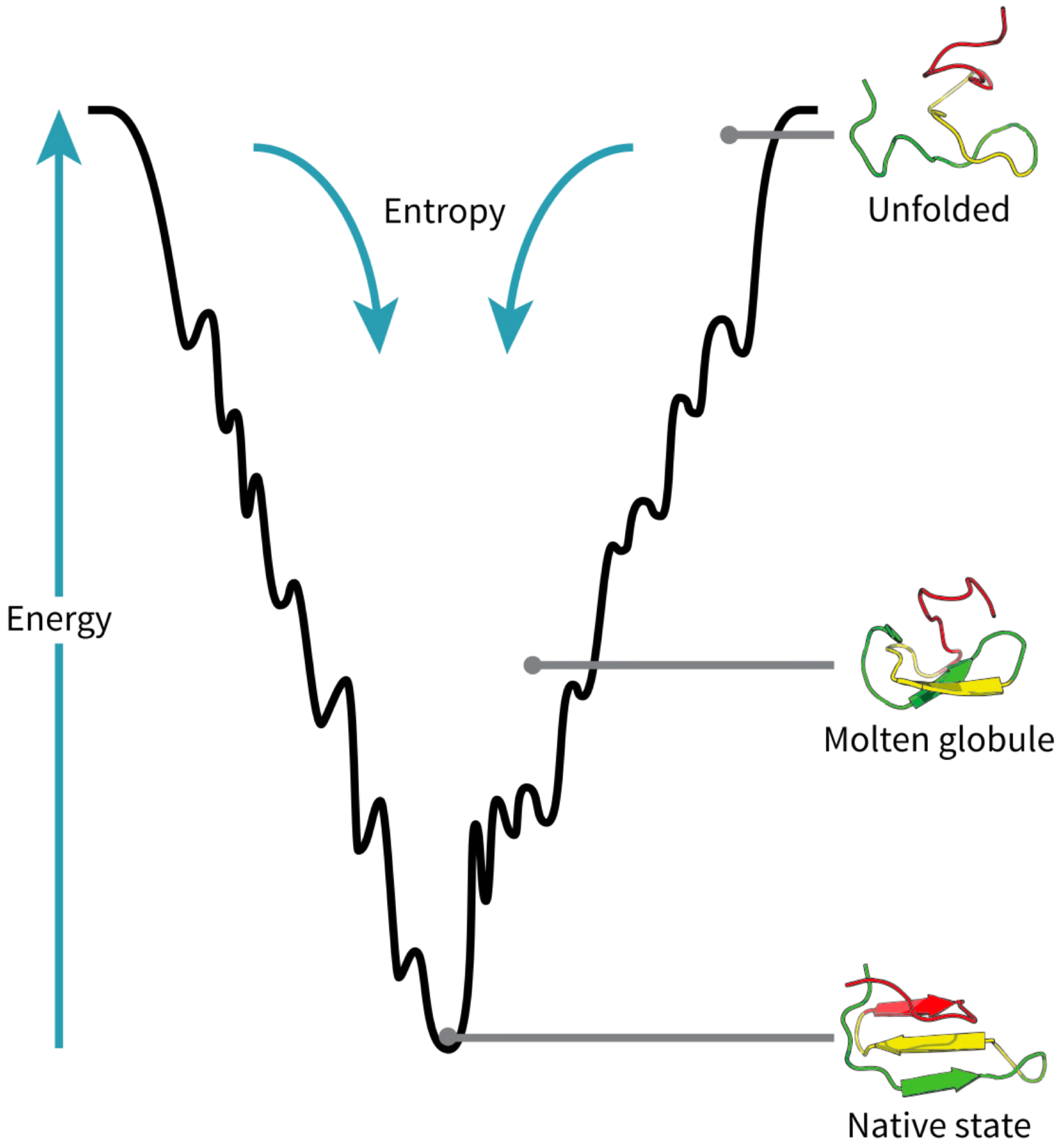


The Central Dogma of Biology



Ribosome during translation

The Central Dogma of Biology



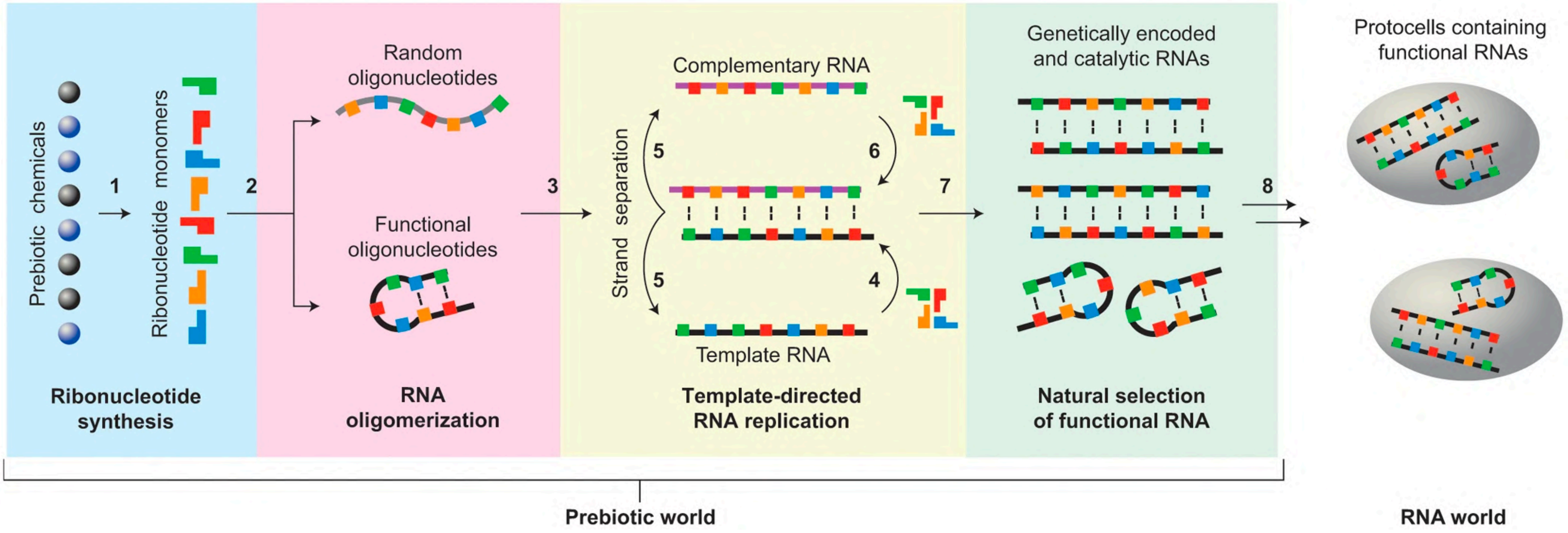
The RNA World Hypothesis

Information storage and transfer

Function

Fulfils **Genetic** and **Catalytic** requirements

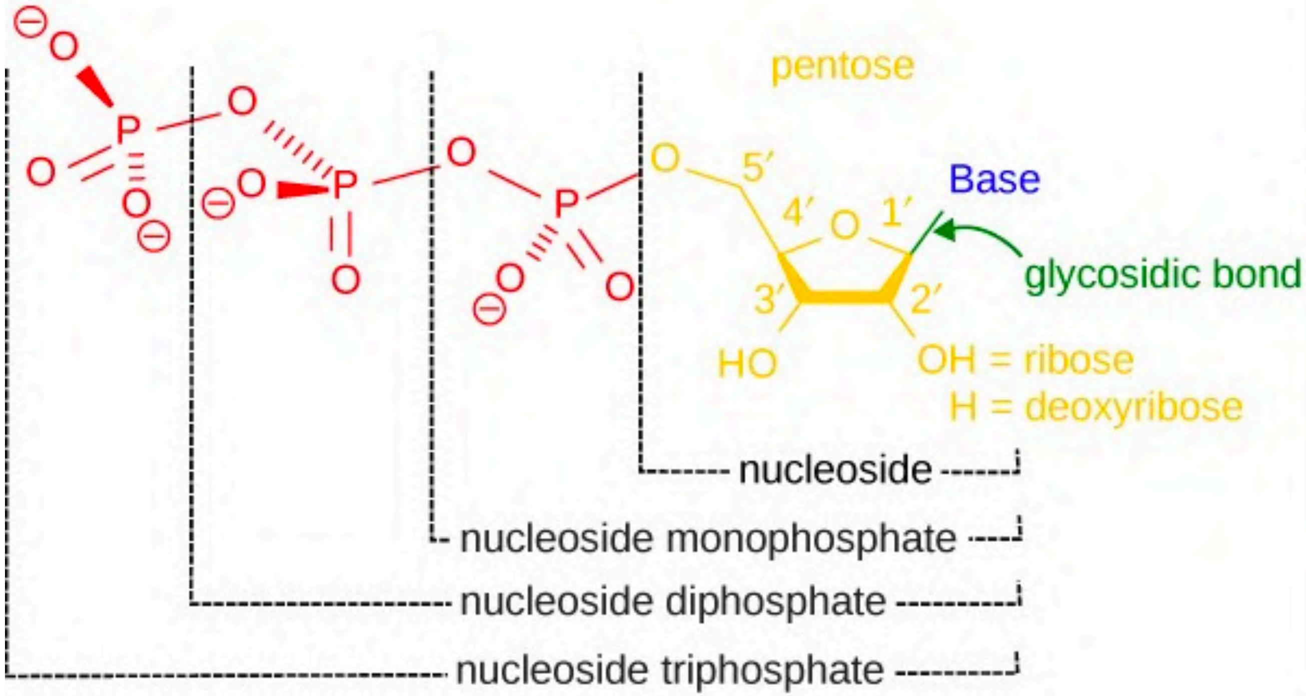
The RNA World Hypothesis

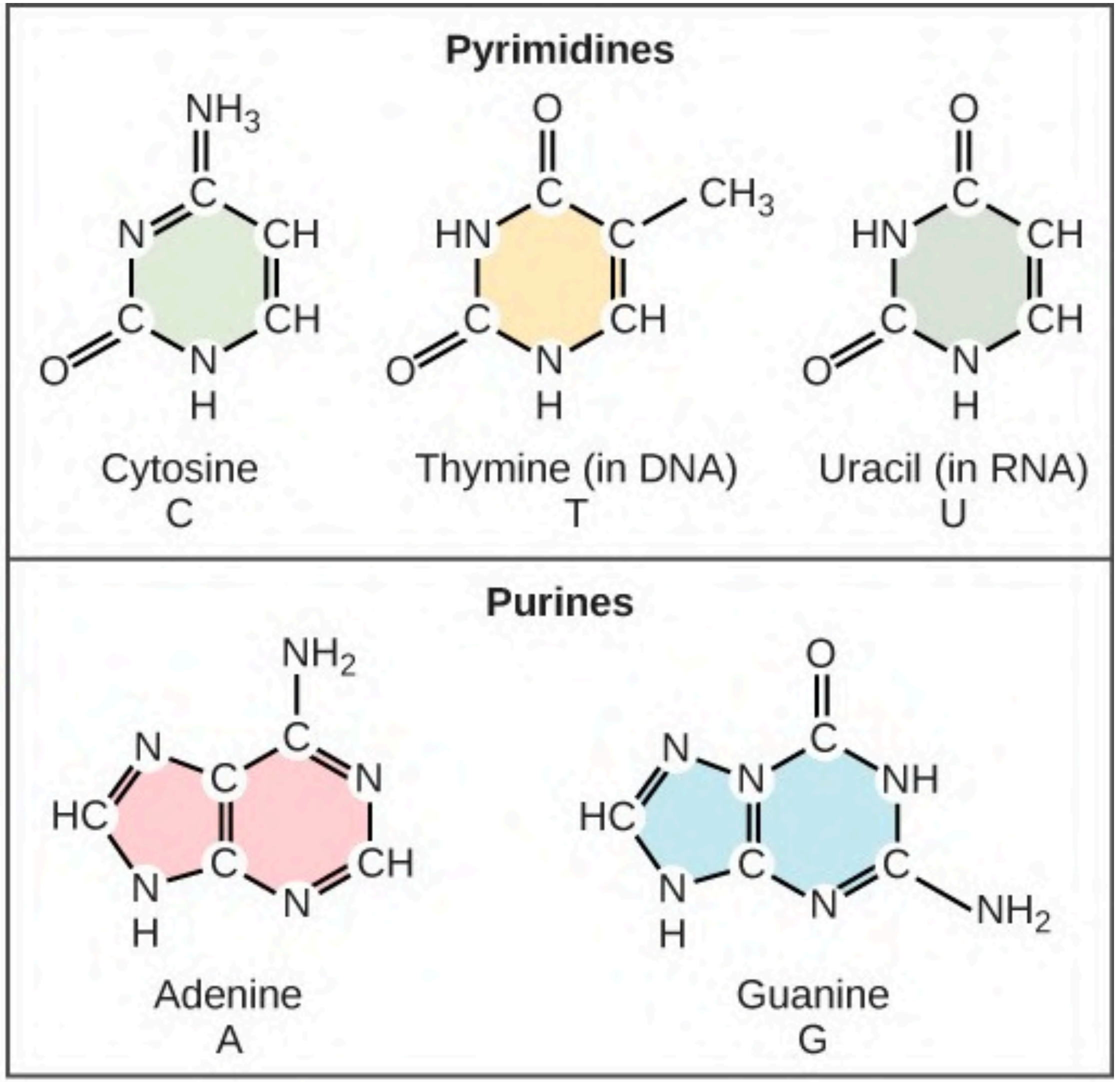


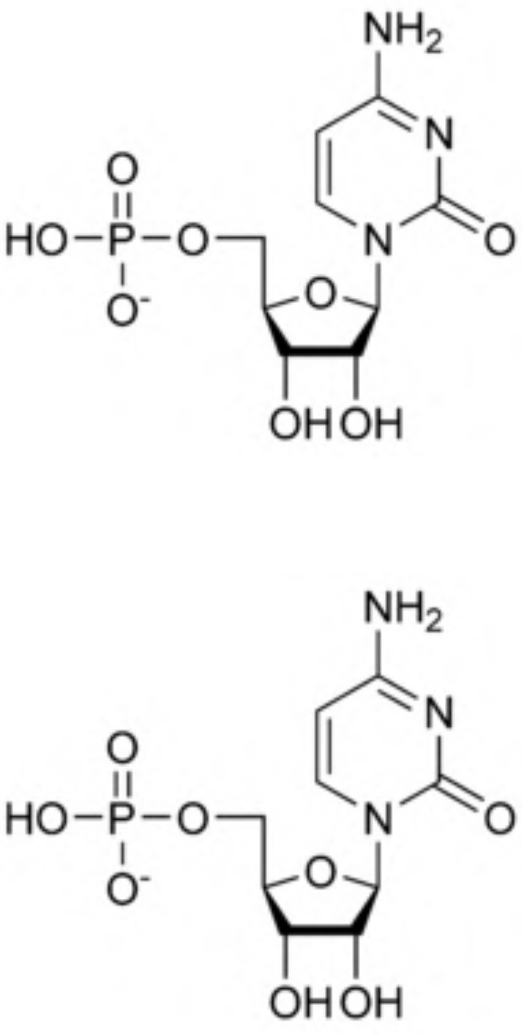
Hernández, A., Piccirilli, J. Prebiotic RNA unstuck. *Nature Chem* **5**, 360–362 (2013)

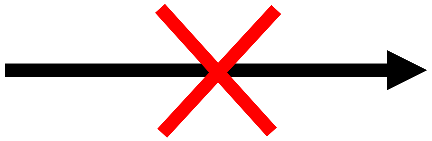
RNA

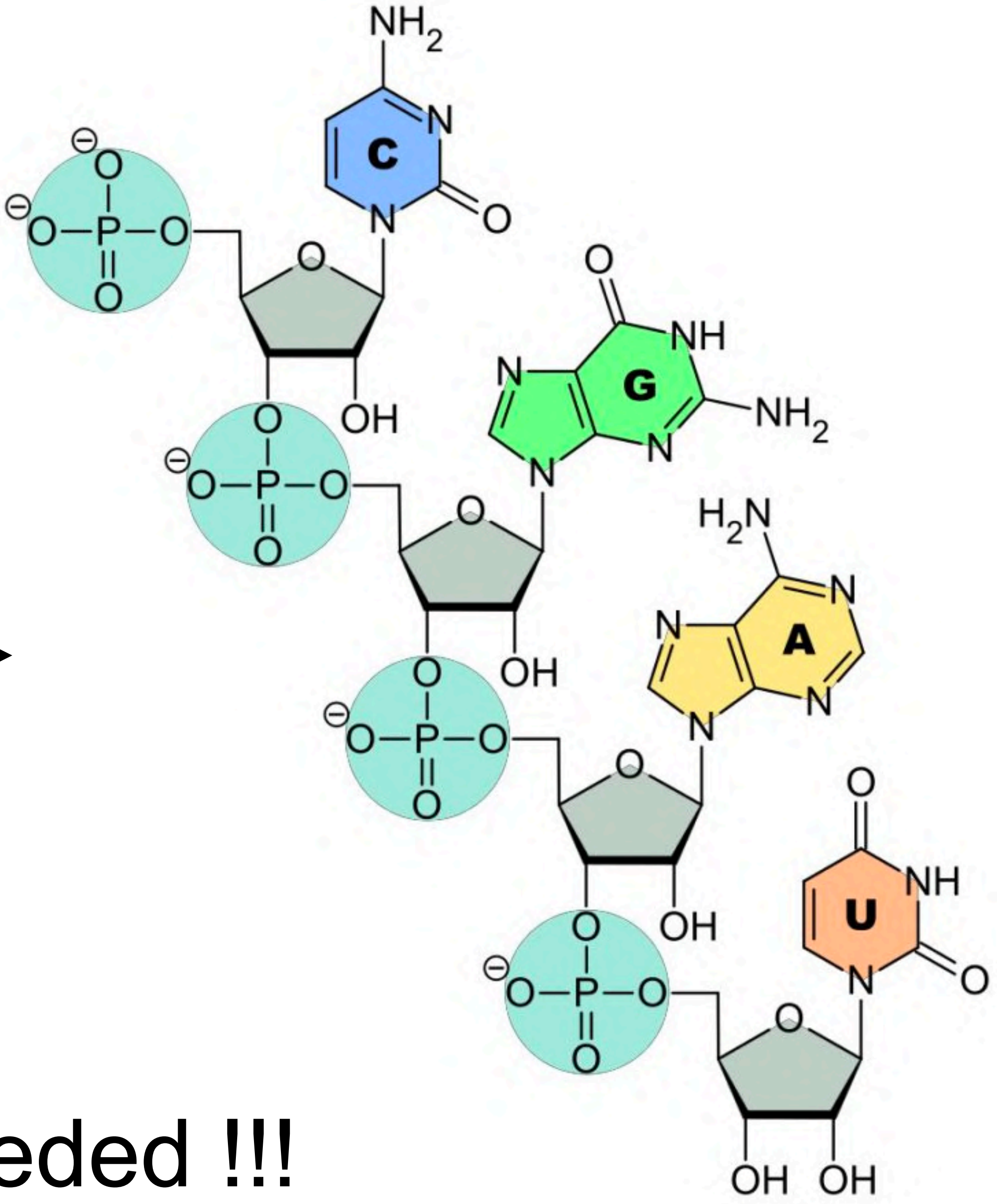
Building blocks





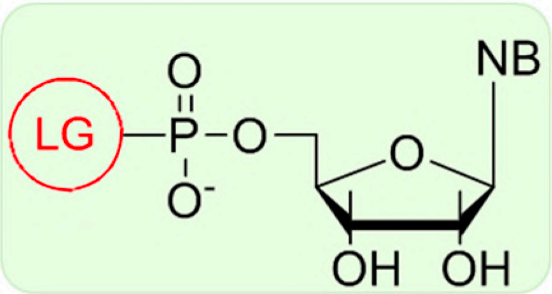




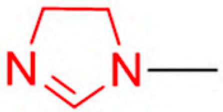


Activation needed !!!

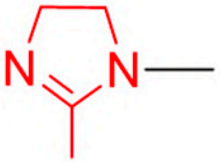
Activated nucleotides



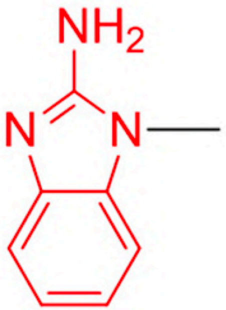
imidazole



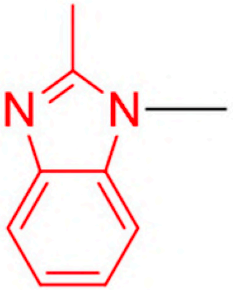
2-methylimidazole



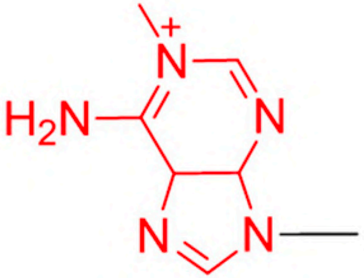
2-amino-benzimidazole



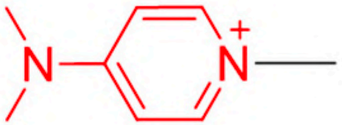
2-methyl-benzimidazole



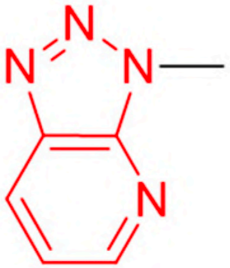
1-methyladenine

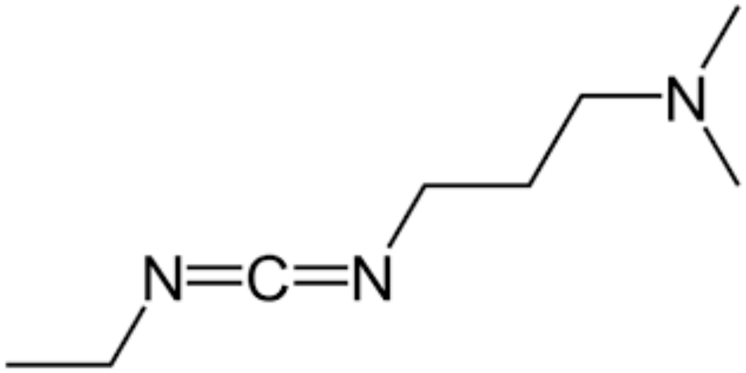


dimethylaminopyridine

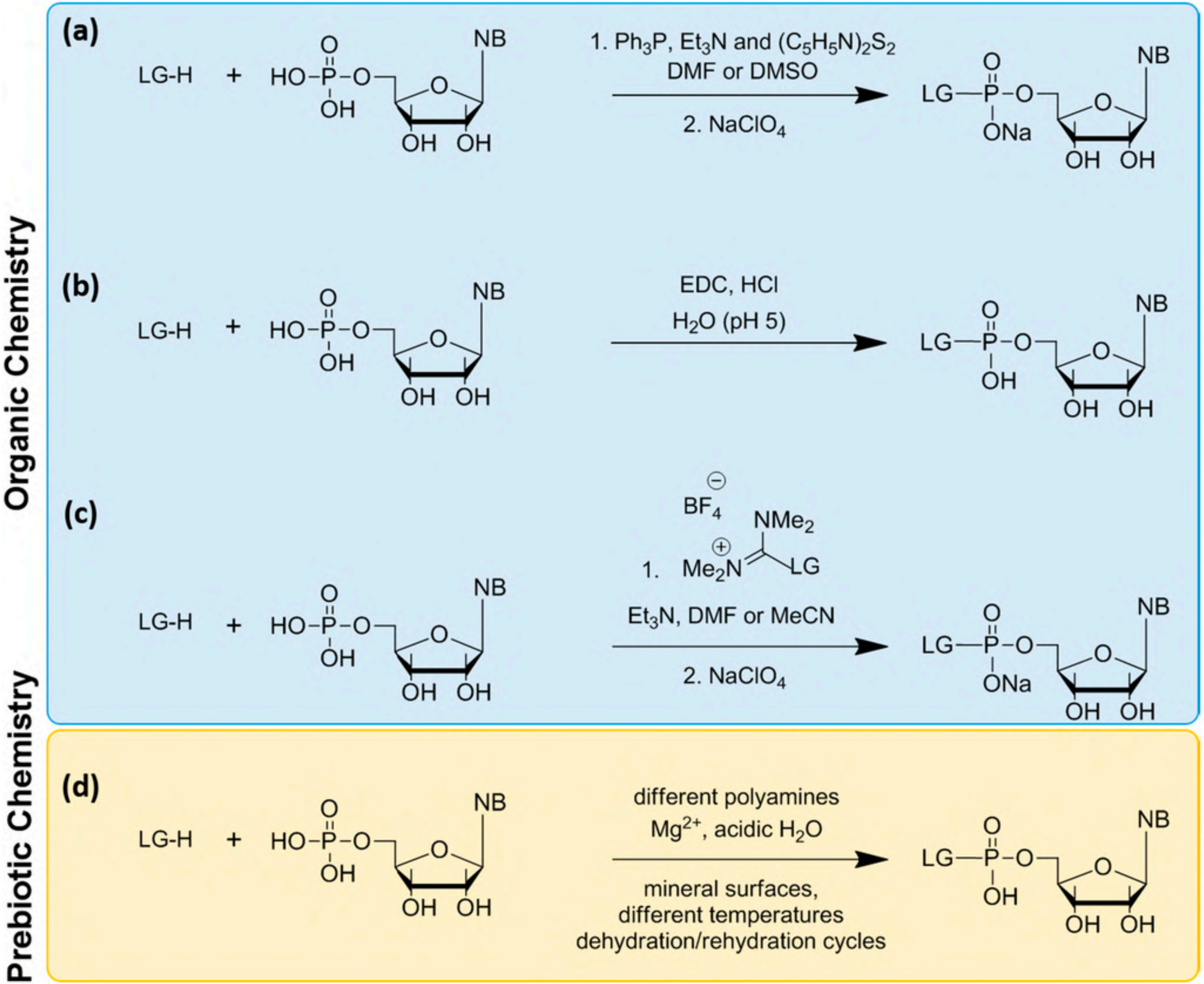


7-aza-1-hydroxybenzotriazole



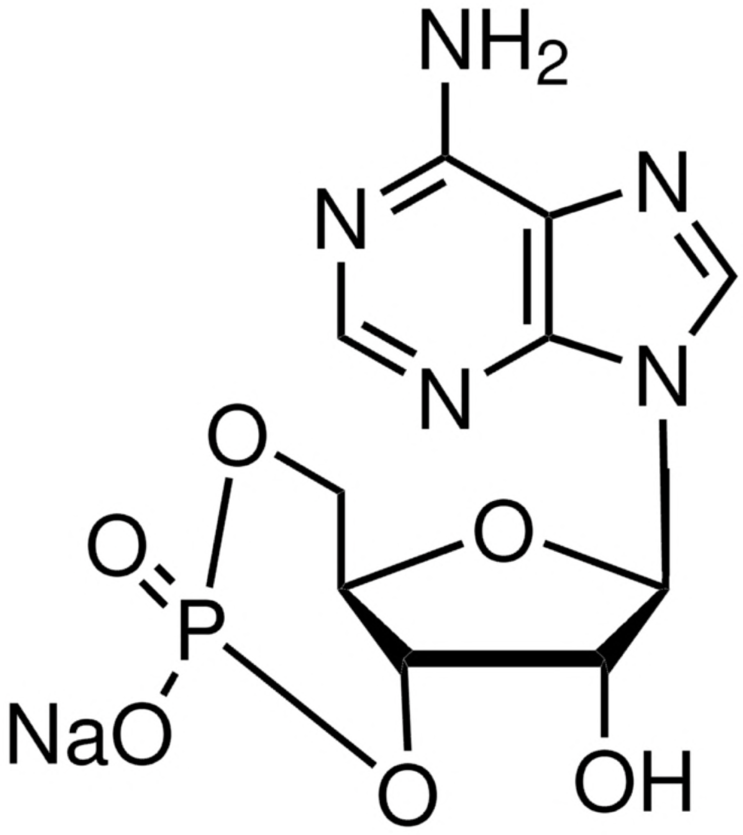


EDC

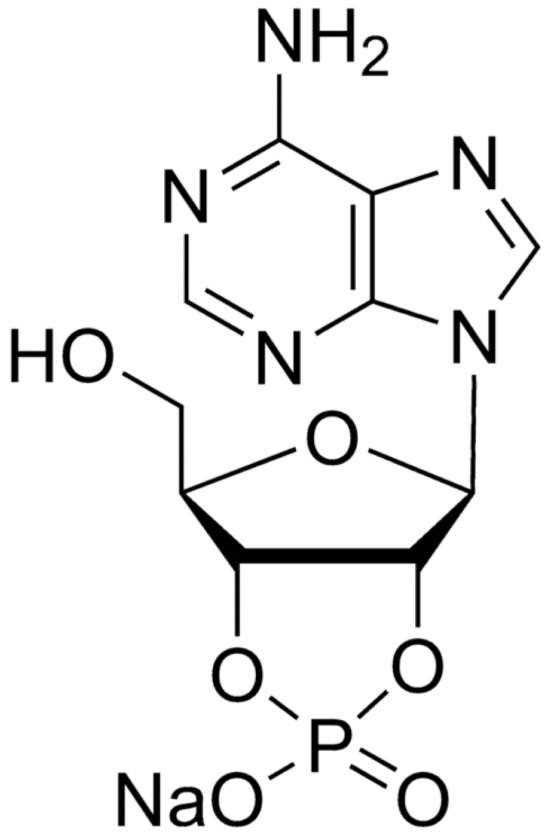


Life **2014**, *4*(4), 598-620

Cyclic nucleotides

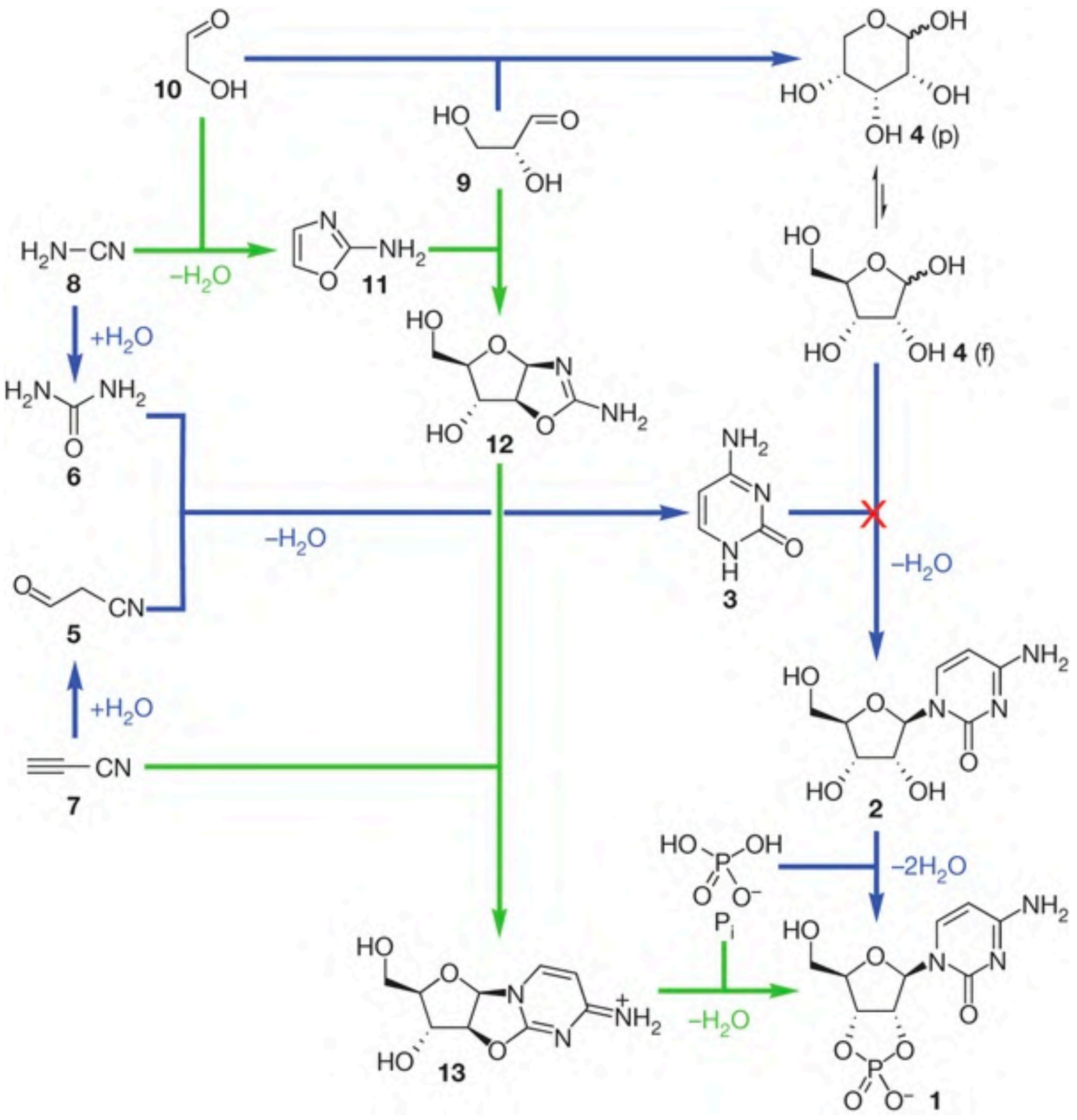


Adenosine 3′,5′-cyclic monophosphate sodium salt



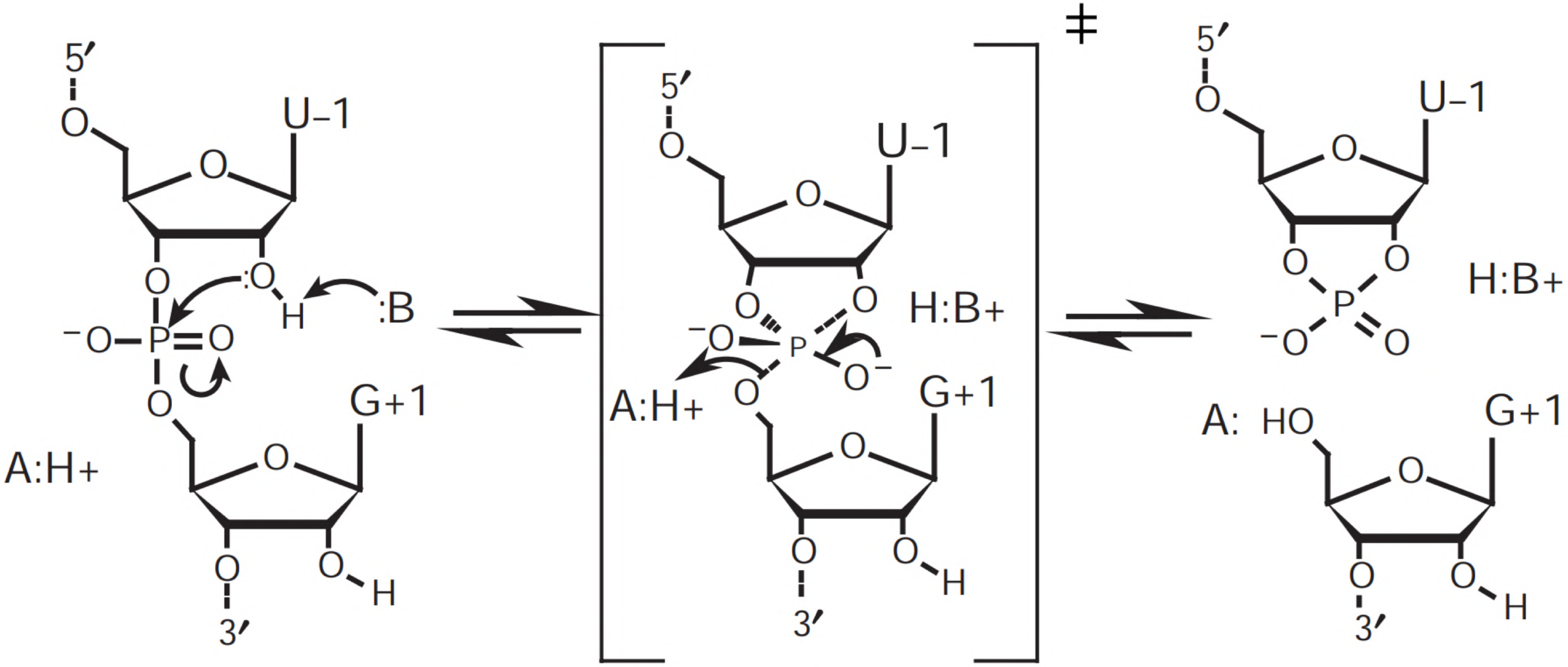
Adenosine 2′,3′-cyclic monophosphate sodium salt

2′,3′-cyclic nucleotides… why are they special ?



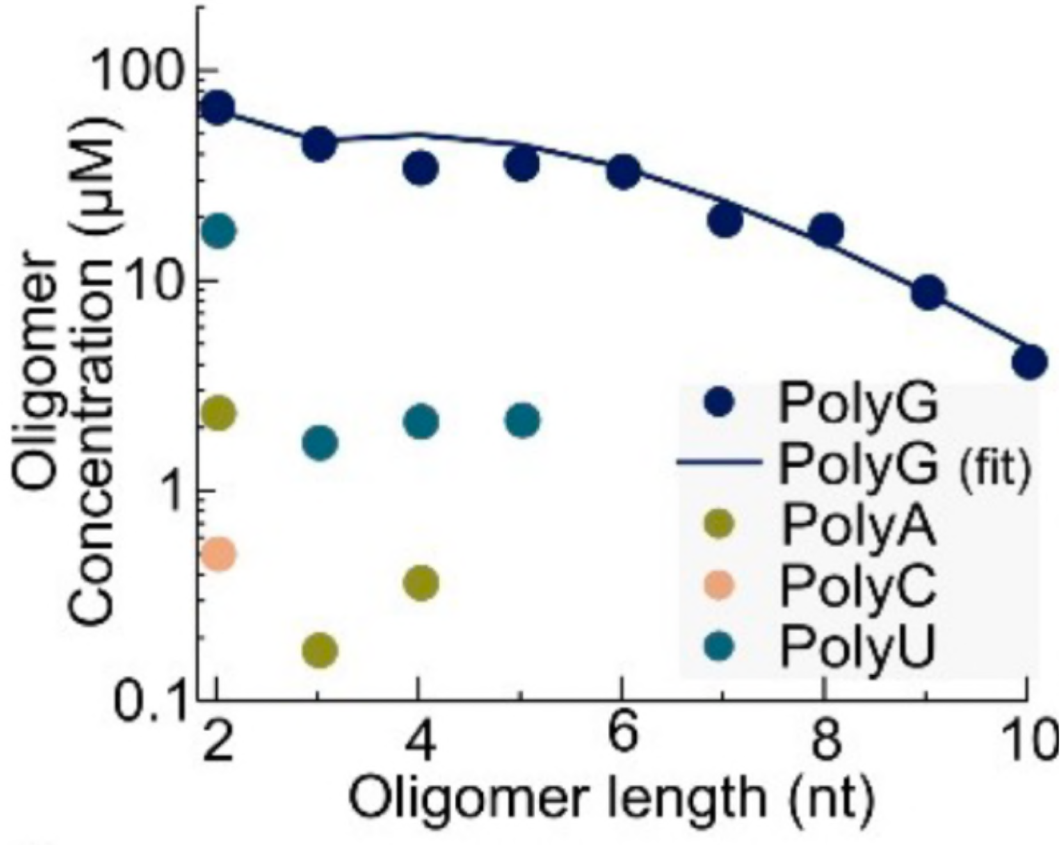
Powner *et al., Nature* **459**, 239–242 (2009)

2′,3′-cyclic nucleotides… why are they special ?



Doudna et al., *Nature* **459**, 239–242 (2009)

RNA oligomerization from 2′,3′-cyclic nucleotides in a dry state



cGMP > cUMP > cAMP > cCMP

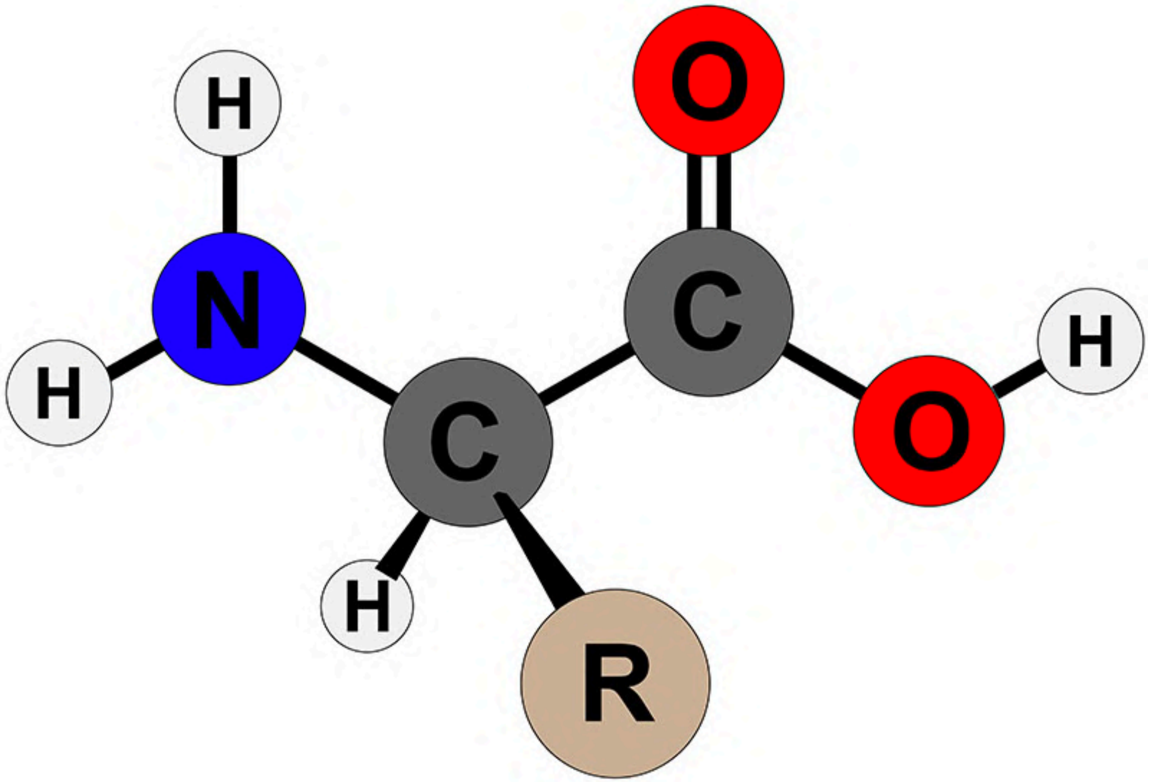
Dass et al., ChemSystemsChem, 2022,e202200026

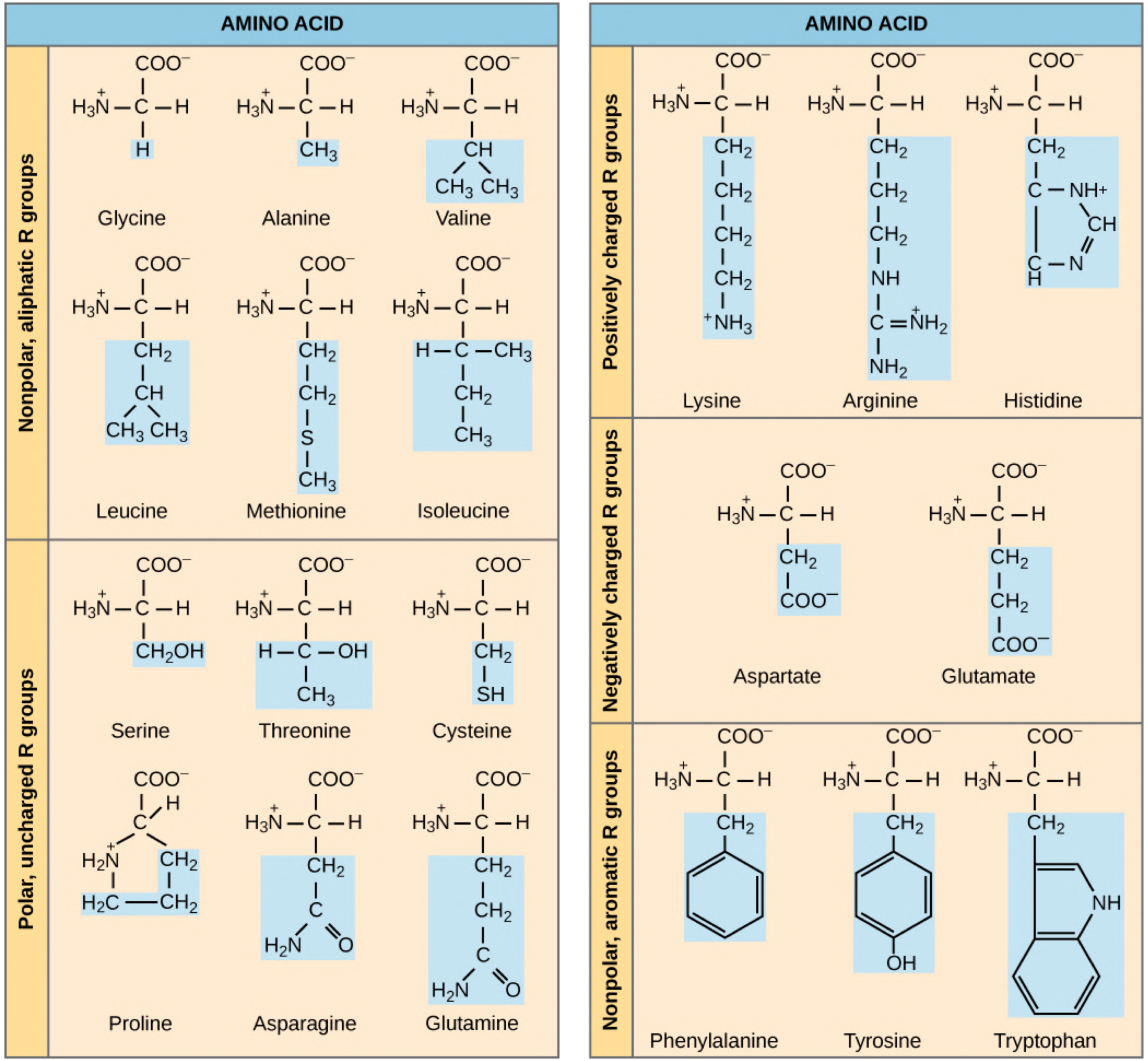
Molecular cooperation on ancient earth

Amino acids

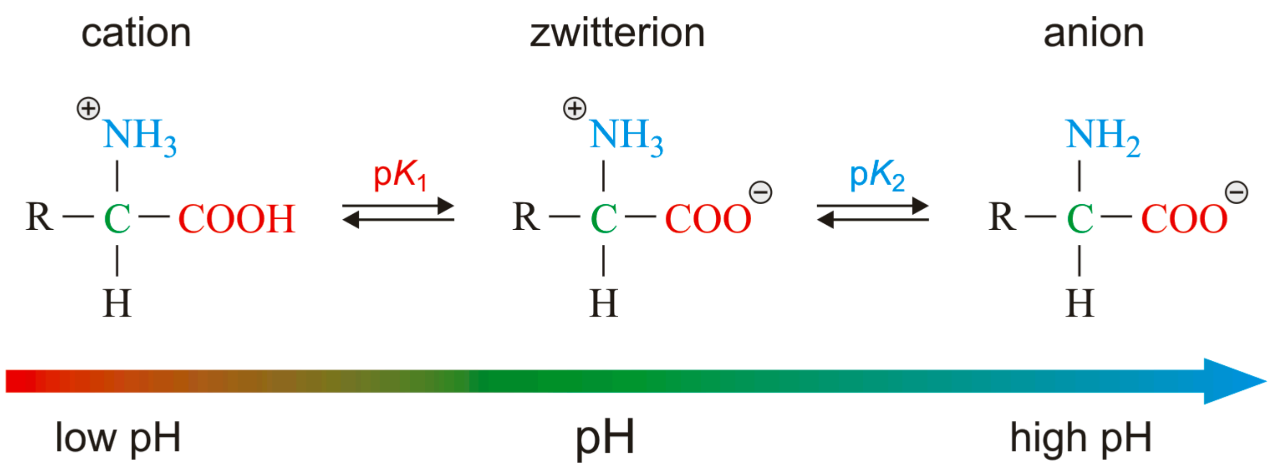
Nucleotides

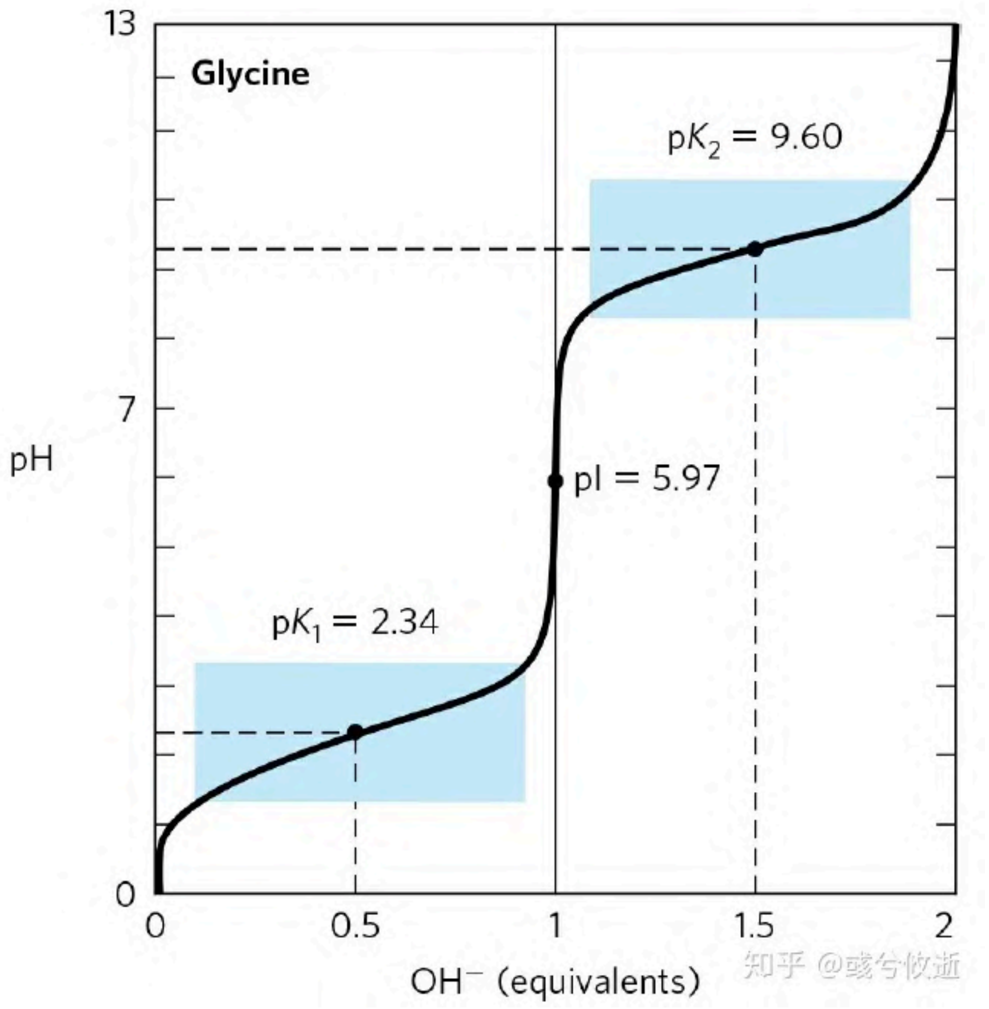
What are amino acids ?

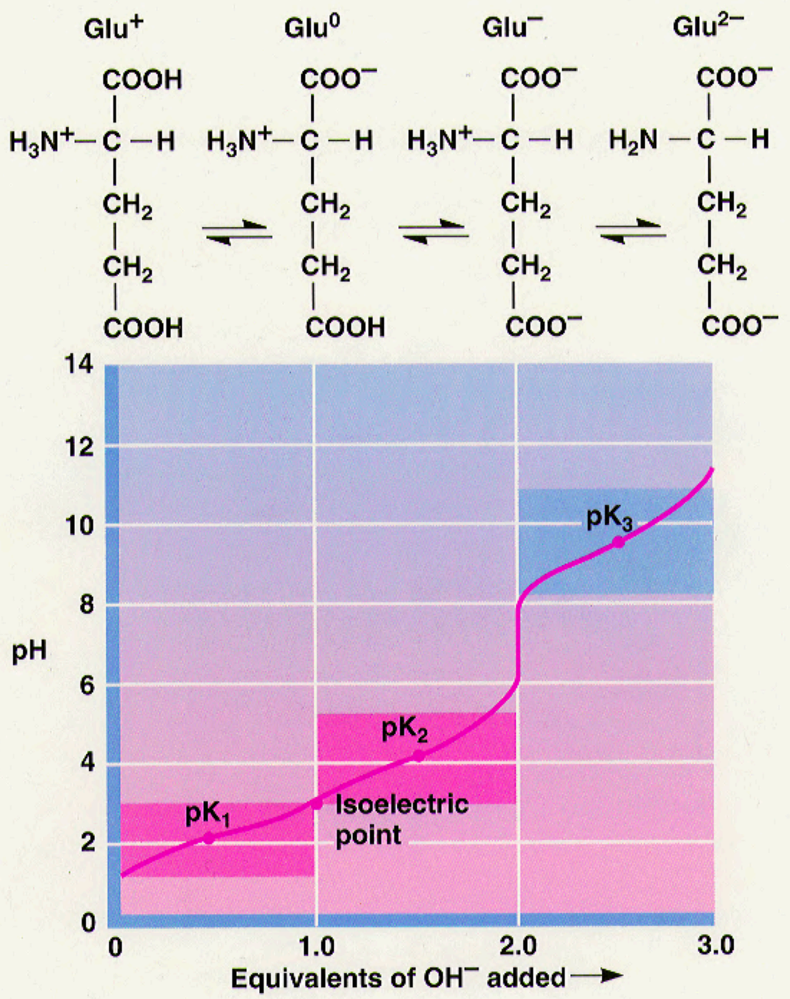

H
N
H
C
H
R
O
C
O
H


AMINO ACID
Nonpolar, aliphatic R groups
Glycine
Alanine
Valine
Leucine
Methionine
Isoleucine
Polar, uncharged R groups
Serine
Threonine
Cysteine
Proline
Asparagine
Glutamine
AMINO ACID
Positively charged R groups
Lysine
Arginine
Histidine
Negatively charged R groups
Aspartate
Glutamate
Nonpolar, aromatic R groups
Phenylalanine
Tyrosine
Tryptophan

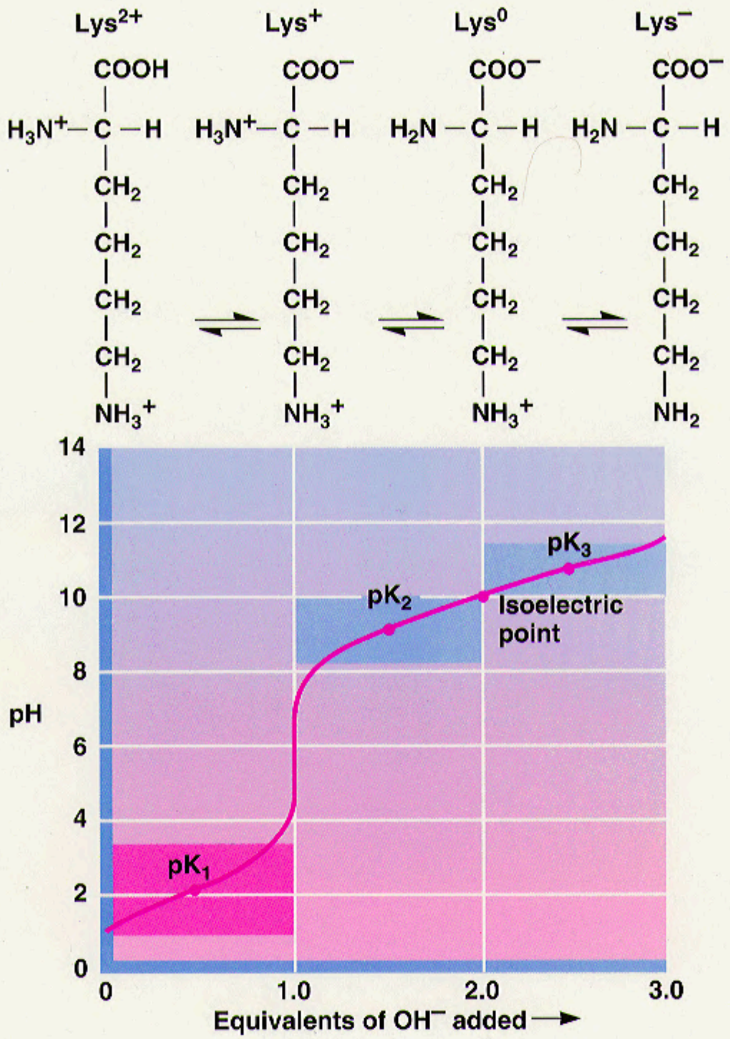
Ionization of amino acids





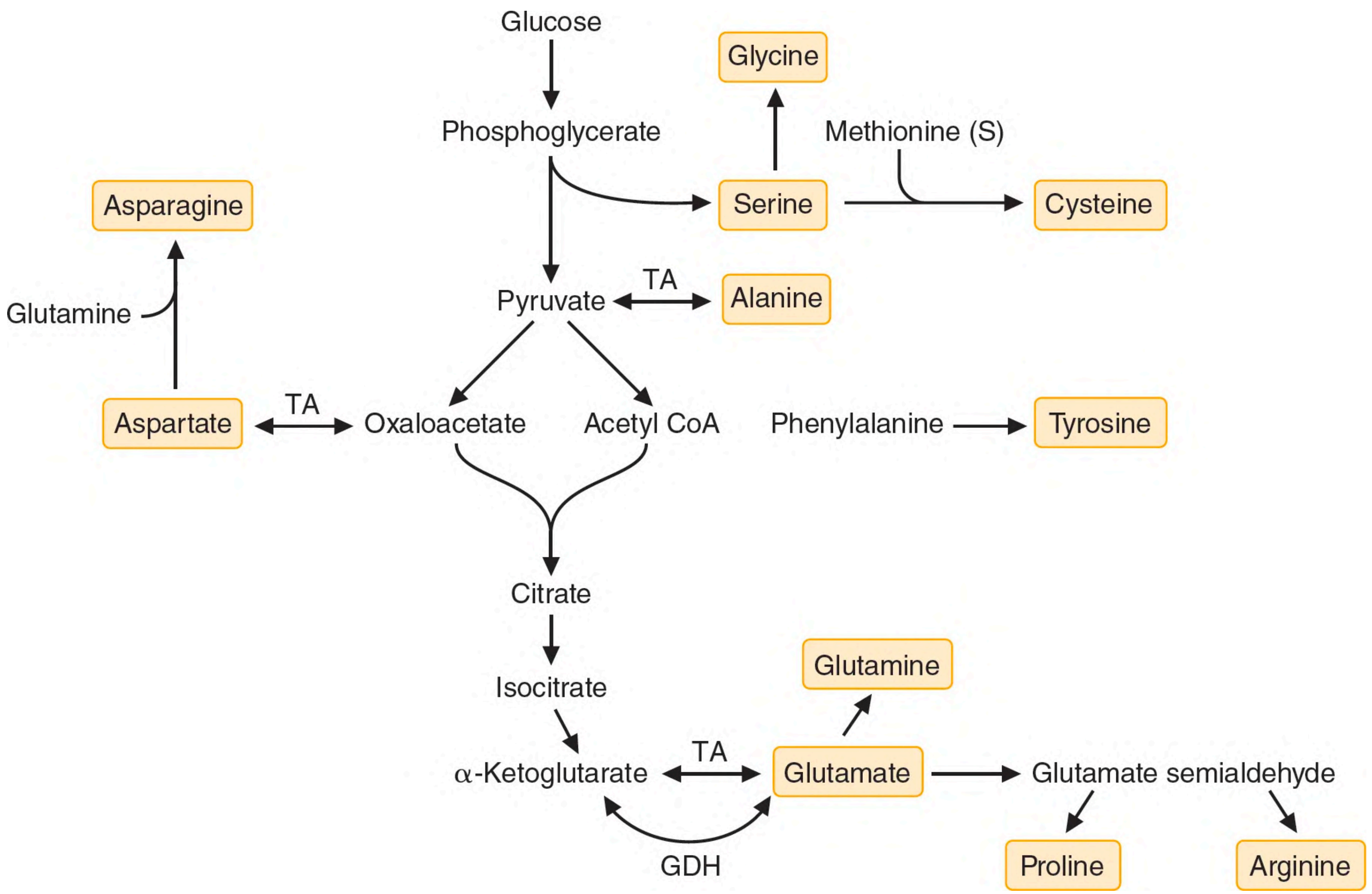


Glu+
Glu0
Glu−
Glu2−
pK1
pK2
pK3
Isoelectric point
pH
Equivalents of OH− added

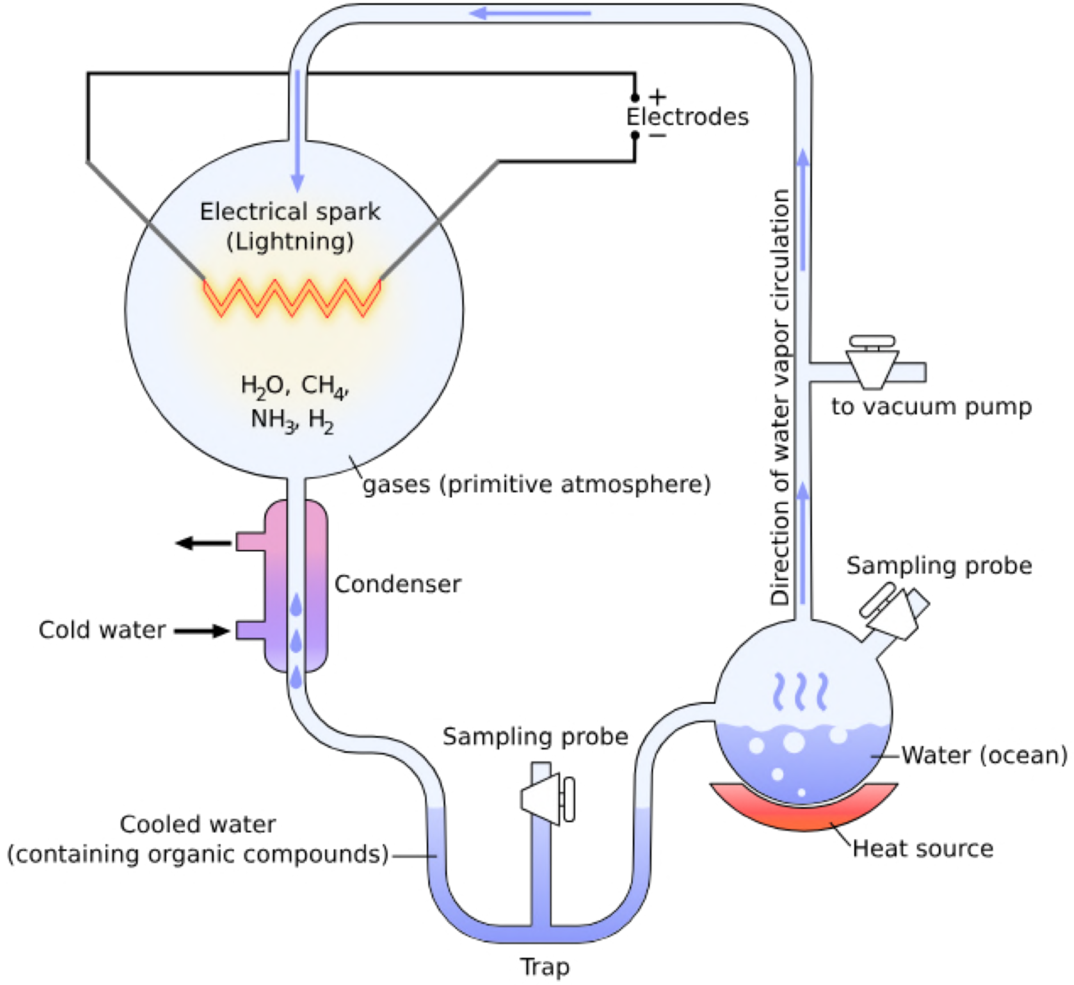


Lys2+
Lys+
Lys0
Lys−
pK1
pK2
pK3
Isoelectric point
pH
Equivalents of OH− added

Bio-synthesis



Prebiotic synthesis

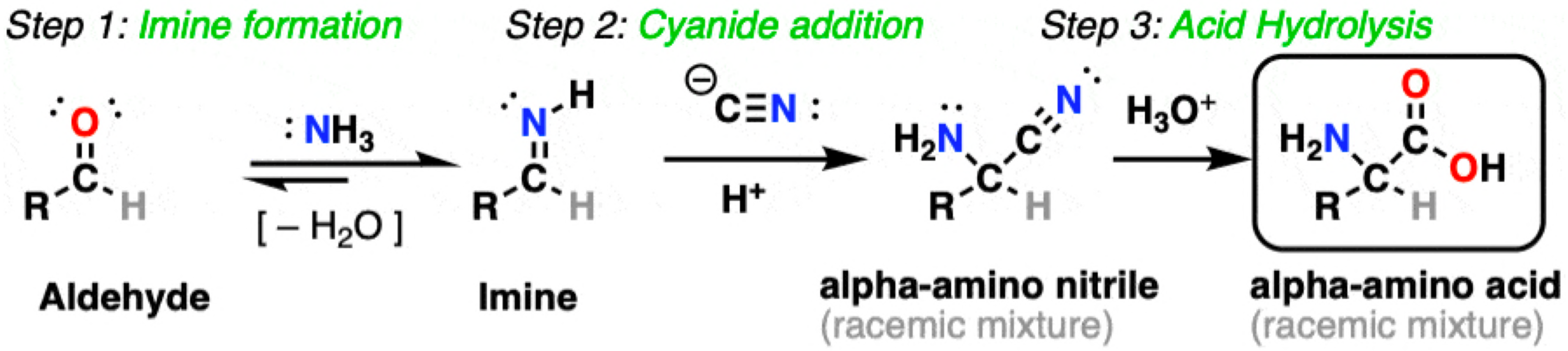


Miller–Urey experiment

Amino Acids	Amines	Peptides
Glycine	Methylamine	Glycyl-alanine
Alanine	Ethylamine	Glycyl-threonine
β-Alanine	Ethanolamine	Glycyl-proline
Serine	Isopropylamine	Prolyl-glycine
Isoserine	N-Propylamine	Glycyl-valine
α-Aminoisobutyric acid	Cysteamine	Valyl-glycine
β-Aminoisobutyric acid		Glycyl-glutamic acid
α-Aminobutyric acid		Glutamyl-glycine
β-Aminobutyric acid		Leucyl-glycine
γ-Aminobutyric acid		cyclo(Glycyl-glycine)
Homoserine		cyclo(Glycyl-Proline)
α-Methylserine		cyclo(Leucyl-Glycine)
Threonine		
Aspartic acid		
β-Hydroxyaspartic acid		
Valine		
Isovaline		
Norvaline		
Ornithine		
Glutamic acid		
α-Methylglutamic acid		
Leucine		
Isoleucine		
α-Aminoadipic acid		
Phenylalanine		
Homocysteic acid		
S-Methylcysteine		
Methionine		
Methionine sulfoxide		
Methionine sulfone		
Ethionine		

Johnson et al., 2008; Parker et al., 2011; Parker et al., 2014.

Strecker synthesis

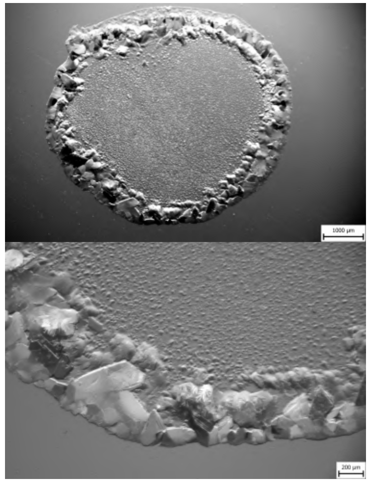


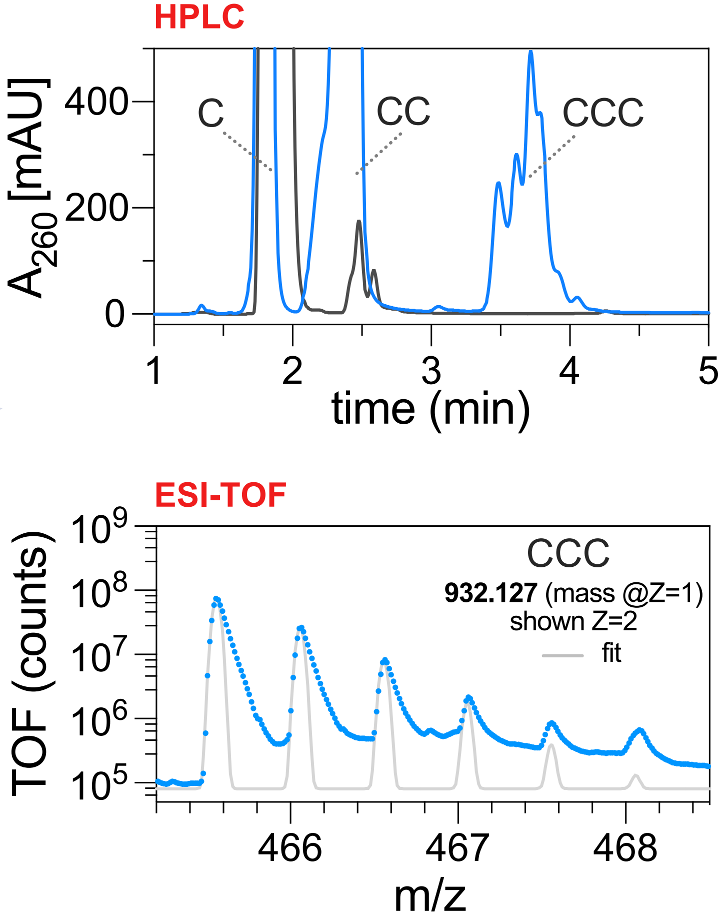
Amino acids as **catalysts** for RNA polymerization

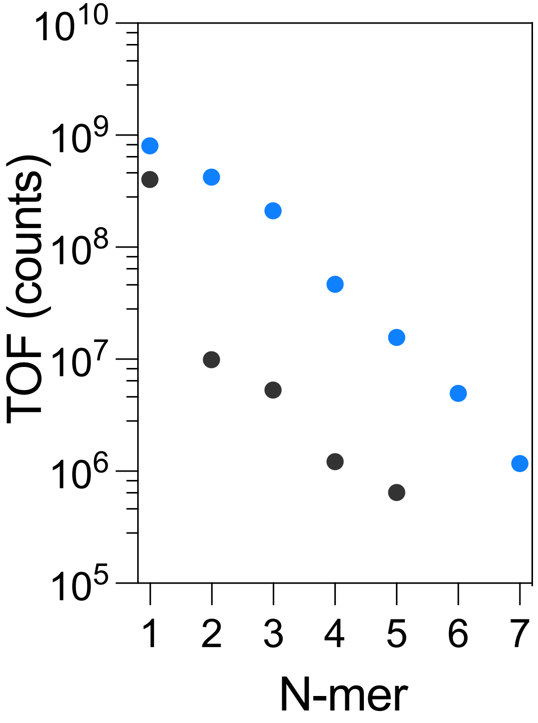
Experimental set up: dry state RNA polymerization

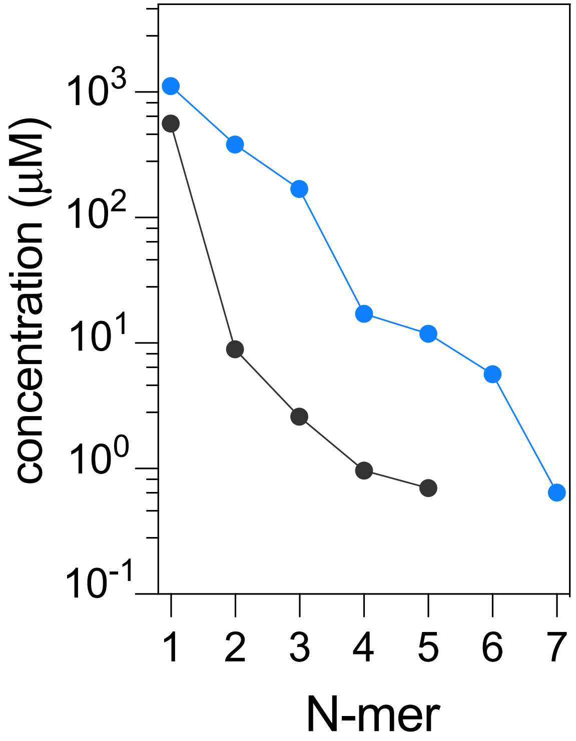
cCMP

cCMP + Valine



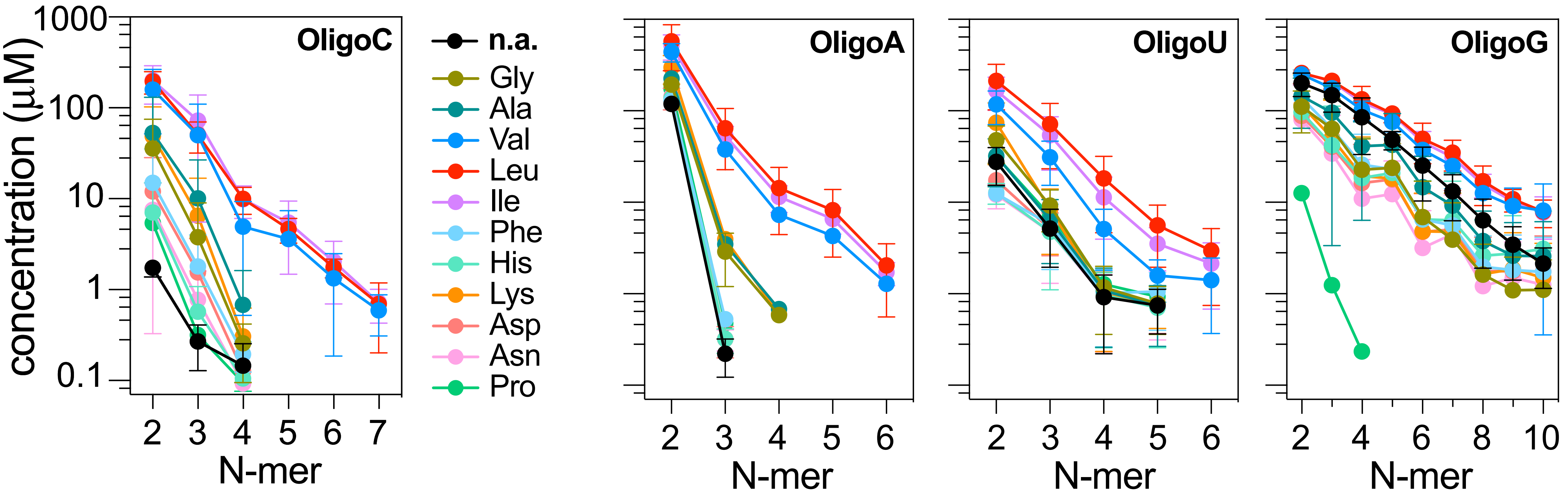






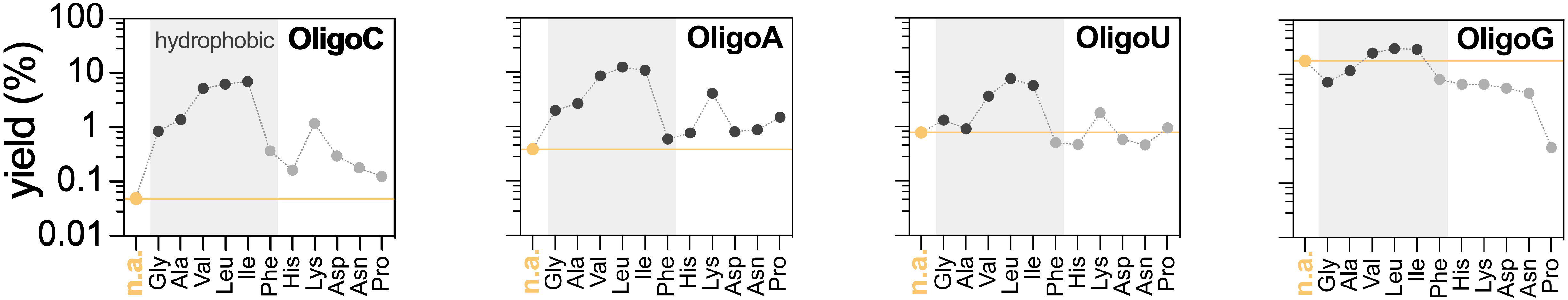
Nucleotide - 10 mM
Amino acid - 50 mM
pH 10 (with KOH)
Dry 20 h

Oligomerization of 2’, 3’-cNMP catalyzed by amino acids



cNMP- 10 mM
Val - 50 mM
pH 10, RT

Oligomerization of 2’, 3’-cNMP catalyzed by amino acids

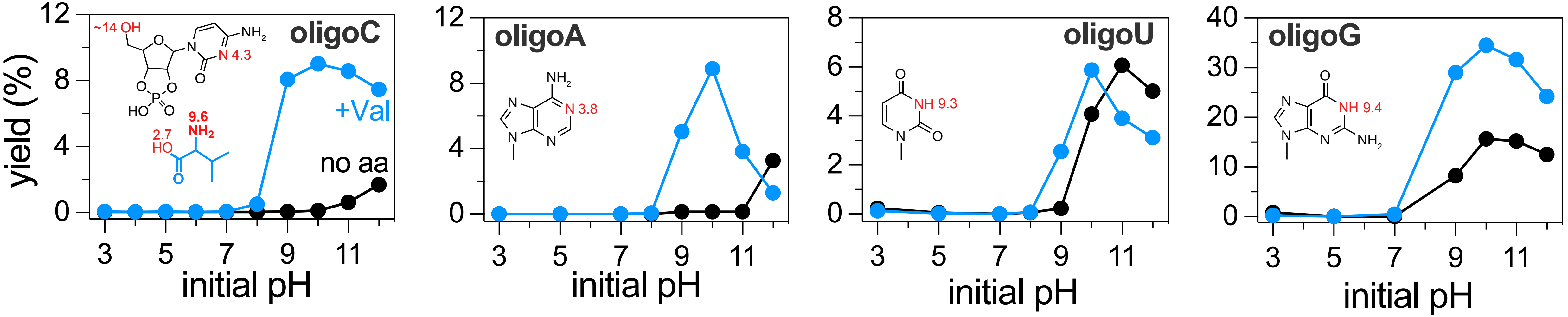


cNMP: C < A < U < G

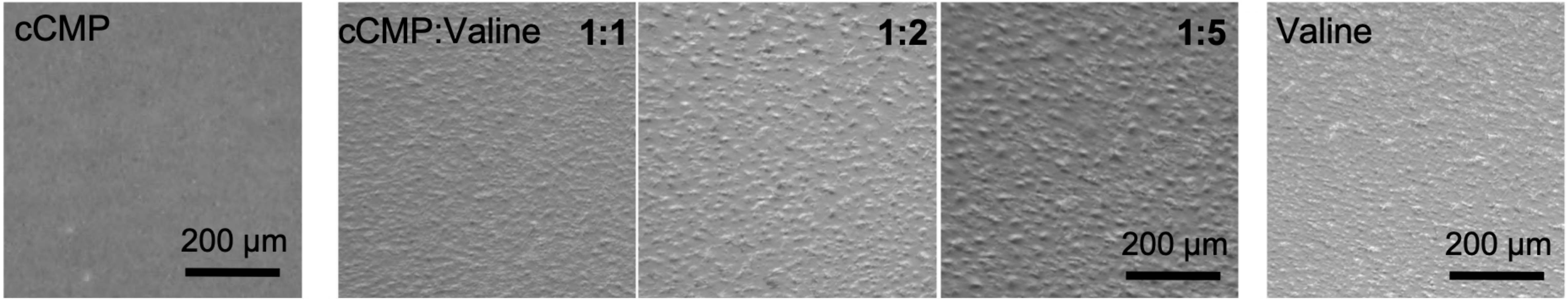
cNMP + Val: C > A > U > G

cNMP- 10 mM
Val - 50 mM
pH 10, RT

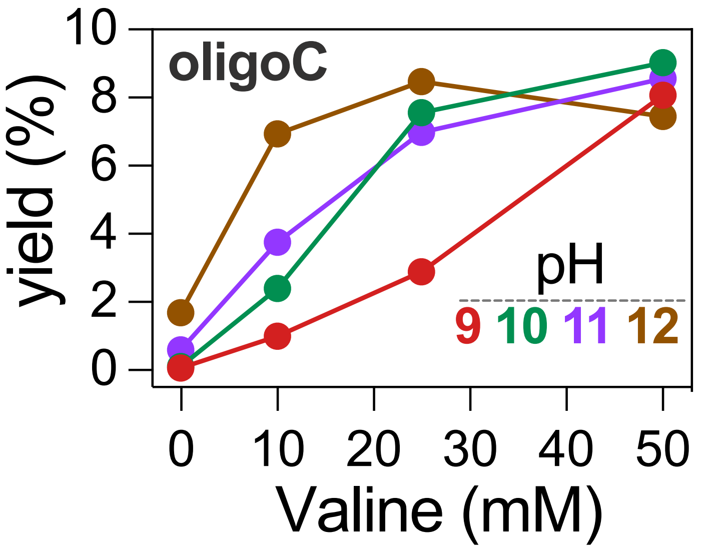
pH dependence of the amino acid-assisted RNA oligomerization

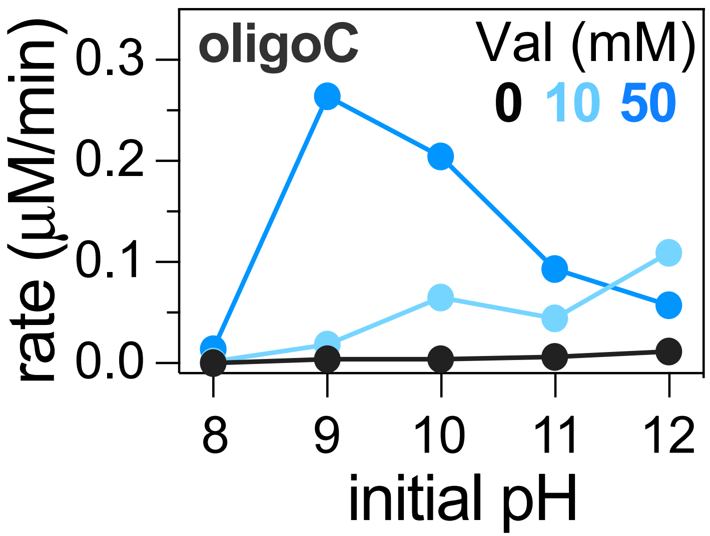


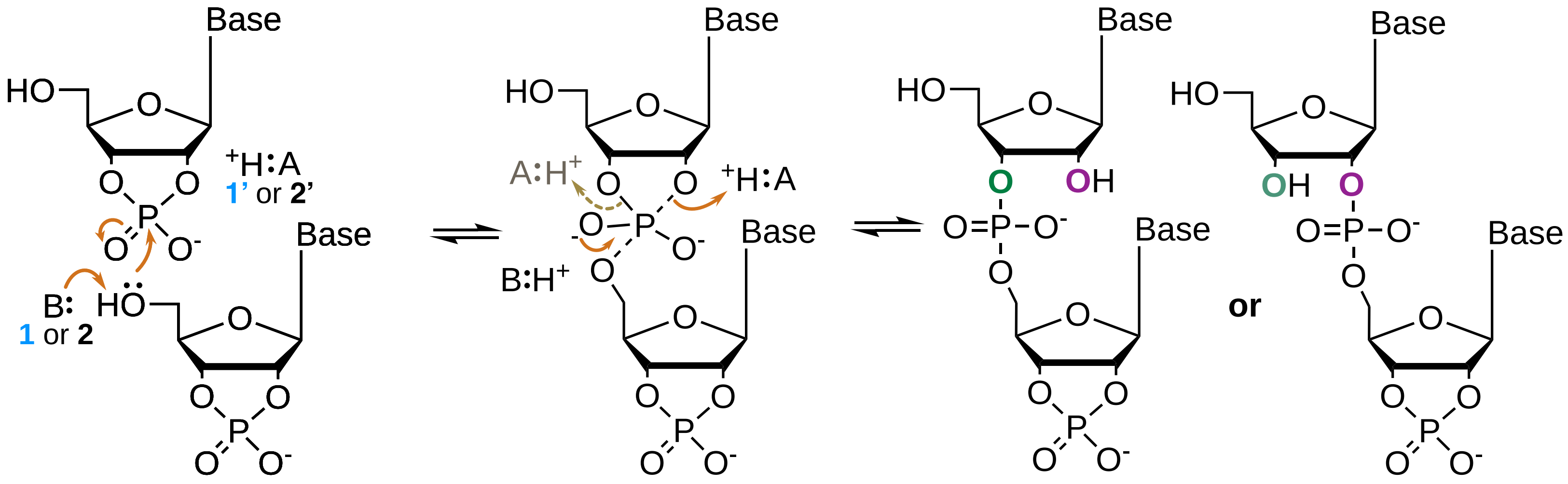
Amino acid concentration dependence of the RNA oligomerization

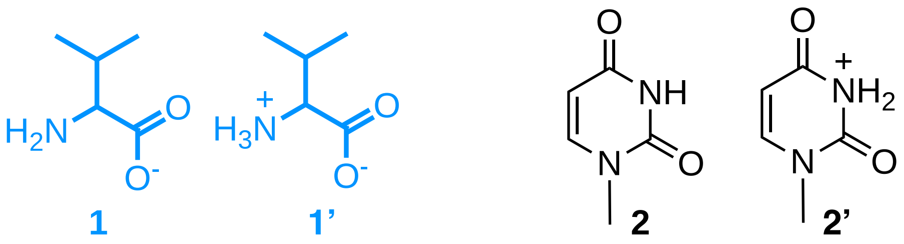


Amino acid concentration dependence of the RNA oligomerization









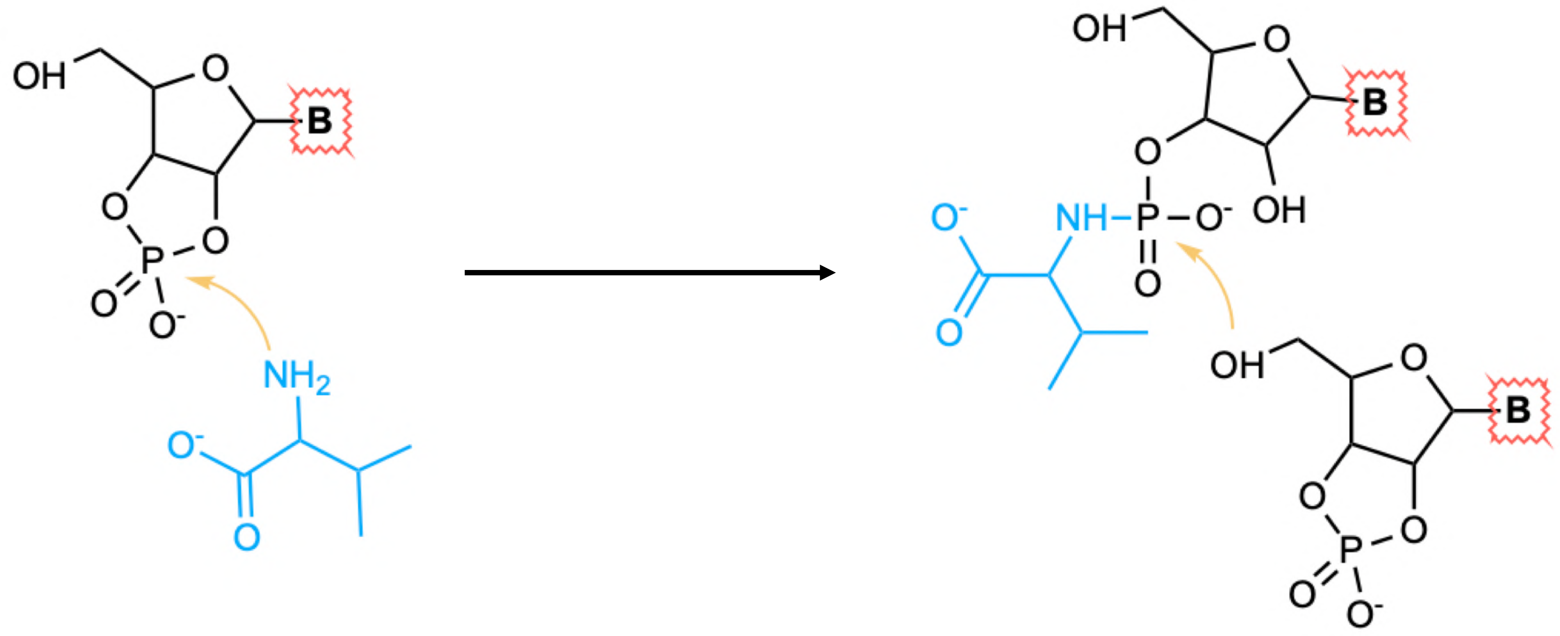
Amino acid: Valine

Nucleobase: Uracil

General base catalysis!

by the amino acids

Another possible mechanism?

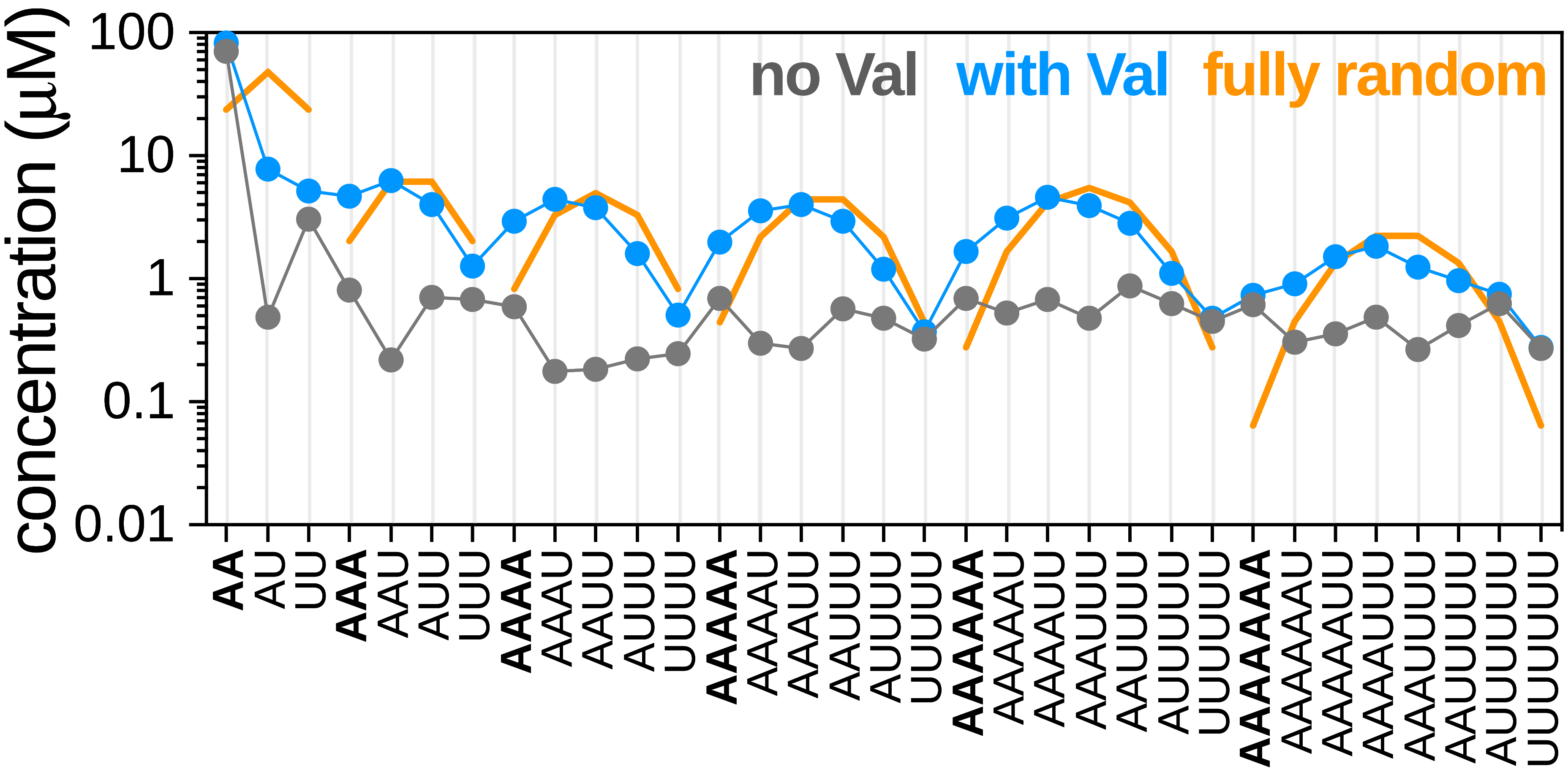


No evidence for this was found

Enhanced compositional diversity of the oligomers

AU oligos

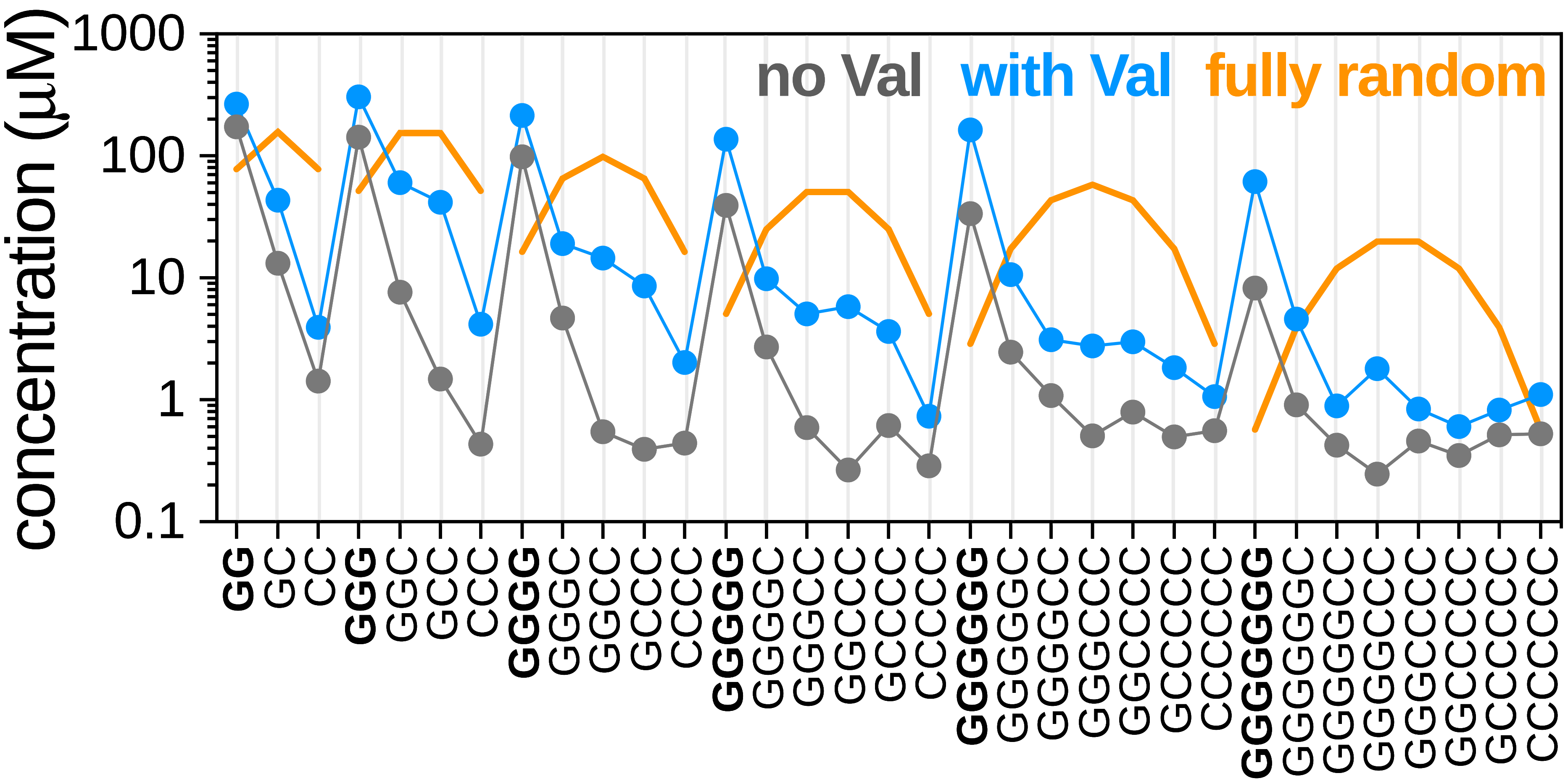
cAMP+cUMP - 40 mM
Valine - 100 mM
pH 10, RT, 20 h



Enhanced compositional diversity of the oligomers

GC oligos

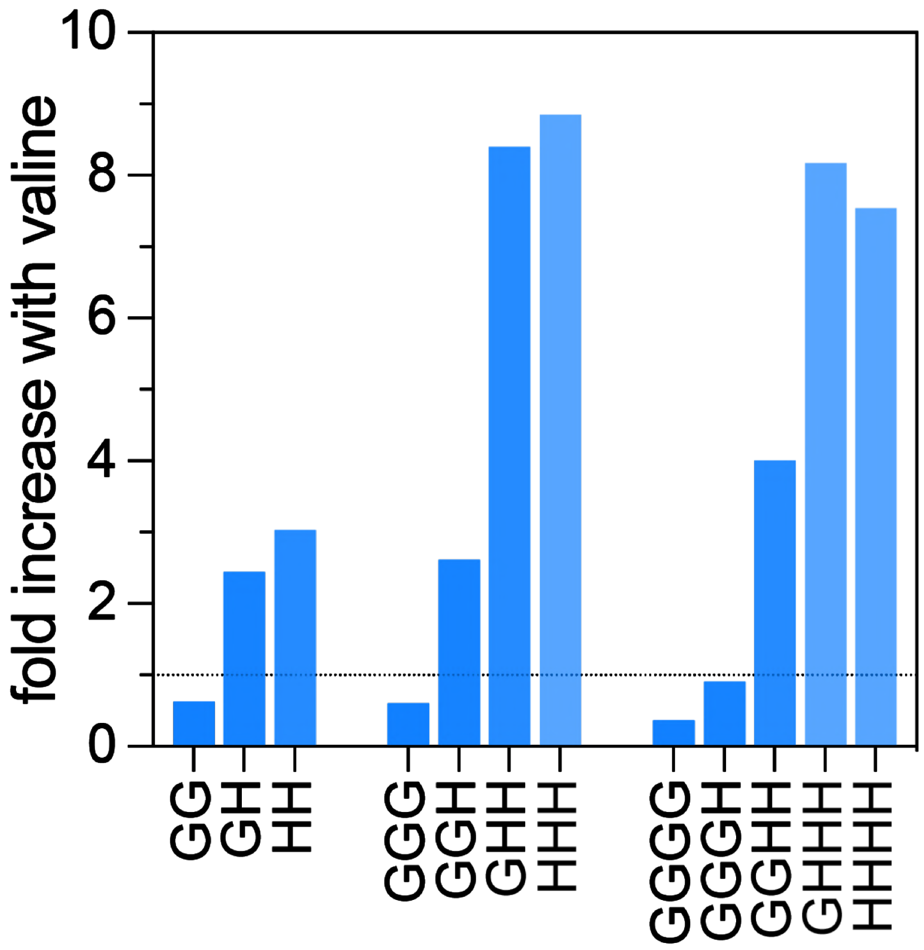
c**G**MP+c**C**MP - 40 mM
Valine - 100 mM
pH 10, RT, 20 h



Enhanced compositional diversity of the oligomers

GCAU oligos

G+C+A+U - 40 mM
Valine - 100 mM
pH 10, RT, 20 h



Enhanced compositional diversity of the oligomers

GCAU oligos

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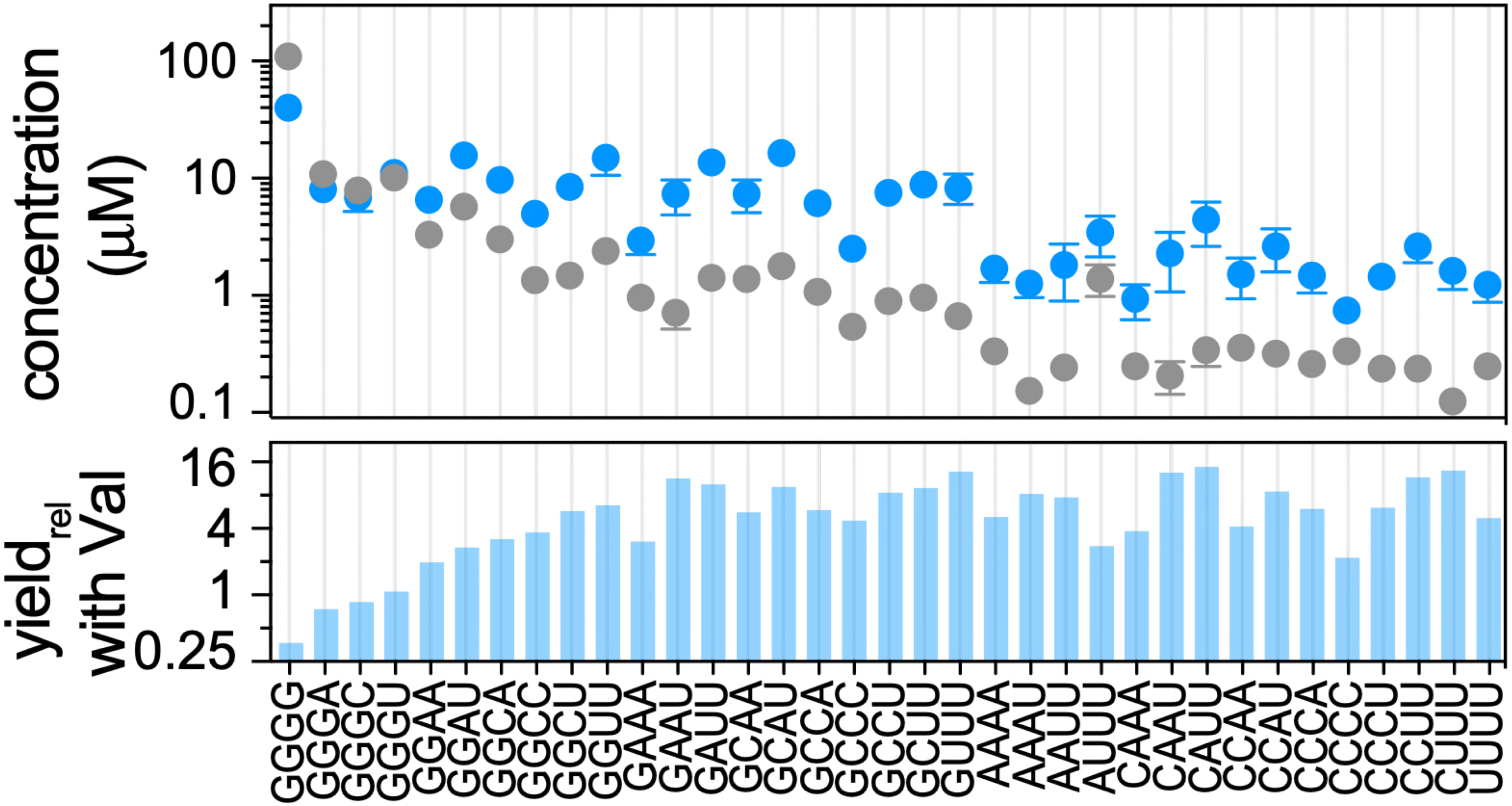
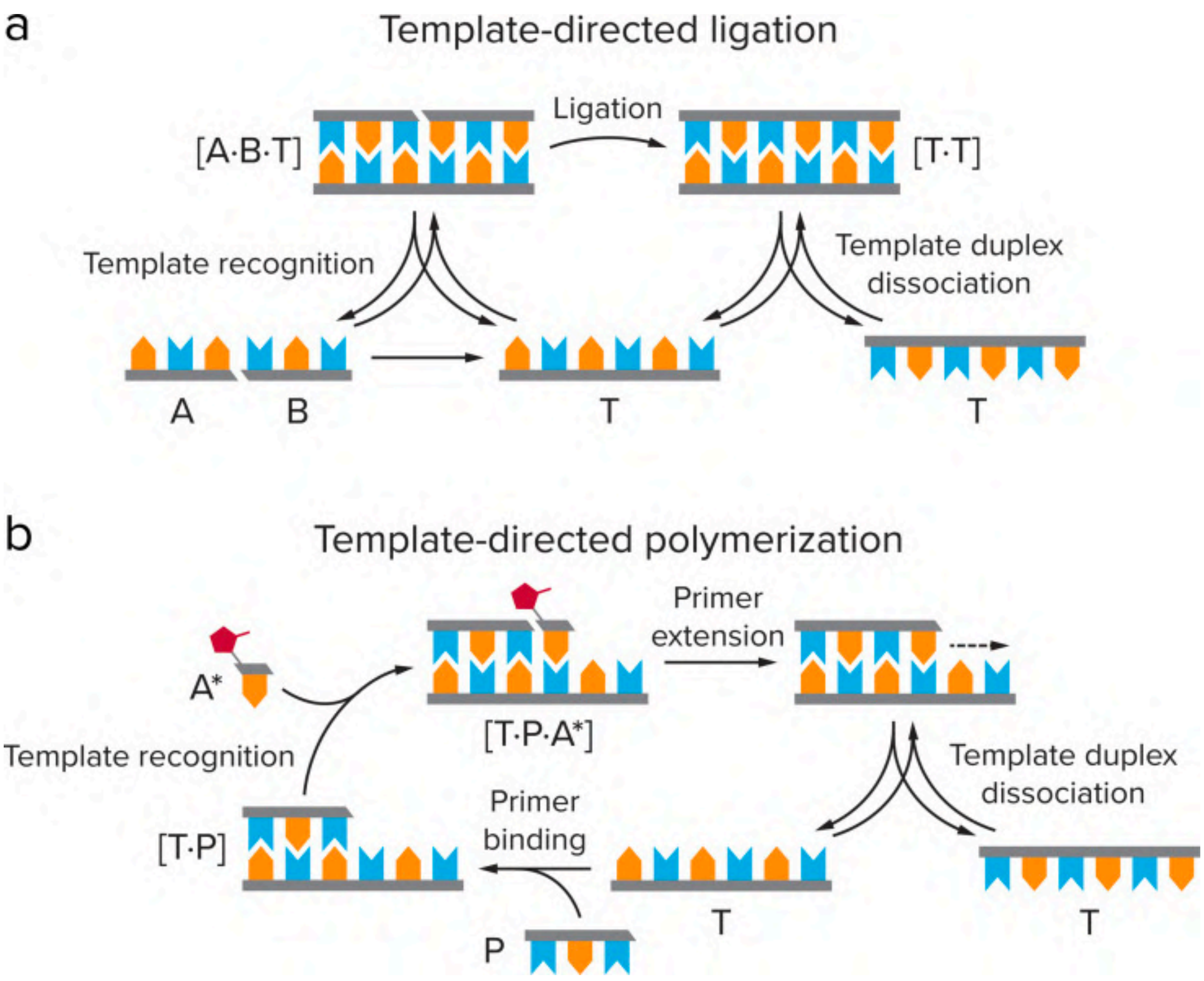
Valine - 100 mM
pH 10, RT, 20 h

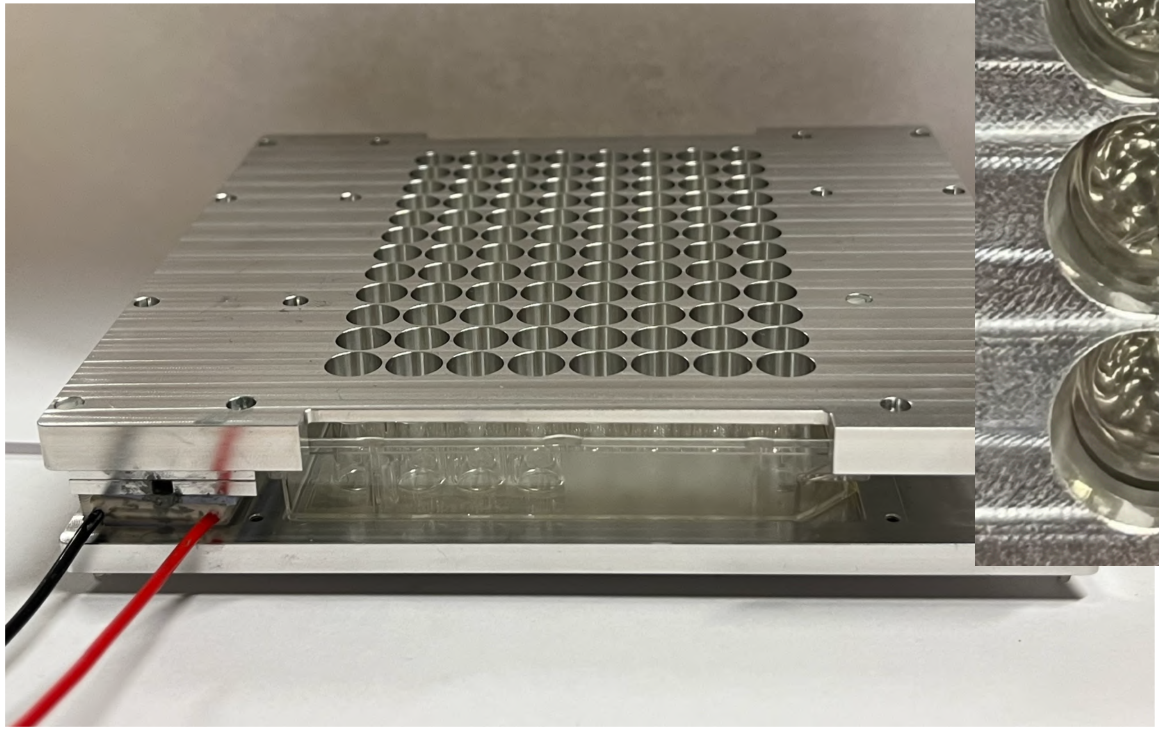
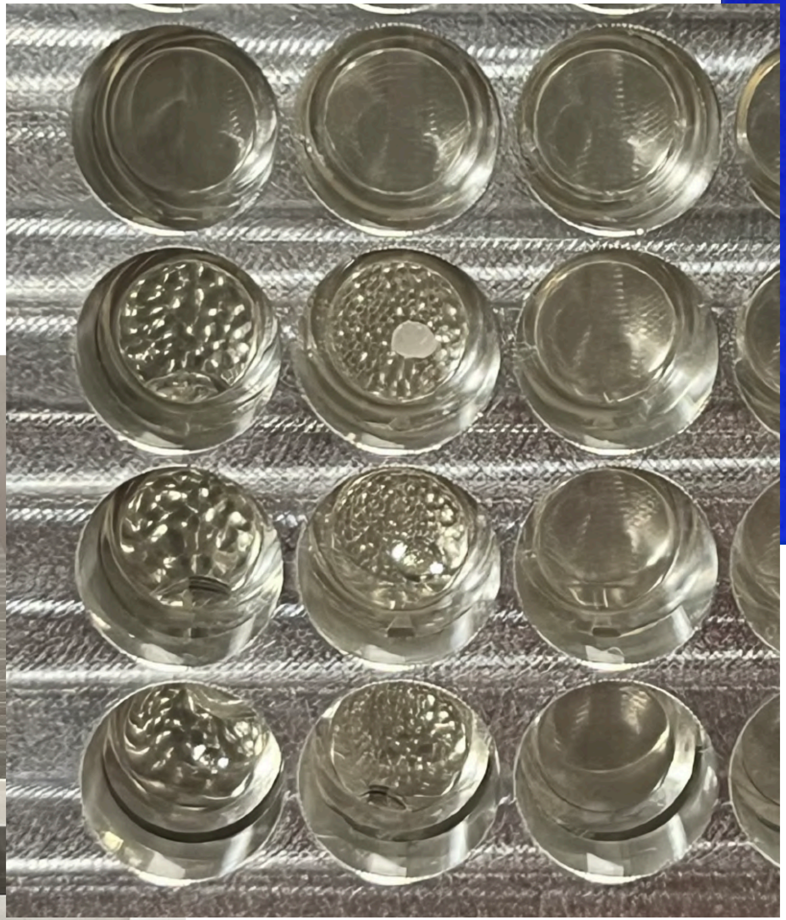
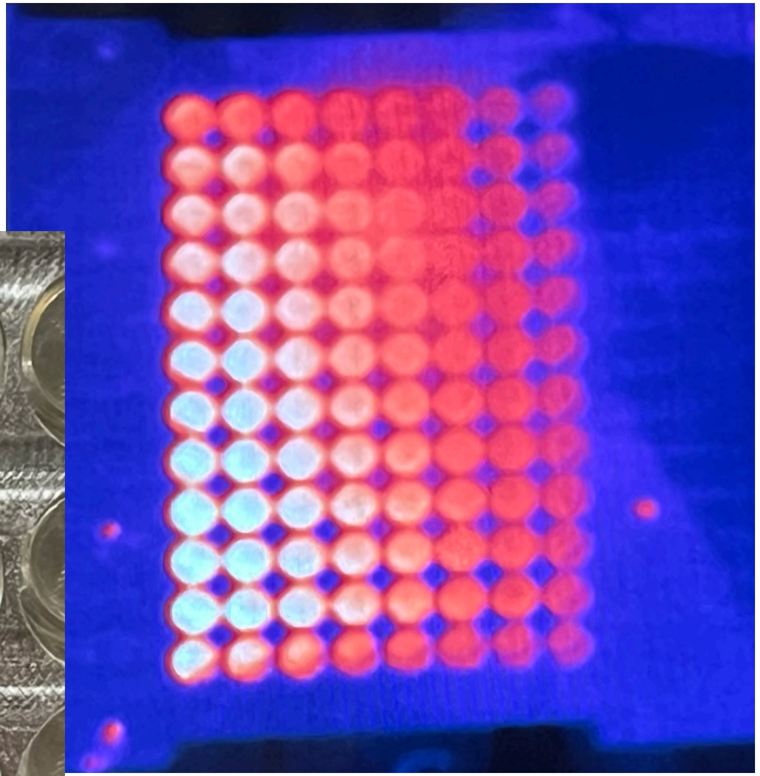


Dry-wet cycles



Spruijt et al., 2022

Dry-wet cycles

Acknowledgement

- Prof. Dieter Braun
- The Braun lab members