The Origins of Life on the Earth

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the timeline of life

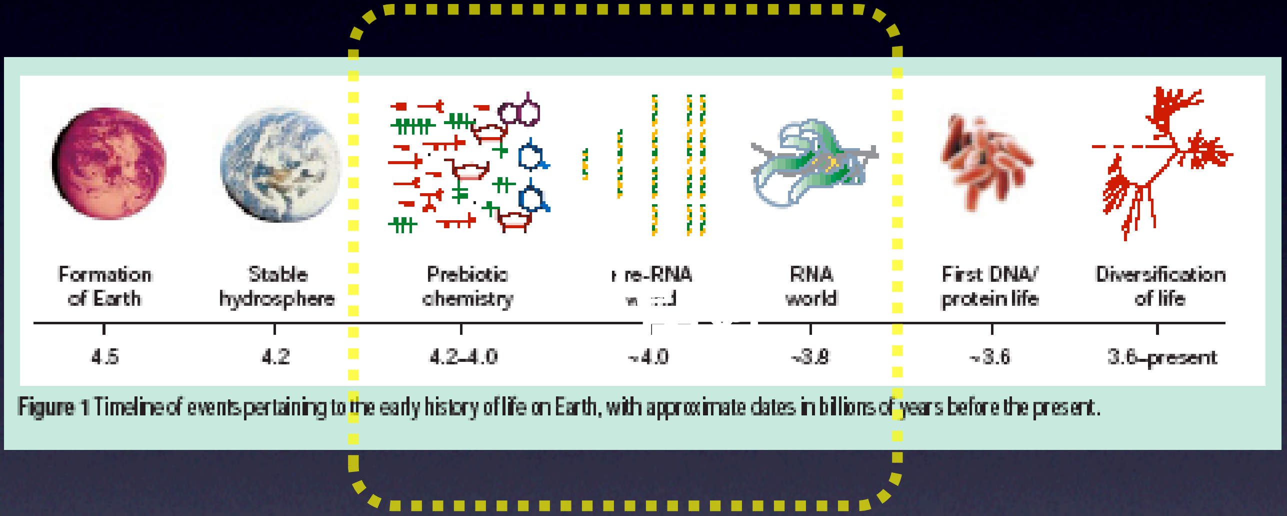


Figure 1 Timeline of events pertaining to the early history of life on Earth, with approximate dates in billions of years before the present.

Joyce (2002) *Nature* **418**, 214-221

LIFE = "a self-sustaining chemical system capable of darwinian evolution" (Joyce/NASA)

life


Capsule
Ribosomes
DNA
Cytoplasm
Cell wall
Plasma membrane
Pili
Flagellum

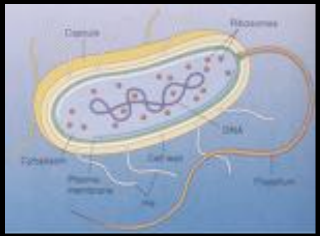
non-life

the non-life-to-life transition
at 4.0 +/– 0.1 billion years ago

a "dead" bag of chemicals

???

an "alive" bag of chemicals



Lehman: "*the origins of life is a chemical problem in a biological context*"

the seven challenges to a prebiotic chemist

1. The origin/source of the elements
2. The origin/source of small molecule precursors
3. The origin/source of monomers
4. The condensation problem
5. The self-replication problem
6. The chirality problem
7. The compartmentalization problem

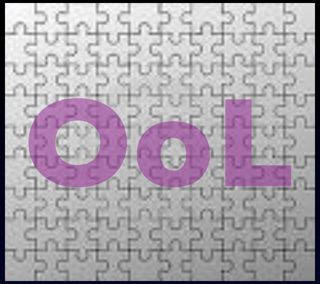
the stuff of life

- proteins (amino acids)
- lipids (alcohols & fatty acids)
- carbohydrates (sugars)
- nucleic acids (nucleotides)
- small molecules (water, metals, ions, *etc.*)

all are polymers formed by condensation reactions

...IN THE "PRIMORDIAL SOUP"?

piecing together the jigsaw puzzle through experimentation



- Stanley Miller (1953) – *made proteins from inert gasses*
- Juan Oró (1961) – *made adenine from hydrogen cyanide*
- Jerry Joyce (1991) – *evolved RNA molecules in a test tube*
- Jim Ferris (1996) – *used clay to make RNA*
- Dave Bartel (2001) – *evolved an RNA replicase*
- Jack Szostak (2003) – *made artificial cells*

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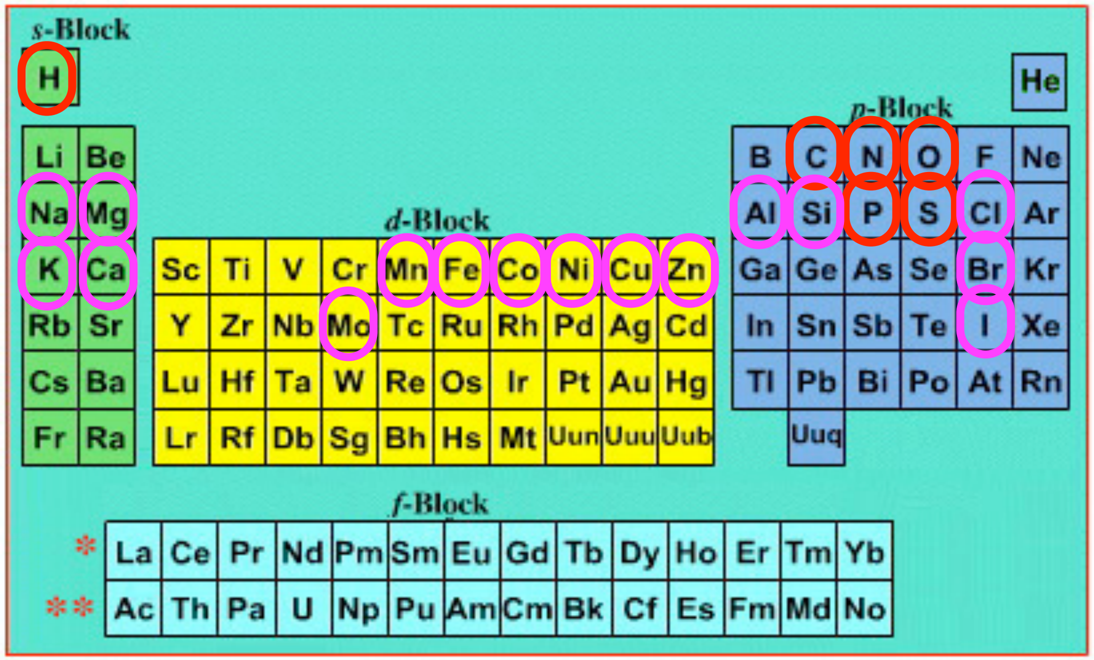
the elements of life



H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Lr	Rf	Db	Sg	Bh	Hs	Mt	Uun	Uuu	Uub		Uuq				

*	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb
**	Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No

sum = about 22 elements

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small molecule precursors

Found in space:

- hydrogen cyanide (HCN)
- acetlyene ($HC \equiv CH$)
- formic acid ($HCOOH$)
- formaldehyde (H_2CO)
- acetic acid (CH_3COOH)
- ammonia (NH_3)
- water

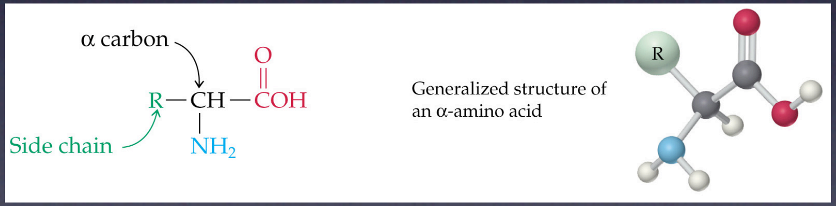
Found in comets & meteorites:

- amino acids
- lipids
- PAHs
- water

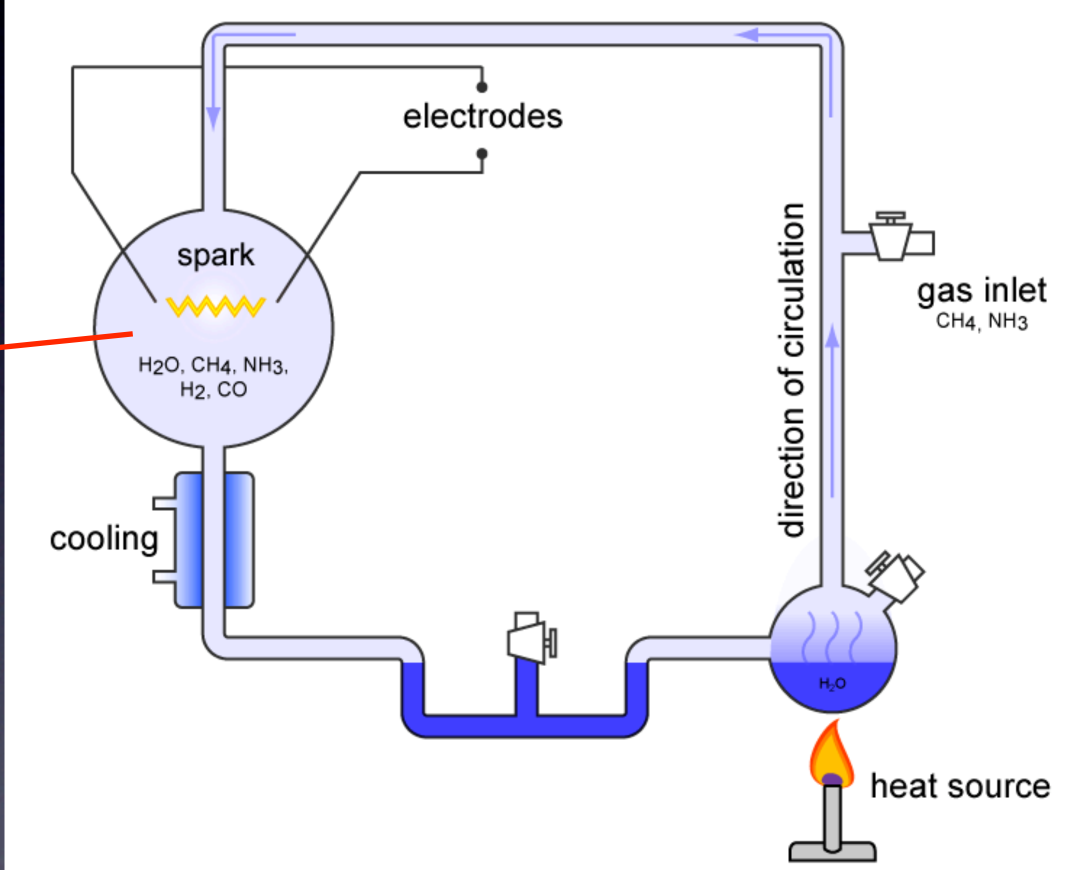
abundant on early Earth: hydrogen sulfide, CO, water, methane, salts, *etc.*

the source of monomers - amino acids

glycine, alanine, aspartic acid, etc.



Generalized structure of an α-amino acid



the Miller-Urey spark-discharge experiments (1953-)

the source of monomers - amino acids

$$H_2 + NH_3 + CH_4 + H_2O \xrightarrow{\textbf{energy}} H_2N - CH_2 - COOH$$

a “dead” bag of chemicals → glycine, an amino acid

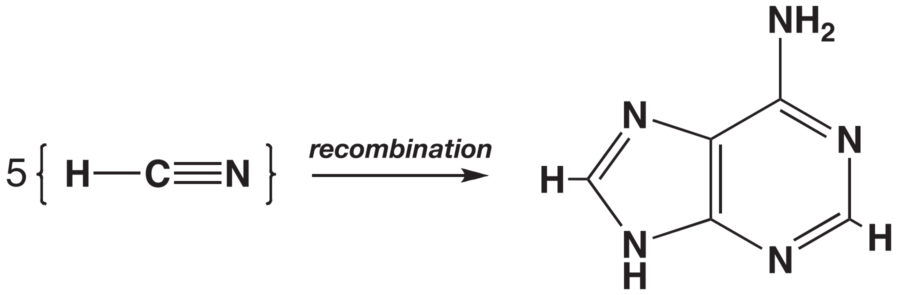
The Miller-Urey spark-discharge experiments (1953-)

Miller's experiment generated instant media attention

"Milk, meat, albumen, bacteria, viruses, lungs, hearts – all are proteins. Wherever there is life there is protein" stated the New York Times in its May 15, 1953 issue. "Protein is of fairly recent origin, considering the hot state of the earth in the beginning. How the proteins and therefore life originated has puzzled biologists and chemists for generations. Accepting the speculations of the Russian scientist A. I. Oparin of the Soviet Academy of Science, Prof. Harold C. Urey assumes that in its early days the earth had an atmosphere of methane (marsh gas), ammonia and water. Oparin suggested highly complex but plausible mechanisms for the synthesis of protein and hence of life from such compounds. In a communication which he publishes in Science, one of Professor Urey's students, Stanley L. Miller, describes how he tested this hypothesis", continued the New York Times, "A laboratory earth was created. It did not in the least resemble the pristine earth of two or three billion years ago; for it was made of glass. Water boiled in a flask so that the steam mixed with Oparin's gases. This atmosphere was electrified by what engineers call a corona discharge. Miller hoped that in this way he would cause the gases in his artificial atmosphere to form compounds that might be precursors of amino acids, these amino acids being the bricks out of which multifarious kinds of protein are built. **He actually synthesized some amino acids and thus made chemical history by taking the first step that may lead a century or so hence to the creationof something chemically like beefsteak or white of egg.** Miller is elated, and so is Professor Urey, his mentor."

the source of monomers - nucleobases

hydrogen cyanide (HCN)



15 atoms &
50 electrons:
5 C-H bonds
5 C-N bonds

present in
interstellar medium

15 atoms &
50 electrons:
2 C-H bonds
9 C-N bonds
3 N-H bonds
1 C-C bond

present in
living systems

adenine

the Oró HCN polymerization experiments (1961-)

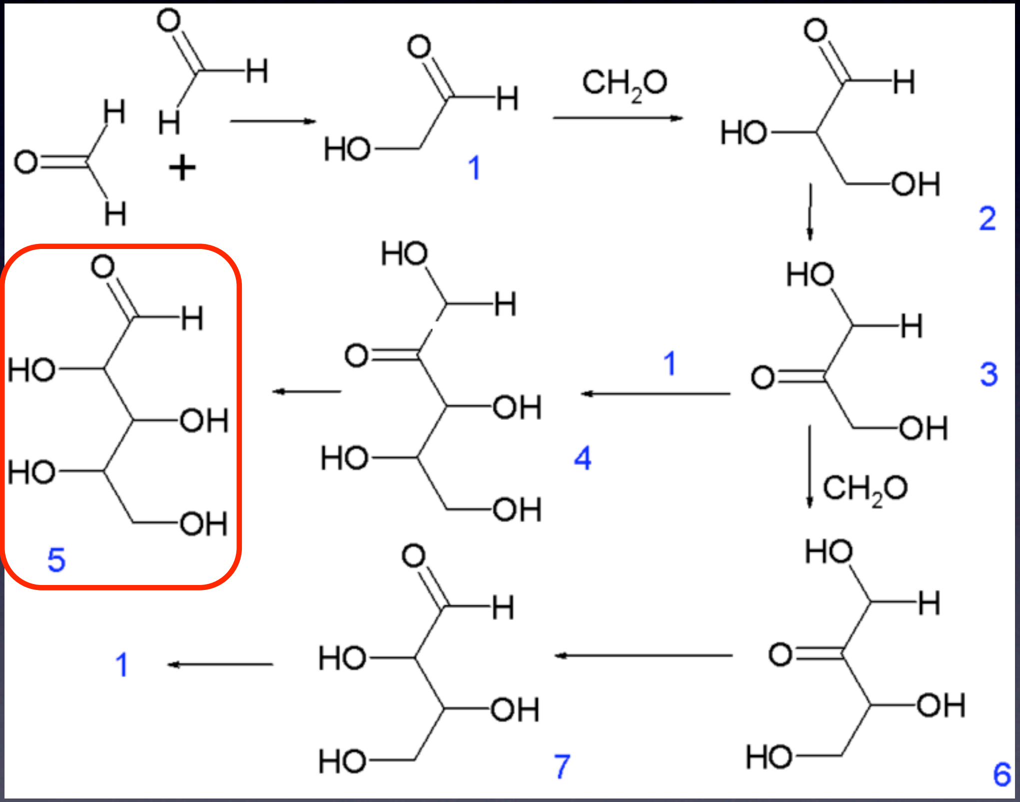
the source of monomers - ribose sugars

glycoaldehyde

formaldehyde

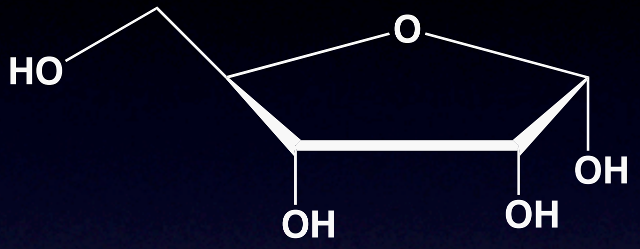
DL-glyceraldehyde

ribose



the "formose reaction" (autocatalytic)

the source of monomers - ribose sugars



The formose reaction can make ribose, but the yield is poor (<<1%) and MANY other products arise

Possible solutions:

- boron complexation (Benner)
- membranes can be selectively permable (Szostak)
- phosphorylating the glycoaldehyde (Eschenmoser)
- alternative backbones: PNA, TNA, *etc.*

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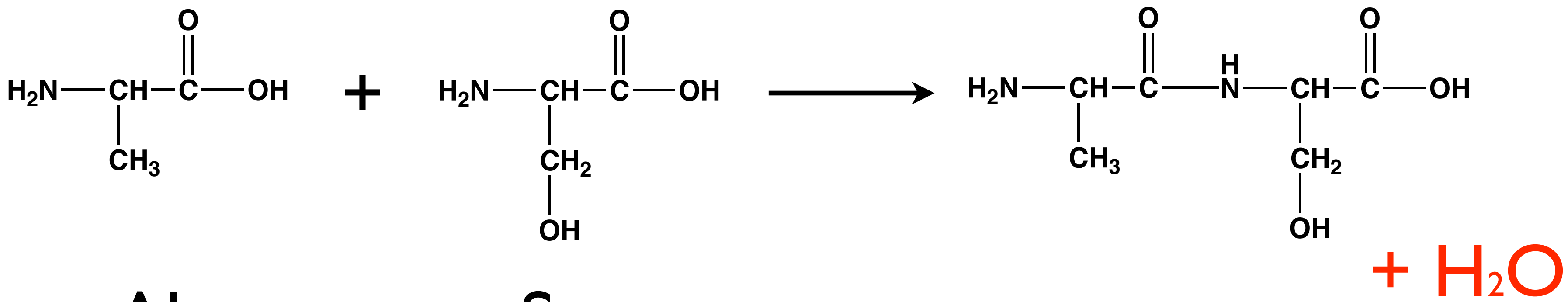
condensation

- polymerizing monomers with the liberation of water ... in water!

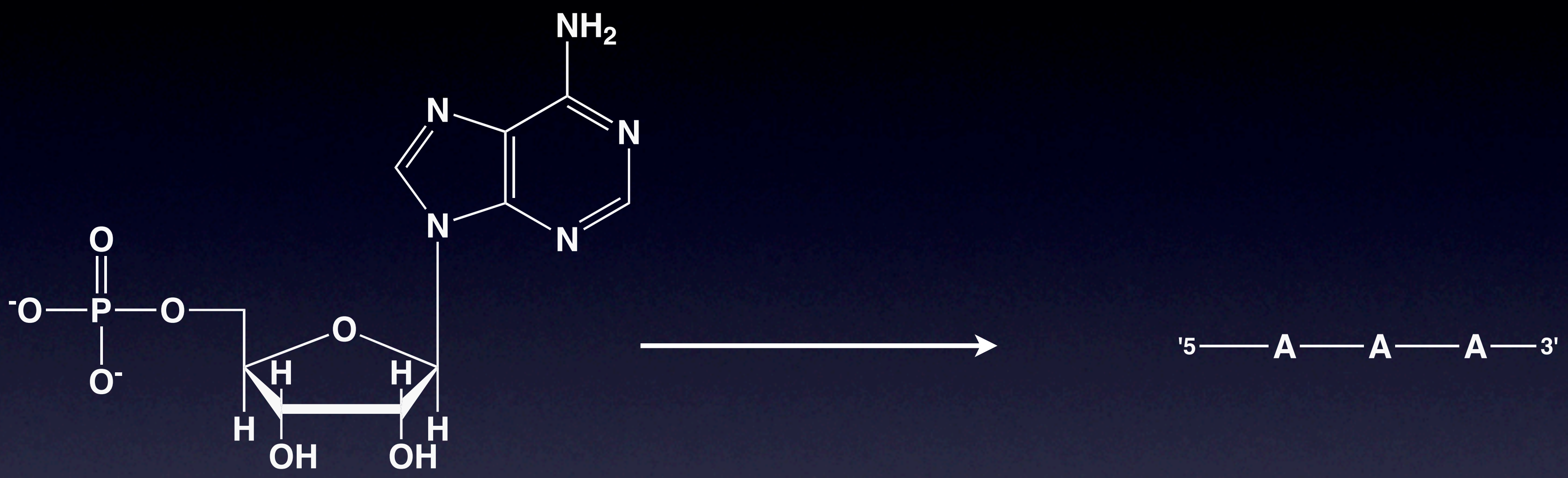


$$H_2N-\underset{\underset{CH_3}{|}}{CH}-\overset{\overset{O}{\|}}{C}-OH + H_2N-\underset{\underset{\underset{OH}{|}}{\underset{CH_2}{|}}}{CH}-\overset{\overset{O}{\|}}{C}-OH \longrightarrow H_2N-\underset{\underset{CH_3}{|}}{CH}-\overset{\overset{O}{\|}}{C}-\overset{H}{N}-\underset{\underset{\underset{OH}{|}}{\underset{CH_2}{|}}}{CH}-\overset{\overset{O}{\|}}{C}-OH + H_2O$$

Ala

Ser

the source of polymers



adenosine phosphate

poly-A (RNA)

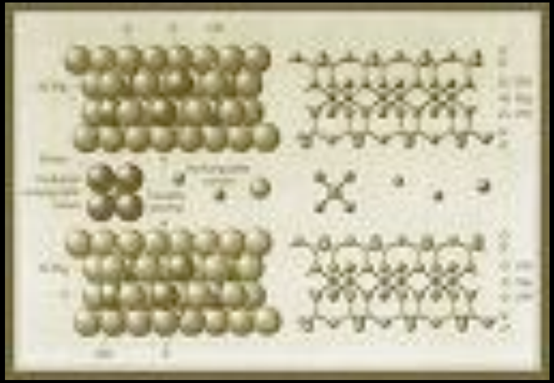
- <u>activation</u> may be needed: triphosphate, imidizole, *etc.*
- templating can help
- dehydration / rehydration cycles can help

clays to the rescue?

- some aluminosilicate sheets have postive charges AND a correct spacing to fit activated nucleotides into pockets
- daily “feeding” of montmorillonite clay & a primer with activated nucleotides leads to polymerization without a template!

Ferris, Hill, Liu, & Orgel (1996) *Nature* **381**, 59-61.

Clays: layers of ions
example: Montmorillonite



Jim Ferris: daily “feeding” of nucleotides to clay results in RNA chains!

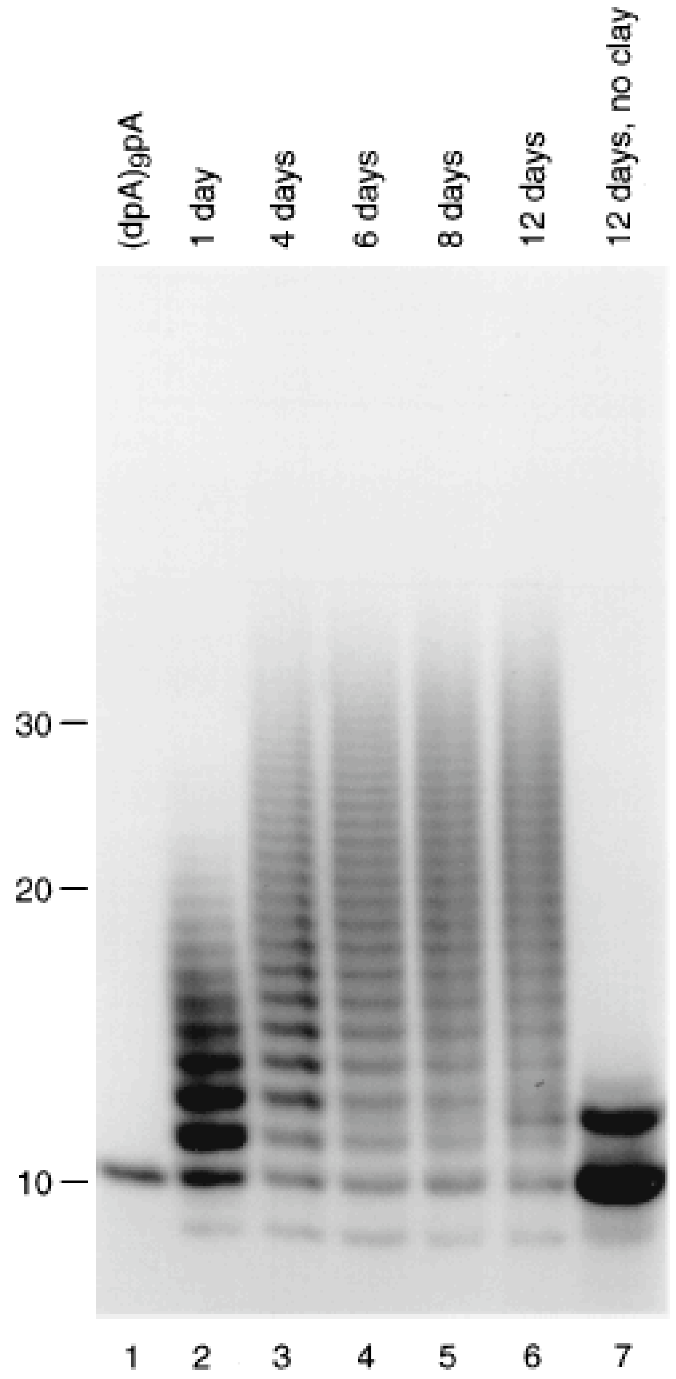
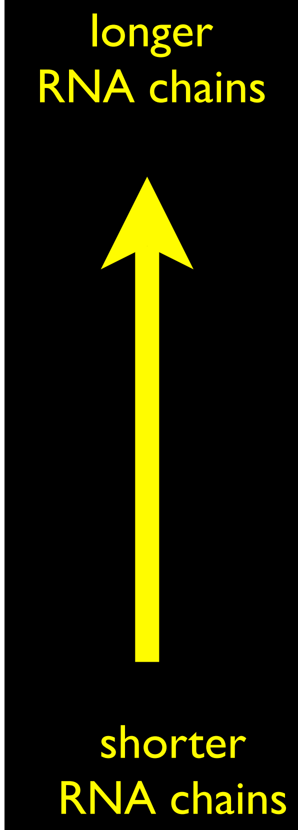


Figure 2. Gel electrophoresis of the elongation of ^{32}pdA(pdA)$_8$pA with ImpA in microcentrifuge tubes. Lane 1, ^{32}pdA(pdA)$_8$pA; lanes 2–6 elongation in the presence of montmorillonite; lane 7, elongation in the absence of montmorillonite.


longer
RNA chains

shorter
RNA chains

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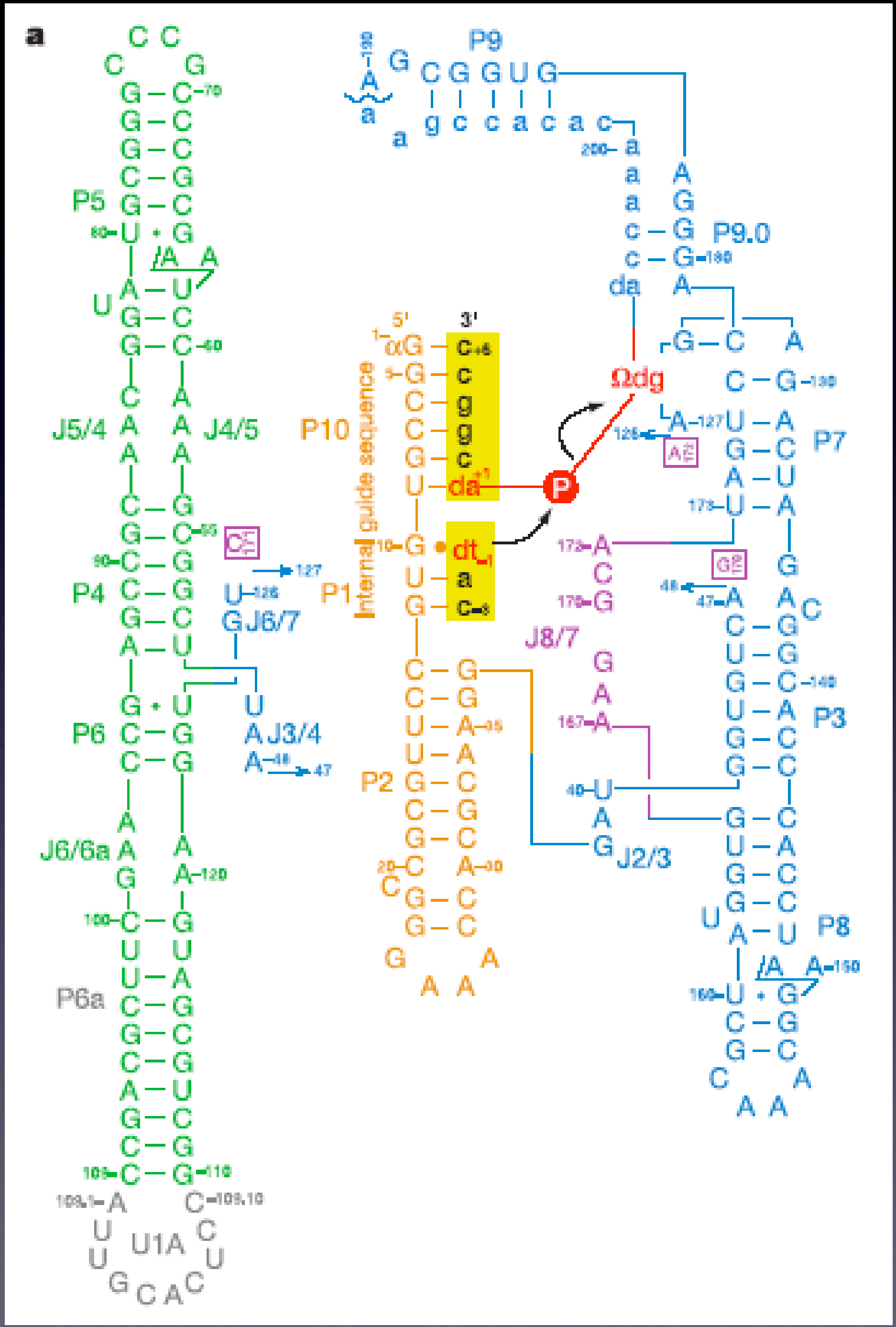
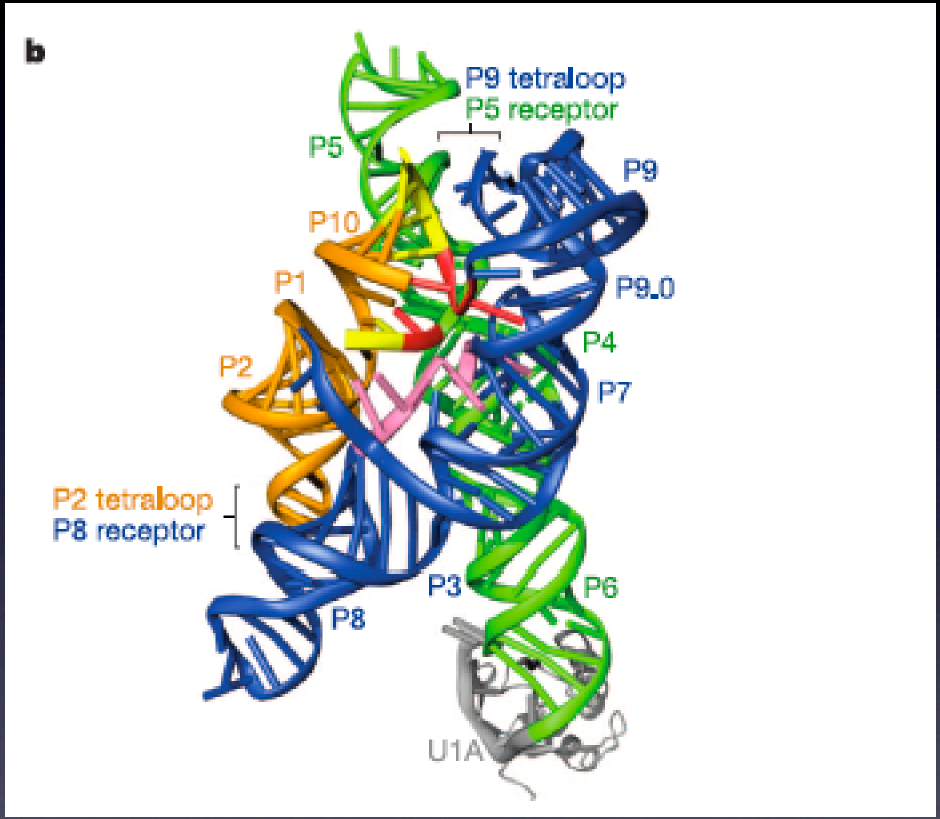
an RNA world?

- a proposed period of time when RNA (or something like RNA) was responsible for all metabolic and information-transmission processes
- RNA has both a genotype AND a phenotype (Cech, Altman: catalytic RNA ... Nobel Prize, 1989) ... unlike DNA or protein
- Catalytic RNA = ribozymes (9 classes)
- The ribosome is a ribozyme (2000)

RNA structure





Azoarcus ribozyme (205 nt)

Adams *et al.* (2004) *Nature* **430**, 45-50.

the catalytic repertoire of RNA

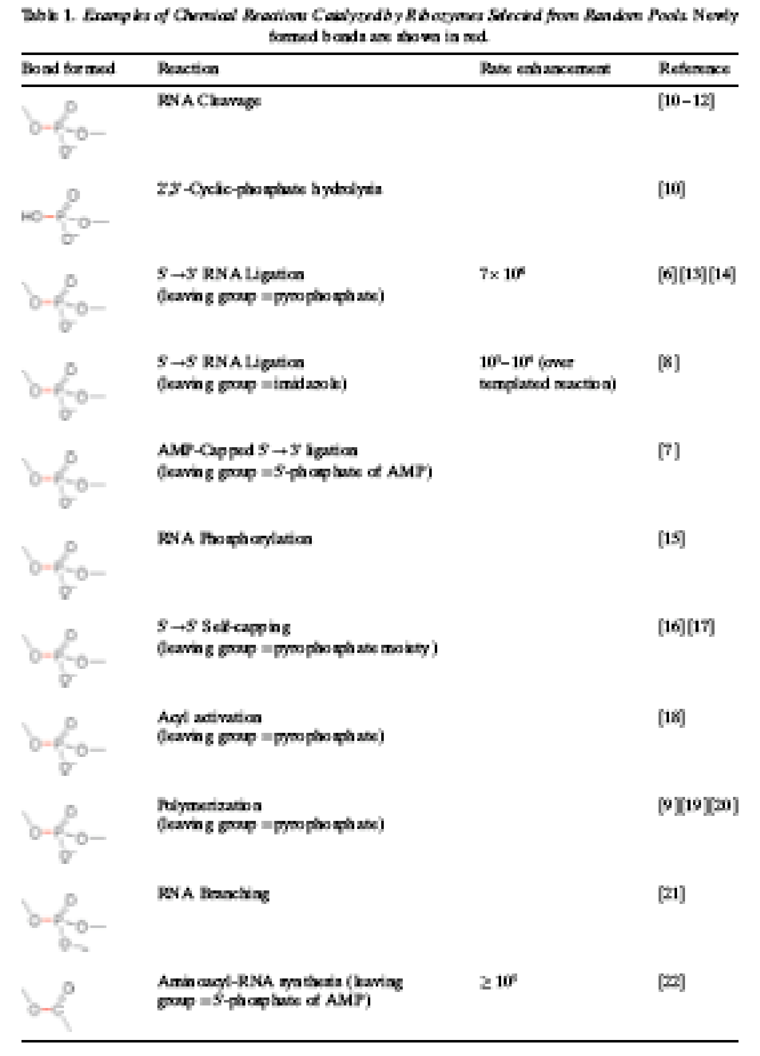


Table 1. *Examples of Chemical Reactions Catalyzed by Ribozymes Selected from Random Pools. Newly formed bonds are shown in red.*

Bond formed	Reaction	Rate enhancement	Reference
	RNA Cleavage		[10–12]
	2',3'-Cyclic-phosphate hydrolysis		[10]
	5'→3' RNA Ligation (leaving group = pyrophosphate)	7× 10^6	[6][13][14]
	5'→5' RNA Ligation (leaving group = imidazole)	10^3–10^4 (over templated reaction)	[8]
	AMP-Capped 5'→3' ligation (leaving group = 5'-phosphate of AMP)		[7]
	RNA Phosphorylation		[15]
	5'→5' Self-capping (leaving group = pyrophosphate moiety)		[16][17]
	Acyl activation (leaving group = pyrophosphate)		[18]
	Polymerization (leaving group = pyrophosphate)		[9][19][20]
	RNA Branching		[21]
	Aminoacyl-RNA synthesis (leaving group = 5'-phosphate of AMP)	≥ 10^5	[22]

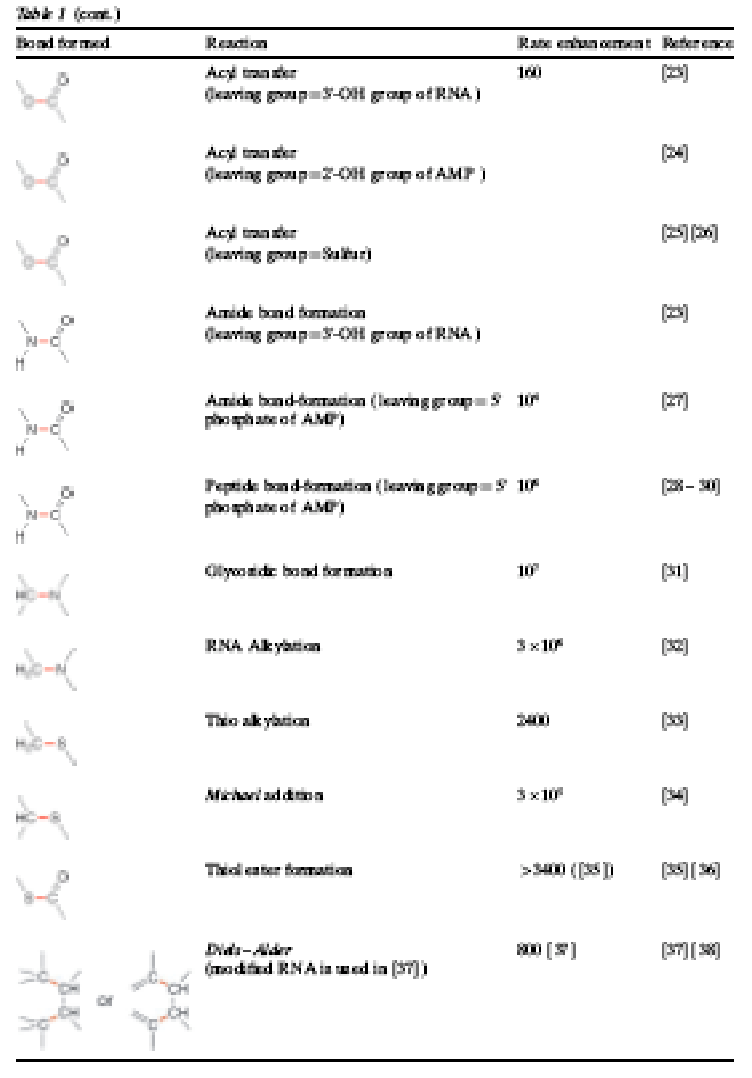


Table 1 (cont.)

Bond formed	Reaction	Rate enhancement	Reference
	Acyl transfer (leaving group = 3'-OH group of RNA)	160	[23]
	Acyl transfer (leaving group = 2'-OH group of AMP)		[24]
	Acyl transfer (leaving group = Sulfur)		[25][26]
	Amide bond formation (leaving group = 3'-OH group of RNA)		[23]
	Amide bond-formation (leaving group = 5' phosphate of AMP)	10^4	[27]
	Peptide bond-formation (leaving group = 5' phosphate of AMP)	10^6	[28–30]
	Glycosidic bond formation	10^7	[31]
	RNA Alkylation	3 × 10^4	[32]
	Thio alkylation	2400	[33]
	Michael addition	3 × 10^5	[34]
	Thiol ester formation	> 3400 ([35])	[35][36]
	Diels–Alder (modified RNA is used in [37])	800 [37]	[37][38]

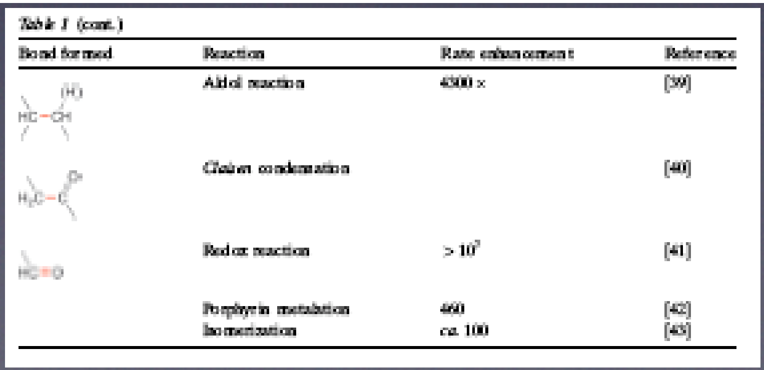
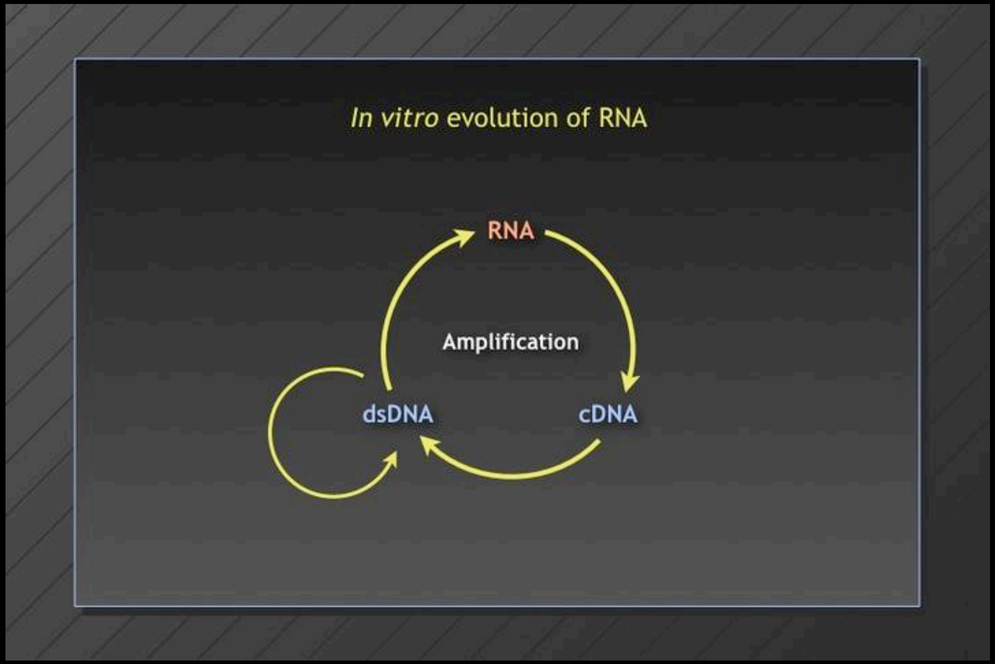


Table 1 (cont.)

Bond formed	Reaction	Rate enhancement	Reference
	Aldol reaction	4300 ×	[39]
	Claisen condensation		[40]
	Redox reaction	> 10^7	[41]
	Porphyrin metalation	460	[42]
	Isomerization	*ca.* 100	[43]

Chen, Li, & Ellington (2007)

RNA can be evolved in a test tube: *in vitro* evolution

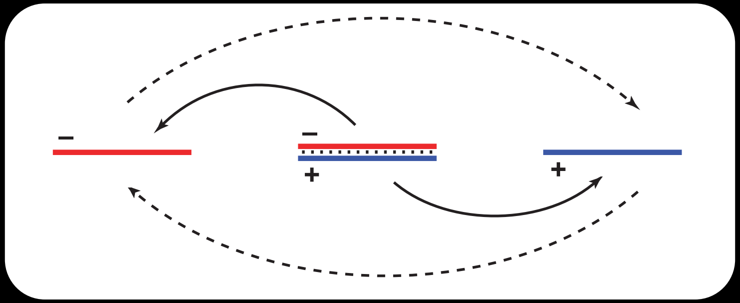


In vitro evolution of RNA

- Jerry Joyce (1991-) has shown how diverse populations of RNA can undergo selection and evolution to generate new sequences and functions
- without cells, RNA can evolve, just like natural populations of organisms

RNA making RNA:

self-replication



- how do you transfer information from one molecule to another?
- balance between fidelity (for information maintenance) and errors (for evolution)

RNA making RNA:

self-replication

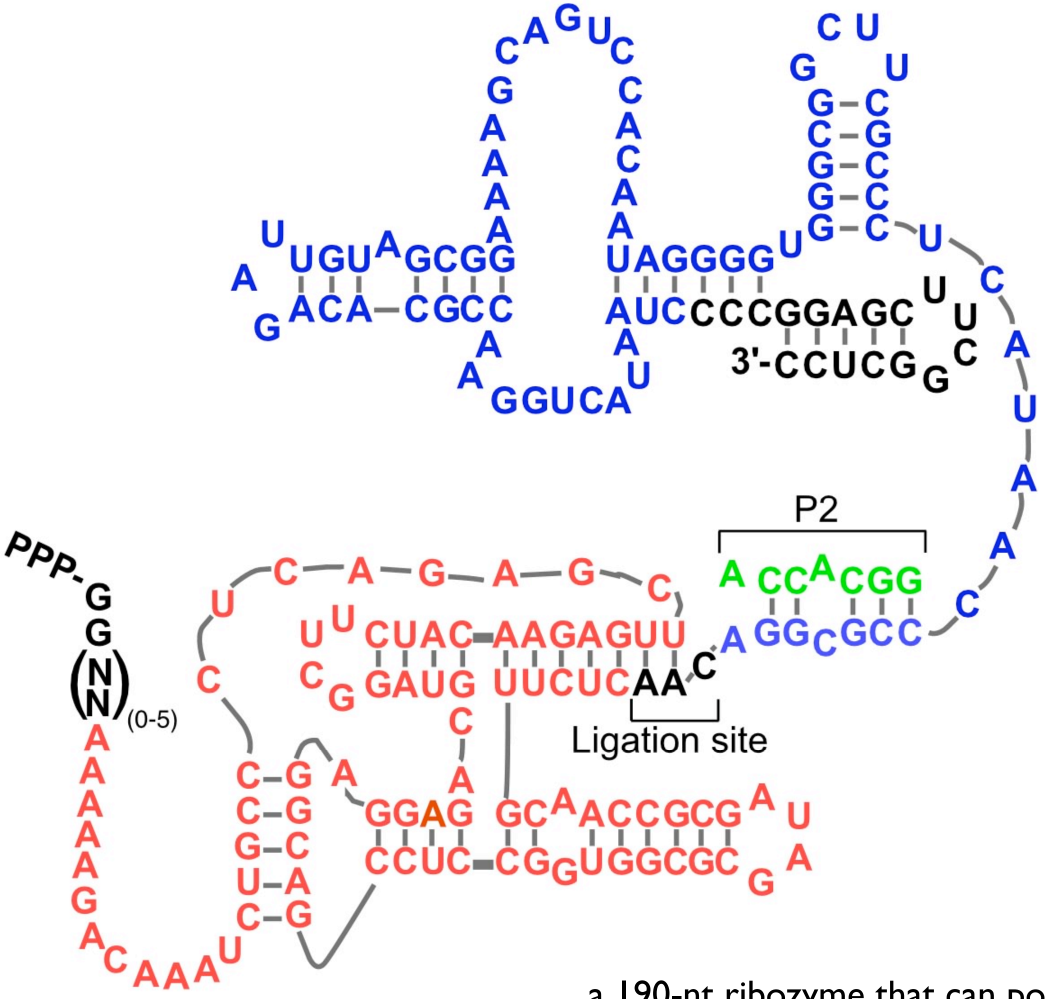
the “holy grail” of prebiotic chemistry:
discovery of an RNA autoreplicase

a significant advance towards this goal:
the Bartel ligase ribozyme

Johnston *et al.* (2001) *Science* **292**, 883-896.
Zaher & Unrau (2007) *RNA* **13**, 1017-1026.

RNA making RNA:

the Bartel/Unrau replicase ribozyme



a 190-nt ribozyme that can polymerize up to 20 nt

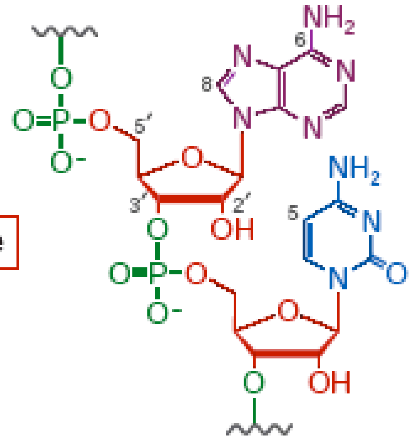
the RNA world

Figure 2 Prebiotic clutter surrounding RNA. Each of the four components of RNA (coloured green, red, purple and blue) would have been accompanied by several closely related analogues (listed in black type), which could have assembled in almost any combination. All possible building blocks for each of the components should be regarded as sorting independently; for example, the phosphodiester linkage may have comprised either a 3′,5′ linkage involving a phosphate or a 2′,5′ linkage involving a pyrophosphate.

3′,5′ Phosphate
2′,5′ Pyrophosphate
2′,2′ Polyphosphate
3′,3′ Alkylphosphate
5′,5′

β D Ribo furanose
α L Lyxo pyranose
Xylo
Arabino

Tetroses
Hexoses
Branched sugars



Adenine, guanine
Diaminopurine
Hypoxanthine
Xanthine
Isoguanine
N6-substituted purines
C8-substituted purines

Cytosine, uracil
Diaminopyrimidine
Dihydrouracil
Orotic acid
C5-substituted pyrimidines

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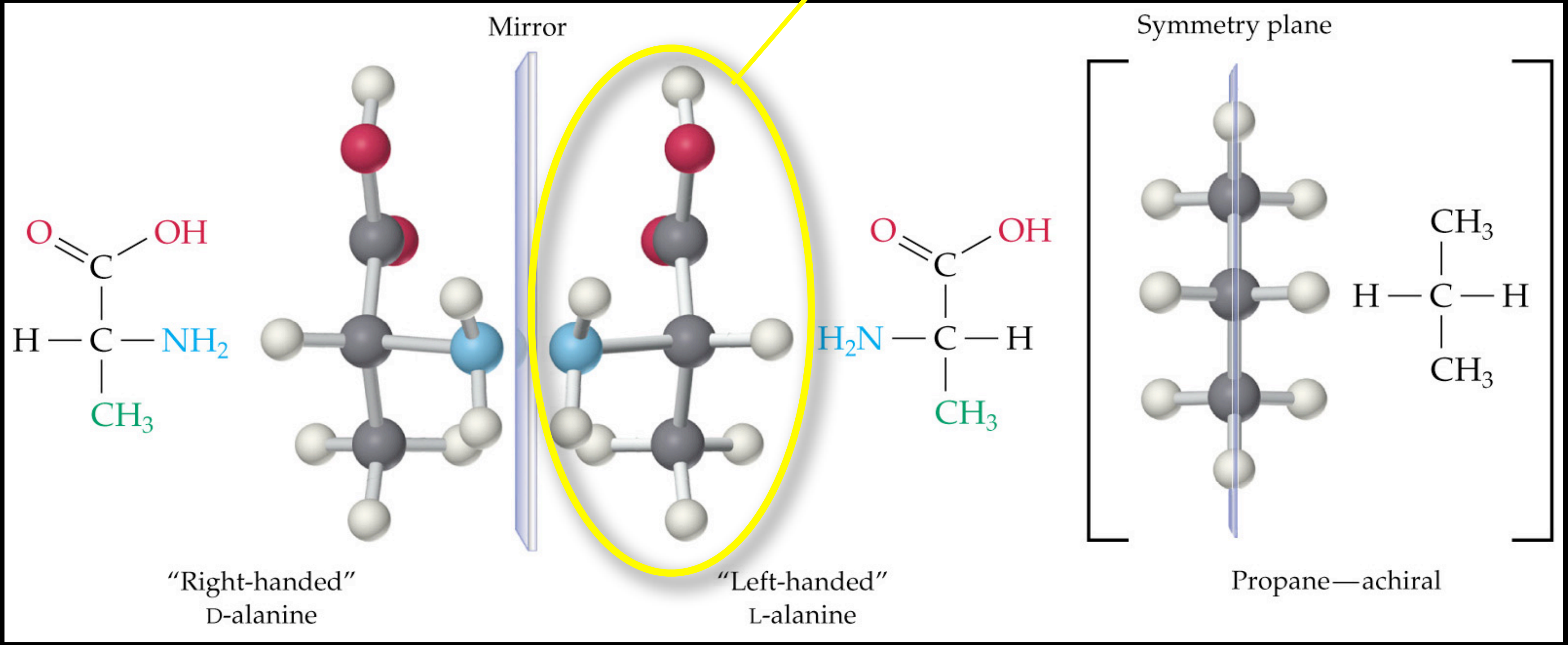
Chirality

chirality

life is chiral; this is a "biosignature"

Earth life:
L-amino acids
and D-nucleotides



abiotic material is achiral or racemic

the origin of chirality

“asymmetry is a hallmark of life”

modern biology:
beta-D-ribonucleotides
&
L-amino acids

it’s not clear how these were selected out of a racemic mixture, but possible solutions include:
assistance from a chiral surface (e.g., quartz),
differential precipitation or solvation,
slightly different energies of the two enantiomers

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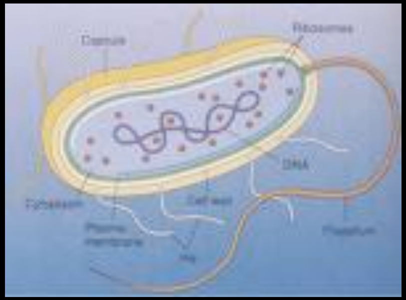
the origin of cells

“linking genotype with phenotype”



compartmentalization would offer life enormous advantages

- keeping water concentrations low
- creating gradients
- allowing genotypes to harvest “the fruits of their labor”

Jack Szostak (Harvard): making artificial cells with life-like properties

Movie

compartmentalization

putting it all together

The Chemical Origins of Life

- the molecular biologists' dream:
“imagine a pool of activated **ß**-D-nucleotides ...”

- the prebiotic chemists' nightmare:
“monomers, polymers, chirality, information, tar ...”

Darwin's
"Warm Little Pond"

"It is often said that all the conditions for the first production of a living organism are now present, which could ever be present. But if (and oh! what a big if) we could conceive in some warm little pond with all sorts of ammonia and phosphoric salts, light, heat, electricity, etc., present, that a protein compound was chemically formed ready to undergo still more complex changes, at the present day, such matter would be instantly devoured or absorbed, which could not have been the case before living creatures were formed."

Darwin, 1871,
unpublished letter