The molecular origins of life

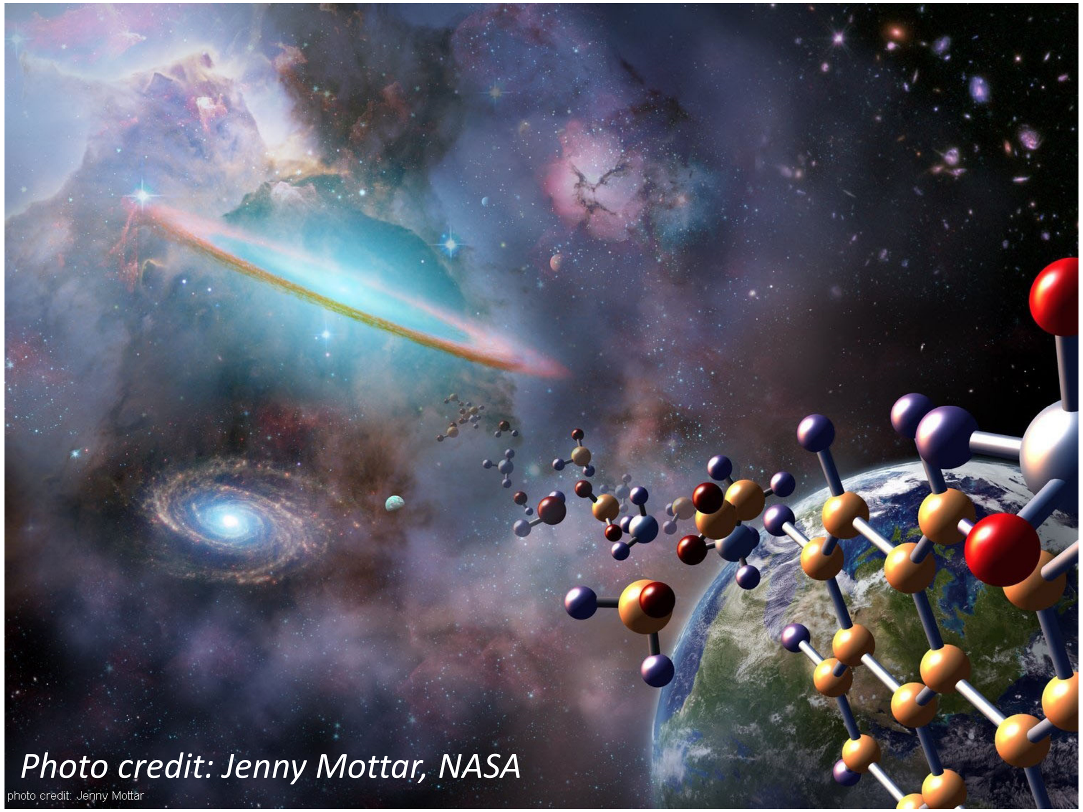


Photo credit: Jenny Mottar, NASA

L1 SoSe 2020

Zbigniew Pianowski

7 lectures (90 min. each) in English, online
Tuesdays 15:45-17:15,
Thursdays (?) 15:45-17:15

1st lecture: 21. April 2020

The most actual dates, handouts – on the website:
http://www.ioc.kit.edu/pianowski/

Mailing list for changes and supplementary information

General references

K. W. Plaxco, M. Gross ***Astrobiology. A brief introduction.*** **2nd Ed.**
(EN, The Jonh Hopkins Univ. Press)
Astrobiologie für Einsteiger (DE, Wiley-VCH)

K. Ruiz-Mirazo, C. Briones, A. Escosura ***Prebiotic Systems Chemistry: New Perspectives for the Origins of Life.***
Chemical Reviews, 2014, 114, pp. 285-366

A. Pross ***What is Life? How Chemistry Becomes Biology.***
(Oxford Univ. Press)

Overview of the course

Origin of the Universe – stars, planets, elements

Origin of biorelevant monomers – primordial soup

Complex chemical processes on the way to living systems

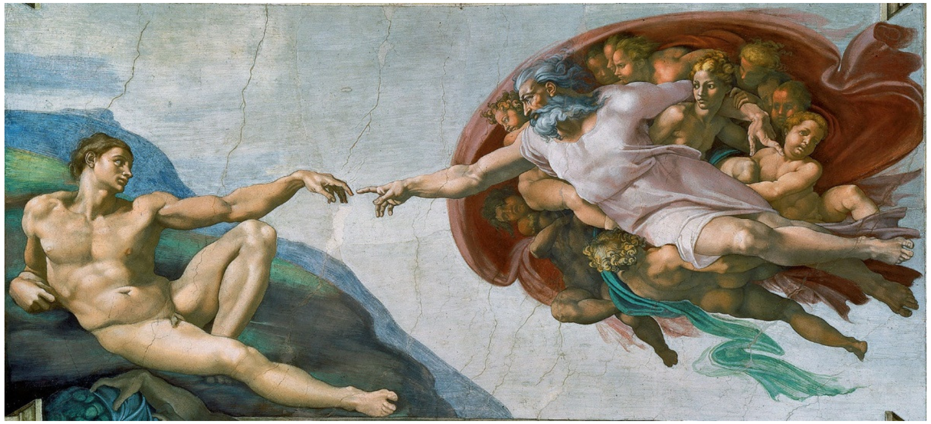
Protocells and LUCA

Overview of the course

Lecture 1	*Introduction to life, The primordial soup – Aminoacids*
Lecture 2	*The primordial soup – Lipids, Sugars*
Lecture 3	*The primordial soup – Nucleobases, cyanosulfidic chemistry*
Lecture 4	*Oligomerization, Systems Chemistry*
Lecture 5	*Self-assembly, RNA world*
Lecture 6	*Metabolism, protocells*
Lecture 7	*LUCA, extremophilic organisms, extraterrestrial life*

People always liked to know...

Where do we come from?



Michelangelo, the Sistine Chapel

Are we alone in the Universe?

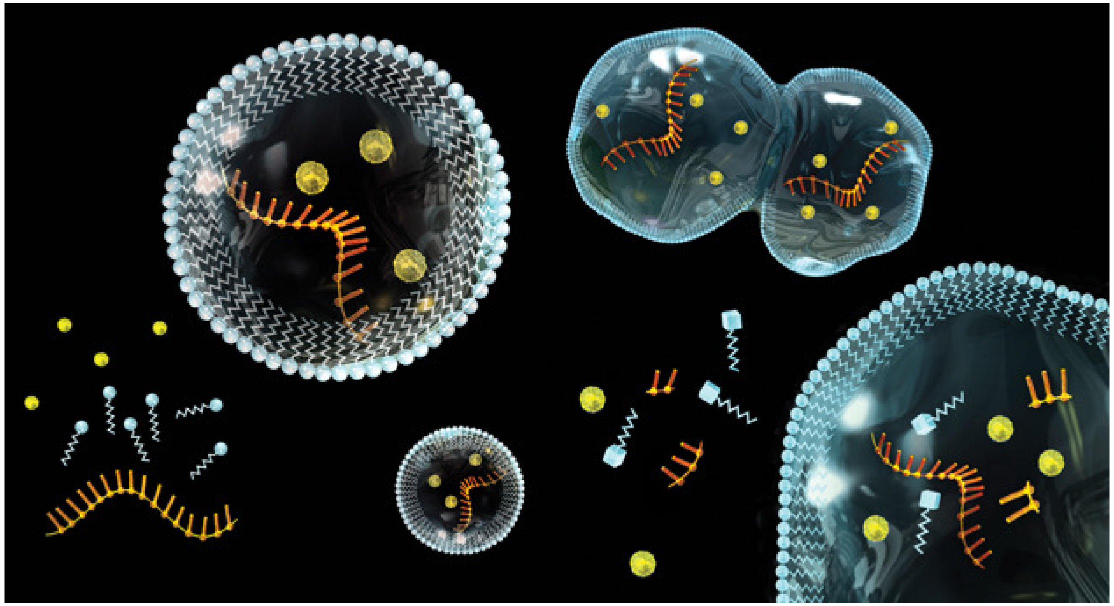
Alien, by Ridley Scott

Can we create life?

Young Frankenstein, by Mel Brooks

Can science give the answers?

Nowadays, molecular sciences and particularly chemistry seem to be in the position to adress these questions



© Henning Dalhoff/Science Photo Library

How science can contribute?

What science can’t do:

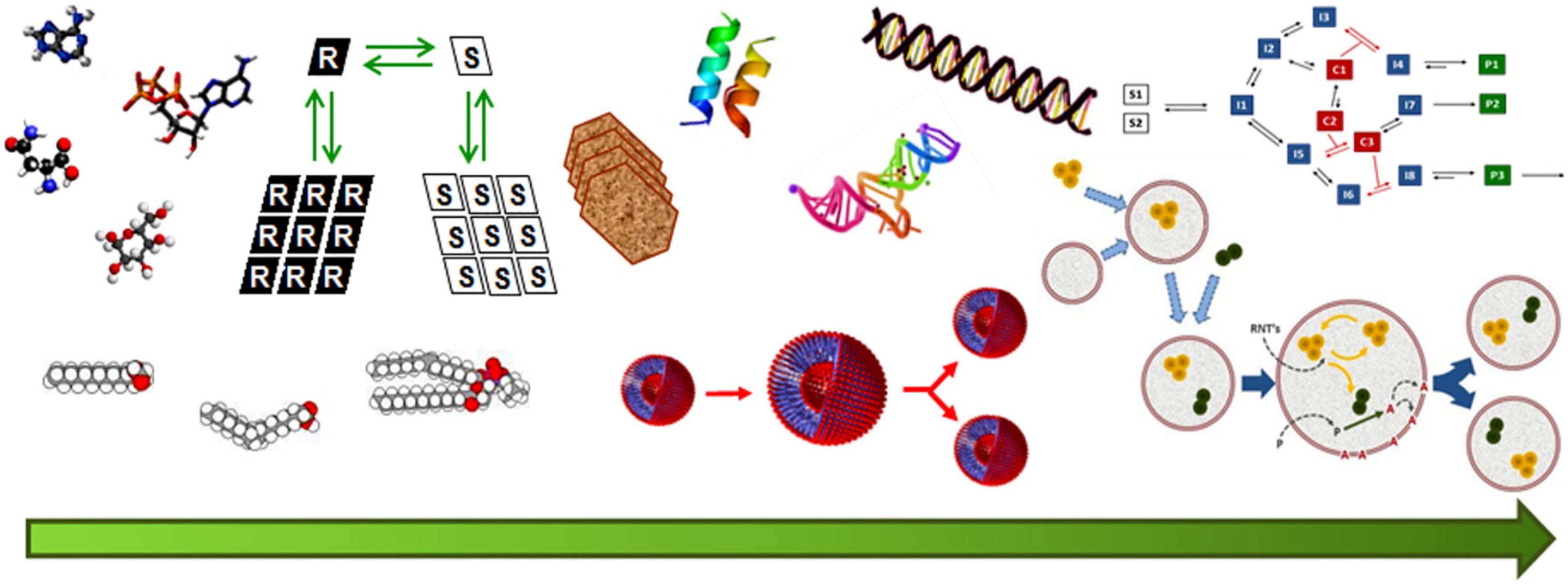
Exactelly repeat creation of the life → not enough time and resources

Science can demonstrate:

- The origin and abundance of elements and small molecules in the Universe
- How the small molecules self-assemble into biopolymers and complex systems
- How to dissect the origin of life into subsequent and overlaping stages
- How the particular stages can be achieved in the lab under abiotic conditions

Important stages of the origin of life

biomolecules – biopolymers – self-replication – metabolism - compartmentalization

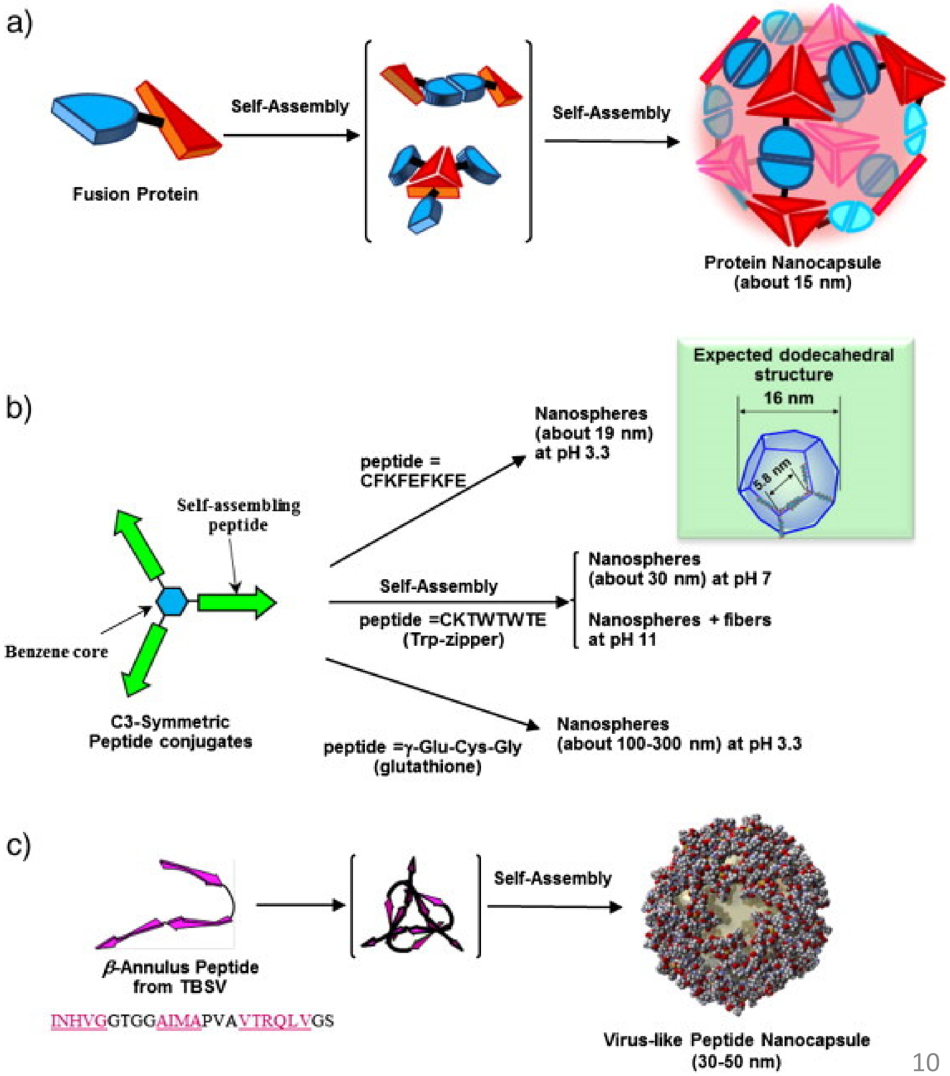


Increasing complexity from molecules to systems

Aspects of chemistry involved:

- Supramolecular chemistry
- Self-assembly
- Autocatalysis
- Organic chemistry
- Biochemistry
- Templated reactions
- Systems chemistry
- Geochemistry
- Astrochemistry

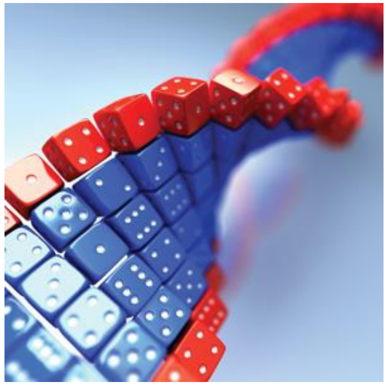
Self assembly



Feedback from:

- Biology
- Physics
- Mathematics and modelling
- Astronomy
- Geology

Modelling approaches



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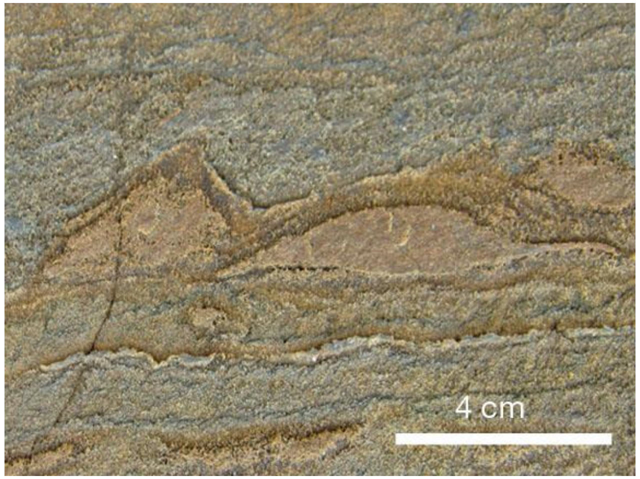
Game theory →
complex life on Earth

Extremophilic organisms

Source: Chemistry World

Metabolism under extreme conditions

Ancient fossils



Source: © Springer Nature

The fossil stromatolites, observable as peaks in the rock,
are the oldest ever found (3.7 billion years old)

Definitions of life


The Nobel Foundation

Erwin Schrödinger (1943):
Life: heredity and thermodynamics

Order from order
genetics

Order from disorder
ordered arrangements of molecules (cells, tissues) within themselves on the expense of increasing disorder of the environment

Definitions of life

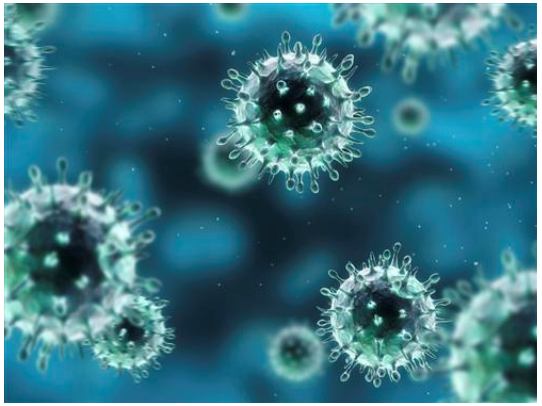
Life is a self-replicating chemical system capable of evolution (NASA, 2009)

Self-replicating: copies itself
Chemical system: based on assembly of molecules
Evolvable: adapt to the surroundings

Mules

Infertile or old animals

Viruses



The definition covers all species, not necessarily individuals

Definitions of life

Life is a self-sustaining kinetically stable dynamic reaction network derived from the replication reaction
(A. Pross, 2012)

Non-living systems → thermodynamic stability
Living systems →dynamic kinetic stability (DKS)
Better at making more of itself (replicating) → more stable in the DKS sense

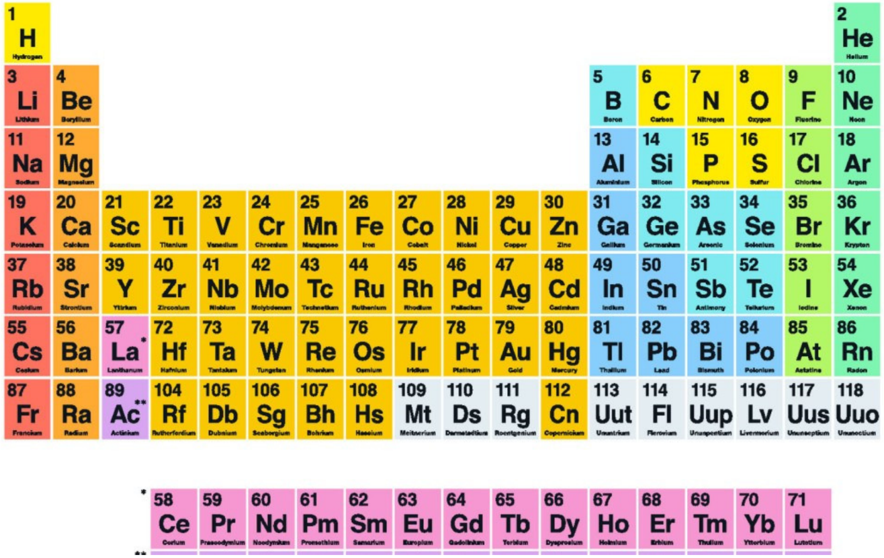
„self-sustaining" - orders itself on the expense of the external world (2nd LT)

Death is reversion of a system from the kinetic, replicative world back to the thermodynamic world

Elements of life

Carbon-based life well-justified:

- self-replicating chemical systems need sufficient complexity
- Carbon is tetravalent and can form complex structures (unlike H, He, Li, O, or F)
- Fourth most common element in the Solar system



1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57 La *	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89 Ac **	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Fl	115 Uup	116 Lv	117 Uus	118 Uuo
		*	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu	
		**															

Silicon is less well suited to support complex chemistry than carbon.

Other atoms are far worse than silicon

Solvents of life

Advantages of water:

- ice floats → nutrient transport, temperature modulation

- High heat capacity 4.2 J/g*^{0}C (3x of rocks or metals),
  heat of vaporization 41 J/g

→ both help to moderate Earth's climate

- Liquidity range – 100^{0}C

- High dielectric constant – water is a very good solvent

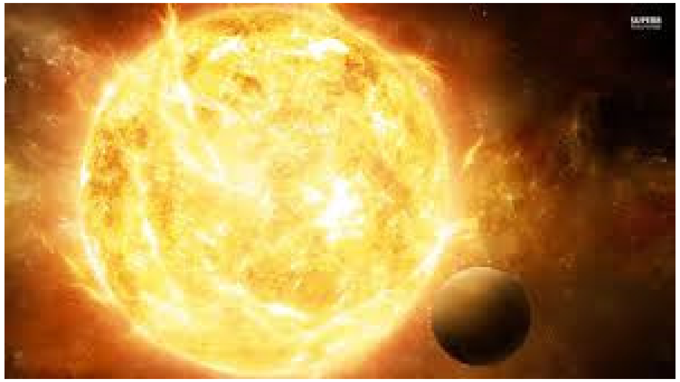
- High molecular density 55.5 mol/L – „hydrophobic effect”:
  H_2O forces dissolved molecules to organize to minimize the enthropic cost

- H, O – very abundant in the Universe (1st, 3rd)
  H_2O – 2nd most abundant after H_2

Alternative solvents
HF, NH_3, CH_4, H_2

Energy for life

The energy of stars

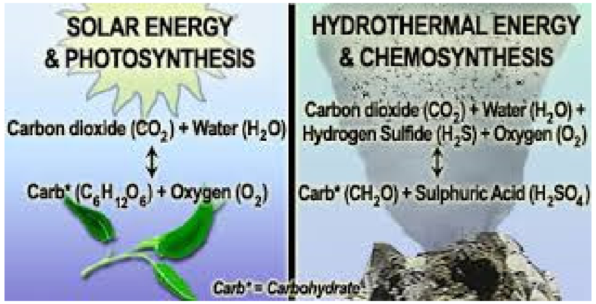


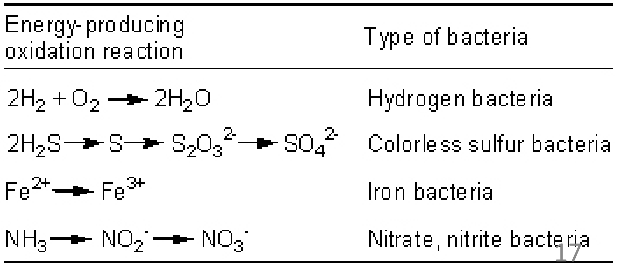
Geothermal/chemical

Life creates order from disorder → need for energy

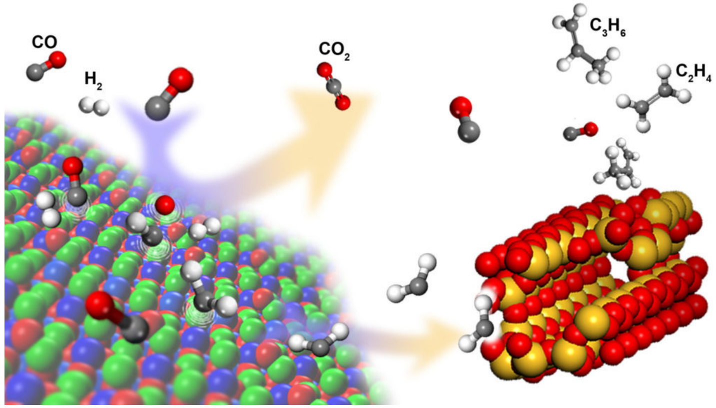
High energy photons absorbed by plants
→ nutrients absorbed by animals;
both patterns used to run metabolic processes

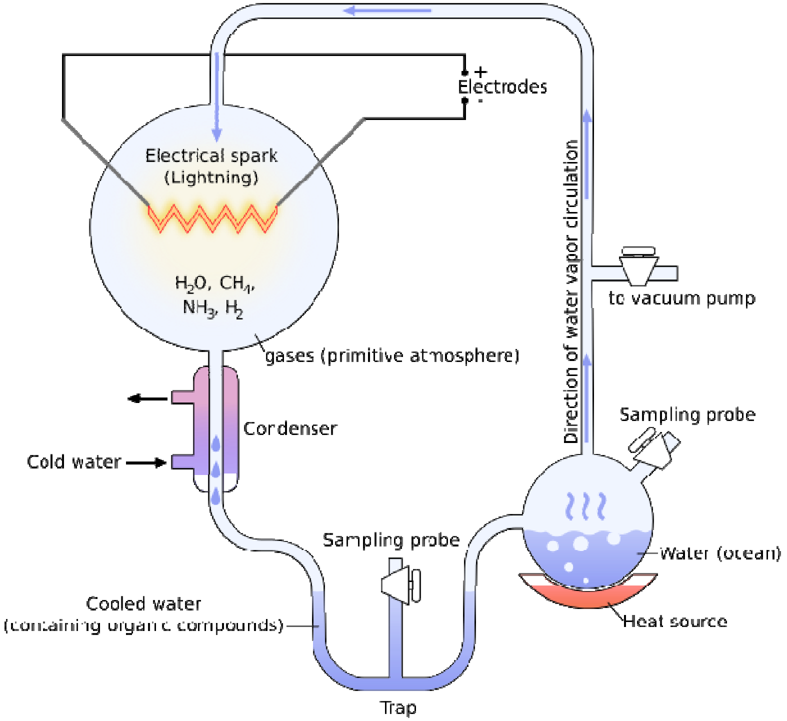
However, not the only available source of energy
→ Further lecture on extremophiles

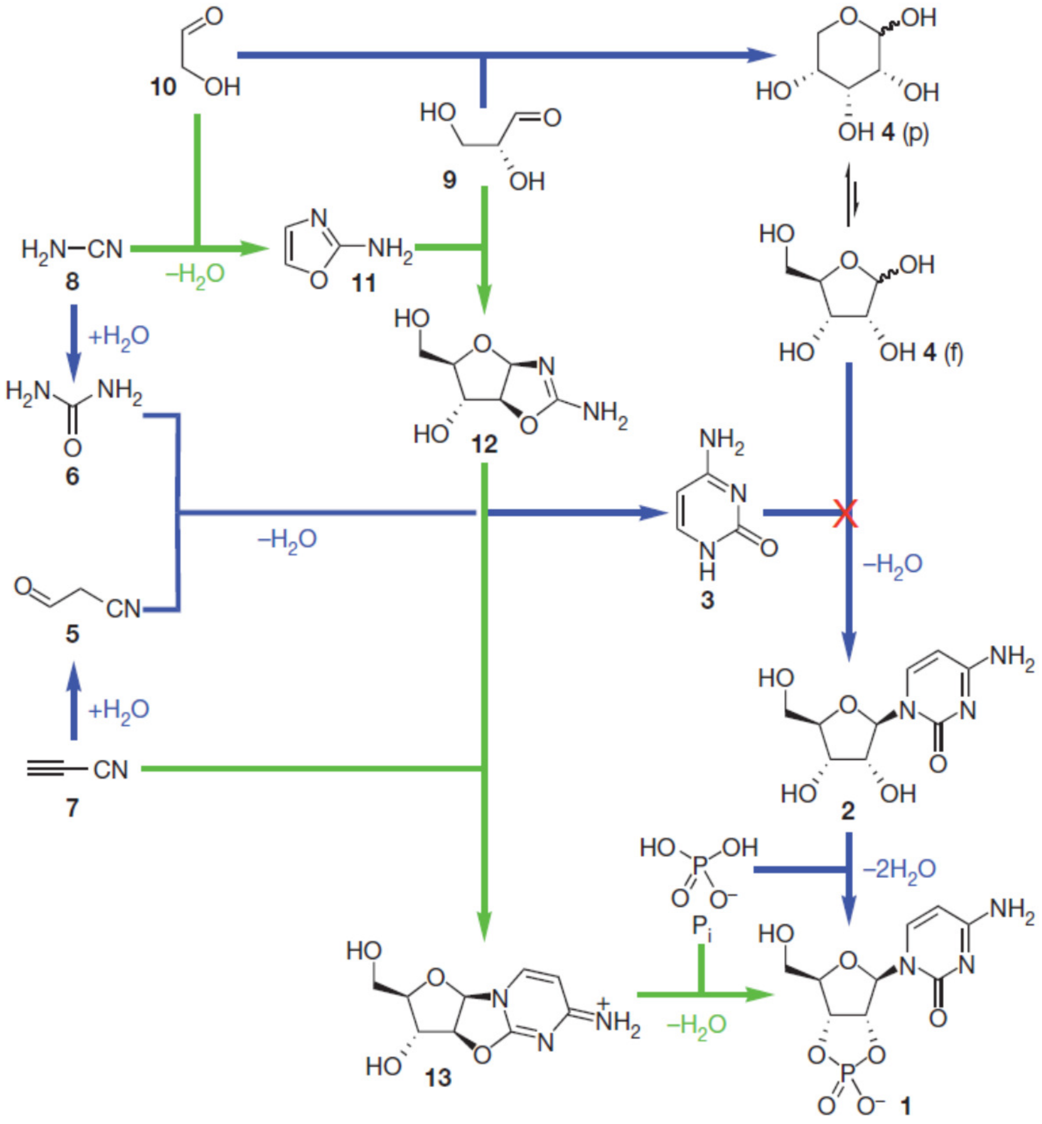




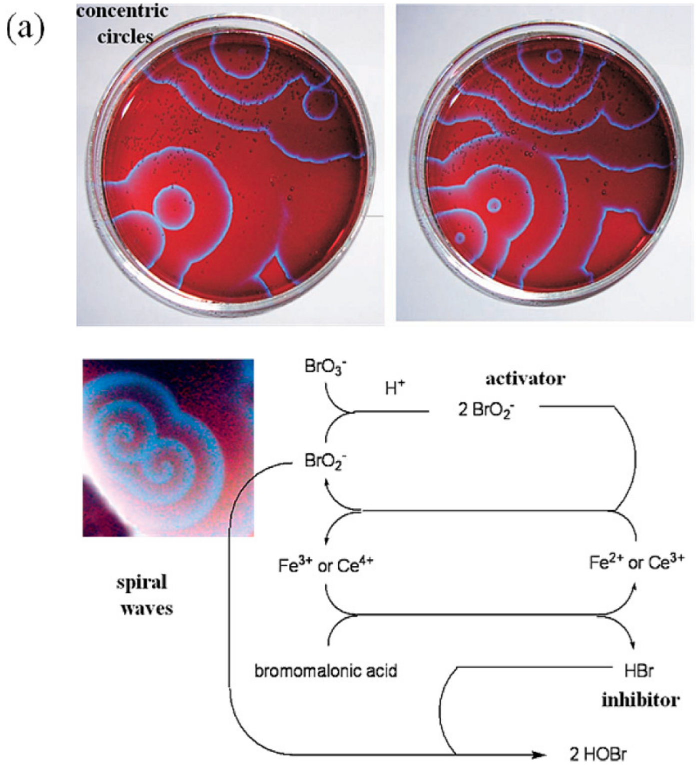
Energy-producing oxidation reaction	Type of bacteria
$2H_2 + O_2 \rightarrow 2H_2O$	Hydrogen bacteria
$2H_2S \rightarrow S \rightarrow S_2O_3^{2-} \rightarrow SO_4^{2-}$	Colorless sulfur bacteria
$Fe^{2+} \rightarrow Fe^{3+}$	Iron bacteria
$NH_3 \rightarrow NO_2^- \rightarrow NO_3^-$	Nitrate, nitrite bacteria


CO
H_2
CO_2
C_3H_6
C_2H_4

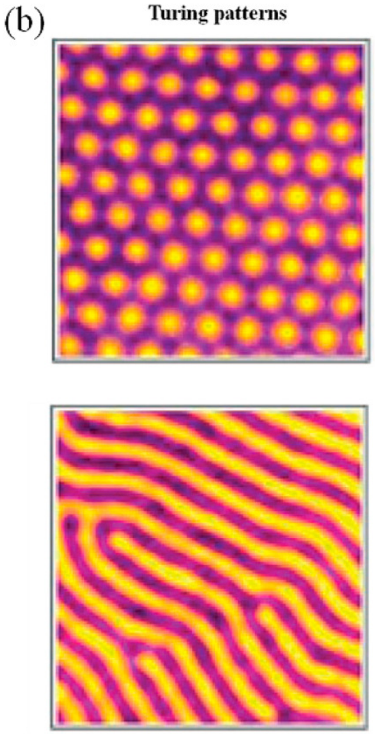

+
Electrodes
-
Electrical spark
(Lightning)
H_2O, CH_4,
NH_3, H_2
gases (primitive atmosphere)
Direction of water vapor circulation
to vacuum pump
Condenser
Cold water
Sampling probe
Sampling probe
Water (ocean)
Heat source
Cooled water
(containing organic compounds)
Trap

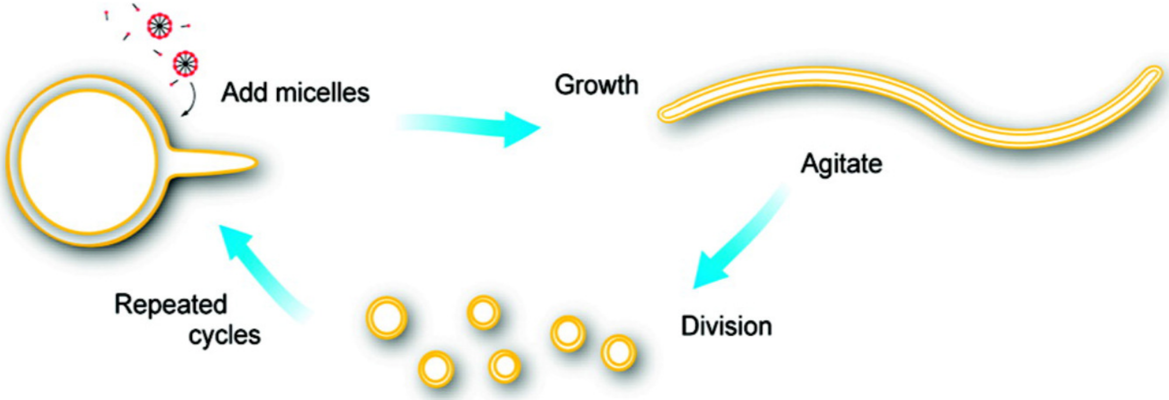

10
9
4 (p)
4 (f)
$H_2N{-}CN$
8
11
12
$-H_2O$
$+H_2O$
6
5
7
3
2
13
1
$-H_2O$
$+H_2O$
$-H_2O$
$-2H_2O$
P_i
$-H_2O$

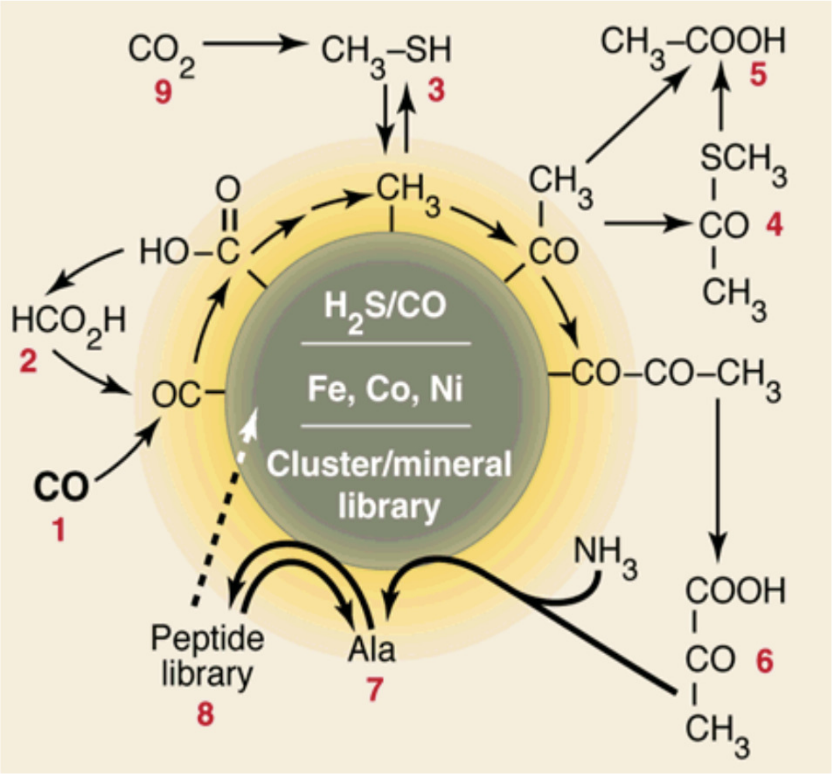
(a)

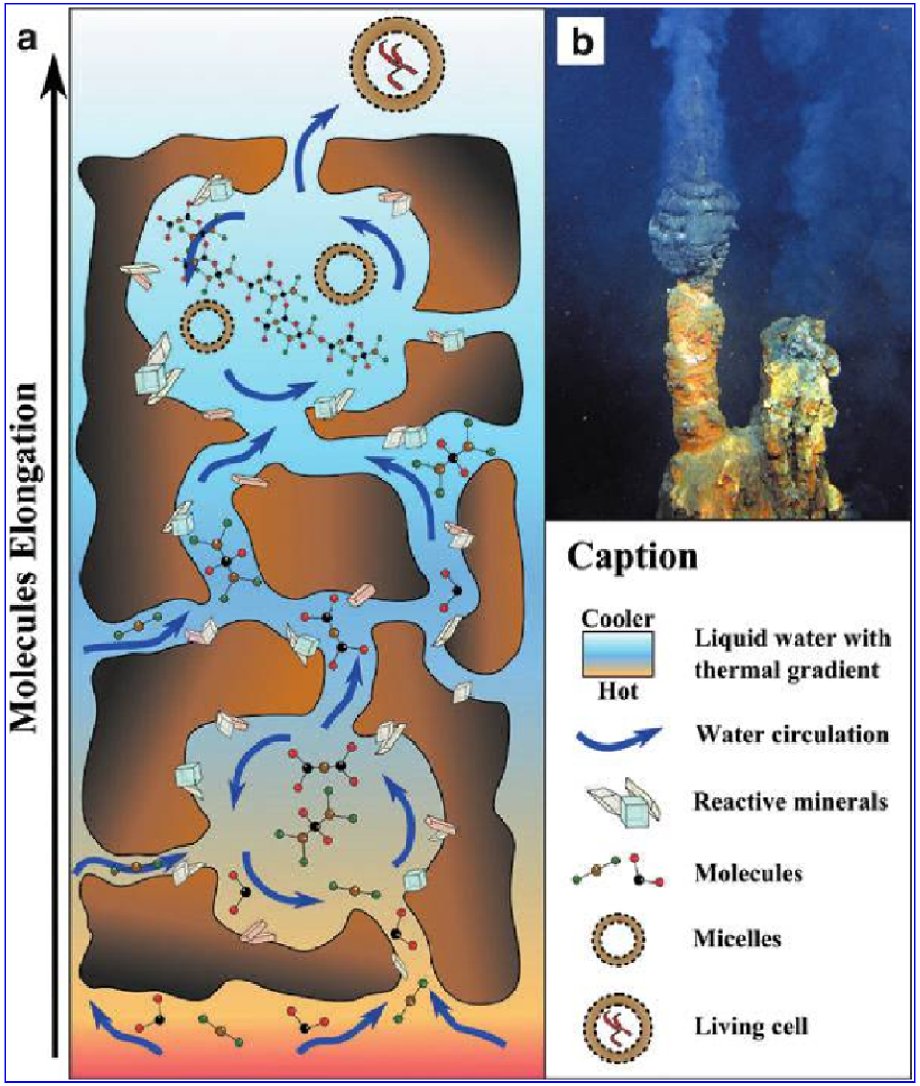

concentric circles
spiral waves
BrO_3^-
H^+
activator
$2\ BrO_2^\cdot$
BrO_2^-
Fe^{3+} or Ce^{4+}
Fe^{2+} or Ce^{3+}
bromomalonic acid
HBr
inhibitor
2 HOBr

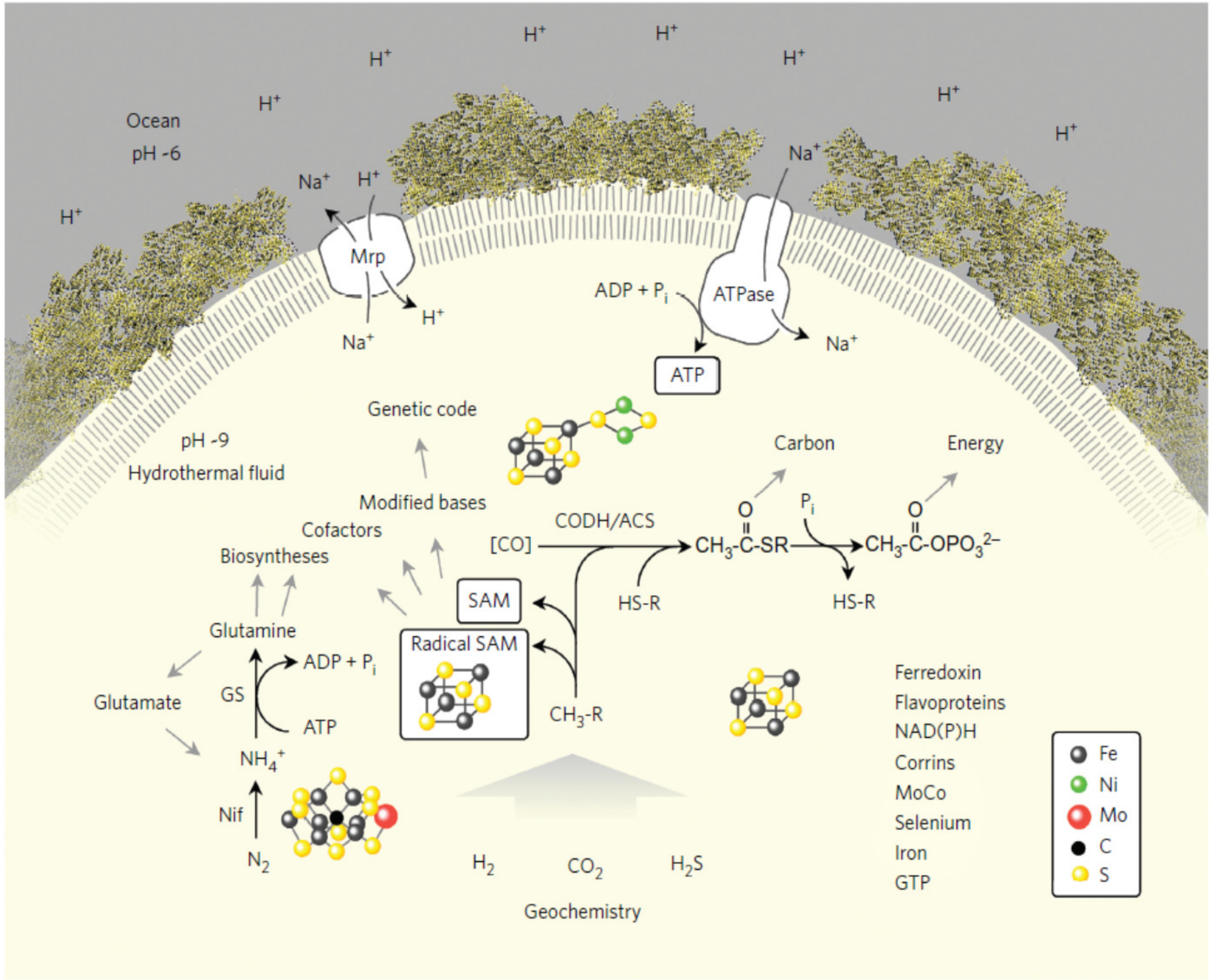
(b)


Turing patterns


Add micelles
Growth
Agitate
Division
Repeated cycles


CO_2 9
$CH_3{-}SH$ 3
$CH_3{-}COOH$ 5
SCH_3
CO 4
CH_3
CH_3
CH_3
CO
O
HO–C
HCO_2H 2
OC–
CO 1
H_2S/CO
Fe, Co, Ni
Cluster/mineral library
–CO–CO–CH_3
NH_3
COOH
CO 6
CH_3
Peptide library 8
Ala 7


a
Molecules Elongation
b
Caption
Cooler
Hot
Liquid water with thermal gradient
Water circulation
Reactive minerals
Molecules
Micelles
Living cell

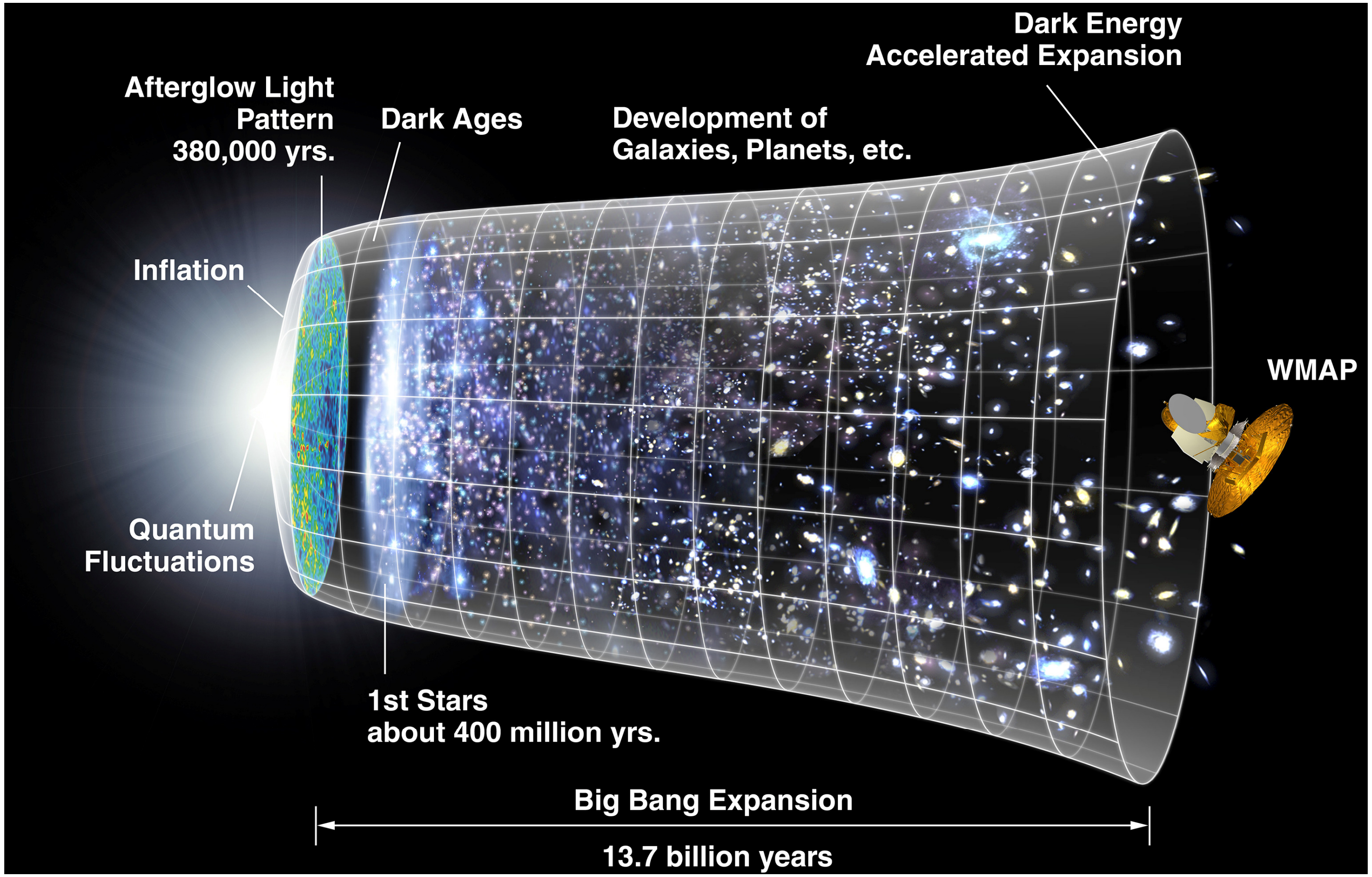

Ocean
pH ~6
H^+
Na^+
Mrp
ATPase
ADP + P_i
ATP
Na^+
pH ~9
Hydrothermal fluid
Genetic code
Modified bases
Cofactors
Biosyntheses
Carbon
Energy
[CO]
CODH/ACS
CH_3-C(=O)-SR
P_i
CH_3-C(=O)-OPO_3^{2-}
HS-R
HS-R
SAM
Radical SAM
CH_3-R
Glutamine
Glutamate
GS
ADP + P_i
ATP
NH_4^+
Nif
N_2
H_2
CO_2
H_2S
Geochemistry
Ferredoxin
Flavoproteins
NAD(P)H
Corrins
MoCo
Selenium
Iron
GTP
Fe
Ni
Mo
C
S

The origin of the habitable Universe and planets

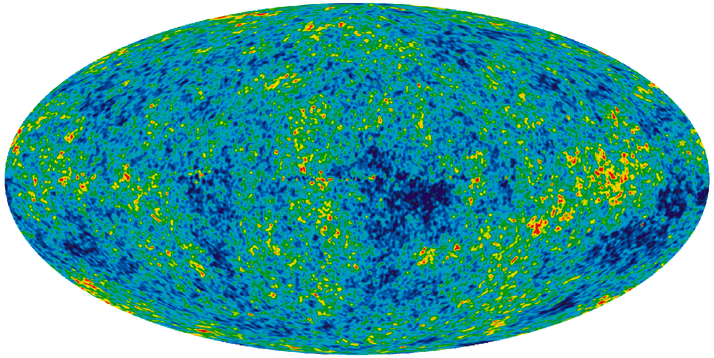
Terry Pratchett: The Discworld

Echoes of the earliest Universe

Red shift of spectral lines in far galaxies (Hubble, 1929)
Theory of the Big Bang – Gamow (1948)

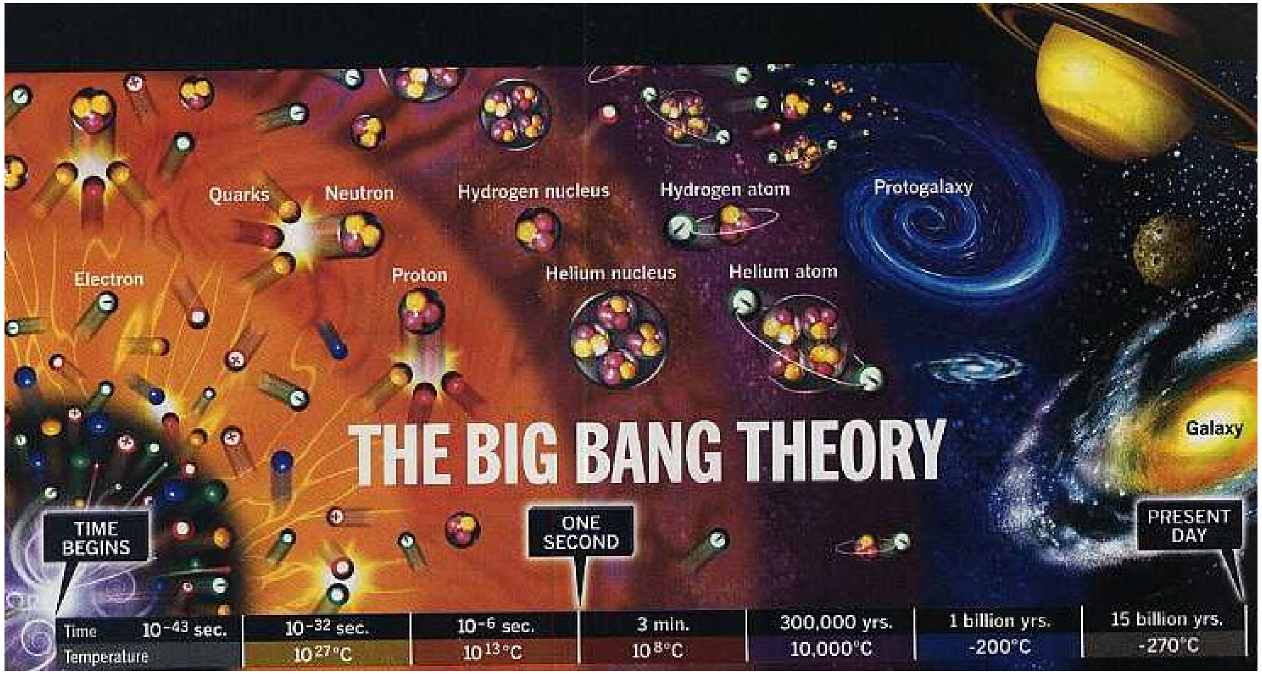


Cosmic microwave background
(Penzias, Wilson,1965 Bell AT&T)



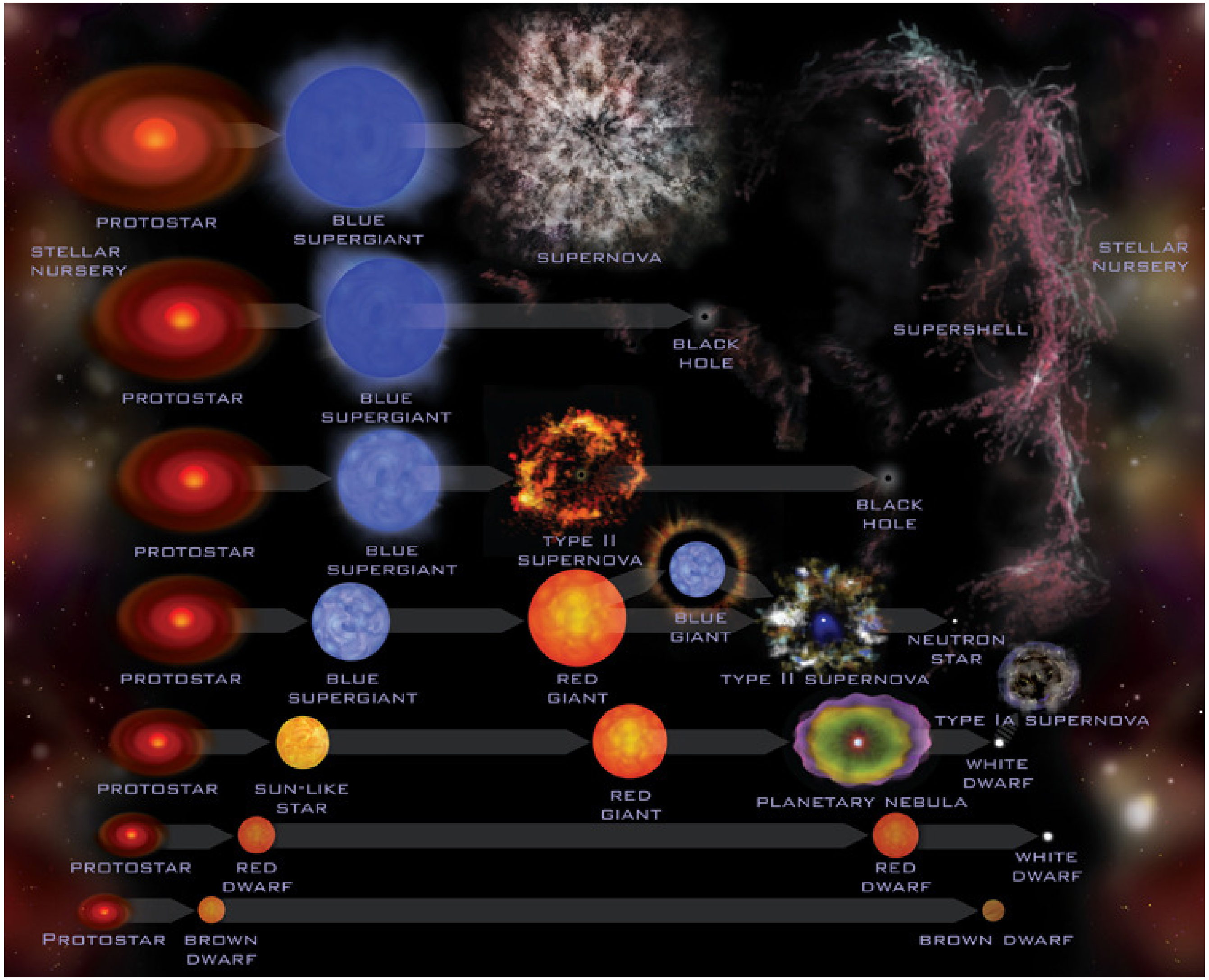
Heat of the Big Bang dissipated in the Universe as the 4 K residual radiation

Origin of the Universe



- Unsymmetric matter/antimatter anihilation
- only H and He elements formed during the Big Bang
- The Universe transparent aftr 377.000 yrs. → background µwave radiation
- Fluctuations registered there → autocatalytic formation of protogalaxies

Stellar evolution



Star that burned all its ^{1}H (red giants), beginns to synthesize ^{12}C and ^{16}O from ^{4}He

Big stars (>8 sun masses) ignite ^{12}C and ^{16}O to form ^{24}Mg, ^{23}Mg ($-^{0}n$), ^{23}Na ($-^{1}H^{+}$), and ^{28}Si
Last step: $2x^{28}Si \rightarrow {}^{56}Fe$

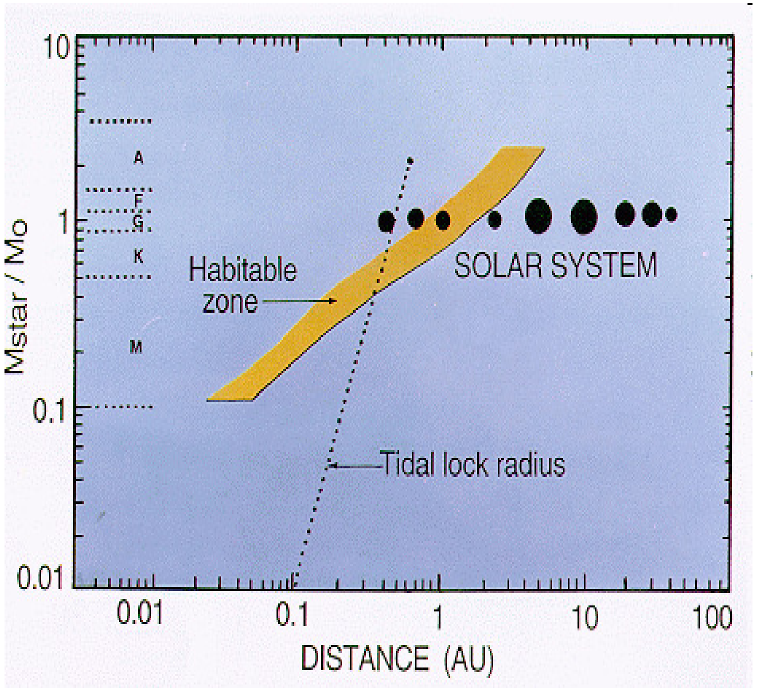
Supernova:
heavier elements synthesized by neutron irradiation of iron

Habitable zone – galactic and star systems

Too close to the center –sterilization by notorious supernova explosions, X-rays from black holes

Far beyond the Sun's orbit – lack of elements > C,O
→ planet formation inhibited

GHZ in the Milky Way → below 5% of stars



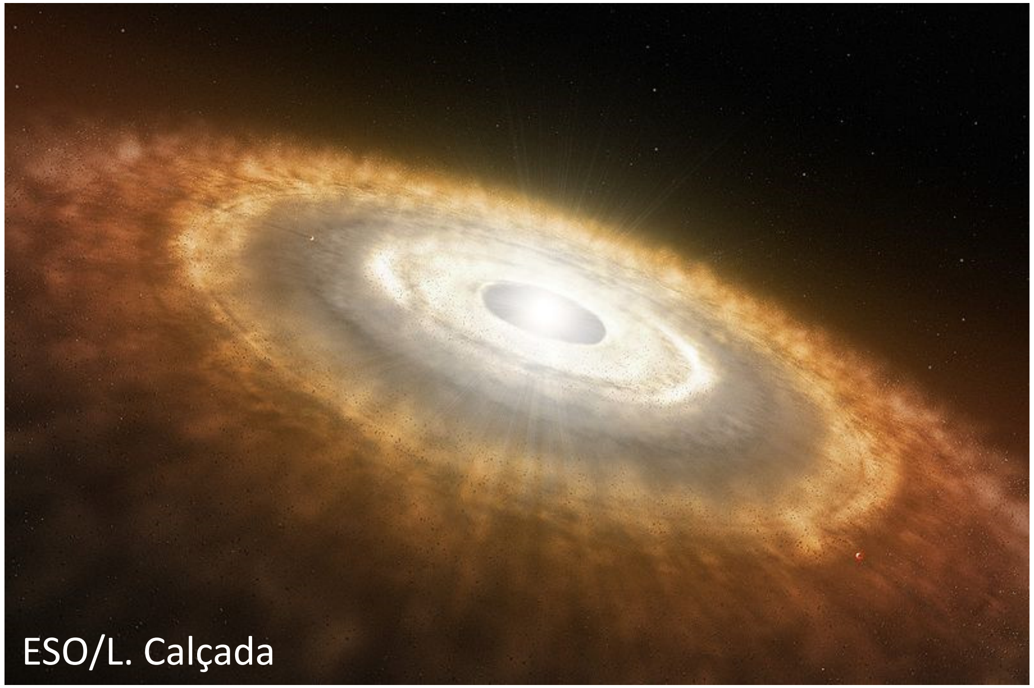
Habitable zone – the region where liquid water can occur

Tidal lock – destructive temperature gradients

→ 0.4-2 Sun mass stars optimal for life development

Evolution of the solar system

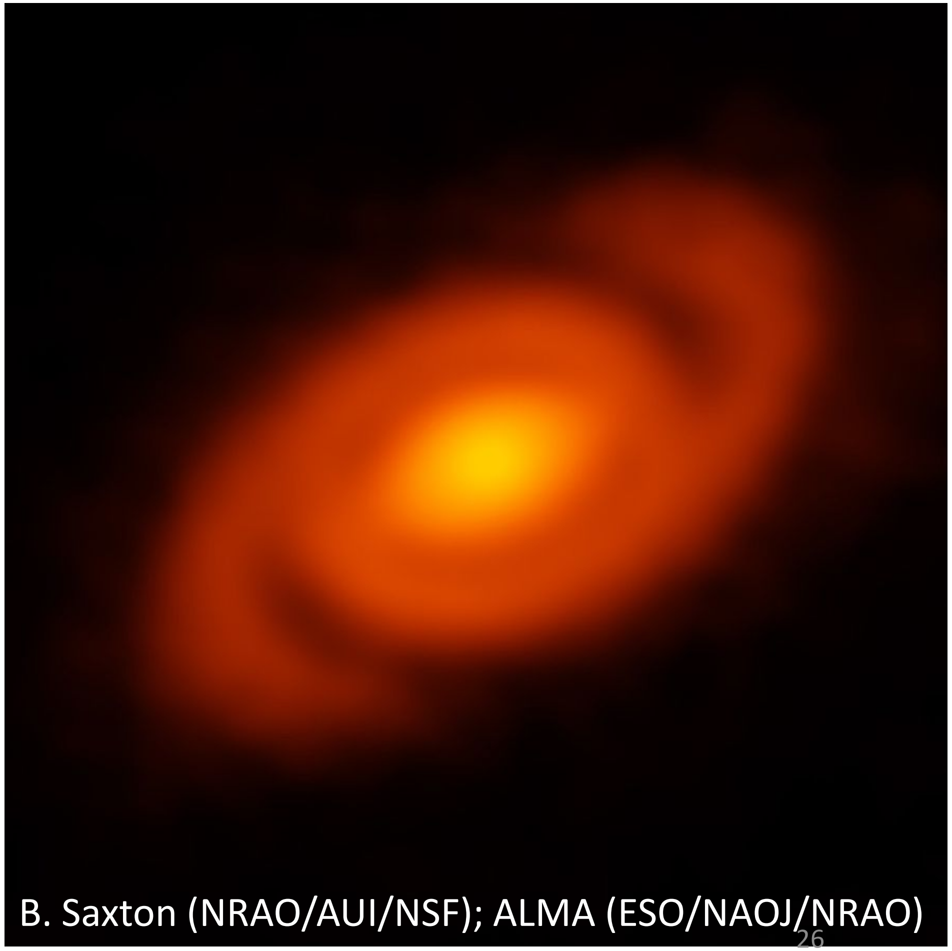
Pre-solar nebula – artistic vision



ESO/L. Calçada

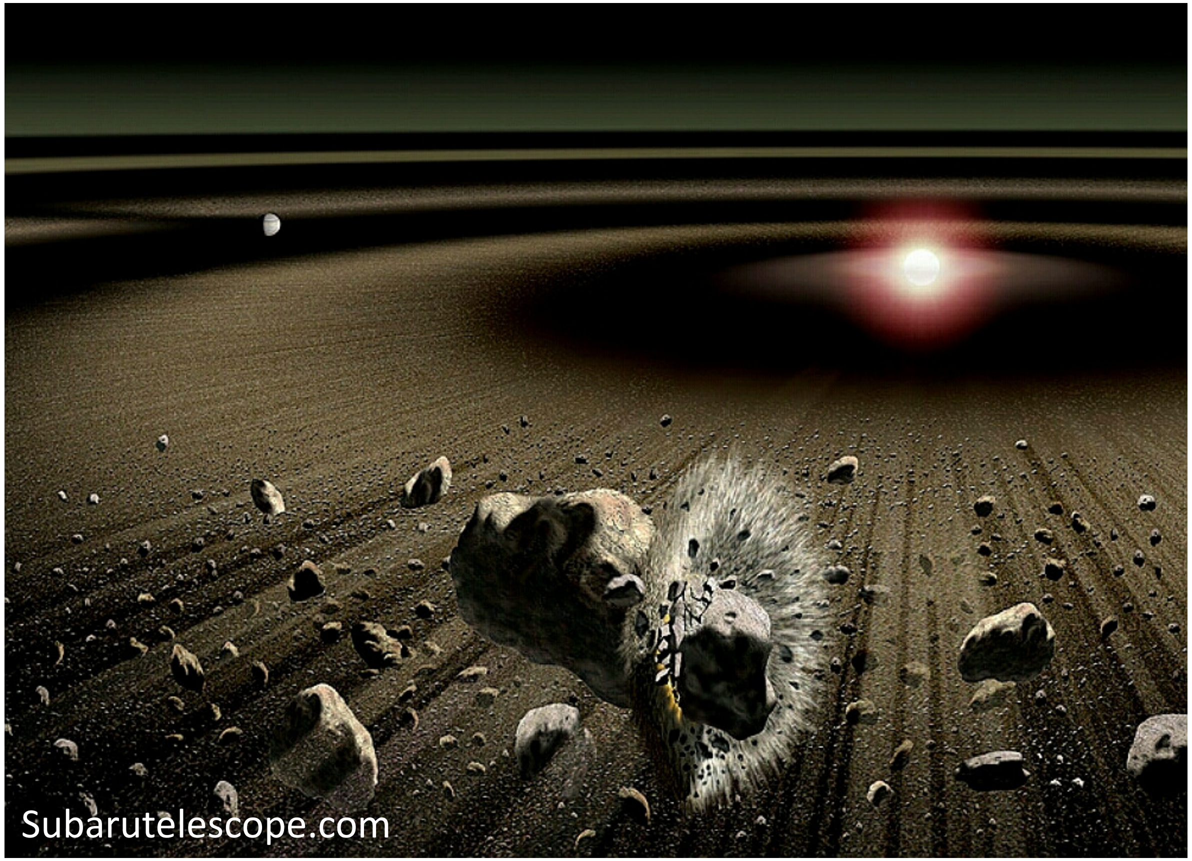
most matter into the proto-sun,
0.1%-2% remained in the acretion disc
Liquids unstable, only sublimation
10 Mio. K → ignition of the star ($^{1}H \rightarrow {}^{4}He$)

Protoplanetary disc surrounding a star
Elias 2-27, 450 light years away



B. Saxton (NRAO/AUI/NSF); ALMA (ESO/NAOJ/NRAO)

Evolution of the solar system



Conglomerations of particles → km-sized planetesimals,
frequent collisions → accretion
the km-sized bodies gravitationally attractive for gases around → growth of proto-planets

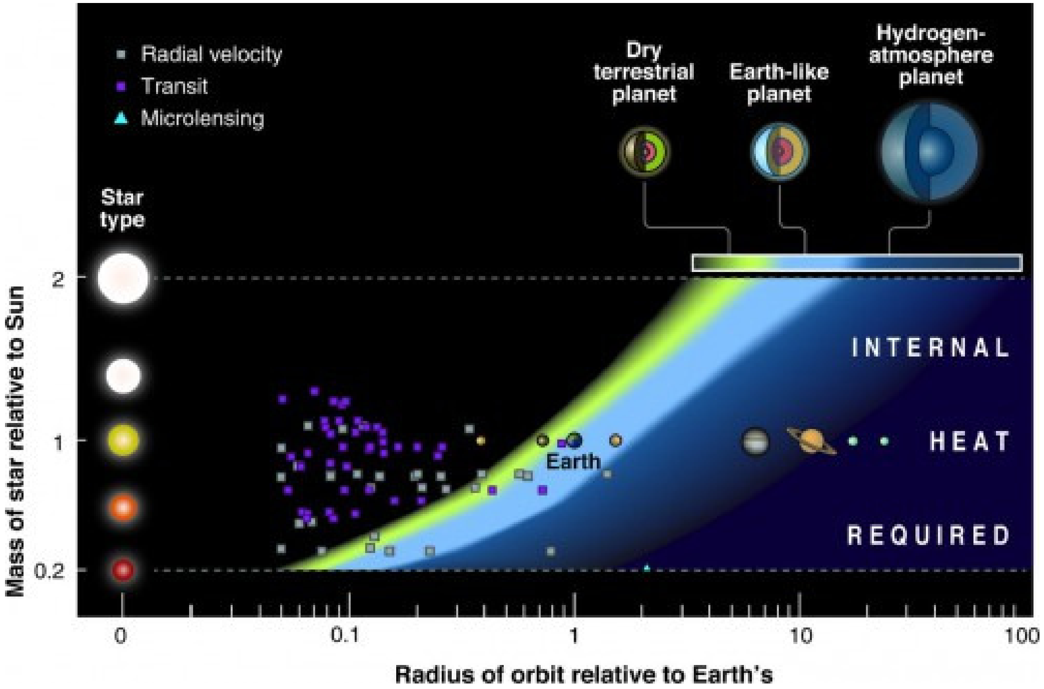
Evolution of the solar system

Composition of planetesimals depends on their distance from the star:

Metal-rich – center

Silicate-rich – middle

Volatile-rich – outer part



The equilibrium condensation model

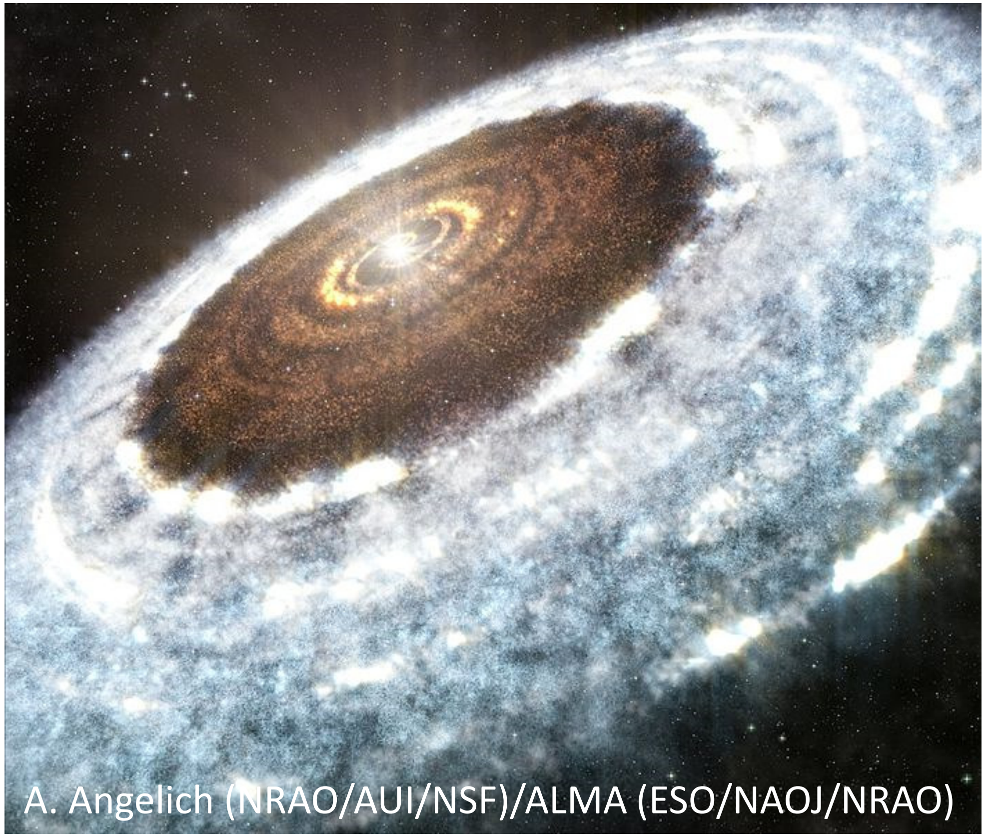
temperature determines equilibrium chemistry which defines the composition

The prediction is rough (scattering)

Exceptions: volatiles on Earth and Venus, composition of the Moon

Composition of the planets in the solar system

Water – a major component of the solar nebula, but under the very low pressure does not condense above 150 K („snow line” in the nebula, 2.7 AU in the Solar system).



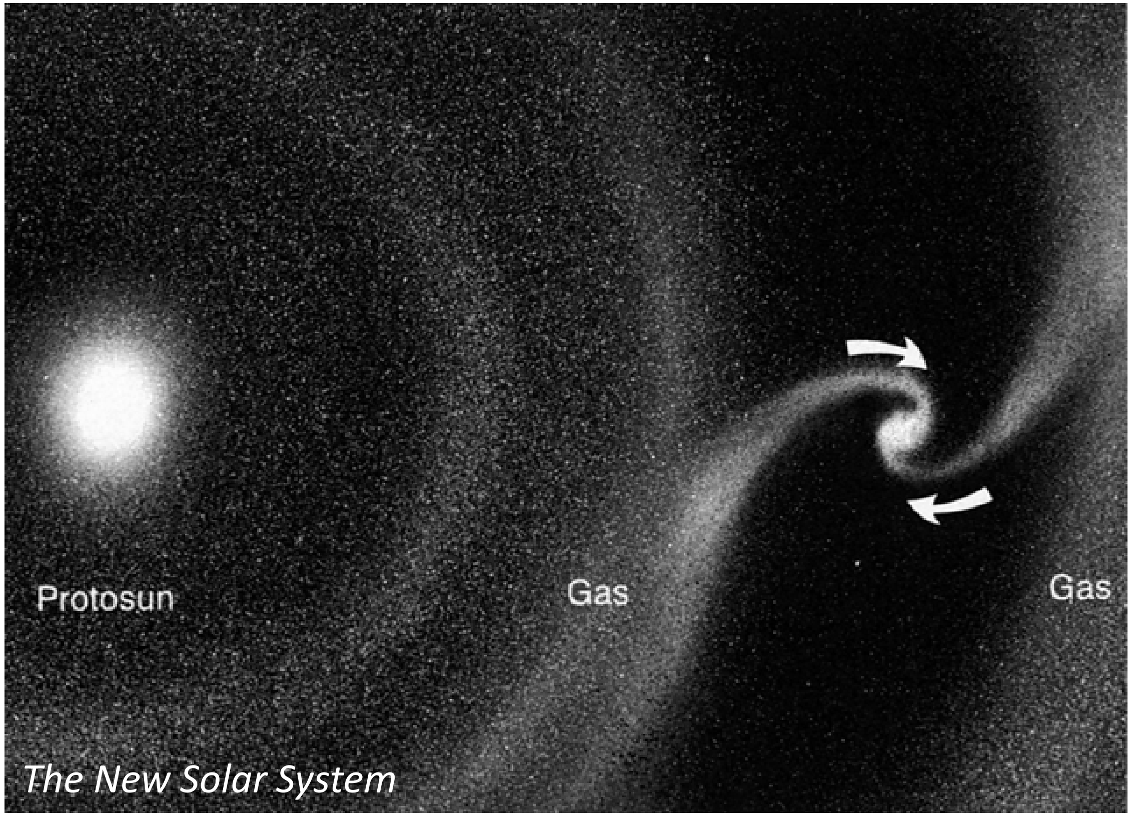
A. Angelich (NRAO/AUI/NSF)/ALMA (ESO/NAOJ/NRAO)

Asteroids that form above 2.7 AU contain significant amount of water

Composition of the planets - Jupiter

Jupiter – 5.21 AU – first planet beyond the snow line – silicates and water condensed in largest amounts of the whole Solar System around a small metal core, and formed a proto-Jupiter
(10-15 Earth masses, fast).

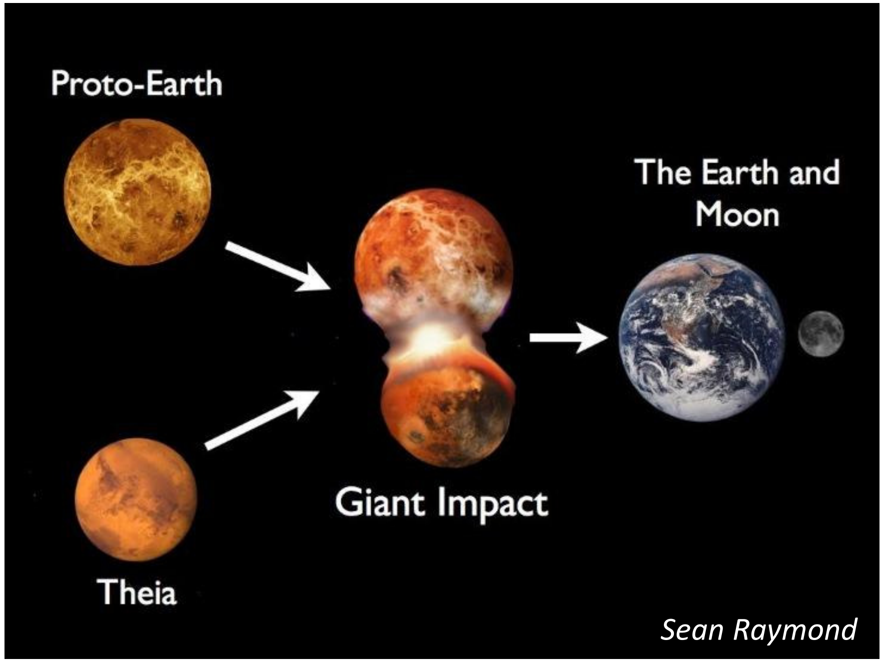
Then gravity strong enough to pull in all available gases around, until it mainly consisted of H_2 and He (strongly pressurized)

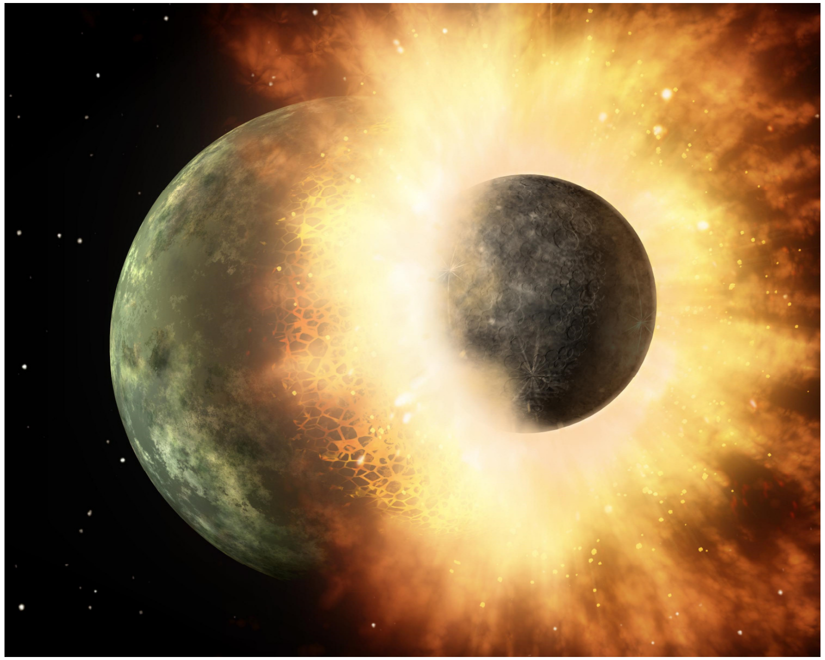


The New Solar System

Origin of the Moon

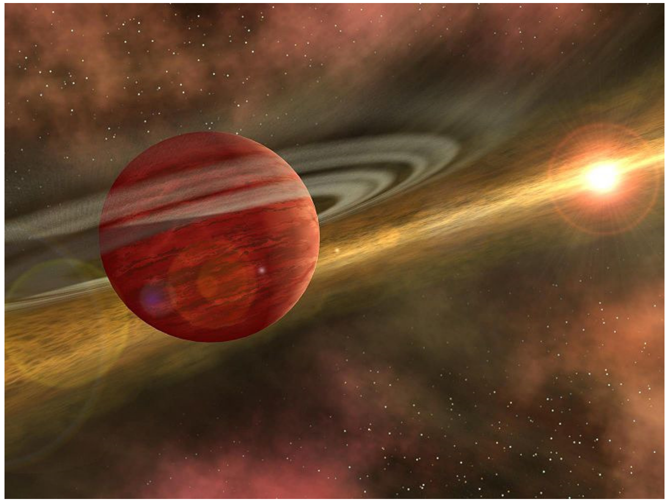
Lunar rock samples (*Apollo* mission): Isotopic distribution like on Earth
Surface of the Moon is different from the Earth surface – lack of „volatile" metals like sodium, the Moon's density only 3.4 g/cm^3 → contains almost entirely silicates





„Daughter-like" Moon's origin – impact of a Mars-size object into Earth splashed a big chunk of liquid rock from its mantle (mostly silicates) into space
Isotope dating (^{182}Hf/^{182}W): Moon formed 30 Mio. Yrs after accretion

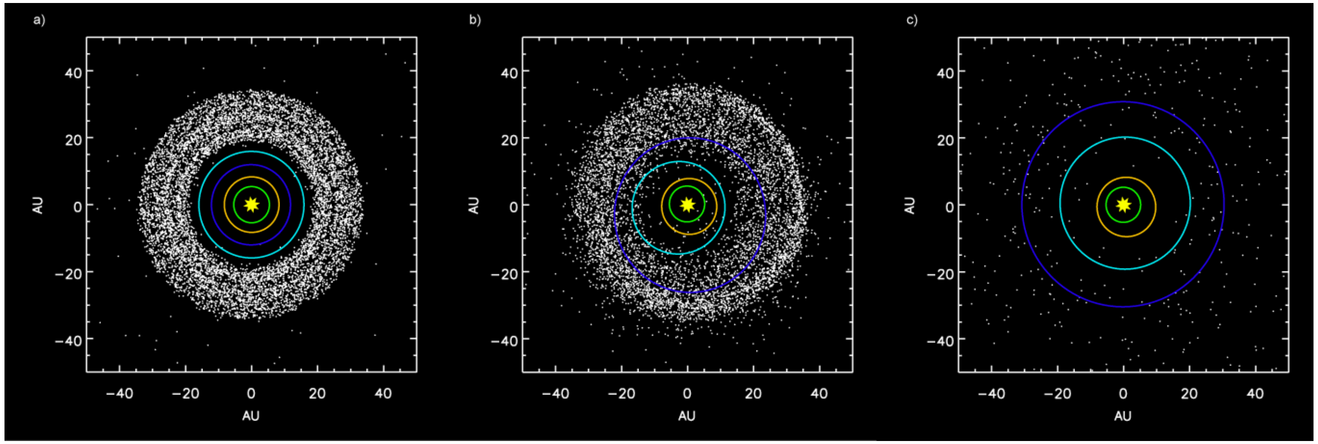
Origin of volatiles on terrestrial planets



Proto-Earth was too hot to condense water
but 0.035% Earth mass is water!!

Water came from beyond the snow line:
Jupiter ejected the remaining planetasimales outwards and inwards: „big cleanup”

The Nice model



Explains the formation of the Kuiper’s Belt, Oort’s Cloud and Planetoid Belt

The ejected planetasimales delivered volatiles to Earth and other terrestrial planets

Late Heavy Bombardment

Tim Wetherell – Australian National University

Late Heavy Bombardment 3.8 Bio. Yrs. ago was the last intensive impact period. Then no more planetasimales.

100-km-wide object can sterilize the surface of the whole planet, but nothing like that happened since.

Origins of a habitable planet - conclusions

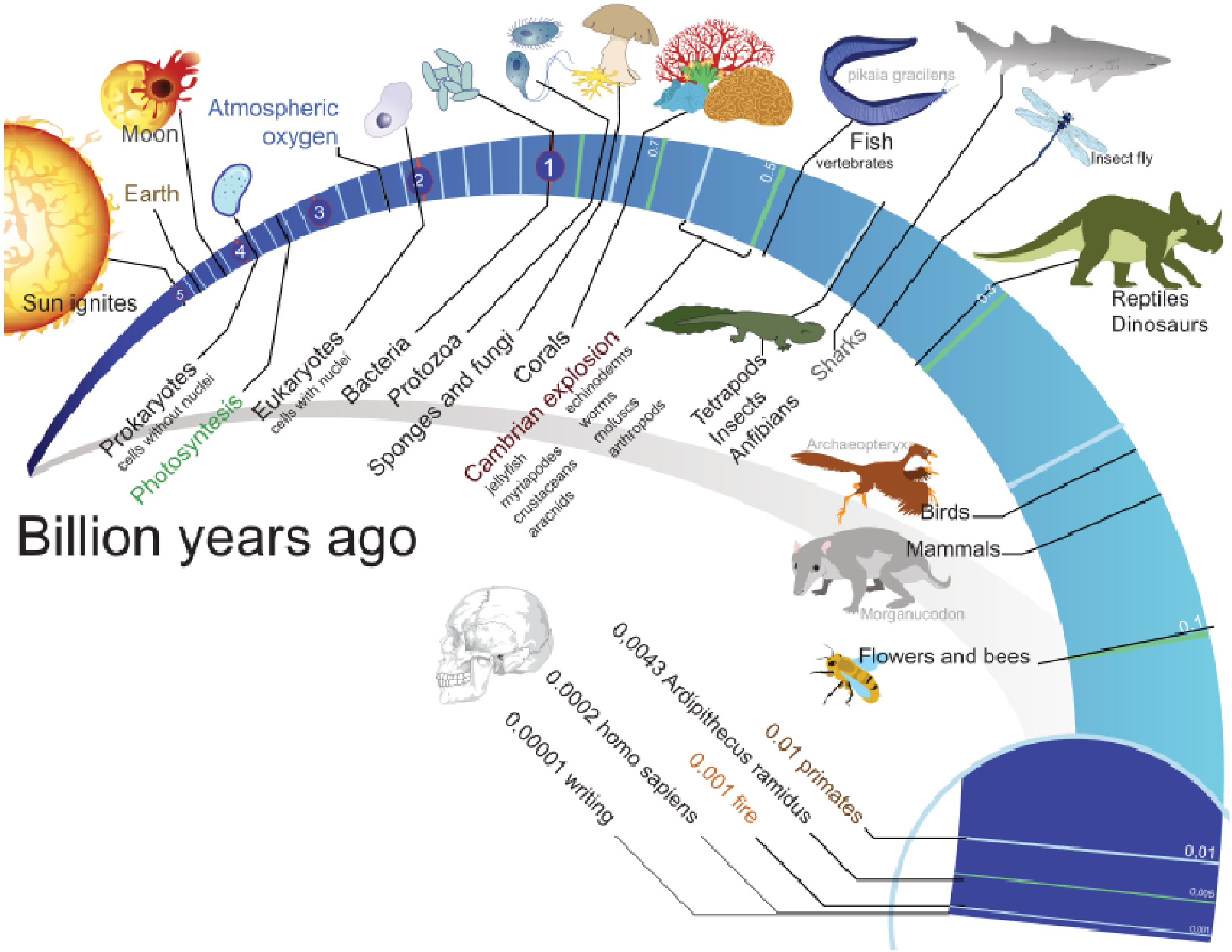
Earth formed in the inner region of the solar nebula
Predominantly composed of refractory metals and silicates – non-biogenic materials
Jupiter provided proto-Earth with icy, volatile-rich material, and allowed cleanup of the Solar System from planetasimales, so no more big, planet-sterilizing impact possible anymore.
Earth is optimally positioned (0.95-1.15 AU) to maintain the acquired water as liquid, and stable surface temperature over billions years.

Topic 2
The primordial soup

The molecular origins of life

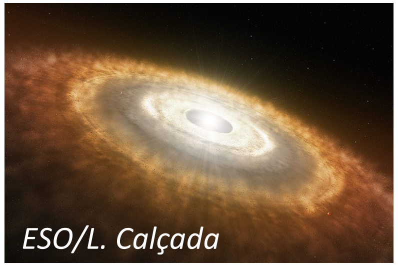
Zibi Pianowski

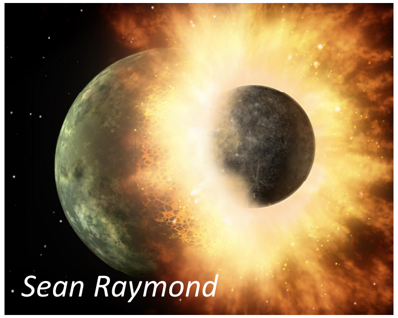
When life originated on Earth?



If life arose relatively quickly on Earth ... then it could be common in the universe."

When life originated on Earth?


ESO/L. Calçada


Sean Raymond

Hadean Eon (4600 Ma - 4000 Ma)
- 4600 Ma – Earth formation
- 4500 Ma – Theia collides Earth → Moon

  Earth's axis of rotation stabilized, which allowed abiogenesis
- 4460 Ma – oldest known lunar rock - Lunar sample 67215, *Apollo 15*
- 4404 Ma – the oldest known material of terrestrial origin – zircon mineral (Australia) –

  isotopic composition of oxygen suggests presence of water on the Earth's surface
- 4374 Ma – the oldest consistently dated zircon

Archean Eon (4000 Ma – 2500 Ma)
- 4031 Ma – formation of the Acastia Gneiss

  - the oldest known intact crustal fragment on Earth
- 4100 Ma - 3800 Ma – Late Heavy Bombardment (LHB)
- 3800 Ma – greenstone belt (Greenland) – isotope frequency

  consistent with presence of life

1 Ma = 1 million years

When life originated on Earth?

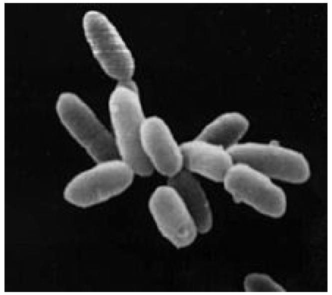
- 4100 Ma – „remains of biotic life” found in zirconites (Australia)
- 3900 Ma – 3500 Ma – cells remaining procaryotes appear

  first chemoautotrophes: oxidize inorganic material to get energy, CO_2 *– carbon source*
- 3700 Ma – oldest evidences for life – biogenic graphite in Isua greenstone belt (Greenland)
- c.a. 3500 Ma – lifetime of the Last Universal Common Ancestor (LUCA)

  split between bacteria and archaea
- 3480 Ma – oldest fossils – microbial mat (bacteria and archaea) fossils – sandstone, Australia
- 3000 Ma – photosynthesizing cyanobacteria evolved – water used as reducing agent

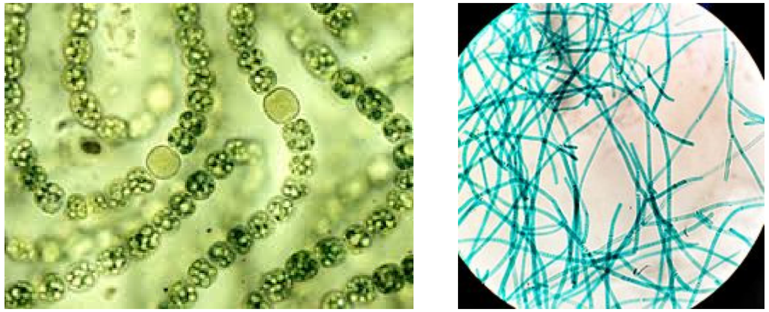
  → production of oxygen → oxidation of iron into iron ore (FeO_x) *(banded iron)*
- 2500 Ma - free oxygen in atmosphere → Great Oxygenation Event („Oxygen catastrophe”)

  extinction of most anaerobic organisms



Archaea (Halobacteria)
extremophiles

cyanobacteria



The origin of life on Earth

- 384-322 BC – Aristotle – *abiogenesis*: spontaneous generation of life forms from unanimated matter (flies from old meat, mice from dirty hay)

- 1665 AC – Robert Hooke (microscope) – discovery of bacteria – considered a proof for spontaneous generation (bacteria division was not observed by then)

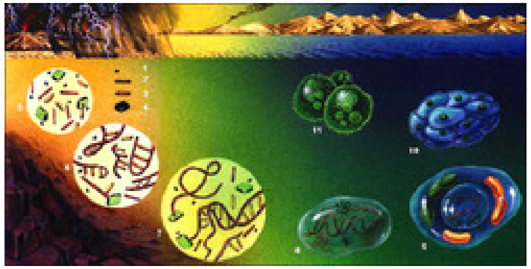
- 1668 – Francisco Redi – *biogenesis*: every life comes from another life

- 1861 – Louis Pasteur – bacteria do not grow in sterilized nutrient-rich medium, unless inoculated from outside; abiogenesis under current conditions regarded as impossible and therefore disproven

Panspermia – idea that life came to Earth from elsewhere in the Universe (e.g. Extremophilic organisms hibernated and traveling inside meteorites) – Anaxagoras (400ts BC), Berzelius, Kelvin, von Helmholtz, Arrhenius...;
Pseudo-panspermia – biorelevant molecules delivered from outside of Earth (meteorites)

The origin of biorelevant molecules on Earth

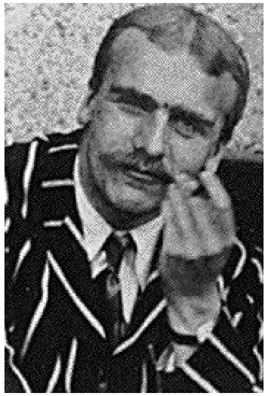
Alexander Oparin
(USSR, 1894-1980)



„atmospheric oxygen prevents the synthesis of certain organic compounds that are necessary building blocks for the evolution of life"

1. *The early Earth had a chemically reducing atmosphere.*
2. *This atmosphere, exposed to energy in various forms, produced simple organic compounds ("monomers").*
3. *These compounds accumulated in a "soup" that may have concentrated at various locations (shorelines, oceanic vents etc.).*
4. *By further transformation, more complex organic polymers - and ultimately life - developed in the soup.*

John B. S. Haldane
(UK, India, 1892-1964)

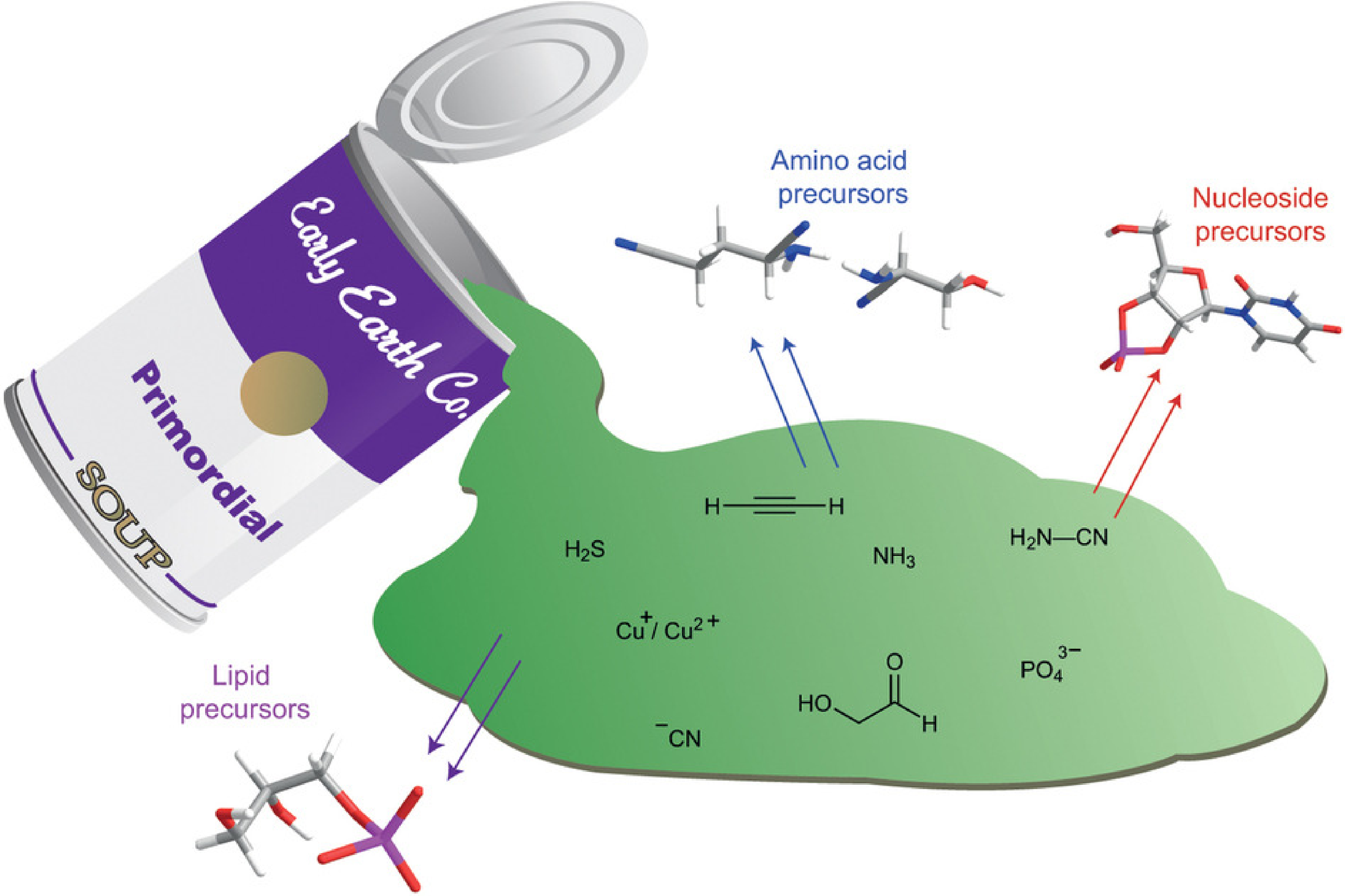


„Primordial soup"

„Biopoeiesis" – prebiotic oceans as „hot diluted soup" under anoxic conditions: e.g. CO_2, NH_3, H_2O

„Life arose through the slow evolution of chemical systems of increasing complexity"

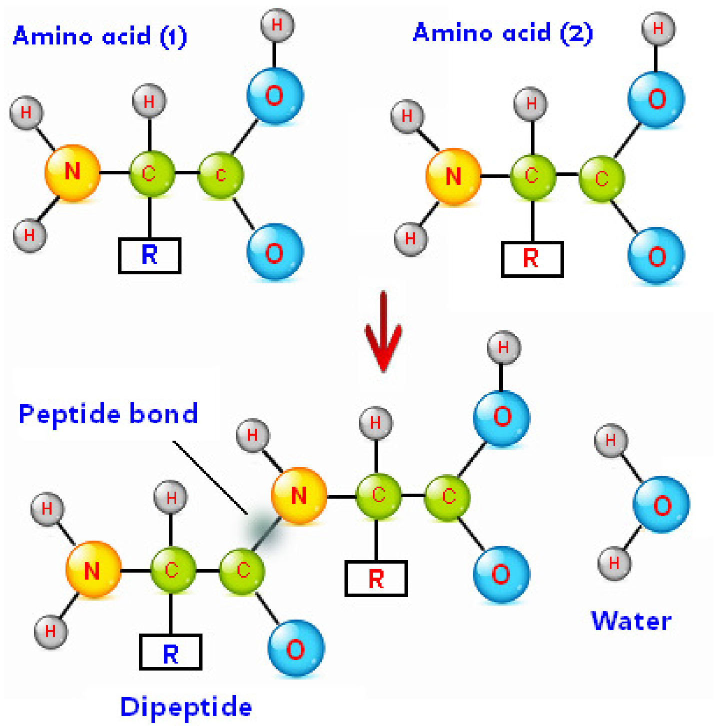
Basic classes of biomolecules



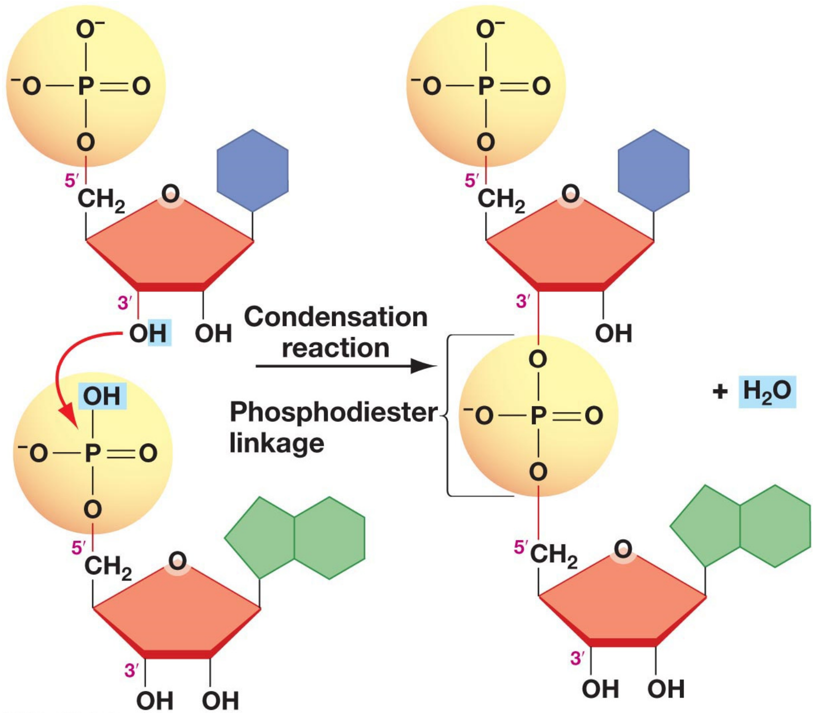
- Aminoacids
- Lipids
- Carbohydrates (sugars)
- Nucleotides
- Nucleosides (sugar+nucleotide)

Vital chemical reactions

Aminoacid polymerization

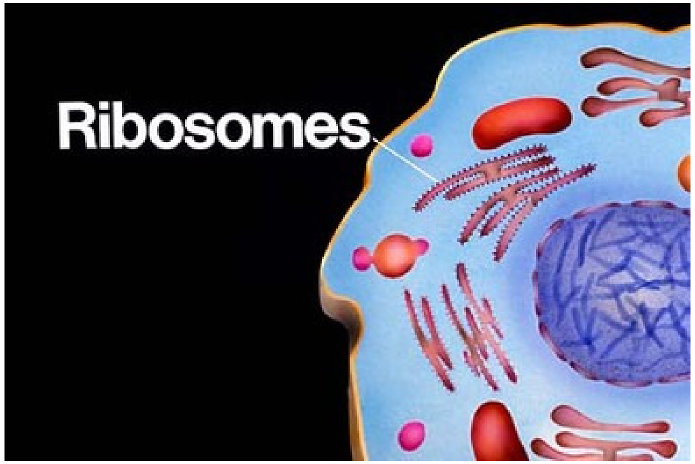


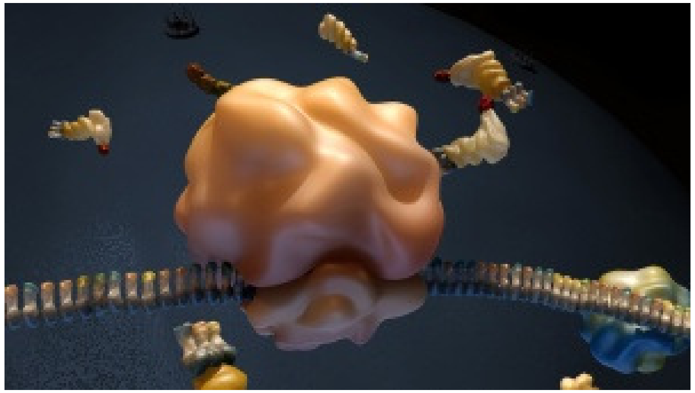
Nucleotide polymerization

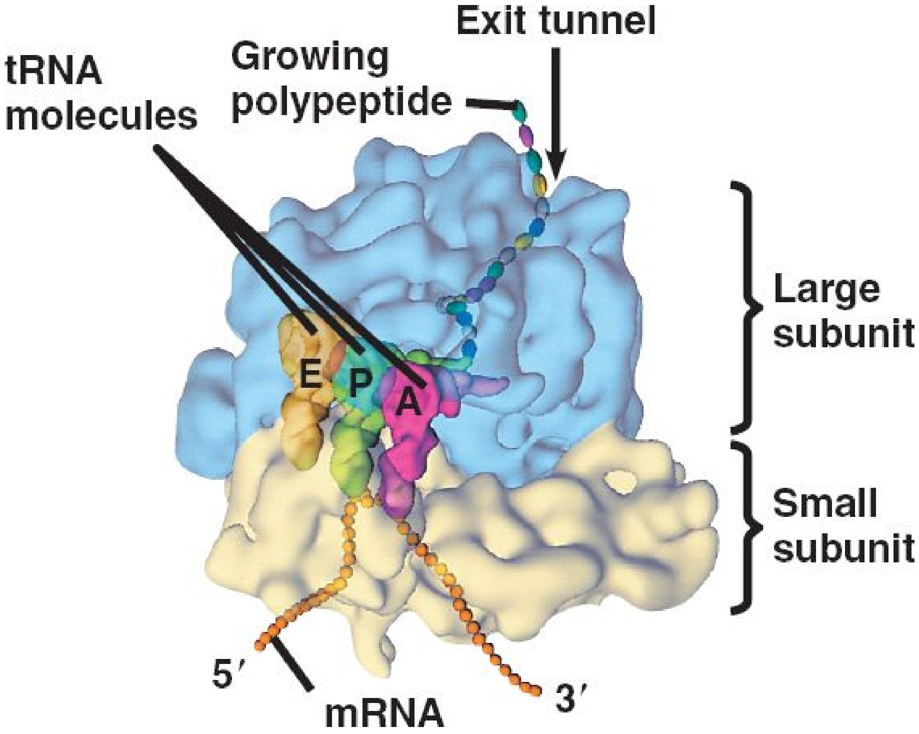


Vital chemical reactions

Aminoacid polymerization → ribosome



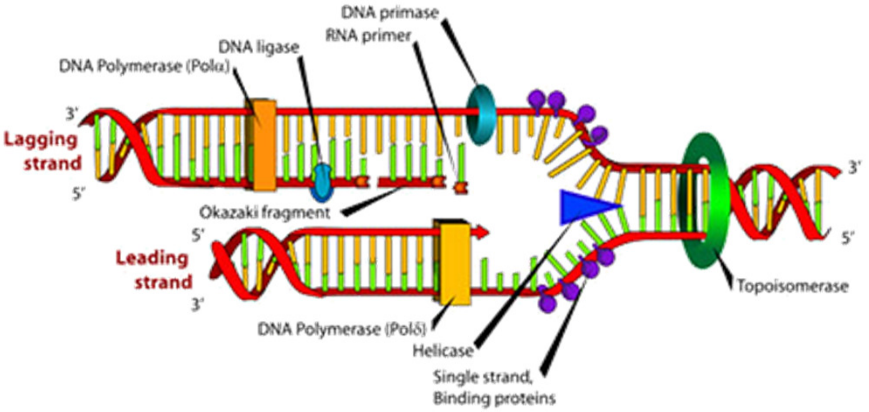




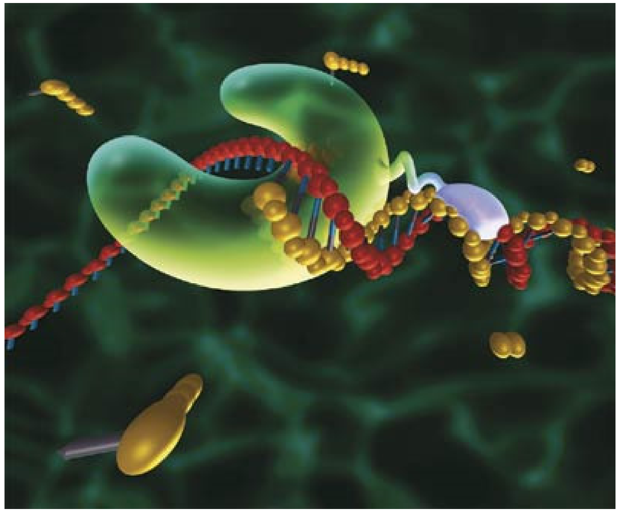
Nature Publishing Group, www.nature.com/nrg/multimedia

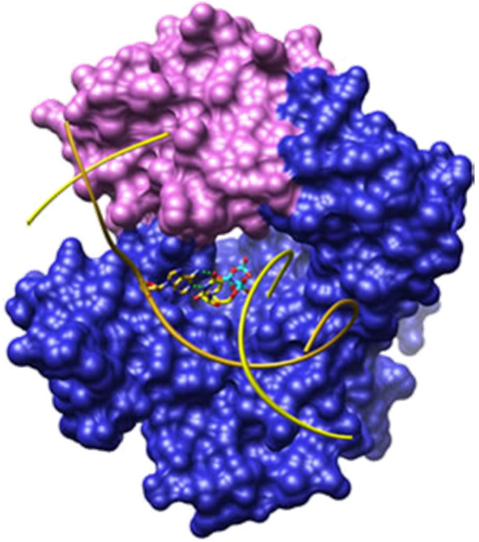
Vital chemical reactions

nucleotide polymerization → DNA/RNA polymerases



dxline.info/img/new_ail/dna-polymerase_1.jpg





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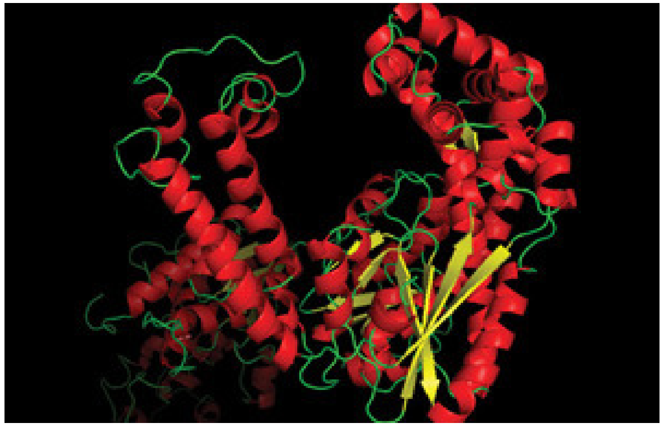

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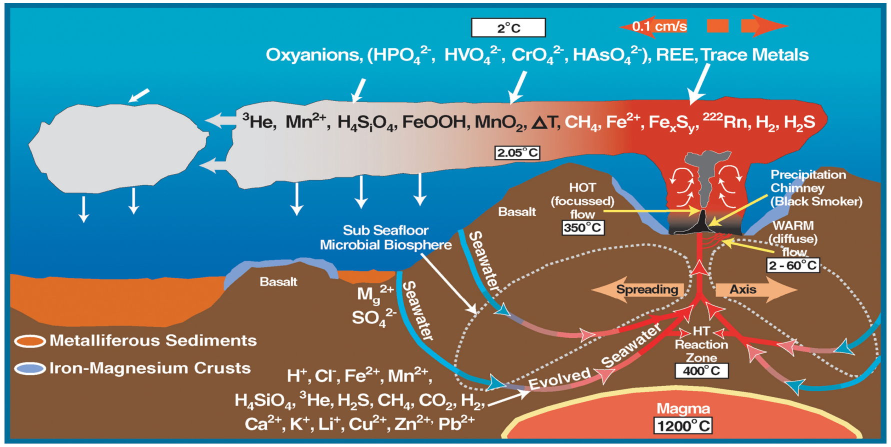
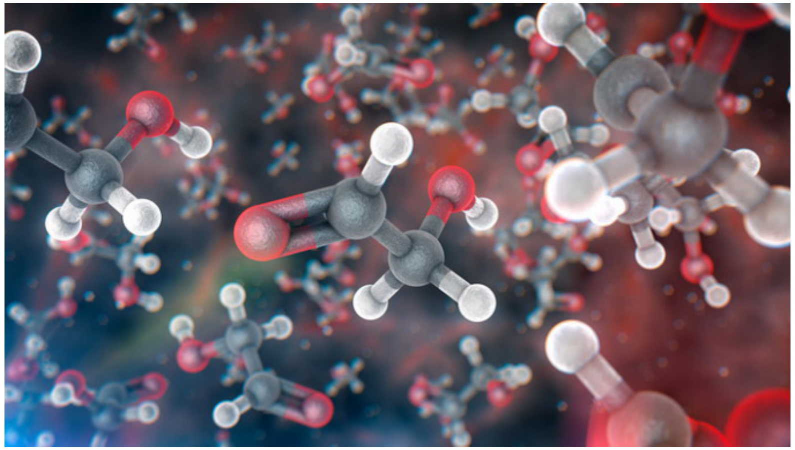
Experimental prebiotic organic chemistry

- Prebiotic chemistry deals with reactive substances (like HCN) often at concentrations much higher than probable in prebiotic environments
- Prebiotic experiments usually performed with very small number of pure substrates
- Early protometabolic processes might have used a broader set of organic compounds than the one contemporary biochemistry



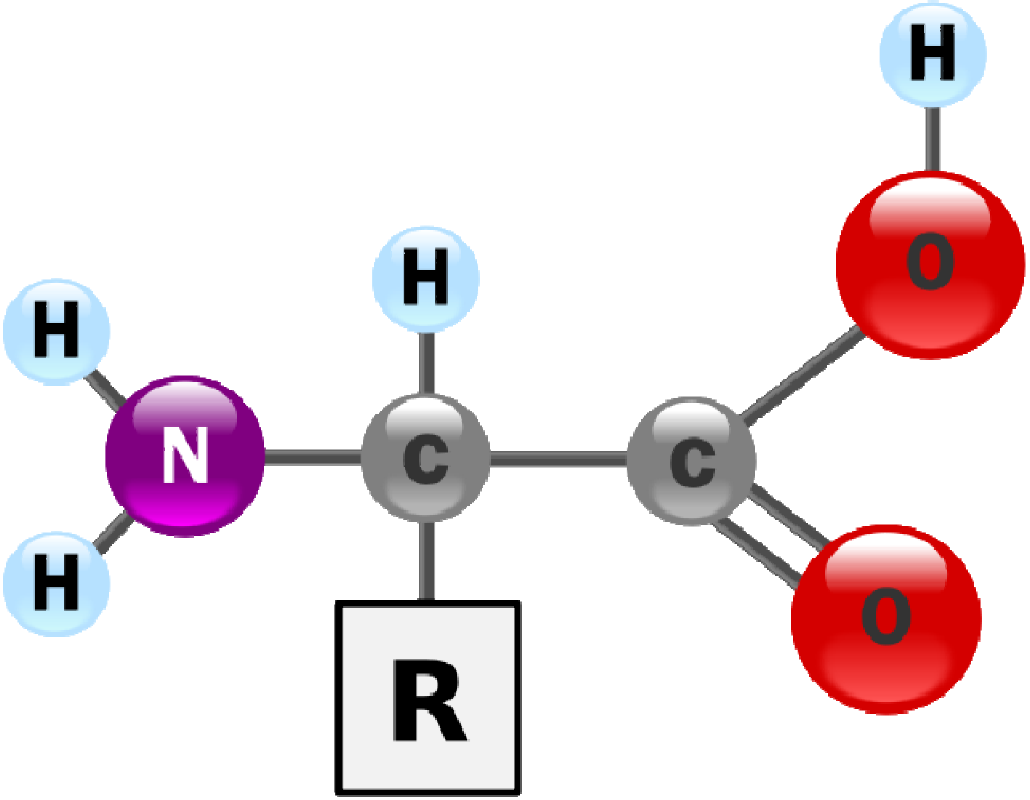


Experimental prebiotic organic chemistry

- No evidences/fossils from that early Earth → we try to SPECULATIVELY fit different examples of chemical reactivity into an EXPECTED OUTCOME which we know as contemporary biochemistry

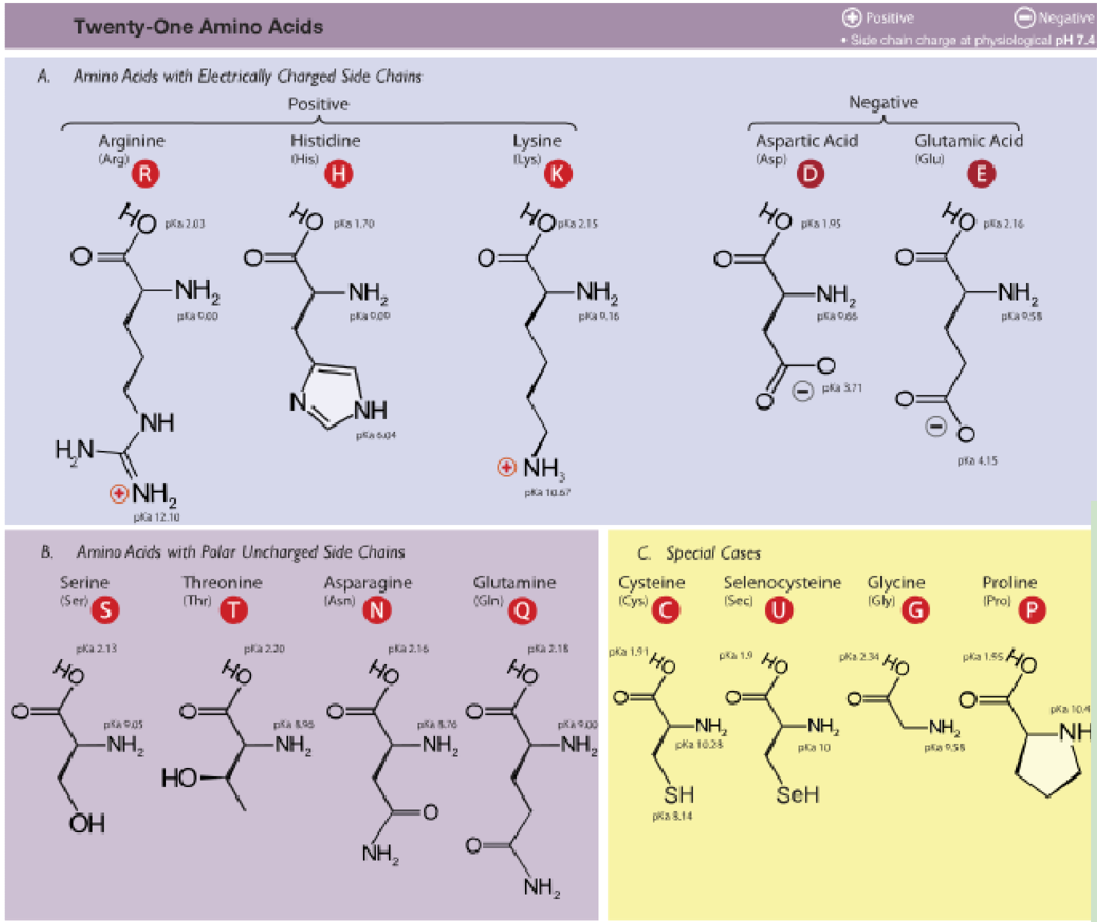
- Most of the discussed transformations are performed by highly specific and evolved enzymes at high speed and efficiency – prebiotic chemistry is supposed to be much slower and less efficient, but more robust and diverse

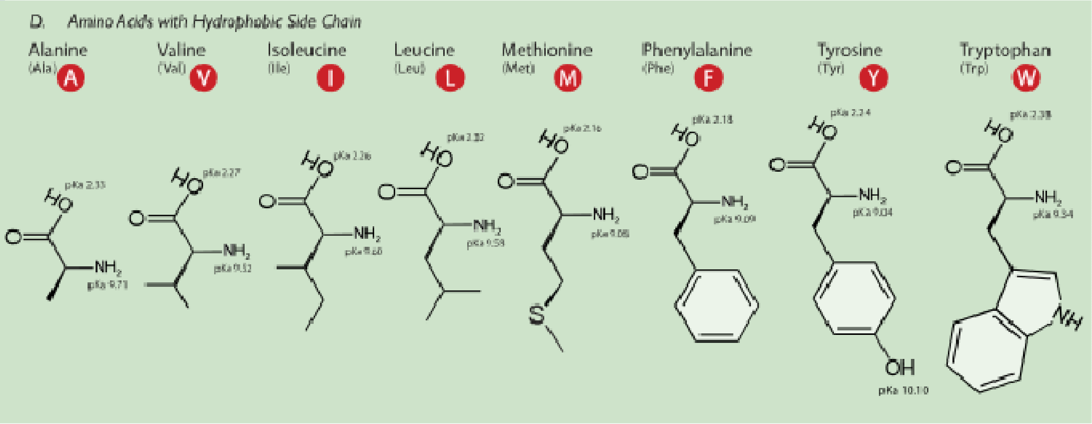
Aminoacids

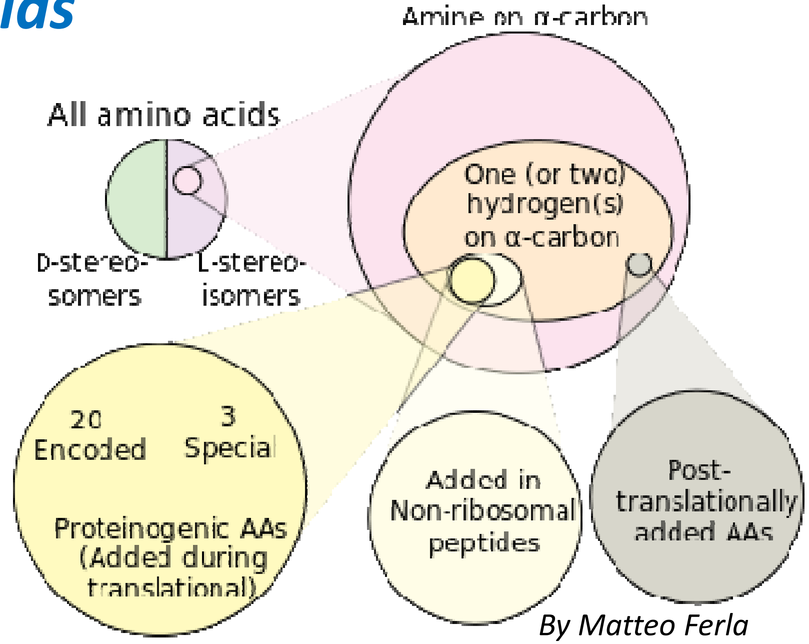


Proteinogenic aminoacids

genetically encoded

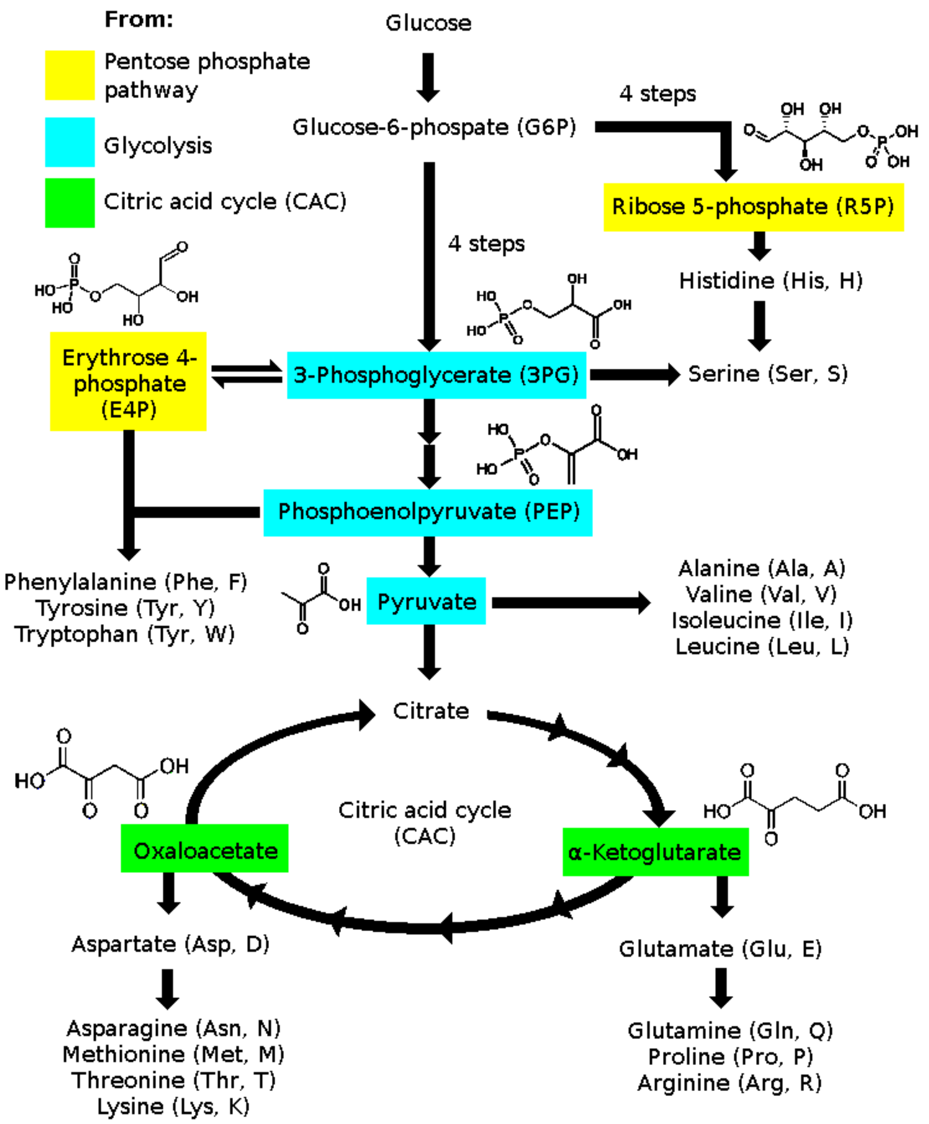






By Matteo Ferla

Biosynthesis of biogenic aminoacids



From:

🟨 Pentose phosphate pathway

🟦 Glycolysis

🟩 Citric acid cycle (CAC)

Glucose

Glucose-6-phospate (G6P)

4 steps

Ribose 5-phosphate (R5P)

Histidine (His, H)

4 steps

Erythrose 4-phosphate (E4P)

3-Phosphoglycerate (3PG)

Serine (Ser, S)

Phosphoenolpyruvate (PEP)

Phenylalanine (Phe, F)
Tyrosine (Tyr, Y)
Tryptophan (Tyr, W)

Pyruvate

Alanine (Ala, A)
Valine (Val, V)
Isoleucine (Ile, I)
Leucine (Leu, L)

Citrate

Citric acid cycle (CAC)

Oxaloacetate

α-Ketoglutarate

Aspartate (Asp, D)

Asparagine (Asn, N)
Methionine (Met, M)
Threonine (Thr, T)
Lysine (Lys, K)

Glutamate (Glu, E)

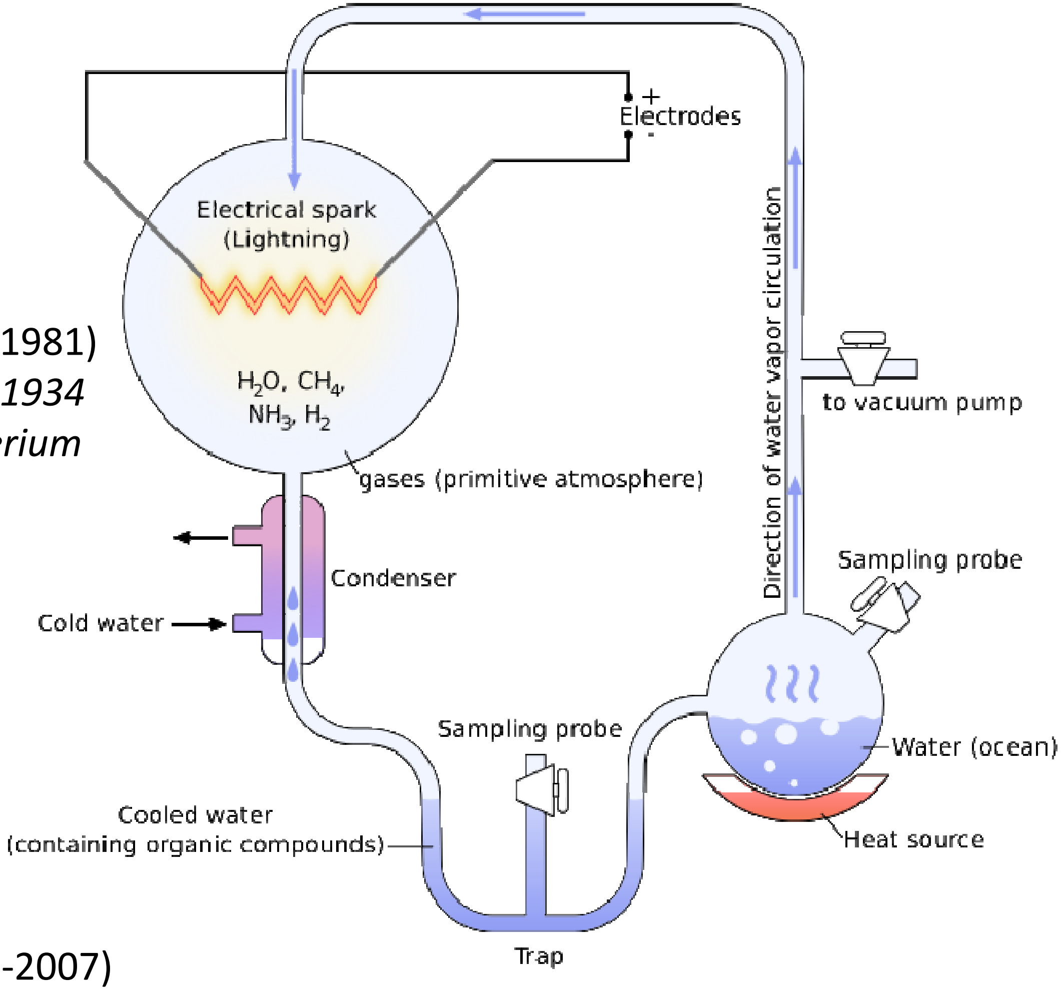
Glutamine (Gln, Q)
Proline (Pro, P)
Arginine (Arg, R)

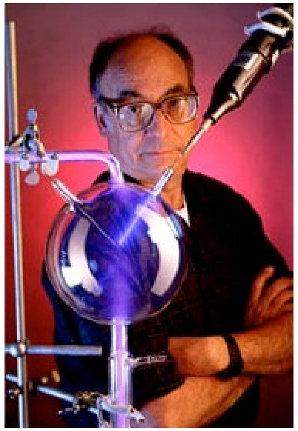
Atmosphere composition for young terrestrial planets

	Reduced	**Neutral**	**Oxic**
Carbon (C)	CH_4	CO, CO_2	CO_2
Nitrogen (N)	NH_3	N_2	N_2
Oxygen (O)	H_2O	H_2O, CO, CO_2	O_2
Hydrogen (H)	H_2, CH_4, NH_3, H_2O	H_2O	H_2O

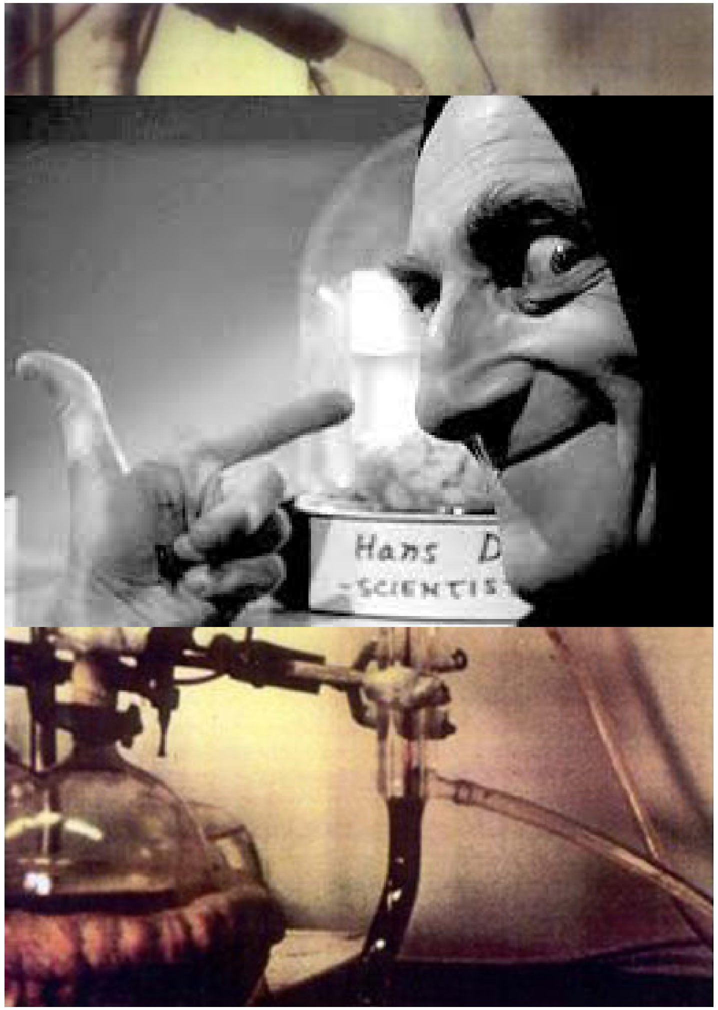
Miller-Urey experiment - 1952

Harold Urey (1893-1981)
UCSD, Nobel prize 1934
Discovery of deuterium

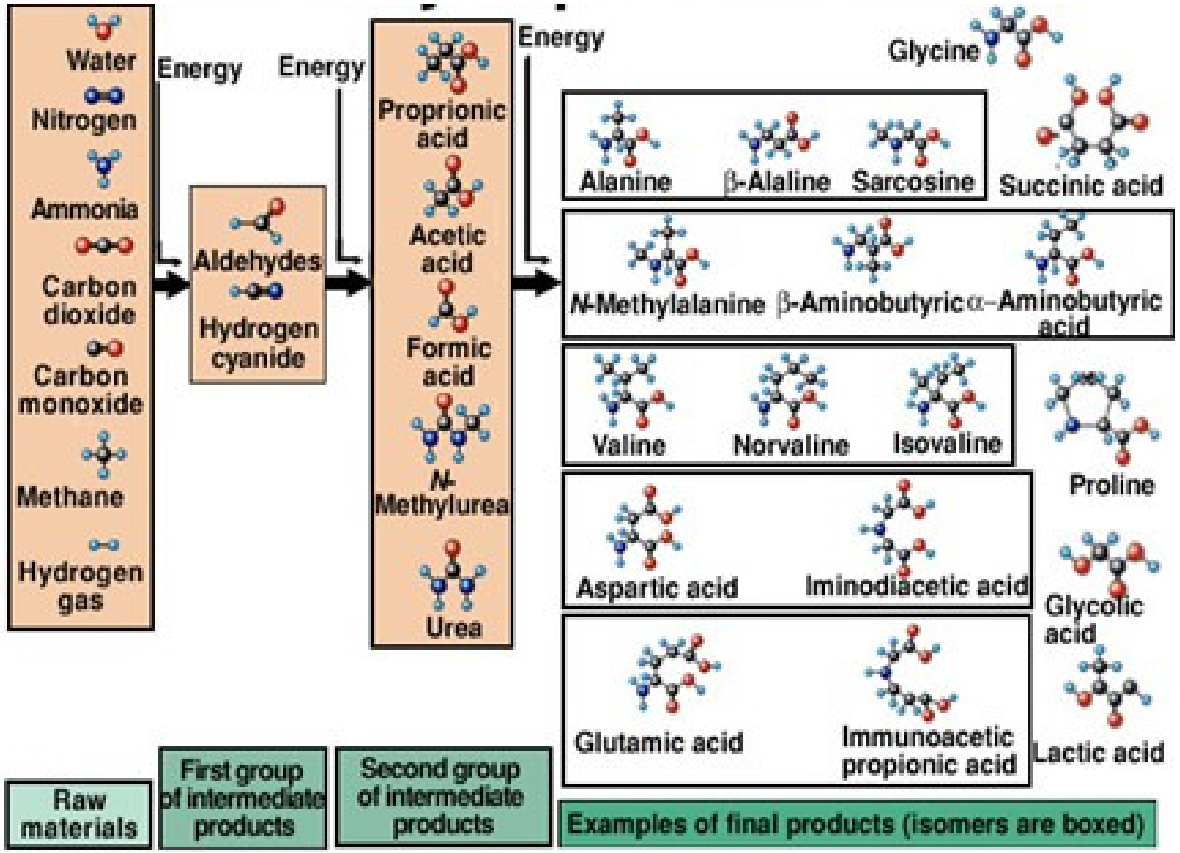




Stanley Miller (1930-2007)
UCSD San Diego, CA, USA



Products of the Miller-Urey experiment



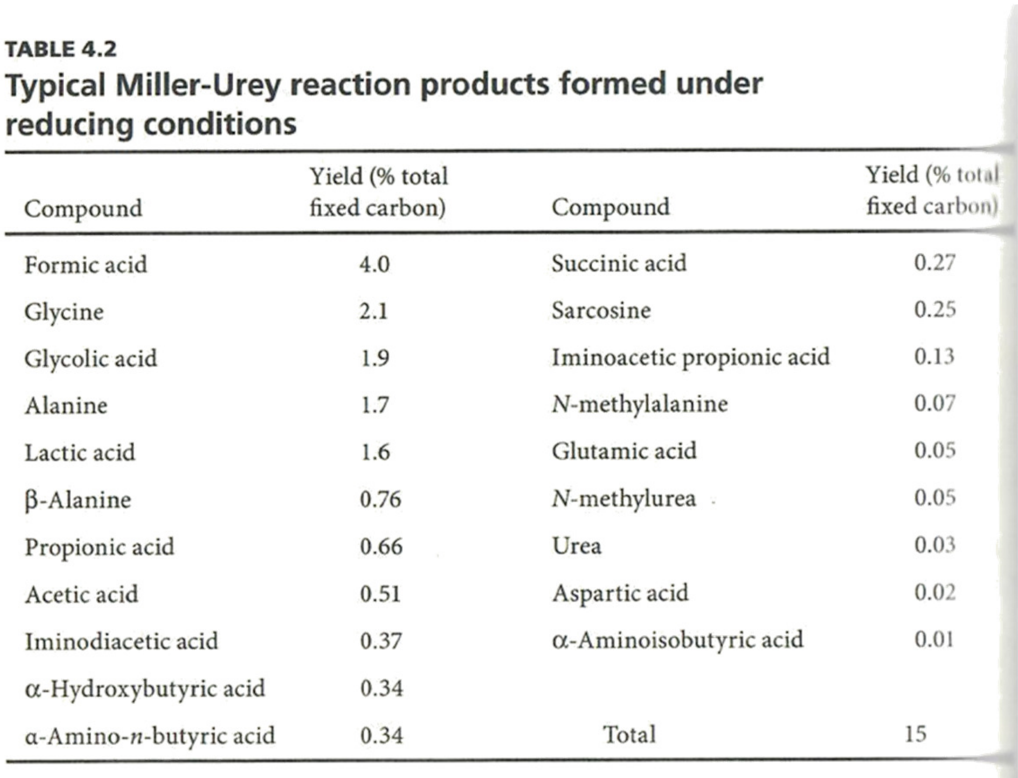


TABLE 4.2

Typical Miller-Urey reaction products formed under reducing conditions

Compound	Yield (% total fixed carbon)	Compound	Yield (% total fixed carbon)
Formic acid	4.0	Succinic acid	0.27
Glycine	2.1	Sarcosine	0.25
Glycolic acid	1.9	Iminoacetic propionic acid	0.13
Alanine	1.7	*N*-methylalanine	0.07
Lactic acid	1.6	Glutamic acid	0.05
β-Alanine	0.76	*N*-methylurea	0.05
Propionic acid	0.66	Urea	0.03
Acetic acid	0.51	Aspartic acid	0.02
Iminodiacetic acid	0.37	α-Aminoisobutyric acid	0.01
α-Hydroxybutyric acid	0.34		
α-Amino-*n*-butyric acid	0.34	Total	15

Cysteine and methionine also present,
when H_2S is added to the reaction mixture

Generation of radicals

$$H_2 \xrightarrow{\text{High-energy electrons or UV light}} 2\ H^\bullet$$

$$H_2O \longrightarrow H^\bullet + HO^\bullet$$

$$CH_4 \longrightarrow {}^\bullet CH_3 + {}^\bullet H$$

Radical reactions

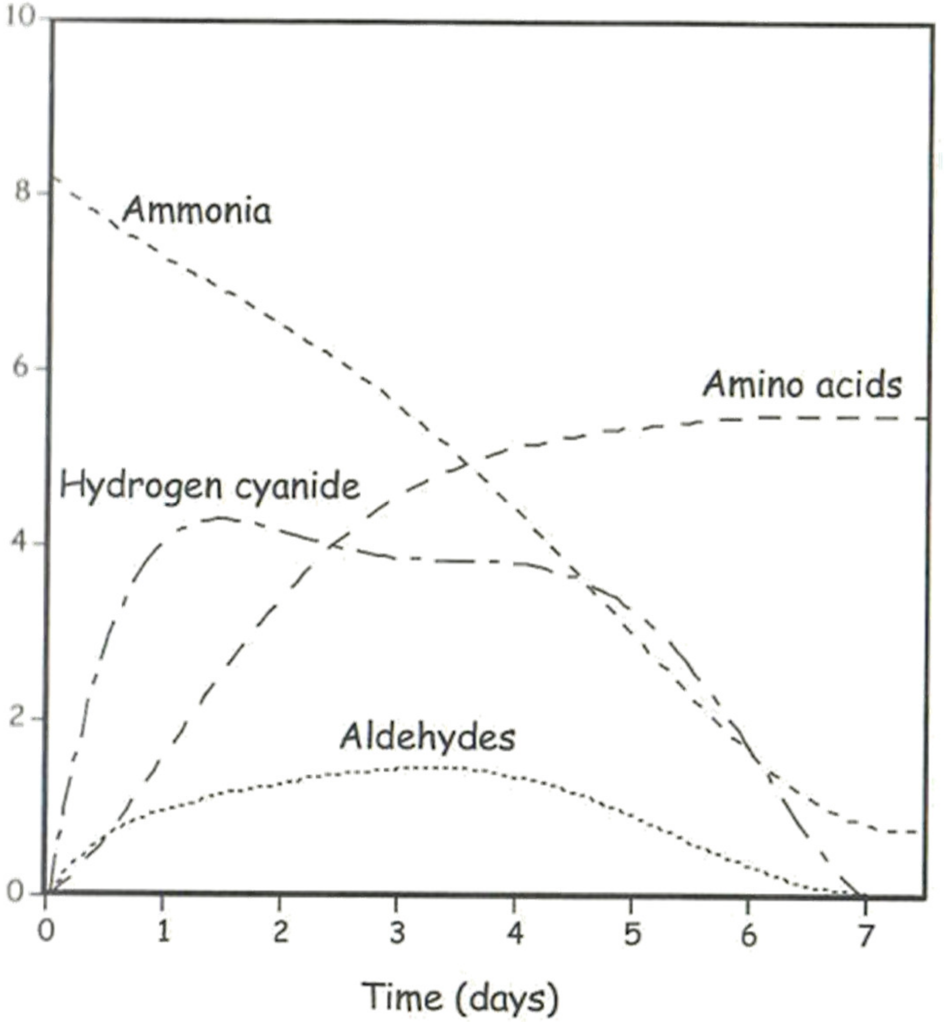
$${}^\bullet CH_3 + H_2O \longrightarrow H_3C{-}O^\bullet + H_2$$

$$H_3C{-}O^\bullet + H^\bullet \longrightarrow H_2C{=}O + H_2$$

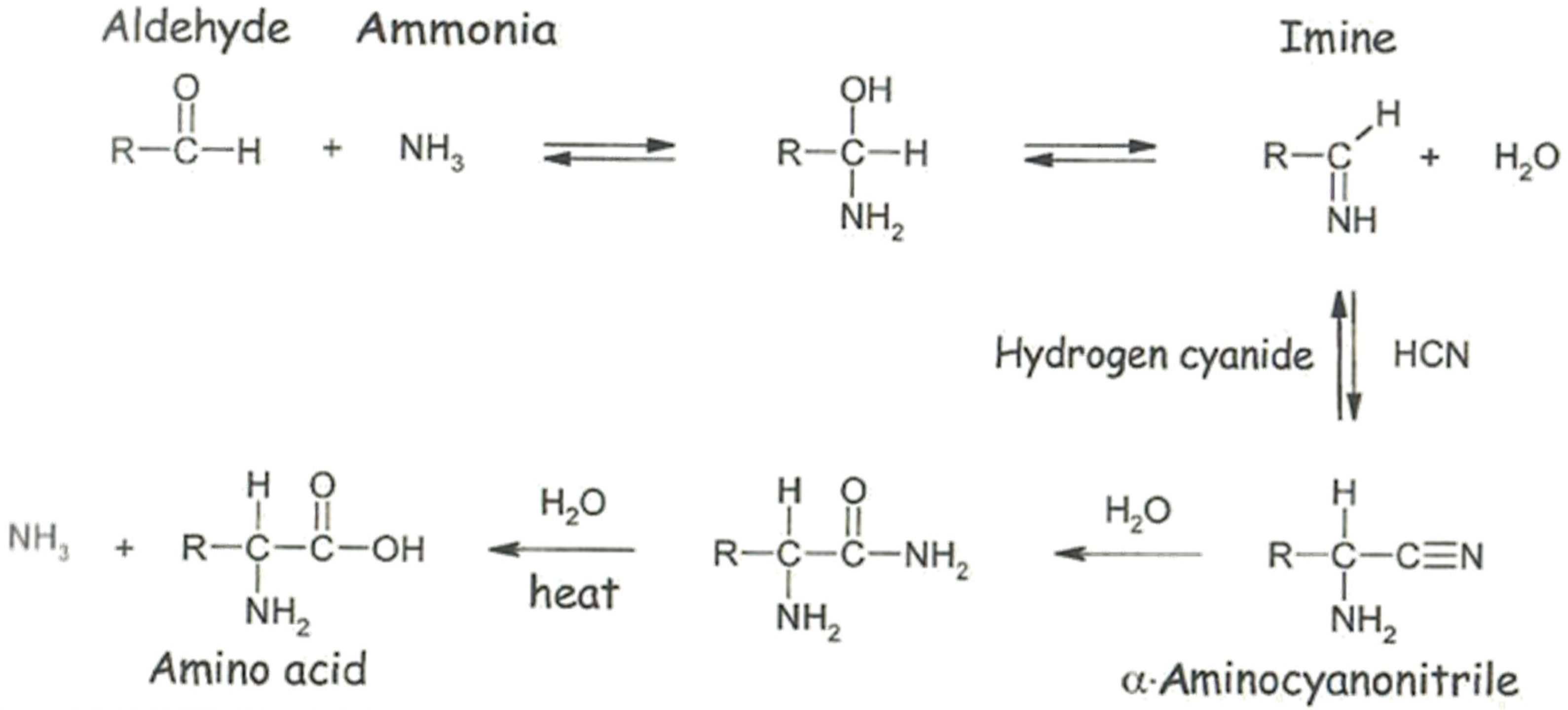
Formaldehyde

$${}^\bullet CH_3 + {}^\bullet CH_3 \longrightarrow H_3C{-}CH_3$$

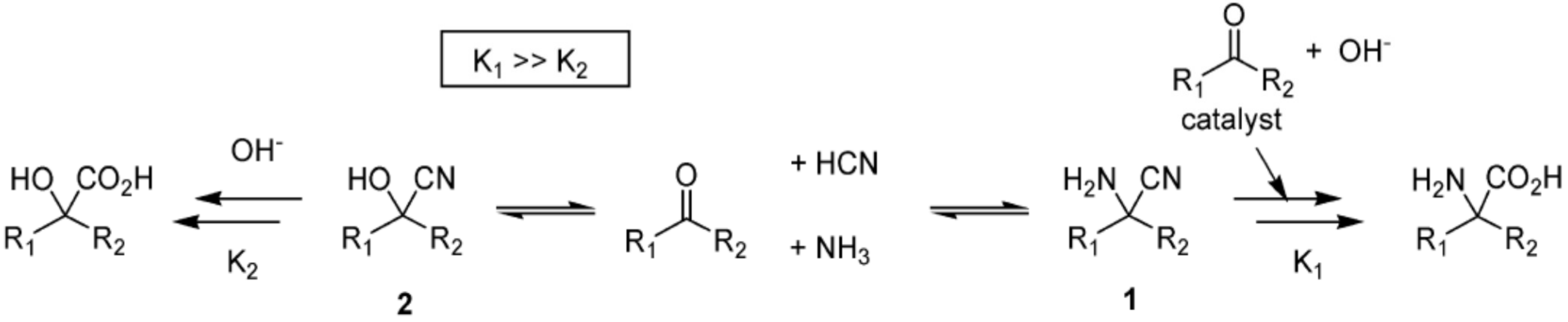
Ethane



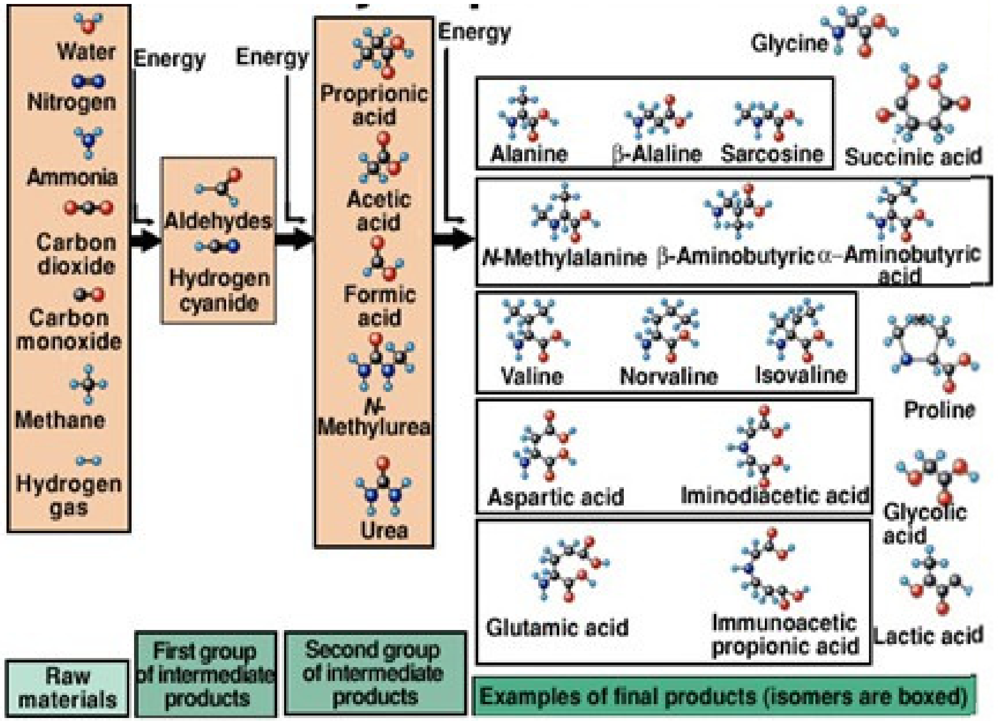
Strecker reaction



Scheme 1. Synthesis of α-Amino Acids through the Strecker Reaction



α-Aminoacid production in the Miller-Urey experiment



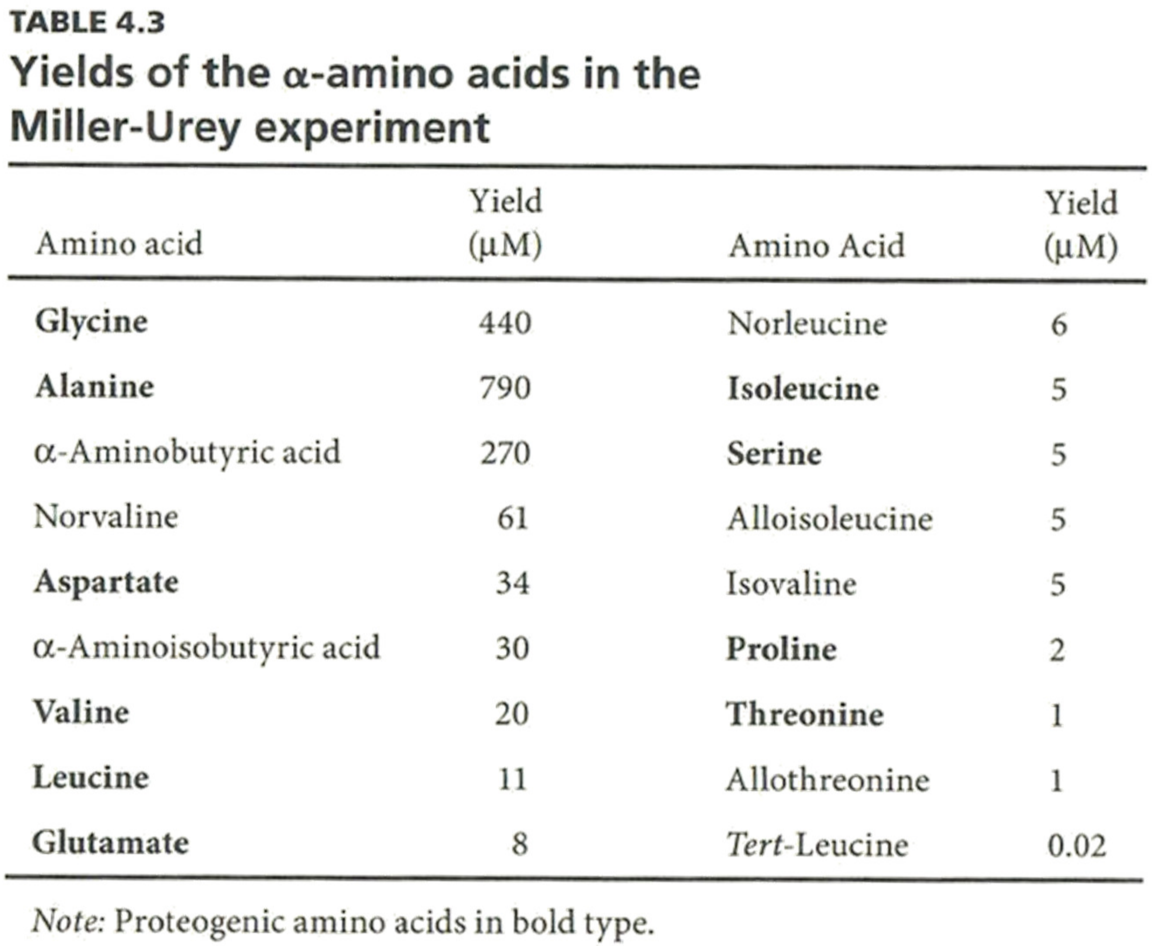


TABLE 4.3

Yields of the α-amino acids in the Miller-Urey experiment

Amino acid	Yield (μM)	Amino Acid	Yield (μM)
Glycine	440	Norleucine	6
Alanine	790	**Isoleucine**	5
α-Aminobutyric acid	270	**Serine**	5
Norvaline	61	Alloisoleucine	5
Aspartate	34	Isovaline	5
α-Aminoisobutyric acid	30	**Proline**	2
Valine	20	**Threonine**	1
Leucine	11	Allothreonine	1
Glutamate	8	*Tert*-Leucine	0.02

Note: Proteogenic amino acids in bold type.

Aminoacid production under hydrothermal conditions

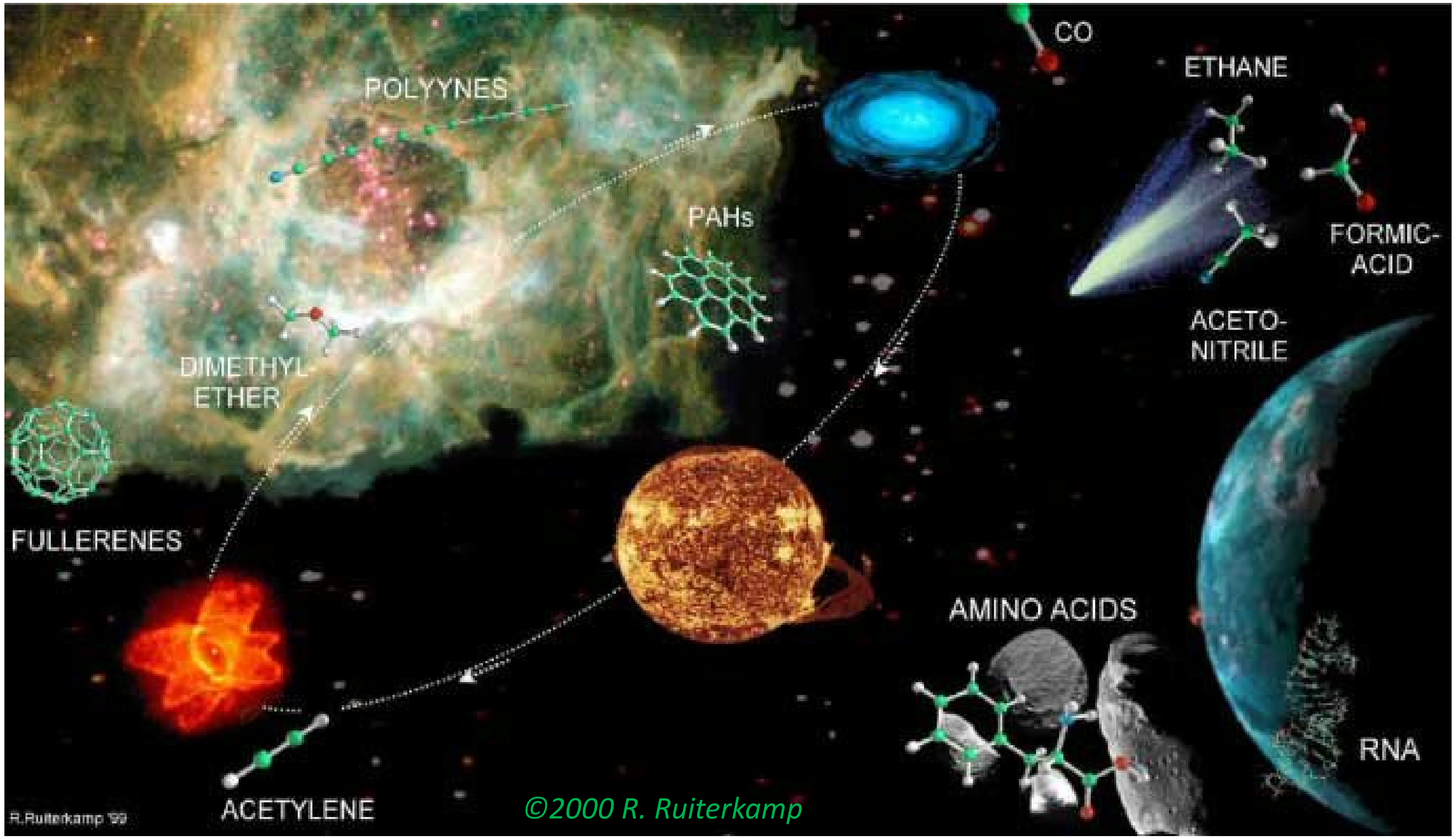
$Ni(OH)_2/KCN/CO$ in alkaline aqueous conditions (80-120^{0}C) → α-amino and α-hydroxyacids

Huber, C.; Wächtershäuser, G. *Science* **2006**, *314*, 630–632

$Ca(OH)_2/NiSO_4/KCN/CO$ in alkaline (pH 9.1-12.9) aqueous conditions (145-280^{0}C) → α-amino and α-hydroxyacids (higher yields): glycine, alanine, serine, glycolate, lactate, glycerate

Huber, C.; Eisenreich, H.; Wächtershäuser, G. *Tetrahedron Lett.* **2010**, *51*, 1069-1071

Extraterrestrial origin of biomolecules



Extraterrestrial origin of biomolecules

Murchison meteorite
chondrite

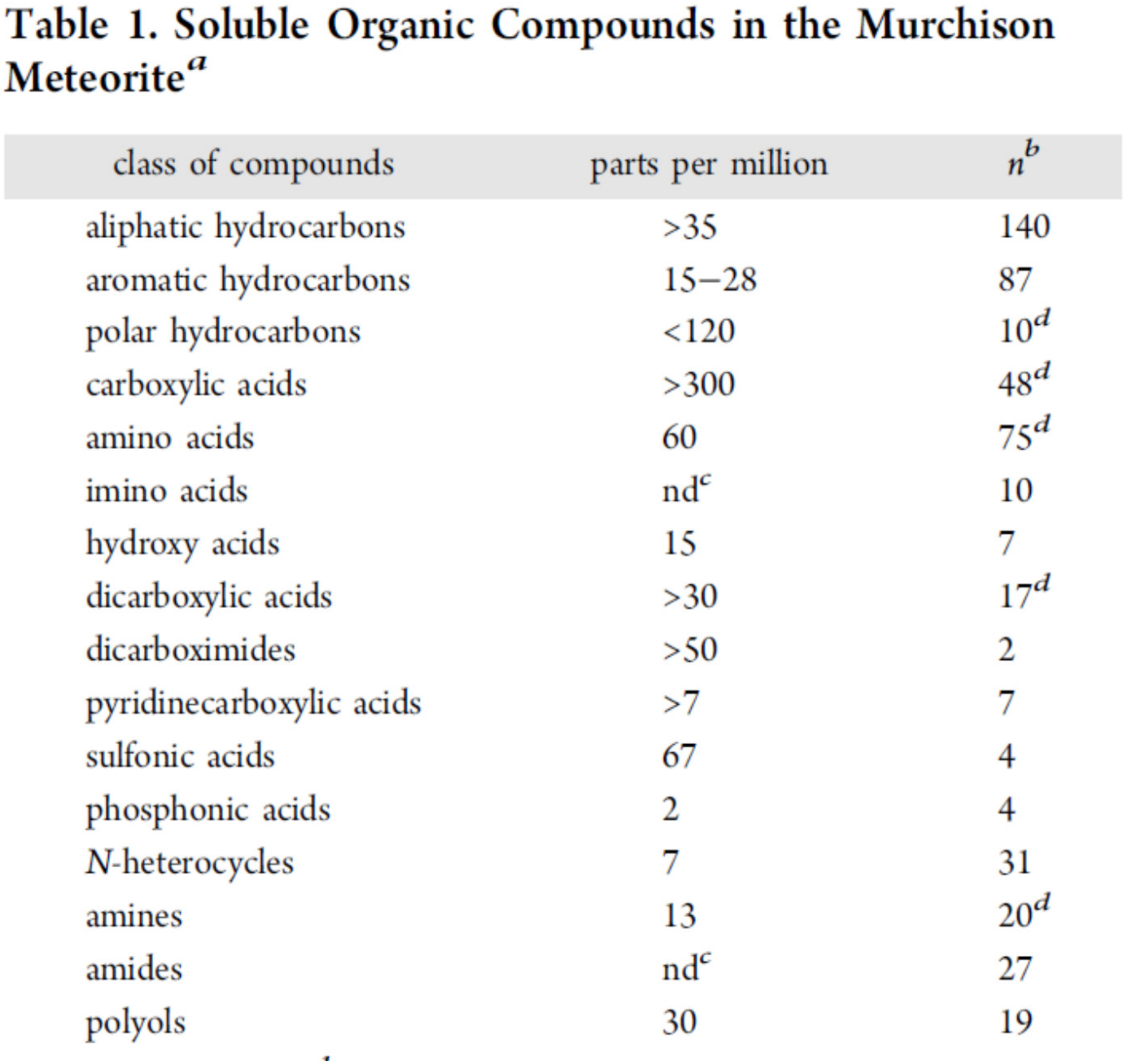
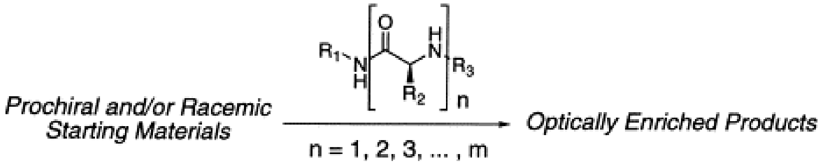


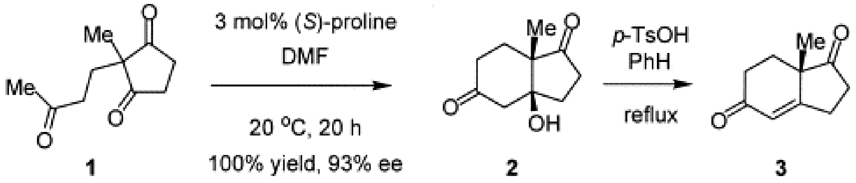
Table 1. Soluble Organic Compounds in the Murchison Meteorite[a]

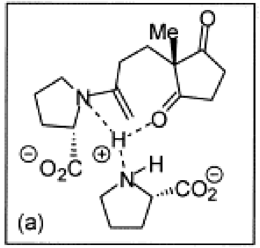
class of compounds	parts per million	n[b]
aliphatic hydrocarbons	>35	140
aromatic hydrocarbons	15–28	87
polar hydrocarbons	<120	10[d]
carboxylic acids	>300	48[d]
amino acids	60	75[d]
imino acids	nd[c]	10
hydroxy acids	15	7
dicarboxylic acids	>30	17[d]
dicarboximides	>50	2
pyridinecarboxylic acids	>7	7
sulfonic acids	67	4
phosphonic acids	2	4
N-heterocycles	7	31
amines	13	20[d]
amides	nd[c]	27
polyols	30	19

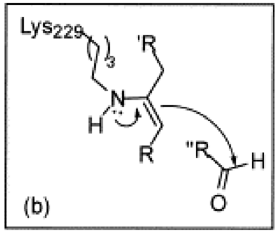
Catalytic properties of aminoacids - organocatalysis



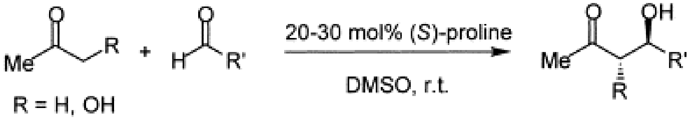
Robinson annulation



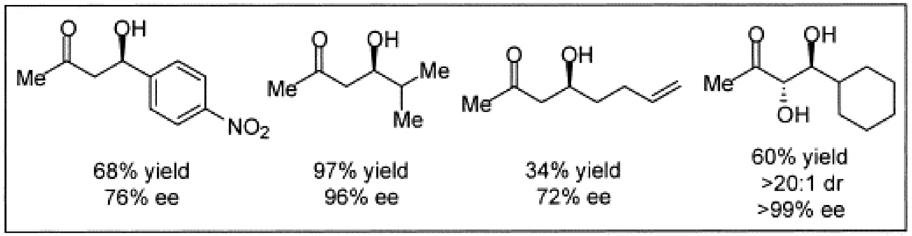


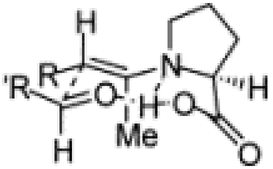


aldol reaction



R = H, OH
20 vol%

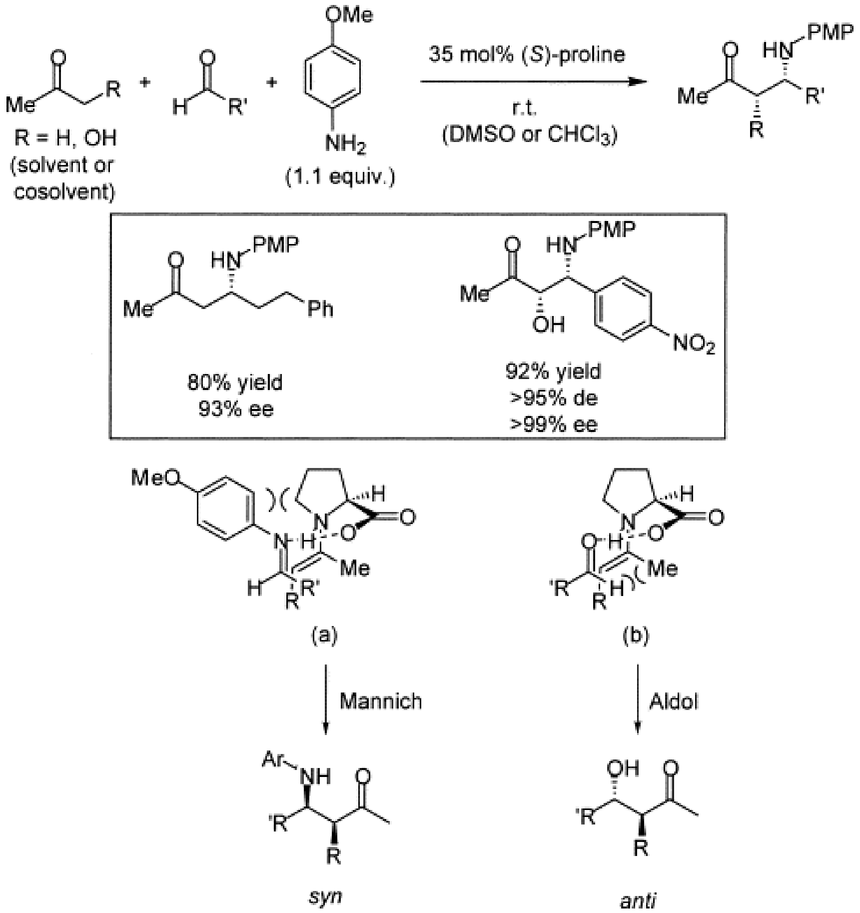




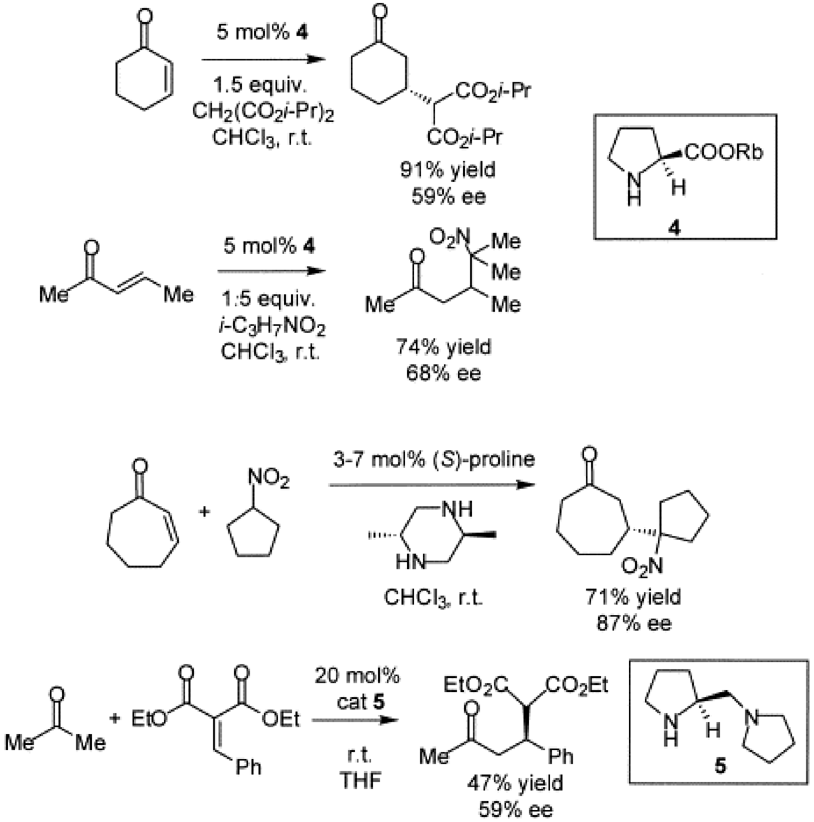
Jarvo, E. R., Miller, S. J. *Tetrahedron* **2002**, *58(13)*, 2481-2495.

Catalytic properties of aminoacids - organocatalysis

Mannich reaction



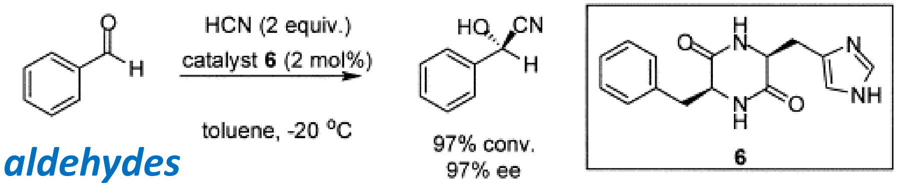
Michael addition



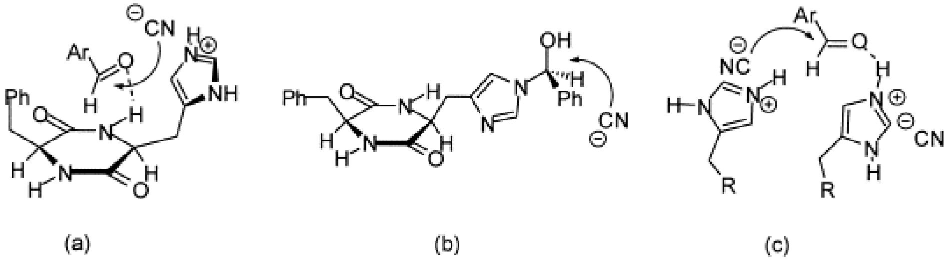
Jarvo, E. R., Miller, S. J. *Tetrahedron* **2002**, *58(13)*, 2481-2495.

Catalytic properties of aminoacids - organocatalysis

Hydrocyanation



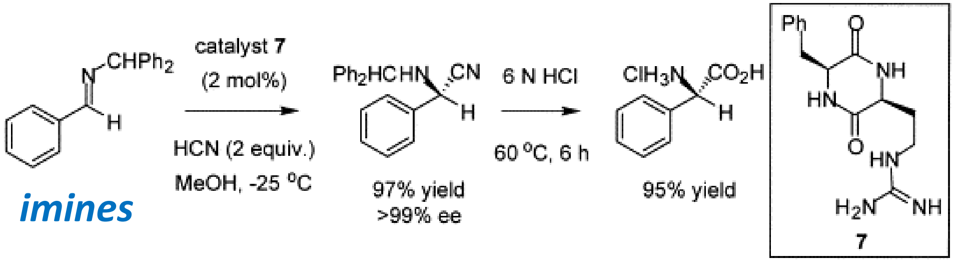
aldehydes



(a)

(b)

(c)

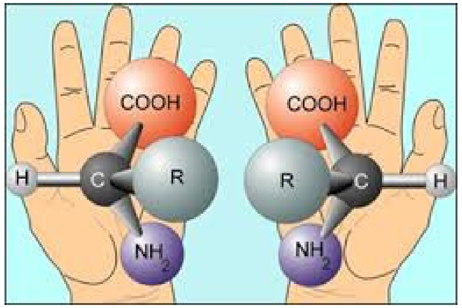


imines

assymetric Strecker reaction!!!

Jarvo, E. R., Miller, S. J. *Tetrahedron* **2002**, *58(13)*, 2481-2495.

The origins of homochirality



Currently known biopolymers are homochiral

Structural propensity and catalytic activity strongly depends on the enantopurity
→ Homochirality must have been involved early in the process of life formation
→ Chiral monomers could be only partially enantioenriched

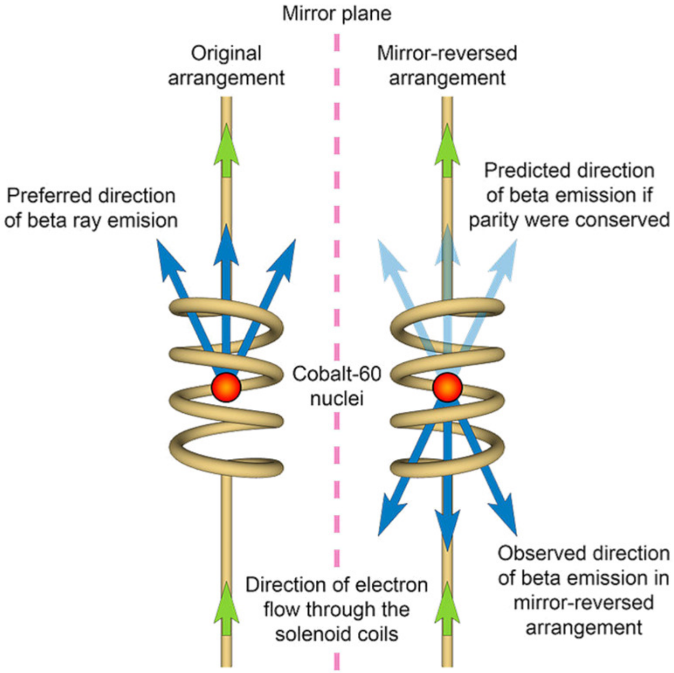
General cause of homochirality:
the initial symmetry breaking + subsequent assymetry amplification:

- ***The pairity violation***
- ***Stochastic symmetry disturbances***

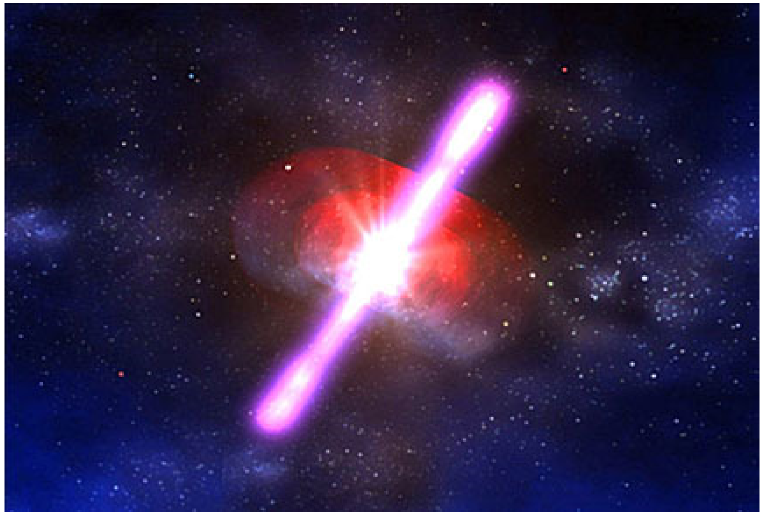
Electroweak interactions and the pairity violation principle cause *L*-aminoacids and *D*-sugars to be SLIGHTLY MORE STABLE than their enantiomers

Differentiation in left and right handedness is inherent property of weak interactions

Chien-Shiung Wu (1956) – experiment on ^{60}Co decay

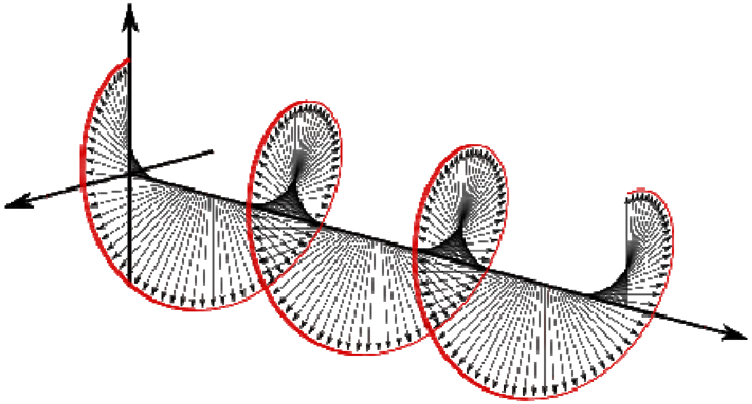


The origins of homochirality

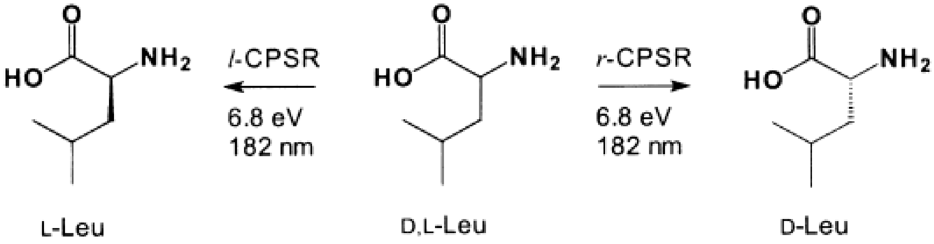


K. Wiersema et al., *Nature* **509** 201, 2014

Circularly polarized light (CPL) from gamma ray bursts



Small enantiomeric excess can be obtained by enantioselective degradation of aminoacids with CPL

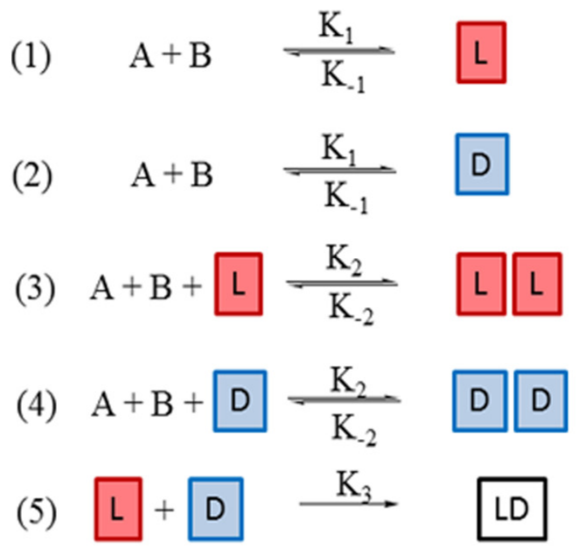


Up to 2.6% ee

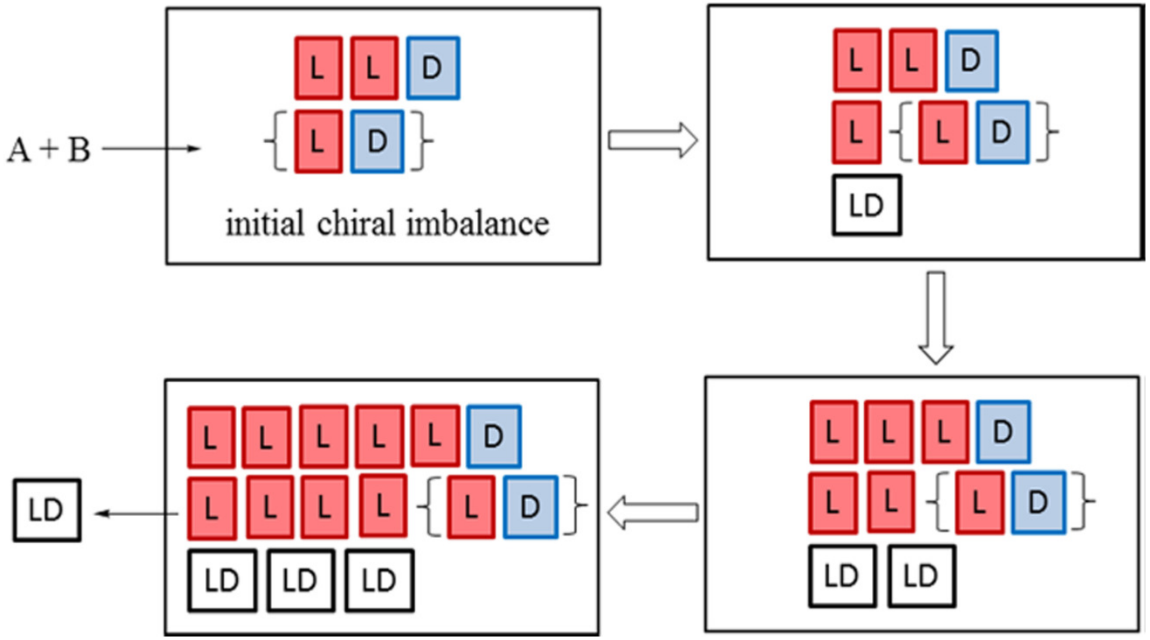
Meierhenrich, U. J.; Nahon, L.; Alcaraz, C.; Bredehoft, J. H.; Hoffmann, S. V.; Barbier, B.; Brack, A. Angew. Chem., Int. Ed. 2005, 44, 5630

Stochastic induction of assymetry – Frank model

Reactions (3) and (4) are autocatalytic

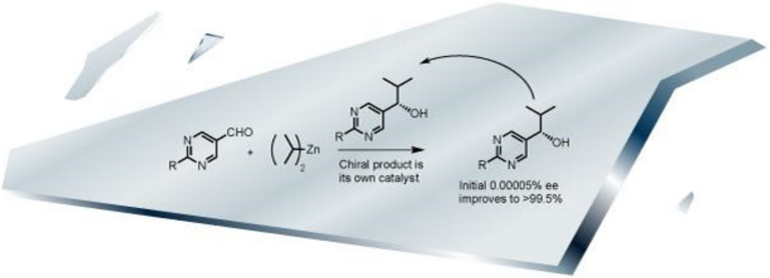


Open flux reactor in non-equilibrium stationary state



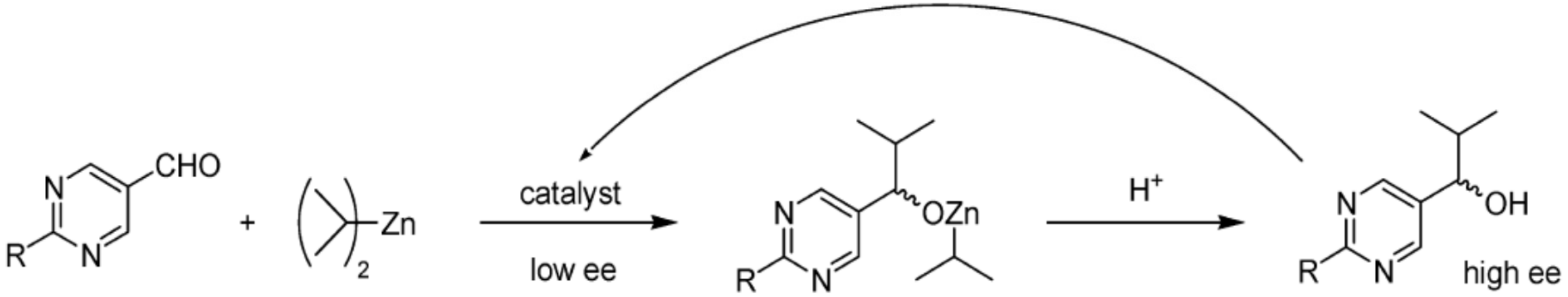
If a chiral dissipative structure catalyzes its own formation and inhibits formation of the opposite enantiomer, any stochastic symmetry breaking in the system will be amplified

autocatalytic Soai reaction – extreme chirality amplification



Organometallic reaction
- NOT prebiotic

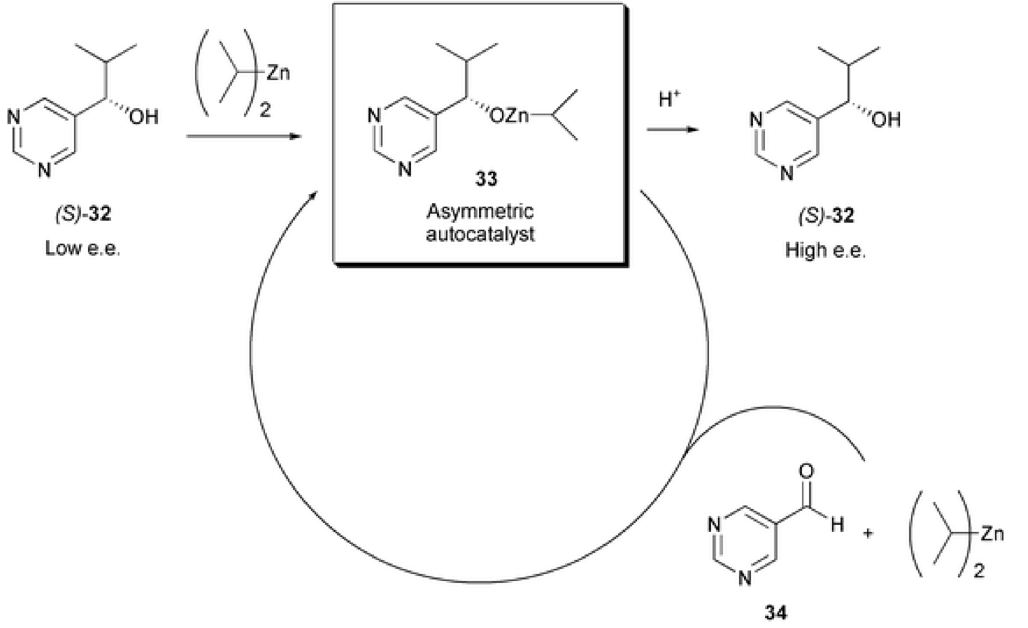
Scheme 9. Soai Autocatalytic Reaction

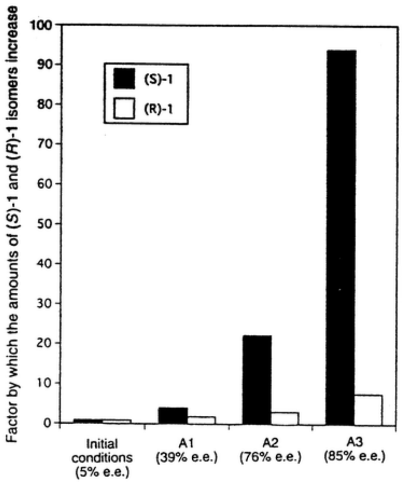


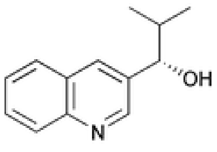
CPL
Aminoacids
$^{12}C/^{13}C$-enantiomers!

Extremelly sensitive
chirality detector

autocatalytic Soai reaction – extreme chirality amplification







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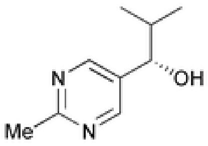
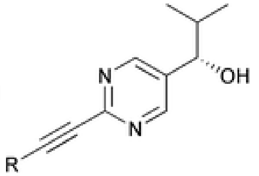


36



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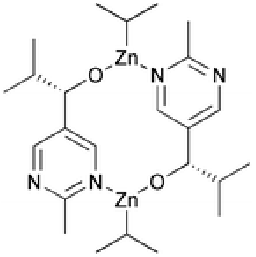
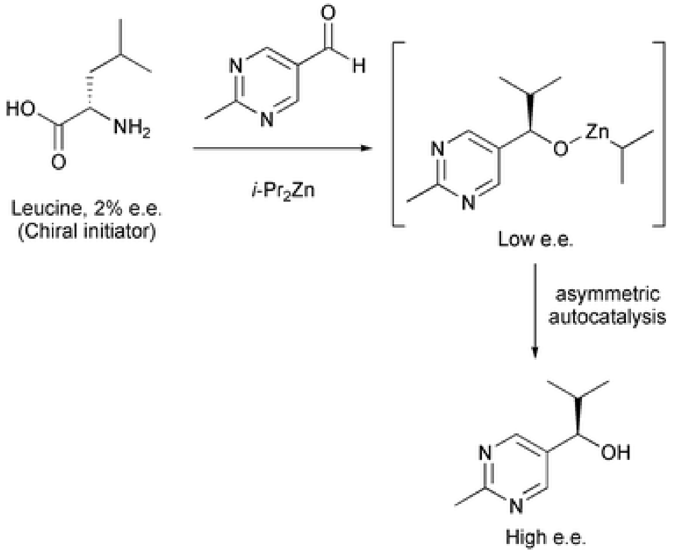
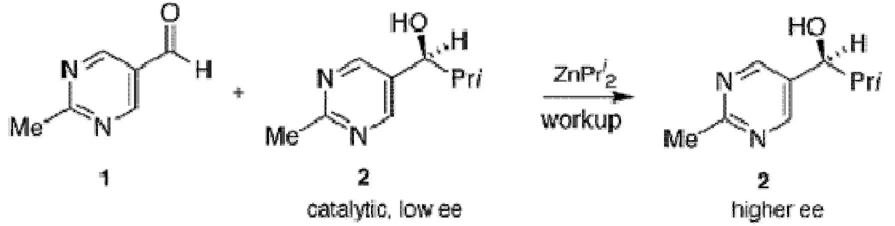
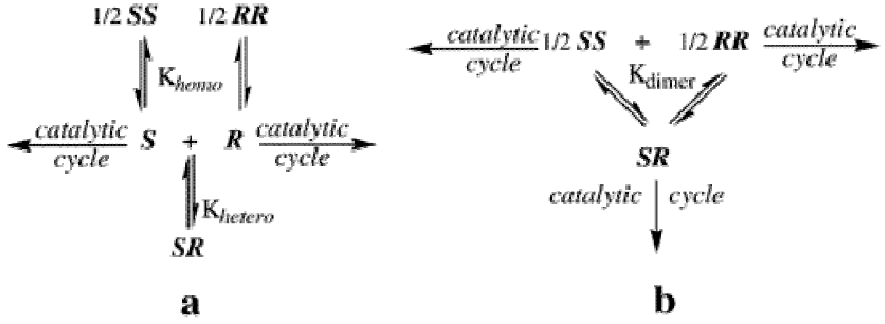


38



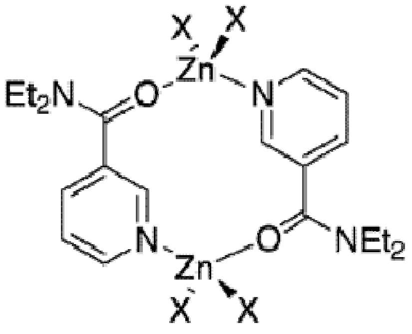
autocatalytic Soai reaction – extreme chirality amplification



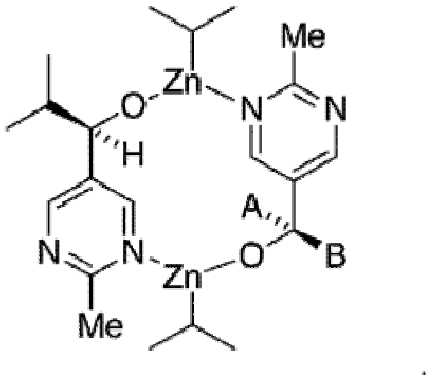


$$g = \frac{\text{activity of } [\boldsymbol{SR}]}{\text{activity of } [\boldsymbol{RR}]} \quad \beta = \frac{[\boldsymbol{SR}]}{[\boldsymbol{RR}] + [\boldsymbol{SS}]} \quad K' = \frac{([\boldsymbol{SR}])^2}{([\boldsymbol{RR}])([\boldsymbol{SS}])}$$

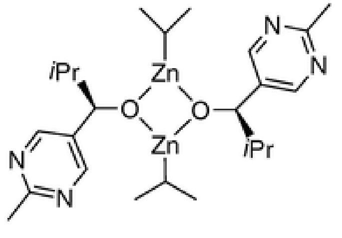
$$\mathrm{ee}_{\mathrm{d}x} = \frac{[\boldsymbol{RR}] - [\boldsymbol{SS}]}{[\boldsymbol{RR}] + [\boldsymbol{SS}] + g[\boldsymbol{SR}]} \quad \mathrm{ee}_{x+\mathrm{d}x} = \frac{\mathrm{ee}_x[\mathbf{2}] + \mathrm{ee}_{\mathrm{d}x}\frac{\mathrm{d}x}{2}[\mathbf{1}]_0}{[\mathbf{2}] + \frac{\mathrm{d}x}{2}[\mathbf{1}]_0} \qquad (2)$$



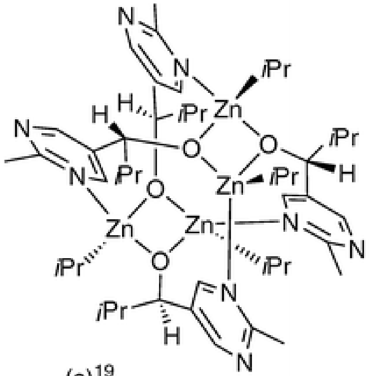
7a, X = Cl,
7b, X = SCN



***(S,S)*-8** A = H, B = Pr^i
***(R,S)*-8** A = Pr^i, B = H



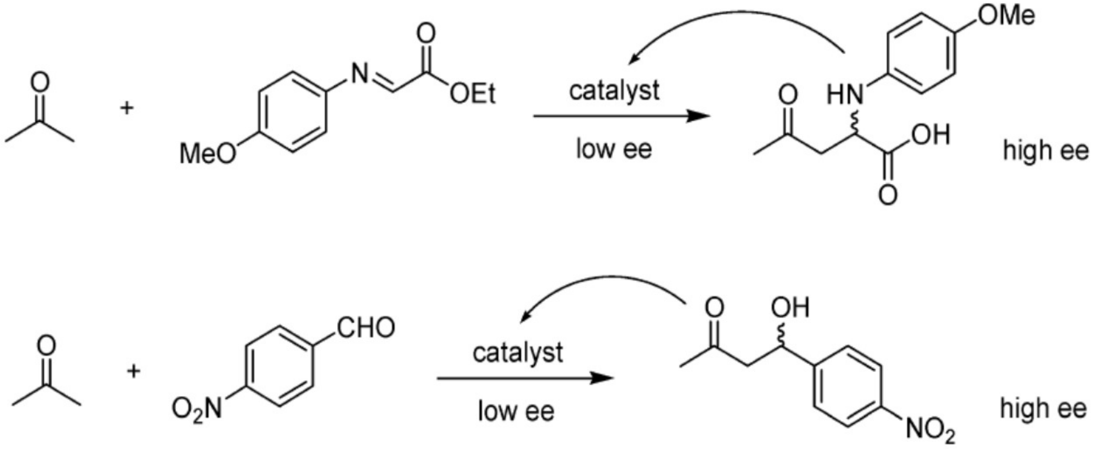
(b)[19]



(c)[19]

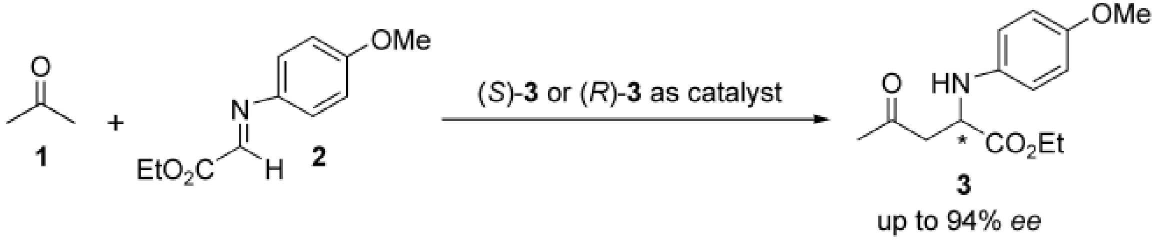
autocatalytic organic reactions

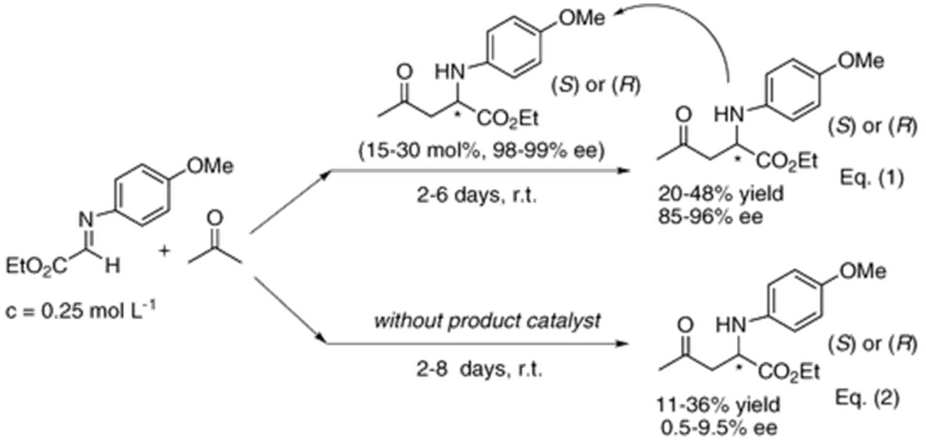
Scheme 10. Mannich and Aldol Autocatalytic Reactions[a]

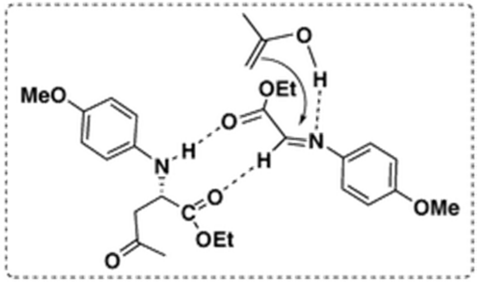


Meaningful transformations for the prebiotic syntheses of aminoacids and sugars

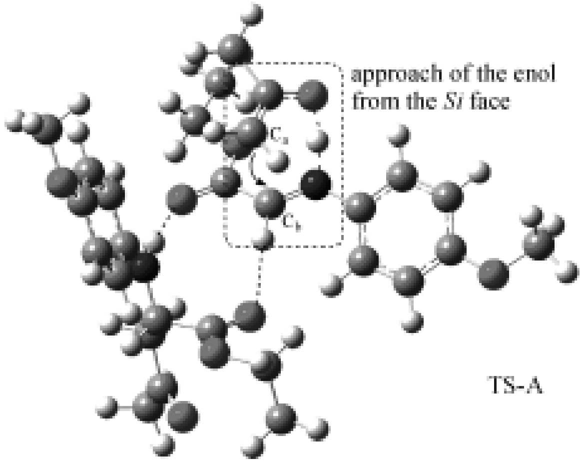
autocatalytic organic reactions

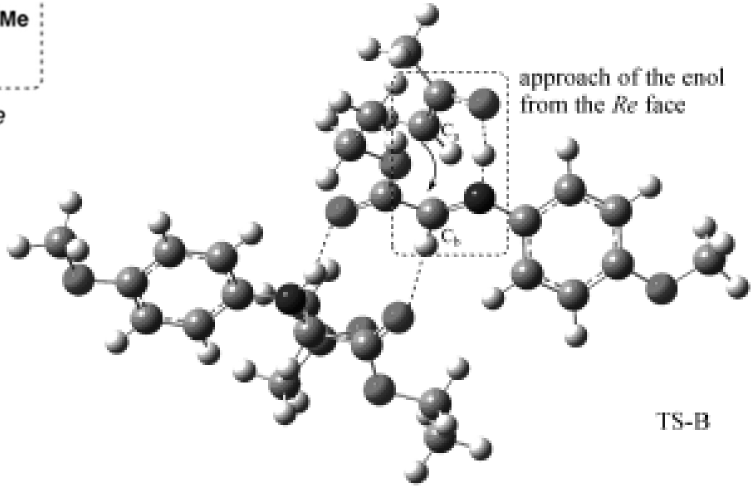






proposed transition-state structure





Organocatalysis – the origin of homochirality

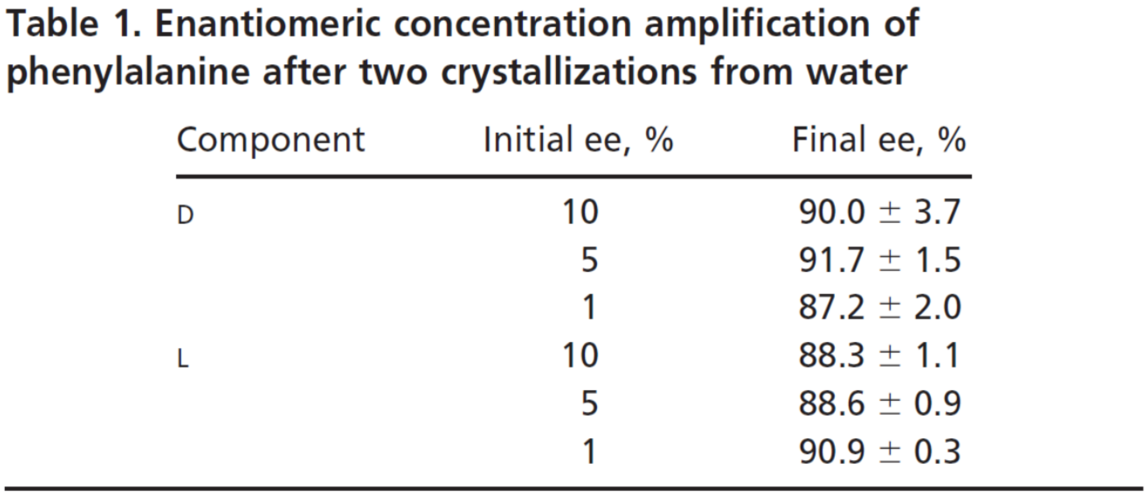
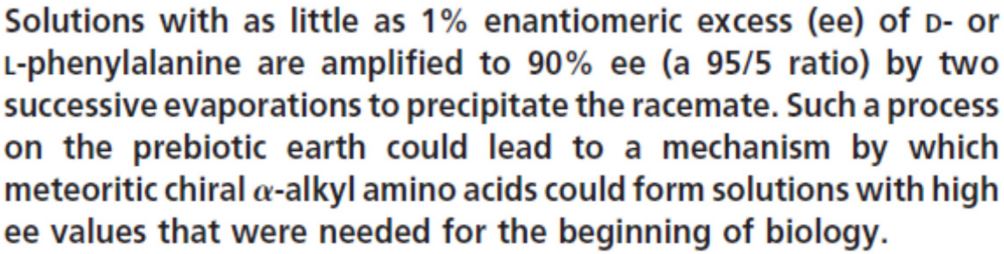


Table 1. Enantiomeric concentration amplification of phenylalanine after two crystallizations from water

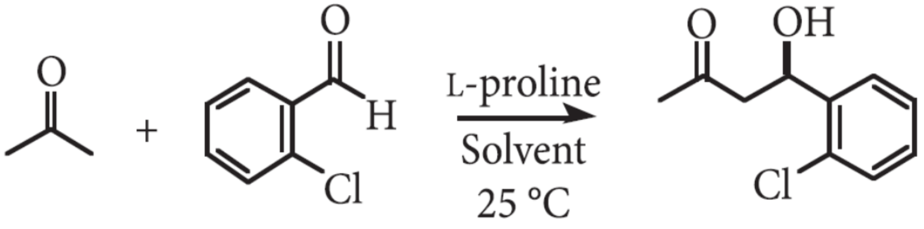
Component	Initial ee, %	Final ee, %
D	10	90.0 ± 3.7
	5	91.7 ± 1.5
	1	87.2 ± 2.0
L	10	88.3 ± 1.1
	5	88.6 ± 0.9
	1	90.9 ± 0.3

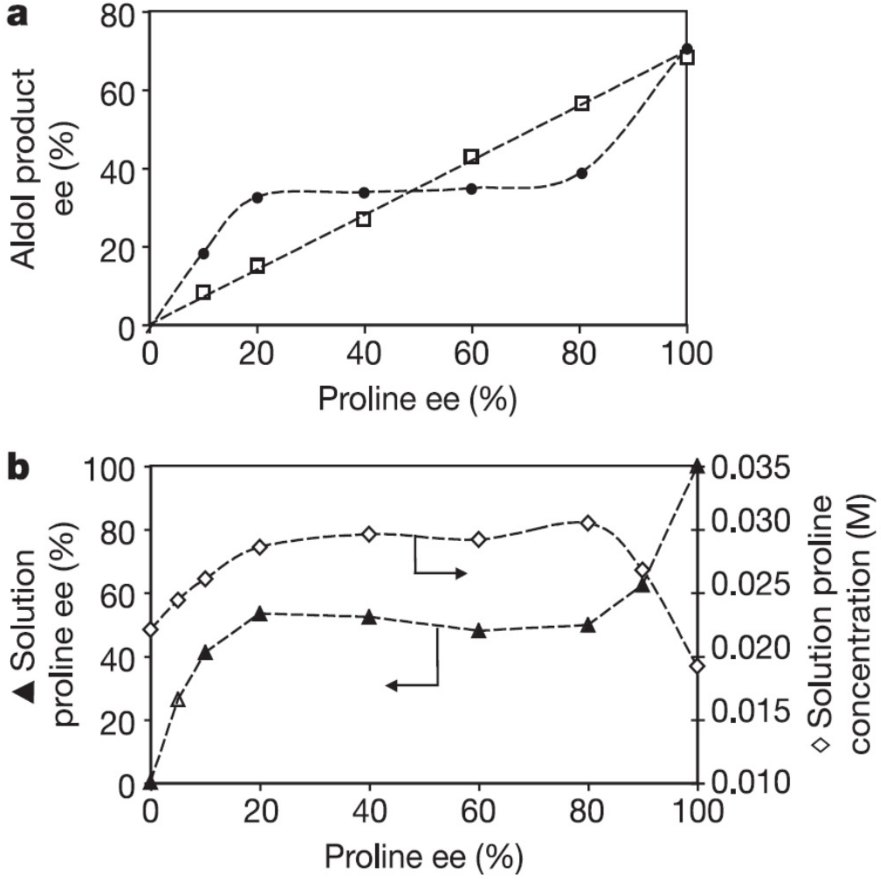


Solutions with as little as 1% enantiomeric excess (ee) of D- or L-phenylalanine are amplified to 90% ee (a 95/5 ratio) by two successive evaporations to precipitate the racemate. Such a process on the prebiotic earth could lead to a mechanism by which meteoritic chiral α-alkyl amino acids could form solutions with high ee values that were needed for the beginning of biology.

Breslow, R., Levine, M. Proc. Natl. Acad. Sci. USA **2006,** *103(35),* 12979-12980

Chirality amplification in biphasic systems





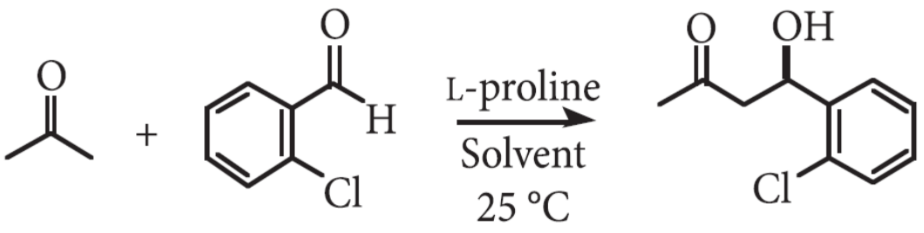
Reaction and solution behaviour as a function of the overall proline enantiomeric excess.

a, Product enantiomeric excess versus proline enantiomeric excess for the aldol reaction of equation

b, Solution proline enantiomeric excess (left axis, triangles) and solution proline concentration (right axis, diamonds) as a function of the overall enantiomeric excess for proline at 0.1 M

Klussmann, M., et al. Nature **2006,** *441,* 621-623

Chirality amplification in biphasic systems



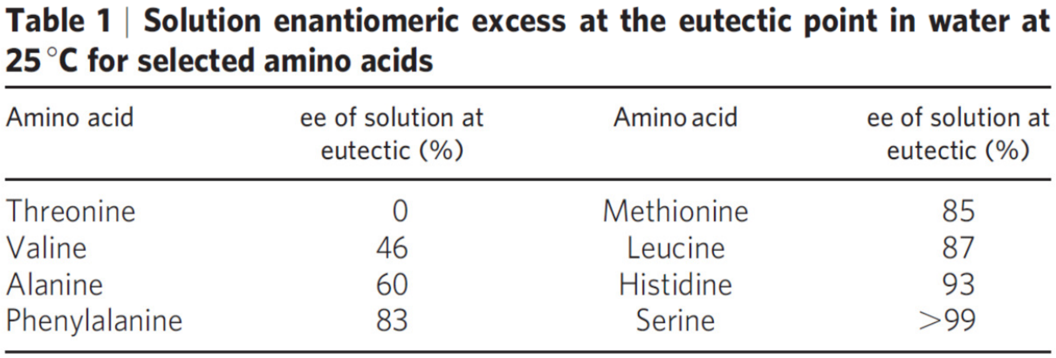
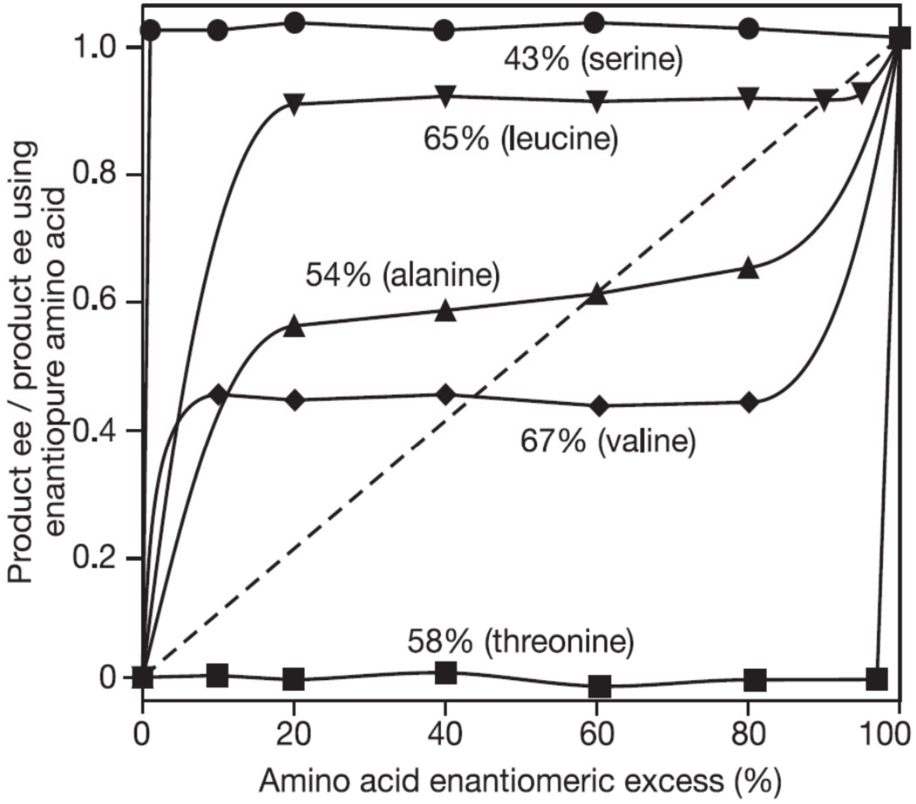


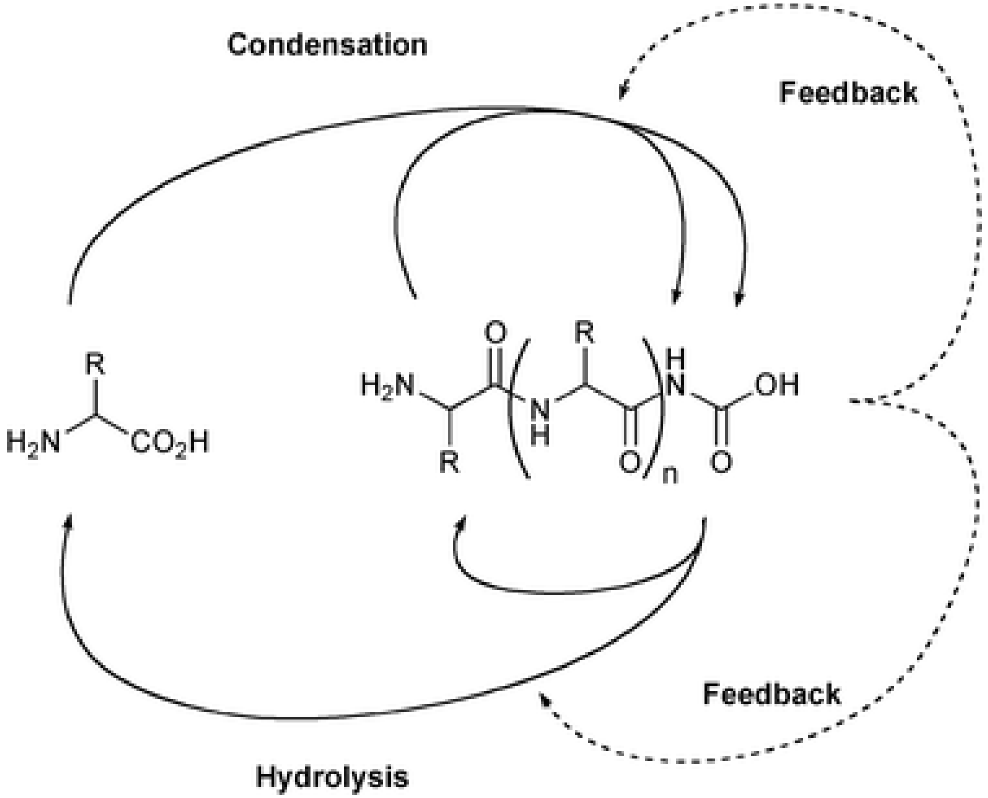
Table 1 | Solution enantiomeric excess at the eutectic point in water at 25 °C for selected amino acids

Amino acid	ee of solution at eutectic (%)	Amino acid	ee of solution at eutectic (%)
Threonine	0	Methionine	85
Valine	46	Leucine	87
Alanine	60	Histidine	93
Phenylalanine	83	Serine	>99

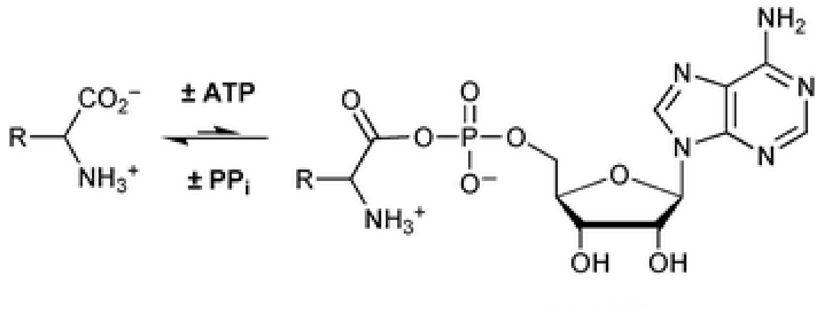


Klussmann, M., et al. Nature **2006,** *441*, 621-623

Condensation of aminoacids into peptides

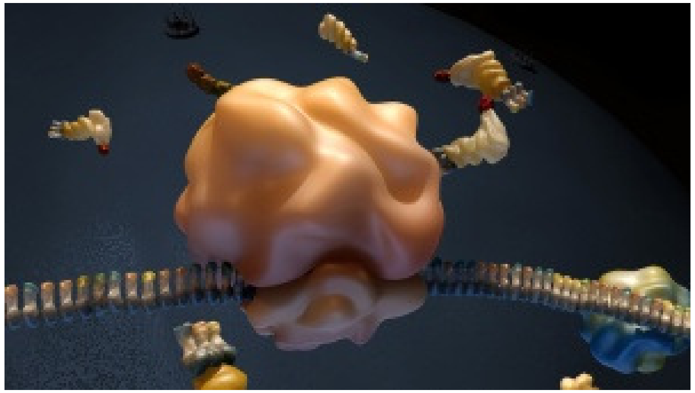


Biochemical condensation of aminoacids into peptides

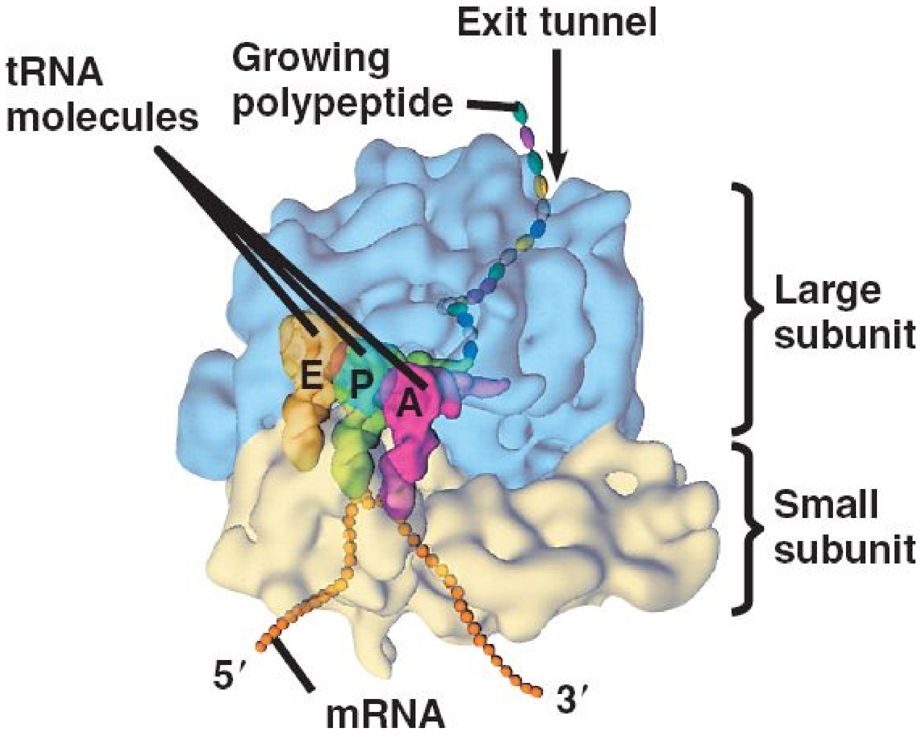


AA-AMP

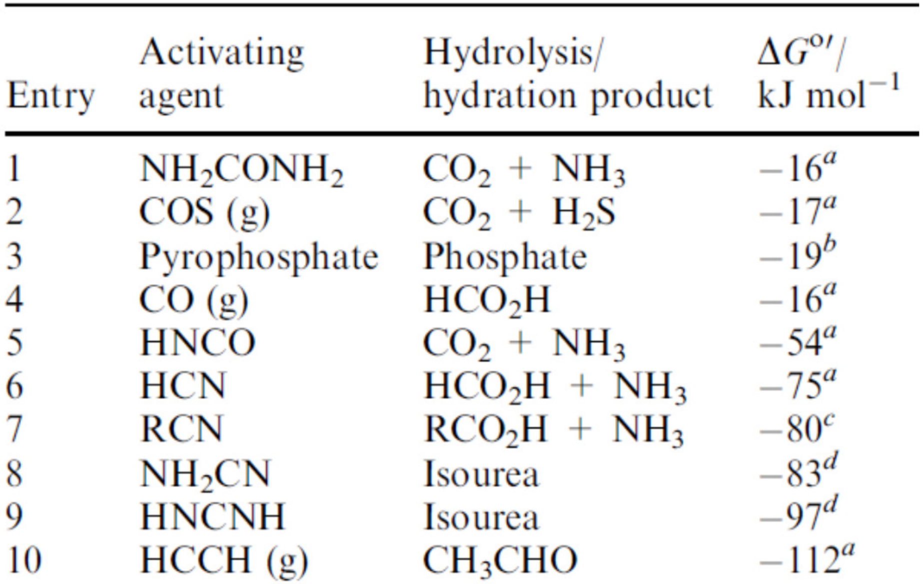
$$\text{AA-AMP} \xrightarrow{+\text{ tRNA}} \text{AA-tRNA} \xrightarrow{\text{Ribosome}} \text{Peptides}$$



Nature Publishing Group, www.nature.com/nrg/multimedia

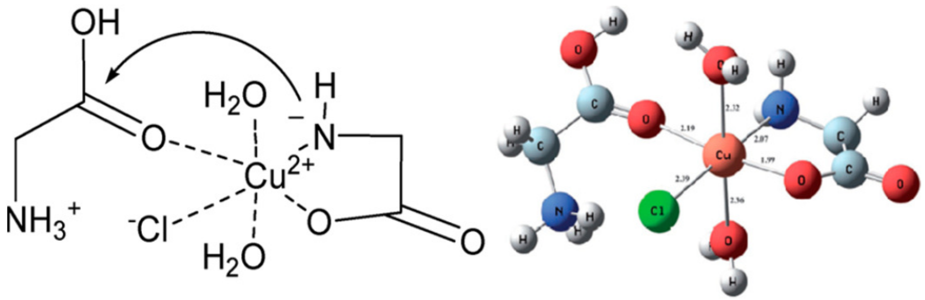


Prebiotically relevant peptide condensation agents



Entry	Activating agent	Hydrolysis/ hydration product	$\Delta G^{o\prime}$/ kJ mol^{-1}
1	NH_2CONH_2	CO_2 + NH_3	-16^a
2	COS (g)	CO_2 + H_2S	-17^a
3	Pyrophosphate	Phosphate	-19^b
4	CO (g)	HCO_2H	-16^a
5	HNCO	CO_2 + NH_3	-54^a
6	HCN	HCO_2H + NH_3	-75^a
7	RCN	RCO_2H + NH_3	-80^c
8	NH_2CN	Isourea	-83^d
9	HNCNH	Isourea	-97^d
10	HCCH (g)	CH_3CHO	-112^a

Danger, G.; Plasson, R.; Pascal, R. *Chem. Soc. Rev.* **2012**, *41*, 5416.

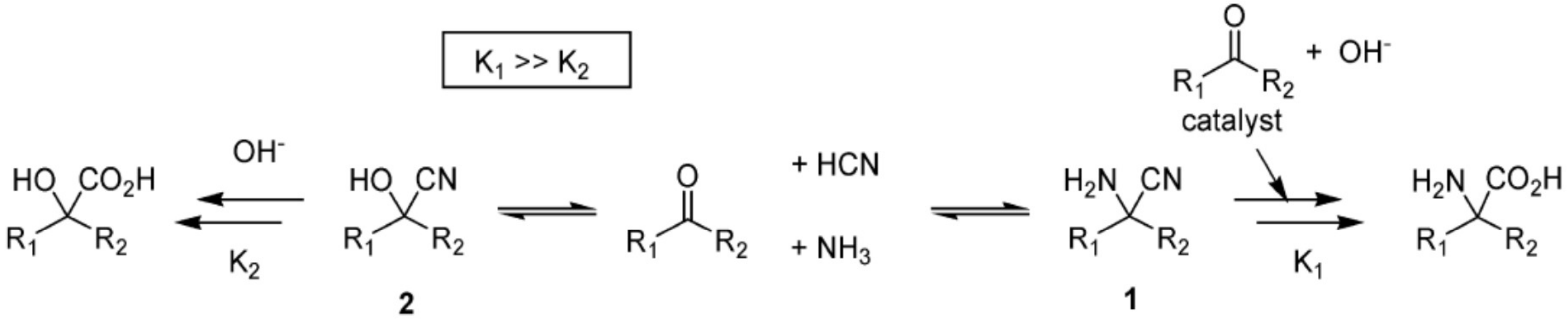


SIPF copper complex geometry with two glycine ligands, optimized by ab initio Hartree–Fock calculations.

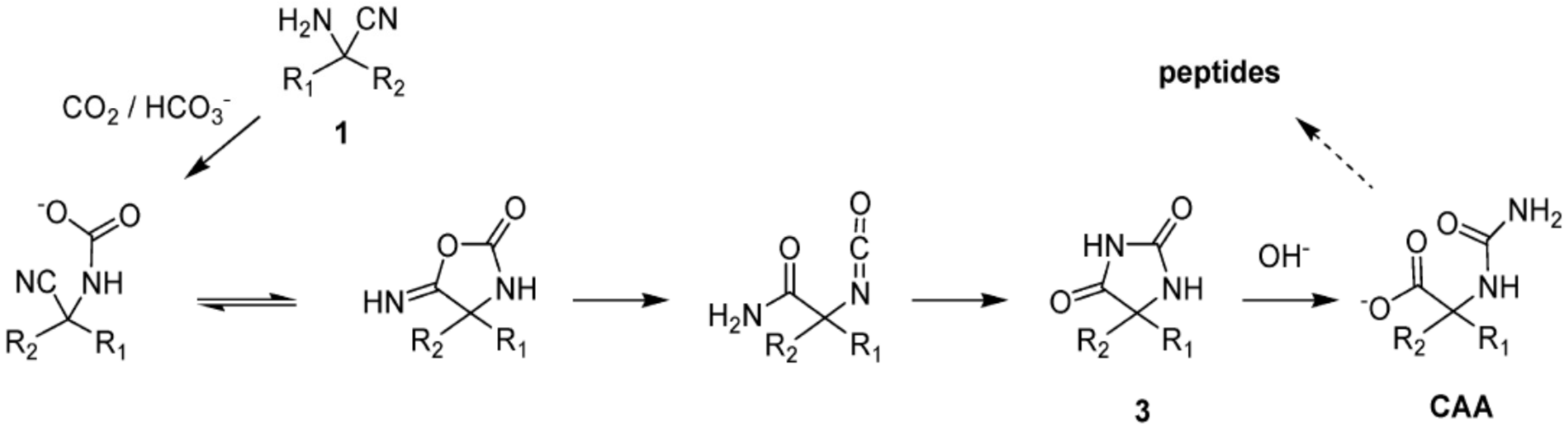
Rode, B. M.; Fitz, D.; Jakschitz, T. Chem. *Biodiversity* **2007**, *4*,2674.

Condensation of aminoacids into peptides

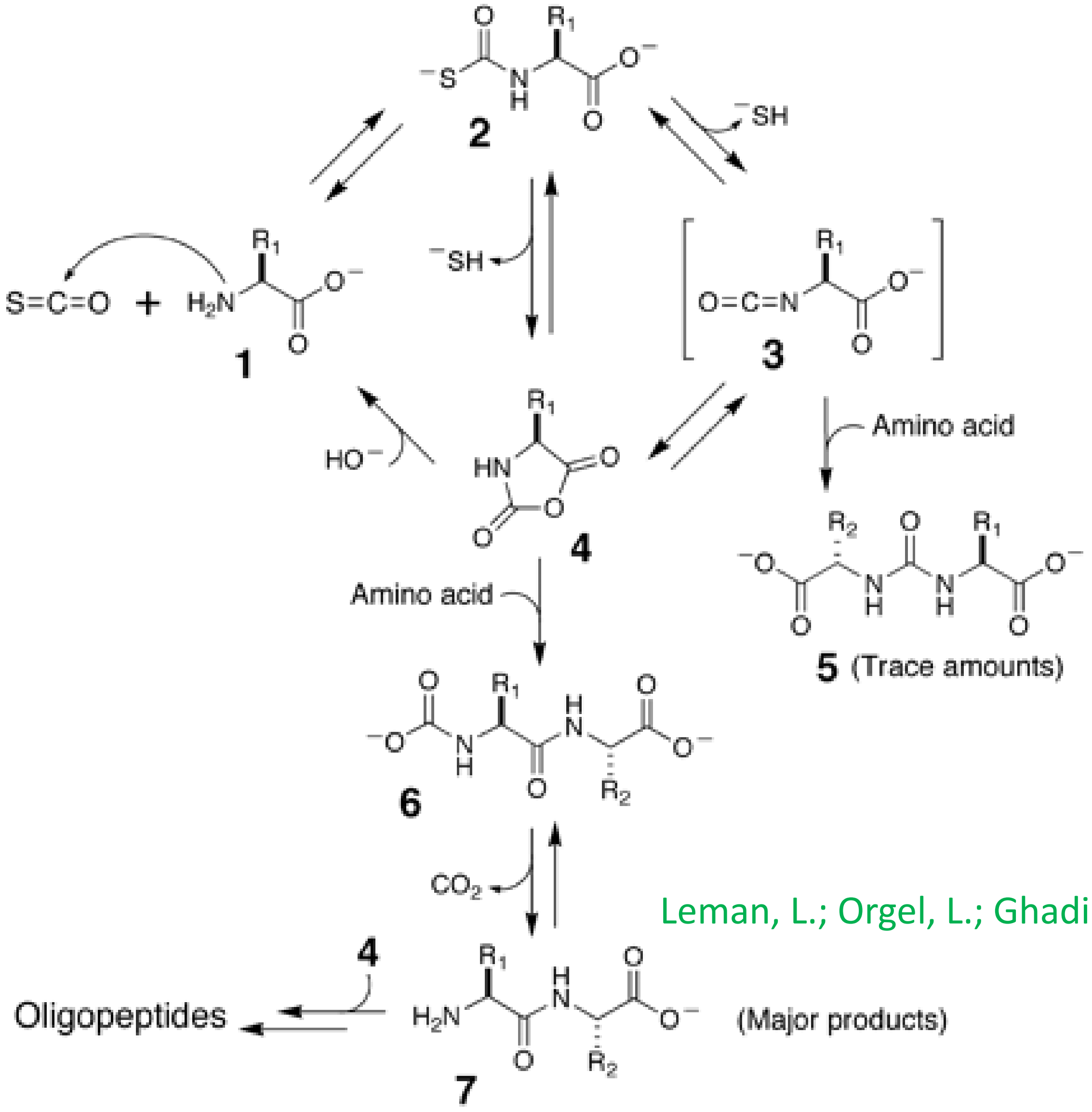
Scheme 1. Synthesis of α-Amino Acids through the Strecker Reaction



Scheme 2. Bücherer–Bergs Hydrolysis of α-Aminonitriles



Carbonyl sulfide – condensing agent



Leman, L.; Orgel, L.; Ghadiri, M. R. *Science* **2004**, *306*, 283-286.

Carbonyl sulfide – condensing agent

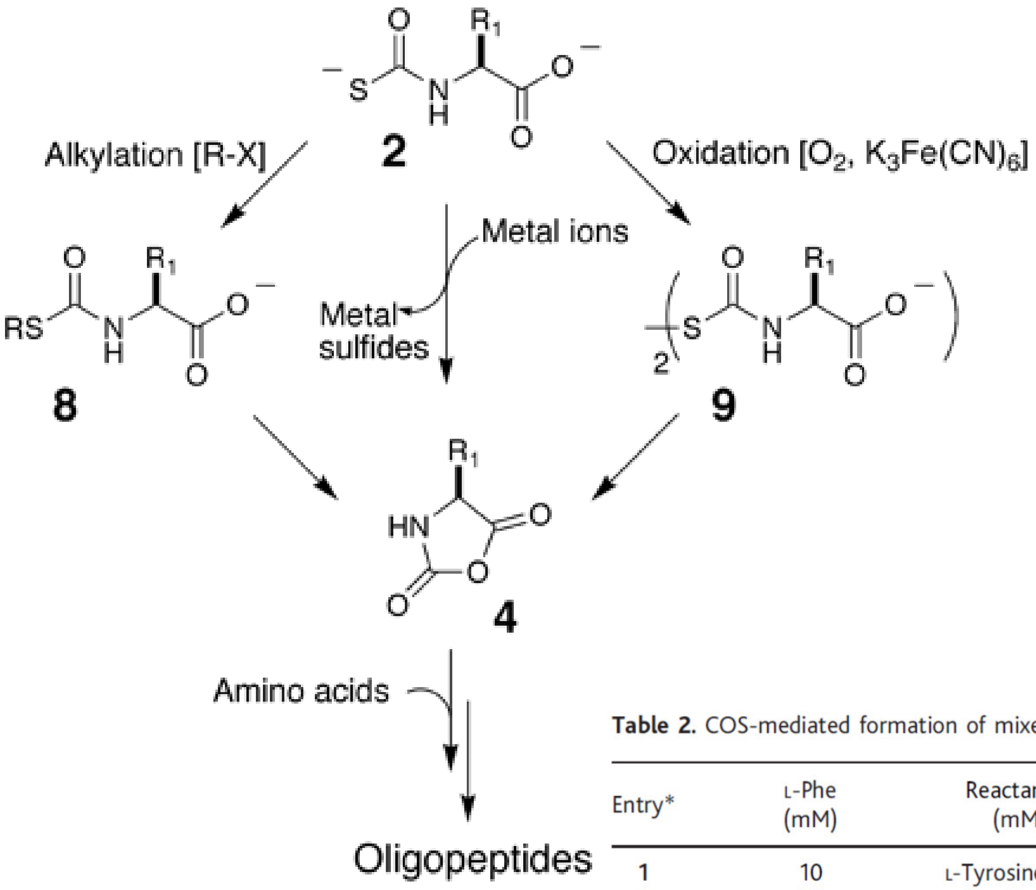


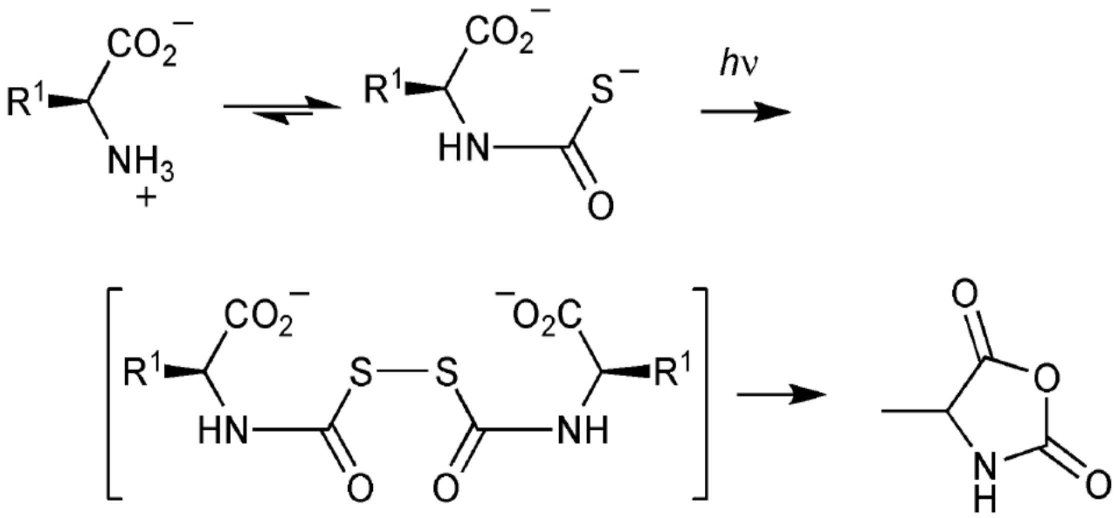
Table 2. COS-mediated formation of mixed peptides. Abbreviations for the amino acid residues: A, Ala; F, Phe; L, Leu; S, Ser; Y, Tyr.

Entry*	L-Phe (mM)	Reactant 2 (mM)	$PbCl_2$ (mM)	Final pH	Time (hours)	Observed dipeptides†	Observed tripeptides†
1	10	L-Tyrosine (10)	20	7.2	3	FF, YY, (YF), (FY)	YYY, (YYF), (YFF), FFF
2	25	L-Leucine (25)	50	7.1	3	FF, LL, (FL)	(LLF), (LFF), FFF
3	25	L-Alanine (25)	50	5.9	3	FF, (AF)	(AAF), (AFF), FFF
4	25	L-Serine (25)	50	6.3	3	SS, FF, SF, FS	SSS, (SFF), FFF

*Each experiment was initiated by admitting ~20 ml of COS gas to an argon-purged reaction vessel containing 2 ml of the reaction mixture indicated dissolved in 500 mM Me_3N buffer, at an initial pH of 9.1. Peptide products were identified by LCMS after quenching the reaction at 3 hours. †Peptides for which product masses were observed but primary amino acid sequences which were not determined are indicated in parentheses.

Leman, L.; Orgel, L.; Ghadiri, M. R. *Science* **2004**, *306*, 283-286.

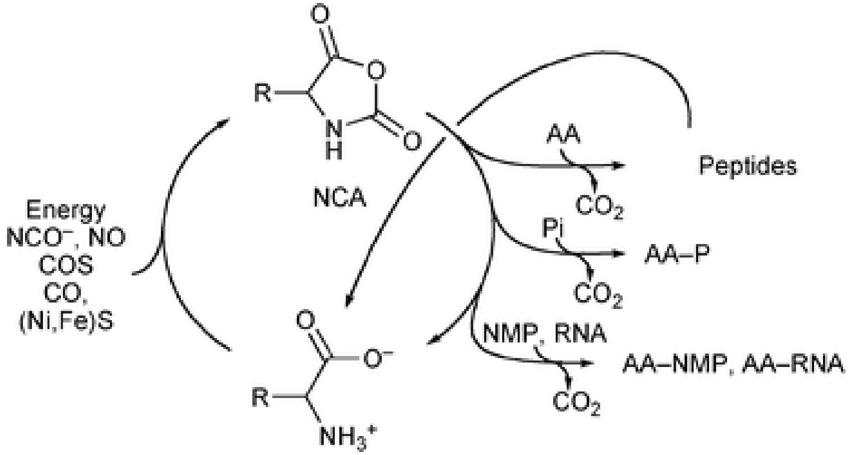
Carbonyl sulfide – photochemical activation



A slow formation of NCAs from free amino acids and COS in the absence of oxidizing or alkylating agents has been reported and studied through theoretical chemistry investigations. However, it seems unlikely that COS (ΔG_0 = 16.9 kJ/mol) could be able to generate NCA (ΔG_0 = 60 kJ/mol) in spite of its cyclic structure.

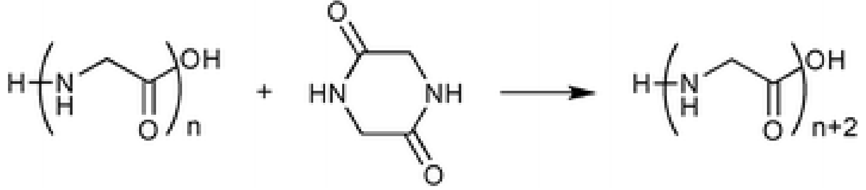
A photochemical activation of thiocarbamate that could take place in a way similar to that of thioacetate in aqueous solution may provide an explanation to this observation. This potential photochemical reaction may also constitute an efficient pathway for the prebiotic formation of NCAs.

Carbonyl sulfide – photochemical activation

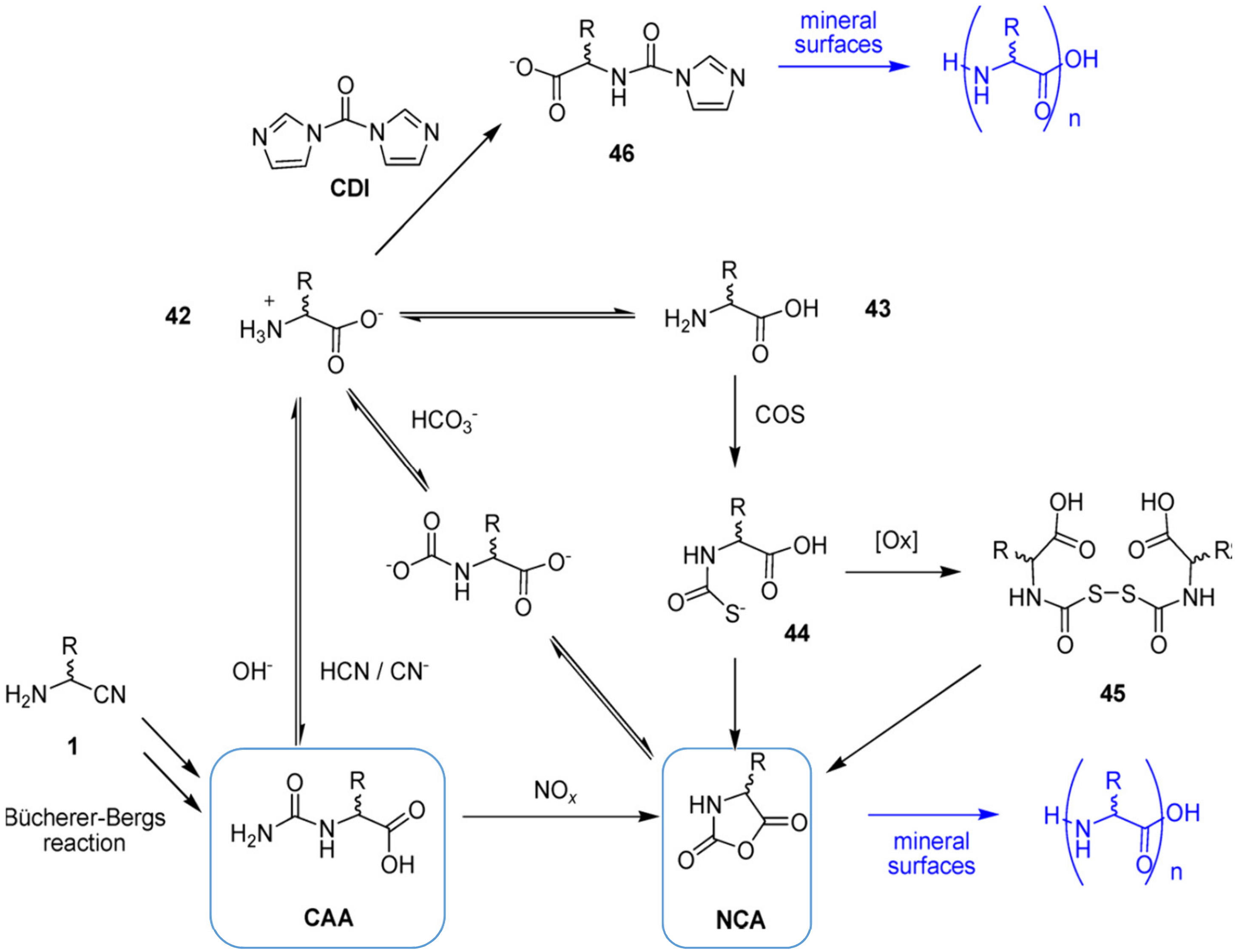


Pathways for the formation of NCAs and further reactions including polymerization and interactions with inorganic phosphate (Pi), nucleotides (NMP), and RNA.

Diketopiperazines as intermediates for peptide condensation



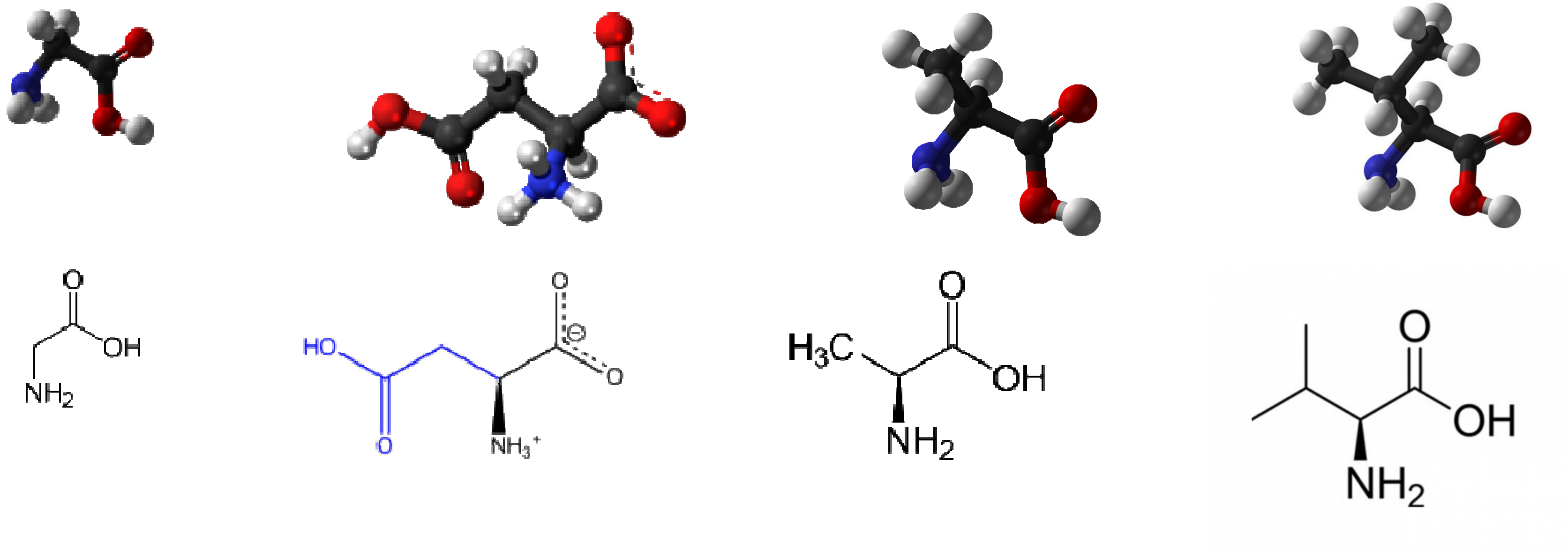
Condensation of aminoacids into peptides



Basic aminoacids for primitive genetic code?

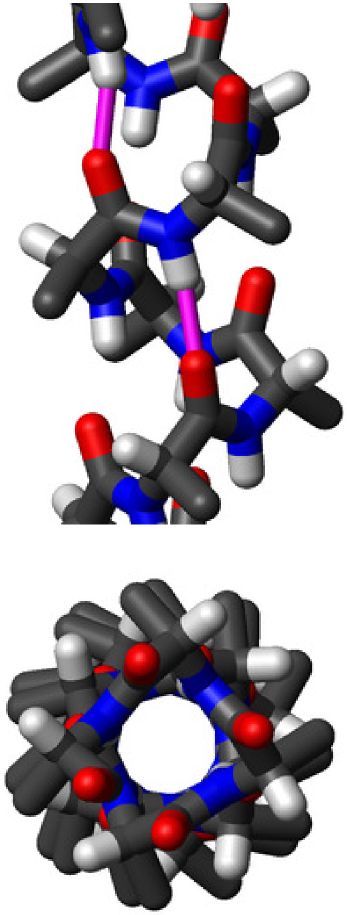
Primordial genetic code might have involved only 4 „GNC" codons:

- *GGC for glycine*
- *GCC for alanine*
- *GAC for aspartic acid*
- *GUC for valine*

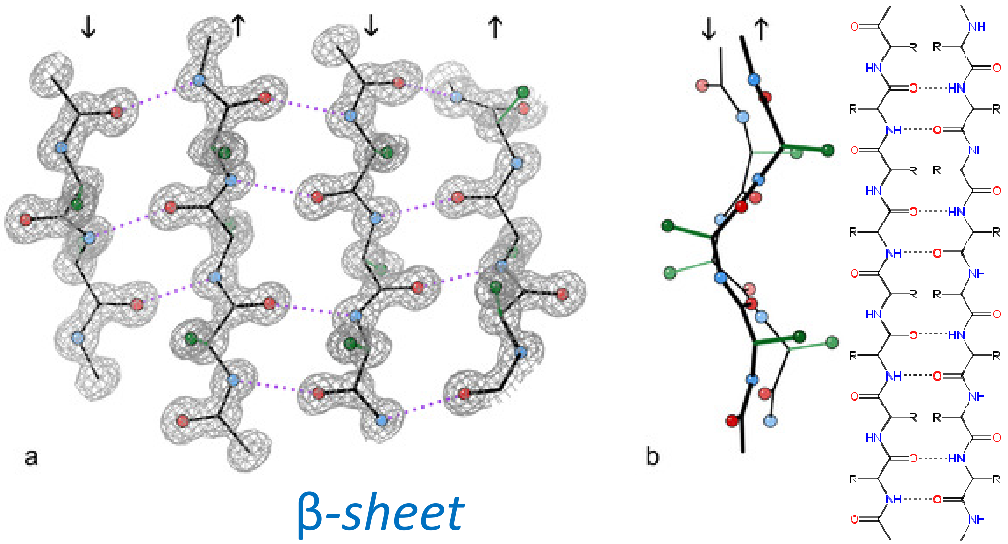


Later, the ‚GNC' code probably evolved into ‚SNS' code (S = G/C, N = A, U, G, C) – 16 codons encoding 10 basic aminoacids (Gly, Ala, Asp, Val, Glu, Leu, Pro, His, Glu, Arg)

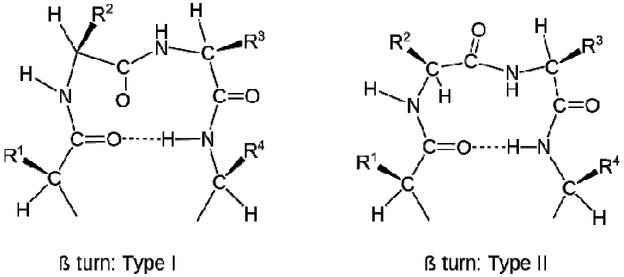
GADV-protein world



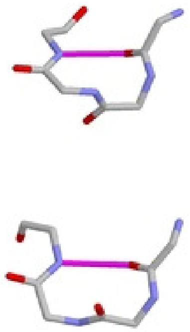
α-helix
(Ala)



β-sheet
(Val)



β-turn (coil)
(Gly)



hydrophilic
and
hydrophobic
structures

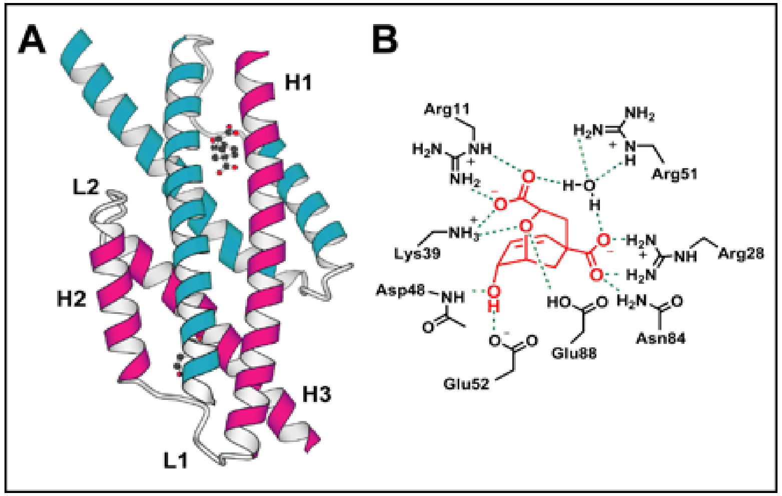
globular
structures

catalytic
activity
(Asp)

Reduced aminoacid alphabet

9-aminoacid alphabet is sufficient to construct functional enzymes

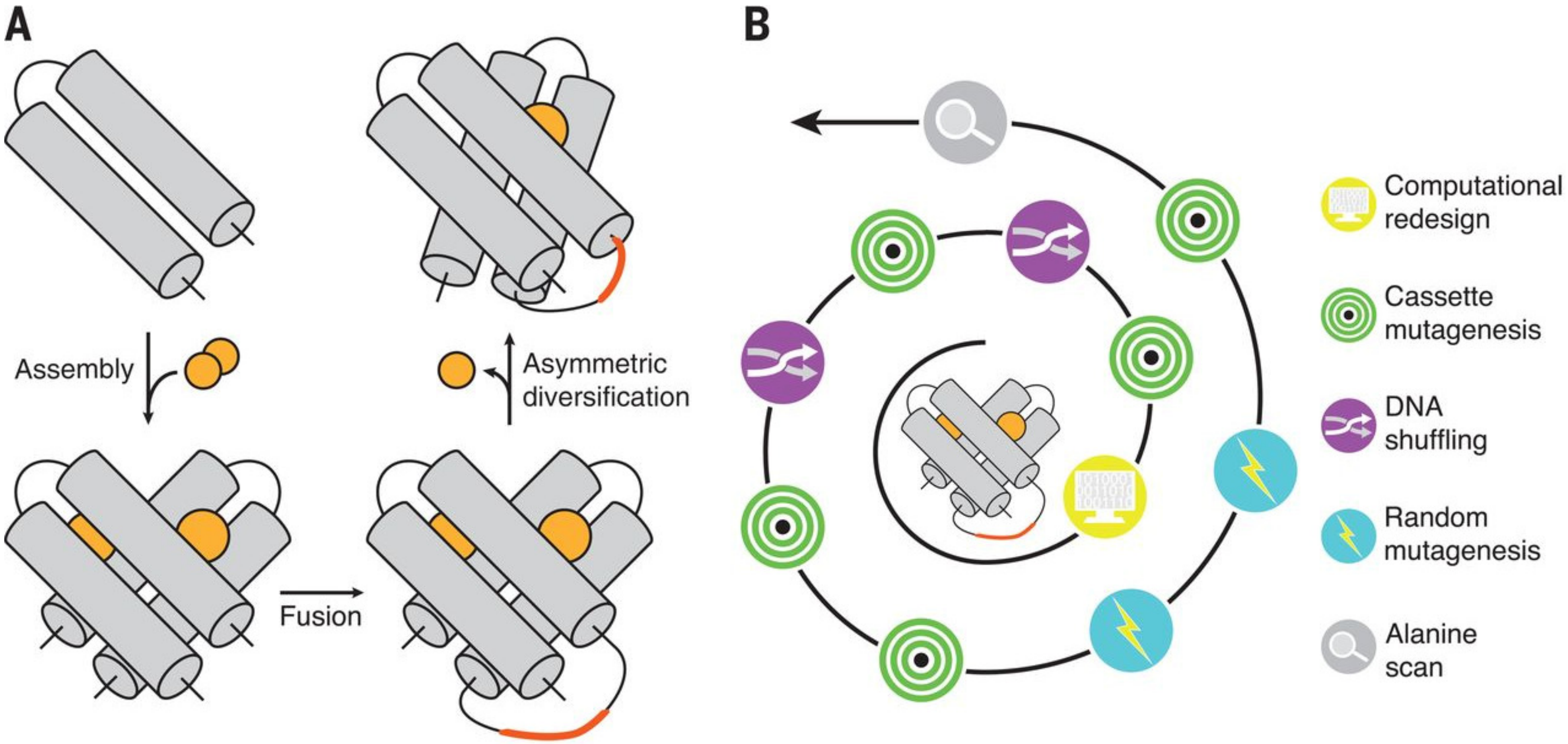
Aminoacids: Asp, Glu, Asn, Lys, Phe, Ile, Leu, Met, Arg



AroQ structure and active site. *A*, the homodimeric EcCM is shown with a transition state analog inhibitor bound at its active sites; the two identical polypeptide chains are colored *blue* and *pink* for clarity. *B*, proposed interactions between residues in the evolved active site of the simplified enzyme and the transition state analog inhibitor, compound **1** (*red*), based on the x-ray structure of EcCM. Residues Gln^{88} and Ser^{84} in EcCM are substituted with Glu^{88} and Asn^{84} in the 9-amino acid enzyme. Residue numbers are referenced to EcCM.

Walter, K. U., Vamvaca, K., Hilvert, D. *J. Biol. Chem.* **2005**, *280*,37742-37749.

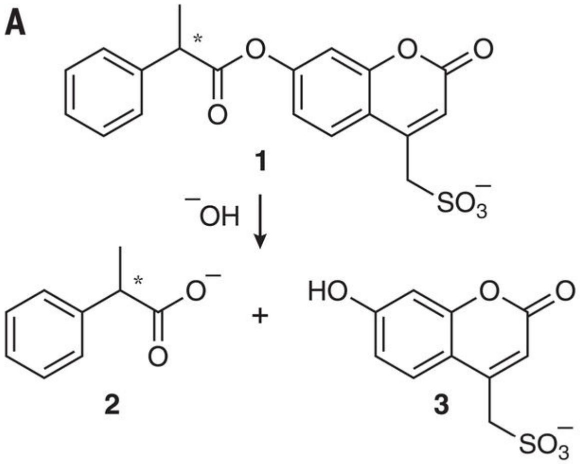
Evolution of a metalloenzyme from short peptides

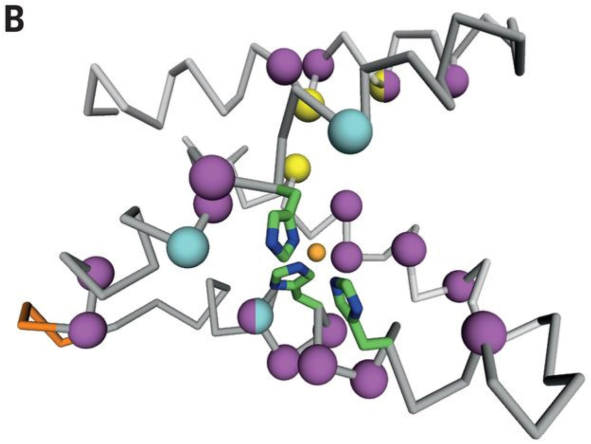


Zinc-mediated assembly of helix-turn-helix fragments, followed by fusion and asymmetric diversification, afforded MID1sc10, an efficient metalloesterase.

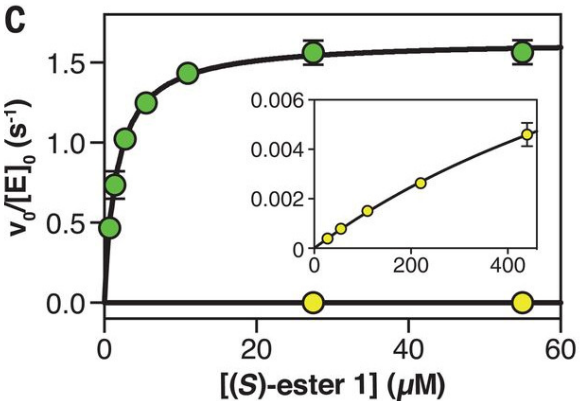
S. Studer, D.A. Hansen, Z. Pianowski, P.R.E. Mittl, A. Debon, S.L. Guffy, B.S. Der, B. Kuhlman, D. Hilvert *Science,* **2018**, *362,* 1285-1288

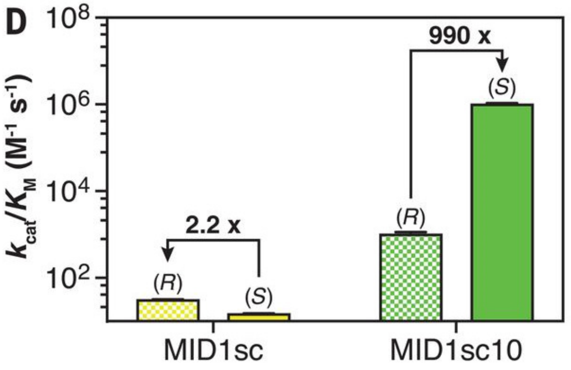
Evolution of a metalloenzyme from short peptides





Crystal structure of MID1sc10
zinc ion - orange sphere,
coordinating histidines - green sticks
linkage of two polypeptides – orange sticks
beneficial mutations - magenta spheres,
residues replaced to prevent competitive zinc
binding modes - cyan spheres).



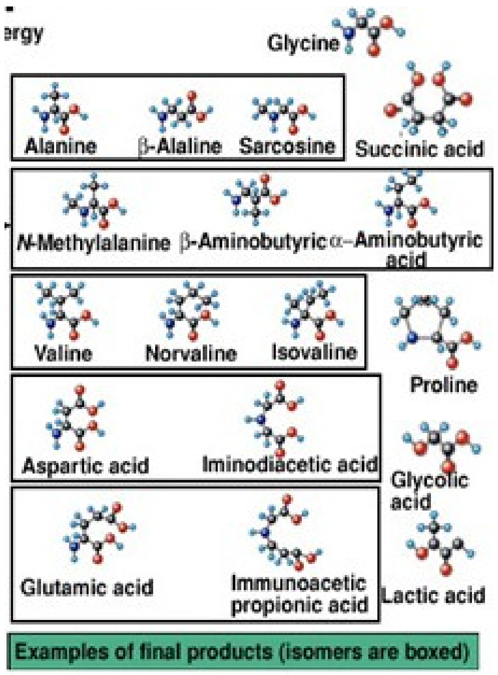


The evolved variant MID1sc10 is highly enantioselective as a consequence of a 2200-fold specificity switch from the modestly (R)-selective starting catalyst MID1sc

Michaelis-Menten plots for **MID1sc** (yellow and inset) and **MID1sc10** (green) show a 70,000-fold improvement in hydrolysis efficiency for (S)-configured **1** after optimization.

S. Studer, D.A. Hansen, Z. Pianowski, P.R.E. Mittl, A. Debon, S.L. Guffy, B.S. Der, B. Kuhlman, D. Hilvert *Science,* **2018**, *362,* 1285-1288

Aminoacids - Summary



Prebiotic generation plausible – variants of the Miller-Urey experiment
Strecker-type of chemistry likely

Aminoacids are good catalysts, can perform various chemical transformations

The origin of homochirality in the Universe caused by the pairity violation and stochastic fluctuations

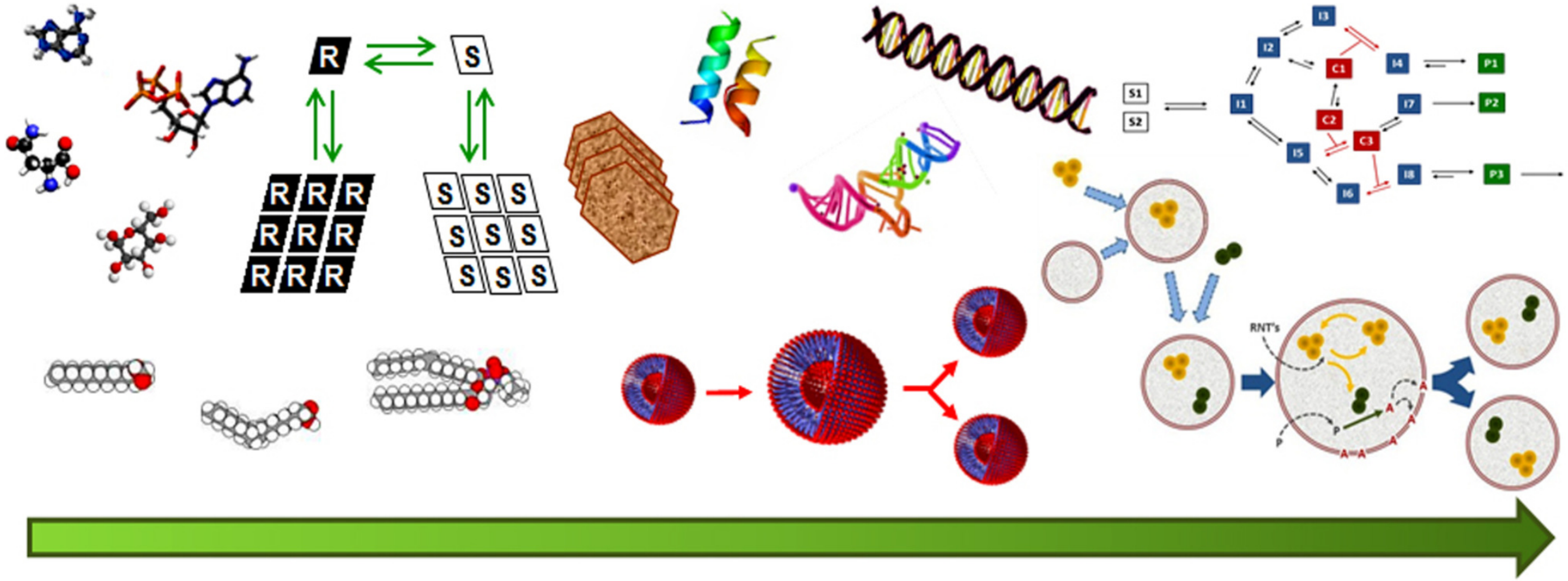
Chirality amplification possible in numerous chemical reactions

Aminoacids can catalyse their own formation with chirality amplification and undergo physical enantioenrichment processes

Condensation of aminoacids into peptides plausible under prebiotic conditions using condensing agents

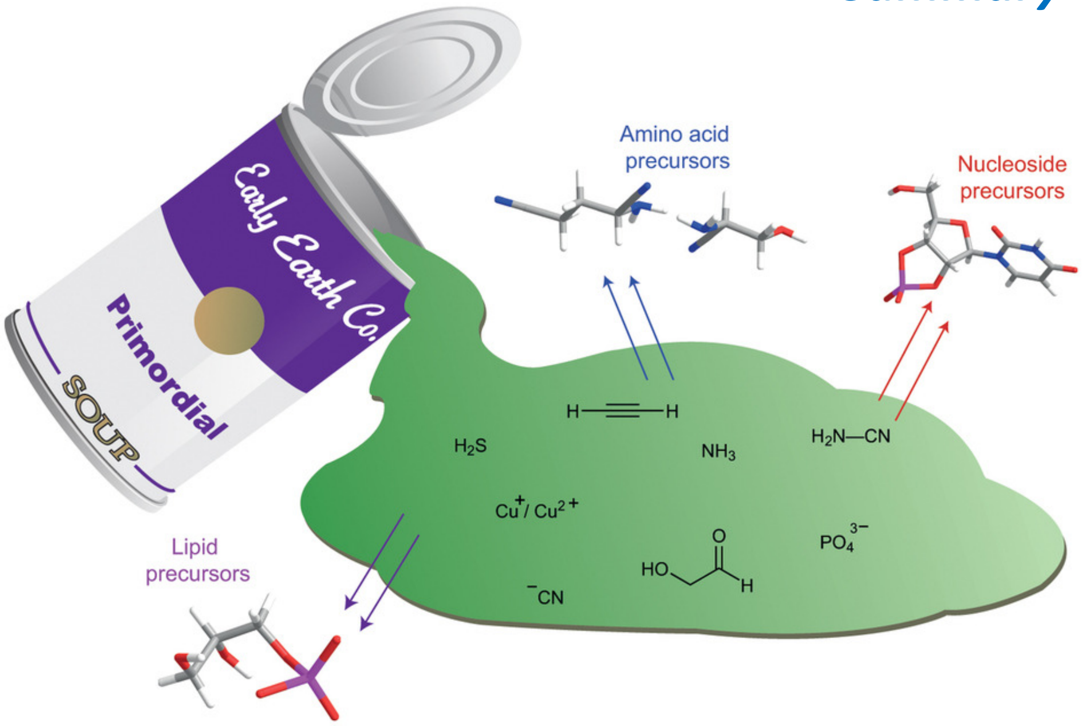
Simple peptides can exhibit broad structural variety,
catalytically active enzymes can be constructed with reduced aminoacid alphabet

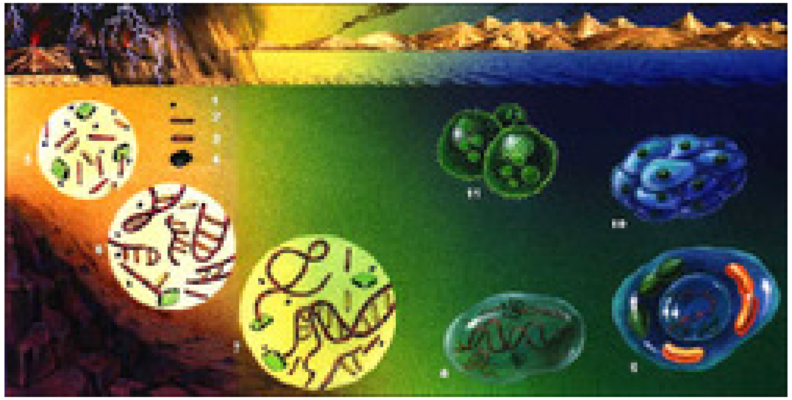
Summary

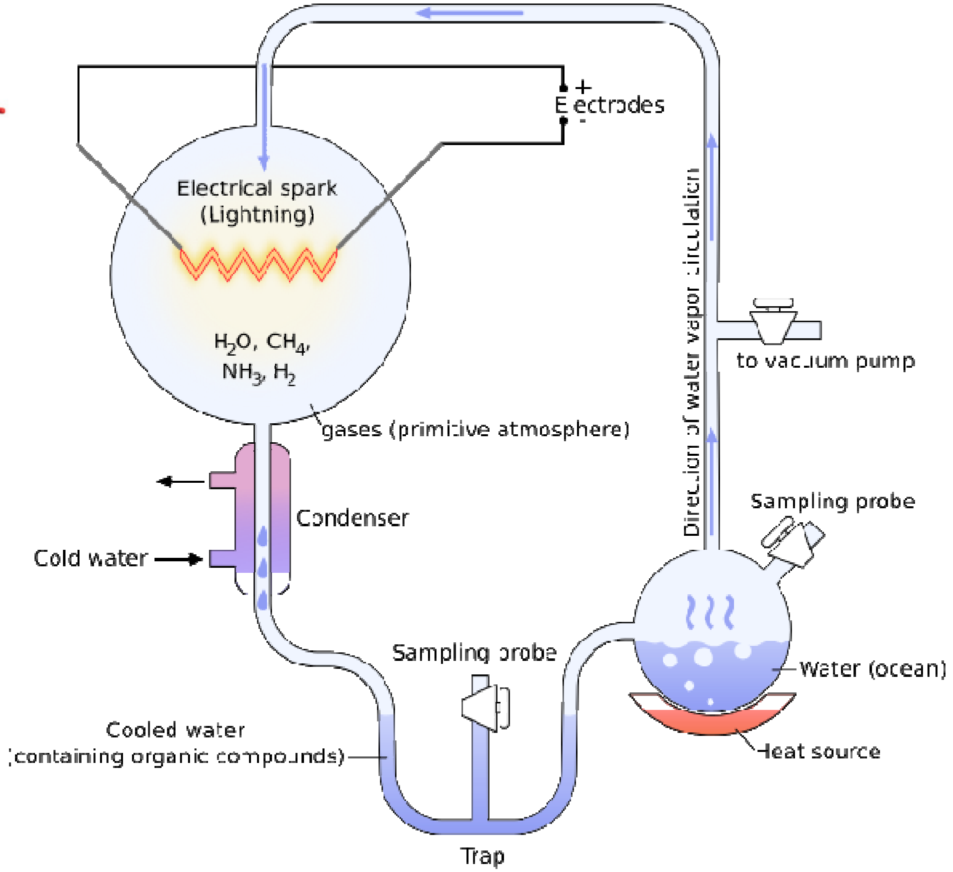


Increasing complexity from molecules to systems

Summary


Early Earth Co.
Primordial
SOUP
Amino acid precursors
Nucleoside precursors
Lipid precursors
H—≡—H
H_2S
NH_3
$H_2N—CN$
Cu^+/Cu^{2+}
PO_4^{3-}
HO
O
H
^-CN




Electrodes
+
-
Electrical spark (Lightning)
H_2O, CH_4, NH_3, H_2
gases (primitive atmosphere)
Condenser
Cold water
Direction of water vapor circulation
to vacuum pump
Sampling probe
Water (ocean)
Heat source
Sampling probe
Cooled water (containing organic compounds)
Trap