The molecular origins of life

L2 SoSe 2020

Zbigniew Pianowski
Definitions of life

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

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

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

Elements of life

Solvents for life

Energy for life

Other limitations
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
Origins of a habitable planet - conclusions

Earth predominantly composed of refractory metals and silicates – non-biogenic materials. Jupiter provided proto-Earth with water, 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.
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
Basic classes of biomolecules

- Aminoacids
- Lipids
- Carbohydrates (sugars)
- Nucleotides
- Nucleosides (sugar+nucleotide)
The origin of biorelevant molecules on Earth

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.

"Primordial soup"

"Biopoeiesis" – prebiotic oceans as "hot diluted soup" under anoxic conditions: e.g. CO₂, NH₃, H₂O

"Life arose through the slow evolution of chemical systems of increasing complexity"
Atmosphere composition for young terrestrial planets

<table>
<thead>
<tr>
<th></th>
<th>Reduced</th>
<th>Neutral</th>
<th>Oxic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon (C)</td>
<td>CH_4</td>
<td>CO, CO_2</td>
<td>CO_2</td>
</tr>
<tr>
<td>Nitrogen (N)</td>
<td>NH_3</td>
<td>N_2</td>
<td>N_2</td>
</tr>
<tr>
<td>Oxygen (O)</td>
<td>H_2O</td>
<td>H_2O, CO, CO_2</td>
<td>O_2</td>
</tr>
<tr>
<td>Hydrogen (H)</td>
<td>H_2, CH_4, NH_3, H_2O</td>
<td>H_2O</td>
<td>H_2O</td>
</tr>
</tbody>
</table>
Miller-Urey experiment - 1952

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

Stanley Miller (1930-2007)
UCSD San Diego, CA, USA
**α-Aminoacid production in the Miller-Urey experiment**

![Diagram of amino acid production](image)

### TABLE 4.3

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

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Yield (µM)</th>
<th>Amino Acid</th>
<th>Yield (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine</td>
<td>440</td>
<td>Norleucine</td>
<td>6</td>
</tr>
<tr>
<td>Alanine</td>
<td>790</td>
<td>Isoleucine</td>
<td>5</td>
</tr>
<tr>
<td>β-Alanine</td>
<td>410</td>
<td>Serine</td>
<td>5</td>
</tr>
<tr>
<td>N-Methylalanine</td>
<td>300</td>
<td>Alloisoleucine</td>
<td>5</td>
</tr>
<tr>
<td>β-Aminobutyric acid</td>
<td>270</td>
<td>Isovaline</td>
<td>5</td>
</tr>
<tr>
<td>N-Methylformamide</td>
<td>30</td>
<td>Proline</td>
<td>2</td>
</tr>
<tr>
<td>β-Aminoisobutyric acid</td>
<td>30</td>
<td>Threonine</td>
<td>1</td>
</tr>
<tr>
<td>Valine</td>
<td>20</td>
<td>Allothreonine</td>
<td>1</td>
</tr>
<tr>
<td>Leucine</td>
<td>11</td>
<td>Tert-Leucine</td>
<td>0.02</td>
</tr>
<tr>
<td>Glutamate</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Proteogenic amino acids in bold type.*
Generation of radicals

High-energy electrons or UV light

\[
\begin{align*}
H_2 & \rightarrow \quad 2H^* \\
H_2O & \rightarrow \quad H^* \quad + \quad HO^* \\
CH_4 & \rightarrow \quad ^*CH_3 \quad + \quad ^*H \\
\end{align*}
\]

Radical reactions

\[
\begin{align*}
^*CH_3 + H_2O & \rightarrow \quad H_3C-O^* \quad + \quad H_2 \\
H_3C-O^* + H^* & \rightarrow \quad H_2C=O \quad + \quad H_2 \\
^*CH_3 + ^*CH_3 & \rightarrow \quad H_3C-CH_3 \\
\end{align*}
\]

Formaldehyde

Ethane

Graph showing the production of ammonia, amino acids, hydrogen cyanide, and aldehydes over time (days).
Scheme 1. Synthesis of α-Amino Acids through the Strecker Reaction

\[
\text{Aldehyde} + \text{Ammonia} \rightleftharpoons \text{Imine} + \text{Water}
\]

\[
\text{Hydrogen cyanide} \rightleftharpoons \text{Imine}
\]

\[
\text{Amino acid} \rightleftharpoons \text{α-Aminocyanonitrile}
\]

\[
K_1 \gg K_2
\]
Aminoacid production under hydrothermal conditions

Ni(OH)$_2$/KCN/CO in alkaline aqueous conditions (80-120$^0$C) $\rightarrow$ 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) $\rightarrow$ α-amino and α-hydroxyacids (higher yields): glycine, alanine, serine, glycolate, lactate, glycerate
Extraterrestrial origin of biomolecules
**Extraterrestrial origin of biomolecules**

### Table 1. Soluble Organic Compounds in the Murchison Meteorite

<table>
<thead>
<tr>
<th>class of compounds</th>
<th>parts per million</th>
<th>( n^b )</th>
</tr>
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<tbody>
<tr>
<td>aliphatic hydrocarbons</td>
<td>&gt;35</td>
<td>140</td>
</tr>
<tr>
<td>aromatic hydrocarbons</td>
<td>15–28</td>
<td>87</td>
</tr>
<tr>
<td>polar hydrocarbons</td>
<td>&lt;120</td>
<td>10(^d)</td>
</tr>
<tr>
<td>carboxylic acids</td>
<td>&gt;300</td>
<td>48(^d)</td>
</tr>
<tr>
<td>amino acids</td>
<td>60</td>
<td>75(^d)</td>
</tr>
<tr>
<td>imino acids</td>
<td>nd(^c)</td>
<td>10</td>
</tr>
<tr>
<td>hydroxy acids</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>dicarboxylic acids</td>
<td>&gt;30</td>
<td>17(^d)</td>
</tr>
<tr>
<td>dicarboximides</td>
<td>&gt;50</td>
<td>2</td>
</tr>
<tr>
<td>pyridinecarboxylic acids</td>
<td>&gt;7</td>
<td>7</td>
</tr>
<tr>
<td>sulfonic acids</td>
<td>67</td>
<td>4</td>
</tr>
<tr>
<td>phosphonic acids</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>N-heterocycles</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td>amines</td>
<td>13</td>
<td>20(^d)</td>
</tr>
<tr>
<td>amides</td>
<td>nd(^c)</td>
<td>27</td>
</tr>
<tr>
<td>polyols</td>
<td>30</td>
<td>19</td>
</tr>
</tbody>
</table>
Catalytic properties of aminoacids - organocatalysis

Robinson annulation

Catalytic properties of aminoacids - organocatalysis

\[
\text{Prochiral and/or Racemic Starting Materials} \xrightarrow{n = 1, 2, 3, \ldots, m} \text{Optically Enriched Products}
\]

**aldol reaction**

\[
\text{MeC} = \text{OR} + \text{HOC} = \text{OR'} \quad \xrightarrow{20-30 \text{ mol}\% (S)-proline} \quad \text{MeC} = \text{OH}
\]

R = H, OH
20 vol%

DMSO, r.t.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeC = OH</td>
<td>68%</td>
<td>76% ee</td>
</tr>
<tr>
<td>MeC = OH</td>
<td>97%</td>
<td>96% ee</td>
</tr>
<tr>
<td>MeC = OH</td>
<td>34%</td>
<td>72% ee</td>
</tr>
<tr>
<td>MeC = OH</td>
<td>60%</td>
<td>&gt;20:1 dr &gt;99% ee</td>
</tr>
</tbody>
</table>

Mannich reaction, organocatalysis, Michael addition

Catalytic properties of amino acids - organocatalysis

Hydrocyanation

**aldehydes**

\[
\text{PhCHO} \xrightarrow{\text{HCN (2 equiv.)}} \text{PhCHCN} \quad (97\% \text{ conv.}, 97\% \text{ ee})
\]

**imines**

\[
\text{PhCHCN} \xrightarrow{6 \text{ N HCl}, 60^\circ C, 6 \text{ h}} \text{PhCHCNCO}_2\text{H} \quad (95\% \text{ yield})
\]

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 asymmetry 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

Circularly polarized light (CPL) from gamma ray bursts

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

Up to 2.6% ee


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

(S)-32
Low e.e.

Asymmetric autocatalyst

(H)Zn

33

H+

(S)-32
High e.e.

Leucine, 2% e.e.
(Chiral initiator)

i-Pr2Zn
Low e.e.

asymmetric autocatalysis

High e.e.

34

35

36

37

38

Factor by which the amounts of (S)-1 and (R)-1 isomers increase

- Initial conditions (5% e.e.)
- A1 (39% e.e.)
- A2 (76% e.e.)
- A3 (85% e.e.)
autocatalytic Soai reaction – extreme chirality amplification

\[
R = \frac{[RX]}{[RR] + [SS] + [SR]}
\]

\[
\beta = \frac{[SR]}{[RR] + [SS]}
\]

\[
e_{ee} = \frac{[SS] - [RR]}{[RR] + [SS] + 2[SR]}
\]

\[
e_{ee,\text{obs}} = \frac{ee_{\text{to}}}{2} + \frac{ee_{\text{ho}}}{2}
\]

7a, \(X = \text{Cl}\)
7b, \(X = \text{SCN}\)

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

(d)\textsuperscript{19}
(c)\textsuperscript{19}
autocatalytic organic reactions

Scheme 10. Mannich and Aldol Autocatalytic Reactions

Meaningful transformations for the prebiotic syntheses of aminoacids and sugars
autocatalytic organic reactions

1 + EtO₂C-H + (S)-3 or (R)-3 as catalyst → 3
up to 94% ee

\[
\begin{align*}
\text{MeO} & \quad \text{H} \\
\text{O} & \quad \text{OEt}
\end{align*}
\]

proposed transition-state structure

approach of the enol from the Si face

TS-A

approach of the enol from the Re face

TS-B

\[
\begin{align*}
\text{c} & = 0.25 \text{ mol L}^{-1} \\
\text{2-6 days, r.t.} & \quad \text{2-8 days, r.t.}
\end{align*}
\]

\[
\begin{align*}
\text{EtO₂C-H} + \text{CO₂Et} & \quad (15-30 \text{ mol\%}, 98-99\% \text{ ee}) \\
\text{20-48\% yield} & \quad 85-96\% \text{ ee}
\end{align*}
\]

Eq. (1)

\[
\begin{align*}
\text{EtO₂C-H} + \text{CO₂Et} & \quad \text{without product catalyst} \\
\text{11-36\% yield} & \quad 0.5-9.5\% \text{ ee}
\end{align*}
\]

Eq. (2)
**Organocatalysis – the origin of homochirality**

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

<table>
<thead>
<tr>
<th>Component</th>
<th>Initial ee, %</th>
<th>Final ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>10</td>
<td>90.0 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>91.7 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>87.2 ± 2.0</td>
</tr>
<tr>
<td>L</td>
<td>10</td>
<td>88.3 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>88.6 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>90.9 ± 0.3</td>
</tr>
</tbody>
</table>

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

Chirality amplification in biphasic systems

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

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>ee of solution at eutectic (%)</th>
<th>Amino acid</th>
<th>ee of solution at eutectic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threonine</td>
<td>0</td>
<td>Methionine</td>
<td>85</td>
</tr>
<tr>
<td>Valine</td>
<td>46</td>
<td>Leucine</td>
<td>87</td>
</tr>
<tr>
<td>Alanine</td>
<td>60</td>
<td>Histidine</td>
<td>93</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>83</td>
<td>Serine</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

Vital chemical reactions

Aminoacid polymerization

Nucleotide polymerization
Condensation of aminoacids into peptides
Biochemical condensation of amino acids into peptides
Condensation of aminoacids into peptides

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

\[
\begin{align*}
\text{HO-CO}_2\text{H} & \quad \overset{K_2}{\rightleftharpoons} \quad \text{HO-CN} \\
\text{R}_1\text{R}_2 & \quad \text{R}_1\text{R}_2 & \quad + \text{HCN} & \quad + \text{NH}_3 \\
\text{K}_1 & \quad >> \quad \text{K}_2
\end{align*}
\]

Scheme 2. Bücherer–Bergs Hydrolysis of α-Aminonitriles

\[
\begin{align*}
\text{CO}_2/\text{HCO}_3^- & \quad \rightarrow \quad \text{H}_2\text{N-CN} \\
\text{R}_1\text{R}_2 & \quad \text{H}_2\text{N-CN} \\
\end{align*}
\]

\[
\begin{align*}
\text{NC} & \quad \overset{\text{NH}}{\rightarrow} \quad \text{HN} \\
\text{CN} & \quad \overset{\text{NH}}{\rightarrow} \quad \text{HN} \\
\text{NH}_2 & \quad \text{OH}^- & \quad \rightarrow \quad \text{O}^- \quad \text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O}^- \quad \text{NH}_2 & \quad \text{O}^- \quad \text{NH}_2 \\
\text{O}^- \quad \text{NH}_2 & \quad \text{O}^- \quad \text{NH}_2 \\
\text{O}^- \quad \text{NH}_2 & \quad \text{O}^- \quad \text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{CAA} & \quad \text{peptides}
\end{align*}
\]
Prebiotically relevant peptide condensation agents

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


Carbonyl sulfide – condensing agent

Carbonyl sulfide – condensing agent

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 ($\Delta G_0 = 16.9$ kJ/mol) could be able to generate NCA ($\Delta G_0 = 60$ 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 amino acids into peptides
Prebiotic peptide condensation in water

GADV-protein world

- α-helix (Ala)
- β-sheet (Val)
- β-turn (coil) (Gly)
- β-sheet (Gly)
- β-sheet (Asp)

hydrophilic and hydrophobic structures

globular structures
catalytic activity (Asp)
Basic amino acids 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 amino acids (Gly, Ala, Asp, Val, Glu, Leu, Pro, His, Glu, Arg)
**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\textsuperscript{88} and Ser\textsuperscript{84} in EcCM are substituted with Glu\textsuperscript{88} and Asn\textsuperscript{84} in the 9-amino acid enzyme. Residue numbers are referenced to EcCM.

---

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

Evolution of a metalloenzyme from short peptides

Crystal structure of MID1sc10
- zinc ion - orange sphere,
- coordinating histidines - green sticks
- linkage of two polypeptides – green 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.

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 parity 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
Lipids

Cholesterol

A free fatty acid

A triglyceride

A phospholipid

By Lmaps

Liposome
Bilayer sheet
Micelle

By Mariana Ruiz Villarreal
Encapsulation – essential for life

Evolving chemical systems require compartments for Darwinian evolution – to compete, to store information and to concentrate reactants/metabolites.

Encapsulation into membranes is considered an early stage in prebiotic chemical evolution and essential requirement for the emergence of life.
Encapsulation – essential for life

Formation of membranes is most easy to explain among major cellular components of the prebiotic Earth. Many amphiphilic organic compounds spontaneously form vesicles in water at sufficiently high concentrations.


The vesicle will encapsulate an aqueous solution inside a thin layer of organic material.
Modern biological membranes consist primarily of phospholipids with embedded transmembrane proteins. Characterized by low permeability – a disadvantage during early evolution.

Encapsulation – essential for life

Fatty acids and fatty alcohols are likely prebiotic lipids
**Fischer-Tropsch synthesis**

Long hydrocarbon chains from CO + H\(_2\) in presence of metal catalysts and high pressure, fatty acids and alcohols are minor by-products

The mixture of D\(_2\) and CO over meteoritic iron or iron ore produced alkanes and n-fatty acids

### Fischer-Tropsch synthesis

<table>
<thead>
<tr>
<th>Main reactions</th>
<th>Side reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Paraffins</td>
<td>3. Water-Gas-Shift (WGS)</td>
</tr>
<tr>
<td>2. Olefins</td>
<td>4. Carbide formation</td>
</tr>
<tr>
<td></td>
<td>5. Alcohols</td>
</tr>
<tr>
<td></td>
<td>6. Boudouard reaction</td>
</tr>
<tr>
<td></td>
<td>7. Catalyst reduction and oxidation</td>
</tr>
<tr>
<td></td>
<td>8. Coking</td>
</tr>
</tbody>
</table>
Hydrothermal Fischer-Tropsch synthesis

Formic or oxalic acid heated in water at 150-250°C (stainless steel reactor) yielded a mixture of C\textsubscript{12}-C\textsubscript{33} lipids


When CO, H\textsubscript{2} and NH\textsubscript{3} are allowed to react at 200-700°C in presence of Ni, Al, or clay catalysts, amino acids are detected:

\textit{glycine, alanine, sarcosine, aspartic acid, glutamic acid, arginine, histidine, lysine and ornithine}

Extraterrestrial origin of biomolecules
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<td>&gt;35</td>
<td>140</td>
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<tr>
<td>aromatic hydrocarbons</td>
<td>15–28</td>
<td>87</td>
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<tr>
<td>polar hydrocarbons</td>
<td>&lt;120</td>
<td>10(^d)</td>
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<tr>
<td>carboxylic acids</td>
<td>&gt;300</td>
<td>48(^d)</td>
</tr>
<tr>
<td>amino acids</td>
<td>60</td>
<td>75(^d)</td>
</tr>
<tr>
<td>imino acids</td>
<td>nd(^c)</td>
<td>10</td>
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<tr>
<td>hydroxy acids</td>
<td>15</td>
<td>7</td>
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<tr>
<td>dicarboxylic acids</td>
<td>&gt;30</td>
<td>17(^d)</td>
</tr>
<tr>
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<tr>
<td>pyridinecarboxylic acids</td>
<td>&gt;7</td>
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</tr>
<tr>
<td>sulfonic acids</td>
<td>67</td>
<td>4</td>
</tr>
<tr>
<td>phosphonic acids</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>N-heterocycles</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td>amines</td>
<td>13</td>
<td>20(^d)</td>
</tr>
<tr>
<td>amides</td>
<td>nd(^c)</td>
<td>27</td>
</tr>
<tr>
<td>polyols</td>
<td>30</td>
<td>19</td>
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Fatty acids have been found in meteorites – plausible prebiotic synthesis pathways existed in the early Solar System. Extracts of meteorites containing these compounds spontaneously form vesicles when hydrated.
The first protocell membranes may have assembled from fatty acids and related single-chain lipids available in the prebiotic environment.

At different concentrations, fatty acids can partition between several different phases, including soluble monomers, micelles, and lamellar vesicles, with higher concentrations favoring larger vesicle aggregates.

Transition: Micelles-Vesicles-Protocells

Vesicle growth and division cycle

- Micelles
- Vesicle growth
- Protocell formation
- Mineral components (Ni, Fe, S)
- Catalysts
- Genetic information

Bacteria
- Archaea
- Bacterial phospholipids
- Archaeal phospholipids

Acellular cenarchester; no membrane

Surface metabolism on pyrite

Mineral (FeS)-compartmented cenarchester; no lipid membrane

Cell-like evolution in mineral compartments within a hydrothermal chimney

Pre-cell stem with heterochiral membrane; non-enzymatic or nonspecific glycerol phosphate synthesis

Eukaryotes
- Bacteria
- Archaea
- Bacterial phospholipids
- Archaeal phospholipids

Cenarchester with heterochiral membrane; enzymatic nonspecific glycerol phosphate synthesis

Chemical evolution

Surface metabolism on pyrite
Jack Szostak

(* November 9, 1952) - Canadian American biologist of Polish British descent,

Nobel Prize laureate 2009 for Physiology and Medicine, for the discovery of how chromosomes are protected by telomeres; Professor of Genetics at Harvard Medical School.

Szostak has made significant contributions to the field of genetics. His achievement helped scientists to map the location of genes in mammals and to develop techniques for manipulating genes.

His research findings in this area are also instrumental to the Human Genome Project.

In the early 90s his laboratory shifted its research direction and focused on studying RNA enzymes, which had been recently discovered by Cech and Altman. He developed the technique of in vitro evolution of RNA (also developed independently by Gerald Joyce) which enables the discovery of RNAs with desired functions through successive cycles of selection, amplification and mutation. He isolated the first aptamer (term he used for the first time). He isolated RNA enzymes with RNA ligase activity directly from random sequence (project of David Bartel).

Currently his lab focuses on the challenges of understanding the origin of life on Earth, and the construction of artificial cellular life in the laboratory.
**Coupled growth and division of model protocell membranes**

The growth of large multilamellar fatty acid vesicles fed with fatty acid micelles, in a solution where solute permeation across the membranes is slow, results in the transformation of initially spherical vesicles into long thread-like vesicles, a process driven by the transient imbalance between surface area and volume growth. Modest shear forces are then sufficient to cause the thread-like vesicles to divide into multiple daughter vesicles without loss of internal contents.

Cycles of vesicle growth and division. (A) Relative surface area after two cycles of addition of 5 equiv of oleate micelles (solid circles) or 5 equiv of NaOH (open circles) to oleate vesicles, each followed by agitation. Inset micrographs show vesicle shapes at indicated times. Scale bar, 10 μm. (B) Vesicle shapes during cycles of growth and division in a model prebiotic buffer (0.2 M Na-glycine, pH 8.5, ~1 mM initial oleic acid, vesicles contain 10 mM HPTS for fluorescence imaging). Scale bar, 20 μm.

Photochemically driven protocell division

The illumination of filamentous fatty acid vesicles rapidly induces pearling and subsequent division in the presence of thiols.

Photochemically generated reactive oxygen species oxidize thiols to disulfide-containing compounds that associate with fatty acid membranes, inducing a change in surface tension and causing pearling and subsequent division.

Alternative route for the emergence of early self-replicating cell-like structures, particularly in thiol-rich surface environments. The subsequent evolution of cellular metabolic processes controlling the thiol:disulfide redox state would have enabled autonomous cellular control of the timing of cell division, a major step in the origin of cellular life.

Oleate vesicle pearling and division.
A. Radical-mediated oxidation of DTT.
B. An oleate vesicle (containing 2 mM HPTS, in 0.2 M Na-glycinamide, pH 8.5, 10 mM DTT) 30 min after the addition of five equivalents of oleate micelles.
C. and D. Under intense illumination (for 2 s and 12 s, respectively), the long thread-like vesicle went through pearling and division.
Scale bar, 10 μm.

Photochemically driven protocell division

Oleate vesicle pearling and division with various thiols in the solution.

(A) 3-mercaptopropionic acid.
(B and C) An oleate vesicle (containing 2 mM HPTS, in 0.2 M Na-bicine, pH 8.5, 10 mM 3-mercaptopropionic acid, 30 min after the addition of five equivalents of oleatemicelles) went through pearling and division under intense illumination (for 3 s and 15 s, respectively).

(D) 3-mercapto-1-propanol.
(E and F) An oleate vesicle as above but in 50 mM 3-mercapto-1-propanol, went through pearling and division under intense illumination (for 2 s and 10 s, respectively).

(G) 1-mercapto-2-propanol.
(H and I) An oleate vesicle as above but in 50 mM 1-mercapto-2-propanol went through pearling and division under intense illumination (for 2 s and 9 s, respectively).

(J) 3-mercapto-1,2,4-triazole.
(K and L) An oleate vesicle as above but in 50 mM 3-mercapto-1,2,4-triazole went through pearling and division under intense illumination (for 3 s and 13 s, respectively).

Scale bar, 20 μm.

Noncovalent nucleotide association with membranes

a) Design of RNA-localizing molecules that include both nonpolar and cationic regions.

b) The change in zeta potential

c) Schematic of the FRET assay used to assess RNA localization to vesicle membranes

d) RNA (5'-FAM-U_{15} and 5'-FAM-A_{15}) shows increasing localization to POPC membranes that contain increased amounts of undecylimidazole.

Microscopy of encapsulated RNA localization to POPC membranes with 2-undecylimidazole. Confocal images of 5'-FAM-U\textsubscript{15} RNA (green) association with giant POPC vesicles membranes in the presence of 2-undecylimidazole. Differential interference contrast (DIC) microscopy images are shown for each vesicle.

a) RNA appears uniformly distributed in the interior of POPC GUVs.

b) The addition of SUVs containing a rhodamine-labeled lipid (red) leads to SUV aggregation and association with the giant vesicle membranes, but RNA (green) remains uniformly encapsulated in the vesicle interior.

c) The addition of SUVs containing a rhodamine-labeled lipid (red) and 40 mol\% 2-undecylimidazole leads to SUV association with vesicle membranes and RNA (green) localizes to the vesicle surface. The scale bar is 20 mm.

**SUV** – small unilamellar vesicle  
**GUV** – giant unilamellar vesicle (5-25 µm)

Peptide-induced RNA–membrane association. A FRET assay reports RNA localization (5′-FAM-U₃) to POPC and oleic acid membranes (7.5 mm) 10 h after the addition of 1 mm of various peptides to the vesicle solution at pH 8. Data is reported as a percentage change from control samples that lack peptide. n=4, error bars represent the standard error of the mean.

Microscopy of peptide-induced RNA–membrane association. Confocal images show RNA localization (5'-AlexaFluor647-labeled 15-mer, cyan) to the outside of oleic acid/POPC (90%/10%) and pure POPC membranes in the presence of R3F3 and R3W3 peptides. Control samples had no peptide added. For each image, the left panel shows the DIC image and the right panel shows AlexaFluor647 fluorescence. The scale bar is 20 mm.

Microscopy of encapsulated RNA localization to POPC membranes with peptides. Confocal images show that RNA (5'-FAMU$_{15}$, green) encapsulated in POPC vesicles (containing a rhodaminelabeled lipid, red) becomes localized to the membrane of certain vesicles after an overnight incubation with R3F3 and R3W3 peptides. The scale bar is 20 mm.

**Schreibersite** is generally a rare iron-nickel phosphide mineral, \((\text{Fe,Ni})_3\text{P}\), though common in iron-nickel meteorites.

Acidic schreibersite corrosion under anaerobic conditions (10% aq. HCl/N\(_2\)) → soluble forms of phosphorus

\[
(\text{Fe,Ni})_3\text{P} + \text{HCl}_{\text{aq}} \rightarrow \text{H}_2\text{PO}_3^- \rightarrow \text{H}_2\text{P}_2\text{O}_5^{2-}
\]

T. P. Kee *et al.* *Geochimica et Cosmochimica Acta.* 2013 109, 90-112

*Image of schreibersite grain present in a thin-section of the enstatite meteorite, KLE 98300.*

*Image of schreibersite rimmed by kamacite.*

*Slice of the Gebel Kamil Meteorite with schreibersite rimmed by kamacite.*
Radical pathway of the corrosion is suggested. In presence of simple organic molecules (e.g. acetic acid) organophosphorous compounds are detected.

Phospholipids

M. Powner, J. Sutherland Phil. Trans. R. Soc. B 2011, 366, 2870–2877
**Lipids - summary**

Many amphiphilic organic compounds spontaneously form vesicles in water at sufficiently high concentrations.

Current phospholipid membranes likely evolved late. Protocells probably encapsulated by fatty acids, fatty alcohols, prenyl oligomers, or phosphorylated alcohols.

Nucleolipids are proposed as intermediates in templated oligonucleotide replication.

Phosphorus was accessible upon corrosion of meteorite materials and could be incorporated into lipids.
**The origin of small reactive intermediates**

*Schreibersite* (Fe,Ni)$_3$P, from iron-nickel meteorites: source of phosphorus, iron and nickel

Under more neutral conditions phosphates recombine with iron → **Fe$_3$(PO$_4$)$_2$$^\text{vivianite}$**

It should be re-solubilized to become accessible for following chemical transformations

HCN – the crucial reactive intermediate – burning of carbon-rich chondrite meteorites into redox-neutral atmosphere containing N$_2$ and water

$$\text{Fe}_3(\text{PO}_4)_2 + 18\text{CN}^- \rightarrow 2\text{PO}_4^{3-} + 3[\text{Fe(CN)}_6]^{4-}$$

Two important functions: solubilization of phosphates and concentration of atmospheric HCN deposited as salts of mono- and divalent cations (Na, K, Mg, Ca)

Similar reactions take place with insoluble copper and nickel sulfides deposited by iron-nickel meteorite impacts (same occurrence as schreibersite, rich mining sources of these metals until today)

$$\text{NiS} + \text{H}_2\text{O} + 6\text{CN}^- \rightarrow [\text{Ni(CN)}_6]^{4-} + \text{HS}^- + \text{OH}^-$$

$$\text{Cu}_2\text{S} + \text{H}_2\text{O} + 6\text{CN}^- \rightarrow 2[\text{Cu(CN)}_3]^{2-} + \text{HS}^- + \text{OH}^-$$
The origin of small reactive intermediates

Thermal decomposition of cyanoferrates (volcanic):

\[
\begin{align*}
\text{(Na,K)}_4[\text{Fe(CN)}_6] & \xrightarrow{700^\circ C} 4(\text{Na/K})\text{CN} + \text{Fe(CN)}_2 \\
3\text{Fe(CN)}_2 & \xrightarrow{700^\circ C} \text{Fe}_3\text{C} + 5\text{C} + 3\text{N}_2 \\
\text{Fe(CN)}_2 & \xrightarrow{700^\circ C} \text{Fe} + 2\text{C} + \text{N}_2 \\
\text{Ca}_2[\text{Fe(CN)}_6] & \xrightarrow{660^\circ C} 2\text{Ca(CN)}_2 + \text{Fe(CN)}_2 \\
\text{Ca(CN)}_2 & \xrightarrow{660^\circ C} \text{CaNCN} + \text{C} \xrightarrow{1000^\circ C} \text{CaC}_2 + \text{N}_2 \\
\text{Mg}_2[\text{Fe(CN)}_6] & \xrightarrow{315^\circ C} 2\text{Mg(CN)}_2 + \text{Fe(CN)}_2 \\
\text{Mg(CN)}_2 & \xrightarrow{395^\circ C} \text{MgCN}_2 + \text{C} \\
3\text{MgCN}_2 & \xrightarrow{420^\circ C} \text{Mg}_3\text{N}_2 + 3\text{C} + 2\text{N}_2
\end{align*}
\]

Action of water (buffered to neutral or slightly acidic) on that mixture produced concentrated HCN solution + cyanamide (from CaNCN) + acetylene (from CaC₂) + ammonia (from Mg₃N₂)

\[
\text{Cu}_2\text{S} + \text{H}_2\text{O} + 6\text{CN}^- \rightarrow 2[\text{Cu(CN)}_3]^{2-} + \text{HS}^- + \text{OH}^- \\
\text{cyancuprates and HS}^- \text{are delivered by this process}
\]

Photoredox cycle based on cyanocuprates may convert HCN into cyanogen

\[
\begin{align*}
\text{Cu}_2\text{S} + \text{H}_2\text{O} + 6\text{CN}^- & \rightarrow 2[\text{Cu(CN)}_3]^{2-} + \text{HS}^- + \text{OH}^- \\
\text{cyancuprates and HS}^- & \text{are delivered by this process}
\end{align*}
\]
Nucleotides - components

Purines
- Adenine
- Guanine

Pyrimidines
- Cytosine
- Uracil
- Thymine

Nitrogenous bases:
- Adenine
- Thymine
- Guanine
- Cytosine

Hydrogen bonds
3' 5'

Sugar-phosphate backbone
Nucleotides - nucleobases + sugars

Deoxyribose used in DNA backbone

Ribose used in RNA backbone

Nitrogenous Bases of RNA

- Uracil
- Cytosine
- Adenine
- Guanine

Key:
- H: Hydrogen
- O: Oxygen
- C: Carbon
Summary

Increasing complexity from molecules to systems
Summary