

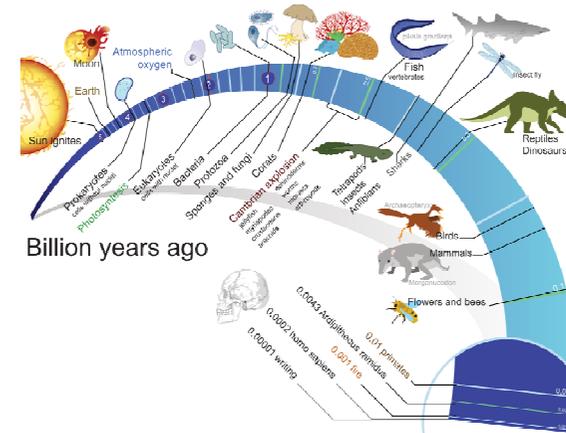
## Topic 2 The primordial soup



WS 2016  
*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."*

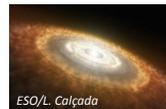
### When life originated on Earth?

#### 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 – 2500 Ma – cells remaining prokaryotes appear  
*first chemoautotrophes: oxidize inorganic material to get energy, CO<sub>2</sub> – 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<sub>x</sub>) (*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“

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



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. CO<sub>2</sub>, NH<sub>3</sub>, H<sub>2</sub>O

„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 → ribosome

nucleotide polymerization → DNA/RNA polymerases

### 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
  - 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

### Proteinogenic aminoacids

genetically encoded

**Twenty-One Amino Acids**

**A. Amino Acids with Electrically Charged Side Chains**

- Positive:** Arginine (Arg), Lysine (Lys), Histidine (His)
- Negative:** Aspartic Acid (Asp), Glutamic Acid (Glu)

**B. Amino Acids with Polar Uncharged Side Chains**

- Serine (Ser), Threonine (Thr), Asparagine (Asn), Glutamine (Gln)

**C. Special Cases**

- Cysteine (Cys), Selenocysteine (Sec), Glycine (Gly), Proline (Pro)

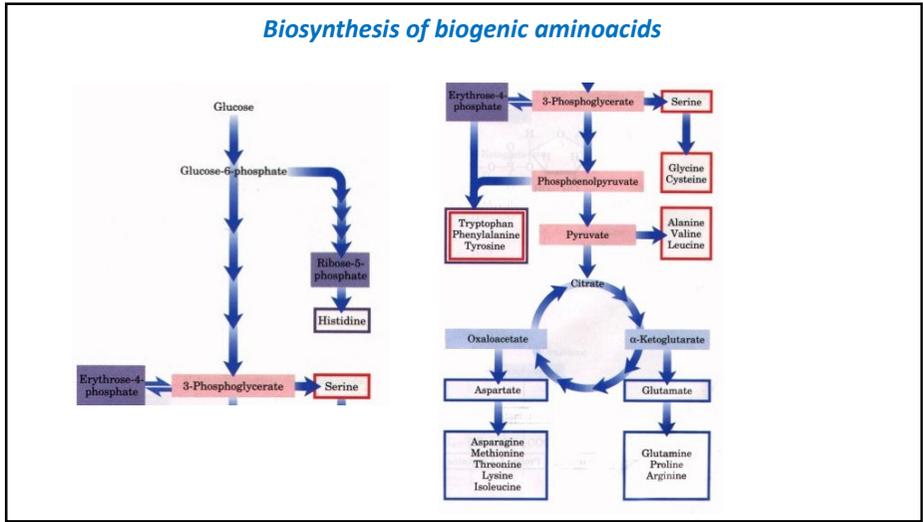
**D. Amino Acids with Hydrophobic Side Chains**

- Alanine (Ala), Valine (Val), Isoleucine (Ile), Leucine (Leu), Methionine (Met), Phenylalanine (Phe), Tyrosine (Tyr), Tryptophan (Trp)

**All amino acids**

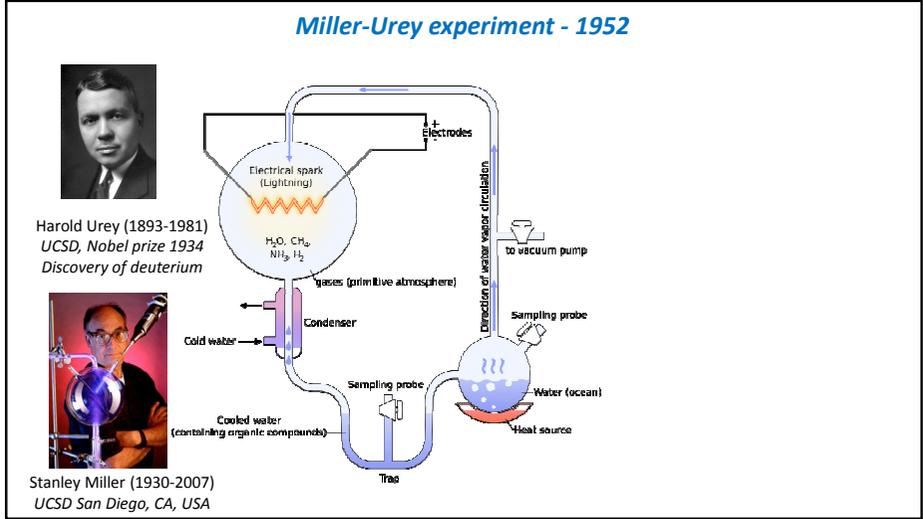
- One (or two) hydrogen(s) on  $\alpha$ -carbon
- L-stereo-isomers (20 Encoded)
- D-stereo-isomers (3 Special)
- Proteinogenic AAs (Added during translational)
- Added in Non-ribosomal peptides
- Post-translationally added AAs

By Matteo Ferla

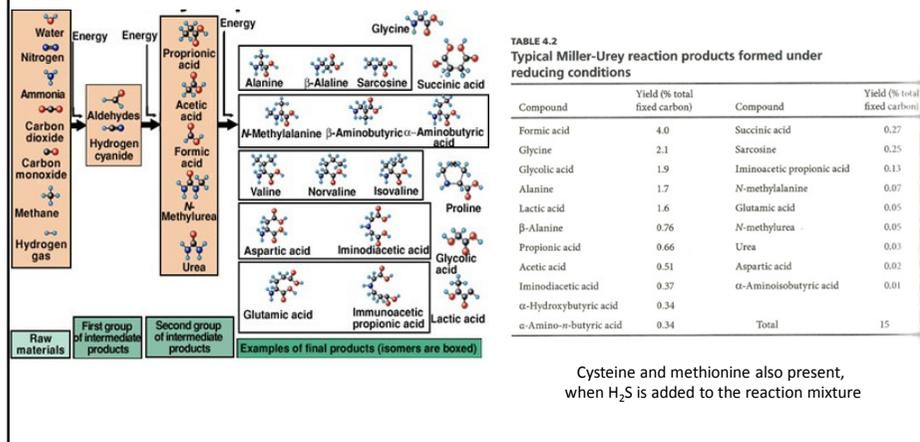


### Atmosphere composition for young terrestrial planets

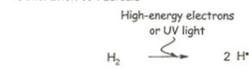
	Reduced	Neutral	Oxic
Carbon (C)	CH <sub>4</sub>	CO, CO <sub>2</sub>	CO <sub>2</sub>
Nitrogen (N)	NH <sub>3</sub>	N <sub>2</sub>	N <sub>2</sub>
Oxygen (O)	H <sub>2</sub> O	H <sub>2</sub> O, CO, CO <sub>2</sub>	O <sub>2</sub>
Hydrogen (H)	H <sub>2</sub> , CH <sub>4</sub> , NH <sub>3</sub> , H <sub>2</sub> O	H <sub>2</sub> O	H <sub>2</sub> O



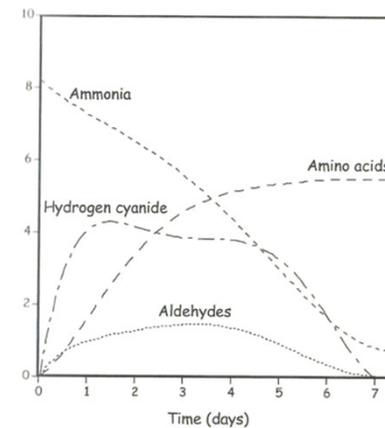
### Products of the Miller-Urey experiment



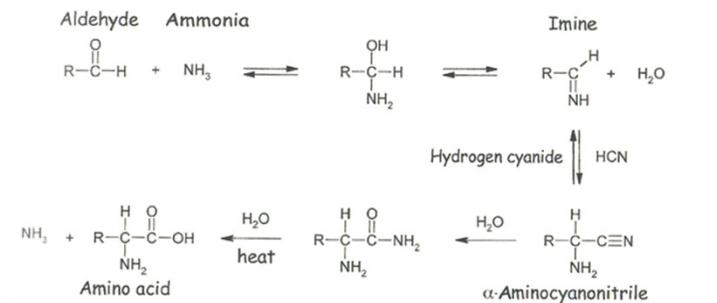
### Generation of radicals



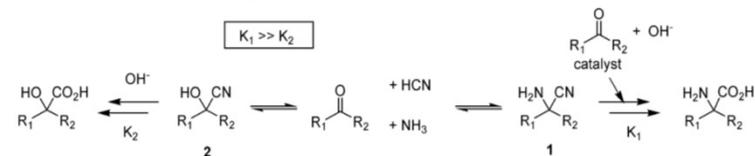
### Radical reactions



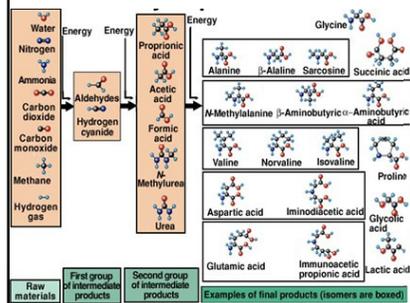
### Strecker reaction



### Scheme 1. Synthesis of $\alpha$ -Amino Acids through the Strecker Reaction



### $\alpha$ -Amino acid production in the Miller-Urey experiment



**TABLE 4.3**  
Yields of the  $\alpha$ -amino acids in the Miller-Urey experiment

Amino acid	Yield ( $\mu$ M)	Amino Acid	Yield ( $\mu$ M)
Glycine	440	Norleucine	6
Alanine	790	<b>Isoleucine</b>	5
$\alpha$ -Aminobutyric acid	270	Serine	5
Norvaline	61	Alloisoleucine	5
Aspartate	34	Isovaline	5
$\alpha$ -Aminoisobutyric acid	30	<b>Proline</b>	2
Valine	20	Threonine	1
Leucine	11	Allothreonine	1
Glutamate	8	<i>Tert</i> -Leucine	0.02

Note: Proteogenic amino acids in bold type.

### Modifications of the Miller-Urey experiment

Researcher(s)	Year	Reactants	Energy source	Results	Probability
Miller	1953	$\text{CH}_4, \text{NH}_3, \text{H}_2\text{O}, \text{H}_2$	Electric discharge	Simple amino acids, organic compounds	unlikely
Abelson	1956	$\text{CO}, \text{CO}_2, \text{N}_2, \text{NH}_3, \text{H}_2, \text{H}_2\text{O}$	Electric discharge	Simple amino acids, HCN	unlikely
Groth and Weysenhoff	1957	$\text{CH}_4, \text{NH}_3, \text{H}_2\text{O}$	Ultraviolet light (1470–1294 ?)	Simple amino acids (low yields)	under special conditions
Bahadur, et al.	1958	Formaldehyde, molybdenum oxide	Sunlight (photosynthesis)	Simple amino acids	possible
Pavolvskaya and Pasynskii	1959	Formaldehyde, nitrates	High pressure Hg lamp (photolysis)	Simple amino acids	possible
Palm and Calvin	1962	$\text{CH}_4, \text{NH}_3, \text{H}_2\text{O}$	Electron irradiation	Glycine, alanine, aspartic acid	under special conditions
Harada and Fox	1964	$\text{CH}_4, \text{NH}_3, \text{H}_2\text{O}$	Thermal energy (900–1200° C)	14 of the "essential" amino acids of proteins	under special conditions
Oró	1968	$\text{CH}_4, \text{NH}_3, \text{H}_2\text{O}$	Plasma jet	Simple amino acids	unlikely
Bar-Nun et al.	1970	$\text{CH}_4, \text{NH}_3, \text{H}_2\text{O}$	Shock wave	Simple amino acids	under special conditions
Sagan and Khare	1971	$\text{CH}_4, \text{C}_2\text{H}_6, \text{NH}_3, \text{H}_2\text{O}, \text{H}_2\text{S}$	Ultraviolet light (>2000 ?)	Simple amino acids (low yields)	under special conditions

### Modifications of the Miller-Urey experiment

Yoshino et al.	1971	$\text{H}_2, \text{CO}, \text{NH}_3$ , montmorillonite	Temperature of 700°C	Glycine, alanine, glutamic acid, serine, aspartic acid, leucine, lysine, arginine	unlikely
Lawless and Boynton	1973	$\text{CH}_4, \text{NH}_3, \text{H}_2\text{O}$	Thermal energy	Glycine, alanine, aspartic acid, ?-alanine, N-methyl-?-alanine, ?-amino-n-butyric acid.	under special conditions
Yanagawa et al.	1980	Various sugars, hydroxylamine, inorganic salts,	Temperature of 105°C	Glycine, alanine, serine, aspartic acid, glutamic acid	under special conditions
Kobayashi et al.	1992	$\text{CO}, \text{N}_2, \text{H}_2\text{O}$	Proton irradiation	Glycine, alanine, aspartic acid, ?-alanine, glutamic acid, threonine, ?-aminobutyric acid, serine	possible
Hanic, et al.	1998	$\text{CO}_2, \text{N}_2, \text{H}_2\text{O}$	Electric discharge	Several amino acids	possible

### Amino acid production under hydrothermal conditions

$\text{Ni}(\text{OH})_2/\text{KCN}/\text{CO}$  in alkaline aqueous conditions (80–120°C)  $\rightarrow$   $\alpha$ -amino and  $\alpha$ -hydroxyacids  
Huber, C.; Wächtershäuser, G. *Science* **2006**, *314*, 630–632

$\text{Ca}(\text{OH})_2/\text{NiSO}_4/\text{KCN}/\text{CO}$  in alkaline (pH 9.1–12.9) aqueous conditions (145–280°C)  $\rightarrow$   $\alpha$ -amino and  $\alpha$ -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

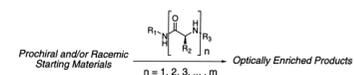


Murchison meteorite  
chondrite

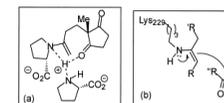
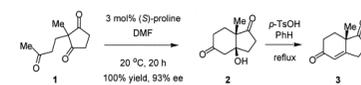
Table 1. Soluble Organic Compounds in the Murchison Meteorite<sup>a</sup>

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

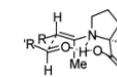
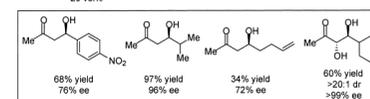
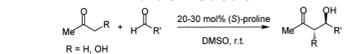
## Catalytic properties of aminoacids - organocatalysis



### Robinson annulation



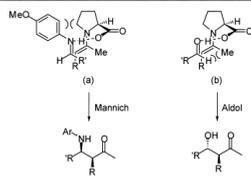
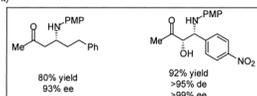
### aldol reaction



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

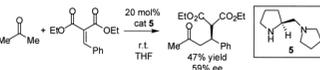
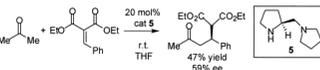
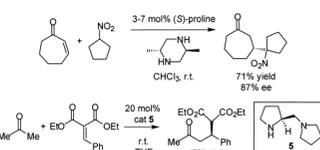
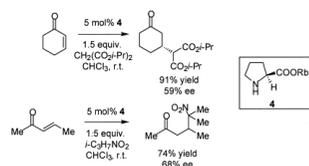
## Catalytic properties of aminoacids - organocatalysis

### Mannich reaction



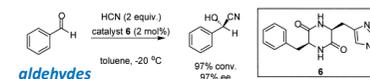
Jarvo, E. R., Miller, S. J. *Tetrahedron* **2002**, *58*(13), 2481-2495.

### Michael addition

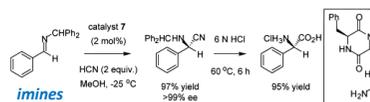
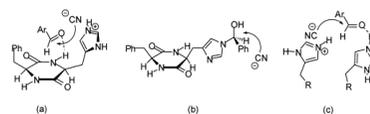


## Catalytic properties of aminoacids - organocatalysis

### Hydrocyanation



aldehydes



imines

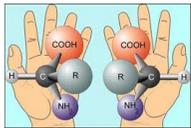
asymmetric Strecker reaction!!!

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 enantio-purity  
 → 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:

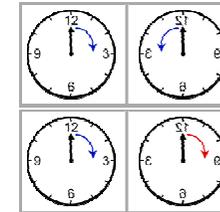
- The parity violation
- Stochastic symmetry disturbances

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

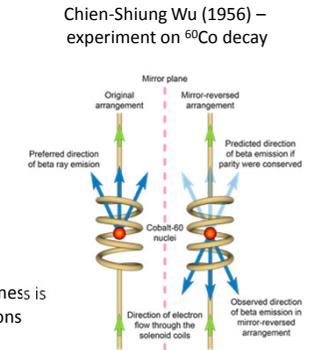
### The parity violation – Wu experiment

Mirror image of the world does not behave exactly like the world itself  
 because **TIME GOES UNIDIRECTIONALLY**

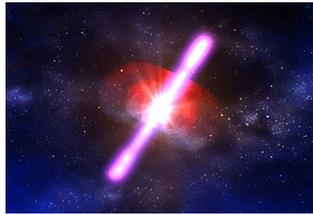
In a mirror, time will not go BACKWARDS!



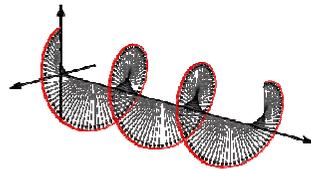
Differentiation in left and right handedness is inherent property of weak interactions



### The origins of homochirality

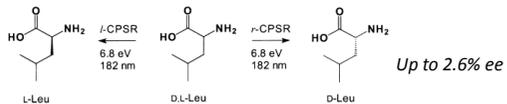


Circularly polarized light (CPL) from gamma ray bursts



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

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



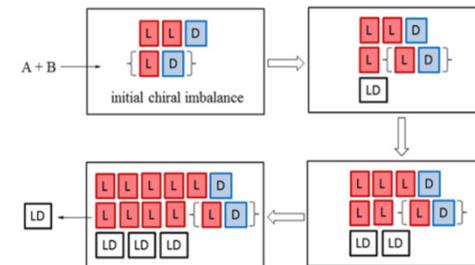
Meierhenrich, U. J.; Nahon, L.; Alcaraz, C.; Bredehoft, J. H.; Hoffmann, S. V.; Barbier, B.; Brack, A. Angew. Chem., Int. Ed. 2005, 44, 5630

### Stochastic induction of asymmetry – Frank model

Reactions (3) and (4) are autocatalytic

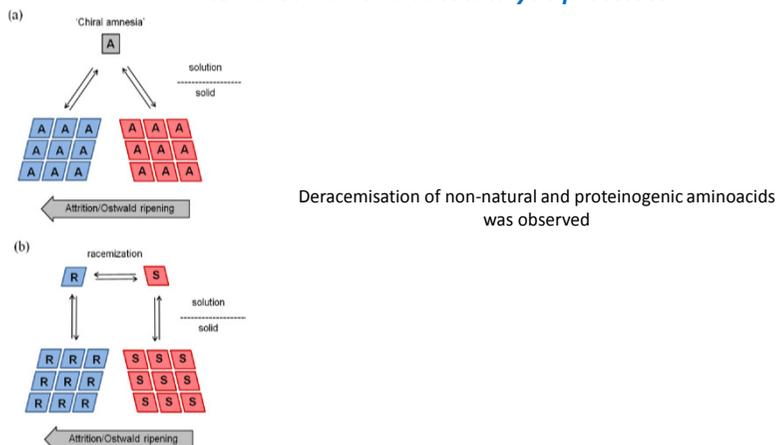
- (1)  $A + B \xrightleftharpoons[K_{-1}]{K_1} \text{L}$
- (2)  $A + B \xrightleftharpoons[K_{-1}]{K_1} \text{D}$
- (3)  $A + B + \text{L} \xrightleftharpoons[K_{-2}]{K_2} \text{L L}$
- (4)  $A + B + \text{D} \xrightleftharpoons[K_{-2}]{K_2} \text{D D}$
- (5)  $\text{L} + \text{D} \xrightleftharpoons[K_{-3}]{K_3} \text{LD}$

Open flux reactor in non-equilibrium stationary state

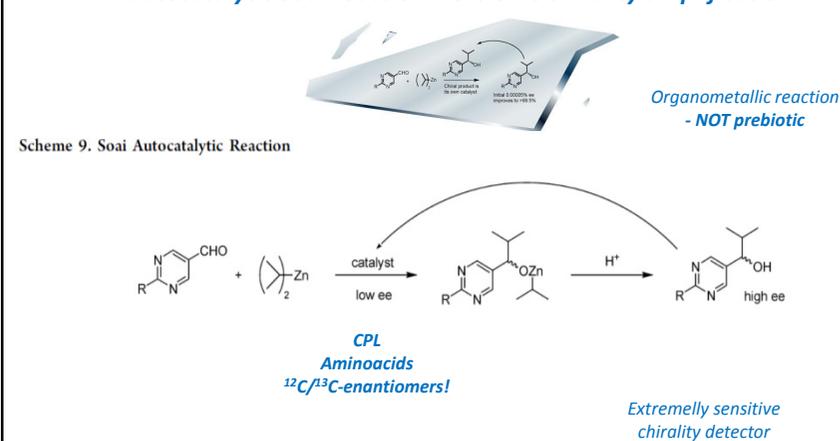


If a chiral dissipative structure catalyzes its own formation and inhibits formation of the opposite enantiomer, any stochastic symmetry breaking in the system will be amplified

### External stimuli and autocatalytic processes

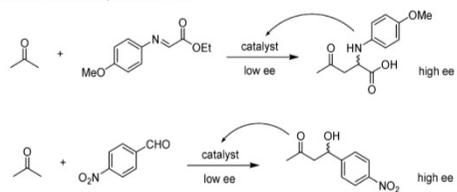


### autocatalytic Soai reaction – extreme chirality amplification



### autocatalytic organic reactions

Scheme 10. Mannich and Aldol Autocatalytic Reactions<sup>47</sup>



Meaningful transformations for the prebiotic syntheses of aminoacids and sugars

### Organocatalysis – the origin of homochirality

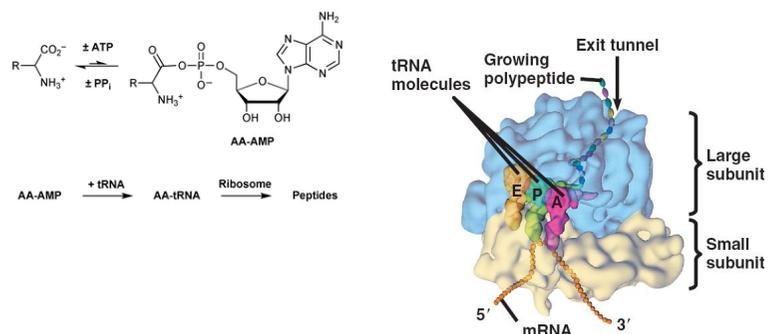
Table 1. Enantiomeric concentration amplification of phenylalanine after two crystallizations from water

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  $\alpha$ -alkyl amino acids could form solutions with high ee values that were needed for the beginning of biology.



### Biochemical condensation of aminoacids into peptides



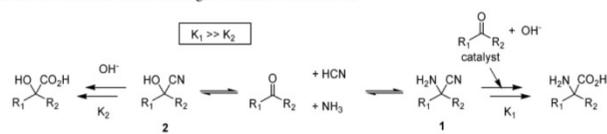
### Prebiotically relevant peptide condensation agents

Entry	Activating agent	Hydrolysis/hydration product	$\Delta G^{0'}$ / kJ mol <sup>-1</sup>
1	NH <sub>2</sub> CONH <sub>2</sub>	CO <sub>2</sub> + NH <sub>3</sub>	-16 <sup>a</sup>
2	COS (g)	CO <sub>2</sub> + H <sub>2</sub> S	-17 <sup>a</sup>
3	Pyrophosphate	Phosphate	-19 <sup>b</sup>
4	CO (g)	HCO <sub>2</sub> H	-16 <sup>a</sup>
5	HNCO	CO <sub>2</sub> + NH <sub>3</sub>	-54 <sup>a</sup>
6	HCN	HCO <sub>2</sub> H + NH <sub>3</sub>	-75 <sup>a</sup>
7	RCN	RCO <sub>2</sub> H + NH <sub>3</sub>	-80 <sup>c</sup>
8	NH <sub>2</sub> CN	Isourea	-83 <sup>d</sup>
9	HNCNH	Isourea	-97 <sup>d</sup>
10	HCCH (g)	CH <sub>3</sub> CHO	-112 <sup>d</sup>

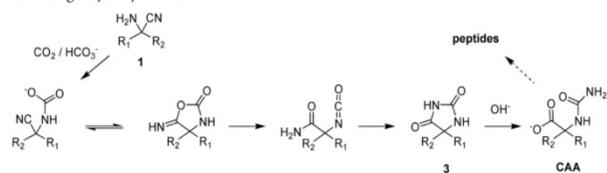
Danger, G.; Plasson, R.; Pascal, R. *Chem. Soc. Rev.* **2012**, *41*, 5416.

### Condensation of aminoacids into peptides

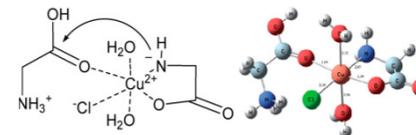
Scheme 1. Synthesis of  $\alpha$ -Amino Acids through the Strecker Reaction



Scheme 2. Bücherer–Bergs Hydrolysis of  $\alpha$ -Aminonitriles

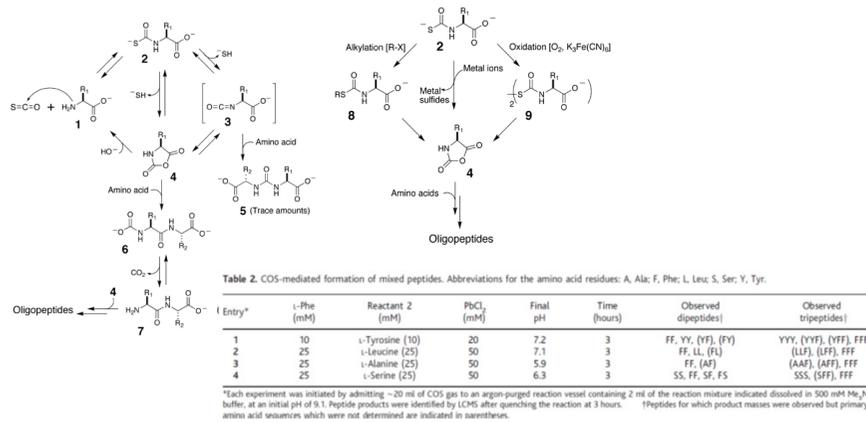


### Salt-induced peptide formation (SPIF)

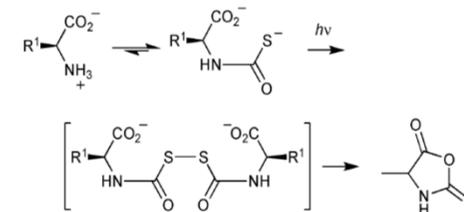


SPIF copper complex geometry with two glycine ligands, optimized by ab initio Hartree–Fock calculations.  
Rode, B. M.; Fitz, D.; Jakschitz, T. *Chem. Biodiversity* **2007**, *4*, 2674.

### Carbonyl sulfide – condensing agent



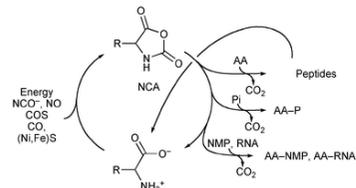
### Carbonyl sulfide – photochemical activation



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 (DGo0 = 16.9 kJ mol<sup>-1</sup>)<sup>37</sup> could be able to generate NCA (DGo0 E 60 kJ mol<sup>-1</sup>)<sup>20</sup> in spite of its cyclic structure.

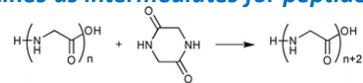
A photochemical activation of thiocarbamate that could take place in a way similar to that of thiocetate in aqueous solution may provide an explanation to this observation. This potential photochemical reaction may also constitute an efficient pathway for the prebiotic formation of NCAs.

### Carbonyl sulfide – photochemical activation

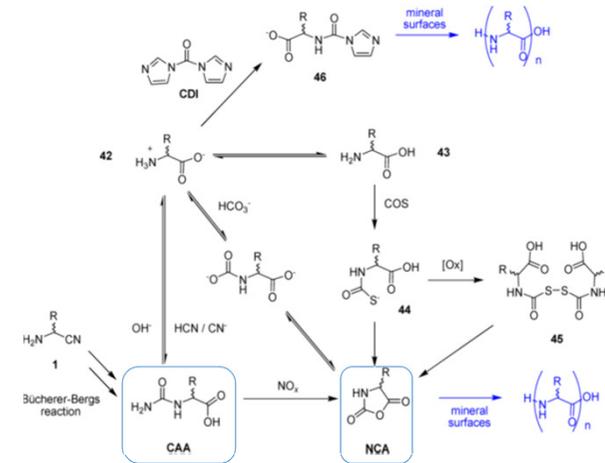


Pathways for the formation of NCAs and further reactions including polymerization and interactions with inorganic phosphate (Pi), nucleotides (NMP), and RNA.

### Diketopiperazines as intermediates for peptide condensation



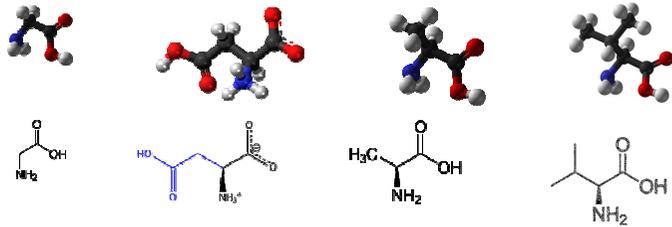
### Condensation of amino acids into peptides



### Basic aminoacids for primitive genetic code?

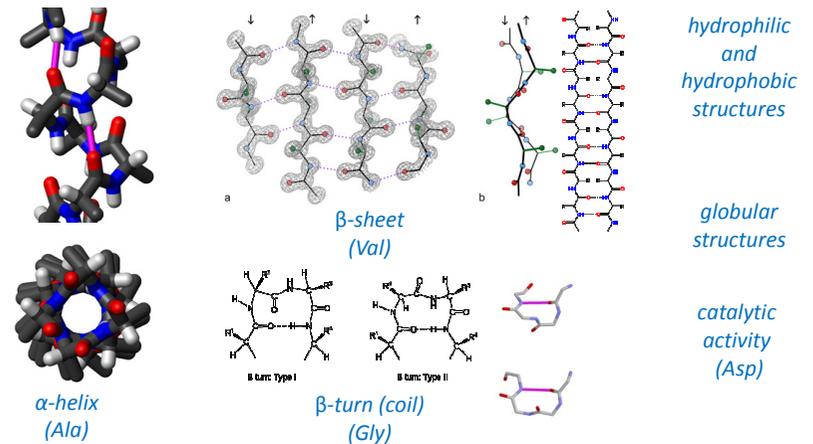
Primordial genetic code might have involved only 4 „GNC” codons:

- 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)

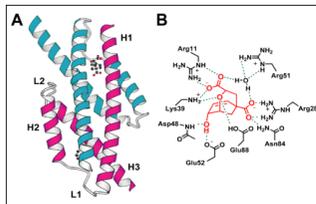
### GADV-protein world



### 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<sup>88</sup> and Ser<sup>84</sup> in EcCM are substituted with Glu<sup>88</sup> and Asn<sup>84</sup> 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.

### 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

