HOMOCHIRALITY, SEED OF TERRESTRIAL LIFE

Hadi Gholami

October 23, 2013
**Chirality**

🌟 1840s - Louis Pasteur studied the crystalline and solution forms of (±)-tartaric acid

🌟 1894 - The introduction of the word “chiral” by Lord Kelvin

**Chiral** comes from the Greek word “Χείρ, Chir” meaning “HAND”

Hands are non-superimposable mirror images

(S) “Sinister” LEFT

(R) “Rectus” RIGHT
Types of Chirality

*Point chirality*

\[
\text{H}_3\text{C} - \text{CO}_2\text{H} \quad \text{(S)}
\]

\[
\text{H}_2\text{N} - \text{NH}_2 - \text{H} \quad \text{(R)}
\]

\[
\text{H}_2\text{N} - \text{H} \quad \text{(S)}
\]

\[
\text{H}_3\text{C} - \text{CO}_2\text{H} \quad \text{(S)}
\]
Types of Chirality

Point chirality

Helical chirality

(S)

(R)

(P)

(M)
Types of Chirality

**Point chirality**

- **H$_3$C$\longrightarrow$NH$_2$**
  - (S)
- **H$_3$C$\longrightarrow$CO$_2$H**
  - (R)

**Helical chirality**

- **[Image](image1.png)**

**Axial chirality**

- **[Image](image2.png)**
- **[Image](image3.png)**
- **[Image](image4.png)**
Different Chirality, Different Properties?

Different Taste
- S,S-isomer of Aspartame
- R,R-isomer of Aspartame

Different Smell
- (R) Spearmint oil
- (S) Caraway oil
- (R) Limonene
- (S) Limonene

Pharmaceuticals: Chirality matters!

(S)-Thalidomide

(R)-Thalidomide

(S)-isomer had the desired antinausea effects

(R)-form caused fetal abnormalities

Pharmaceuticals: Chirality matters!

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Homochirality and Life

**Homochirality**: Nature selects almost exclusively one enantiomer over the other as building blocks for living organisms.
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Homochirality: Nature selects almost exclusively one enantiomer over the other as building blocks for living organisms.


Progression of Homochirality on Earth

Inducing Initial Enantio Imbalance → Amplification of Initial $ee$ → Expansion of Chiral Pool
Progression of Homochirality on Earth

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Progression of Homochirality on Earth

Inducing Initial Enantio Imbalance -> Amplification of Initial ee -> Expansion of Chiral Pool

By chance ..... 

Circularly Polarized Light (Chiral Light) 

and many more ...
It’s all about light?  
From Prebiotic Soup to Chiral Organisms...

Enantiomeric imbalance was induced by **polarized light**, either somewhere in the universe (extraterrestrial) or directly on earth (terrestrial) resulting in small excess of one enantiomer of the biological building blocks over the other (chiral excess).

3.6-3.8 billion years ago
Stanley Miller’s Experiment

Light Storm

Energy from the spark drives the reaction between molecules

Water vapor was provided into the artificial atmosphere

Organic molecules including some **amino acids** were detected after a few days

http://www.studyblue.com/notes/n/exam-3-flashcards/deck/2577056
Revised Stanley Miller’s Experiment

UV photolysis of the mixture on ice
\[ \text{H}_2\text{O}:\text{CH}_3\text{OH}:\text{NH}_3:\text{HCN} \]
20:2:1:1

Revised Stanley Miller’s Experiment

UV photolysis of the mixture on ice

\[ \text{H}_2\text{O} : \text{CH}_3\text{OH} : \text{NH}_3 : \text{HCN} \]

20:2:1:1

- Light can induce biological building block formation.
- Non-chiral light cannot induce enantio excess (Homochirality)

What is Chiral Light?

Light → Polarizing Filter → Linear Polarized Light
What is Chiral Light?

Linear Polarized Light

http://www.photophysics.com/tutorials/circular-dichroism-cd-spectroscopy/1-understanding-circular-dichroism
What is Chiral Light?

Linear Polarized Light

Circularly Polarized Light (Chiral Light)

http://www.photophysics.com/tutorials/circular-dichroism-cd-spectroscopy/1-understanding-circular-dichroism
Induction of Chirality on Molecules by Circularly Polarized Light

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Wavelength Irradiated (nm)</th>
<th>Circularity of Light, %</th>
<th>Optical yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>410</td>
<td>75 (RCP)</td>
<td>2.00</td>
</tr>
<tr>
<td>2</td>
<td>390</td>
<td>75 (RCP)</td>
<td>1.96</td>
</tr>
<tr>
<td>3</td>
<td>370</td>
<td>75 (RCP)</td>
<td>1.77</td>
</tr>
<tr>
<td>4</td>
<td>290</td>
<td>75 (LCP)</td>
<td>-0.42</td>
</tr>
</tbody>
</table>

RCP, Right Handed Circular Polarized Light / LCP, Linear Polarized Light

But is There Any Circularly Polarized Light in the Universe?

Creation of Chiral Excess by Circularly Polarized Light
#### Measured Enantiomeric Excesses for $^{13}$C-Alanine

<table>
<thead>
<tr>
<th>Polarization Type</th>
<th>ee L-Ala (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linearly polarized light (LPL)</td>
<td>-0.04</td>
</tr>
<tr>
<td>Left-handed circularly polarized light (L-CPL)</td>
<td>+0.71</td>
</tr>
<tr>
<td>Right-handed circularly polarized light (R-CPL)</td>
<td>-1.34</td>
</tr>
</tbody>
</table>

Can you Induce Chiral Excess in a Racemic Solution Using Circularly Polarized Light?

Enantiomeric excesses obtained after irradiation of racemic leucine with circularly polarized light.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Irradiation</th>
<th>ee (D-Leucine) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0.00</td>
</tr>
<tr>
<td>2</td>
<td>L-CPL</td>
<td>-0.88</td>
</tr>
<tr>
<td>3</td>
<td>R-CPL</td>
<td>2.60</td>
</tr>
</tbody>
</table>

Why Enantiomers Interact Differently with Circularly Polarized Light

\[ g = 2 \frac{\varepsilon_R - \varepsilon_S}{\varepsilon_R + \varepsilon_S} = 2 \frac{k_R - k_S}{k_R + k_S} \]

\( g \) : anisotropy factor
\( \varepsilon \) : extinction coefficient

Thick lines: Anisotropy spectra
Thin lines: corresponding \( e \theta \)

d-Val (orange) and l-Val (black)

H\(_2\)N-\( \text{Valine} \)-CO\(_2\)H

α-methyl L-amino acids were found on meteorites

2 proposed pathways:

**Autocatalysis**: Increase of ee via autocatalytic reactions

**Crystallization**:  
i. Enrichment of enantiomeric purity by conglomerate crystallization in solid phase  
ii. Racemic crystallization driven enantio-enrichment of the liquid phase
Demonstration of Autocatalysis

**Autocatalysis:** The chiral substrate acts as a catalyst for its self-production while suppressing synthesis of its enantiomer.

Proposed reaction scheme of asymmetric autocatalyst of (S)-1


Demonstration of Autocatalysis

Asymmetric autocatalysis of chiral alkanol (1).

Demonstration of Autocatalysis

Asymmetric autocatalysis of chiral alkanol (1).

Relation between the ee of catalyst (S)-1 and ee of the newly formed product (S)-1 in asymmetric autocatalytic reaction of (S)-1.
Racemic crystallization: crystals contain a 1 : 1 ratio of D : L enantiomers.

Conglomerate crystallization: A compound can be crystallized in purely one form of its enantiomer from its racemic mixture in liquid phase. Molecules in the crystal have a greater affinity for the same enantiomer than for the opposite enantiomer.

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Random Chiral Symmetry Breaking During Conglomerate Crystallization

Random D or L homochirality from initial symmetric mixtures of D and L crystals.

sodium chlorate (NaClO$_3$), Racemic solution.

Solid-Solution Equilibrium for an Intrinsically Achiral Molecule

Chiral crystals, L or D in the sample (%)

Na$^+$[\(\text{O} \quad \text{O}^{-} \quad \text{Cl}^{-}\)]

Controlled Chiral Symmetry Breaking During Conglomerate Crystallization

sodium chlorate (NaClO₃)

Any small initial crystal enantiomeric excess (CEE) eventually gives rise to total crystal purity disappearing the less abundant enantiomer (100% CEE)

Conglomerate Crystallization for Molecules with Intrinsic Chirality

Solid-Solution Equilibrium for an Intrinsically Achiral Molecule

Conglomerate Crystallization for Molecules with Intrinsic Chirality

Solid-Solution Equilibrium for an Intrinsically Achiral Molecule

Solid-Solution Equilibrium for a Chiral Molecule Undergoing Solution-Phase Racemization

Single Solid Chiral State from a Nearly Racemic Amino Acid Derivative

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Chemical and Physical Equilibria in the Racemization and Crystallization / Dissolution Processes for 1.

Solid-Solution Equilibrium for a Chiral Molecule Undergoing Solution-Phase Racemization

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Single Solid Chiral State from a Nearly Racemic Amino Acid Derivative

\[ \text{DBU} \quad \text{MeOH or MeCN} \quad 25^\circ \text{C} \]

\[ (S)-1 \]  
\[ (R)-1 \]

\[ (S)-1 \text{ (solid)} \]  
\[ (R)-1 \text{ (solid)} \]

Attrition-enhanced evolution of solid-phase ee for 1 in MeCN: starting from initial ee values of 1 as shown.

Evolution of Solid Phase Homochirality for a Natural Amino Acid

Evolution of Solid Phase Homochirality for a Natural Amino Acid

Racemic Crystallization Driven Liquid Phase ee Amplification

- Many compounds, including amino acids, their racemates are less soluble than the pure enantiomers.

\[
\text{Ph} \begin{array}{c} \text{CO}_2\text{H} \\ \text{NH}_2 \end{array}
\]

L-phenylalanine 1% ee, ≈500 mg

\[
\text{slow evaporation}
\]

Racemic crystals (≈ 400 mg)

\[
\text{solid removal}
\]

solution with 40% ee L-phenylalanine

Racemic Crystallization Driven Liquid Phase ee Amplification

- Many compounds, including amino acids, their racemates are less soluble than the pure enantiomers.

**L-phenylalanine**

- 1% ee, ≈500 mg
- 40% ee, ≈500 mg

**Racemic crystals**

- (≈ 400 mg)
- (≈ 100 mg)

**Solution**

- water solution with 40% ee L-phenylalanine
- water solution with 90% ee L-phenylalanine

Enantiomeric concentration amplification of phenylalanine after two crystallizations from water.

Racemic Crystallization Driven Liquid Phase ee Amplification

A solution with a small ee of an amino acid component were allowed to evaporate, there would be selective precipitation of the racemate crystals, leading to amplification of the ee concentration in solution.

<table>
<thead>
<tr>
<th>Component</th>
<th>Initial ee, %</th>
<th>Final ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-Phenylalanine</td>
<td>10</td>
<td>90.0</td>
</tr>
<tr>
<td>L-Phenylalanine</td>
<td>5</td>
<td>91.7</td>
</tr>
<tr>
<td>D-Phenylalanine</td>
<td>1</td>
<td>87.2</td>
</tr>
<tr>
<td>L-Phenylalanine</td>
<td>10</td>
<td>88.3</td>
</tr>
<tr>
<td>L-Phenylalanine</td>
<td>5</td>
<td>88.6</td>
</tr>
<tr>
<td>L-Phenylalanine</td>
<td>1</td>
<td>90.9</td>
</tr>
</tbody>
</table>

Enantiomeric concentration amplification of phenylalanine after two crystallizations from water.

Application of chiral amino acid to catalyze the prebiotic synthesis of other biological building blocks.
Chirality Transfer From $\alpha$-Methyl Amino Acids

$\alpha$-methyl L-valine + $\alpha$-keto carboxylates

Cu$^{2+}$

- CO$_2$

H$^+$ transfer from $\alpha$-methyl valine

Natural L-amino acids

Sugars Synthesis Catalyzed with $\alpha$-Methyl Amino Acids

\[
\text{glycoaldehyde} + \text{S-isovaline} \\
\text{Asymmetric aldol}
\]

\[
\begin{align*}
\text{L-thereose} & : \text{HO} \cdots \text{OH} \\
\text{D-thereose} & : \text{HO} \cdots \text{OH} \\
\text{L-erythrose} & : \text{HO} \cdots \text{OH} \\
\text{D-erythrose} & : \text{HO} \cdots \text{OH}
\end{align*}
\]

Sugars Synthesis Catalyzed with α-Methyl Amino Acids

\[
\text{glycoaldehyde} + \text{S-isovaline} \xrightarrow{\text{Asymmetric aldol}} \begin{cases} \text{L-thereose} \\ \text{D-thereose} \\ \text{L-erythrose} \\ \text{D-erythrose} \end{cases}
\]

Sugars Synthesis Catalyzed with $\alpha$-Methyl Amino Acids

\[
\text{glycoaldehyde} + \text{S-isovaline} \xrightarrow{\text{Asymmetric aldol}} \text{L-thereose} \quad \text{D-thereose} \quad \text{L-erythrose} \quad \text{D-erythrose}
\]

Enantiomeric excess (%) of amino acid catalysts:

- S-Iva (100%)
- R-Iva (100%)
- R-Iva (75%)
- R-Iva (50%)
- R-Iva (25%)
- R-Iva (10%)
- R-Iva (5%)
- DL-Ala (0%)
- D-Ala (100%)
- L-Ala (100%)

Sugars Synthesis Catalyzed with α-Methyl Amino Acids

\[
\text{glycoaldehyde} + \text{S-isovaline} \rightarrow \text{Asymmetric aldol}
\]

\[
\begin{align*}
\text{L-thereose} & \quad \text{D-thereose} \\
\text{L-erythrose} & \quad \text{D-erythrose}
\end{align*}
\]

Enantiomeric excess (%) of amino acids catalyzed with α-Methyl Amino Acids:

- L-(s)-Isovaline: 100%
- D-(s)-Valine: 100%
- L-(s)-Valine: 100%
- L-(s)-Isoleucine: 100%

**Sugars Synthesis Catalyzed with Amino Acids**

![Chemical structures and reactions](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Amino acid</th>
<th>Glyceraldehyde ratio D/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CH₂OH</td>
<td>L-erine</td>
<td>50.3/49.7</td>
</tr>
<tr>
<td>-CH₃</td>
<td>L-alanine</td>
<td>50.8/49.2</td>
</tr>
<tr>
<td>-CH(CH₃)₂</td>
<td>L-valine</td>
<td>52.2/47.8</td>
</tr>
<tr>
<td>-CH₂-C₆H₅</td>
<td>L-phenylalanine</td>
<td>52.2/47.8</td>
</tr>
<tr>
<td>-CH₂-CH(CH₃)₂</td>
<td>L-leucine</td>
<td>54.4/45.6</td>
</tr>
<tr>
<td>-CH₂CH₂CO₂H</td>
<td>L-glutamic acid</td>
<td>60.7/39.3</td>
</tr>
<tr>
<td>♂</td>
<td>L-proline</td>
<td>28.9/71.1</td>
</tr>
</tbody>
</table>

pH Dependent Proline Catalyzed Amination of Aldehydes

\[ \text{R}^1\text{CHO} + \text{R}^2\text{O}_2\text{C}-\text{N}^2\text{N}-\text{CO}_2\text{R}^2 \rightleftharpoons \overset{1)}{\text{Catalyst}} \overset{2)}{\text{NaBH}_4} \overset{3)}{\text{NaOH}} \rightarrow \overset{*}{\text{N-HCO}_2\text{R}^2} \]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>ee, %</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CO}_2\text{H} )</td>
<td>85%</td>
<td>(R)</td>
</tr>
<tr>
<td>( \text{CO}_2\text{H} ), DBU</td>
<td>48%</td>
<td>(S)</td>
</tr>
<tr>
<td>( \Theta \text{CO}_2\text{Bu}_4\text{N} )</td>
<td>60%</td>
<td>(S)</td>
</tr>
</tbody>
</table>

Enantiomeric Excess of Glyceraldehyde in the Presence of Proline and Prolinate Catalysts

Glycoaldehyde + Formaldehyde

L-proline

\begin{align*}
\text{L-Glyceraldehyde} & : (8\% \text{ ee}) \\
\text{D-Glyceraldehyde} & : (13\% \text{ ee})
\end{align*}

\begin{align*}
\text{Glycoaldehyde} & + \text{Formaldehyde} \\
\text{L-proline} & \quad \rightarrow \\
\text{L-Glyceraldehyde} & \quad (8\% \text{ ee}) \\
\text{D-Glyceraldehyde} & \quad (13\% \text{ ee})
\end{align*}

\begin{align*}
\text{Glycoaldehyde} & + \text{Formaldehyde} \\
\text{L-proline} & \quad \rightarrow \\
\text{L-Glyceraldehyde} & \quad (17\% \text{ ee})
\end{align*}

Conclusion

- We are all surrounded by chiral objects.
- Circularly polarized light can be a chiral template to induce chirality into biologically building blocks.
- L-Amino acids (natural and/or unnatural (α-methyl) amino acids) can be one of the primary chiral product formed in small ee under influence of chiral light.
- Small ee can be amplified via chemical and physical processes.
- L-Amino acids can act as chiral templates to induce chirality into other biological building blocks (D-sugars).
- It has been proposed that the observed homochirality on earth (L-amino acids and D-sugars) was selected to match with the overall chirality of this part of the universe.
Acknowledgements

Professor Babak Borhan

Professor Xuefei Huang

Dr. Chryssoula Vassiliou

Group members:

Arvind, Kumar, Carmin, Calvin

Tanya, Ipek, Maisam, Nastaran, Bardia, Yi,

Eddie, Elizabeth, Jun, Wei, Ding.

Mina

and

All of you for your attention.