"Deducing the mechanism of the origin of life on earth has always remained a fascinating but unsolved puzzle. Some have even considered it too difficult for scientific study, because the direct evidence is long gone, and we can only work by plausible inference."


"It's a long way from slime to Mozart."

D.G. Blackmond quoting G.M. Whitesides (Scripps Lecture, 2008)

"...Among the scientists engaged in active research on the problem of biogenesis, native synthetic organic chemists are a small minority; scientists actively moving behind a merely passive interest in this basic problem are mostly biologists, biochemists, physical chemists, physicists, earth and planetary scientists. The situation is in a way reminiscent of the DNA structure problem, which had been attacked and solved by non-chemists and, in retrospect, revealed itself as one that would have been a major, if not the major problem that nature had in store for natural products chemistry."

"Biogenesis, as a problem of science, is lastly going to be a problem of synthesis. The origin of life cannot be 'discovered', it has to be re-invented."


1. **Primitive Chemical Synthesis**: What is possible in a laboratory setting?
2. **Chirality**: How and where did it come from?
**Origins of organic compounds:**

This would appear simple in theory:

A. They came here

or

B. They were made here

**Murchison Meteorite**

At 11 am (local time) on September 28th, 1969 a large type carbonaceous chondrite type meteorite fell in the small town of Murchison in Victoria, Australia. Its organic composition has spawned a flurry of interest that continues even into the 21st century

"Evidence for Extraterrestrial Amino-Acids and Hydrocarbons in the Murchison Meteorite"


-Analysis of the meteorite indicated glycine, alanine, glutamic acid, valine, and proline, 2-methylalanine, sarcosine, and a "complex mixture of alkanes."

-Both enantiomers (in nearly equal amounts) were detected for each amino acid

"The unique distribution of amino-acids in the Murchison meteorite cannot be explained satisfactorily on the basis of contamination by human hands."

"Distribution and Enantiomeric composition of amino acids in the Murchison Meteorite"


enantiomeric enrichment of several proteogenic amino acids are reported, while some others (non-proteo) are reported racemic

"On the reported optical activity of amino acids in the Murchison Meteorite"


This paper calls into question Engels data regarding ee's of the amino acids and points to contamination.

"Isotopic Evidence for Extraterrestrial non-racemic amino acids in the Murchison Meteorite"


^15^N abundance shows murchison enantiomers amino acids are not from earth, thus L-amino acids are preferred not only on earth
Atmospheric Conundrum

There is no general agreement on the composition of the primitive earth, with the exception that it was most likely not highly oxidizing (No O₂)

<table>
<thead>
<tr>
<th>Strongly Reducing</th>
<th>Neutral:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₄ + N₂ + H₂O or CH₄ + NH₃ + H₂O</td>
<td>CO₂ + N₂ + H₂O</td>
</tr>
<tr>
<td>favored by prebiotic chemists</td>
<td>favored by</td>
</tr>
<tr>
<td></td>
<td>atmospheric chemists</td>
</tr>
</tbody>
</table>

"Reduction of Carbon Dioxide in Aqueous Solutions by Ionizing Radiation"


General Experiments:

\[ ^{14}\text{CO}_2 + \text{H}_2\text{O} \xrightarrow{\text{He ions (40-meV)}} \ ^{14}\text{CO}_2\text{H} \]

\[ ^{14}\text{CO}_2 + \text{H}_2\text{O} + \text{FeSO}_4 \xrightarrow{\text{He ions (40-meV)}} \ ^{14}\text{CH}_2\text{O} + ^{14}\text{CO}_2\text{H} \]

Conclusion:
- CO₂ can be reduced to CO₂H using solely radiation and H₂O
- The Process can be somewhat efficient in the presence of inorganic additives (in the FeSO₄ experiments, ~25% of the dissolved CO₂ was reduced to a mixture of CO₂H and CH₂O
Prebiotic Chemistry I

**The Urey-Miller Experiment (1953)**

S. L. Miller, *Science*, 1953, 117, 528

"Although Oparin's "prebiotic soup" theory had gained popularity with biologists, it had gone unnoticed in other fields of science."

\[
\text{CH}_4 + \text{NH}_3 + \text{H}_2 \xrightarrow{\text{electric discharge}} \text{H}_2\text{O} \rightarrow \begin{array}{c}
\text{NH}_2 \\
\text{H}_2 \text{N} - \text{CH}_{2} - \text{COOH} \\
\text{H}_2 \text{N} - \text{CH} - \text{CH}_2 - \text{COOH} \\
\text{H}_2 \text{N} - \text{CH}_{2} - \text{COOH} \\
\end{array}
\]
**Prebiotic Amino Acid Chemistry**

- HCN readily forms a oligomeric structures by base catalysis
- As early as 1876, it was shown that mild alkaline hydrolysis of these oligomers yields glycine (R. Wipperman, *Ber.*, 1876, 767. T. Volker, *Angew. Chem.* 1960, 72, 379)

\[
\text{HCN} \xrightarrow{\text{basic pH}} \text{"oligomers"} \xrightarrow{\text{hydrolysis}} \text{H}_2\text{N-COOH}
\]

- This chemistry was extended to show the formation of even more aa's by Oro

"Amino-acid Synthesis from Hydrogen Cyanide under Possible Primitive Earth Conditions"

Like the Oro study this paper concerns the study of Cyanide as a possible precursor to amino acids, however they report additional compounds in the mixture

"Synthesis of Purines Under Possible Primitive Earth Conditions. I. Adenine From Hydrogen Cyanide."
- This is the seminal paper in the field of base pair prebiotic synthesis.

HCN $\xrightarrow{\text{NH}_3 \text{(aq.)}}$ \[ \xrightarrow{70^\circ \text{C}} \text{Adenine} \]

1 L of 11.1 M HCN could yield 685 mg. adenine.

"Synthesis of Purines Under Possible Primitive Earth Conditions. II. Purine Intermediates From Hydrogen Cyanide."

The disclosure of byproducts formed in the previous communication:

4-aminoimidazole-5-carboxamide
4-aminoimidazole-5-carboxamide
formamide
formamidine
glycaminde
glycine
alanine
aspartic acid

"and a large number of other unidentified ultra-violet absorbing and fluorescent compounds"

"An Unusual Photochemical Rearrangement in the Synthesis of Adenine from Hydrogen Cyanide."
**Prebiotic Base Pair Chemistry**

- The identity of the HCN oligomers are now known and their chemistry has been extensively studied.

- Of particular interest is the photochemistry of the tetramer:

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- Eschenmoser has studied the chemistry of the highly reactive dimer 2.

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<table>
<thead>
<tr>
<th>purine</th>
<th>adenine</th>
<th>guanine</th>
<th>hypoxanthine</th>
<th>xanthine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>theobromine</th>
<th>caffeine</th>
<th>uric acid</th>
<th>isoguanine</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

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- The identity of the HCN oligomers are now known and their chemistry has been extensively studied.
Prebiotic Chemistry

Prebiotic Amino Acid Chemistry
- Prebiotic experiments relating to the pyrimidine synthesis have been in general less successful, but some exceptions are noted

"An Efficient Prebiotic Synthesis of Cytosine and Uracil"

\[
\text{HO-MCN} + \text{H}_2\text{NCONH}_2 \xrightarrow{100^\circ C \ 30 \ h} \ \text{NH}_2
\]

53%
Prebiotic Carbohydrate Chemistry

- In 1861 Bulerow noted that sugar-like substances are formed when formaldehyde is treated with mild base
- The Formose reactions appears to be the most likely pre-biotic route to early carbohydrates (eg. ribose, deoxyribose)
- The mechanism was studied by Breslow in the 1950's
- As you can imagine, prebiotic carbohydrate synthesis are extremely low yielding, "messy" reactions

Formose Reaction:

- Reaction proceeds only under the action of metal ions or basic pH's
- Redistilled formaldehyde does not yield sugars
- Addition of glycoaldehyde initiates an autocatalytic cycle based on sequential aldol reactions thereby generating more glyco-aldehyde.

Oro and Cox have shown that deoxyribose could also originate via a similar pathway.
Prebiotic Peptide Bond Formation

"Peptide Formation in the Prebiotic Era: Thermal Condensation of Glycine in Fluctuating Clay Environments."

It has been proposed that a fluctuating environment of water content and temperature combined with a catalytically active surface, and the opportunity for redistribution of the organic may be ideal for condensation reactions in the prebiotic era.

As geological relevant models of prebiotic environments, mixtures of clay, H₂O, and amino acids were subject to cyclic variations in temperature and H₂O content.

Consider the complex equilibrium that could exist with only a single amino acid:

\[
\begin{align*}
\text{H}_2\text{N}-\text{CONH}_2 + \text{H}_2\text{O} &\rightleftharpoons \text{H}_2\text{N}-\text{CONH}-\text{CH}_2\text{COOH} + \text{H}_2\text{O} \\
\text{H}_2\text{N}-\text{CONH}_2 + \text{H}_2\text{O} &\rightleftharpoons \text{H}_2\text{N}-\text{CONH}-\text{CONH}_2 + \text{H}_2\text{O}
\end{align*}
\]

Results:
1. Without clay, trace amounts of diglycine formed after lengthy heating. With clay, diglycine readily detected after 1 week at 94°C and further heating increased the amount of diglycine and larger peptides. At 60°C only trace amounts of diglycine could be detected after 35 days.
2. WDTF exp. enhanced peptide synthesis over the TF exp. oligomers up to pentaglycine could be detected.
3. Clay composition affected oligomer length.
4. Increasing Glycine-to-Clay ratio produced higher yield and lengths.
5. There appeared to be very little change in peptide length and yield after ~11 cycles.
6. Yields in general are very low.

Conclusion:
The dynamic balance of peptide bond formation and destruction over a large number of cycles provides a mechanism for selective generation of oligomers, i.e. chemical evolution.
Prebiotic Peptide Bond Formation

"Montmorillonite Catalyzed Peptide Bond Formation: The Effect of Exchangeable Cations"

The effect of additives on clay-based oligomerization is studied using the WDTF method

Reactions Studied:

<table>
<thead>
<tr>
<th>Clay + H$_3$N-CONH$_2$OH</th>
<th>Various counterions</th>
<th>Dipeptides (racemization occurs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clay + H$_2$N-CONH$_2$</td>
<td>Various counterions</td>
<td></td>
</tr>
</tbody>
</table>

counterions screened: Li, Na, K, Rb, Cs, Mg, Ca, Sr, Ba, Al, NH$_4$
results:
1. ratios of DKP : gly$_3$ : gly$_4$ vary with metal source
2. Diketopiperazine (DKP) always largely predominates
3. Poor yields

Conclusion: There must be another way nature makes peptide bonds!

"Peptides by Activation of Amino Acids with CO on (Ni,Fe)S Surfaces: Implications for the origin of Life"

Reactions Studied:

<table>
<thead>
<tr>
<th>CO + FeS (2 eq.) + NiS (2 eq.)</th>
<th>H$_2$S or MeSH (1 eq.)</th>
<th>100°C (pH 7-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA's</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gly</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Possible mechanisms:

"Leuchs anhydride"

"Dipeptides were formed if we replaced CO and H$_2$S with COS, but not in the absence of NiS and FeS."

Results:
1. No peptides were detectable if any of the reagents were absent
2. Control experiments show that dipeptides hydrolyze under the reaction conditions
3. Low yields
4. Strong pH dependence (8-9.5 optimal)
5. Only minor amounts of DKP’s formed

Conclusions:
Supports theory of thermophilic origin of life
pH control must have been one of the primary concerns for early peptide-synthesizing organisms

Note: It should be mentioned that previously Hirschmann, in studying the synthesis of peptides using 2,5-Thiazolinediones, mentioned as a footnote that COS "would seem to offer another pathway to peptide formation under prebiotic conditions" see: Hirschmann et al., J. Org. Chem. 1971, 36, 49-59.
Prebiotic Peptide Bond Formation


- Ghadiri and co-workers postulated that COS might have a played a more general role in prebiotic chemistry than previous work has been able to show
- To date, this work has been the most thorough from a chemical standpoint with regard to scope and mechanism in COS-mediated prebiotic bond formation

The authors propose the following:

\[
\text{OCS} + H_2N\text{R}O^- \leftrightarrow -S\text{R}N\text{R}O^- \\
\text{R}\text{N}\text{R}O^- + \text{AA} \rightarrow -S\text{R}N\text{R}O^-
\]

\[
\text{R}\text{N}\text{R}O^- + \text{COS} \rightarrow \text{R}\text{N}\text{R}O^- \rightarrow \text{oligopeptides}
\]

\[
\text{R}\text{N}\text{R}O^- + \text{COS} \rightarrow \text{R}\text{N}\text{R}O^- \rightarrow \text{oligopeptides}
\]

NMR studies:

\[
\text{H}_2\text{N}\text{R}O^- \rightarrow \text{COS} \rightarrow \text{H}_2\text{N}\text{R}O^- \rightarrow \text{oligopeptides}
\]

- quantitative by \(^1\text{H} NMR
- stable under Rxn. Conditions

key experiment:

\[
\text{S}\text{R}N\text{R}O^- \rightarrow \text{H}_2\text{N}\text{R}O^- \rightarrow \text{peptide! 6-7%}
\]

This experiment definitively shows that COS alone can act as a simple peptide-bond forming reagent!
Prebiotic Chemistry I

Prebiotic Peptide Bond Formation

Considering that the thiolate anion is a poor leaving group, could simple reagents accelerate Leuchs Anhydride formation, and thus lead to more efficient peptide bond formation.

Consider the following alternatives:

Selected results:

<table>
<thead>
<tr>
<th>Metal</th>
<th>(Phe)₂</th>
<th>(Phe)₃</th>
<th>(Phe)₄</th>
<th>(Phe)₅</th>
<th>(Phe)₆</th>
<th>rxn time</th>
</tr>
</thead>
<tbody>
<tr>
<td>PbCl₂</td>
<td>22%</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
<td>27 h</td>
</tr>
<tr>
<td>CdCl₂</td>
<td>48%</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td>16 h</td>
</tr>
<tr>
<td>FeCl₂</td>
<td>23%</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
<td>64 h</td>
</tr>
<tr>
<td>FeCl₃</td>
<td>14%</td>
<td>n.d.</td>
<td></td>
<td></td>
<td></td>
<td>53 h</td>
</tr>
<tr>
<td>ZnCl₂</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metal</th>
<th>(Phe)₂</th>
<th>(Phe)₃</th>
<th>(Phe)₄</th>
<th>(Phe)₅</th>
<th>(Phe)₆</th>
<th>rxn time</th>
</tr>
</thead>
<tbody>
<tr>
<td>K₃Fe(CN)₆</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH = 8.9 5 mins</td>
<td>63%</td>
<td>13%</td>
<td>3%</td>
<td></td>
<td>traces</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metal</th>
<th>(Phe)₂</th>
<th>(Phe)₃</th>
<th>(Phe)₄</th>
<th>(Phe)₅</th>
<th>(Phe)₆</th>
<th>rxn time</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrEtOAc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH = 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>l-Phe (mM)</th>
<th>Reactant 2 (mM)</th>
<th>PbCl₂ (mM)</th>
<th>Final pH</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>l-Tyrosine (10)</td>
<td>20</td>
<td>7.2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>l-Leucine (25)</td>
<td>50</td>
<td>7.1</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>l-Alanine (25)</td>
<td>50</td>
<td>5.9</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>l-Serine (25)</td>
<td>50</td>
<td>6.3</td>
<td>3</td>
</tr>
</tbody>
</table>

COS gas (20 ml) bubbled in, Me₃N buffer, pH = 9.1, reactions quenched after 3 hours, ( ) = sequence not determined
Origins of the study of Chirality

A Brief Refresher:

1. Optical activity was first demonstrated in 1812, when French physicist Jean Baptiste Biot discovered that quartz crystals could rotate a beam of plane-polarized light. He also determined that many natural products (ex. turpentine, camphor, tartaric acid) also had this property.

2. In 1848, Pasteur separated sodium ammonium tartrate crystals into two different forms (now known as enantiomers) and showed that they had identical properties with the exception of the rotation of polarized light.

   Since both the salt as well as dissolved solutions of the salt displayed optical activity, this demonstrated that optical activity was not a property of the crystals, but rather a property of the molecules themselves.

3. In 1874, Jacobus Van't Hoff and Joseph Le Bel proposed the concept of the tetrahedral carbon, stereocenters, and chirality.

"Pasteur himself was absolutely fearless. Anxious to secure a sample of saliva straight from the jaws of a rabid dog, I once saw him with the glass tube held between his lips draw a few drops of the deadly saliva from the mouth of a rabid bull-dog, held on the table by two assistants, their hands protected by leather gloves."

   - Axel Munthe, The Story of San Michelle.

When the young Pasteur announced his discovery, an aging Jean Baptiste Biot showed up from the French Academy of Science. "Show me!" he demanded. Together, Pasteur and Biot ran the experiment. When it worked, Biot seized Pasteur's hand and, in a voice charged with emotion, said "I have loved science so much during my life, that this touches my very heart."

Some words to live by in the lab (courtesy of Pasteur)

"Let me tell you the secret that has led me to my goal. My strength lies solely in my tenacity."

"There are no such things as applied sciences, only applications of science."

"In the field of observation, chance favors only the prepared mind."

Origins of Chirality

Some questions to consider:

1. Is homochirality an inevitable consequence of universal fundamental physical processes relating to symmetry breaking?

2. Is polarized light responsible?

3. Is a pure chiral medium necessary for the origin of life or is chiral uniformity a consequence of life?

4. How can enantiomeric excess be enriched?

5. How can enantiomeric excess be maintained?
Origins of Chirality

1. Polarized Light

Le Bel and Van’t Hoff considered circularly polarized light as a way to create optical activity found in biology as early as 1874.

Circular dichroism (CD): Homochiral substances have different absorption intensities for left and right circularly polarized light.

Asymmetric Destruction of a racemic Mixture:

Basic idea: Photolysis (destruction by light) requires absorption
- $R$ and $S$ enantiomers absorb polarized light differently
- Thus one enantiomer can be destroyed faster, leaving enantiomeric excess

If we consider a racemic mixture at $t = 0$, with $R$ and $S$ enantiomers undergoing photochemical absorptions (and likely photochemistry) at differing rates $K_R$ and $K_S$, we can easily obtain the following:

$$ee = \frac{[R] - [S]}{[R] + [S]} = \tanh \left(\frac{1}{2} (K_S - K_R)t\right)$$

The Good News:

Recall: hyperbolic tangent function always increases. Therefore even if $K_S$ and $K_R$ are very similar (i.e. minimal stereoselectivity) the enantiomeric purity will approach 100%!

The Bad News:

- **All known reactions induced by circularly polarized light are weakly stereoselective**
- **We must consider that as the enantiomeric excess approaches 100% ee, the yield approaches 0%!**
- Magnitude as well as sign of a CD are light frequency dependent, thus resolution can only occur with CP light over a narrow frequency window. If a large range of frequencies are used, the enantiodiscrimination effects would cancel.

Proof of principal:

- **50% conver.**
- **0.5% ee**

20% ee but 99% of SM destroyed!
Origins of Chirality

Recall there are 4 fundamental forces in physics: gravitation, electromagnetism, weak interaction, and strong interaction. Of the 4, the weak interaction is unique in that it violates parity conservation (space-reflection symmetry).

In physics, if a phenomenon is not identical to its mirror image it is said to be chiral. For example the spin of a particle may be used to define the handedness for that particle. The symmetry transformation between the two is called parity.

It was discovered at Columbia in 1956 while studying the decay of $^{60}$CO nuclei, that parity is violated in the weak interaction. Thus the known elementary particles respect rotation, translation, but not mirror reflection symmetry (i.e. parity). Symmetry = lack of any visible change under any kind of transformation, i.e. from one reference frame to another. As Shown in the experiment, more electrons and neutrinos are ejected opposite the direction of the mangetic field (and therefore opposite the nuclear spin). Therefore neutrinos are left-handed!

Only the left-handed components of particles and the right-handed components of antiparticles participate in weak interactions. Thus parity is not a symmetry of our universe, unless a hidden mirror sector exists in which parity is violated in the opposite way. (Mirror matter, aka shadow matter, aka Alice Matter is a hypothetical counterpart to ordinary matter.)

"In weak decays, like $\beta$-decay, the particles which carry spin, like the neutrino and the electron, come out with a spin tending toward the left. The parity of the charge is violated, and that charge-parity violation. So this is completely anomalous, as symmetry is not preserved, and by extrapolation we can question whether in fact there is something special about the direction that time flows, and this would start to explain things about the way the universe looks."


"The idea that nature at a very fundamental can tell the difference between "left-handed" and "right-handed" systems is a radical one"

"For a while Yang had tried experimental physics, but it was not to be. Other graduate students had teased him, "Where there was a bang there was Yang."

"Lee was a theorist from the start."

"Arriving at Berkeley in 1936 from Shanghai, Wu was one of the most ardently pursued coeds on campus. But she was also a hard worker who abhorred the marked absence of women from the American scientific establishment. She says, "... it is shameful that there are so few women in science... In China there are many, many women in physics. There is a misconception in America that women scientists are all dowdy spinsters. This is the fault of men. In Chinese society, a woman is valued for what she is, and men encourage her to accomplishments --- yet she retains eternally feminine."

"She is a slave driver. She is the image of the militant woman so well known in Chinese literature as either empress or mother."
**Amplitcations of Chirality**

- It's a long way from having a small amount of chiral material (wherever it come from) to large biomolecules with numerous stereocenters as single enantiomers.
- Chiral amplification is rarely used to explain how mixtures of low enantiomeric excess can be increased or how a catalyst of low ee can yield products of high ee.
- Asymmetric Autocatalytic systems were first proposed by Frank in 1953 (Frank, F. C.).

"Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule."

![Reaction Studied Diagram](image)

---

**TABLE 1** Asymmetric autocatalysis of chiral pyrimidyl alcohol 1

<table>
<thead>
<tr>
<th>Run*</th>
<th>Catalyst 1 (% e.e.)</th>
<th>Time (h)</th>
<th>Mixture of catalyst 1 and product 1</th>
<th>Factor by which the amount of (S)-1 has increased</th>
<th>Newely formed product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series A‡</td>
<td></td>
<td></td>
<td>Yield (%) e.e. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>5 (S)</td>
<td>74</td>
<td>62 39 (S)</td>
<td>4.1</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>A2</td>
<td>39 (S)</td>
<td>60</td>
<td>86 76 (S)</td>
<td>22</td>
<td></td>
<td>55</td>
</tr>
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<td>68</td>
<td>80 85 (S)</td>
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<tr>
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<td>66</td>
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<tr>
<td>A5</td>
<td>89 (S)</td>
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<td>81 89 (S)</td>
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<tr>
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<td>2 (S)</td>
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<tr>
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<td>96</td>
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<tr>
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<tr>
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<td>79 88 (S)</td>
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<tr>
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<td></td>
<td>Yield (%) e.e. (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>10 (R)</td>
<td>70</td>
<td>81 53 (R)</td>
<td>61</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>C2</td>
<td>30 (R)</td>
<td>65</td>
<td>79 72 (R)</td>
<td>59</td>
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<tr>
<td>Run D</td>
<td>Racemate</td>
<td>55</td>
<td>68 BDL</td>
<td>48</td>
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</table>
\textbf{Amplifications of Chirality}

How does this work?
"Origins of Asymmetric Amplification in Autocatalytic Alkylzinc Additions."

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Proposed mechanisms for asymmetric alkylation of aldehydes.}
\end{figure}

\begin{align*}
\text{Reaction Studied by heat flow kinetics}
\end{align*}

In Case A: $SR$, $SS$, $RR$, are unreactive heterodimers and only the monomeric catalysts can enter the catalytic cycle. Amplification occurs if $K_{\text{hetero}} > 2K_{\text{homo}}$. Data showed that $K_{\text{hetero}} = 2K_{\text{homo}}$ thus this model cannot explain autocatalysis.

In Case B: $SS$, $RR$, and $SR$ can all serve as competent catalysts. \textit{This is exactly the scenario we want for chiral amplification, i.e. the minor enantiomer is suppressed in the catalytic cycle.}

\begin{align*}
\text{"Achieving high selectivity by capitalizing on stability differences between complex species is a common tool in modern asymmetric catalyst design; however, it is one that is unlikely to have been available to the simple molecules present in the prebiotic world. Thus, amplification without this requirement, as demonstrated by our studies, may provide an important clue toward the understanding of the biochemical origin of homochirality."}
\end{align*}

\begin{align*}
\text{"the Soai reaction is a template-directed self-replicating system which successfully maintains ideal exponential growth kinetics, and therefore high autocatalytic efficiency, over many turnovers."}
\end{align*}

Lower Catalytic activity?
\begin{itemize}
\item \textit{or}
\item More stable?
\end{itemize}
**Amplifications of Chirality**

"Chiral Symmetry Breaking in Sodium Chlorate Crystallization"

- Sodium Chlorate (NaClO₃) crystals are optically active (P₂₁3 space group) although the molecules of the compound are not chiral.

- As can be expected, when crystallized from aqueous solution a statistical mixture of L and D crystals are made.

---

**If the Solution was Stirred While Crystallizing, almost all of the crystals (99.7%)**

*were found to be either all D or all L*

- This phenomenon can be referred to as total spontaneous resolution

Consider crystal growth cycle:

**First Step:** Primary nucleation, aka the growth of a new crystal (not caused by existing crystal nuclei)
**Second step:** secondary nucleation, existing crystals perpetuate crystal growth (recall "seeding")

Secondary nucleation has been studied extensively by researchers of continuous crystallization.

**Empirical rates:**

\[ R_{\text{sec}} = k(c - c_0)^\alpha \]

\( c = \text{concentration} \)
\( c_0 = \text{concentration at saturation} \)
\( k = \text{factor that depends on rate of stirring, } \alpha > 1 \)

- Secondary nucleation alone cannot explain this phenomenon, because secondary nucleation must also be accompanied by suppression of nucleation of the other hand.

- However recall that primary nucleation is extremely sensitive to [NaClO₃], so as time proceeds \( R_{\text{prim}} \) will decrease for both enantiomers. Thus at time proceeds \( R_{\text{sec}} \gg R_{\text{prim}} \) if \( k \) is large. Thus the first crystal to form (statistically equal chance of D or L) is ultimately the "mother crystal" which determines the chirality of the daughters.

---

"Chiral Symmetry Breaking During Crystallization: Complete Chiral Purity Induced by Nonlinear Autocatalysis and Recycling"

This paper demonstrated the first experimental case where total symmetry breaking and complete chiral purity is achieved from a system where both enantiomers are present since the beginning.

Therefore this new process cannot be explained using the "mother crystal" idea above, and the demonstration of "chiral amnesia" emerges.

---

**Basic experiment**

<table>
<thead>
<tr>
<th>racemic NaClO₃ crystals 12g</th>
<th>add H₂O 10 mol</th>
<th>saturated NaClO₃ solution (&gt;2g remain undissolved)</th>
<th>add glass beads</th>
<th>stir at room temp</th>
<th>Check ee of crystals</th>
</tr>
</thead>
</table>

Results:

1) If no beads are put in (but stirring is still used), the crystals maintain their initial ee.

2) The time required to achieve chiral purity depends on the number of glass bead. With equal numbers, the time required depends on the speed of agitation.

3) A racemic mixture with 4g glass balls can be upgraded to optical purity in 24 hours (statistically equal chance of D or L)
Amplifications of Chirality

"Chiral Symmetry Breaking During Crystallization: Complete Chiral Purity Induced by Nonlinear Autocatalysis and Recycling"

Grinding the mixture promotes a dynamic dissolution/ crystallization process. Crushing the crystals is like a second nucleation

These guys “forgot” what enantiomer they were part of as soon as they dissolve. Chiral Amnesia!

total surface area is a driving force for crystal growth

Gibb’s Thompson rule:

*Considering that solubility of smaller particles is greater than that of larger ones, a slight concentration gradient will exist between particles of different size even near equilibrium.*

- In a saturated solution, this leads to large crystals growing faster than small ones regardless of their handedness.

"Emergence of a Single Solid Chiral State from a Nearly Racemic Amino Acid Derivative"

Can this idea by carried over to molecules whose monomers are themselves chiral? (e.g. organic compounds)

**Consider the analogy below**

**system studied:**

\[
\begin{align*}
\text{DBU} & \quad \text{MeOH or MeCN 25°C} \\
(S)-M & \quad \text{MeOH or MeCN 25°C} \\
& \quad \text{R}-M
\end{align*}
\]

\[
\begin{align*}
\text{(S)-solid} & \quad \text{MeOH or MeCN 25°C} \\
& \quad \text{(R)-solid}
\end{align*}
\]

achiral

chiral, but interconvertible (racemization!!)

Chiral amnesia!

Crystals cannot racemize out of solution
Chirality transfer

"Prebiotic Amino Acids as Asymmetric Catalysts"

Prebiotic Chemistry I

Baran Lab

Tom Maimone

H₂N\[\text{Me}\]|\[O\]  +  HO\[-\text{CH₃}\]  →  aq. Et₃N-HOAc buffer  

pH = 5.4
50°C
10 h

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>L-Threose (%)</th>
<th>D-Threose (%)</th>
<th>L-Erythrose (%)</th>
<th>D-Erythrose (%)</th>
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</thead>
<tbody>
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<td>L-Valine</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>R-Valine</td>
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<td>R-Valine</td>
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<td>L-Valine</td>
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<td>R-Valine</td>
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<td>100</td>
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</table>

"Catalysis by proline, which has been observed in related reactions involving imine intermediates in organic solvents was not seen under our reaction conditions."
**Conclusions:**

1. We have shown that very simple organic (and even inorganic) compounds can be converted to a variety of the basic building blocks of life under laboratory conditions, and discussed other possible origins of these compounds.
2. We have discussed the origins or chirality and shown that nearly racemic organic mixtures can become nearly enantiopure under certain conditions (autocatalysis).
3. We have shown that simple chiral compounds can transfer their chirality to other simple compounds.

**Some Questions to Ponder:**

*(Prelude to Prebiotic Chemistry II: prebiotic to biological chemistry)*

1. How might chirality have been maintained in aqueous, racemizing environments?
2. Is chirality a requirement for life or a result of it?
3. What might have been the requirements for the first biopolymers?
4. What molecules can fulfill these requirements?
5. Molecular Recognition, Self-Assembly, and information storage