The primordial soup – the final sip

L4 SoSe 2019 HD
The origin of small reactive intermediates

Thermal decomposition of cyanoferrates (volcanic):

\[
\begin{align*}
&(\text{Na,K})_4[\text{Fe}(\text{CN})_6] \xrightarrow{700^\circ\text{C}} 4(\text{Na/K})\text{CN} + \text{Fe}(\text{CN})_2 \\
&3\text{Fe}(\text{CN})_2 \xrightarrow{700^\circ\text{C}} \text{Fe}_3\text{C} + 5\text{C} + 3\text{N}_2 \\
&\text{Fe}(\text{CN})_2 \xrightarrow{700^\circ\text{C}} \text{Fe} + 2\text{C} + \text{N}_2 \\
&\text{Ca}_2[\text{Fe}(\text{CN})_6] \xrightarrow{660^\circ\text{C}} 2\text{Ca}(\text{CN})_2 + \text{Fe}(\text{CN})_2 \\
&\text{Ca}(\text{CN})_2 \xrightarrow{660^\circ\text{C}} \text{CaNCN} + \text{C} \xrightarrow{1000^\circ\text{C}} \text{CaC}_2 + \text{N}_2 \\
&Mg_2[\text{Fe}(\text{CN})_6] \xrightarrow{315^\circ\text{C}} 2\text{Mg}(\text{CN})_2 + \text{Fe}(\text{CN})_2 \\
&Mg(\text{CN})_2 \xrightarrow{395^\circ\text{C}} \text{MgCN}_2 + \text{C} \\
&3\text{MgCN}_2 \xrightarrow{420^\circ\text{C}} \text{Mg}_3\text{N}_2 + 3\text{C} + 2\text{N}_2
\end{align*}
\]

Action of water (buffered to neutral or slightly acidic) on that mixture produced concentrated HCN solution + cyanamide (from CaNCN) + acetylene (from CaC\(_2\)) + ammonia (from Mg\(_3\)N\(_2\))

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

Photoredox cycle based on cyanocuprates may convert HCN into cyanogen
Cyanosulfidic chemistry for the Kiliani-Fischer homologation

J. Sutherland, *Nature Reviews Chemistry* 2017, 1, Article 0012, doi:10.1038/s41570-016-0012
Prebiotic route to pyrimidine nucleotides

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Cyanosulfidic chemistry

First signs of a linkage between all subsystems through cyanosulfidic chemistry.

glyceraldehyde 5 is a precursor of pyrimidine nucleotides (RNA), Upon isomerization to 53 and reduction to glycerol 54, it can be phosphorylated to yield phospholipids (from 56 and 57)...

J. D. Sutherland, et al. Nature Chem. 2015, 7, 301-307
**Lipids**

**d.** TEM image of a sample (15 mg in 1 ml water) from the crude reaction in b, showing the formation of vesicle-like structures with a diameter of ∼9.2 μm.

**e.** TEM image of a sample (1 mg in 1 ml water) of authentic phospholipid 26 from Fig. 2c showing the formation of vesicle-like structures with a diameter of ∼3.5 μm.

**f–h.** Confocal laser scanning microscopy fluorescence images of vesicles prepared with authentic phospholipid 26 (1 mg in 0.1 ml water) with dye encapsulation.

- In **f**, green fluorescence indicates hydrophilic pyranine dye encapsulated within the cavity of the liposome.
- In **g**, red fluorescence indicates rhodamine B dye labelling the bilayer phospholipid membrane of the liposome.
- In **h**, a fluorescence merged image is shown of a phospholipid vesicle prepared with both rhodamine B dye and pyranine dye.
Photoredox systems chemistry with hydrosulfide as the stoichiometric reductant. a) (Over-)reduction of glycolonitrile 45 to glycolaldehyde 4 (and acetaldehyde 49), b) reductive homologation of 4 (and 49) to 5 (and 51), c) most of the aldehydes produced by this chemistry as Strecker amino acid precursors (boxed) and the self-destruction (as regards potential Strecker chemistry) of the cyanohydrin 52.

J. D. Sutherland, *et al.* Nature Chem. 2015, 7, 301-307
Cyanosulfidic chemistry

Cyanohydrins undergo photoreduction to α-hydroxyaldehydes. α-hydroxythioamides first undergo photodeoxygenation to thioamides, and then photoreduction to aldehydes.

J. D. Sutherland, *et al.* Nature Chem. 2015, 7, 301-307
Cyanosulfidic chemistry

J. D. Sutherland, et al. Nature Chem. 2015, 7, 301-307
Cyanosulfidic chemistry

First signs of a linkage between all subsystems through cyanosulfidic chemistry.

Glyceraldehyde 5 is a precursor of pyrimidine nucleotides (RNA). Upon isomerization to 53 and reduction to glycerol 54, it can be phosphorylated to yield phospholipids (from 56 and 57)...

The side product – acetone 55 – seems to be meaningful in the potentially prebiotic route for branched aminoacids Val and Leu.

J. D. Sutherland, et al. Nature Chem. 2015, 7, 301-307
Synthesis of cyanoacetylene 18 and reactions leading to amino acid precursors of Asp/Asn and Glu/Gln.
Synthesis of acrylonitrile 71 and reactions leading to amino acid precursors therefrom.
Cyanosulfidic chemistry

Chemistry in a post-meteoritic-impact scenario.
A series of post-impact environmental events are shown along with the chemistry (boxed) proposed to occur as a consequence of these events.

Dissolution of atmospherically produced hydrogen cyanide results in the conversion of vivianite (the anoxic corrosion product of the meteoritic inclusion schreibersite) into mixed ferrocyanide salts and phosphate salts, with counter cations being provided through neutralization and ion-exchange reactions with bedrock and other meteoritic oxides and salts.
Cyanosulfidic chemistry

Chemistry in a post-meteoritic-impact scenario. A series of post-impact environmental events are shown along with the chemistry (boxed) proposed to occur as a consequence of these events.

Partial evaporation results in the deposition of the least-soluble salts over a wide area, and further evaporation deposits the most-soluble salts in smaller, lower-lying areas.
Cyanosulfidic chemistry

After complete evaporation, impact or geothermal heating results in thermal metamorphosis of the evaporite layer, and the generation of feedstock precursor salts (in bold).

\[
\begin{align*}
\text{(Na,K)}_4\text{[Fe(CN)]}_6 & \xrightarrow{700 \degree C} 4\text{(Na/K)CN} + \text{Fe(CN)}_2 \\
3\text{Fe(CN)}_2 & \xrightarrow{700 \degree C} \text{Fe}_3\text{C} + 5\text{C} + 3\text{N}_2 \\
\text{Fe(CN)}_2 & \xrightarrow{700 \degree C} \text{Fe} + 2\text{C} + \text{N}_2 \\
\text{Mg}_2\text{[Fe(CN)]}_6 & \xrightarrow{315 \degree C} 2\text{Mg(CN)}_2 + \text{Fe(CN)}_2 \\
\text{Mg(CN)}_2 & \xrightarrow{395 \degree C} \text{MgCN}_2 + \text{C} \\
3\text{MgCN}_2 & \xrightarrow{420 \degree C} \text{Mg}_3\text{N}_2 + 3\text{C} + 2\text{N}_2 \\
\text{Ca}_2\text{[Fe(CN)]}_6 & \xrightarrow{660 \degree C} 2\text{Ca(CN)}_2 + \text{Fe(CN)}_2 \\
\text{Ca(CN)}_2 & \xrightarrow{660 \degree C} \text{CaNCN} + \text{C} \xrightarrow{1,000 \degree C} \text{CaC}_2 + \text{N}_2
\end{align*}
\]
Rainfall on higher ground (left) leads to rivulets or streams that flow downhill, sequentially leaching feedstocks from the thermally metamorphosed evaporite layer. Solar irradiation drives photoredox chemistry in the streams. Convergent synthesis can result when streams with different reaction histories merge (right), as illustrated here for the potential synthesis of arabinose aminooxazoline (5) at the confluence of two streams that contained glycolaldehyde (1), and leached different feedstocks before merging.
Cyanosulfidic chemistry system

Table 1 | Yields for the part of the reaction network shown in Fig. 1b.

<table>
<thead>
<tr>
<th>Conversion</th>
<th>Number of steps</th>
<th>Yield (%)</th>
<th>Conversion</th>
<th>Number of steps</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 → 17</td>
<td>1</td>
<td>59</td>
<td>26 → 28</td>
<td>1</td>
<td>57</td>
</tr>
<tr>
<td>17 → 18+</td>
<td>1</td>
<td>29</td>
<td>28 → 29</td>
<td>1</td>
<td>75</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 → 24</td>
<td>2</td>
<td>62</td>
<td>26 → 29</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>24 → 25</td>
<td>1</td>
<td>41</td>
<td>29 → 30</td>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>25 → 26</td>
<td>2</td>
<td>78</td>
<td>30 → 31</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>26 → 27</td>
<td>1</td>
<td>42</td>
<td>19 → 21+</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>22</td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

Table 2 | Yields for the parts of the reaction network shown in Fig. 1c,d.

<table>
<thead>
<tr>
<th>Conversion</th>
<th>Number of steps</th>
<th>Yield (%)</th>
<th>Conversion</th>
<th>Number of steps</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 → 34</td>
<td>1</td>
<td>83</td>
<td>38 → 41+</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38 → 42</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>34 → 35</td>
<td>1</td>
<td>55</td>
<td>38 → 44</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>34 → 37</td>
<td>2</td>
<td>77</td>
<td>44 → 47</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>34 → 36</td>
<td>1</td>
<td>45</td>
<td>45 → 46</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>37 → 39</td>
<td>1</td>
<td>77</td>
<td>6 → 48+</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49+</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>37 → 40</td>
<td>2</td>
<td>~100</td>
<td>48 → 51</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>37 → 43</td>
<td>3</td>
<td>~70</td>
<td>51 → 52</td>
<td>1</td>
<td>89</td>
</tr>
<tr>
<td>37 → 45</td>
<td>5</td>
<td>~50</td>
<td>52 → 53</td>
<td>1</td>
<td>~100</td>
</tr>
<tr>
<td>36 → 38</td>
<td>1</td>
<td>~100</td>
<td>52 → 54</td>
<td>2</td>
<td>~70</td>
</tr>
</tbody>
</table>
Cyanosulfidic chemistry system
Cyanosulfidic chemistry system
Remaining challenges of prebiotic nucleotide synthesis

Homochirality of currently known biomolecules

Prebiotic synthesis of purine nucleotides and deoxyribonucleotides

Prebiotic polymerization
Polymerization of $D$-nucleotides is suppressed in presence of $L$-nucleotides – the problem of “enantiomeric cross-inhibition”

Incorporation of $L$-enantiomers into growing chains of $D$-oligonucleotides $\rightarrow$ families of diastereomers for each sequence $\rightarrow$ problematic development of phenotypic RNA properties

Without access to highly enantioenriched sugars, the nucleotides formed during the ‘cyanosulfidic chemistry’ synthesis would not lead to informational polymers capable of establishing a genetic code

Chiral amplification and the origins of homochirality

Enantioenriched amino acids present in meteorites (up to 18% ee L-isomers). Further enantioenrichment is possible by manipulation of amino acid phase behavior:

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 evaporation 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.

Eutectic solutions over enantioenriched aminoacids

Mixtures of enantiomers can crystallize as conglomerates (a single crystal contains only molecules of one handedness) or racemates (a single crystal is racemic).

Enantioenriched mixtures give mixtures of crystals which would have the same ee value upon re-solubilization.

Highly enantioenriched solutions may be obtained from a small initial enantiomeric imbalance for many aminoacids, including proline, via physical amplification processes that sequester the minor enantiomer as racemic solid.

Manipulation of eutectic ee value by formation of a solvate that reduces the solubility of the racemic compound.

D. Blackmond Phil. Trans. R. Soc. B 2011, 366, 2878-2884
Eutectic solutions over enantioenriched aminoacids

D. Blackmond Phil. Trans. R. Soc. B 2011, 366, 2878-2884
Eutectic solutions over enantioenriched amino acids

\[
\text{aldol product ee} (\%) = f(\text{proline ee} (\%))
\]

\[
\text{solution proline ee} (\%) = f(\text{proline ee} (\%))
\]

<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>

Cyanosulfidic chemistry

The recently uncovered route to activated pyrimidine nucleotides 2.

The nucleobase ribosylation problem is circumvented by the assembly proceeding through 2-aminooxazole 21, which can be thought of as the chimera of half a pentose sugar and half a nucleobase. The second half of the pentose - glyceraldehyde 5 - and the second half of the nucleobase—cyanoacetylene 7—are then added sequentially to give the anhydronucleoside 23.

Phosphorylation and rearrangement of 23 then furnishes 2 (B=C), and UV irradiation effects the partial conversion of 2 (B=C) to 2 (B=U).

M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* 2009, 459, 239–242
Cytosine-2',3’cP – step 2: pentose-amino-oxazolines

M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* 2009, 459, 239–242
**Enantiomeric excess in the cyanosulfidic chemistry**

**a**, In the presence of an enantioenriched L-proline (3o), the diastereoselective formation of a three-component side product (6) effectively sequesters the unnatural L-glyceraldehyde (L-1).

**b**, The side reaction acts as a kinetic resolution of glyceraldehyde, giving enantiorichment of greater than 90% e.e. D-1, which reacts with 2 to form the enantioenriched amino-oxazoline RNA precursors D-4 and D-5. e.e. values are ±2%.

1% e.e. L-proline (3o) is suspended in solvent (either CHCl₃ or EtOH). After equilibration, the remaining solid is removed and the solvent is evaporated from the supernatant. Racemic glyceraldehyde DL-1 and amino-oxazole 2b are then added and the mixture is dissolved in water. The ensuing reaction produces amino-oxazolines 4 and 5 in 20–80% e.e. Cooling the mixture to 4 °C induces crystallization of enantiopure ribo-amino-oxazoline crystals.

Chiral sugars drive enantioenrichment in prebiotic aminoacid synthesis

D. G. Blackmond et al., ACS Cent. Sci., 2017, 3, 322-328
**Chiral sugars drive enantioenrichment in prebiotic aminoacid synthesis**

![Chemical reactions and structures](image)

**Table 1. Enantioenrichment of Amino Acid Precursors Driven by D-Sugars (Scheme 3)\(^a\)**

<table>
<thead>
<tr>
<th>Sugar</th>
<th>Ala-II e.e.(%)</th>
<th>Phe-II e.e.(%)</th>
<th>Trp-II e.e.(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-ribose</td>
<td>65 (D)</td>
<td>70 (D)</td>
<td>33 (D)</td>
</tr>
<tr>
<td>D-lyxose</td>
<td>83 (L)</td>
<td>83 (L)</td>
<td>59 (L)</td>
</tr>
<tr>
<td>D-xylose</td>
<td>45 (D)</td>
<td>35 (D)</td>
<td>11 (D)</td>
</tr>
<tr>
<td>D-arabinose</td>
<td>58 (L)</td>
<td>48 (L)</td>
<td>38 (L)</td>
</tr>
<tr>
<td>D-deoxyribose</td>
<td>29 (D)</td>
<td>32 (D)</td>
<td>33 (D)</td>
</tr>
<tr>
<td>D-ribose + D-lyxose</td>
<td>45 (L)</td>
<td>14 (L)</td>
<td>18 (L)</td>
</tr>
<tr>
<td>D-xylose + D-arabinose</td>
<td>47 (L)</td>
<td>18 (L)</td>
<td>20 (L)</td>
</tr>
</tbody>
</table>

**Table 2. Opposite Sense of Enantioenrichment of Phe-II for L-Sugars\(^a\)**

<table>
<thead>
<tr>
<th>Sugar</th>
<th>Phe-II e.e.(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-ribose</td>
<td>69 (L)</td>
</tr>
<tr>
<td>L-lyxose</td>
<td>81 (D)</td>
</tr>
<tr>
<td>L-xylose</td>
<td>31 (L)</td>
</tr>
<tr>
<td>L-arabinose</td>
<td>43 (D)</td>
</tr>
</tbody>
</table>

Chiral sugars drive enantioenrichment in prebiotic aminoacid synthesis

Table 3. Effect of Sugar Concentration on Phe-II ee (%) for Reaction Mediated by D-Ribose

<table>
<thead>
<tr>
<th>[d-ribose] (M)</th>
<th>d-ribose (equiv)</th>
<th>Phe-II e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.025</td>
<td>0.1</td>
<td>9 (a)</td>
</tr>
<tr>
<td>0.050</td>
<td>0.2</td>
<td>14 (a)</td>
</tr>
<tr>
<td>0.10</td>
<td>0.4</td>
<td>23 (a)</td>
</tr>
<tr>
<td>0.25</td>
<td>1</td>
<td>43 (a)</td>
</tr>
<tr>
<td>0.5</td>
<td>2</td>
<td>43 (a)</td>
</tr>
<tr>
<td>1.0</td>
<td>4</td>
<td>43 (a)</td>
</tr>
<tr>
<td>2.0</td>
<td>8</td>
<td>42 (a)</td>
</tr>
</tbody>
</table>

Table 4. Effect of Solution pH on Phe-II ee (%) for Reaction Mediated by D-Ribose

<table>
<thead>
<tr>
<th>NaOH (M)</th>
<th>Effective pH</th>
<th>Temperature (°C)</th>
<th>Phe-II e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000010</td>
<td>10</td>
<td>22-24</td>
<td>36 (a)</td>
</tr>
<tr>
<td>0.00010</td>
<td>10</td>
<td>37</td>
<td>36 (a)</td>
</tr>
<tr>
<td>0.00010</td>
<td>10</td>
<td>37</td>
<td>36 (a)</td>
</tr>
</tbody>
</table>

D. G. Blackmond et al., ACS Cent. Sci., 2017, 3, 322-328
Chiral sugars drive enantioenrichment in prebiotic aminoacid synthesis

D. G. Blackmond et al., ACS Cent. Sci., 2017, 3, 322-328
Nucleoside synthesis – further development

![Chemical structures and reactions](image-url)
The synthesis of activated pyrimidine ribonucleotides 29 and 30 is dependent on the controlled formation of pentose aminooxazolines 31 (black), but the synthesis of 31 is wholly reliant on the ordered introduction of pure glycolaldehyde 14 (to cyanamide 33) and glyceraldehyde 20 (to 2-aminooxazole 32) to prevent the formation of numerous deleterious by-products (red). Ribonucleotide synthesis fails without the adherence to this order of synthetic steps. Glyceraldehyde 20 is highly susceptible to equilibration with dihydroxyacetone 22, especially in phosphate buffer, which results in diminishing amounts of pentose aminooxazolines 31 being formed (inset).

S. Islam, M. W. Powner *Chem* 2017, 2, 470-501
2-Aminothiazole-Controlled Aldehyde Sequestration

S. Islam, M. W. Powner *Chem* 2017, 2, 470-501
2-Aminothiazole-Controlled Aldehyde Sequestration

S. Islam, M. W. Powner *Chem* 2017, 2, 470-501
Analysis of the prebiotic amino acid and nucleotide syntheses reveal that glycolaldehyde $\text{14}$—a serine and ribonucleotide precursor—lies at a generational node between these two metabolite classes. The same analysis applied to cysteine suggested that $\text{b-mercaptoacetaldehyde} \ 47$ would be as important as glycolaldehyde $\text{14}$ and that the reactivity of $\text{2-aminothiazole} \ 44$ might have key implications for the concomitant prebiotic synthesis of amino acid and nucleotides.

S. Islam, M. W. Powner Chem 2017, 2, 470-501
Strategies toward Enantio-enriched Glyceraldehyde and Ribonucleotide Precursors

A

\[
\text{L-Pro} + \text{20} + \text{32} \rightarrow \text{D-31} \quad \gg \quad \text{L-31}
\]

\[
\text{51} \quad > > \quad \text{52}
\]

B

\[
\text{20} \overset{\text{crystallization and ee amplification}}{\longrightarrow} \text{49} \overset{\text{crystals}}{\longrightarrow} \text{51}
\]

\[
\text{D-20} \overset{\text{syrup}}{\longrightarrow} \text{50}
\]

S. Islam, M. W. Powner Chem 2017, 2, 470-501
Purine nucleoside synthesis via cyanosulfidic chemistry
8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry

Prebiotic feedstocks $\rightarrow$ 1a

b

10a $\rightarrow$ Pyrimidines

16 $\rightarrow$ Purines
8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry
8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry

Divergence B:

- 2a: \( \text{NH}_3 \) + \( \text{R} = \text{CHCHCN} \) \( \rightarrow \) 10a
- 1a: \( \text{R} = \text{H} \)
- 1b: \( \text{R} = \text{CHCHCN} \)
- 1c: \( \text{R} = \text{Me} \)
- 8: \( \text{MeSH} \)

Convergence:

- 10a: \( \text{R} = \text{CHCHCN} \) \( \rightarrow \) 16b: \( \text{R}' = \text{CN} \)
- 10a: \( \text{R} = \text{Me} \) \( \rightarrow \) 16c: \( \text{R}' = \text{CONH}_2 \)

11: \( \text{CO(NH}_2)_2 \) + \( \text{HCONH}_2 \) \( \rightarrow \) 3C: \( \text{B} = \text{cytosine} \)

3U: \( \text{B} = \text{uracil} \)

3OA: \( \text{B} = \text{8-oxo-adenine} \)

3OI: \( \text{B} = \text{8-oxo-hypoxanthine} \)

17A: \( \text{Y} = \text{NH}_2 \)

17I: \( \text{Y} = \text{OH} \)
8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry

\[ \text{HO-} \begin{array}{c} \text{N} \\
\text{HO} \\
\text{O} \\
\text{C} \\
\text{S} \\
\text{NH} \\
\text{HO} \end{array} \text{a} \rightarrow \text{b} \xrightarrow{1b} \begin{array}{c} \text{HO} \\
\text{O} \\
\text{C} \\
\text{S} \\
\text{NH} \\
\text{HO} \end{array} \]

\[ \begin{array}{c} \text{HO} \\
\text{C} \\
\text{S} \\
\text{NH} \\
\text{HO} \end{array} \xrightarrow{\text{NH}_3} \begin{array}{c} \text{HO} \\
\text{O} \\
\text{C} \\
\text{S} \\
\text{NH} \end{array} \xrightarrow{2a} \]

\[ \begin{array}{c} \text{HO} \\
\text{O} \\
\text{C} \\
\text{S} \\
\text{NH} \end{array} \]

\[ \begin{array}{c} \text{HO} \\
\text{C} \\
\text{S} \\
\text{NH} \\
\text{HO} \end{array} \]

\[ \begin{array}{c} \text{HO} \\
\text{C} \\
\text{S} \\
\text{NH} \\
\text{HO} \end{array} \]

\[ \begin{array}{c} \text{HO} \\
\text{C} \\
\text{S} \\
\text{NH} \\
\text{HO} \end{array} \]

\[ \begin{array}{c} \text{HO} \\
\text{C} \\
\text{S} \\
\text{NH} \\
\text{HO} \end{array} \]
8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry

$$\text{16b} \quad R = \text{CN}$$

$$\text{16c} \quad R = \text{CONH}_2$$

$$\text{HC(NH)NH}_2$$

$$\text{HC(O)NH}_2$$

$$\text{17A} \quad Y = \text{NH}_2$$

$$\text{17I} \quad Y = \text{OH}$$
8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry

(a) Urea and $\text{H}_2\text{PO}_4^-$ react to form nucleosides with $X=\text{NH}_2$ and $X=\text{OH}$.

(b) Conversion of 17A at pH 11 to 19, and of 19 at pH 13 to 20.
8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry

\[
\begin{align*}
\text{180A } X=\text{NH}_2 \\
\text{180I } X=\text{OH} \\
\text{C} \\
\text{30A } X=\text{NH}_2 \\
\text{30I } X=\text{OH} \\
\text{3C}
\end{align*}
\]

\[
\text{Urea} \quad \text{H}_2\text{PO}_4^- \quad \text{d}
\]

\[\text{11} \quad \text{17A} \quad \text{17I} \quad \text{19} \quad \text{20}\]
Canonical purine nucleoside synthesis via cyanosulfidic chemistry

![Chemical structures of purine nucleosides](image_url)
Cyanosulfidic chemistry

Multicomponent Assembly of Hydrogen Cyanide Tetramers

Proposed Development of Activated Pyrimidine Synthesis To Concurrently Yield Purine Precursors.

J. Am. Chem. Soc. 2010, 132, 16677-16688
Cyanosulfidic chemistry

beta-Ribofuranosyl-pyrimidine nucleotide assembly and potential stepwise, regioselective beta-ribofuranosyl-purine assembly
Pathway via the intermediacy of tetrahydroimidazo[1′,3′]-2′′-aminooxazolo[1′,2′]-pyrimidines

M. W. Powner, J. D. Sutherland, J. W. Szostak J. Am. Chem. Soc. 2010, 132, 16677-16688
Purine nucleoside synthesis - alternatives
Prebiotic synthesis of purine nucleosides –FaPY pathway

Prebiotic syntheses of aminopyrimidines

\[ \text{H}_2\text{N}-\text{C}≡\text{N} + \text{NH}_3 \rightarrow \text{H}_2\text{N}-\text{NH}_2\text{NH}_2 \]  

\[ \text{H}_2\text{N} \rightarrow \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \rightarrow \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \]  

\[ \text{aminomalononitrile} \rightarrow \text{guanidine} \]  

\[ \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \rightarrow \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \rightarrow \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \]  

\[ \text{amines} \rightarrow \text{triaminopyrimidines} \]  

\[ \text{H}_2\text{N} \rightarrow \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \rightarrow \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \]  

\[ \text{amines} \rightarrow \text{triaminopyrimidines} \]  

\[ \text{malononitrile} + \text{S} \text{H}_2\text{N} \text{NH}_2 \rightarrow \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \rightarrow \text{H}_2\text{N} \text{C}≡\text{C}≡\text{N} \]  

\[ \text{thiourea} \rightarrow \text{condensation} \rightarrow \text{nitrosation} \rightarrow \text{reduction} \]  

\[ \text{amines} \rightarrow \text{triaminopyrimidines} \]  

Prebiotic synthesis of purine nucleosides –FaPY pathway

Prebiotic synthesis of purine nucleosides – FaPY pathway

T. Carell, Nature 2016, 352(6287), 833-836
Prebiotic synthesis of deoxyribonucleosides
Prebiotic synthesis of deoxyribonucleosides

D. J. Ritson, J. D. Sutherland J. Mol. Evol. 2014, 38, 245-250
Prebiotic synthesis of deoxyribonucleosides

Prebiotic synthesis of deoxyribonucleosides

proposed multicomponent ribonucleotide syntheses

Prebiotic synthesis of deoxyribonucleosides

proposed multicomponent deoxyribonucleotide syntheses

Prebiotic synthesis of deoxyribonucleosides

Strecker-Type Synthesis of Amino Acids

Azole Synthesis in Water

Prebiotic synthesis of deoxyribonucleosides

Three-Component Reaction of 2-Aminothiazole 7, 4-Aminoimidazole-5-carboxamide 16, and Glyceraldehyde 22
Prebiotic synthesis of deoxyribonucleosides

Crystallization of Bis-(2-aminothiazole)-aminals of Glycolaldehyde 3 and D-Glyceraldehyde 22 from Water at pH 7

Prebiotic phosphorylations
Selective Phosphorylation of Glycolaldehyde and Aldol Reactions of Glycolaldehyde Phosphate

S. Islam, M. W. Powner Chem 2017, 2, 470-501
Prebiotic Reconstruction of the Triose Glycolysis Pathway by Selective $\alpha$-Phosphorylation of Sugars

S. Islam, M. W. Powner Chem 2017, 2, 470-501
Prebiotic soup - summary

Fischer-Tropsch chemistry - lipids

Strecker chemistry - aminoacids

Dehydrating agents (COS, NO) – condensation of AAs to peptides
Prebiotic soup - summary

Formose chemistry - carbohydrates

Phosphorus reactivity - phosphates

Formaldehyde + Glyceraldehyde →

Acetone + Formaldehyde

H₂C-C-O

R

R'

R''

R'''

Acetone + Formaldehyde

H₂C-C-O

R

R'

R''

R'''

H₂C-C-O

R

R'

R''

R'''

H₂C-C-O

R

R'

R''

R'''

H₂C-C-O

R

R'

R''

R'''

H₂C-C-O

R

R'

R''

R'''

H₂C-C-O

R

R'

R''

R'''

H₂C-C-O

R

R'

R''

R'''

H₂C-C-O

R

R'

R''

R'''

H₂C-C-O

R

R'

R''

R'''
Prebiotic soup - summary

The Traditional Modular Retrosynthetic Analyses Disconnect RNA to Ribofuranosyl Sugar, Inorganic Phosphate, and Canonical RNA Nucleobases.

S. Islam, M. W. Powner *Chem* 2017, 2, 470-501
The Three Pillars of Prebiotic Chemistry

(A) The spark discharge aminonitrile synthesis (The Miller-Urey experiment.),
(B) Nucleobase synthesis by HCN oligomerization, and
(C) Sugar synthesis by the formose reaction.

S. Islam, M. W. Powner Chem 2017, 2, 470-501
Prebiotic soup - summary

Summary of Sutherland’s Cyanosulfidic Protometabolism

S. Islam, M. W. Powner Chem 2017, 2, 470-501
Prebiotic soup - summary

Summary of the Prebiotic Syntheses of the Activated Pyrimidine Ribonucleotides

S. Islam, M. W. Powner Chem 2017, 2, 470-501
Prebiotic soup - summary

Conversion of Ribose Aminooxazoline to Activated Pyrimidine Ribonucleotides

S. Islam, M. W. Powner Chem 2017, 2, 470-501
Prebiotic soup - summary

Simultaneous pH-Controlled Multicomponent Assembly of Purine and Pyrimidine Nucleotide Precursors

HCN tetramers AICA 40 and AICN 41 participate in a high-yielding pH-dependent three-component reaction with glyceraldehyde 20 and 2-aminooxazole 32. This produces potential purine ribonucleotide precursors 39. The Mannich-type reactivity results in N9-purination with absolute regiospecificity. At pH 6–6.5, both purine 39 and pyrimidine 31 ribonucleotide precursors are observed, suggesting that a divergent synthesis of purine and pyrimidine ribonucleotides from within one pool of reagents is an enticing prospect.

S. Islam, M. W. Powner Chem 2017, 2, 470-501