Basic classes of biomolecules

- Aminoacids
- Lipids
- Carbohydrates (sugars)
- Nucleobases
- Nucleosides (sugar+nucleobase)
Nucleotides - components

- Nucleoside
- Nucleoside monophosphate
- Nucleoside diphosphate
- Nucleoside triphosphate

- Pentose: ribose, deoxyribose
- Base: Adenine, Guanine, Cytosine, Uracil, Thymine

- Glycosidic bond

- Sugar-phosphate backbone

- Nitrogenous bases: Adenine, Thymine, Guanine, Cytosine

- Hydrogen bonds

- 3' to 5' orientation
Activated ribonucleotides in the potentially prebiotic assembly of RNA. Potential P–O bond forming polymerization chemistry is indicated by the curved arrows.
Phosphorylation reagents

**Phosphorylation reagents**

Phosphorylation of sugars

Phosphorylation of sugars

Nucleosides - nucleobases + sugars

- **Deoxyribose** used in DNA backbone
- **Ribose** used in RNA backbone

**Nitrogenous Bases of RNA**
- **Uracil**
- **Cytosine**
- **Adenine**
- **Guanine**

*Key: Hydrogen, Oxygen, Carbon*
Carbohydrates
The reaction begins with two formaldehyde molecules condensing to make glycolaldehyde 1 which further reacts in an aldol reaction with another equivalent of formaldehyde to make glyceraldehyde 2. An aldose-ketose isomerization of 2 forms dihydroxyacetone 3 which can react with 1 to form ribulose 4, and through another isomerization ribose 5. Molecule 3 also can react with formaldehyde to produce tetrulose 6 and then aldoltetrose 7. Molecule 7 can split into 2 in a retro-aldol reaction.
Formaldehyde condensation

Nu = Nucleophilic catalyst
**Aldol reaction**

\[
\begin{align*}
&\text{R} & & \text{R}' & & \text{H} & & \text{H} \\
&\text{R'} & & \text{R}'' & & \text{R}''' & & \rightarrow \\
&\text{R} & & \text{R}' & & \text{H} & & \text{H} \\
\end{align*}
\]

\[
\text{R} & & \text{R}' & & \text{R}'' & & \text{R}''' & & \text{H}_{2}O
\]

ENOL mode

\[
\begin{align*}
&\text{R} & & \text{C} & & \text{CH}_{3} \\
&\text{C} & & \text{CH}_{2} & & \text{H} & & \text{H} \\
\end{align*}
\]

ENOLATE mode

\[
\begin{align*}
&\text{R} & & \text{C} & & \text{CH}_{3} \\
&\text{C} & & \text{CH}_{2} & & \text{H} & & \text{H} \\
\end{align*}
\]

enol

enolate

aldol addition product

aldol condensation product
Aldol reaction

Base catalyzed aldol reaction (shown using $\text{OCH}_3$ as base)

\[
\begin{align*}
\text{RCH=O} & \xrightarrow{\text{OCH}_3^-} \text{RCH(OH)}-\text{CH}_2\text{R} \\
(\text{Lost H shown for clarity}) & \xrightarrow{\text{enolate}} \text{RCH(OH)}-\text{CH}_2\text{R} \\
 & \xrightarrow{\text{Aldol}} \text{RCH(OH)}-\text{CH}_2\text{R} \\
\end{align*}
\]

Acid catalyzed aldol reaction

\[
\begin{align*}
\text{RCH=O} & \xrightarrow{\text{H}^+} \text{RCH(OH)}-\text{CH}_2\text{R} \\
(\text{Protonated carbonyl (electrophilic)}) & \xrightarrow{\text{Enol (nucleophilic)}} \text{RCH(OH)}-\text{CH}_2\text{R} \\
(\text{Enol (nucleophilic)}) & \xrightarrow{\text{Aldol}} \text{RCH(OH)}-\text{CH}_2\text{R} \\
\end{align*}
\]

Base catalyzed dehydration (sometimes written as a single step)

\[
\begin{align*}
\text{RCH(OH)}-\text{CH}_2\text{R} & \xrightarrow{\text{Loses } \text{OH}^-} \text{RCH(O)}-\text{CH}_2\text{R} \\
(\text{Enolate of aldol (shown as carbanion)}) & \xrightarrow{\text{\alpha,\beta-unsaturated aldehyde}} \text{RCH(O)}-\text{CH}_2\text{R} \\
\text{CH}_3\text{O}^- & \xrightarrow{\text{Lost H shown for clarity}} \text{RCH(O)}-\text{CH}_2\text{R} \\
\end{align*}
\]

Acid catalyzed dehydration

\[
\begin{align*}
\text{RCH(OH)}-\text{CH}_2\text{R} & \xrightarrow{\text{H}^+} \text{RCH(OH)}-\text{CH}_2\text{R} \\
(\text{Protonated carbonyl (electrophilic)}) & \xrightarrow{\text{H}_2\text{O}^-} \text{RCH(OH)}-\text{CH}_2\text{R} \\
(\text{Lost H shown for clarity}) & \xrightarrow{\text{\alpha,\beta-unsaturated aldehyde}} \text{RCH(OH)}-\text{CH}_2\text{R} \\
\end{align*}
\]

Reversible process $\rightarrow$ retro-aldol reaction
**Formose reaction as an autocatalytic process**

Formose reaction starts in concentrated alkaline aqueous solutions of formaldehyde. Alkali are typically calcium, magnesium or lead.
**Detailed conditions for the formose reaction**

Formose reaction starts in concentrated alkaline aqueous solutions of formaldehyde; alkali are typically calcium, magnesium or lead.
Formose reaction – substrate modifications
Formose reaction – substrate modifications

c)

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{3} \\
\overset{\text{O}}{\text{C}} & \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{O}}{\text{PO}_3^{2-}} \\
\text{10} & \quad \overset{\text{O}}{\text{C}} & \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{O}}{\text{PO}_3^{2-}} \\
\text{11} & \quad \overset{\text{O}}{\text{C}} & \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{O}}{\text{PO}_3^{2-}} \\
\text{11(p)} & \quad \overset{\text{O}}{\text{C}} & \quad \overset{\text{O}}{\text{C}} \quad \overset{\text{O}}{\text{PO}_3^{2-}}
\end{align*}
\]
Formose reaction under standard basic catalysis
**Formose reaction in presence of borates**

**Pentose formation in the presence of borate**

With borate (left)
Without borate (right)
Colemanite (background)

By NMR, the ribose borate complex 8 has the structure shown; cyclic structures for other pentoses are speculative.

**DL-glyceraldehyde**
(D-enantiomer shown)

With borate:

- Still electrophilic
- No longer acidic due to anionic borate
- No longer nucleophilic
- Negative boron

**diglyceraldehyde borate complex**

**Formose reaction in presence of borates**

Formose reaction in presence of borates

with borate

D,L-glyceraldehyde

Ca^{2+}

diglyceraldehyde borate complex

D-ribose (open form)
D-arabinose (open form)
D-xylose (open form)
D-lyxose (open form)
**Interstellar origin of carbohydrates**

Simulations of photo- and thermochemistry of interstellar ice (silicate/carbon grains surrounded by ice H$_2$O, CH$_3$OH and NH$_3$) exposed on UV light, low pressure ($10^{-7}$ bar) and temperature (78K) delivers a mixture of sugars

<table>
<thead>
<tr>
<th>C-2</th>
<th>Aldoses</th>
<th>Ketoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{R} = \text{CH}_2\text{OH}$, Ethylene glycol (550 ppm)</td>
<td>= CH$_3$, Glycolaldehyde (2390 ppm)</td>
<td>= COOH, Glycolic acid (6330 ppm)</td>
</tr>
</tbody>
</table>

| C-3 | R = CH$_2$OH, Glycerol (2860 ppm) | = CH$_3$, Glyceraldehyde (302 ppm) |

| C-4 | R = CH$_2$OH, Erythritol (5070 ppm) | = CH$_3$, Erythrose (< q.i.) |

| C-5 | R = CH$_2$OH, Ribitol (560 ppm) | = CH$_3$, Ribose (260 ppm) |

Interstellar origin of carbohydrates

Homologation routes to simple sugars from formaldehyde 1.

a, Direct homologation of formaldehyde 1 is problematic, because the first dimerization step (dashed) requires umpolung, and because the trimer is more stable as the ketose 4 than the aldose 3 under conditions where 3 can be formed from 1 and 2. b, Kiliani–Fischer homologation of 1 in conventional synthetic chemistry involves favourable formation of the cyanohydrin 6 by reaction of 1 with hydrogen cyanide 5, followed by the selective reduction of 6 using very specific conditions.
Kiliani-Fischer homologation

1 + 2 HCN → 2b

2b + 2 H₂O → 3b

3b + 2 HO⁻ → 4b

4b + Na/Hg → 5b

H⁺ + H₂O → H₂ + H⁺
Cyanosulfidic chemistry for the Kiliani-Fischer homologation

\[ \text{Cu}_2\text{S} + \text{H}_2\text{O} + 6\text{CN}^- \rightarrow 2[\text{Cu(CN)}_3]^{2-} + \text{HS}^- + \text{OH}^- \]

Photoredox cycle based on cyanocuprates may convert HCN into cyanogen
In absence of HS⁻ glycolaldehyde 2 ends up mainly as a cyclic derivative 13
Cyanosulfidic chemistry for the Kiliani-Fischer homologation

J. Sutherland, Nature Reviews Chemistry 2017, 1, Article 0012, doi:10.1038/s41570-016-0012
**Carbohydrates - summary**

Formose reaction gives access to numerous C$_2$-C$_5$ and higher carbohydrates, but is difficult to direct towards particular outcome, and ultimately turns into polymeric tar if overcooked.

In presence of borates, the formose reaction tends to deliver protected pentoses in high yields and stable form.

Although formaldehyde is the simplest starting material, the reaction is autocatalytic in glycolaldehyde and without it long incubation period is required.

Carbohydrate synthesis can also occur under simulated extraterrestrial conditions – by UV-light irradiation of cometary ice.

Alternative prebiotic synthesis of simple carbohydrates involves Kiliani-Fischer homologation process based on HCN in presence of copper ions and hydrosulfides – all accessible by the meteorite-derived cyanide-metal chemistry.

The same type of chemistry can also deliver a set of reactive intermediates like cyanogen, acetylene, ammonia, and activated forms of phosphate – the latest can derivatize sugars and, after redox processes, deliver numerous building blocks present in currently known metabolic cycles.