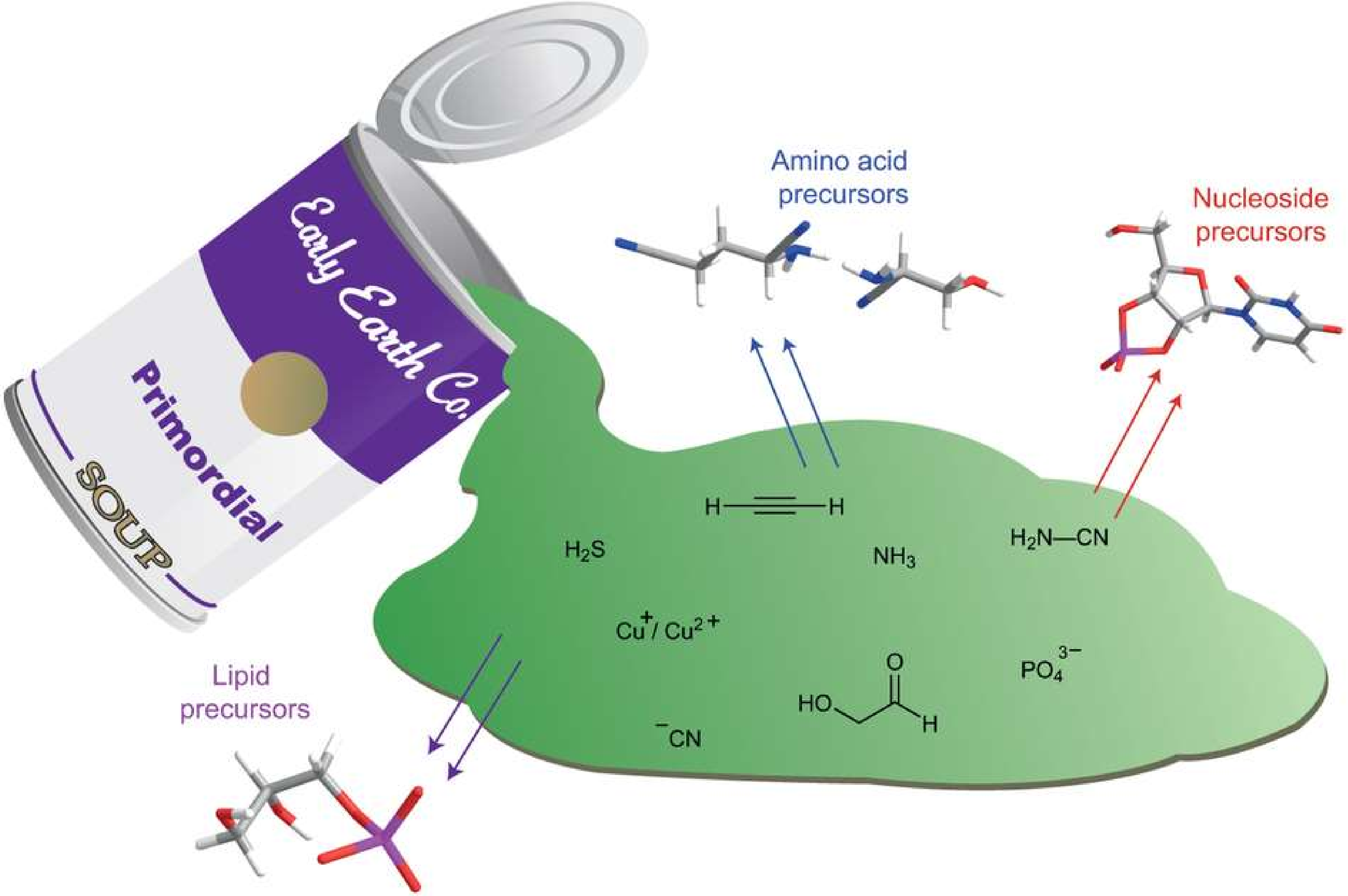
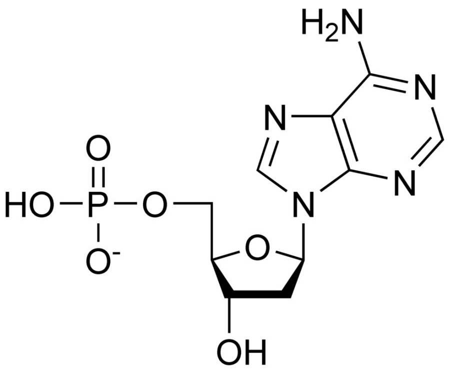
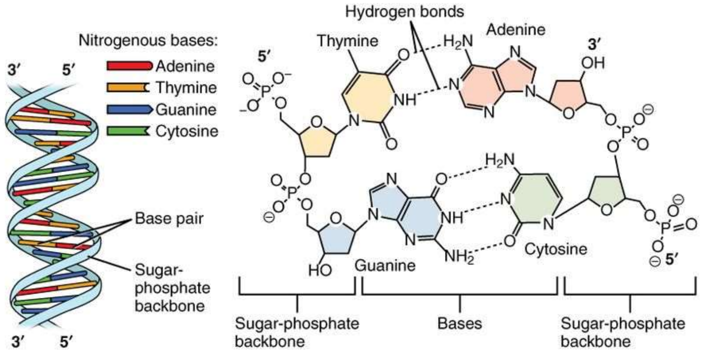
Basic classes of biomolecules

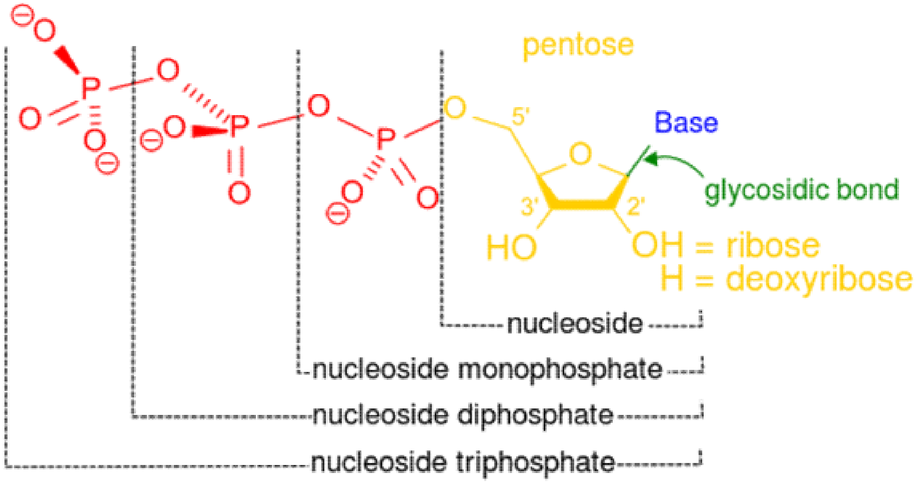


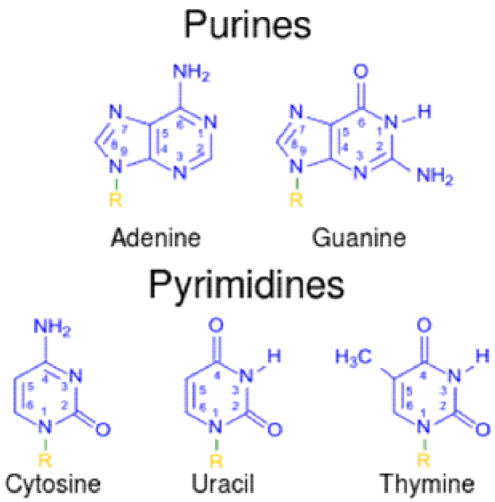
- Aminoacids
- Lipids
- **Carbohydrates (sugars)**
- **Nucleobases**
- **Nucleosides (sugar+nucleobase)**

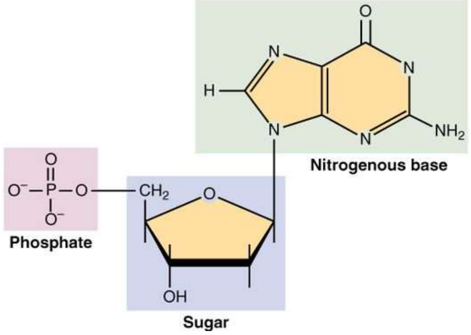
Nucleotides - components



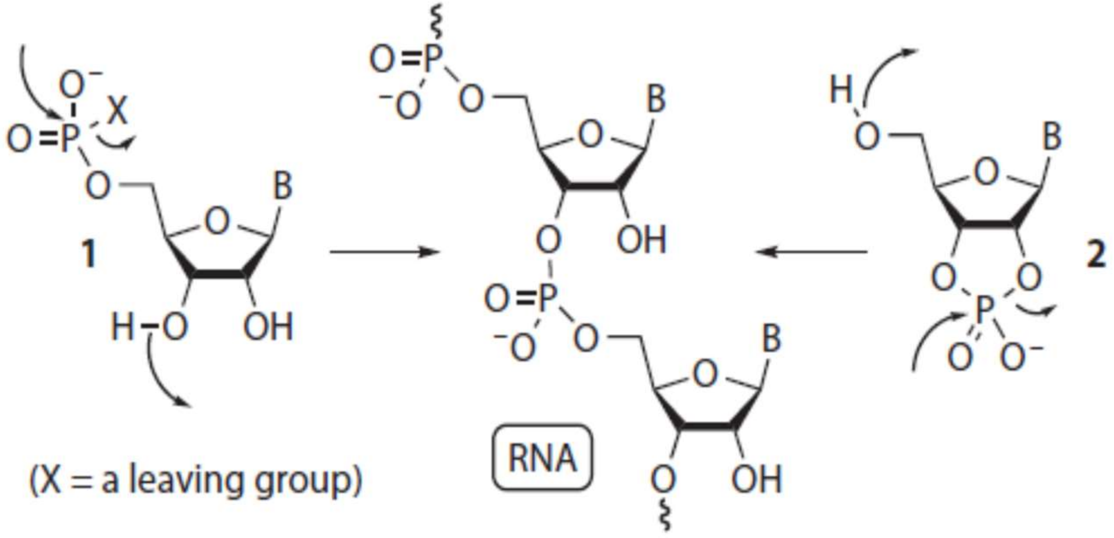






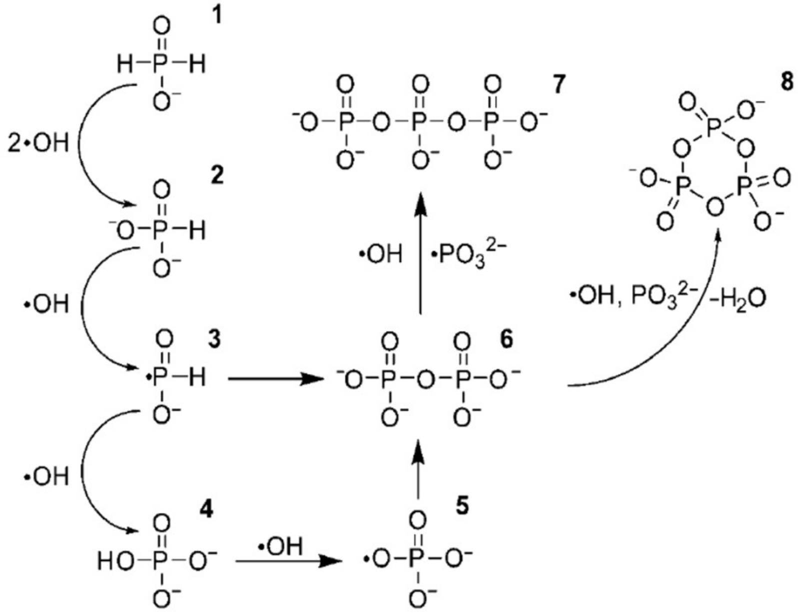


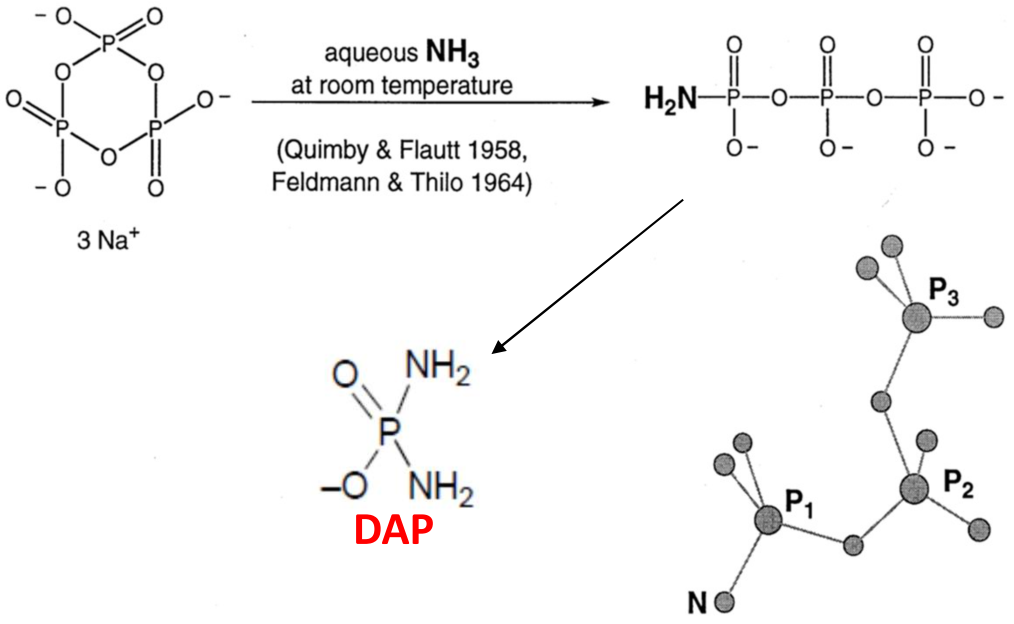
Phosphates and the prebiotic synthesis of oligonucleotides



Activated ribonucleotides in the potentially prebiotic assembly of RNA. Potential P–O bond forming polymerization chemistry is indicated by the curved arrows.

Phosphorylation reagents



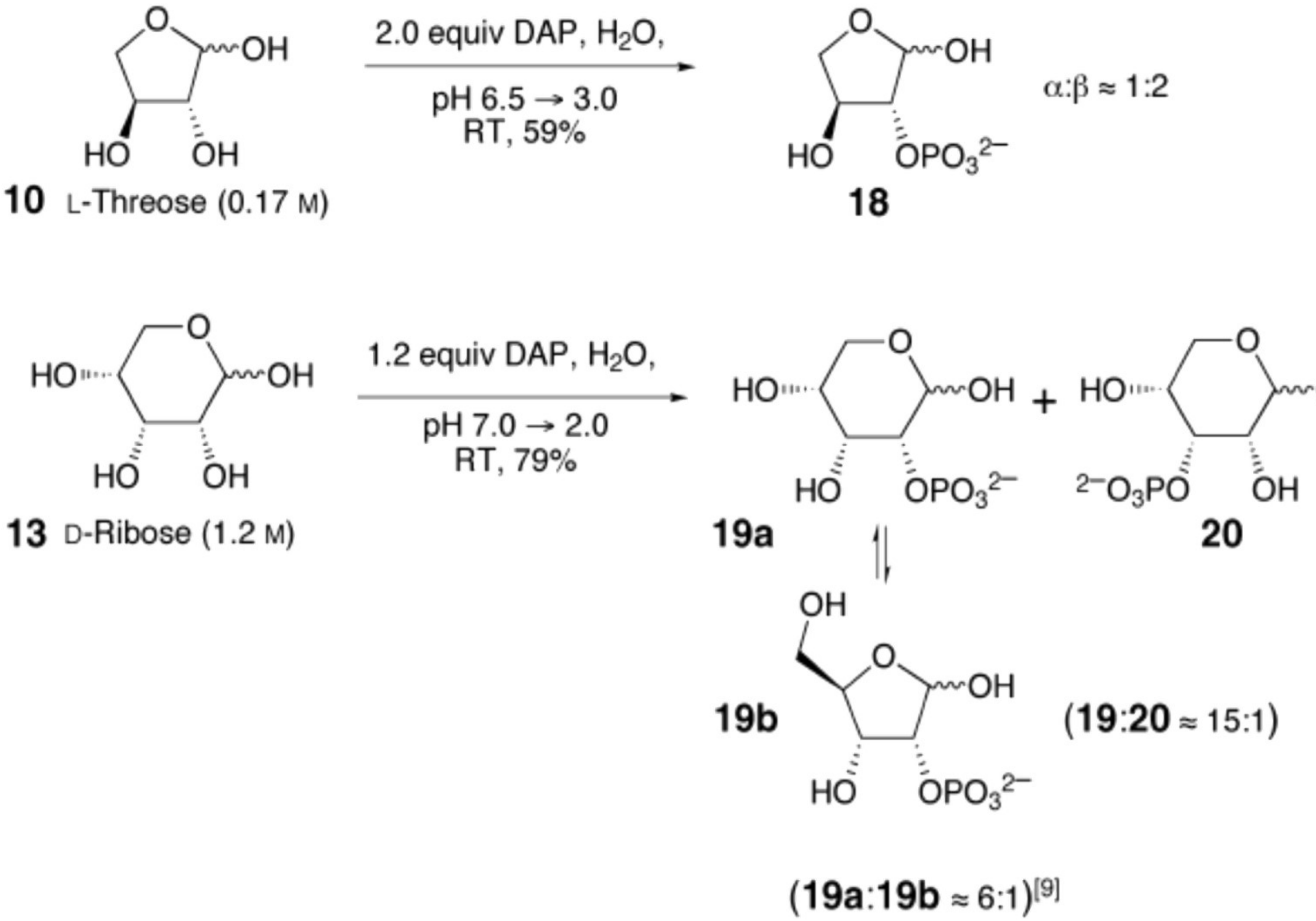


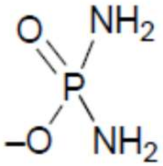
(Quimby & Flautt 1958, Feldmann & Thilo 1964)

x-ray structure of $K_4(P_3O_9NH_2)$ (Hilmer, 1965)

M. A. Pasek, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7918-7920 A. Eschenmoser, *et al. Orig. Life Evol. Biosph.* **1999**, *29*, 333-354

Phosphorylation reagents

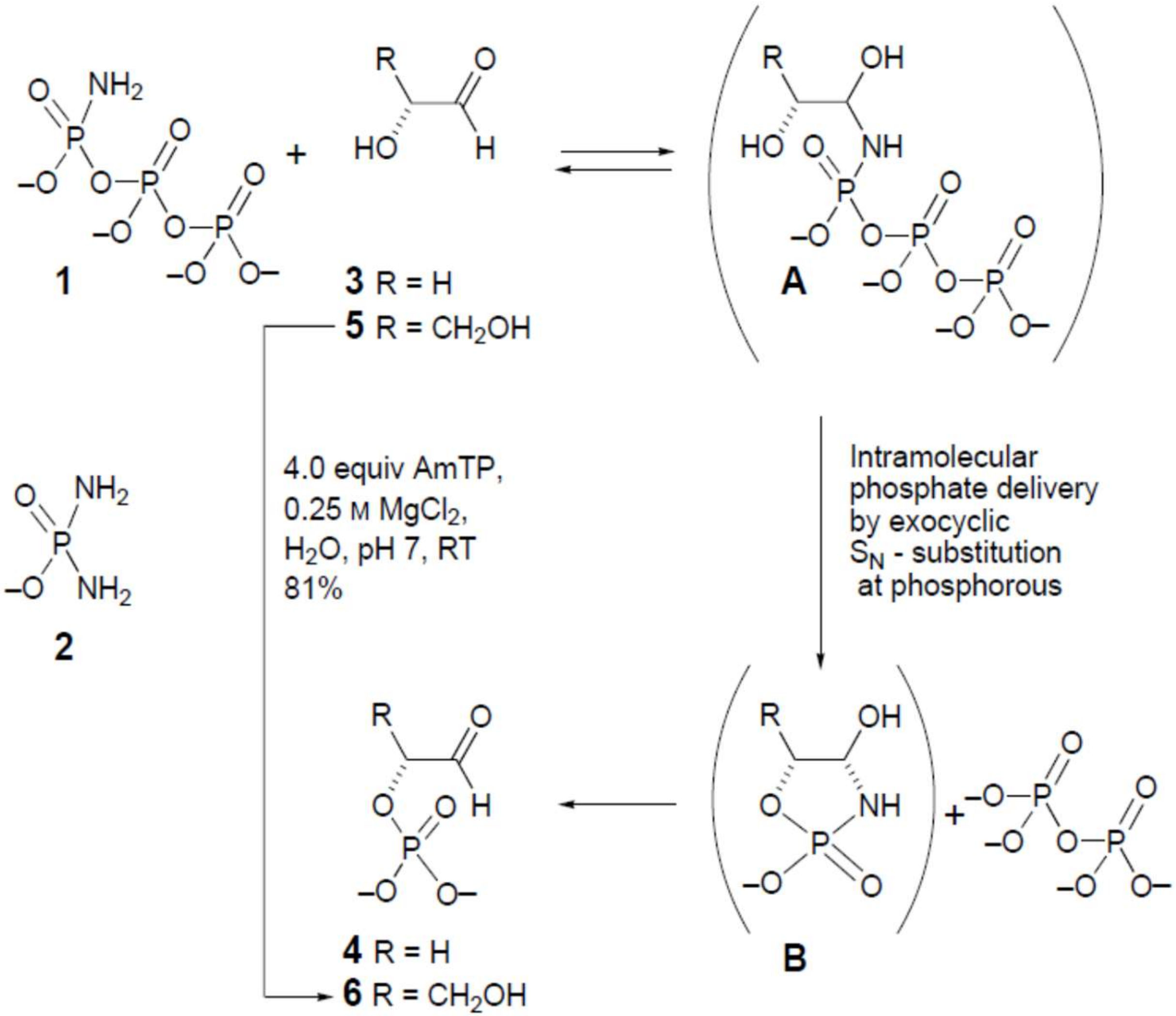




DAP

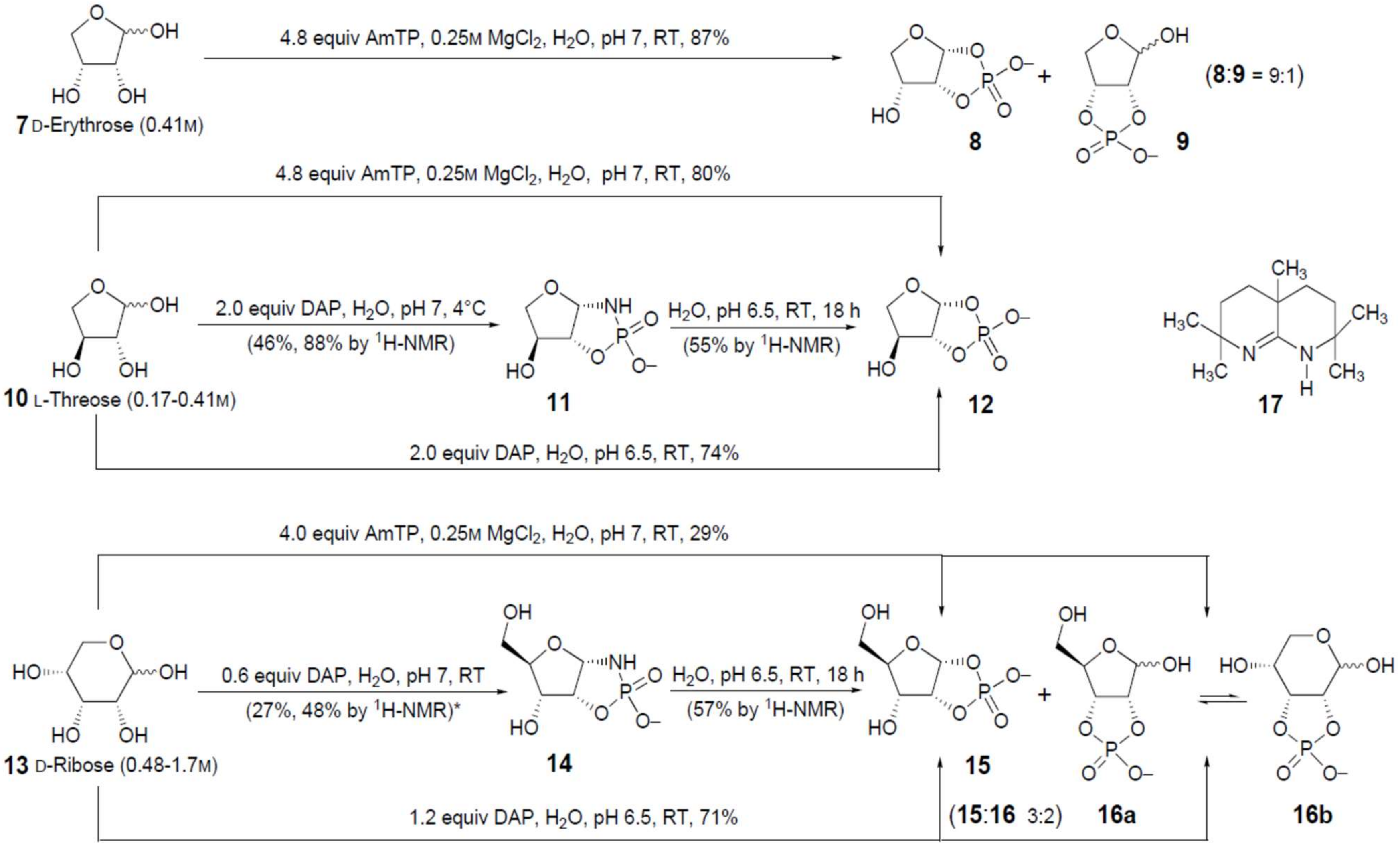
M. A. Pasek, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7918-7920 A. Eschenmoser, *et al. Orig. Life Evol. Biosph.* **1999**, *29*, 333-354

Phosphorylation of sugars



A. Eschenmoser, *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2281-2285

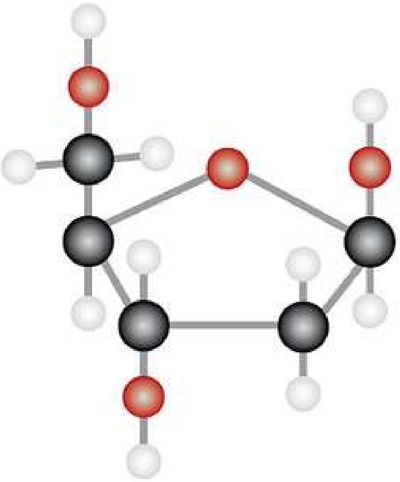
Phosphorylation of sugars



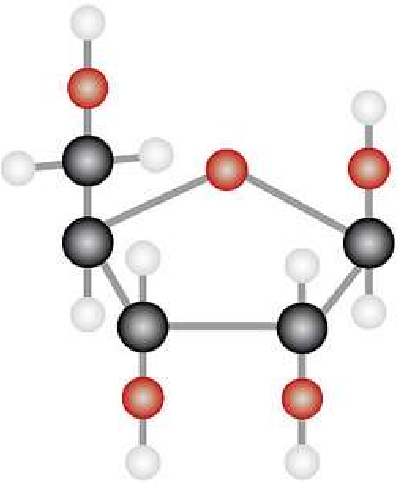
A. Eschenmoser, *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2281-2285

(**16a**:**16b** 3:1)[9]

Nucleosides - nucleobases + sugars

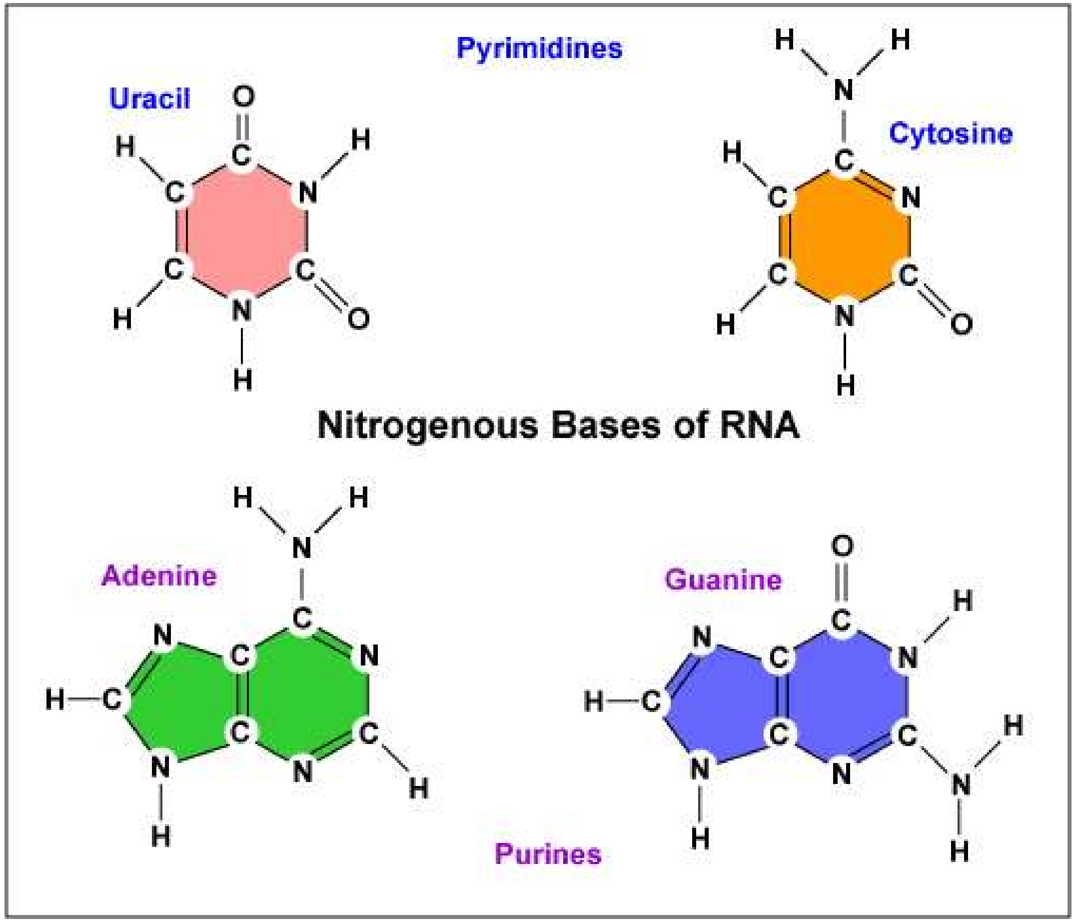


Deoxyribose
used in DNA backbone

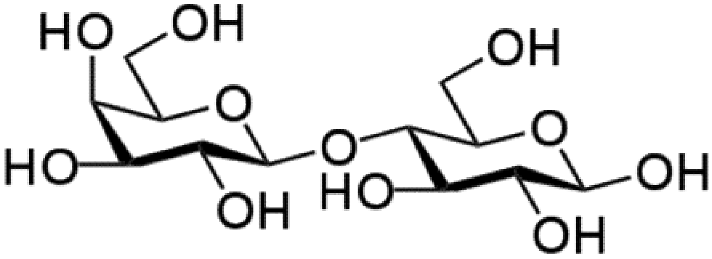


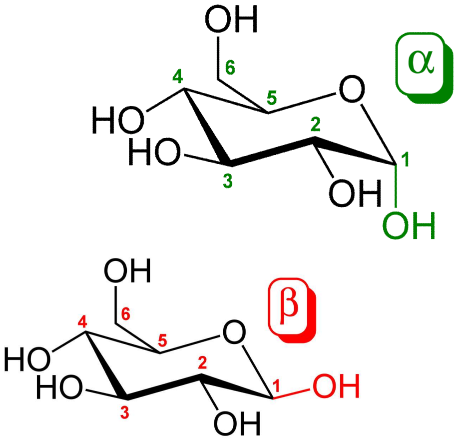
Ribose
used in RNA backbone

Key
○ Hydrogen
🔴 Oxygen
● Carbon

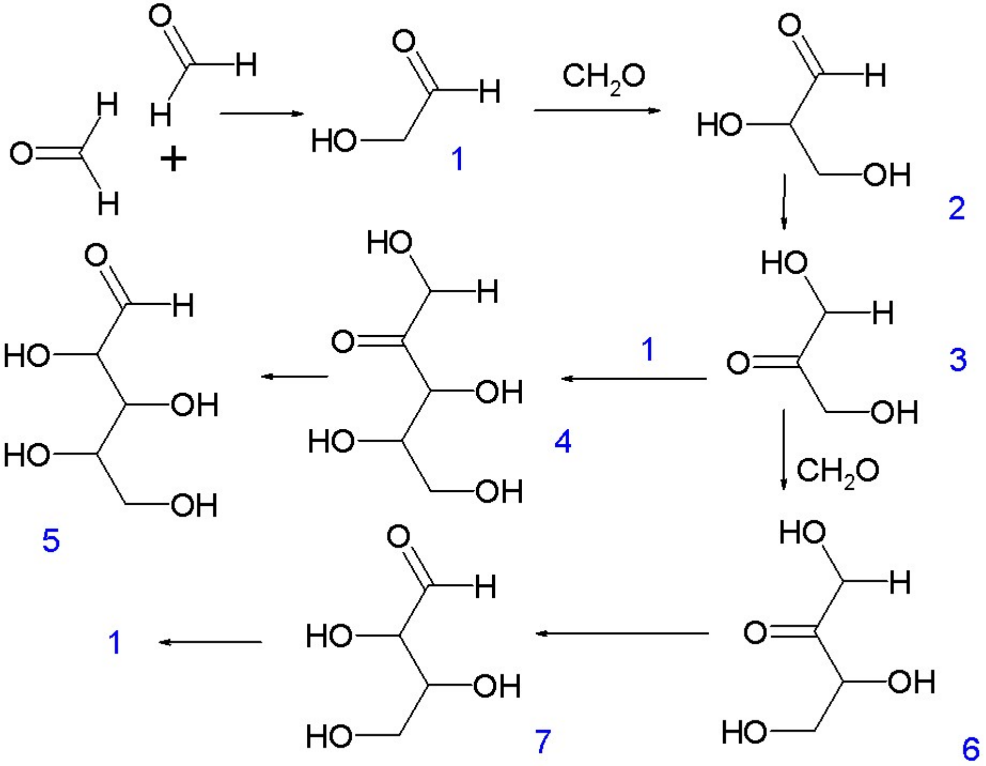


Carbohydrates





Formose reaction

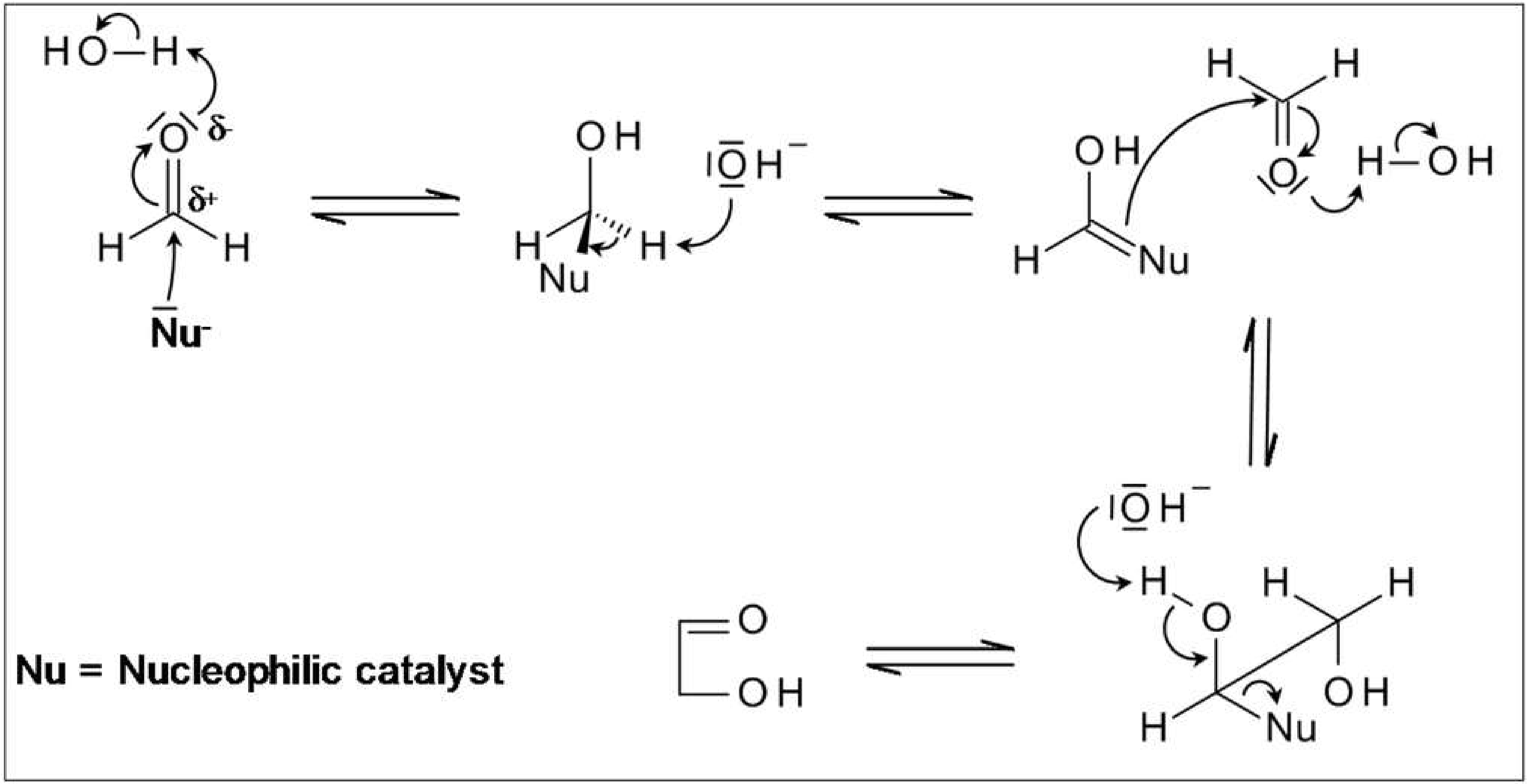


The reaction begins with two formaldehyde molecules condensing to make glycolaldehyde **1** which further reacts in an aldol reaction with another equivalent of formaldehyde to make glyceraldehyde **2**. An aldose-ketose isomerization of **2** forms dihydroxyacetone **3** which can react with **1** to 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.

Alexander Butlerov (1828-1886)
St. Petersburg, Kazan, Russia

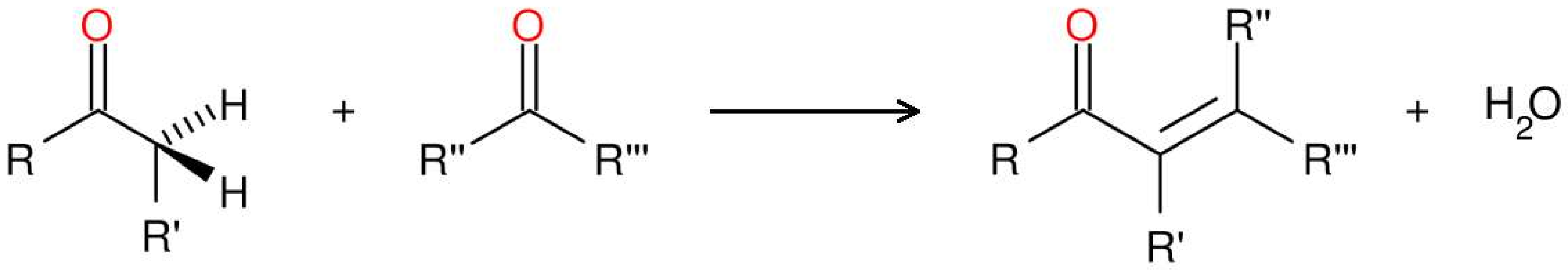
Ronald Breslow (1931-)
Columbia University, USA

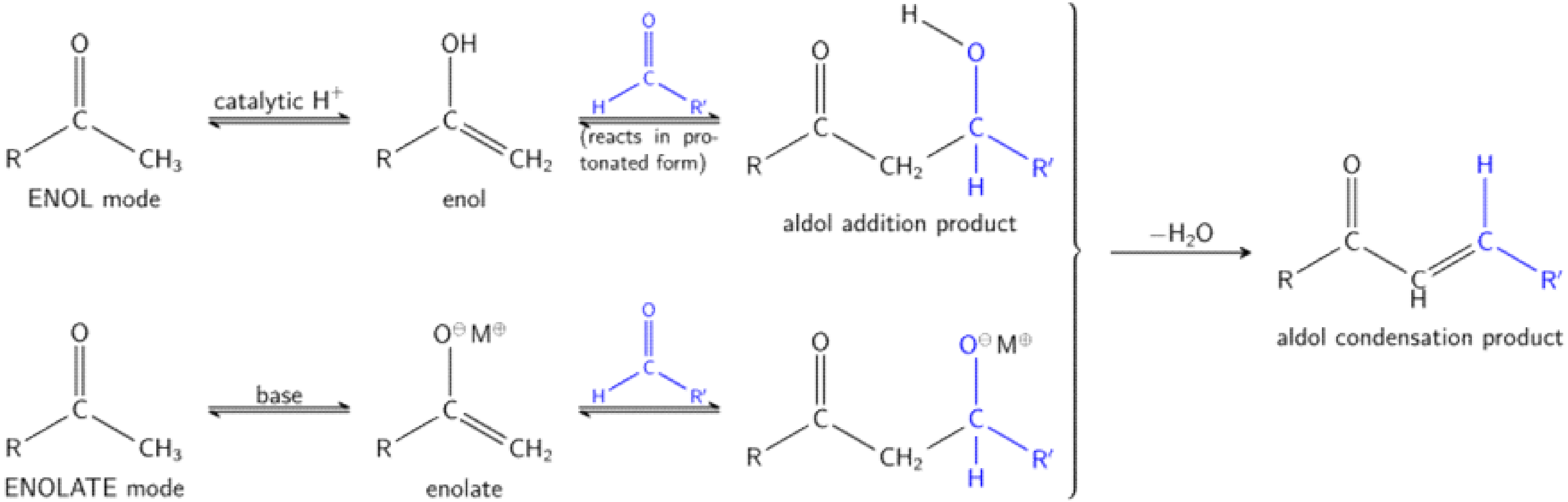
Formaldehyde condensation



Nu = Nucleophilic catalyst

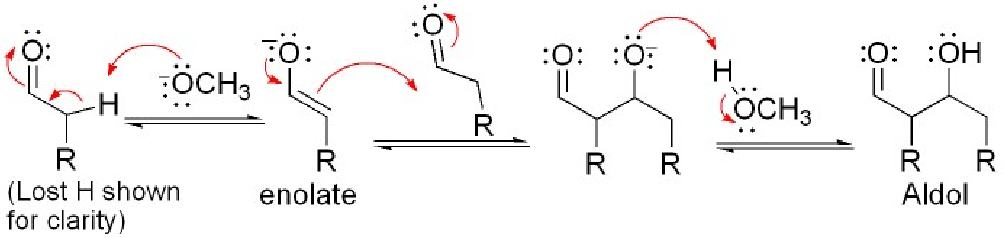
Aldol reaction



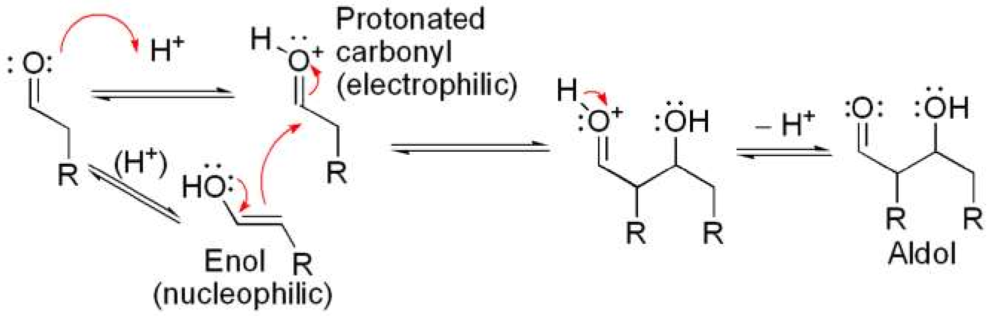


Aldol reaction

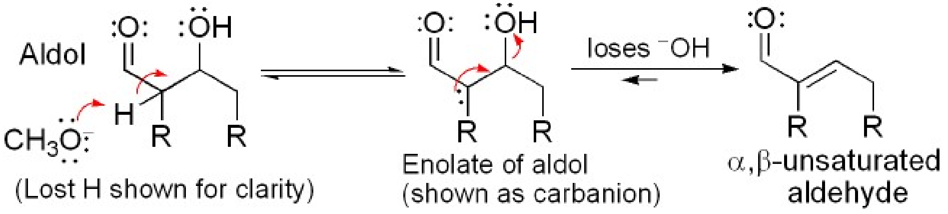
Base catalyzed aldol reaction (shown using $^{-}OCH_3$ as base)



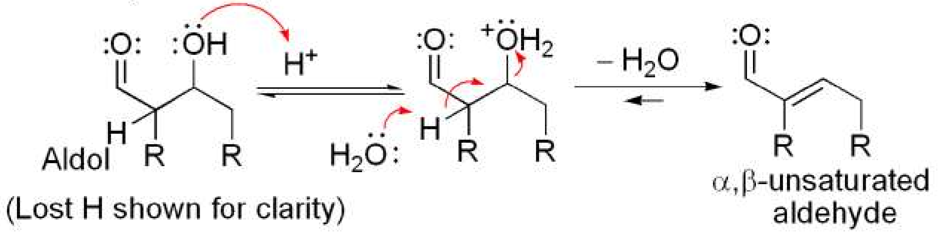
Acid catalyzed aldol reaction



Base catalyzed dehydration (sometimes written as a single step)

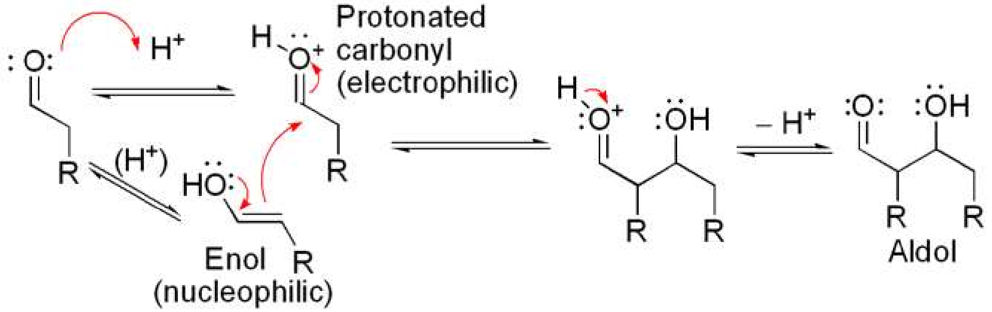


Acid catalyzed dehydration



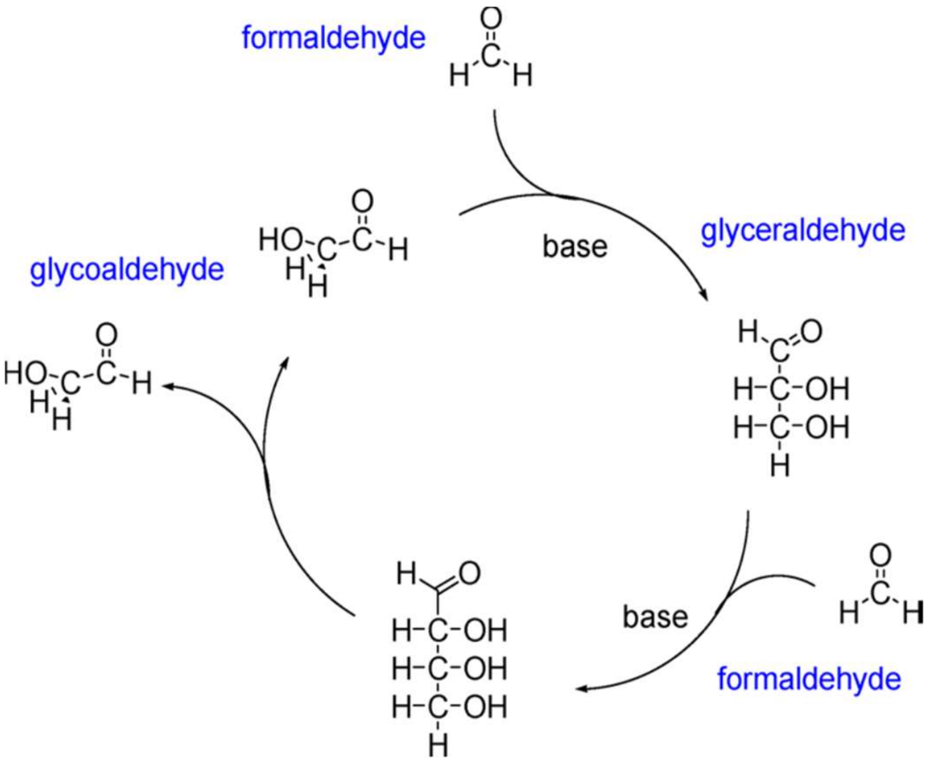
Reversible process
→ retro-aldol reaction

Acid catalyzed aldol reaction



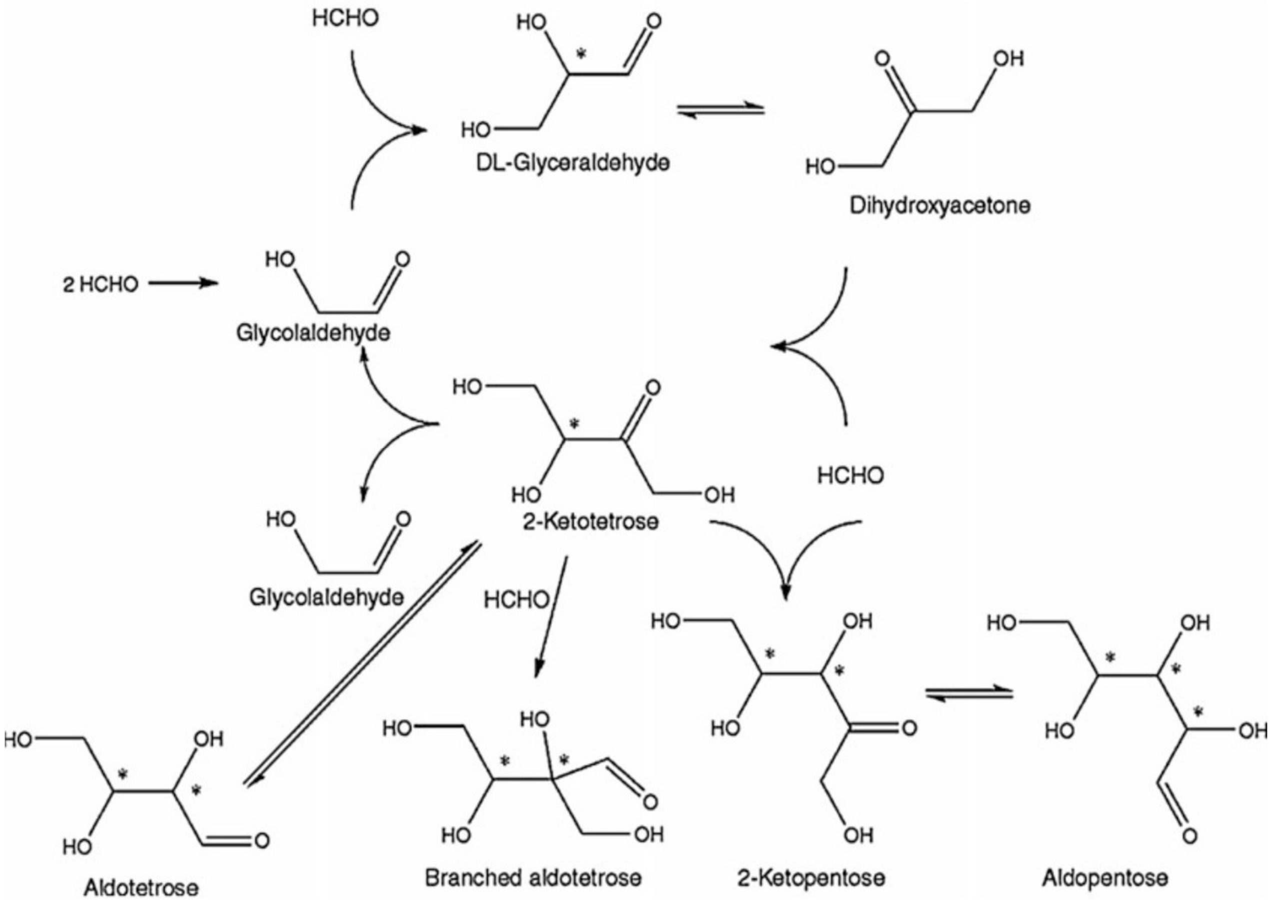
Formose reaction as an autocatalytic process

Formose reaction starts in concentrated alkaline aqueous solutions of formaldehyde
alkali are typically calcium, magnesium or lead



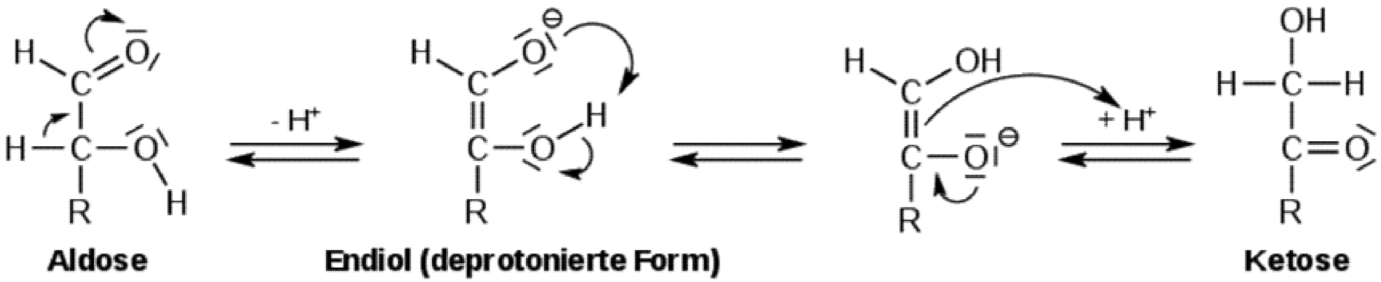
Detailed conditions for the formose reaction

Formose reaction starts in concentrated alkaline aqueous solutions of formaldehyde alkali are typically calcium, magnesium or lead

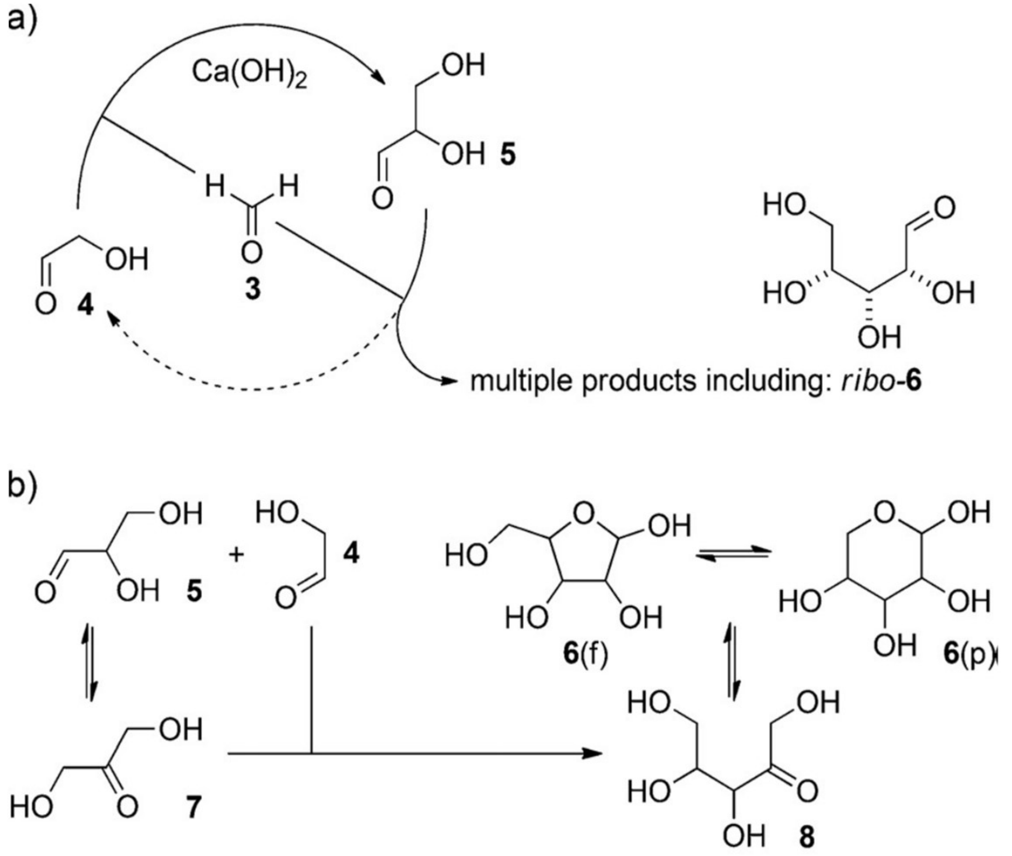


Aldose-ketose isomerization

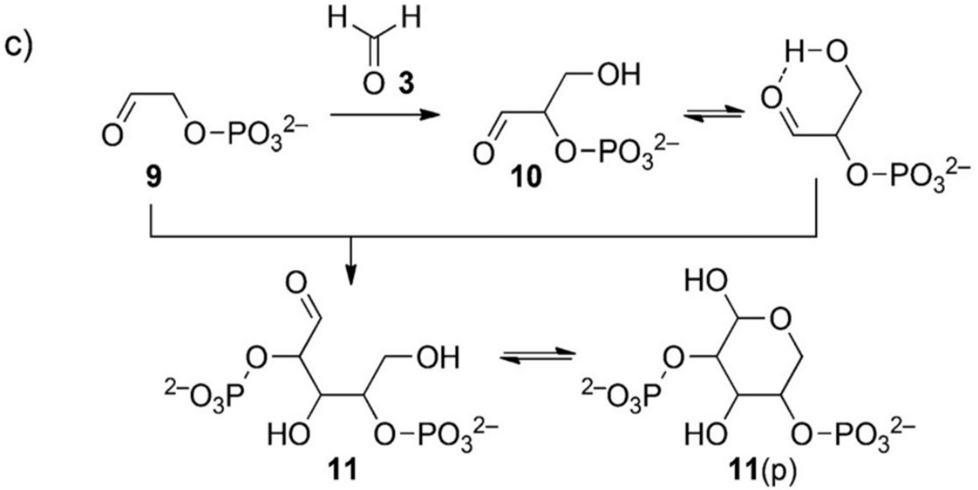
Lobry de Bruyn(–Alberda)-van Ekenstein transformation



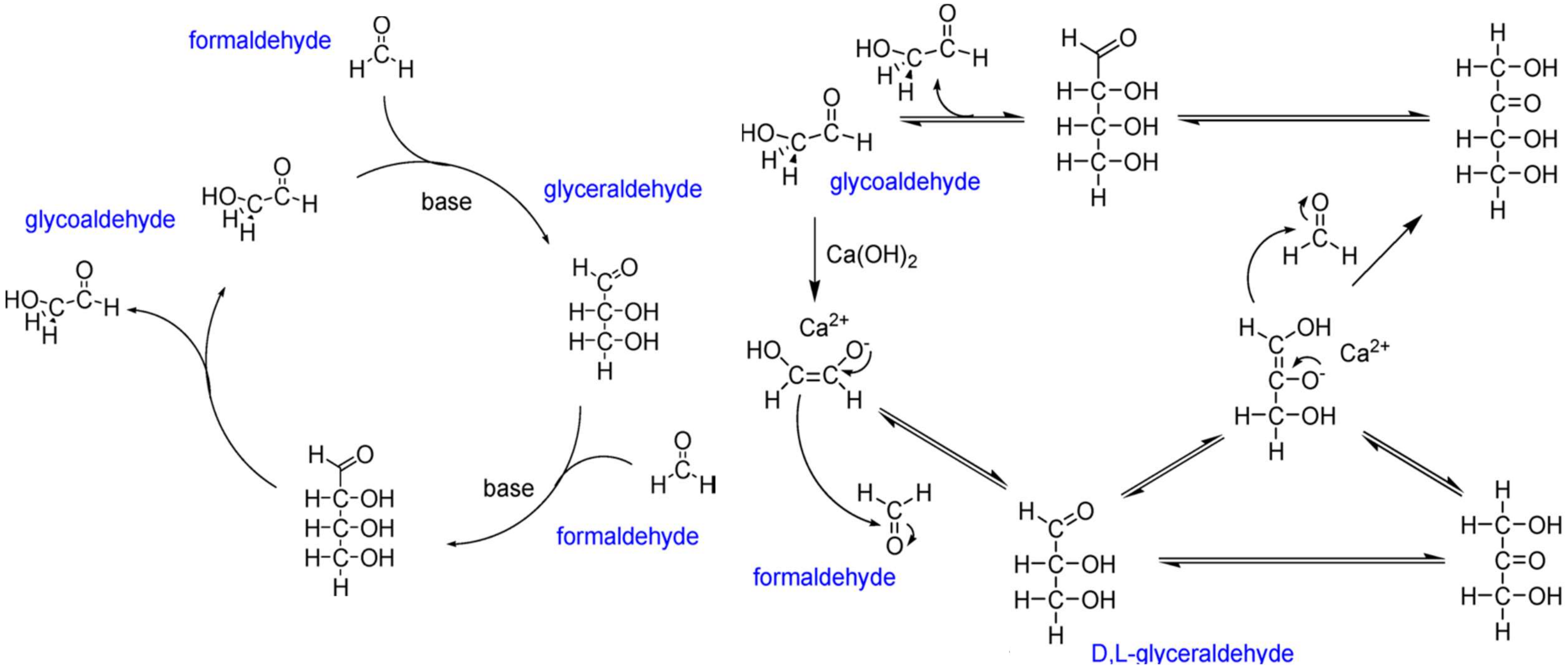
Formose reaction – substrate modifications



Formose reaction – substrate modifications

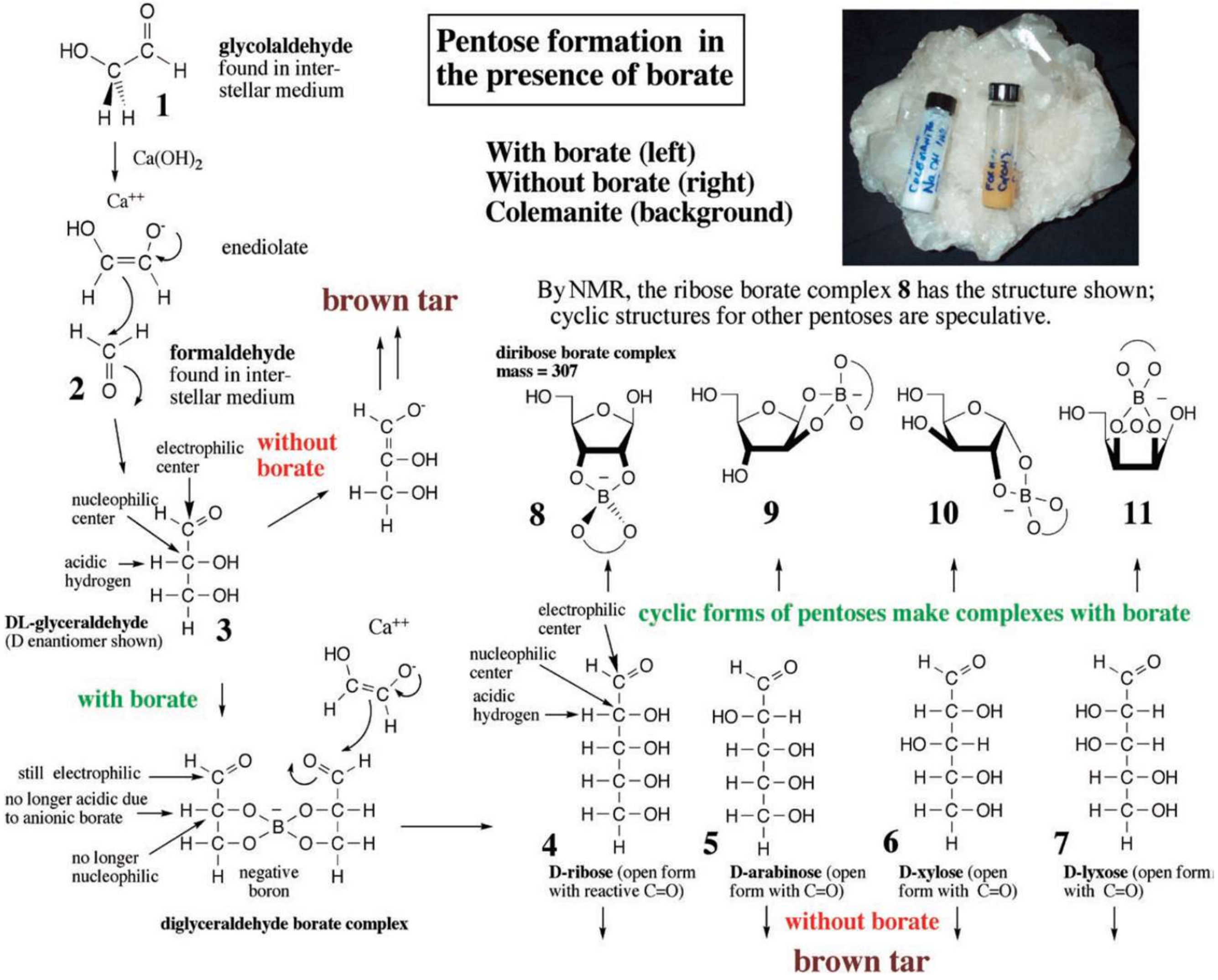


Formose reaction under standard basic catalysis



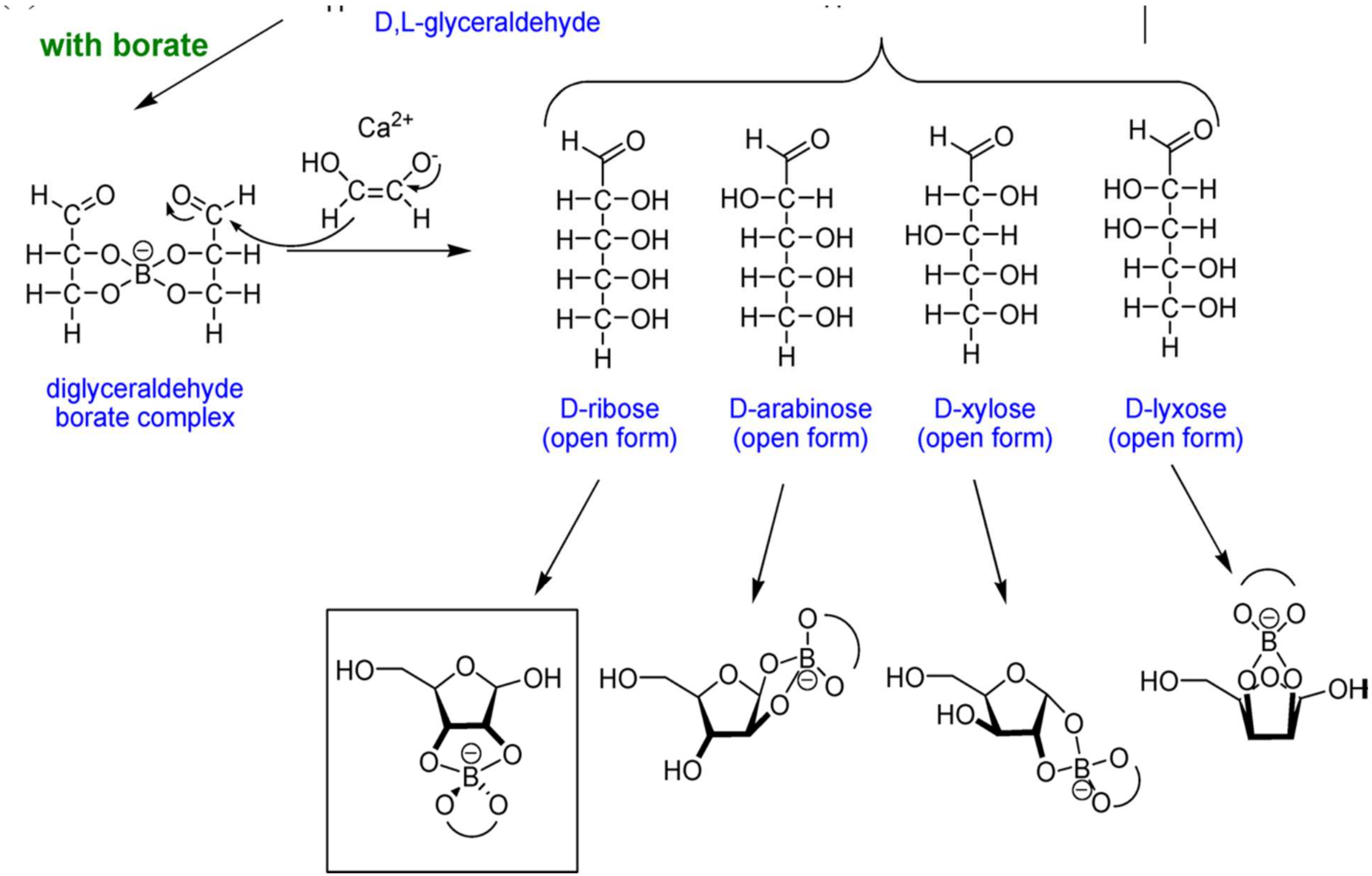
Escosura

Formose reaction in presence of borates



A. Ricardo, M. A. Carrigan, A. N. Olcott, S. A. Benner *Science* **2004**, *303*, 196

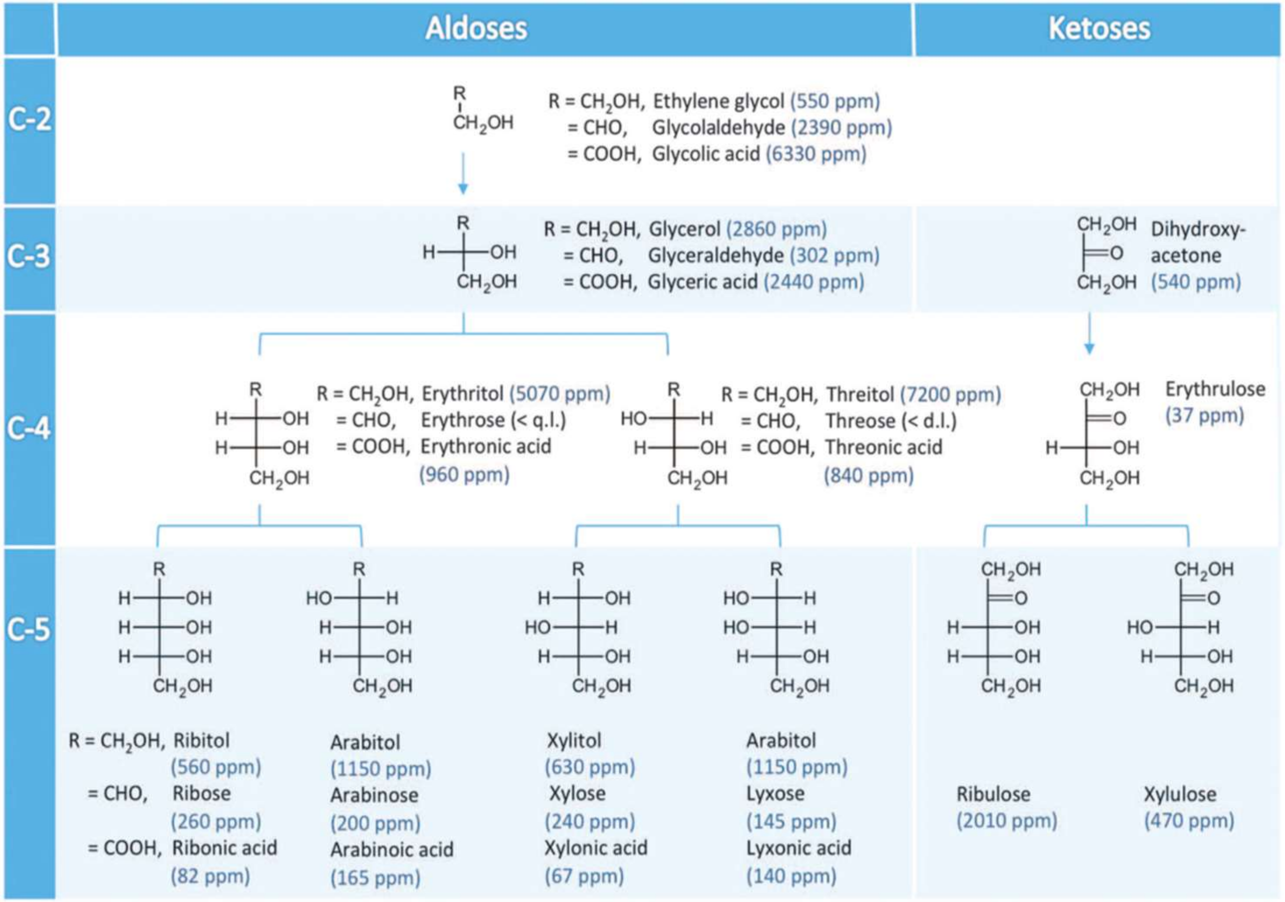
Formose reaction in presence of borates



Escosura

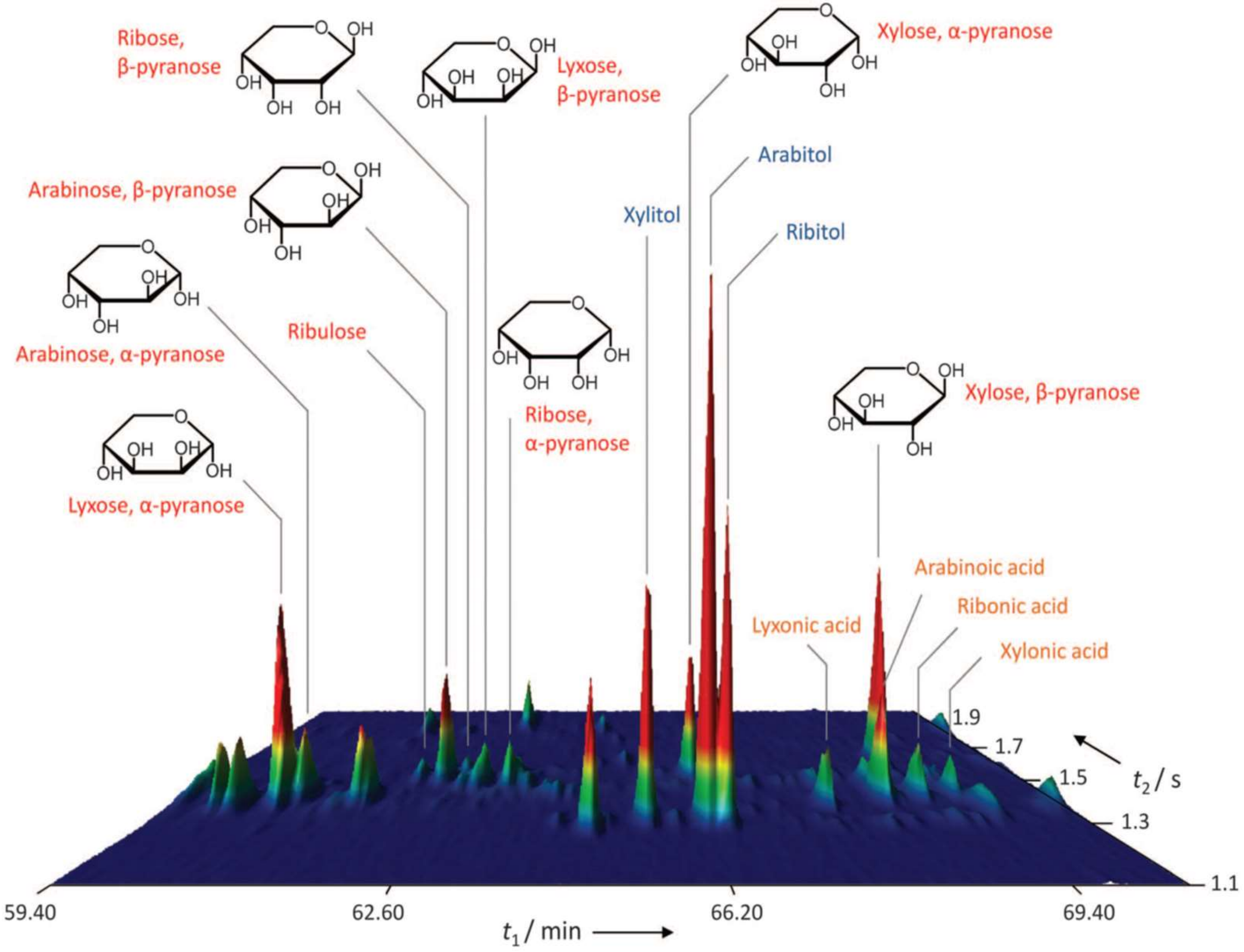
Interstellar origin of carbohydrates

Simulations of photo- and thermochemistry of interstellar ice (silicate/carbon grains surrounded by ice H_2O, CH_3OH and NH_3) exposed on UV light, low pressure (10^{-7} bar) and temperature (78K) delivers a mixture of sugars



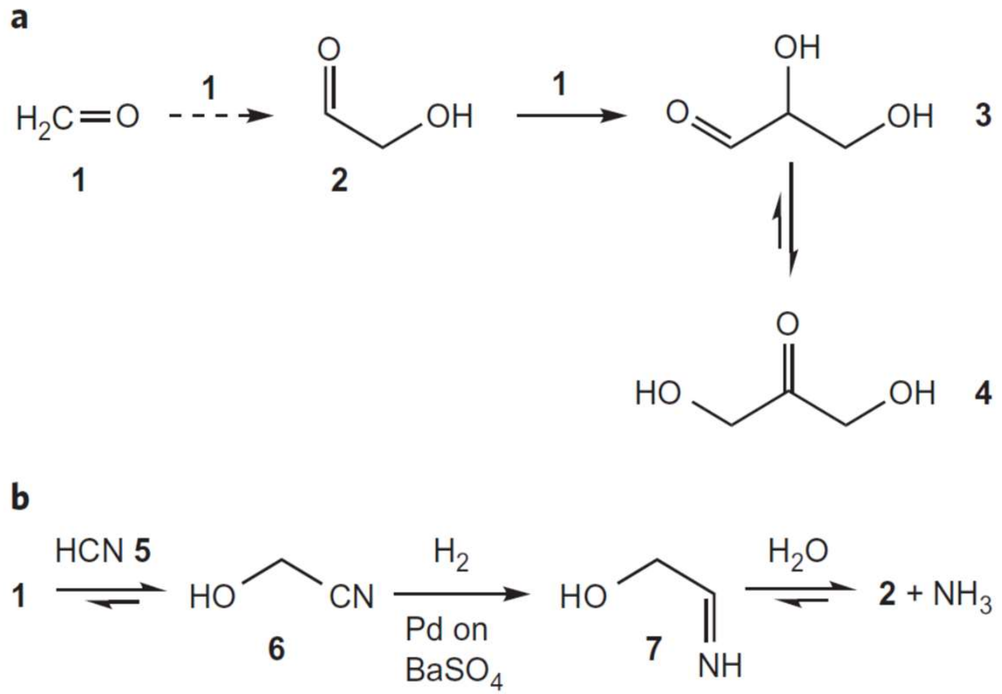
U. Meierhenrich, *et al. Science* **2016**, *352(6282)*, 208-212

Interstellar origin of carbohydrates



U. Meierhenrich, *et al. Science* **2016**, *352(6282)*, 208-212

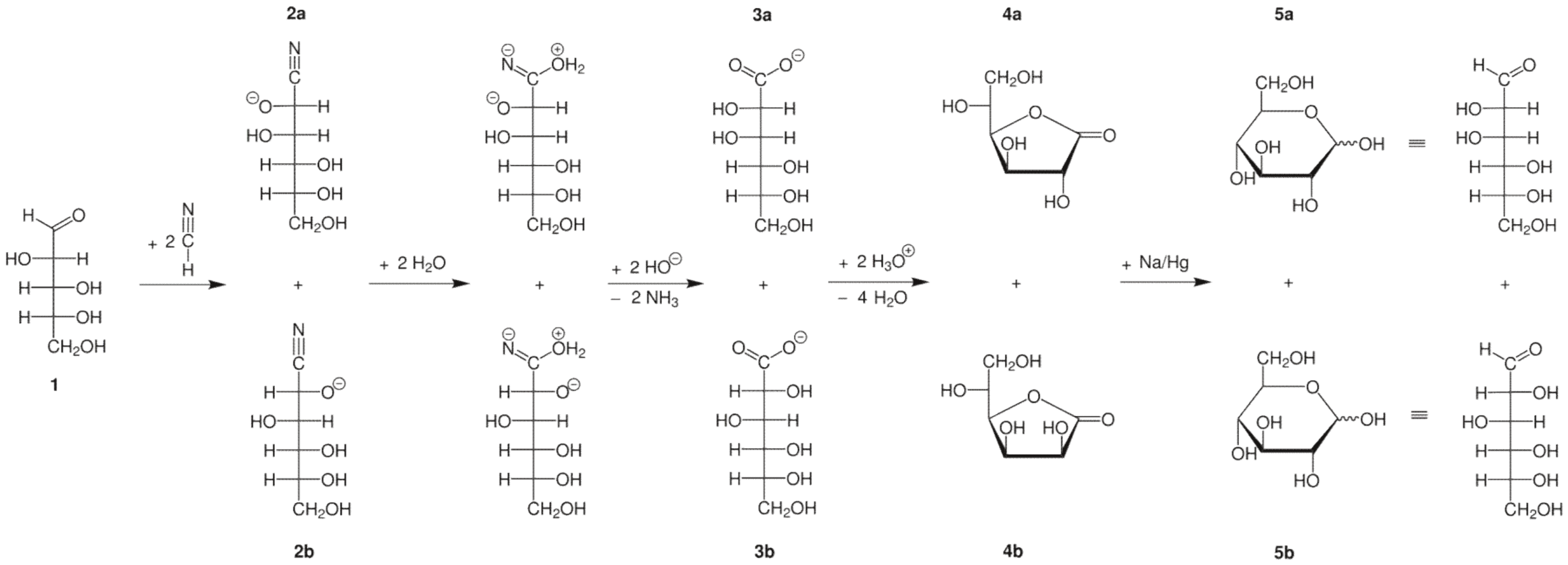
Prebiotically plausible alternatives to formose process

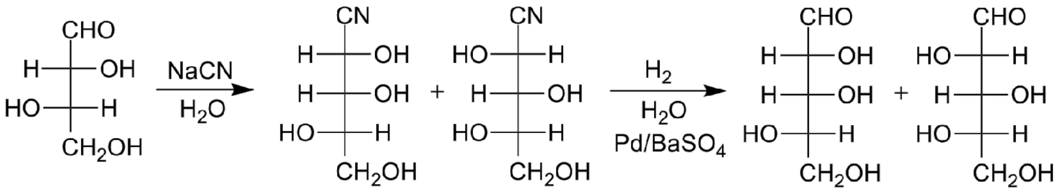


Homologation routes to simple sugars from formaldehyde **1**.

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

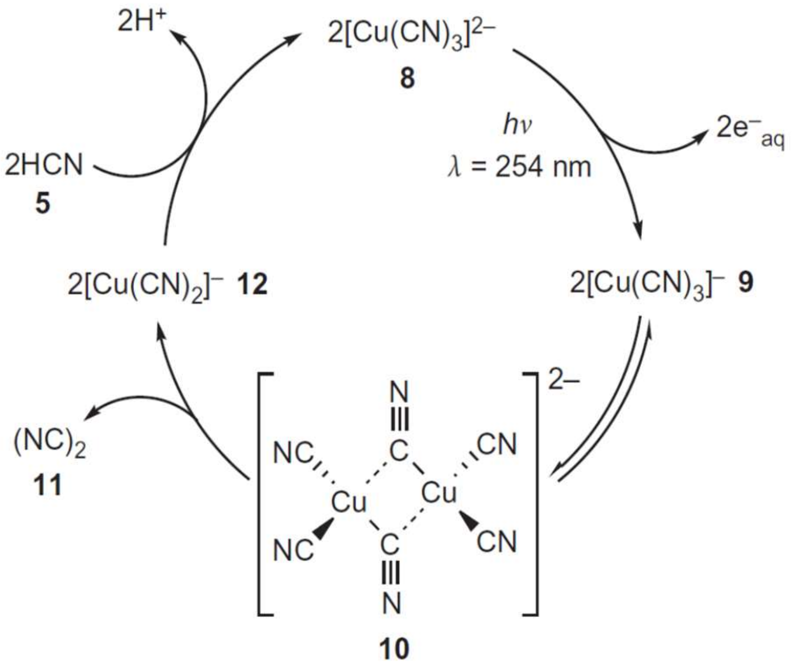


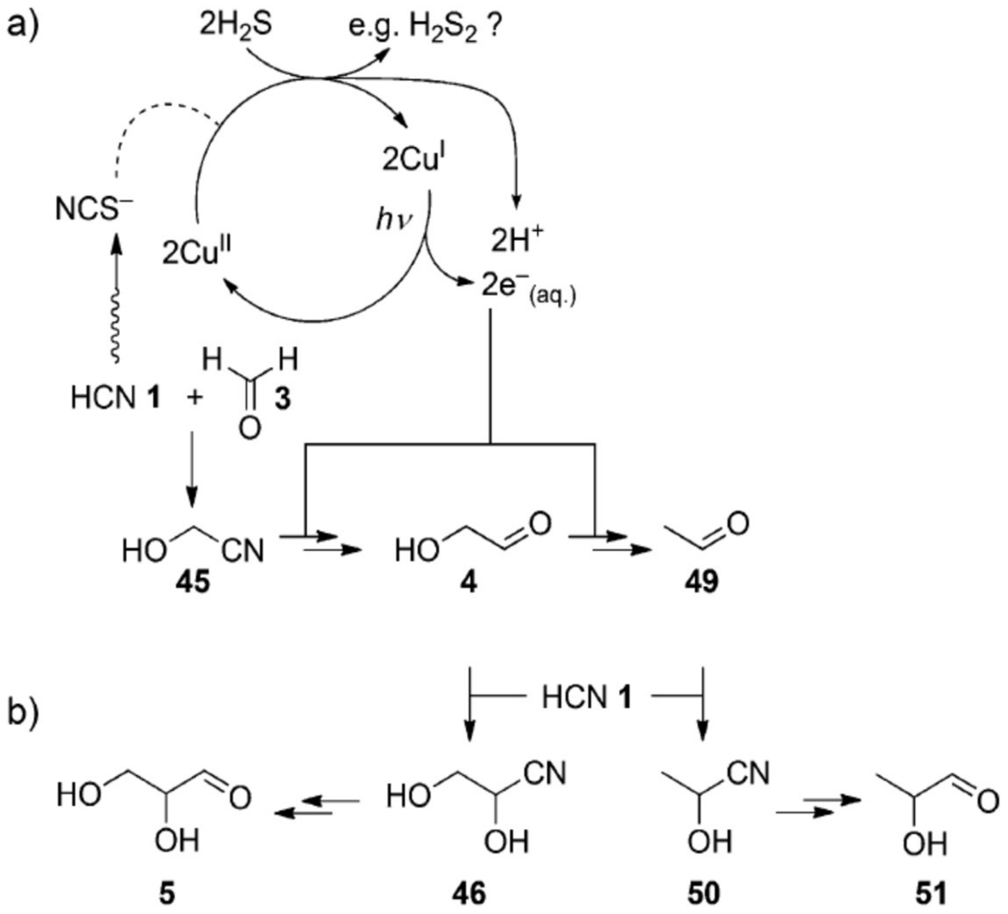


Cyanosulfidic chemistry for the Kiliani-Fischer homologation

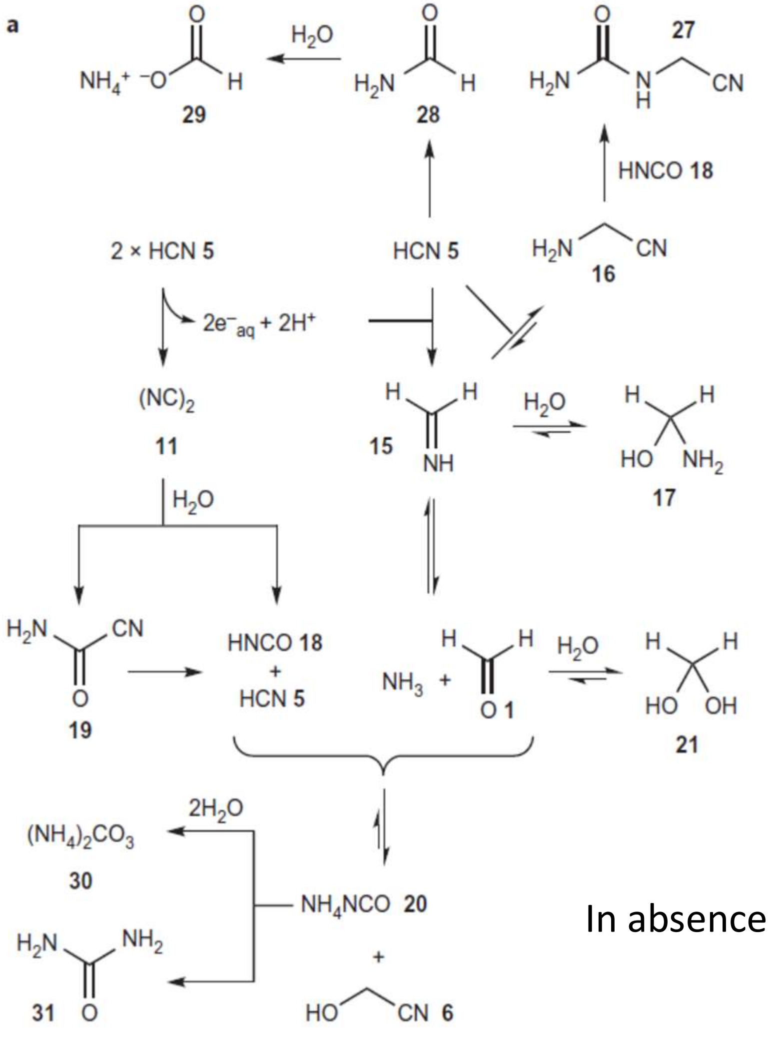
$Cu_2S + H_2O + 6CN^- \rightarrow 2[Cu(CN)_3]^{2-} + HS^- + OH^-$

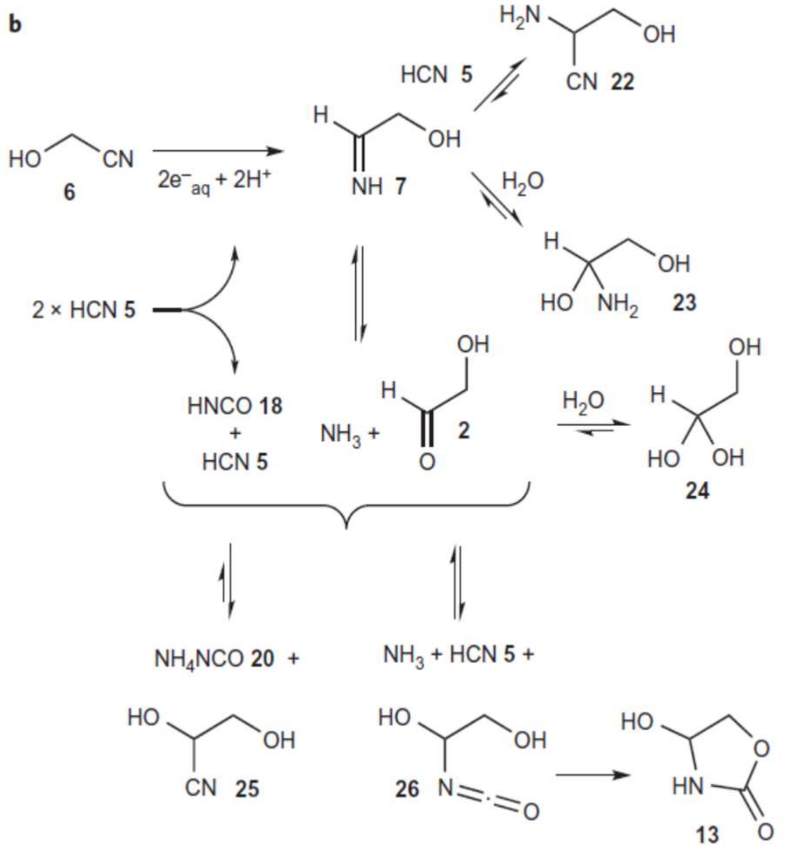
Photoredox cycle based on cyanocuprates may convert HCN into cyanogen





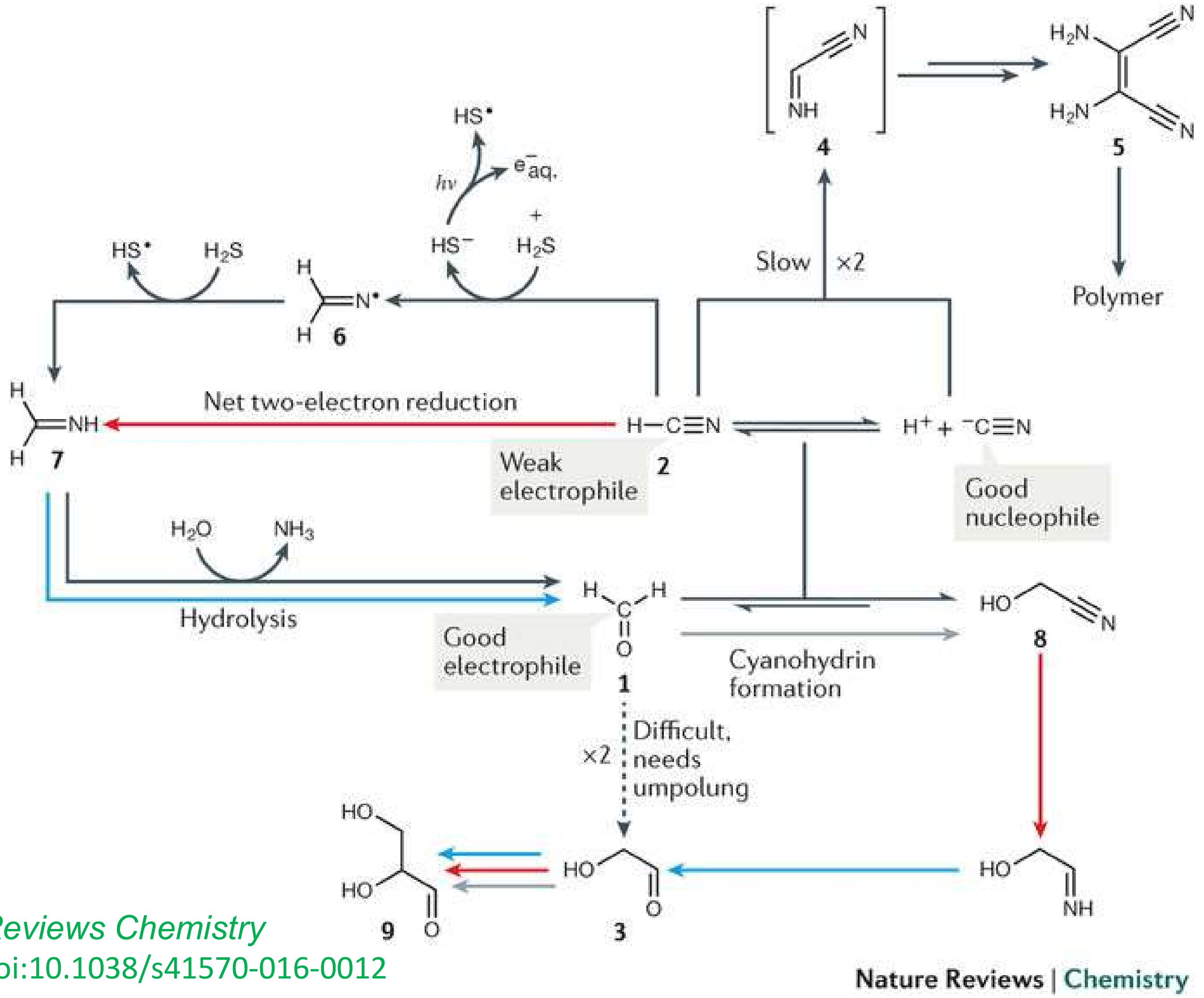
Cyanosulfidic chemistry for the Kiliani-Fischer homologation





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