The molecular origins of life

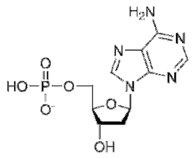
SoSe 2017 HD

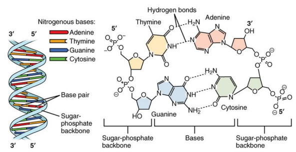
Zbigniew Pianowski

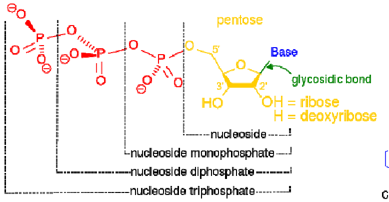
Basic classes of biomolecules

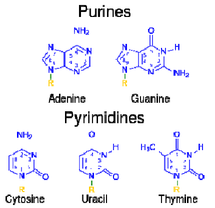
- Aminoacids
- Lipids
- Carbohydrates (sugars)
- Nucleotides
- Nucleosides
  (sugar+nucleotide)

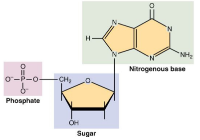
Nucleotides - components



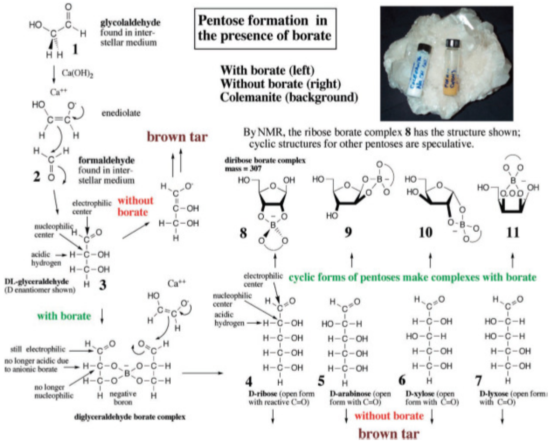








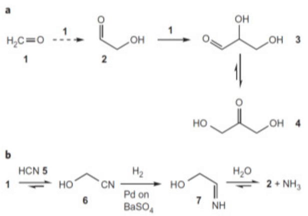
Formose reaction in presence of borates



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

Prebiotically plausible alternatives to formose process

Step **1** → **2** (dashed) requires umpolung
→ Slow trimer more stable as the ketose **4** than the aldose **3**



Kiliani–Fischer homologation of **1** favourable formation of the cyanohydrin **6** by reaction of **1** with HCN **5**,
It requires the selective reduction of **6**.

Phosphates

Source: Google Images

Wikimedia , Butcherbird

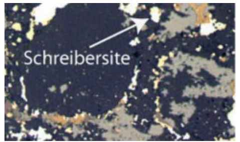
slice of the Gebel Kamil Meteorite with schreibersite rimmed by kamacite

Schreibersite is generally a rare iron-nickel phosphide mineral, $(Fe,Ni)_3P$, though common in iron-nickel meteorites

Acidic schreibersite corrosion under anaerobic conditions (10% aq. HCl/N_2) → soluble forms of phosphorus

$$(Fe,Ni)_3P + HCl_{aq} \rightarrow H_2PO_3^- \rightarrow H_2P_2O_5^{2-}$$

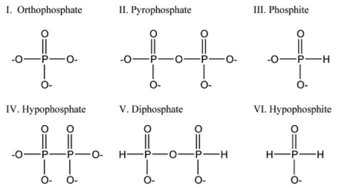
T. P. Kee *et al.Geochimica et Cosmochimica Acta.* ***2013*** *109,* 90-112

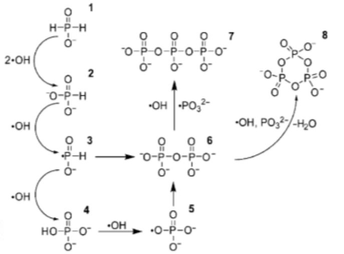


Virginia Smith, UA Lunar & Planetary Laboratory

Image of schreibersite grain present in a thin-section of the enstatite meteorite, KLE 98300.

The origin of phosphates





$Fe_3P + 7H_2O \rightarrow Fe_3O_4 + H_3PO_3 + 5\tfrac{1}{2}H_2(g)$

$H_3PO_3 + H_2O \rightarrow H_3PO_4 + H_2(g)$

$2H_3PO_3 \rightarrow H_4P_2O_6 + H_2(g)$

$H_4P_2O_6 + H_2O \rightarrow H_4P_2O_7 + H_2(g)$

$H_4P_2O_7 + H_2O \rightarrow 2H_3PO_4$

vivianite

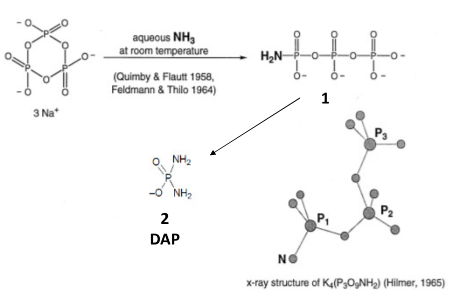
Wikimedia , Carles Millan

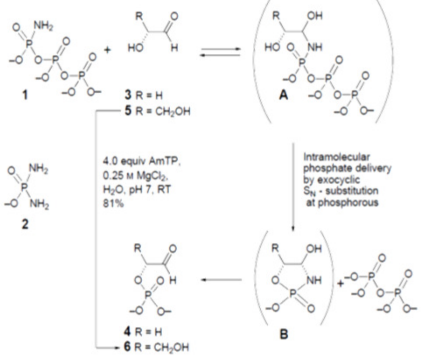
Under more neutral conditions phosphates recombine with iron → $Fe_3(PO_4)_2$ (**vivianite**)

HCN – burning of carbon-rich meteorites into redox-neutral atmosphere (N_2 and H_2O)

$Fe_3(PO_4)_2 + 18CN^-_{aq} \rightarrow 2PO_4^{3-} + 3[Fe(CN)_6]^{4-}$

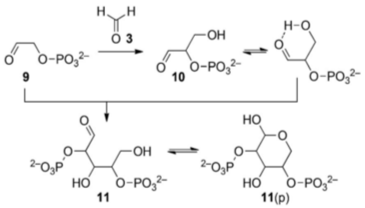
Phosphorylation reagents

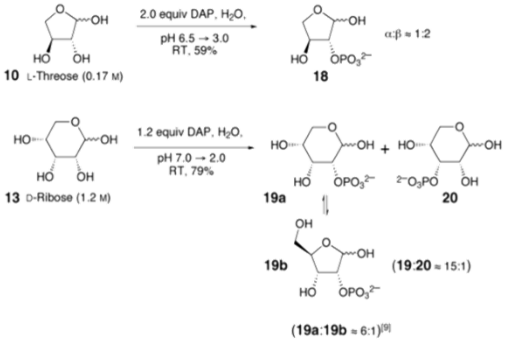




M. A. Pasek, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7918-7920 A. Eschenmoser, *et al. Orig. Life Evol. Biosph.* **1999**, *29*, 333-354

Phosphorylation of carbohydrates

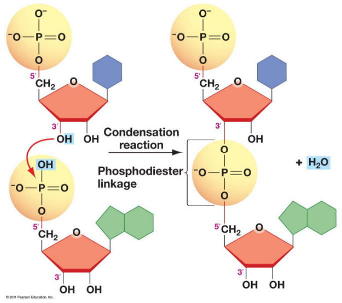




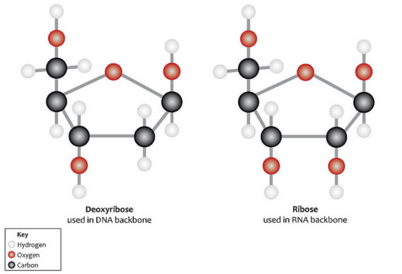
M. A. Pasek, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7918-7920 A. Eschenmoser, *et al. Orig. Life Evol. Biosph.* **1999**, *29*, 333-354

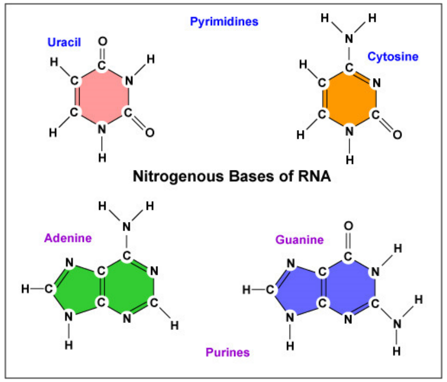
Nucleotide polymerization

Regioselective formation of 3'-5' phosphodiester bonds between nucleotides



Nucleotides - nucleobases + sugars





Since 1950's – assumed separate synthesis of sugars and nucleobases, followed by regio- and diastereoselective glycosidation → monomeric nucleotides

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Literature sources

J. Oro, *Biochem. Biophys. Res. Commun.* **1960**, *2*, 407–412.

J. D. Sutherland, *Cold Spring Harbor Perspect. Biol.* **2010**, 2, a005439.

M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242

J. D. Sutherland, *Angew. Chem. Int. Ed.* **2016**, *55*, 104-121.

B. H. Patel, C. Percivalle, D. J. Ritson, C. D. Duffy, J. D. Sutherland, *Nat. Chem*. **2015**, *7*, 301–307.

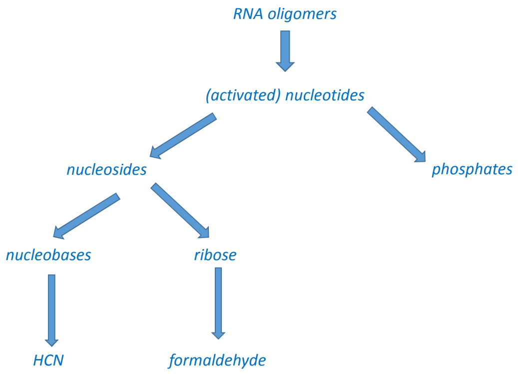
J. D. Sutherland, *et al. Nat. Chem*. **2013**, *5*, 383–389.

L. E. Orgel, *Crit. Rev. Biochem. Mol. Biol.* **2004**, *39*, 99-123.

Powner, M. W.; Sutherland, J. D.; Szostak, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 16677

T. Carell, *Nature* **2016**, *352(6287)*, 833-836

RNA oligomers – prebiotic disconnections



RNA oligomers

(activated) nucleotides

nucleosides

phosphates

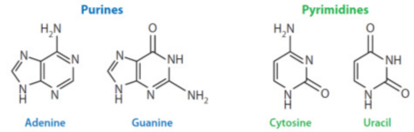
nucleobases

ribose

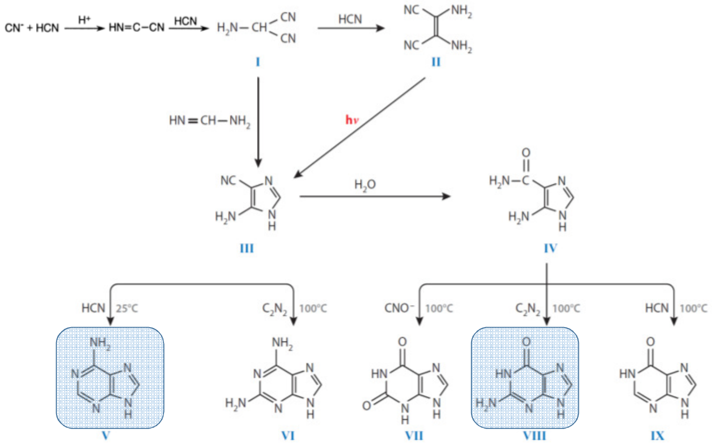
HCN

formaldehyde

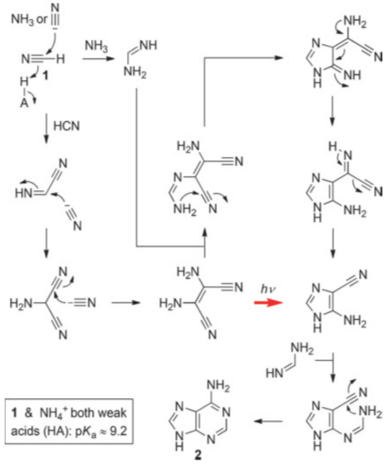
Prebiotic synthesis of nucleobases



Prebiotic synthesis of purines



Prebiotic synthesis of adenine



1960 - Oró's synthesis of adenine **2** from hydrogen cyanide **1** and ammonia (general acid–base catalysis, presumed to operate in most steps, is only shown once).

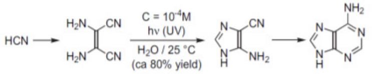
Heating ammonium cyanide at 70^{0}C for a few days
→ 0.5% adenine

Heating HCN with liquid ammonia in a sealed tube → 20% adenine

The photochemical shortcut discovered by Ferris and Orgel is shown by the red arrow.

Optimized yields – up to 20% for adenine, 3% for guanine

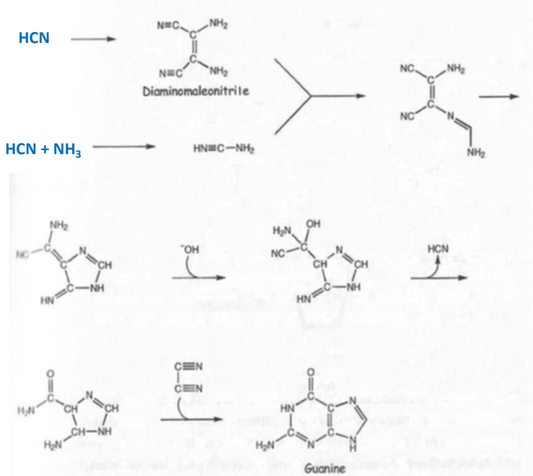
Eutectic freezing (-20^{0}C) increases the yield of DAMN formation by concentrating HCN between pure ice crystals



J. Oro *Biochem. Biophys. Res. Commun.* **1960**, *2*, 407.

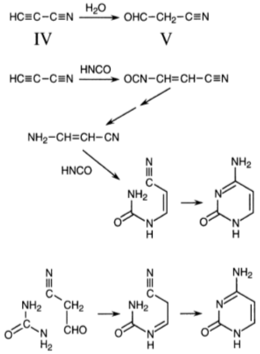
J. P. Ferris, L. E. Orgel, *J. Am. Chem. Soc.* **1966**, *88*, 1074

Prebiotic synthesis of purines



Prebiotic synthesis of pyrimidines

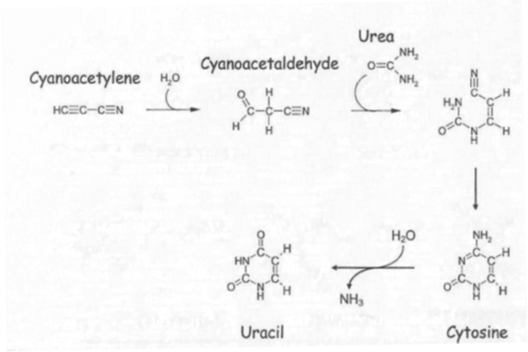
Cyanoacetylene is a major product of electric discharges in the mixture of nitrogen and methane



Cyanoacetylene incubated with saturated solution of urea yields up to 50% cytosine.
Other methods typically yield up to 5% cytosine.It is further converted to uracil by hydrolysis.

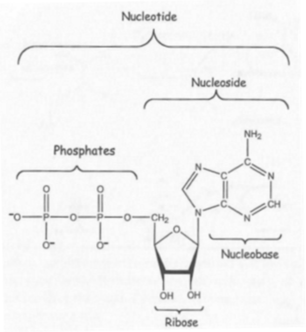
Prebiotic synthesis of pyrimidines

Cyanoacetylene can be hydrolysed to cyanoacetaldehyde. That compound can condense with urea to form cytosine

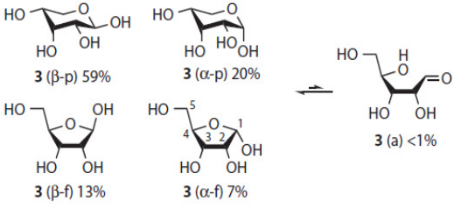


R. Shapiro *PNAS* **1999**, *96*, 4396-4401

Prebiotic synthesis of nucleosides



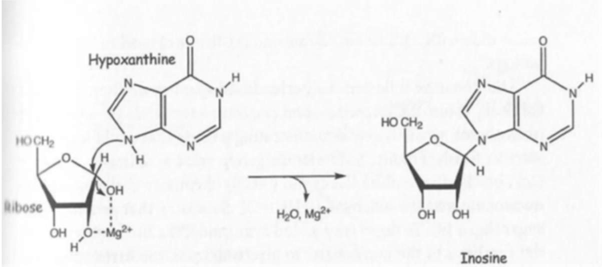
Prebiotic synthesis of nucleosides



The difficulties of assembling beta-ribonucleosides by nucleobase ribosylation:

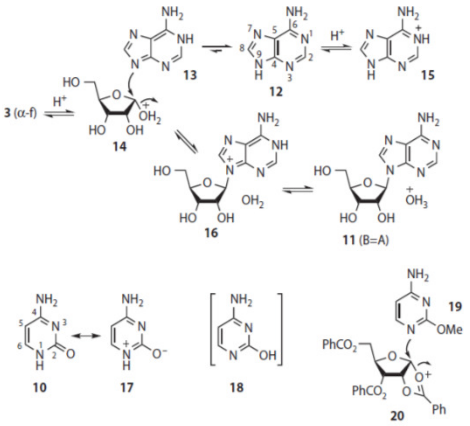
The many different forms of ribose **3** adopted in aqueous solution. The pyranose (p) and furanose (f) forms interconvert via the open-chain aldehyde (a), which is also in equilibrium with an open-chain aldehyde hydrate (not shown).

Prebiotic synthesis of nucleosides



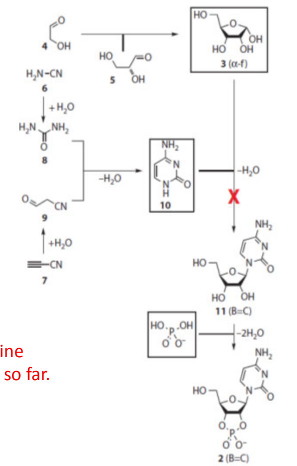
Heating purines with ribose and magnesium salts yields beta-nucleosides, although with low yields
β-inosine – 8%, β-adenosine – 4%, β-guanosine – 9%
Other isomers (e.g. alpha-glycosides) also present.

W. Fuller, R. Sanchez, L. Orgel *J. Mol. Biol.* **1972**, *67, 25-33*



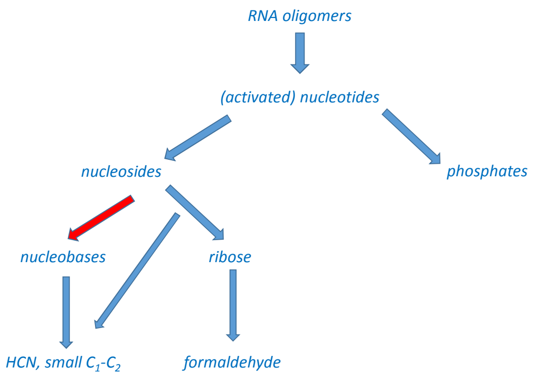
Adenine tautomerism and the ribosylation step necessary to make the adenosine **11** thought to be needed for RNA assembly. The low abundance of the reactive entities **13** and **14** is partly responsible for the low yield of **11**. The reason for the lower nucleophilicity of *N1* of the pyrimidines, and the conventional synthetic chemist's solution to the problems of ribosylation.

Prebiotic synthesis of pyrimidine nucleosides



No direct synthesis of pyrimidine nucleosides from ribose reported so far.

RNA oligomers – prebiotic disconnections



RNA oligomers

(activated) nucleotides

nucleosides

phosphates

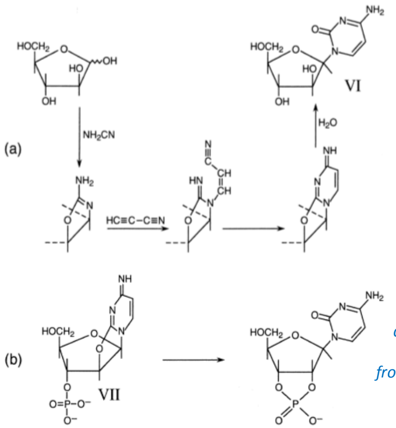
nucleobases

ribose

HCN, small C_1-C_2

formaldehyde

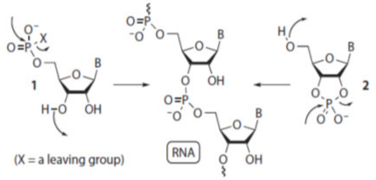
Prebiotic synthesis of nucleosides



cytosine arabinoside synthesis

cytosine riboside (as a cyclic phosphate) is obtained from a phosphorylated substrate

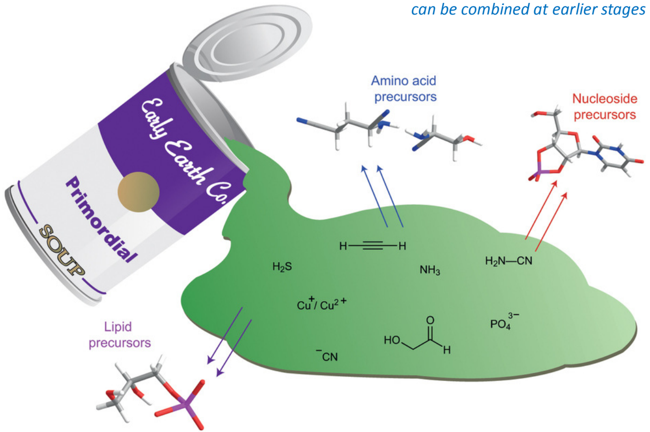
Prebiotic synthesis of oligonucleotides



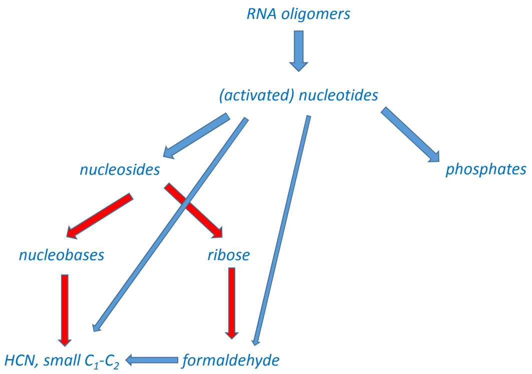
Activated ribonucleotides in the potentially prebiotic assembly of RNA. Potential P–O bond forming polymerization chemistry is indicated by the curved arrows.

Cyanosulfidic chemistry

The aldol chemistry of sugars and cyanide chemistry of nucleobases can be combined at earlier stages than glycosylation.



RNA oligomers – prebiotic disconnections



RNA oligomers

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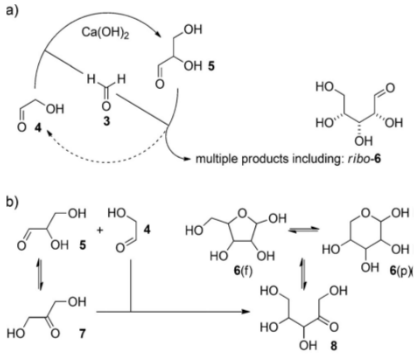
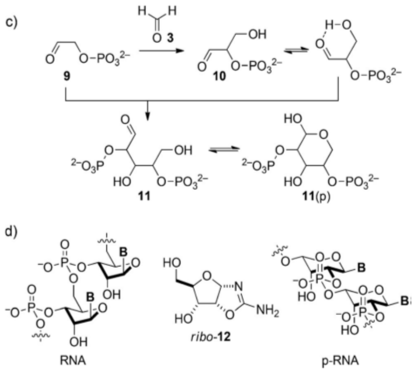
Cyanosulfidic chemistry



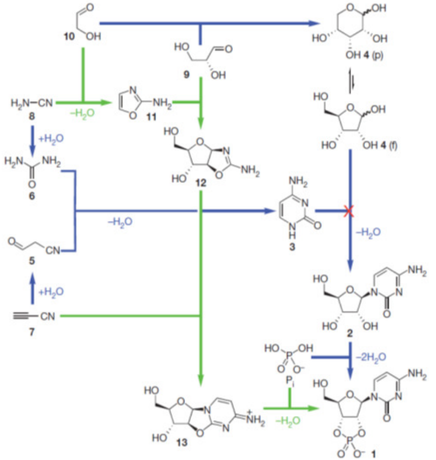
Sugars and the informational subsystem.
a) Ribose as an unfavoured product of the formose reaction proper,
b) inherently favoured aldolisation of C_2- and C_3-sugars,

Cyanosulfidic chemistry

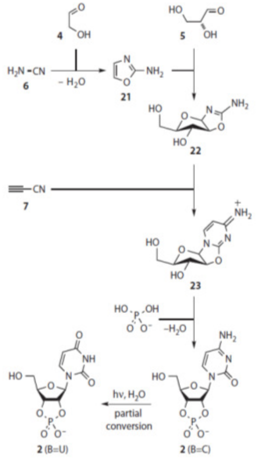


c) aldolisation favoured through restriction of other chemistries by α-hydroxyaldehyde phosphorylation
d) (stabilised) ribose derivatives. **B**=canonical nucleobase.

Cyanosulfidic chemistry



Cyanosulfidic chemistry

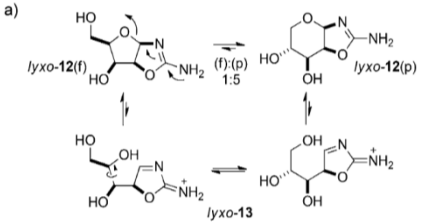


The recently uncovered route to activated pyrimidine nucleotides **2**.

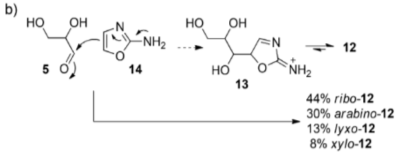
The nucleobase ribosylation problem is circumvented by the assembly proceeding through 2-aminooxazole **21**, which can be thought of as the chimera of half a pentose sugar and half a nucleobase. The second half of the pentose - glyceraldehyde **5** -and the second half of the nucleobase—cyanoacetylene **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).

Cyanosulfidic chemistry

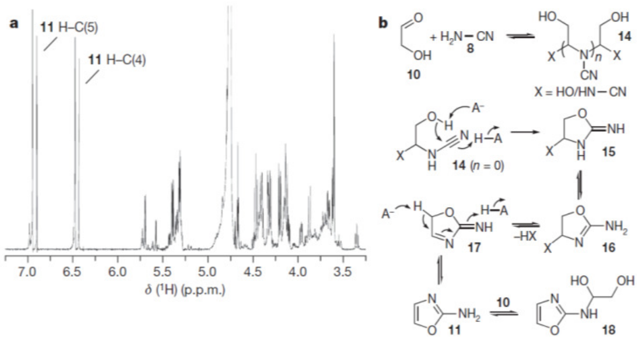


The interconversion of furanose and pyranose forms of *lyxo*-**12**,

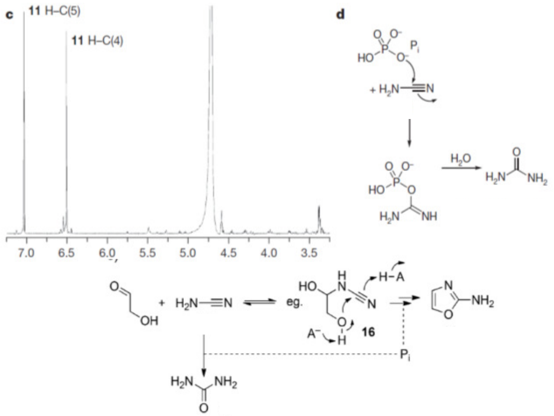


reaction of 2-aminooxazole **14** and glyceraldehyde **5**,

Cyanosulfidic chemistry

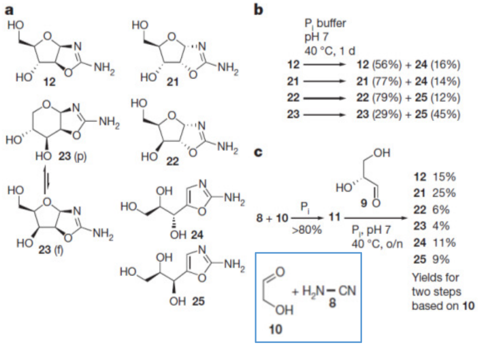


Cyanosulfidic chemistry



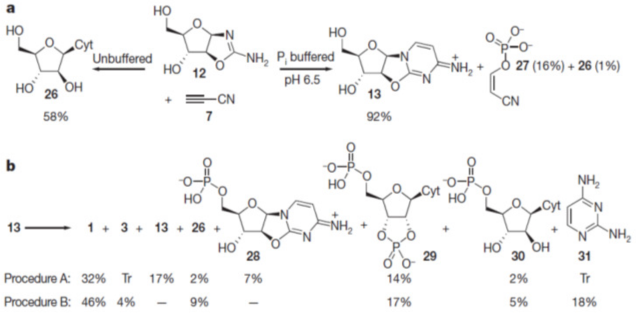
phosphate as a catalyst in the reactions of cyanamide;
catalysis indicated by dashed lines. P_i=inorganic phosphate, HA=general acid

Cyanosulfidic chemistry



Pentose amino-oxazoline stability, and assembly chemistry.
a, Structures of the arabinose (**12**), ribose (**21**), xylose (**22**) and lyxose (**23**) amino-oxazolines and their elimination products **24** and **25**.
b, Relative stabilities of the amino-oxazolines in the presence of phosphate.
c, Formation of amino-oxazolines by addition of glyceraldehyde **9** to a solution of 2-amino-oxazole **11**, with the latter freshly formed in situ from cyanamide **8** and glycolaldehyde **10**. P_i, inorganic phosphate; o/n, overnight

Cyanosulfidic chemistry

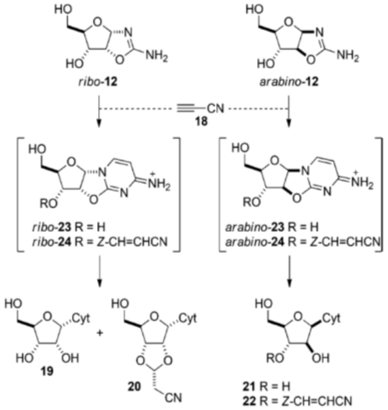


Formation and phosphorylation of the arabinose anhydronucleoside **13**.

a, Major products isolated from the reaction of arabinose amino-oxazoline **12** and cyanoacetylene **7** in the presence and absence of phosphate.

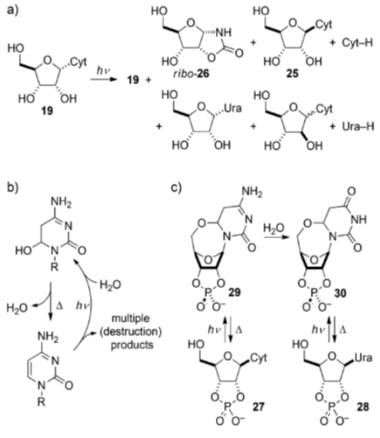
b, Products of phosphorylation of **13** using pyrophosphate and urea in the dry state (procedure A) or inorganic phosphate and urea in formamide solution (procedure B).

Cyanosulfidic chemistry



Cyanovinylation of pentose aminooxazolines **12**. Cyt=N-1-linked cytosinyl.

Cyanosulfidic chemistry



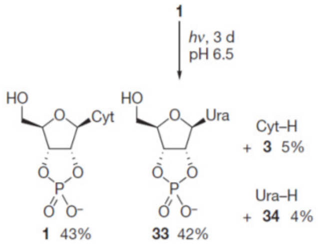
Orgel reported photoanomerization of alpha-cytidine **19** to the beta-anomer **25**, but the reaction was very low-yielding and combined with massive decomposition

R. A. Sanchez, L. E. Orgel, *J. Mol. Biol.* **1970**, *47*, 531-543

UV light tends to destroy most of phosphorylated cytidine derivatives (by photohydration and followed decomposition).
EXCEPTION: beta-cytidine-2’,3’-cyclic phosphate **27**
→ Partial conversion to the uridine nucleotide **28**, but both are stable on further irradiation

Photochemistry of cytidine nucleosides and nucleotides. Ura=N-1-linked uracilyl.

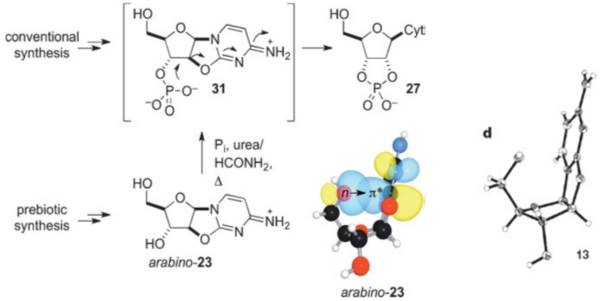
Cyanosulfidic chemistry



Photochemistry of *beta*-ribocytidine-2’,3’-cyclic phosphate **1**. Under conditions of irradiation that destroy most other pyrimidine nucleosides and nucleotides, **1** undergoes partial hydrolysis and slight nucleobase loss. Ura, N1-linked uracil; Cyt–H, cytosine; Ura–H, uracil.

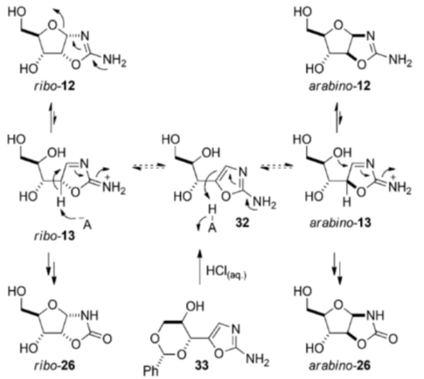
Cyanosulfidic chemistry

Rearrangement of **31**, the 3’-phosphate of *arabino*-**23**, to **1** by intramolecular nucleophilic substitution.



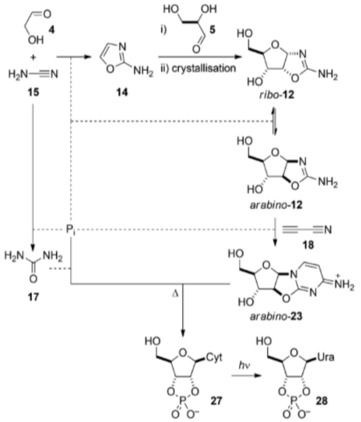
Cyanosulfidic chemistry

Interconversion of pentose aminooxazoline stereoisomers.



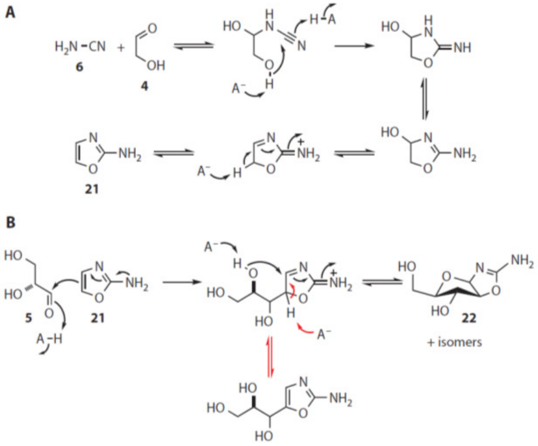
The „side product" *ribo*-**12** can be converted to the expected *arabino*-**12** by general acid-base catalysis in phosphate buffer, although with some decomposition to **26**

Cyanosulfidic chemistry

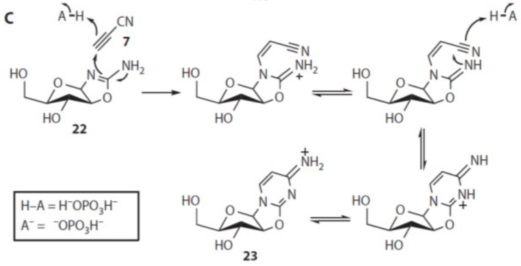


Potentially prebiotic synthesis of activated pyrimidine ribonucleotides. Catalysis, and reaction control through pH and chemical buffering, is indicated by dashed lines.

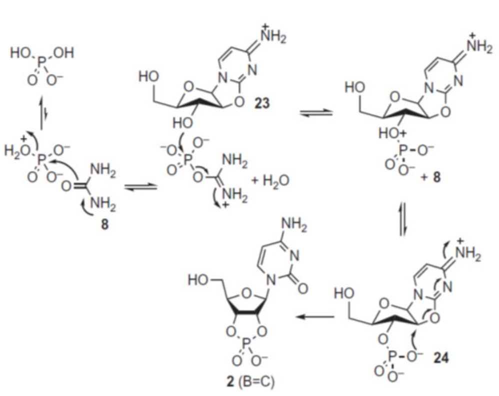
Cyanosulfidic chemistry – ribonucleotide synthesis



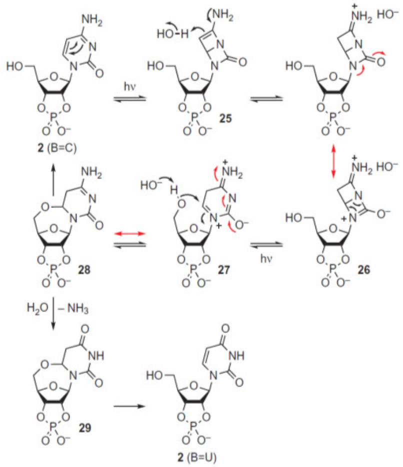
Cyanosulfidic chemistry – ribonucleotide synthesis



Cyanosulfidic chemistry – ribonucleotide synthesis



Cyanosulfidic chemistry – ribonucleotide synthesis



The origin of small reactive intermediates

Thermal decomposition of cyanoferrates (volcanic):

$(Na,K)_4[Fe(CN)_6] \xrightarrow{700^oC} 4(\mathbf{Na/K})\mathbf{CN} + Fe(CN)_2$

$3Fe(CN)_2 \xrightarrow{700^oC} Fe_3C + 5C + 3N_2$

$Fe(CN)_2 \xrightarrow{700^oC} Fe + 2C + N_2$

$Ca_2[Fe(CN)_6] \xrightarrow{660^oC} 2Ca(CN)_2 + Fe(CN)_2$

$Ca(CN)_2 \xrightarrow{660^oC} \mathbf{CaNCN} + C \xrightleftharpoons{1000^oC} \mathbf{CaC_2} + N_2$

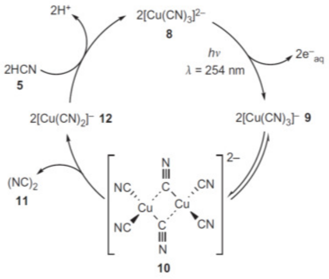
$Mg_2[Fe(CN)_6] \xrightarrow{315^oC} 2Mg(CN)_2 + Fe(CN)_2$

$Mg(CN)_2 \xrightarrow{395^oC} MgCN_2 + C$

$3MgCN_2 \xrightarrow{420^oC} \mathbf{Mg_3N_2} + 3C + 2N_2$

$Cu_2S + H_2O + 6CN^- \rightarrow 2[Cu(CN)_3]^{2-} + HS^- + OH^-$
cyanocuprates and HS^- are delivered by this process

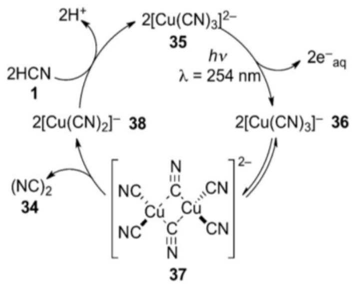
Photoredox cycle based on cyanocuprates may convert HCN into cyanogen



Action of water (bufferred to neutral or slightly acidic) on that mixture produced concentrated HCN solution + cyanamide (from CaNCN) + acetylene (from CaC_2) + ammonia (from Mg_3N_2)

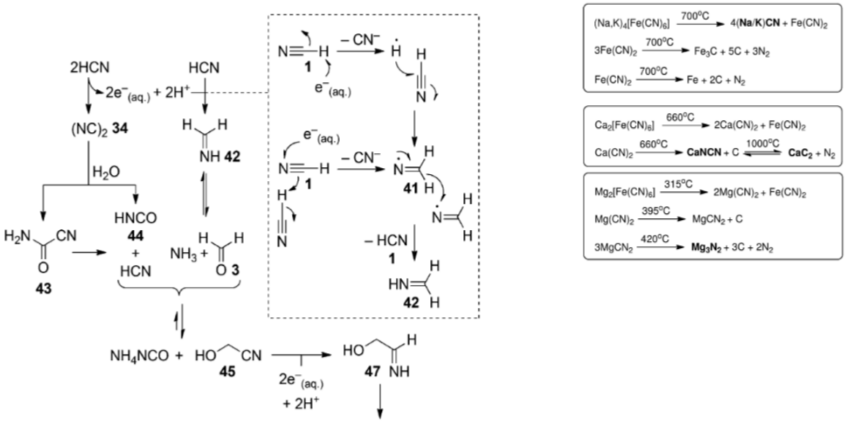
Cyanosulfidic chemistry

Hydrogen cyanide–cyanocuprate photoredox chemistry.
Cyanocuprate photoredox cycle



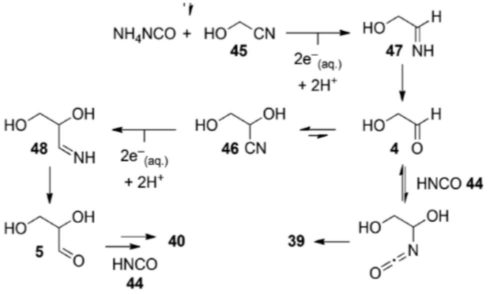
Cyanosulfidic chemistry

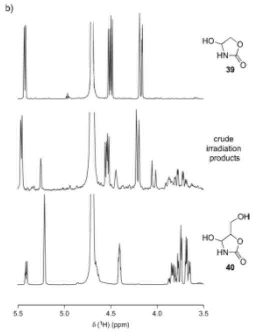
Hydrogen cyanide–cyanocuprate systems photochemistry.



Cyanosulfidic chemistry

Hydrogen cyanide–cyanocuprate systems photochemistry.





^{1}H NMR spectrum of the crude products of irradiation of hydrogen cyanide **1** and copper(I) cyanide along with spectra of **39** and **40**, the isocyanate adducts of glycolaldehyde **4** and glyceraldehyde **5** respectively

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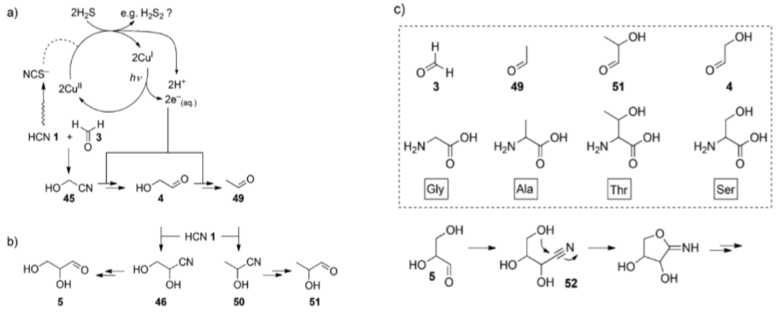
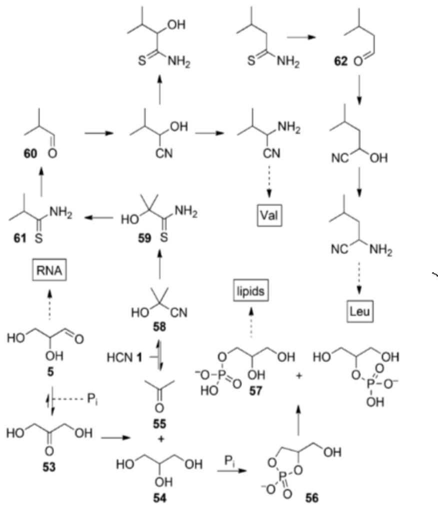
Cyanosulfidic chemistry



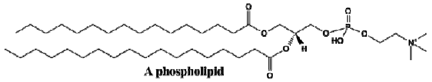
Photoredox systems chemistry with hydrosulfide as the stoichiometric reductant. a) (Over-)reduction of glycolonitrile **45** to glycolaldehyde **4** (and acetaldehyde **49**), b) reductive homologation of **4** (and **49**) to **5** (and **51**), c) most of the aldehydes produced by this chemistry as Strecker amino acid precursors (boxed) and the self-destruction (as regards potential Strecker chemistry) of the cyanohydrin **52**.



Cyanosulfidic chemistry

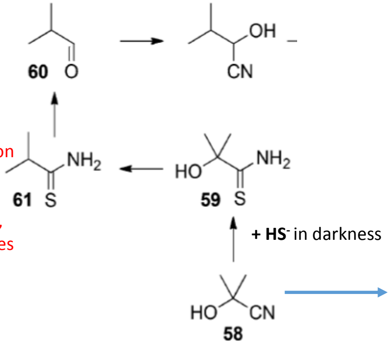
First signs of a linkage between all subsystems through cyanosulfidic chemistry:

Sugars, nucleotides, lipids, aminoacids



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

Cyanosulfidic chemistry

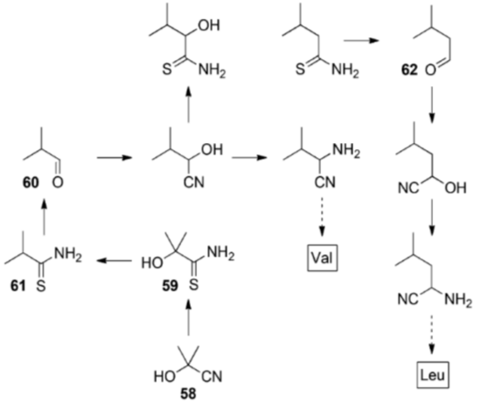


+ **HS**⁻ in darkness

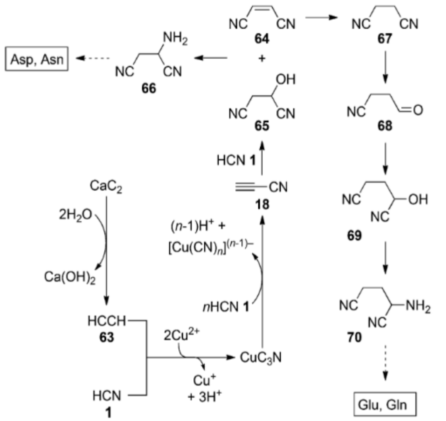
Cyanohydrins undergo photoreduction to α-hydroxyaldehydes.
α-hydroxythioamides first undergo photodeoxygenation to thioamides, and then photoreduction to aldehydes

Not reduced under applied conditions

Cyanosulfidic chemistry

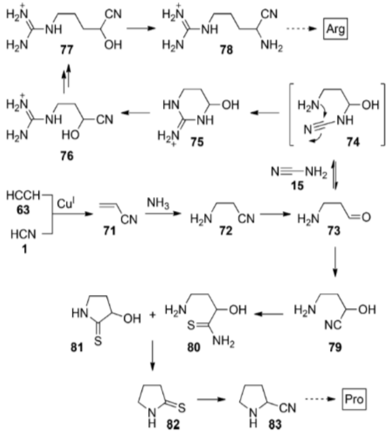


Cyanosulfidic chemistry



Synthesis of cyanoacetylene **18** and reactions leading to amino acid precursors of Asp/Asn and Glu/Gln.

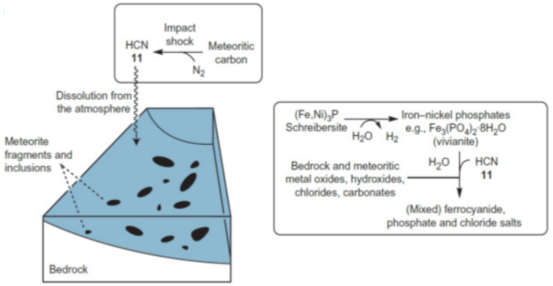
Cyanosulfidic chemistry



Synthesis of acrylonitrile **71** and reactions leading to amino acid precursors therefrom.

Cyanosulfidic chemistry

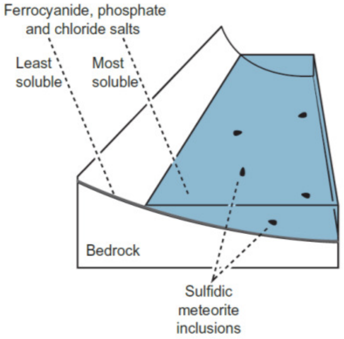
Chemistry in a post-meteoritic-impact scenario.
A series of post-impact environmental events are shown along with the chemistry (boxed) proposed to occur as a consequence of these events.



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).

$$(Na,K)_4[Fe(CN)_6] \xrightarrow{700\ °C} 4(\mathbf{Na/K)CN} + Fe(CN)_2$$

$$3Fe(CN)_2 \xrightarrow{700\ °C} Fe_3C + 5C + 3N_2$$

$$Fe(CN)_2 \xrightarrow{700\ °C} Fe + 2C + N_2$$

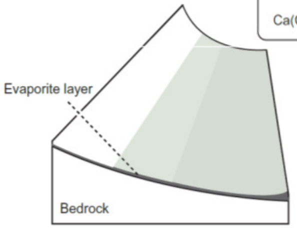
$$Mg_2[Fe(CN)_6] \xrightarrow{315\ °C} 2Mg(CN)_2 + Fe(CN)_2$$

$$Mg(CN)_2 \xrightarrow{395\ °C} MgCN_2 + C$$

$$3MgCN_2 \xrightarrow{420\ °C} \mathbf{Mg_3N_2} + 3C + 2N_2$$

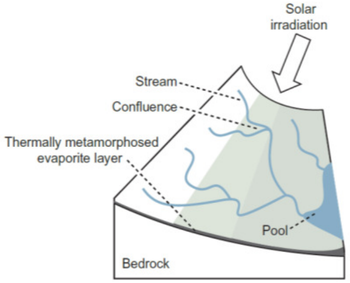
$$Ca_2[Fe(CN)_6] \xrightarrow{660\ °C} 2Ca(CN)_2 + Fe(CN)_2$$

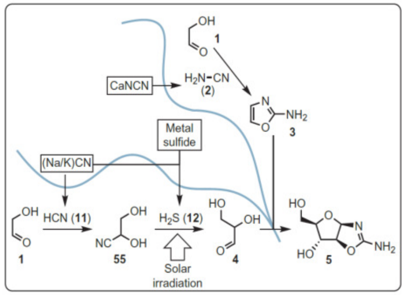
$$Ca(CN)_2 \xrightarrow{660\ °C} \mathbf{CaNCN} + C \xrightleftharpoons{1,000\ °C} \mathbf{CaC_2} + N_2$$



Cyanosulfidic chemistry

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

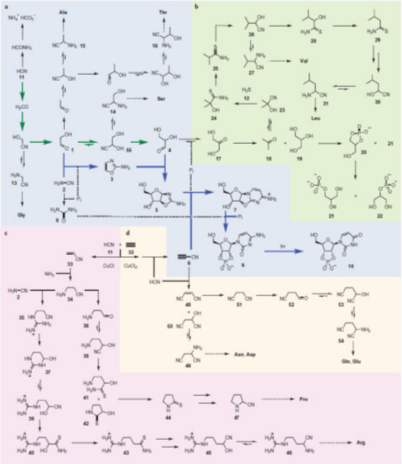


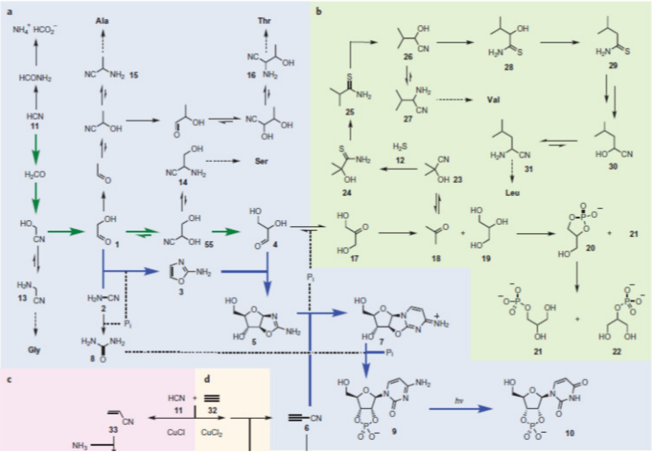
Table 1 | Yields for the part of the reaction network shown in Fig. 1b.

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

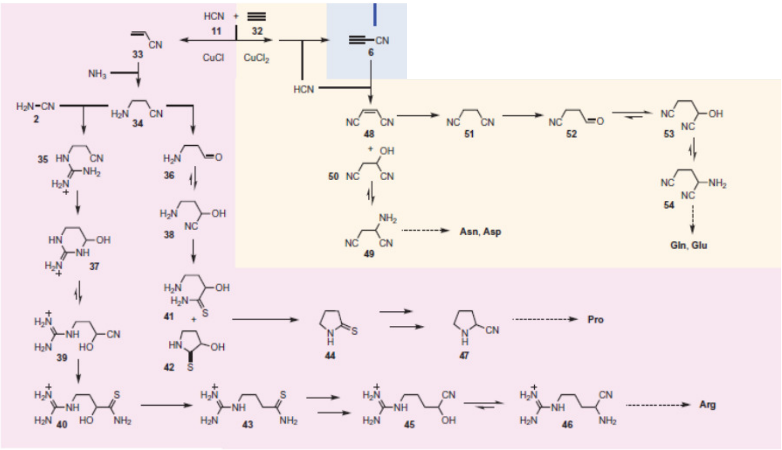
Table 2 | Yields for the parts of the reaction network shown in Fig. 1c,d.

Conversion	Number of steps	Yield (%)	Conversion	Number of steps	Yield (%)
33 → 34	1	83	38 → 41 +	1	30
			42		60
34 → 35	1	55	38 → 44	2	70
34 → 37	2	77	44 → 47	2	32
34 → 36	1	45	45 → 46	1	90
37 → 39	1	77	6 → 48 +	1	50
			49 +		25
			50		16
37 → 40	2	~100	48 → 51	1	90
37 → 43	3	~70	51 → 52	1	89
37 → 45	5	~50	52 → 53	1	~100
36 → 38	1	~100	52 → 54	2	~70

Cyanosulfidic chemistry system



Cyanosulfidic chemistry system



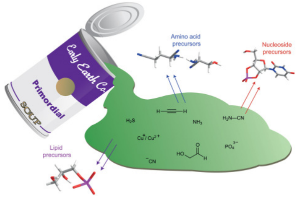
Summary

Small biorelevant building blocks:
HCN, NC-CN, cyanamide, cyanoacetylene, ammonia, H_2S, phosphates, formaldehyde
available on the early Earth due to meteorite delivery (Late Heavy Bombardment), condensation in water,
precipitation as cyanometalic complexes and thermal metamorphosis thereof.

Systematic access to simple carbohydrates possible under uncomplicated set of conditions

Systemic access to all groups of biomolecules by periodic delivery of simple reagents combined with UV light irradiation

activated pyrimidine nucleotides (cyclic), sugars, aminoacids and lipid precursors possibly available together



Primordial soup:
stinky and toxic (to us),
but provides most interesting
components in „one pot"