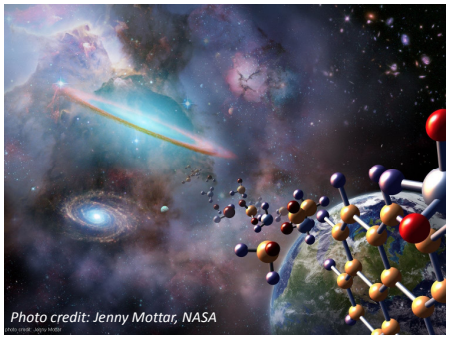
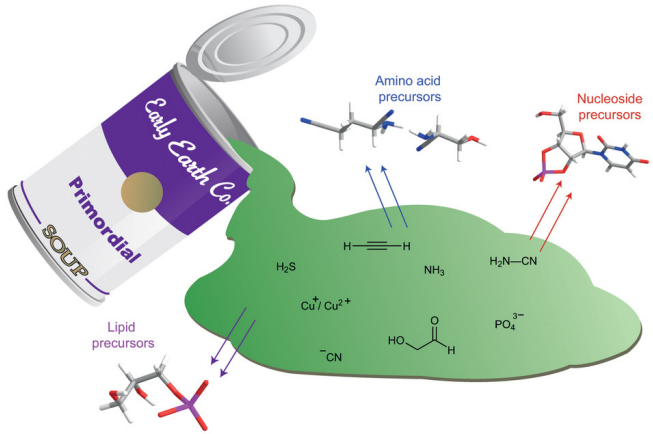
The molecular origins of life



WS 2016

Zbigniew Pianowski

The primordial soup – the final sip



The origin of small reactive intermediates

Thermal decomposition of cyanoferrates (volcanic):

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

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

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

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

$Ca(CN)_2 \xrightarrow{660^oC} CaCN + C \underset{}{\overset{1000^oC}{\rightleftharpoons}} CaC_2 + N_2$

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

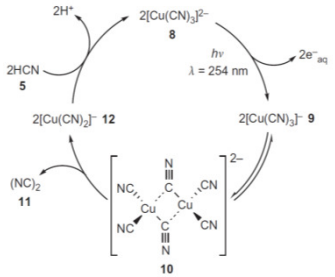
$Mg(CN)_2 \xrightarrow{395^oC} MgCN_2 + C$

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

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

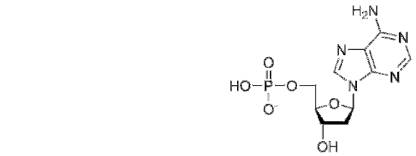
cyanocuprates and HS^- are delivered by this process

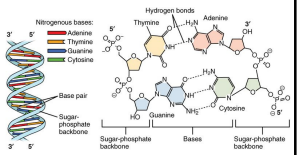
Photoredox cycle based on cyanocuprates may convert HCN into cyanogen

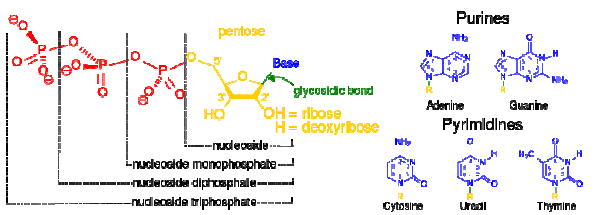


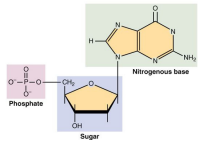
Action of water (bufferred to neutral or slightly acidic) on that mixture produced concentrated HCN solution + cyanamide (from CaNCN) + acetylene (from CaC_2) + ammonia (from Mg_3N_2)

Nucleotides - components

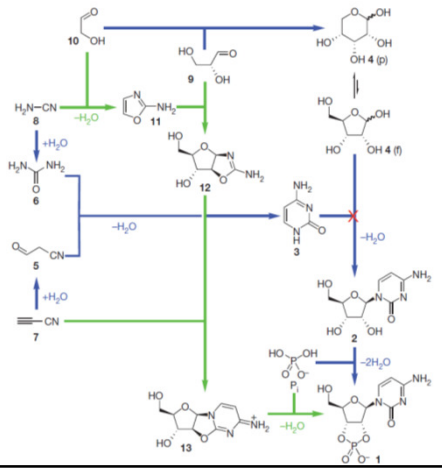




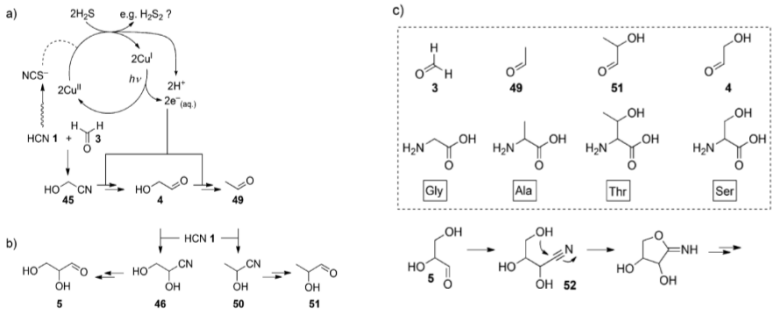




Prebiotic route to pyrimidine nucleotides



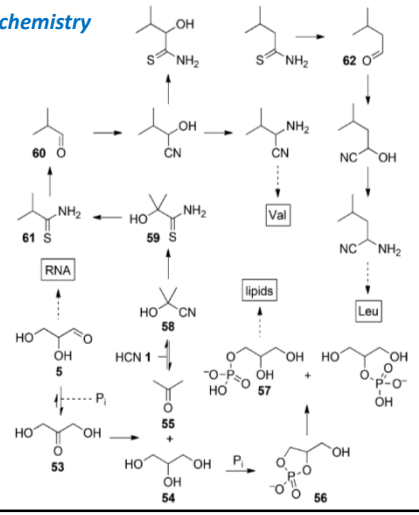
Cyanosulfidic chemistry



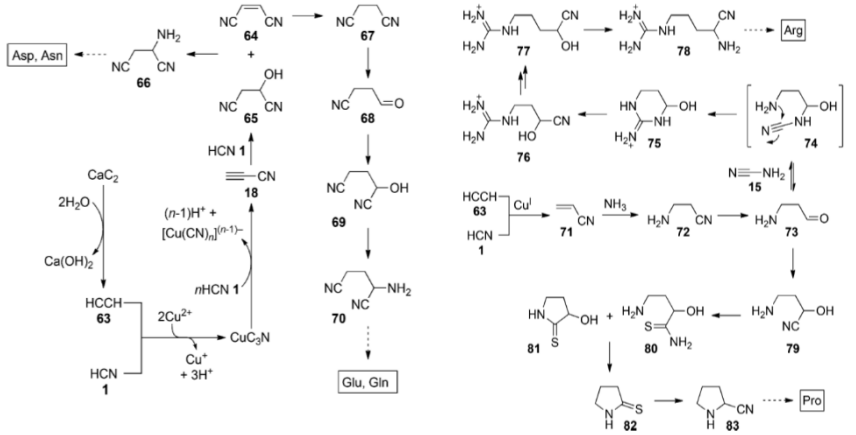
Photoredox systems chemistry with hydrosulfide as the stoichiometric reductant. a) (Over-)reduction of glycolonitrile **45** to glycolaldehyde **4** (and acetaldehyde **49**), b) reductive homologation of **4** (and **49**) to **5** (and **51**), c) most of the aldehydes produced by this chemistry as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

Cyanosulfidic chemistry

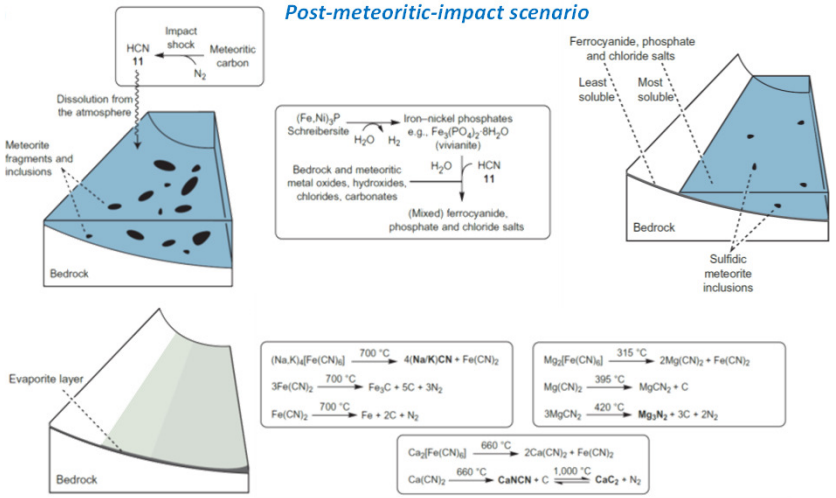
The side product – acetone **55** – seems to be meaningful in the potentially prebiotic route for branched aminoacids Val and Leu



Cyanosulfidic chemistry

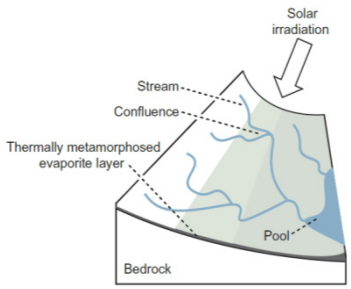


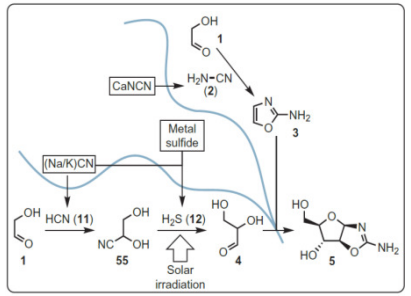
Post-meteoritic-impact scenario



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

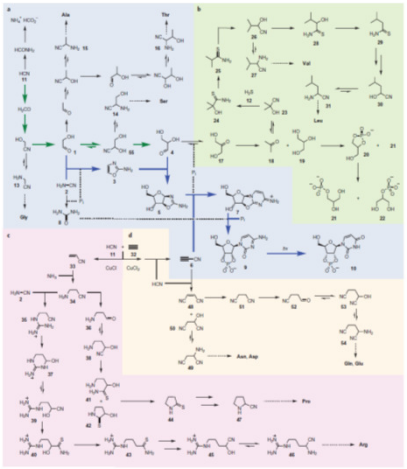


Table 1 | Yields for the part of the reaction network shown in Fig. 1b.

Conversion	Number of steps	Yield (%)	Conversion	Number of steps	Yield (%)
4 → 17	1	59	26 → 28	1	57
17 → 18 + 19	1	29 34	28 → 29	1	75
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 + 22	2	31 40

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

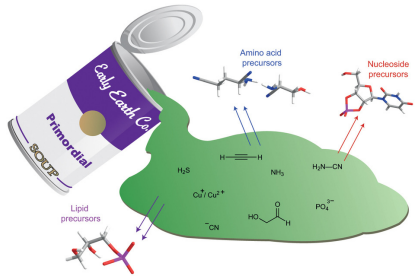
Conversion	Number of steps	Yield (%)	Conversion	Number of steps	Yield (%)
33 → 34	1	83	38 → 41 + 42	1	30 60
34 → 35	1	55	38 → 44	2	70
34 → 37	2	77	44 → 47	2	32
34 → 36	1	45	45 → 46	1	90
37 → 39	1	77	6 → 48 + 49 + 50	1	50 25 16
37 → 40	2	~100	48 → 51	1	90
37 → 43	3	~70	51 → 52	1	89
37 → 45	5	~50	52 →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

Remaining challenges

Homochirality of currently known biomolecules

Prebiotic synthesis of purine nucleotides and deoxyribonucleotides

Prebiotic polymerization



Chiral amplification and the origins of homochirality

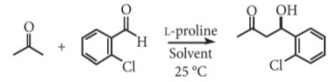
Table 1. Enantiomeric concentration amplification of phenylalanine after two crystallizations from water

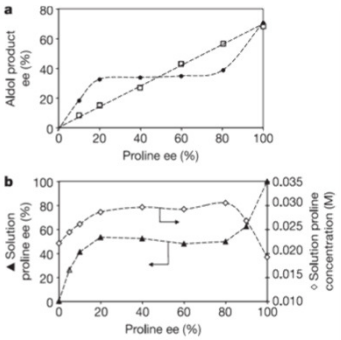
Component	Initial ee, %	Final ee, %
D	10	90.0 ± 3.7
	5	91.7 ± 1.5
	1	87.2 ± 2.0
L	10	88.3 ± 1.1
	5	88.6 ± 0.9
	1	90.9 ± 0.3

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 evaporations 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.

Breslow, R., Levine, M. Proc. Natl. Acad. Sci. USA **2006,** *103(35),* 12979-12980

Eutectic solutions over enantioenriched aminoacids





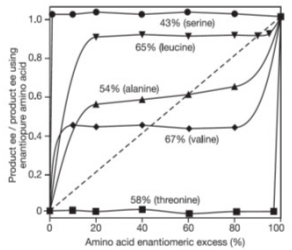
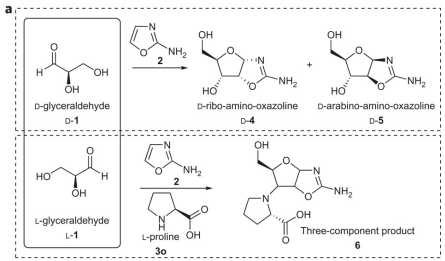


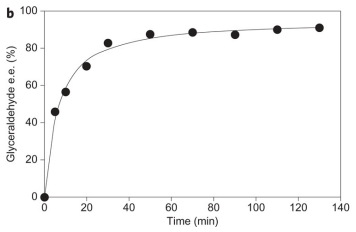
Table 1 | Solution enantiomeric excess at the eutectic point in water at 25 °C for selected amino acids

Amino acid	ee of solution at eutectic (%)	Amino acid	ee of solution at eutectic (%)
Threonine	0	Methionine	85
Valine	46	Leucine	87
Alanine	60	Histidine	93
Phenylalanine	83	Serine	>99

Klussmann, M., et al. Nature **2006,** *441,* 621-623

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%.

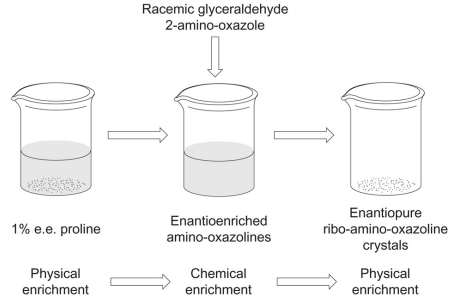
J. E. Hein, E. Tse, D. G. Blackmond, *Nature Chem.*, **2011**, *3*, 704-706

Enantiomeric excess in the cyanosulfidic chemistry

Table 1 | Formation of enantioenriched amino-oxazolines in the presence of L-amino acids.

Amino acid	Three-component product* 6	Ribose amino-oxazoline D-4 (% e.e.)	Arabinose amino-oxazoline D-5 (% e.e.)
Ala (3a)	++	8.9	8.1
Arg (3b)	++	4.1	7.3
Asn (3c)	+	1.1	0.5
Asp (3d)	+	2.1	1.4
Cys (3e)	+++	n.a.	1.4
Gln (3f)	+	1.2	1.1
Glu (3g)	+	0.8	0.1
Gly (3h)	++	-	-
His (3i)	++	7.5 (L)	8.1 (L)
Ile (3j)	+	2.1	0.5 (L)
Leu (3k)	+	1.1	2.1
Lys (3l)	+++	n.a.	n.a.
Met (3m)	+++	n.a.	n.a.
Phe (3n)	+++	2.5	5.4
Pro (3o)	++	55	58
Ser (3p)	+++	3.0	1.9
Thr (3q)	++	1.1	2.6
Trp (3r)	++	10.2	9.8
Tyr (3s)	+	0.5	2.6
Val (3t)	++	2.0	1.0 (L)

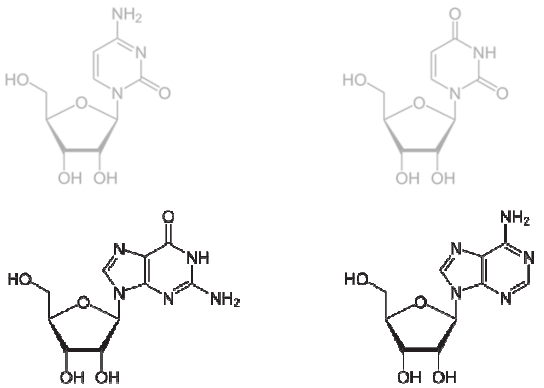
*Yield of side product 6: +, low; ++, medium; +++, high. n.a., no products isolated or observed by chiral LC



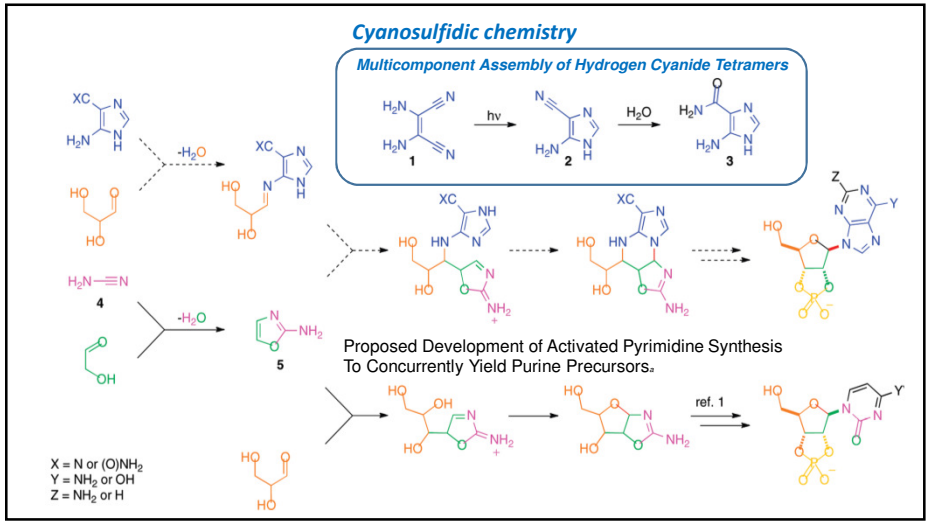
1% e.e. L-proline (3o) is suspended in solvent (either $CHCl_3$ or EtOH). After equilibration, the remaining solid is removed and the solvent is evaporated from the supernatant. Racemic glyceraldehyde DL-**1** and amino-oxazole **2b** are then added and the mixture is dissolved in water. The ensuing 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.

J. E. Hein, E. Tse, D. G. Blackmond, *Nature Chem.*, **2011**, *3*, 704-706

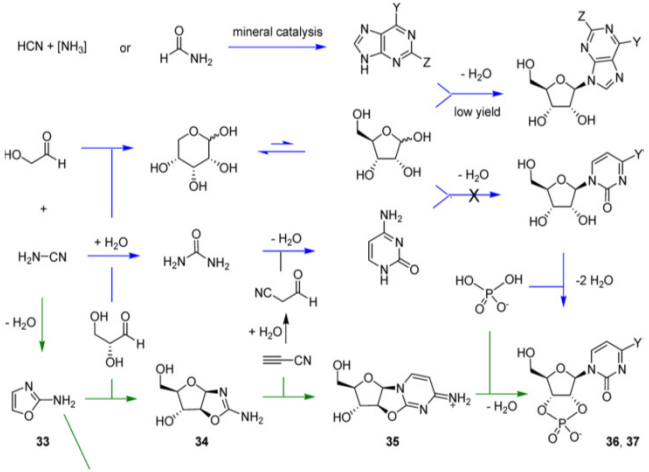
Purine nucleoside synthesis via cyanosulfidic chemistry



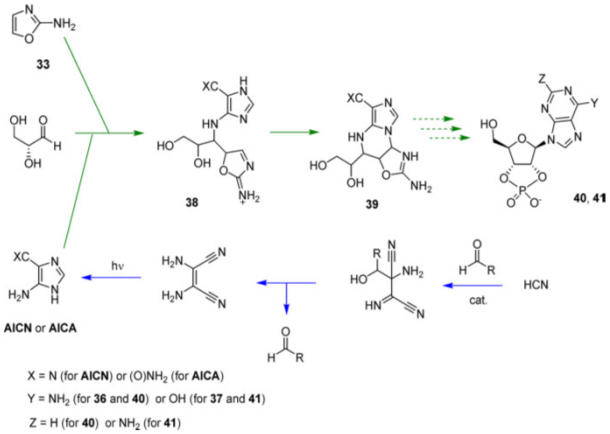
Cyanosulfidic chemistry



Modular vs. systems synthesis

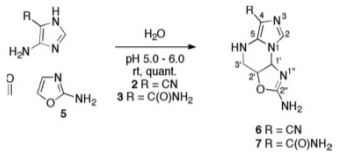


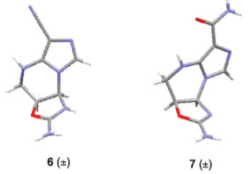
Modular vs. systems synthesis



Cyanosulfidic chemistry

One-Pot Multicomponent Assembly of *rac*-Tetrahydroimidazo[1,3]-2-aminooxazolo[1,2]-pyrimidines **6** and **7**

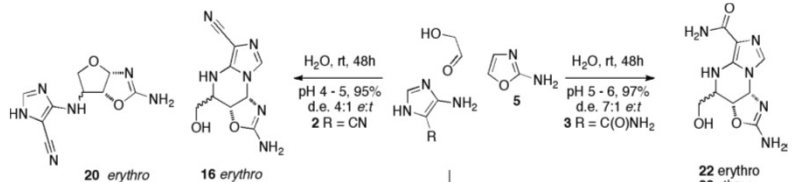


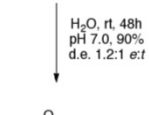


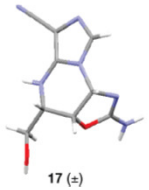
6 (±) **7** (±)

Cyanosulfidic chemistry

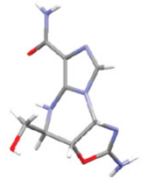
One-pot multicomponent assembly of *rac*-3-(Hydroxymethyl)tetrahydroimidazo[1,3]-2-aminooxazolo[1,2]-pyrimidines from glycolaldehyde, AICN **2** or AICA **3**, and 2AO **5**, with crystal structures of **17** and **22**







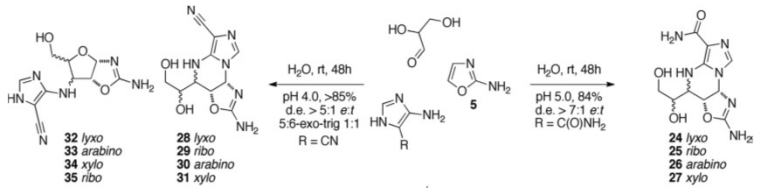
17 (±)

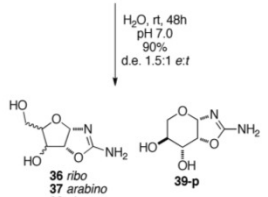


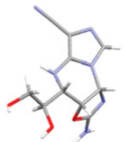
22 (±)

Cyanosulfidic chemistry

One-pot multicomponent [3*R*,4*R*]-selective assembly of *rac*-3-(Dihydroxyethyl)tetrahydroimidazo-2-aminooxazolopyrimidines from glyceraldehyde with crystal structures of **24** and **30**







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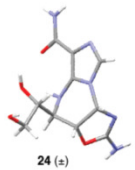
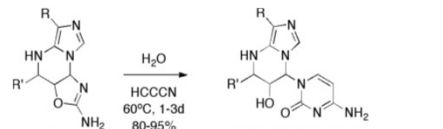
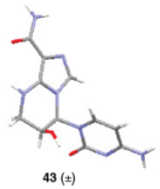


24 (±)

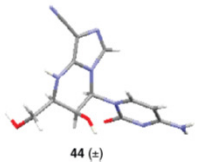
Cyanosulfidic chemistry

cyanovinylation of tetrahydroimidazo[1,3]-2-aminooxazolo[1,2]-pyrimidines with unbuffered aqueous cyanoacetylene





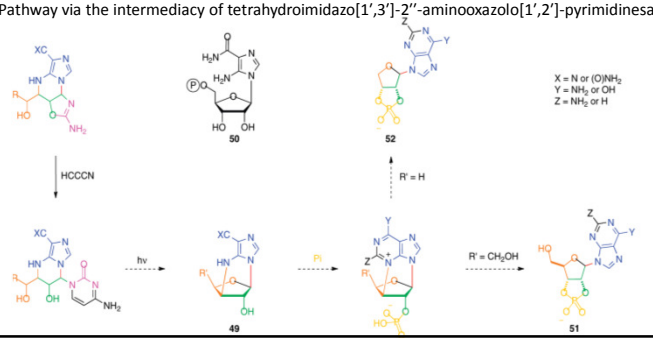
43 (±)



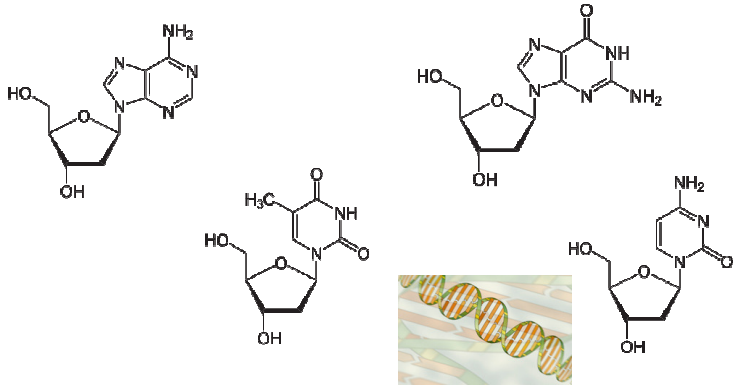
44 (±)

Cyanosulfidic chemistry

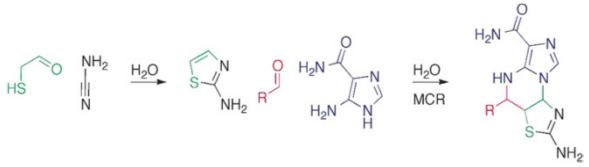
beta-Ribofuranosyl-pyrimidine nucleotide assembly and potential stepwise, regioselective beta-ribofuranosyl-purine assembly
Pathway via the intermediacy of tetrahydroimidazo[1′,3′]-2′′-aminooxazolo[1′,2′]-pyrimidinesa



Prebiotic synthesis of deoxyribonucleosides

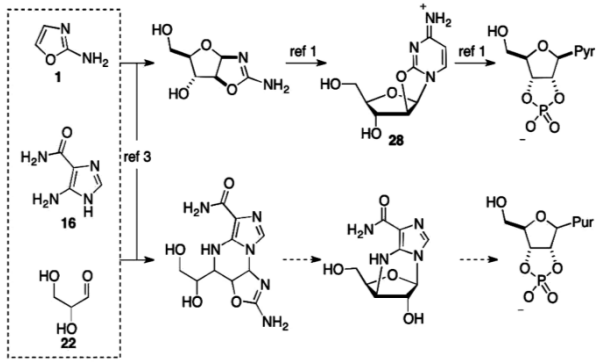


Prebiotic synthesis of deoxyribonucleosides



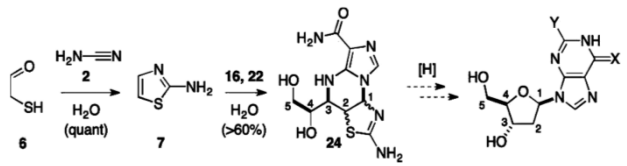
Prebiotic synthesis of deoxyribonucleosides

proposed multicomponent ribonucleotide syntheses

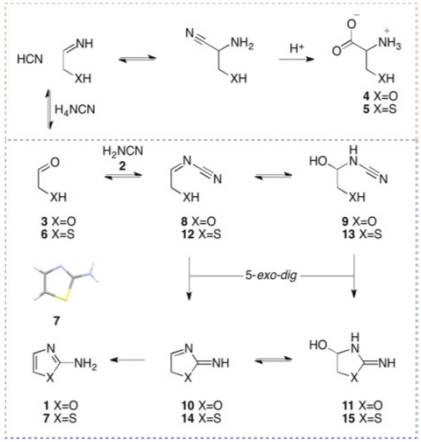


Prebiotic synthesis of deoxyribonucleosides

proposed multicomponent deoxyribonucleotide syntheses



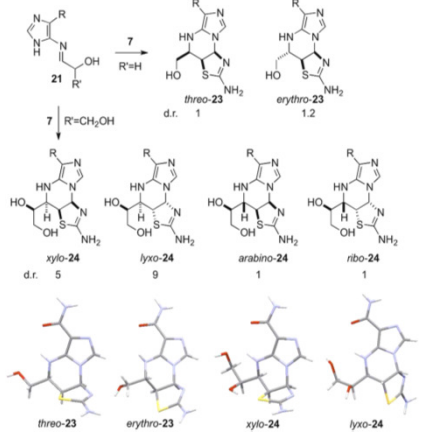
Prebiotic synthesis of deoxyribonucleosides



Strecker-Type Synthesis of Amino Acids (Red Box) and Azole Synthesis in Water (Blue Box)

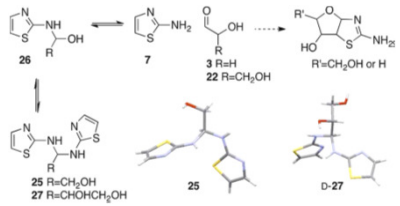
Prebiotic synthesis of deoxyribonucleosides

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

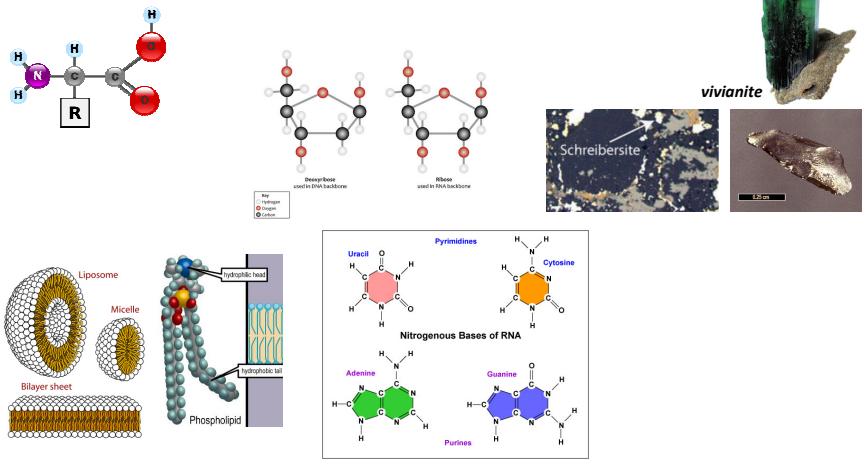


Prebiotic synthesis of deoxyribonucleosides

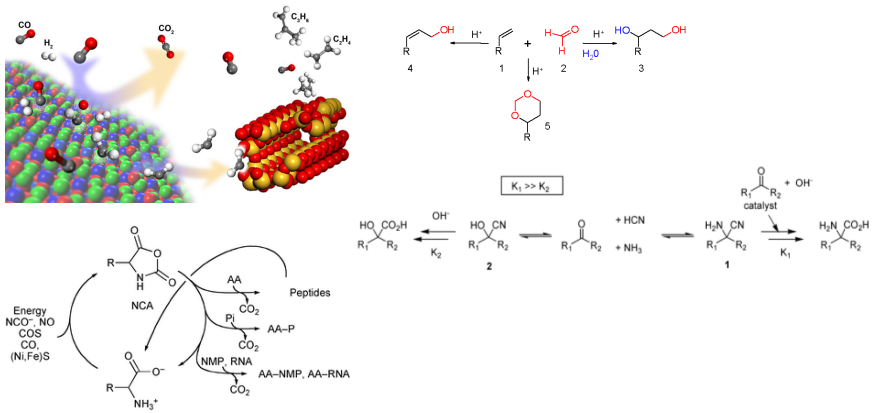
Crystallization of Bis-(2-aminothiazole)-aminals of Glycolaldehyde **3** and D-Glyceraldehyde **22** from Water at pH 7

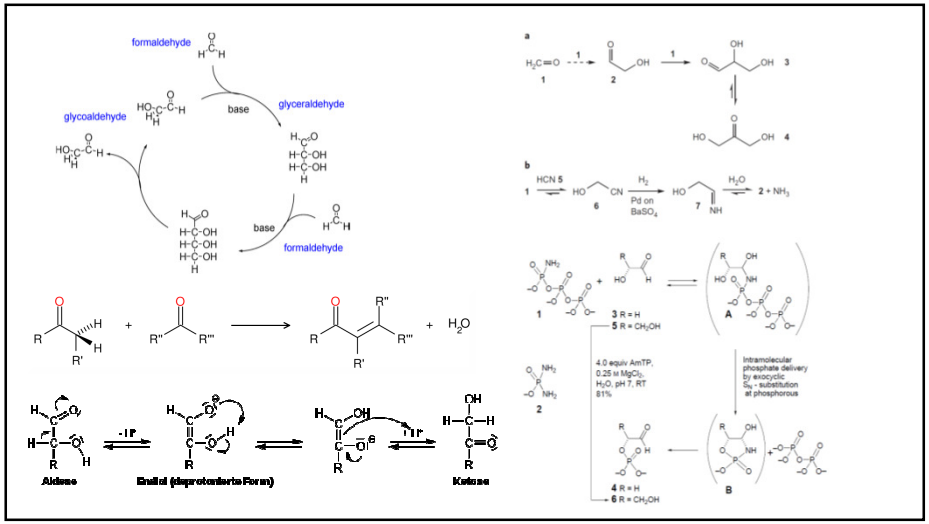


Prebiotic soup - summary



Prebiotic soup - summary





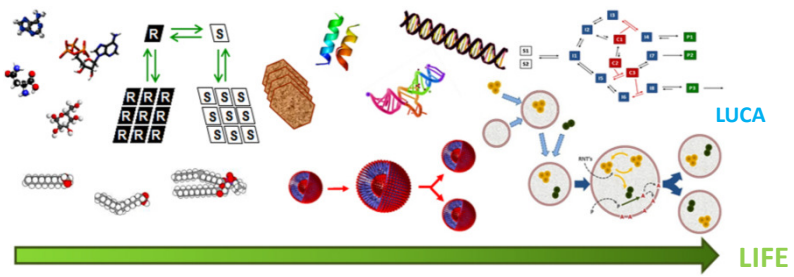
Origin of the Universe – stars, planets, elements

Origin of biorelevant monomers – primordial soup

Complex chemical processes on the way to living systems

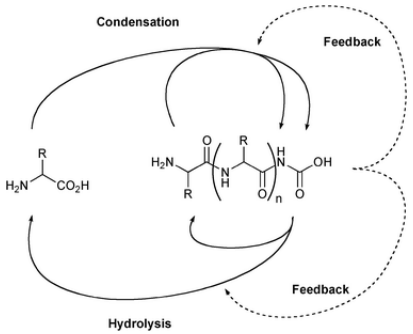
Protocells and LUCA

Self-organization of molecules and chemical reactions

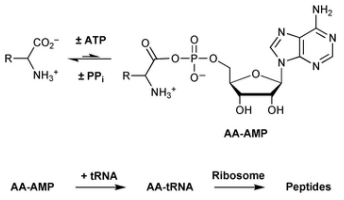


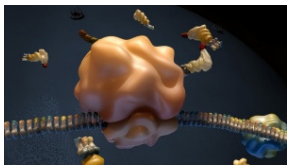
Increasing complexity from molecules to systems

Condensation of aminoacids into peptides

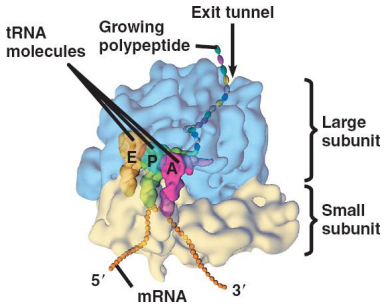


Biochemical condensation of aminoacids into peptides

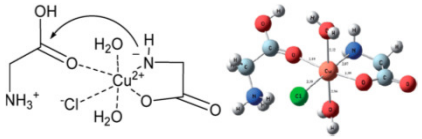




Nature Publishing Group, www.nature.com/nrg/multimedia



Spontaneous vs. assisted dehydratation

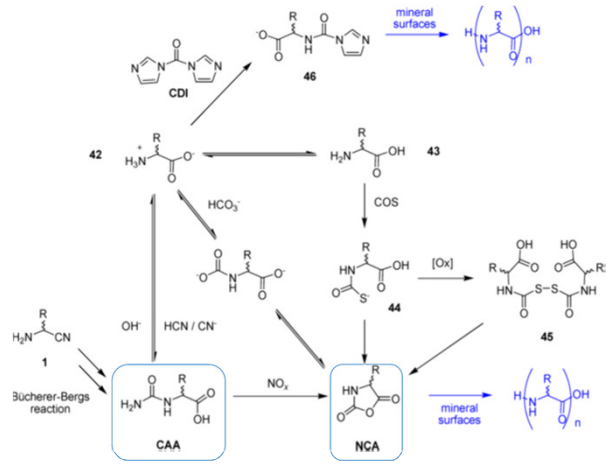


Rode, B. M.; Fitz, D.; Jakschitz, T. Chem. *Biodiversity* **2007**, *4*,2674.

Activating agent	Hydrolysis/ hydration product	$\Delta G^{o\prime}$/ kJ mol^{-1}
NH_2CONH_2	$CO_2 + NH_3$	-16^a
COS (g)	$CO_2 + H_2S$	-17^a
Pyrophosphate	Phosphate	-19^b
CO (g)	HCO_2H	-16^a
HNCO	$CO_2 + NH_3$	-54^a
HCN	$HCO_2H + NH_3$	-75^a
RCN	$RCO_2H + NH_3$	-80^c
NH_2CN	Isourea	-83^d
HNCNH	Isourea	-97^d
HCCH (g)	CH_3CHO	-112^a

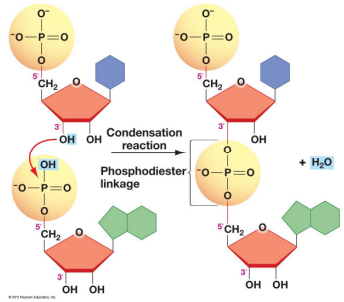
Danger, G.; Plasson, R.; Pascal, R. *Chem. Soc. Rev.* **2012**, *41*, 5416.

Condensation of aminoacids into peptides

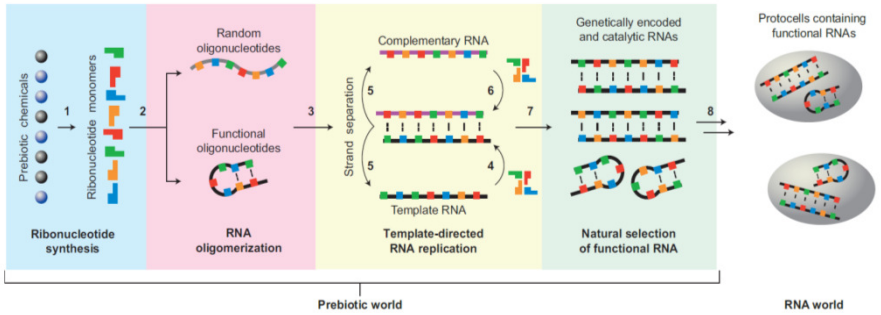


Nucleotide polymerization

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

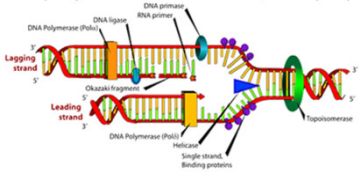


Nucleotide polymerization – sequence control

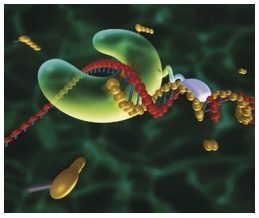


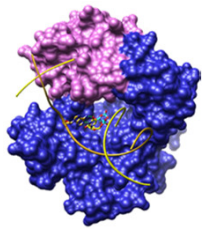
Vital chemical reactions

nucleotide polymerization → DNA/RNA polymerases

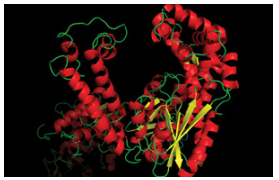


dxline.info/img/new_ail/dna-polymerase_1.jpg



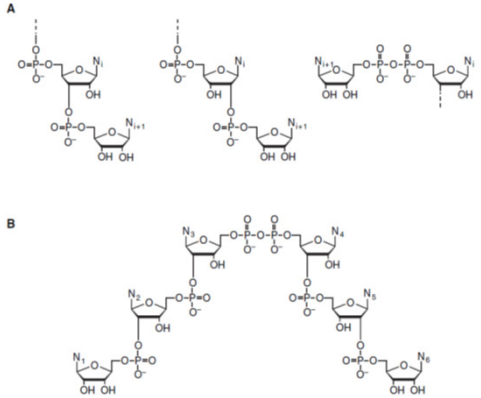


niehs.nih.gov



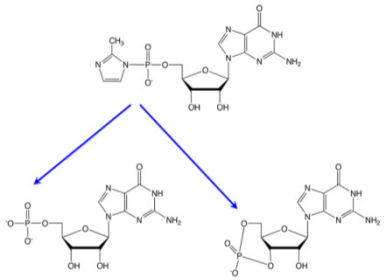
www.neb.com

Products of chemical condensation of nucleotides



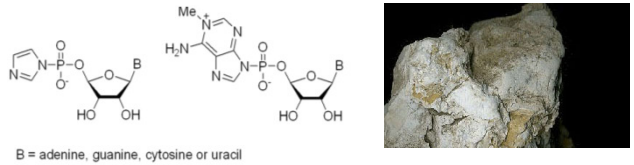
(**A**) Reaction of an activated mononucleotide (N_{i+1}) with an oligonucleotide (N_1–N_i) to form a 3',5'-phosphodiester (left), 2',5'-phosphodiester (middle), or 5',5'-pyrophosphate linkage (right).
(**B**) Typical oligomeric product resulting from chemical condensation of activated mononucleotides

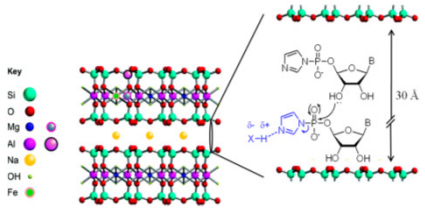
Degradation of activated nucleotides



hydrolysis 3',5'-cyclization

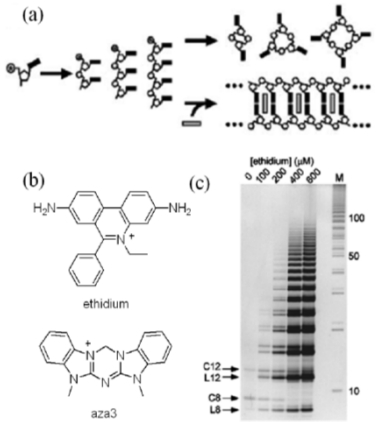
Montmorillonite



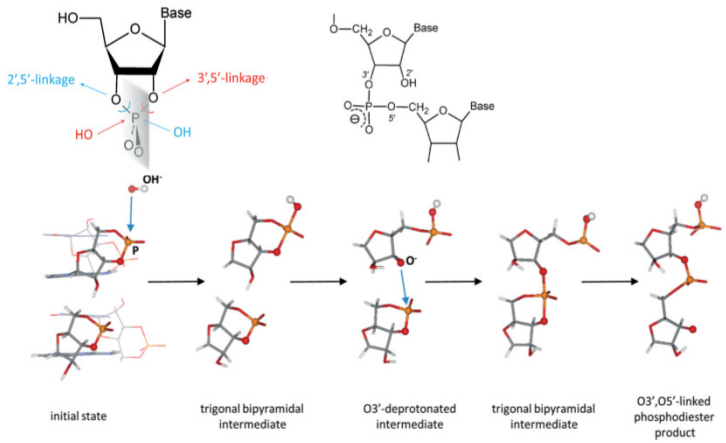


(Top) Structure of ribonucleotide 5′-phosphoimidazolides (left) and ribonucleotide 5′-phosphoro-1-methyladeninium (right). (Bottom) Unit cell of montmorillonite and phosphodiester bond formation within the clay interlayers, as proposed by Ferris and coworkers (right). XH, depicted in blue in the cartoon, is any undifferentiated protic species inside the clay galleries.

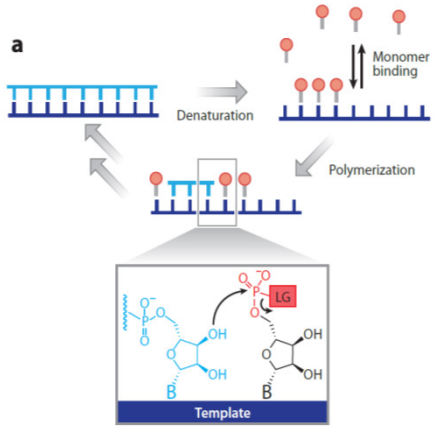
Intercalating agents



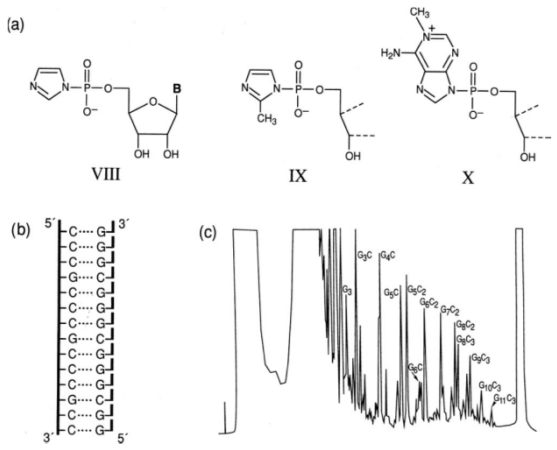
Oligomerization of cyclic nucleotides

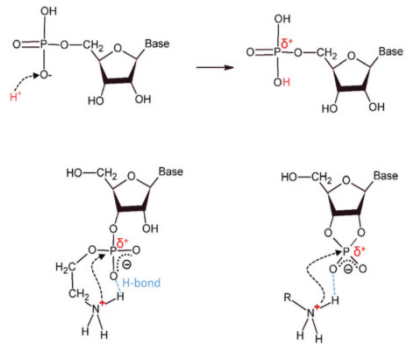


Template-directed synthesis

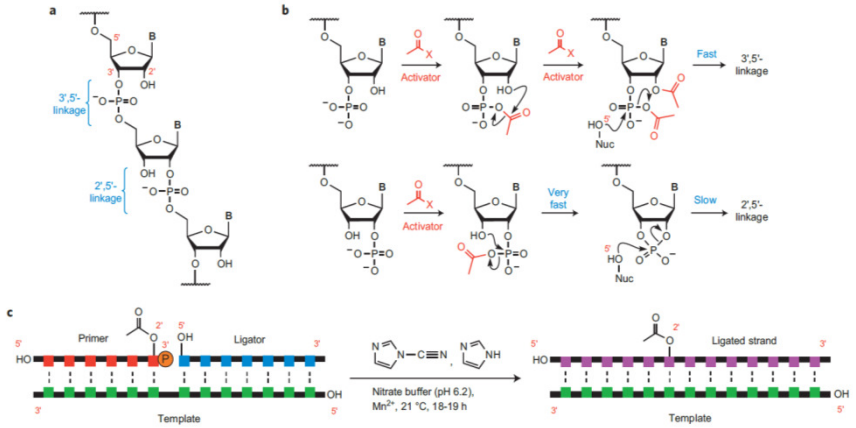


Template-directed synthesis



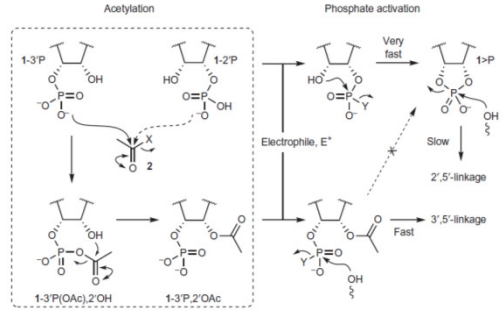


Regioselective ribonucleotide ligation



J. Sutherland *et al. Nature Chem.* **2013,** 383-389

Regioselective ribonucleotide ligation



Protection of the 2'-OH group of **1**-3'P facilitates rapid template-directed 3',5'-ligation after electrophilic phosphate activation. The 3'-OH group of **1**-2'P is protected to a lesser extent, such that **1**>P is the major product of phosphate activation and slow template-directed 2',5'-ligation follows.
X = leaving group, Y = leaving group generated by electrophilic activation of phosphate oxygen with or without a subsequent nucleophilic displacement

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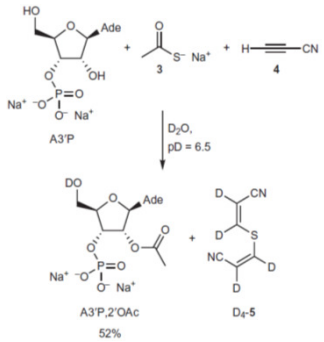
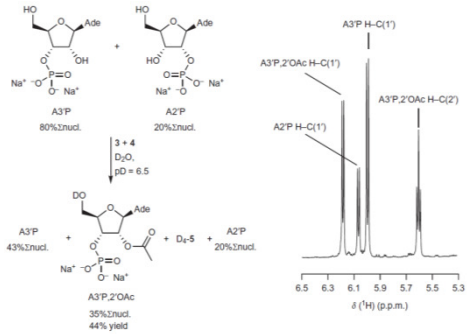
Regioselective ribonucleotide ligation



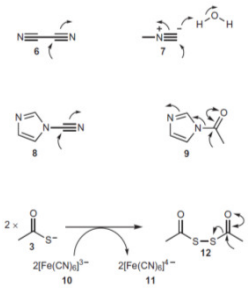
Treatment of A3'P (100 mM) with sodium thioacetate 3 (100 mM) and cyanoacetylene 4 (200 mM) in D_2O at neutral pD for 24 hours results in selective acetylation of the 2-OH group. Curly arrows indicate electrophilic activation/acetylation steps. Yields were judged by ^1H NMR integration. Ade = N9-linked adenine.

J. Sutherland *et al. Nature Chem.* **2013,** 383-389

Regioselective ribonucleotide ligation



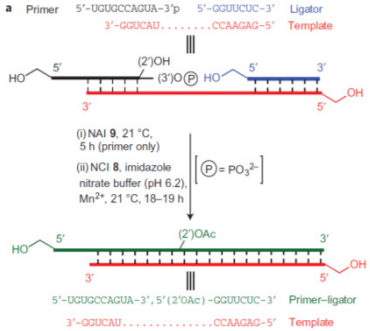
Treatment of A3'P (80 mM) and A2'P (20 mM) as given before results in the exclusive 2-acetylation of the former nucleotide. Partial ^1H NMR spectrum of the reaction products.



Additional electrophiles 6–8 shown to drive the acetylation of ribonucleotides with thioacetate 3. Direct acetylation with 9 is also possible, as is oxidative activation of 3 with errycanide 10 to afford ferrocyanide 11 and a dimeric acetylating agent 12. Curly arrows indicate electrophilic activation/acetylation steps.

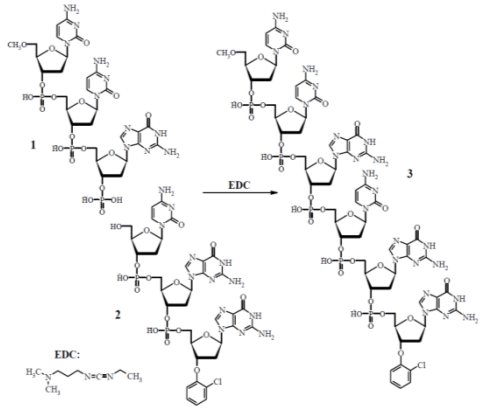
Regioselective ribonucleotide ligation

Chemoselective acetylation of 39P-oligoribonucleotides expedites templated ligation



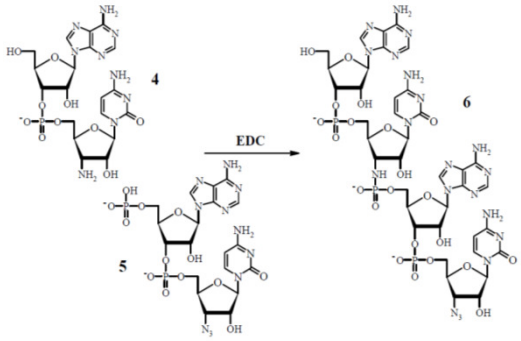
Sequences and reaction conditions employed for acetylation (i) and subsequent templated ligation (ii). The acetylation mixture contained 80 mM primer and 50 mM NAI 9; the ligation mixture contained 4 mM primer from the acetylation reaction, 25 mM template, 30 mM ligator, 200 mM imidazole nitrate buffer (pH 6.2), 10 mM $MnCl_2$ and 100 mM NCI 8. Ligation conditions were based on those reported previously for the conversion of A3'P into A>P (ref. 35) and for the ligation of oligomers with 5P and 2,3-diol termini.

First non-enzymatic self-replicating system



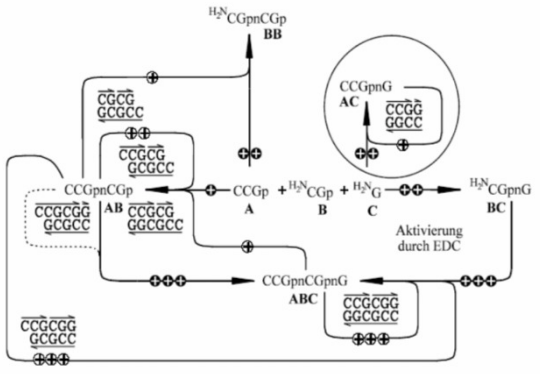
V. Patzke, G. von Kiedrowski *ARKIVOC* **2007** 293-310

Non-enzymatic self-replication of oligonucleotide analogues



Zielinski, W. S.; Orgel, L. E. *Nature* **1987,** *327*, 346

A self-replicating system with three starting materials



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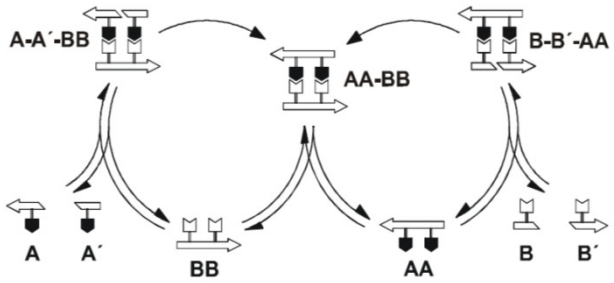
Minimal cross-catalytic self-replicating system representation



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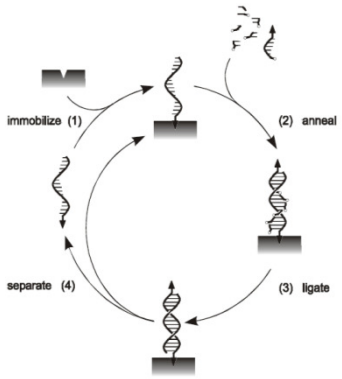
SPREAD – Surface-Promoted Replication and Exponential Amplification of DNA Analogues



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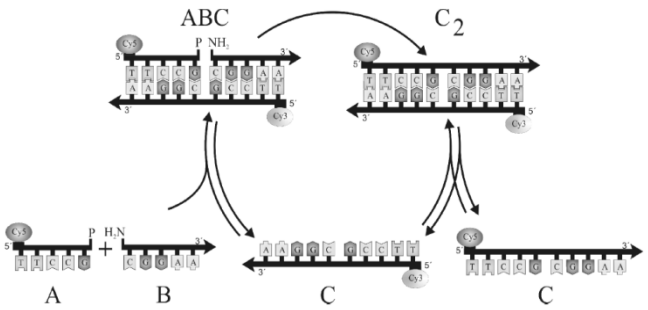
A self-replicating system analysis by FRET



V. Patzke, G. von Kiedrowski *ARKIVOC* **2007** 293-310