

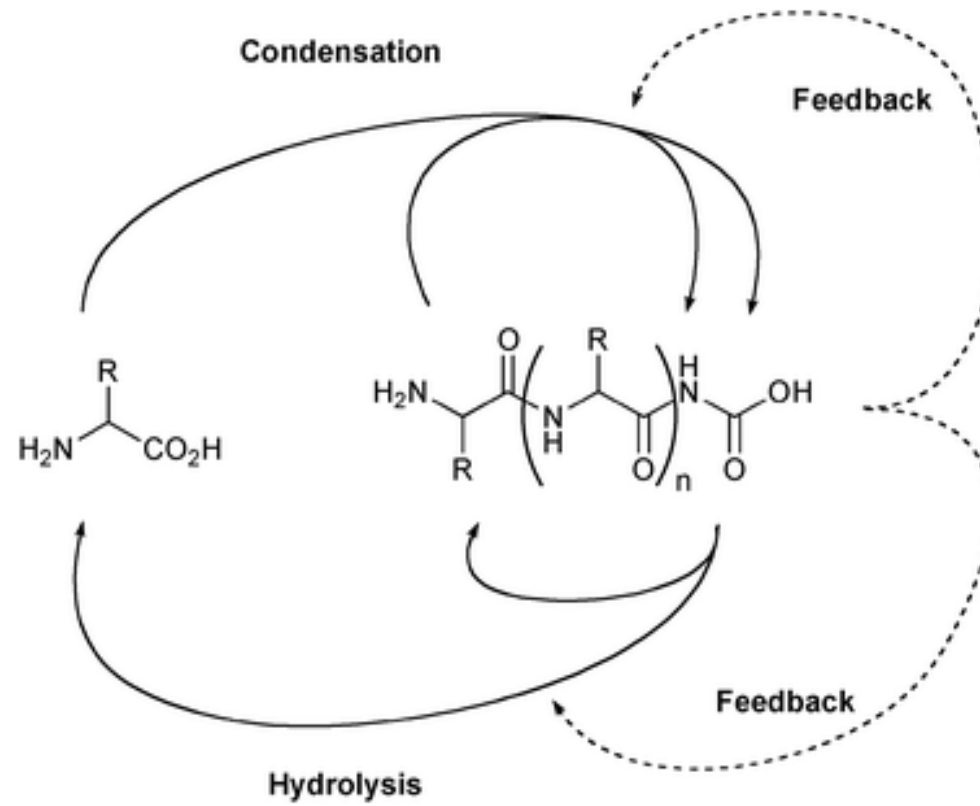
*Origin of the Universe – stars, planets, elements*

*Origin of biorelevant monomers – primordial soup*

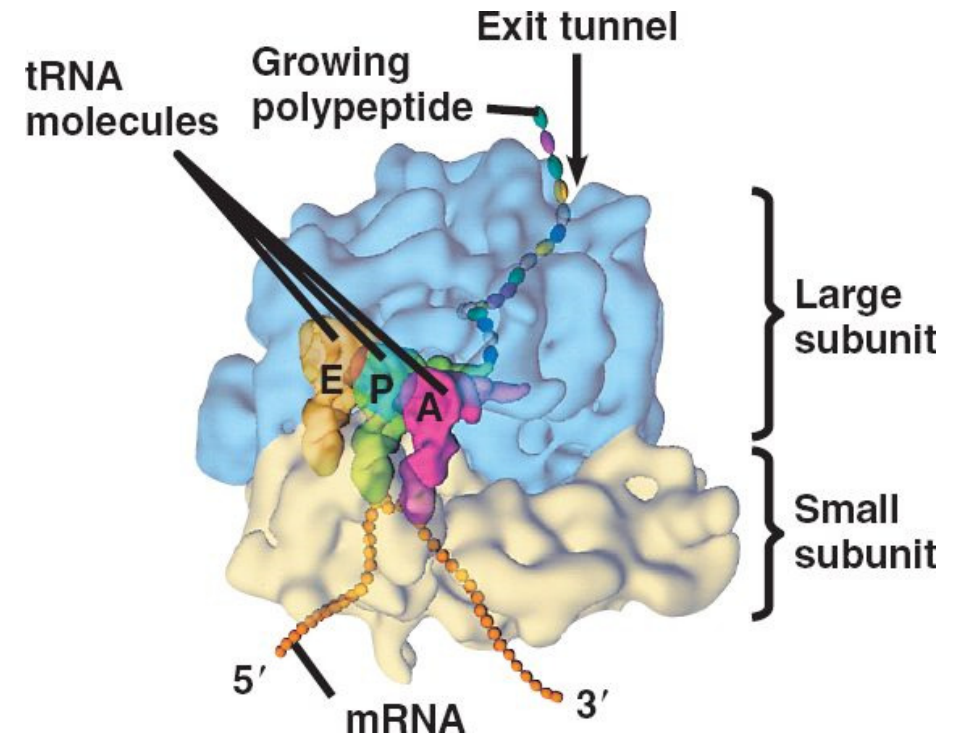
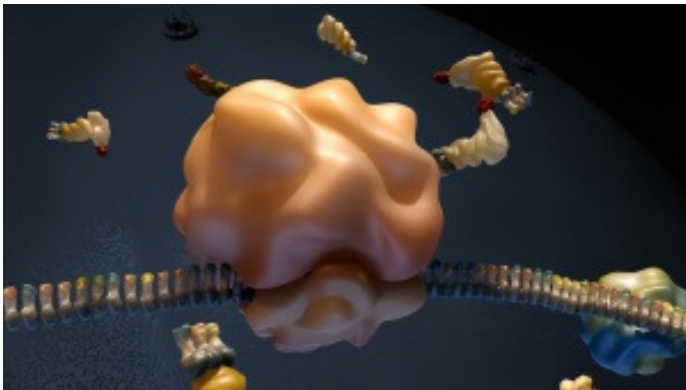
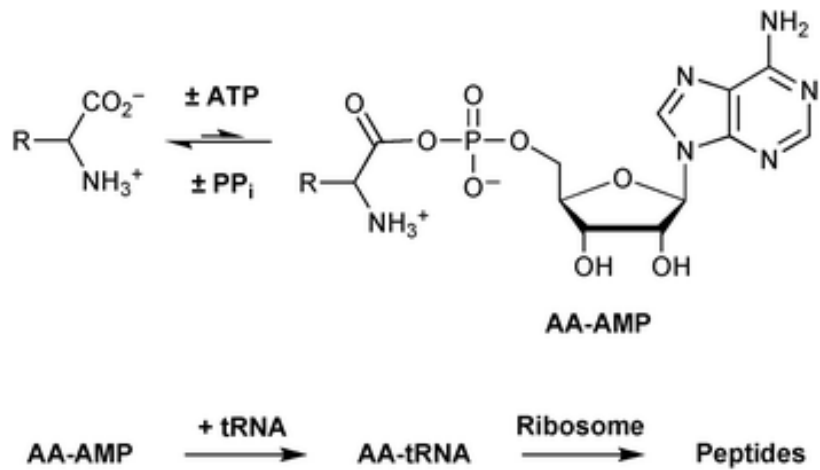
*Complex chemical processes on the way to living systems*

*Protocells and LUCA*

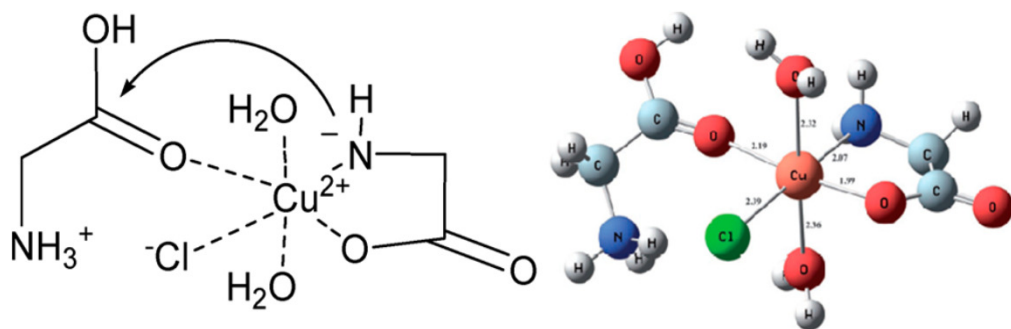
## Condensation of aminoacids into peptides



## Biochemical condensation of amino acids into peptides



## Spontaneous vs. assisted dehydration

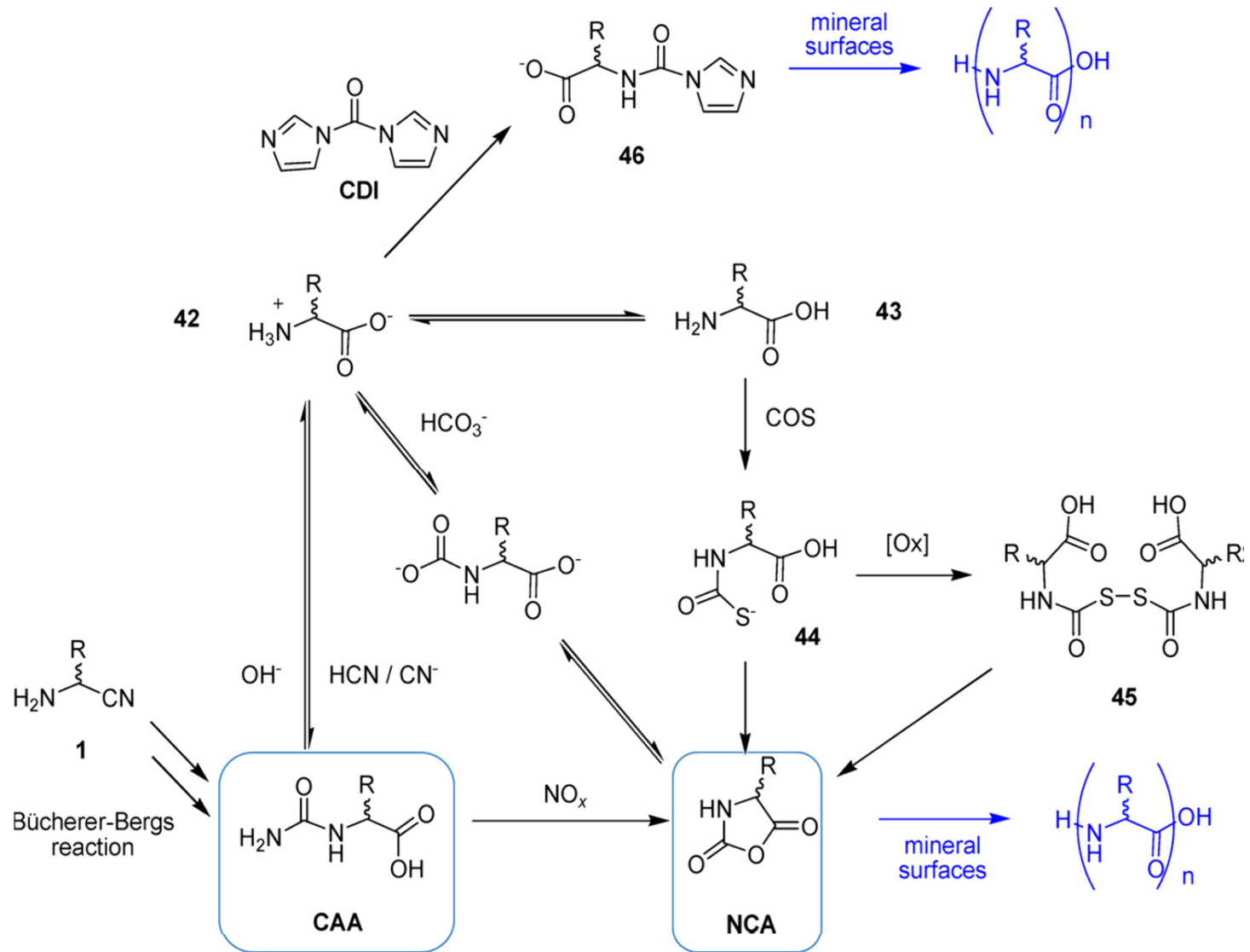


Rode, B. M.; Fitz, D.; Jakschitz, T. *Chem. Biodiversity* **2007**, *4*, 2674.

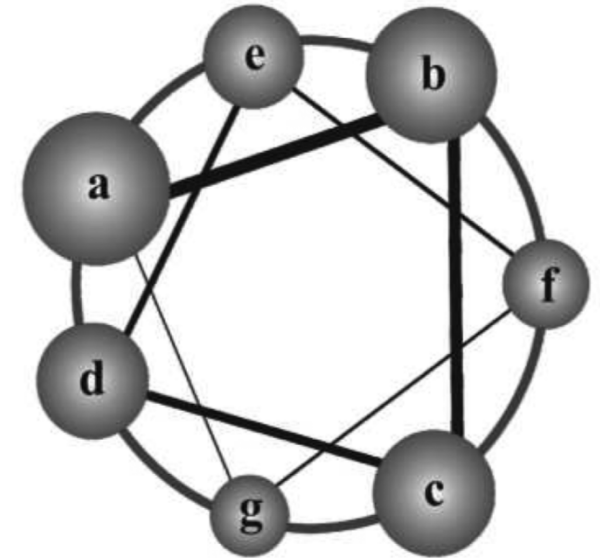
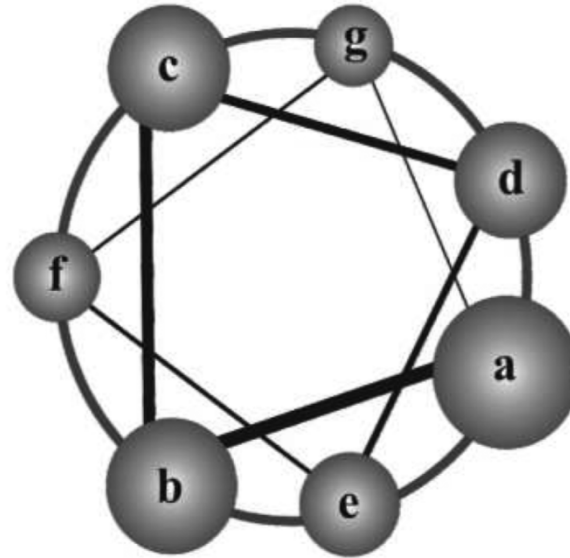
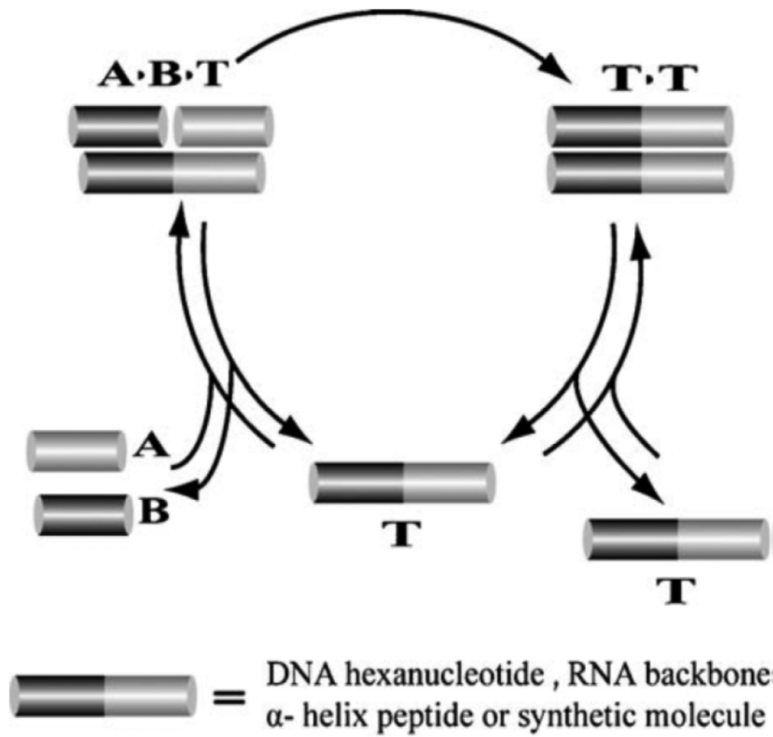
Activating agent	Hydrolysis/ hydration product	$\Delta G^{\circ}$ / kJ mol <sup>-1</sup>
NH <sub>2</sub> CONH <sub>2</sub>	CO <sub>2</sub> + NH <sub>3</sub>	-16 <sup>a</sup>
COS (g)	CO <sub>2</sub> + H <sub>2</sub> S	-17 <sup>a</sup>
Pyrophosphate	Phosphate	-19 <sup>b</sup>
CO (g)	HCO <sub>2</sub> H	-16 <sup>a</sup>
HNCO	CO <sub>2</sub> + NH <sub>3</sub>	-54 <sup>a</sup>
HCN	HCO <sub>2</sub> H + NH <sub>3</sub>	-75 <sup>a</sup>
RCN	RCO <sub>2</sub> H + NH <sub>3</sub>	-80 <sup>c</sup>
NH <sub>2</sub> CN	Isourea	-83 <sup>d</sup>
HNCNH	Isourea	-97 <sup>d</sup>
HCCH (g)	CH <sub>3</sub> CHO	-112 <sup>a</sup>

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

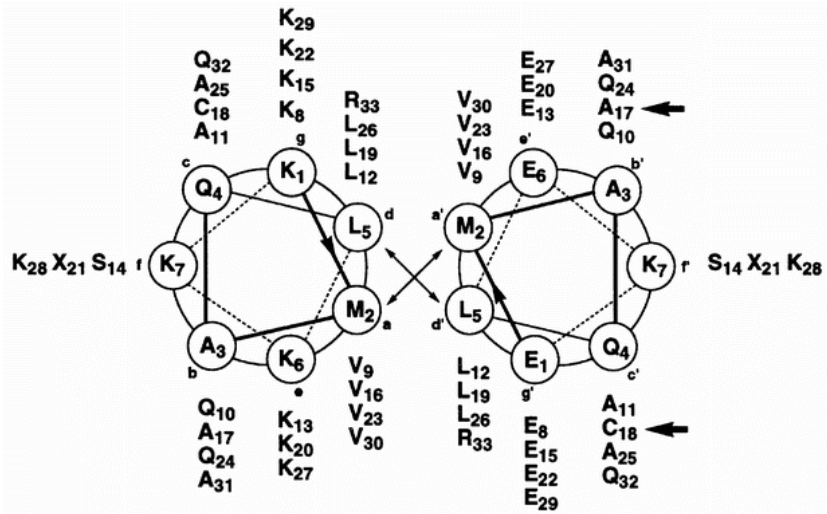
# Condensation of aminoacids into peptides



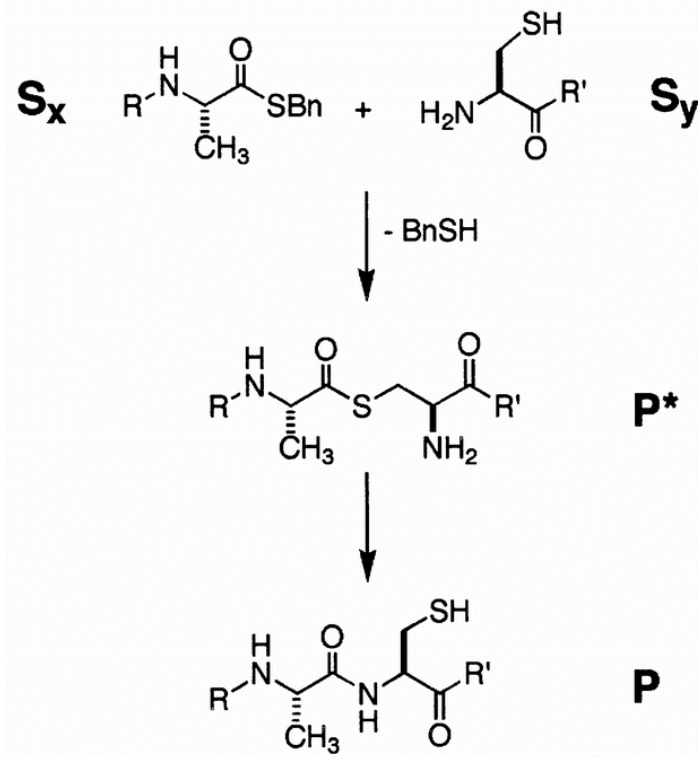
## Peptide self-replication



# Peptide self-replication



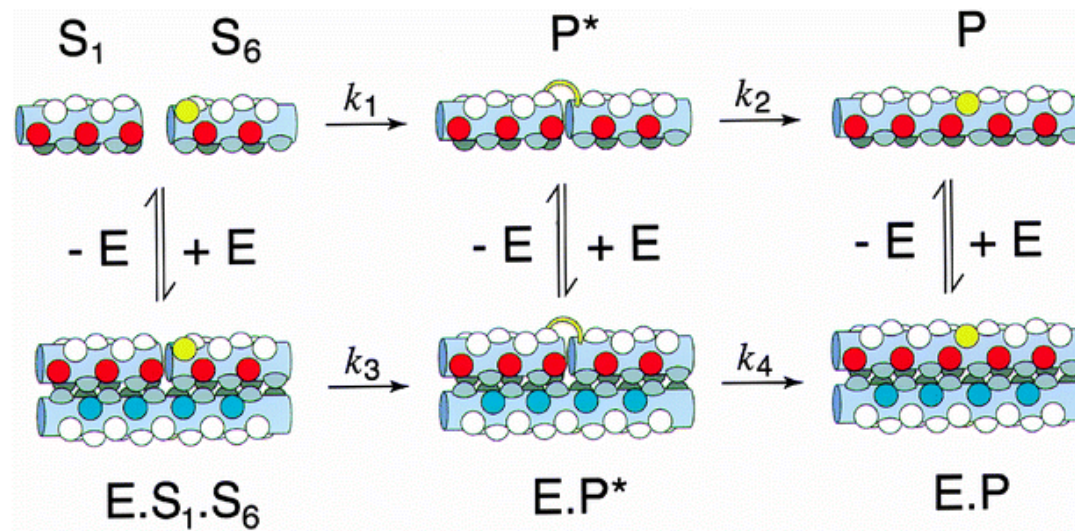
- E:** Ar-KMAQLKKKVQALKSKVA-CLKXKVQALKKKVAQR-CONH<sub>2</sub>  
**E\*:** Ar-KMAQLKKKVQALKSKVA-SLKXKVQALKKKVAQR-CONH<sub>2</sub>  
**S<sub>1</sub>:** Ar-EMAQLEKEVQALESEVA-COSBn  
**S<sub>2</sub>:** Ar-EMAQLEKEVQALESEVA-COS(CH<sub>2</sub>)<sub>2</sub>CONH<sub>2</sub>  
**S<sub>3</sub>:** Ar-EMAQLEKEVQALESEVA-CONHOH  
**S<sub>4</sub>:** Ar-RMKQLEEKVYELLSKVA-COSBn  
**S<sub>5</sub>:** Ar-KMAQLKKKVQALKSKVA-COSBn  
**S<sub>6</sub>:** H<sub>2</sub>N-CLEXEVQALEKEVAQR-CONH<sub>2</sub>  
**S<sub>7</sub>:** H<sub>2</sub>N-CLEXEVARLKKLVGE-CONH<sub>2</sub>  
**S<sub>8</sub>:** H<sub>2</sub>N-(d-C)LEXEVQALEKEVAQR-CONH<sub>2</sub>  
**S<sub>9</sub>:** H<sub>2</sub>N-GLEXEVARLKKLVGE-CONH<sub>2</sub>



K. Severin, D. H. Lee, A. J. Kennan and M. Reza Ghadiri *Nature* **1997**, *389*, 706-709



## Peptide self-replication

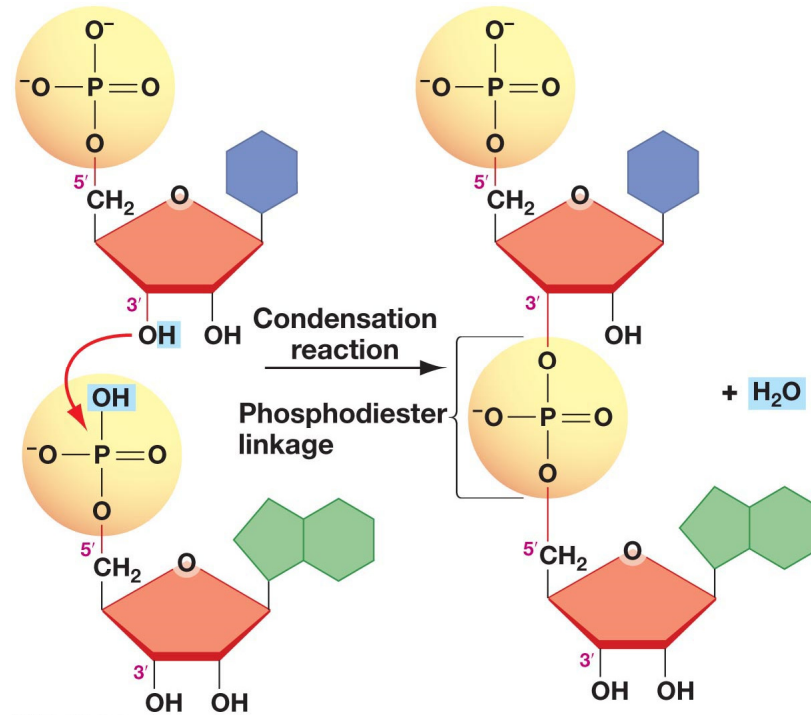


K. Severin, D. H. Lee, A. J. Kennan and M. Reza Ghadiri *Nature* **1997**, *389*, 706-709



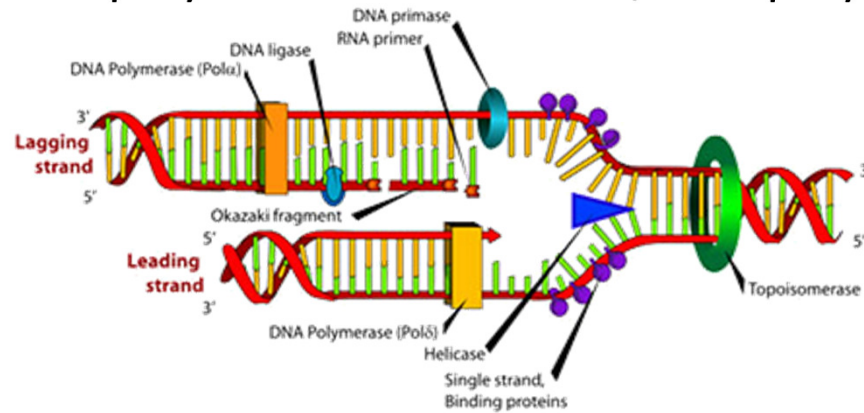
# Nucleotide polymerization

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

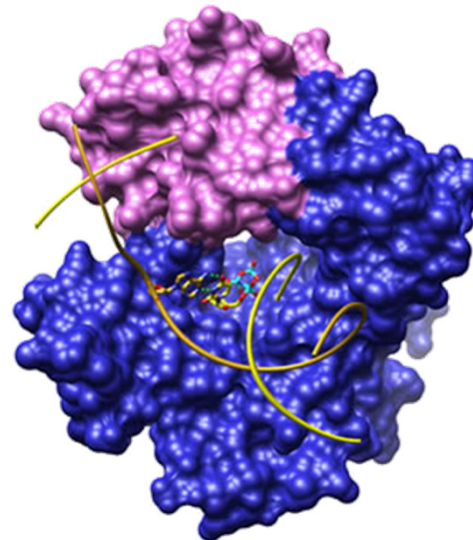
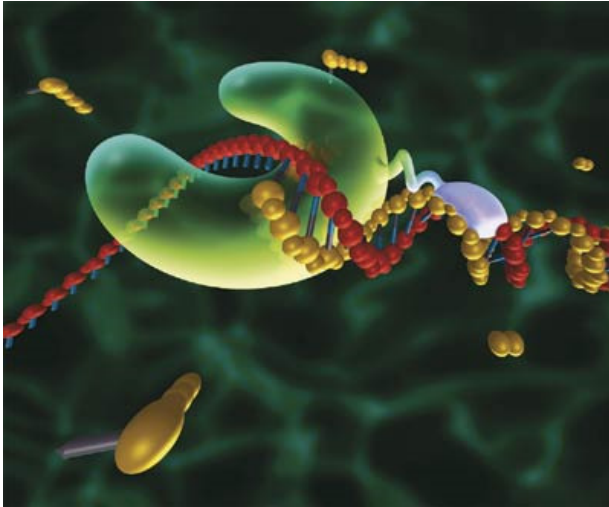


## Vital chemical reactions

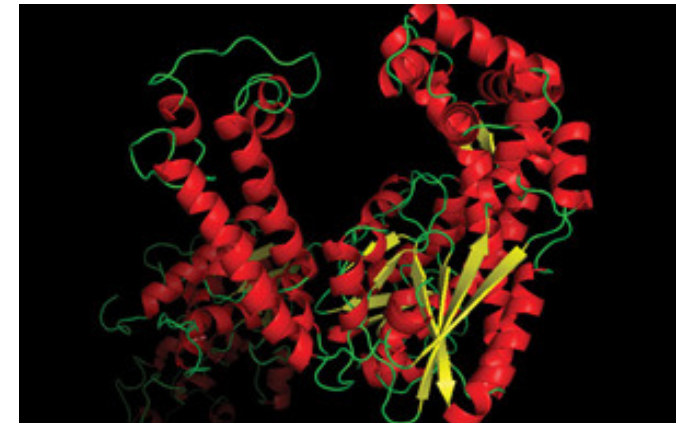
nucleotide polymerization → DNA/RNA polymerases



[dxline.info/img/new\\_ail/dna-polymerase\\_1.jpg](http://dxline.info/img/new_ail/dna-polymerase_1.jpg)

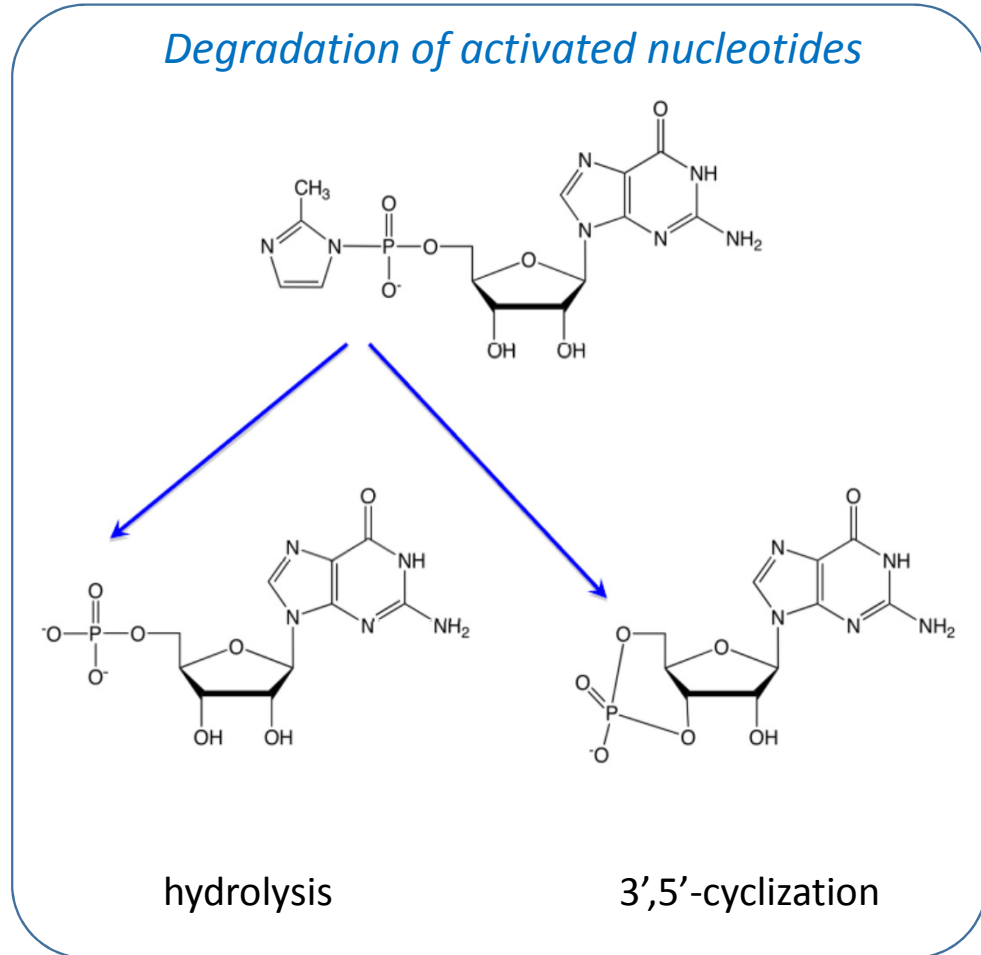
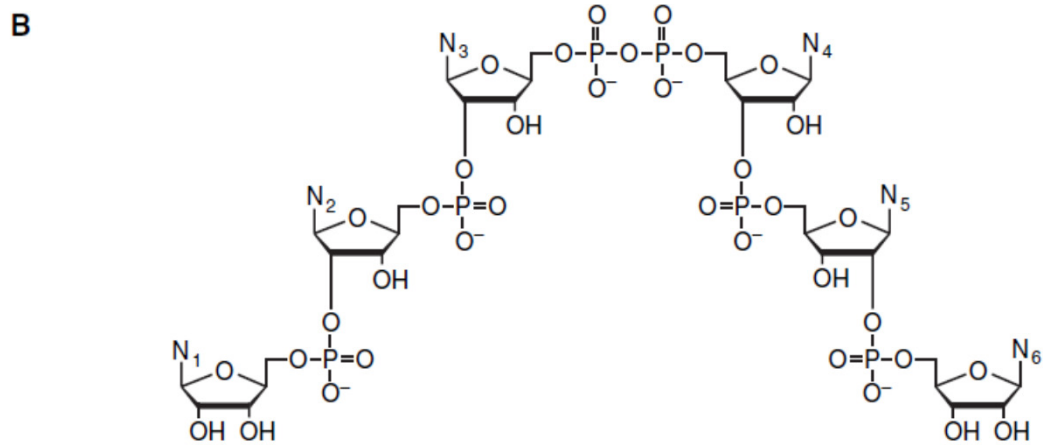
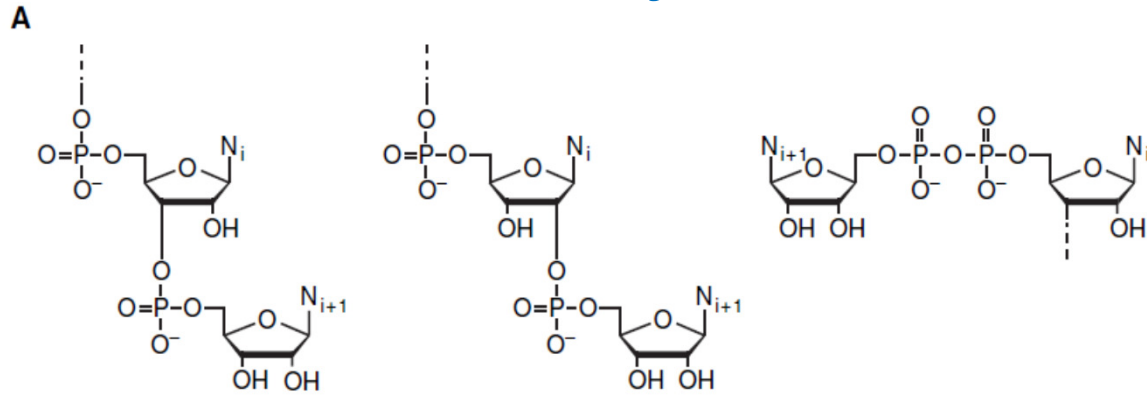


[niehs.nih.gov](http://niehs.nih.gov)



[www.neb.com](http://www.neb.com)

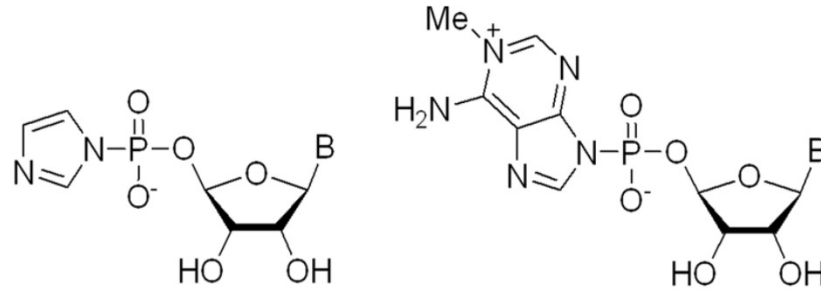
## Products of chemical condensation of nucleotides



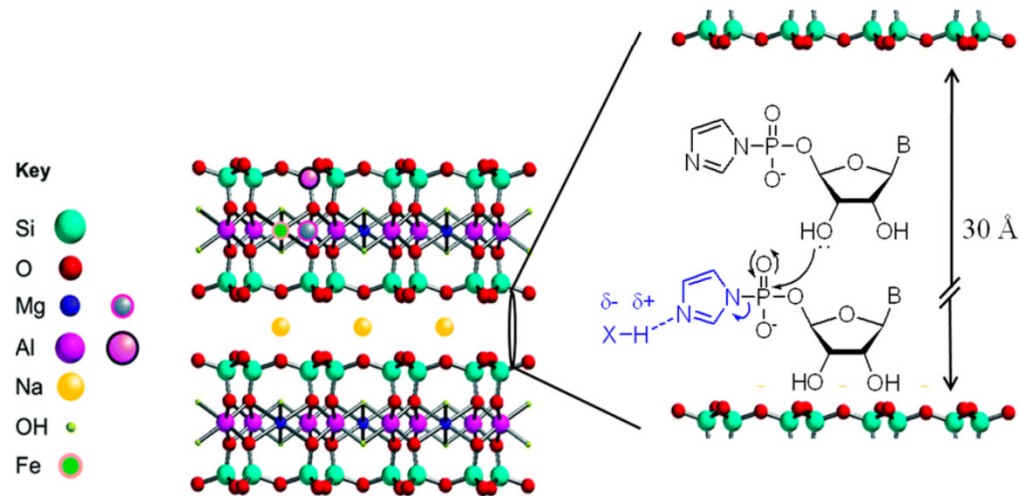
**(A)** Reaction of an activated mononucleotide ( $N_{i+1}$ ) with an oligonucleotide ( $N_1-N_i$ ) to form a 3',5'-phosphodiester (left), 2',5'-phosphodiester (middle), or 5',5'-pyrophosphate linkage (right).

**(B)** Typical oligomeric product resulting from chemical condensation of activated mononucleotides

## Montmorillonite

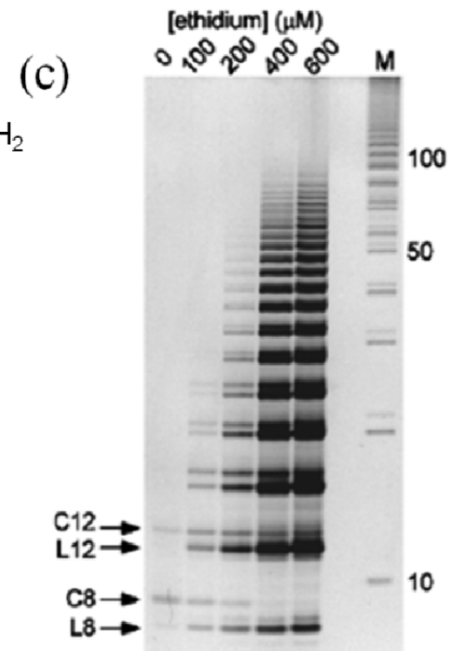
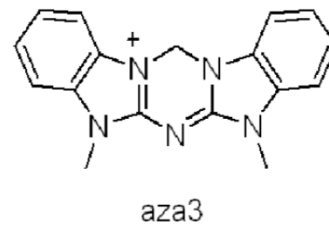
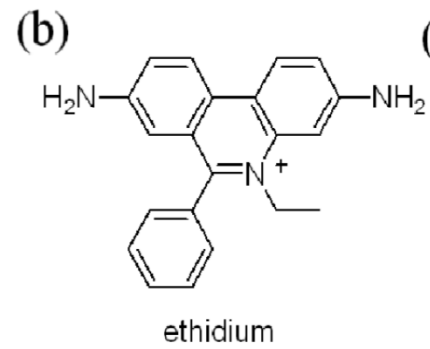
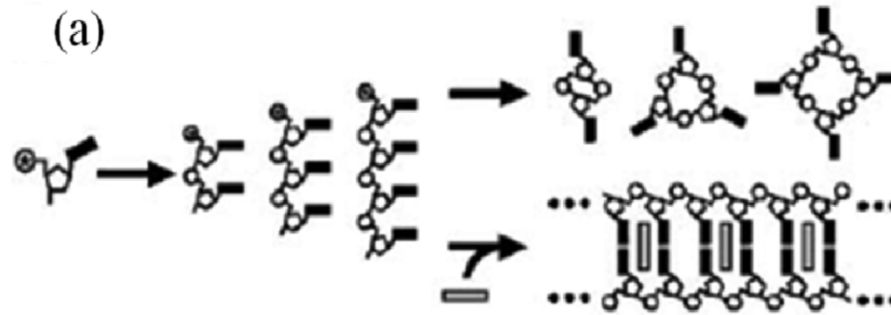


B = adenine, guanine, cytosine or uracil

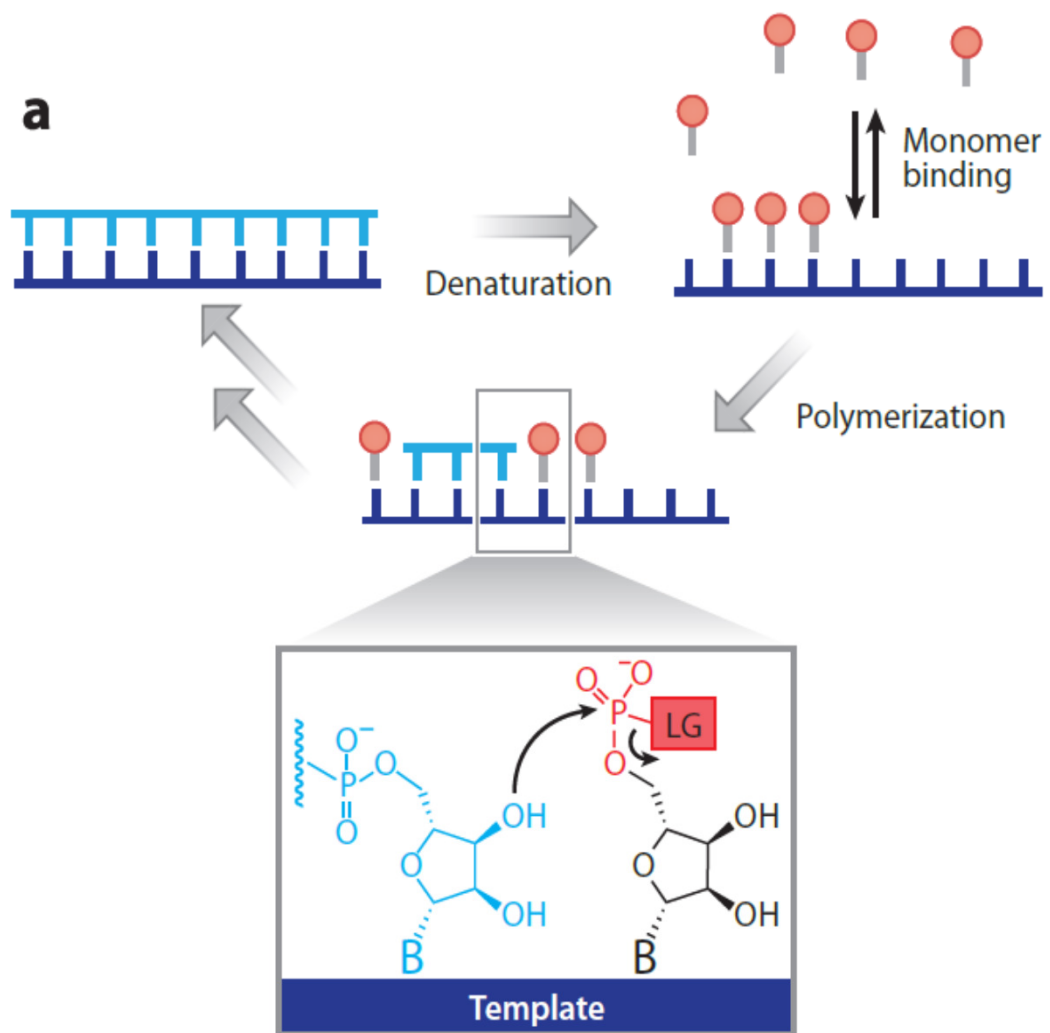


(Top) Structure of ribonucleotide 5'-phosphoimidazolides (left) and ribonucleotide 5'-phosphoro-1-methyladeninium (right). (Bottom) Unit cell of montmorillonite and phosphodiester bond formation within the clay interlayers, as proposed by Ferris and coworkers (right). XH, depicted in blue in the cartoon,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

## Intercalating agents

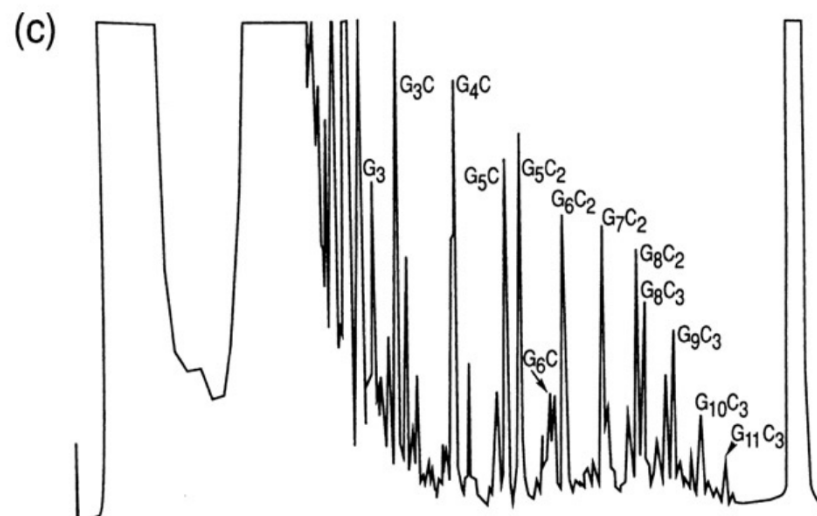
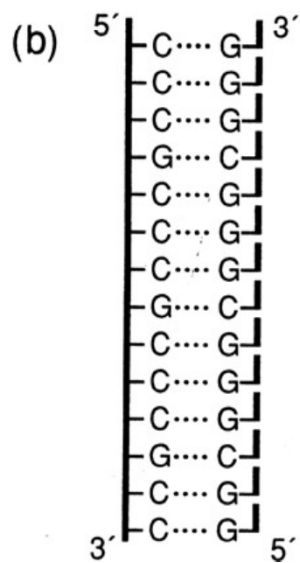
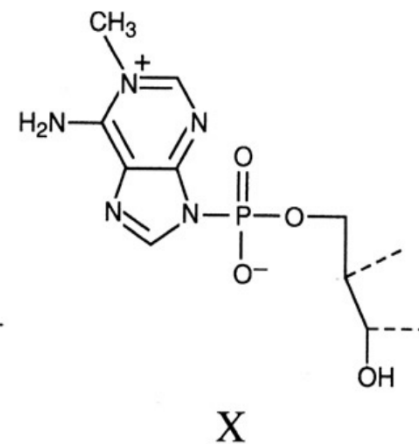
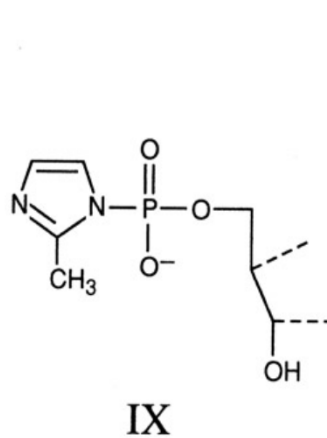
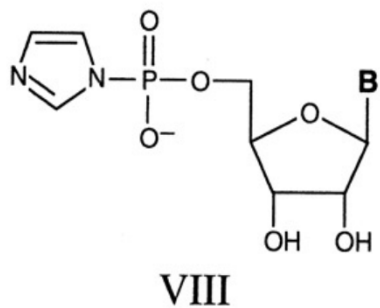


## Template-directed synthesis



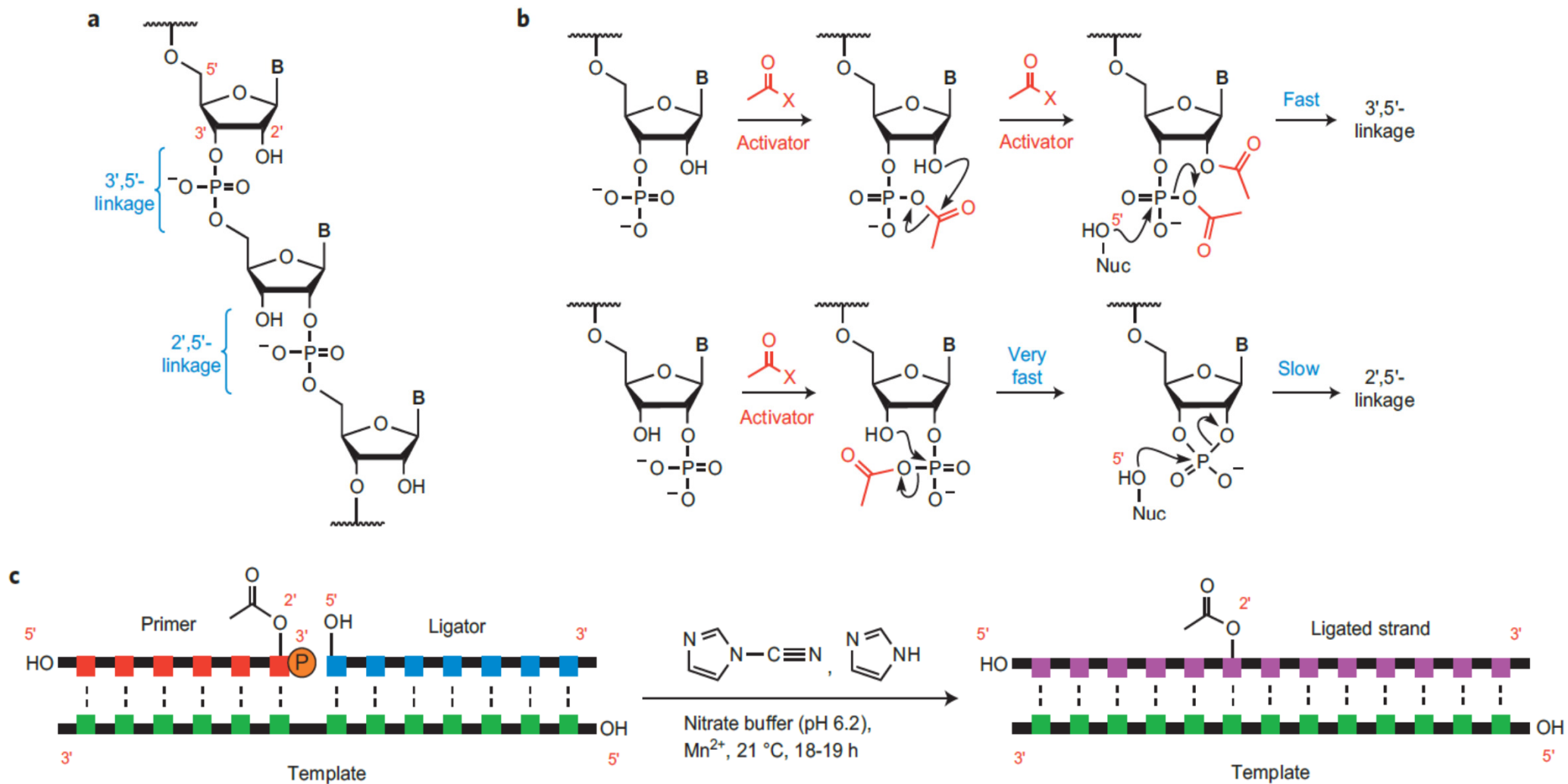
## Template-directed synthesis

(a)



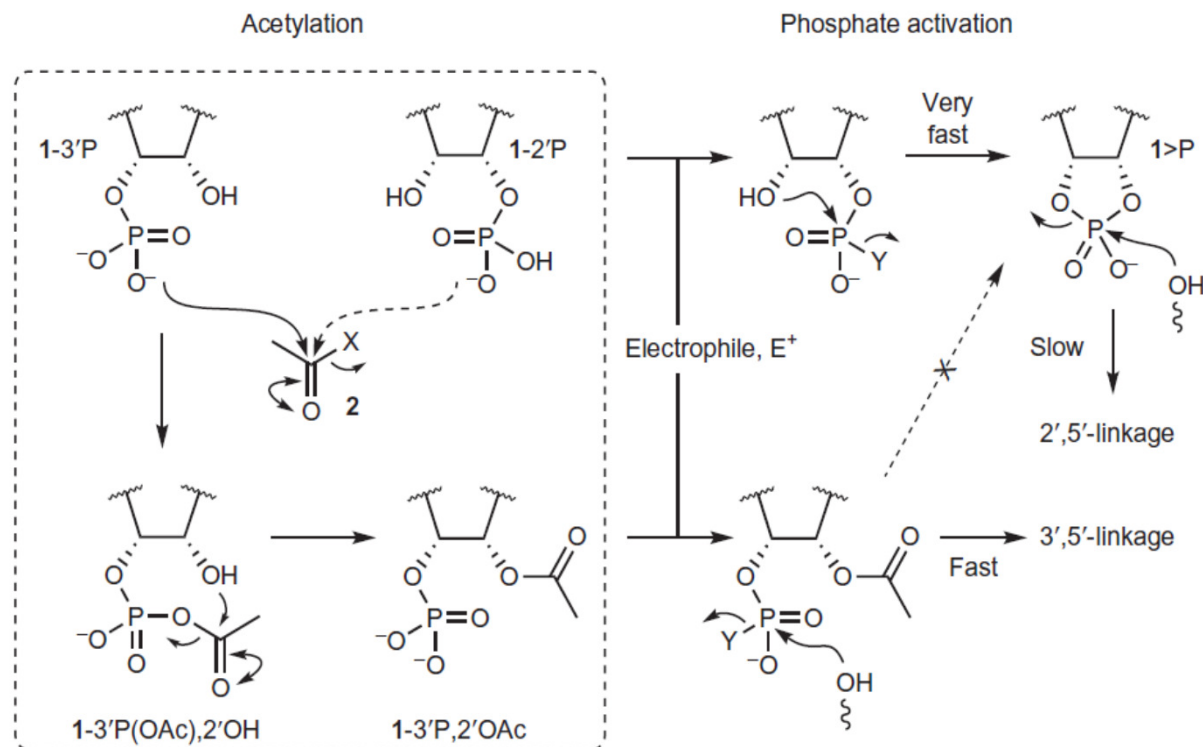


## Regioselective ribonucleotide ligation



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

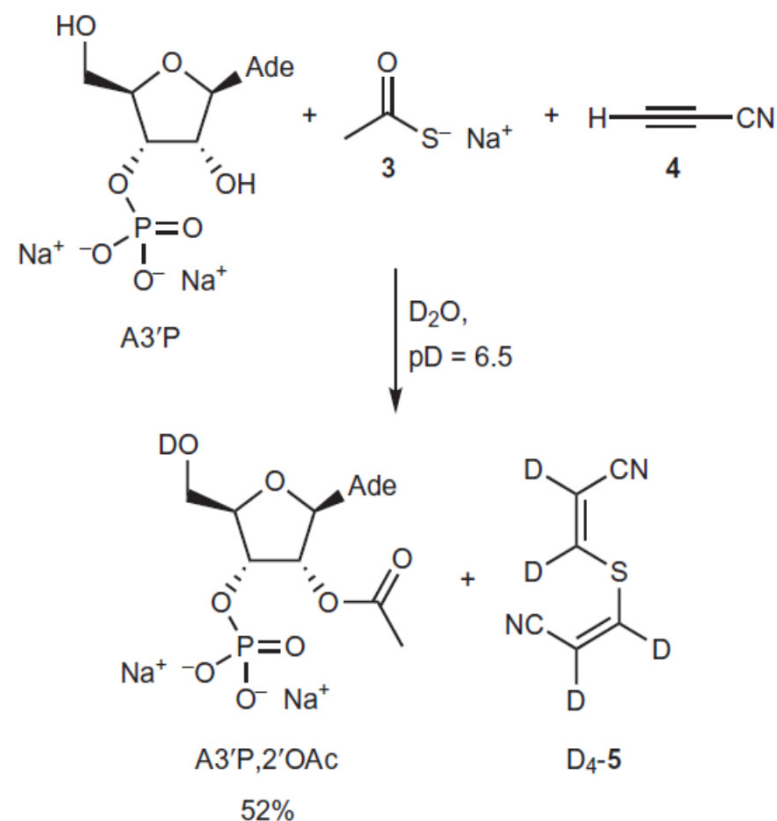
## Regioselective ribonucleotide ligation



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

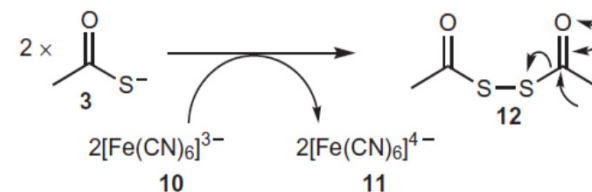
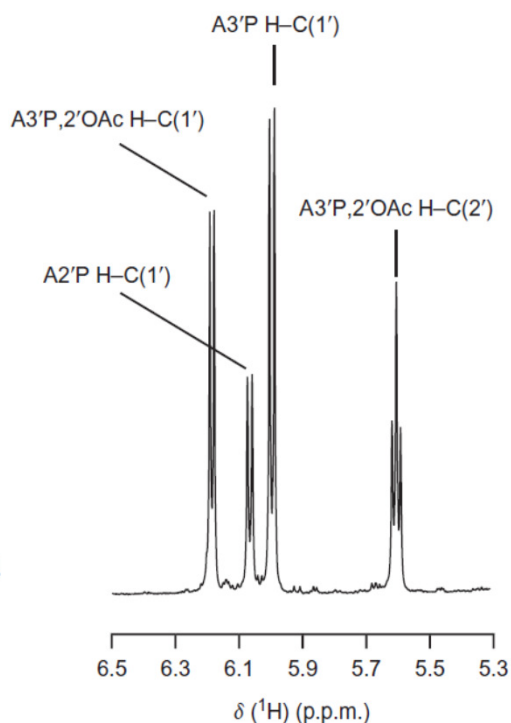
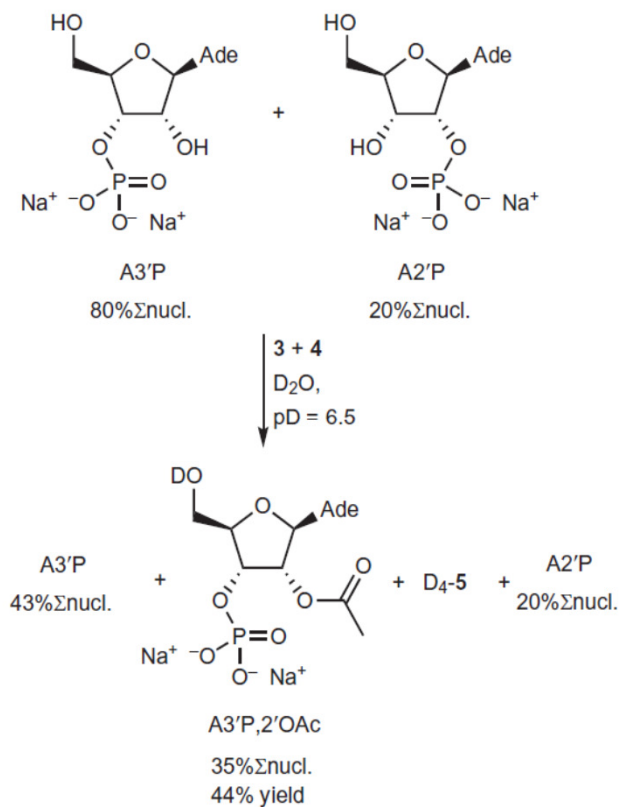
## Regioselective ribonucleotide ligation



Treatment of **A3'P** (100 mM) with sodium thioacetate **3** (100 mM) and cyanoacetylene **4** (200 mM) in D<sub>2</sub>O 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 <sup>1</sup>H NMR integration. Ade = N9-linked adenine.

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

## Regioselective ribonucleotide ligation



Additional electrophiles **6–8** shown to drive the acetylation of ribonucleotides with thioacetate **3**.

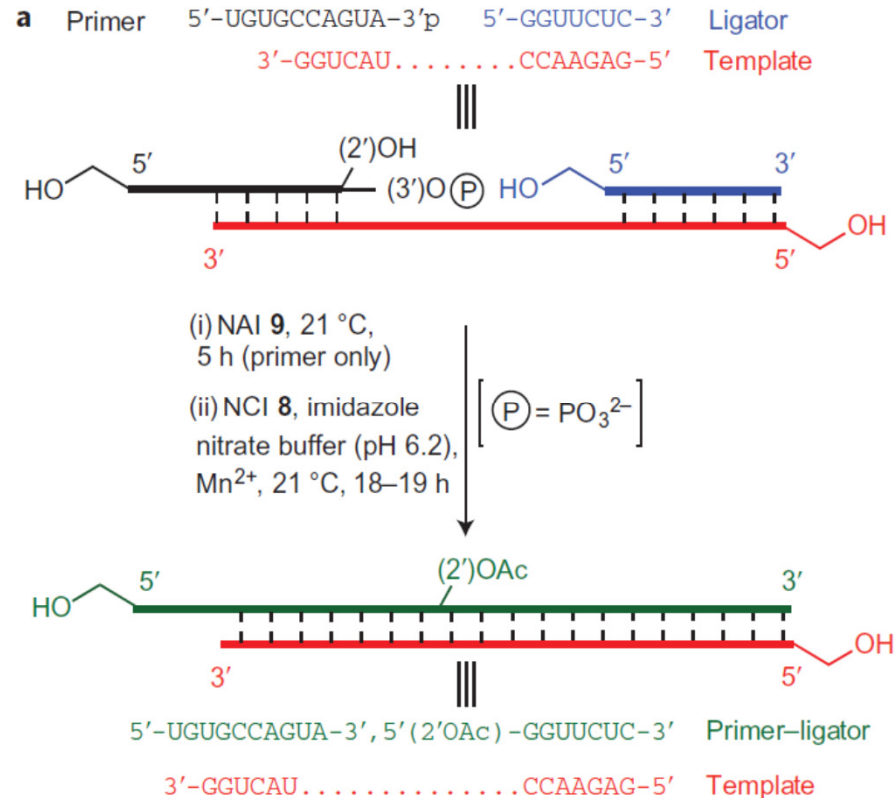
Direct acetylation with **9** is also possible, as is oxidative activation of **3** with ferricyanide **10** to afford ferrocyanide **11** and a dimeric acetylating agent **12**.

Curly arrows indicate electrophilic activation/acetylation steps.

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  $^1\text{H}$  NMR spectrum of the reaction products.

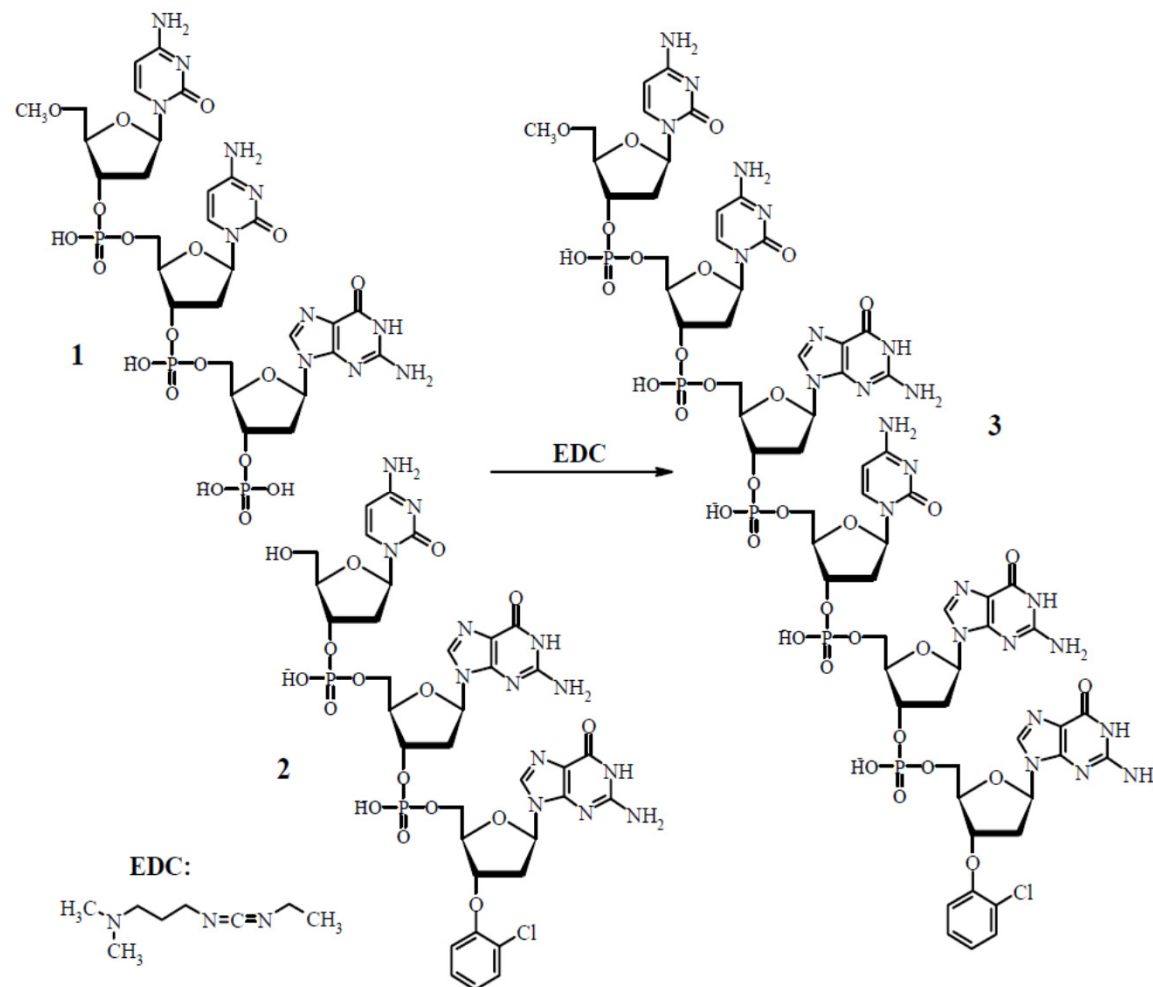
## Regioselective ribonucleotide ligation

Chemoselective acetylation of 3'-P-oligoribonucleotides expedites templated ligation



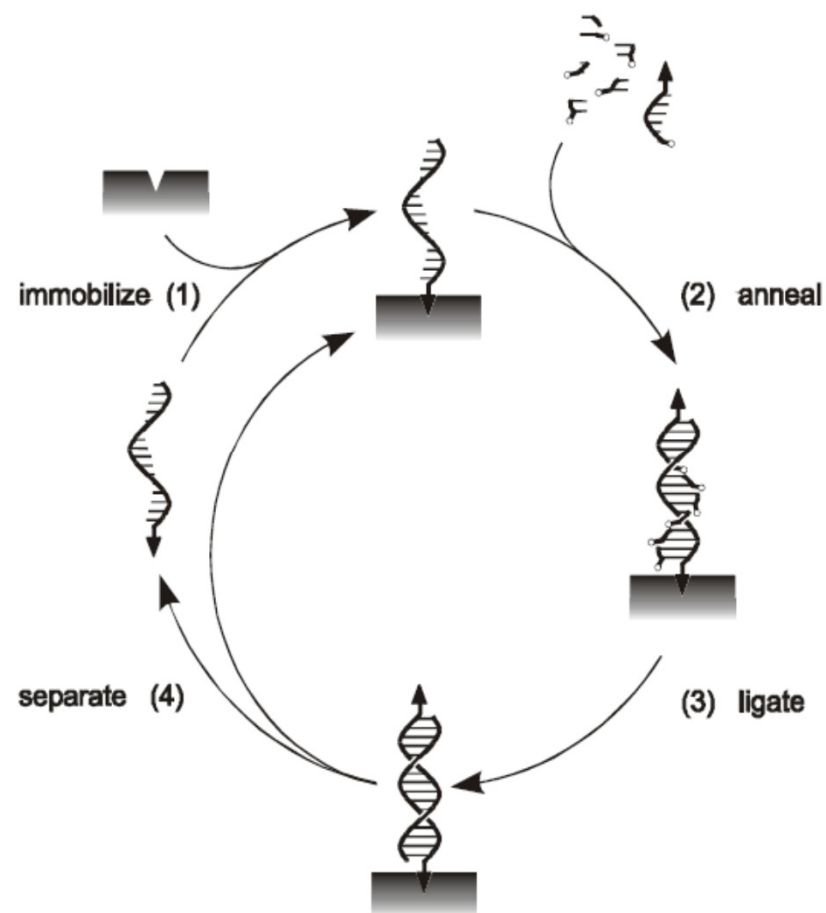
Sequences and reaction conditions employed for acetylation (i) and subsequent templated ligation (ii). The acetylation mixture contained 80 mM primer and 50 mM NAI **9**; the ligation mixture contained 4 mM primer from the acetylation reaction, 25 mM template, 30 mM ligator, 200 mM imidazole nitrate buffer (pH 6.2), 10 mM MnCl<sub>2</sub> 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 5-P and 2,3-diol termini.

## First non-enzymatic self-replicating system



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

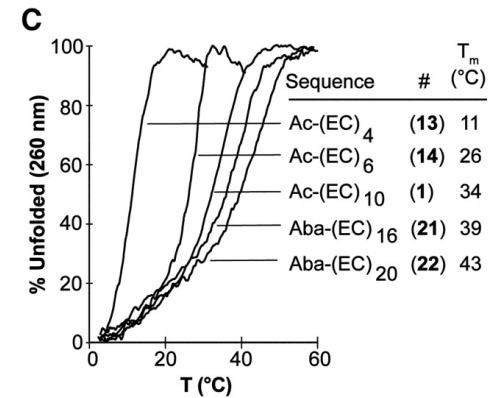
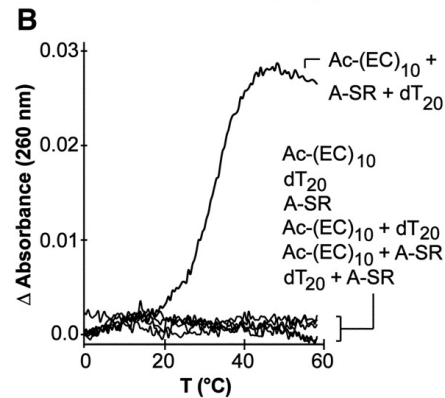
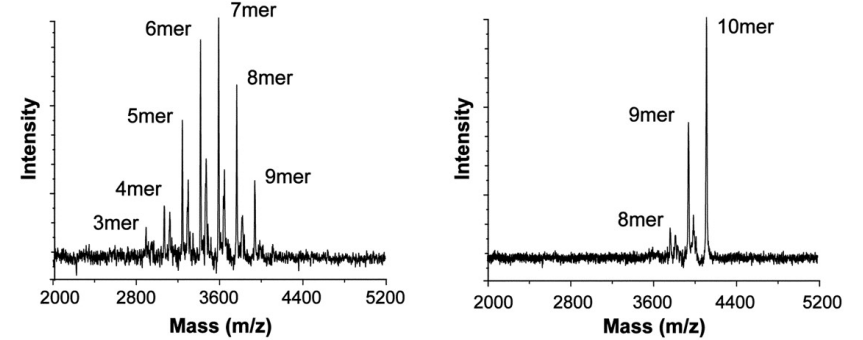
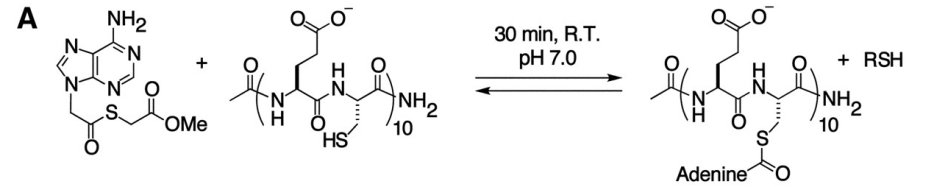
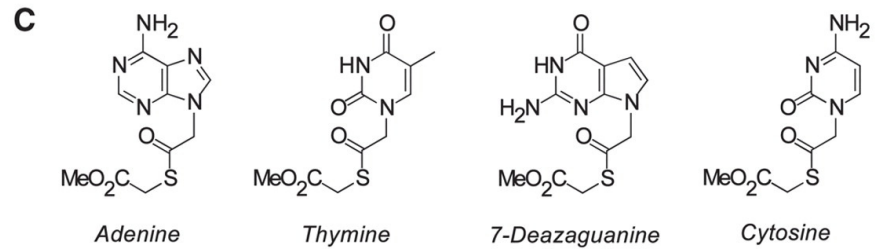
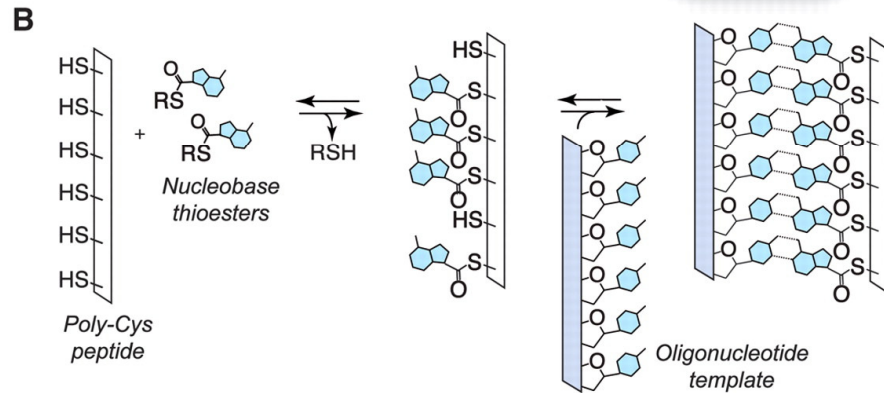
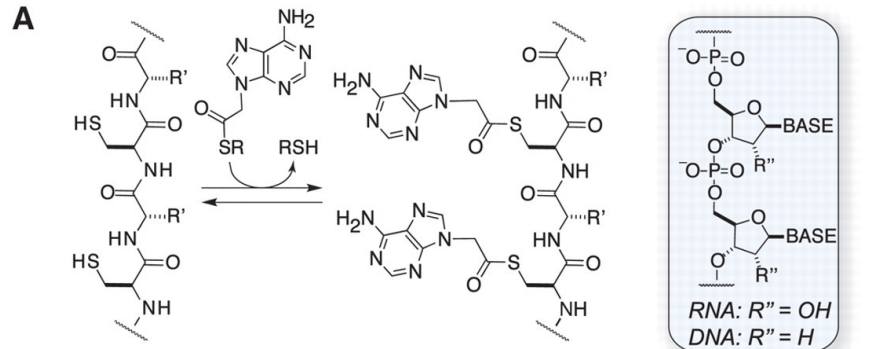
## SPREAD – Surface-Promoted Replication and Exponential Amplification of DNA Analogues



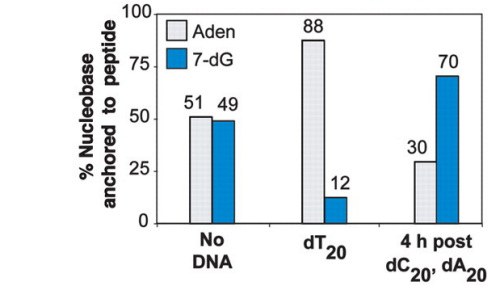
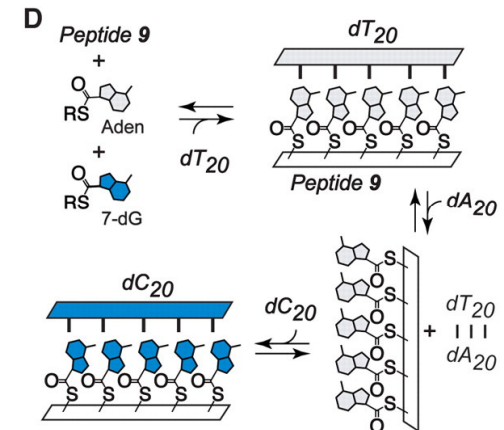
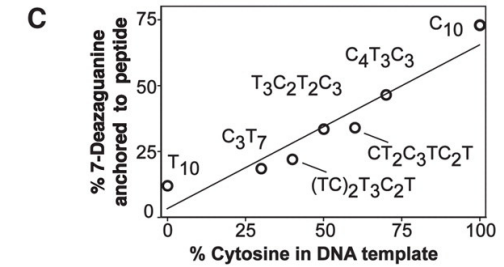
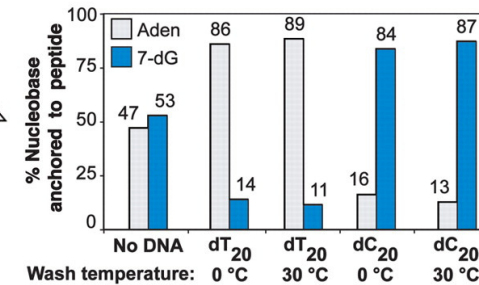
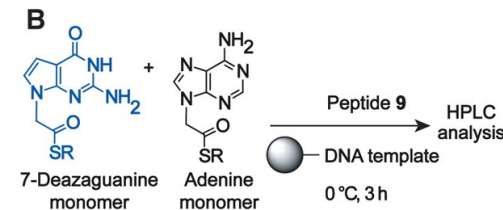
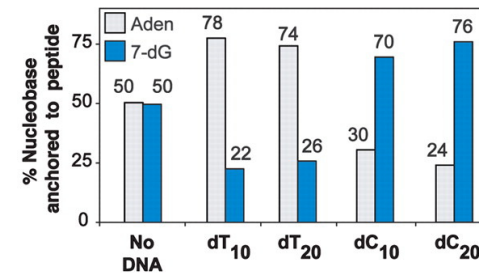
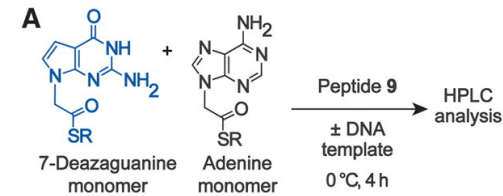
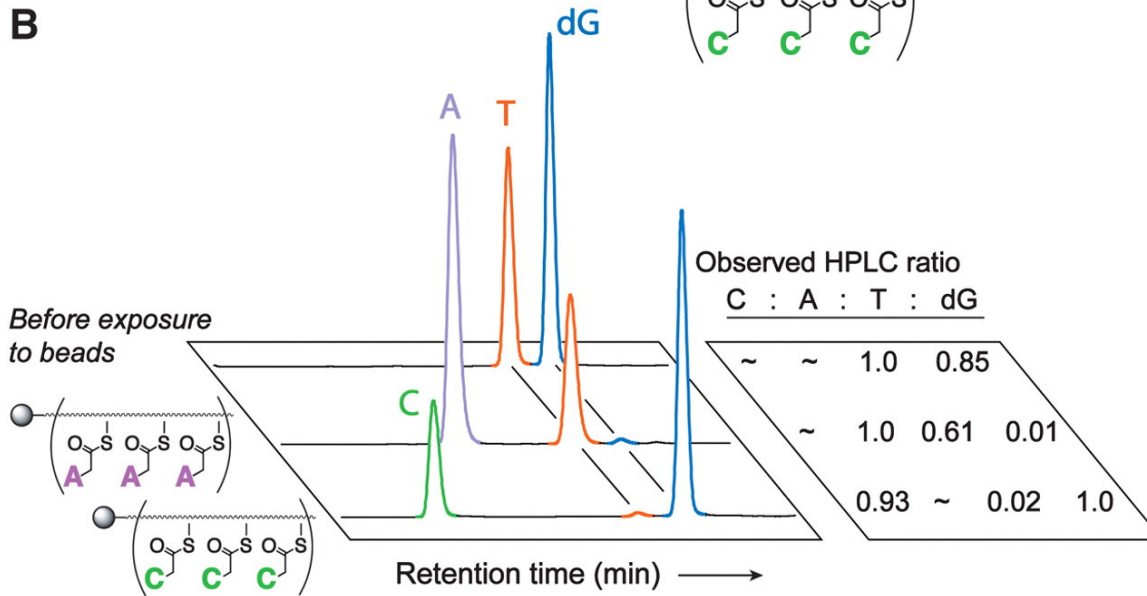
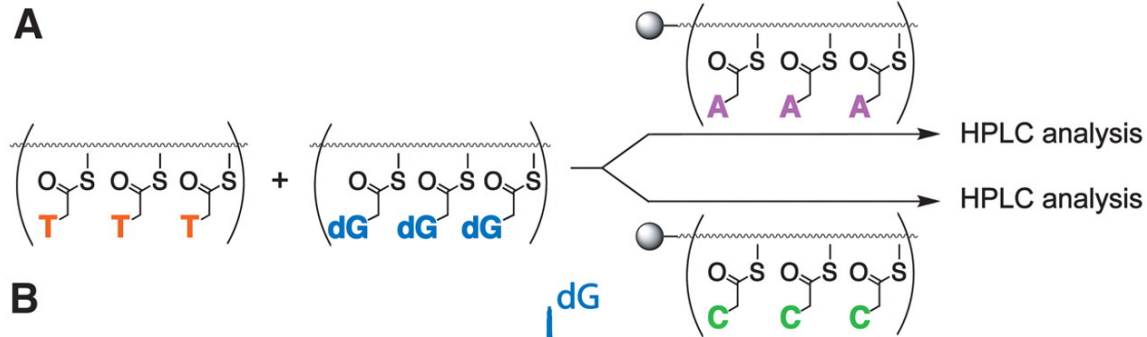
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# Dynamic oligonucleotide analogue sequence-specific assembly



# Dynamic oligonucleotide analogue sequence-specific assembly



M. R. Ghadiri *et al.* *Science* 2009, 325, 73-77