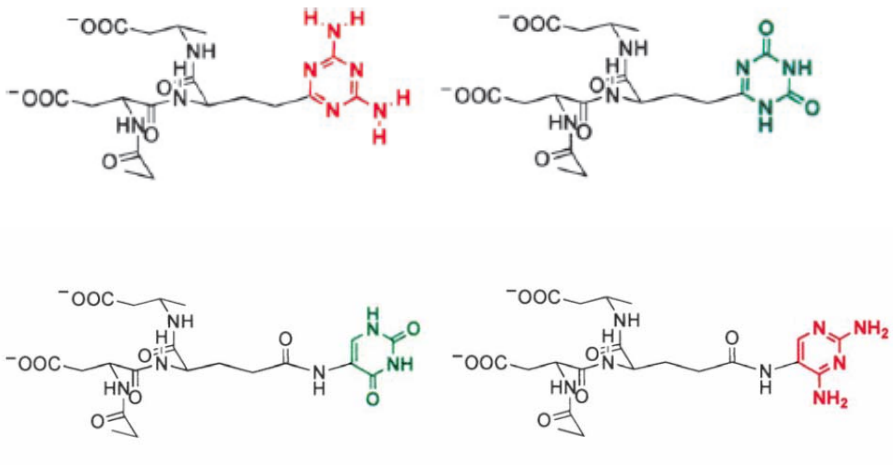
Current Literature Meeting

Mapping the Landscape of Potentially Primordial Informational Oligomers



Leading References:

A. Eschenmoser *Angew. Chem. Int. Ed.*, EarlyView

DOI: 10.1002/anie.200603207

10.1002/anie.200603209

Maciej A. Walczak

November 25, 2006

Thinking about Life…

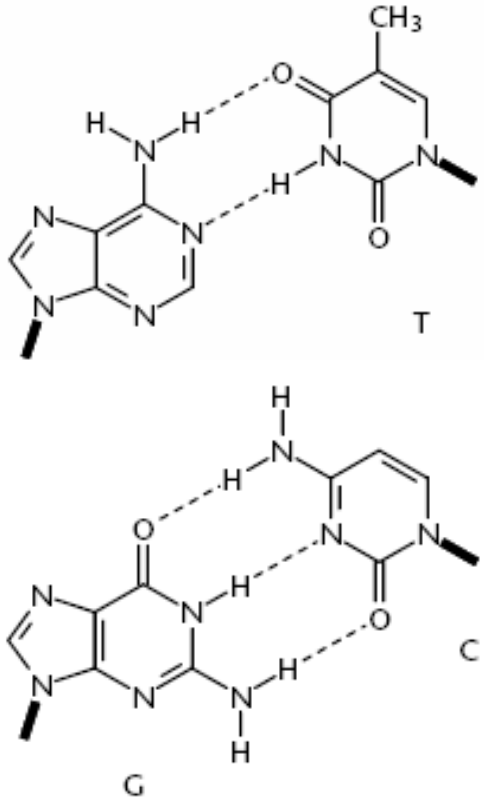
On Earth, live probably appeared 4 billion years ago.

Primitive Earth's atmosphere consisted of simple volatile molecules (CO_2, N_2, H_2O).

Miller's study in 1953 demonstrated experimentally possibility of formation of some amino acids from these substrates using electric discharges.

Many experimental studies convincingly showed a catalytic activity of RNA (ribozyme as the first living organism?).

It is reasonable to speculate that some simpler molecules capable of storage and replication of biological information preceded the "RNA world".



Watson-Crick Pairing

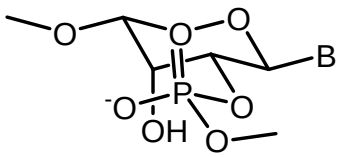
Chemical Etiology

Pentopyranosyl (2'-4') oligonucleotides form one of the strongest oligonucleotide-based binding systems.

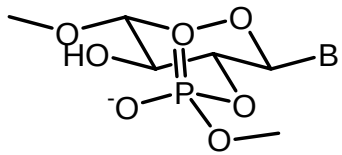
Extensive studies showed that insertion of 2'-OH imposes significant steric hindrance on the oligonucleotide backbone.

TNAs ((L)-α-threofuranosyl nucleic acids) contain 4-carbon backbone are capable of binding to natural RNA and DNA

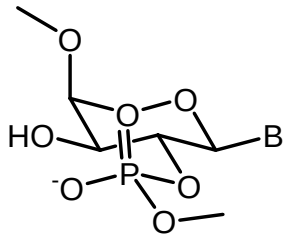
Optimization not maximization might be a determinant of RNA's selection by the Nature



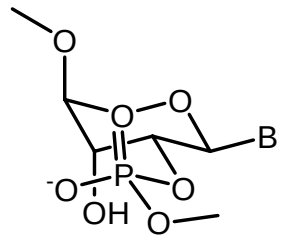
D-β-RIBO-pyranosyl



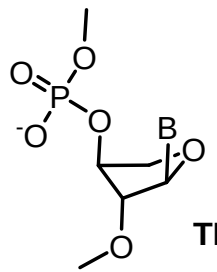
D-β-XYLO-pyranosyl



L-α-LYXO-pyranosyl



L-α-ARABINO-pyranosyl



TNA

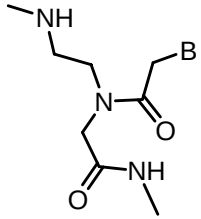
Science **1999**, *283*, 699
Science **1999**, *284*, 2118
Science **2000**, *290*, 1347

Searching for Alternative Backbones - PNA

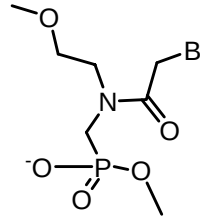
PNA adopt helical structure with a large pitch (18b) but is able to adjust it structure to DNA/RNA backbone in a triplex complex

Ability of PNA to bind to native DNA and RNA made them interesting anlytical tools

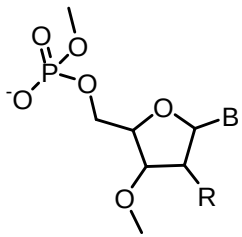
PNA's are very efficient in vitro inhibitors of mRNA (antisense therapy) and bind as well to dsDNA (antigene therapy)



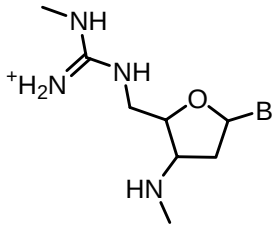
PNA



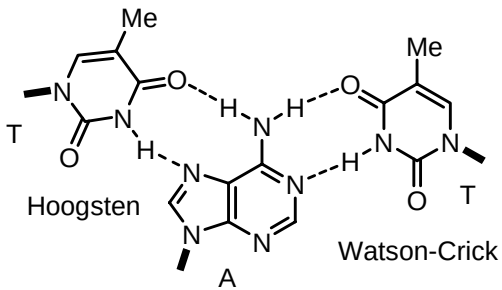
PPNA

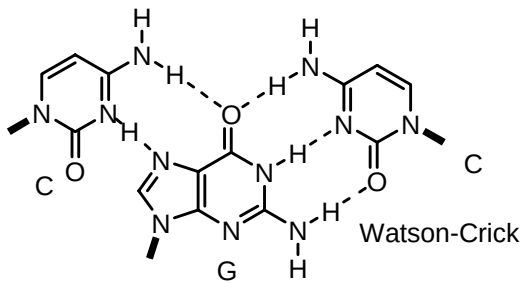


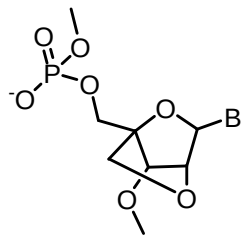
2'-ODN



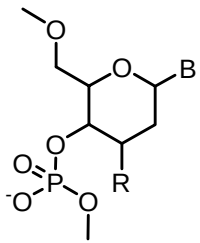
DNG



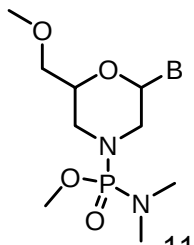




LNA



HNA



Morpholino

Acc. Chem. Res. **2005**, *38*, 404

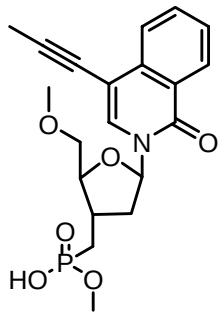
Acc. Chem. Res. **1999**, *32*, 624

Purine and Purimidine Variations

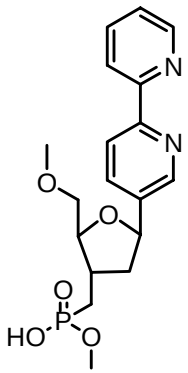
Modification of bases is a major chemical mutation studied

Rationale of this approach was/is to develop nucleoside substituents as potential anti-cancer agents.

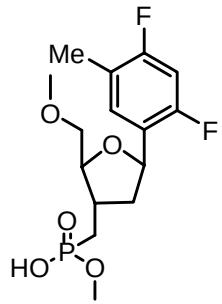
Fundamental studies on the physical properties of nucleic acids or development of practical analytical tools were also the motivation of these studies.



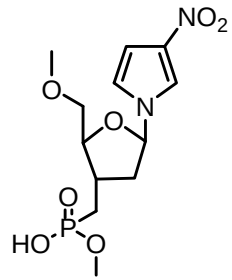
Stabilization by Hydrophobic Interactions
J. Am. Chem. Soc. **1999**, *121*, 11585



Metal Binding Oligonucleotide



Dipole Complementarity



Increased Stacking Ability

Kool *Acc. Chem. Res.* **2002**, *35*, 936

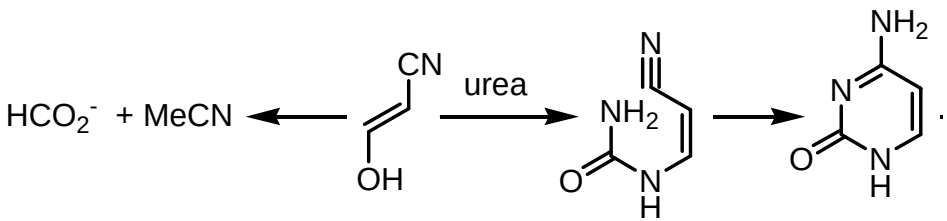
HCN – A Common Precursor to Purines and Pyrimidines

Various experiments show that common nucleotide bases can be obtained by polymerization of HCN

Incorporaton of oxygen functionalities results f hydrolysis of amino derivatives

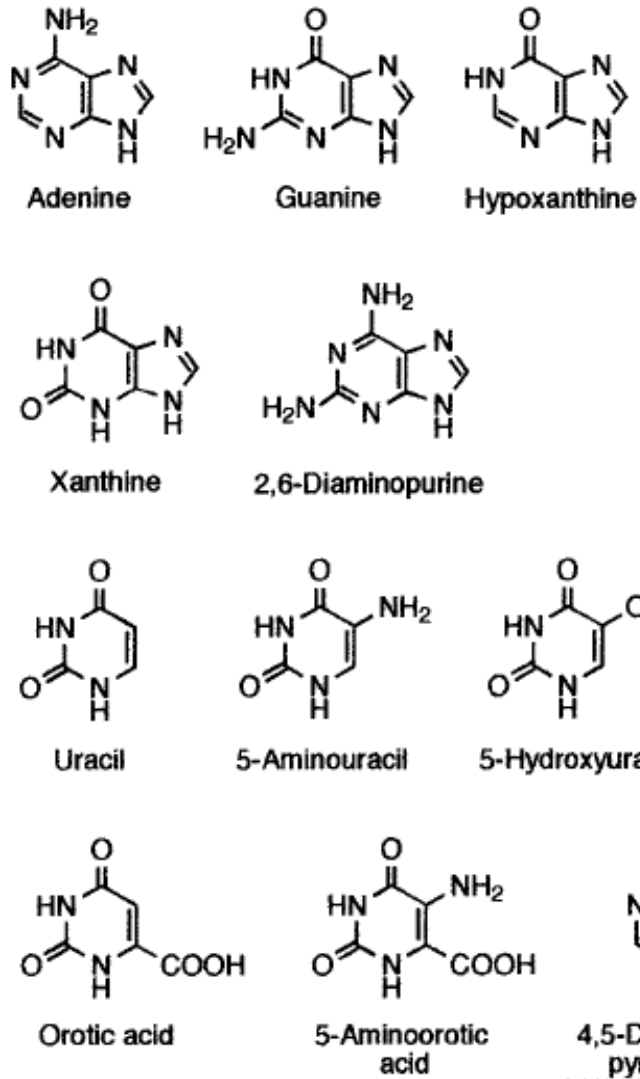
Importantly, formation of pyrimidines require reductive step whereas purines and 5-aminopyrimidine do not.

Other small molecules such as cyanoacetylene (urea are also plausible building bocks in the synthesis of uracil

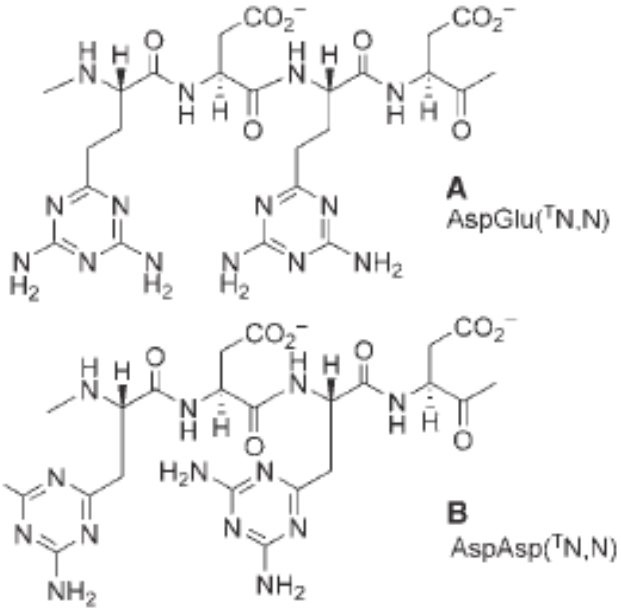


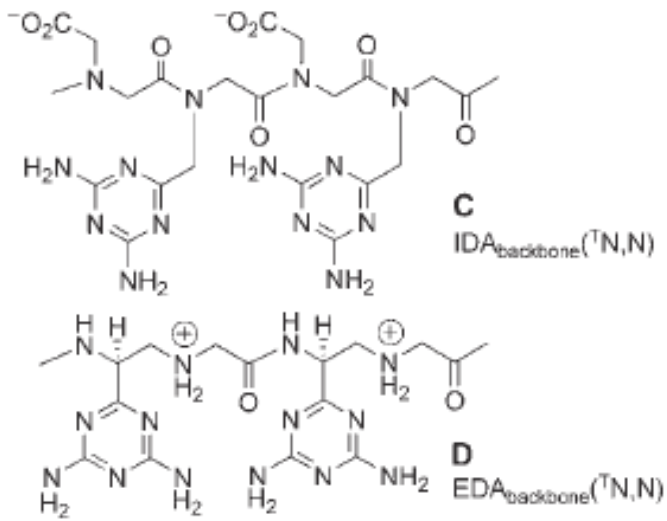
Miller *Nature* **1995**, *375*, 772

Common Products of Oligomerization of HCN



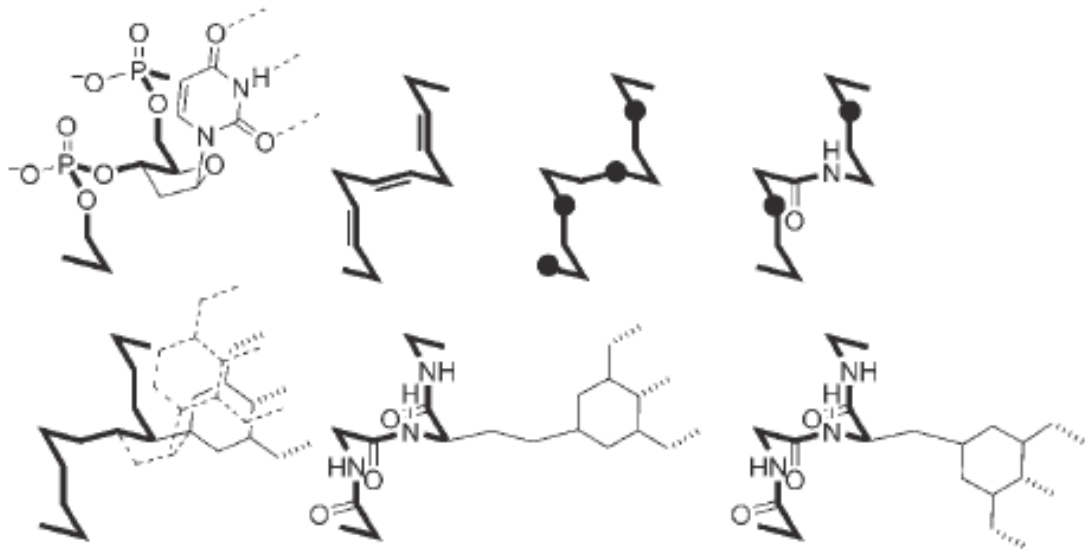
Experiment Design



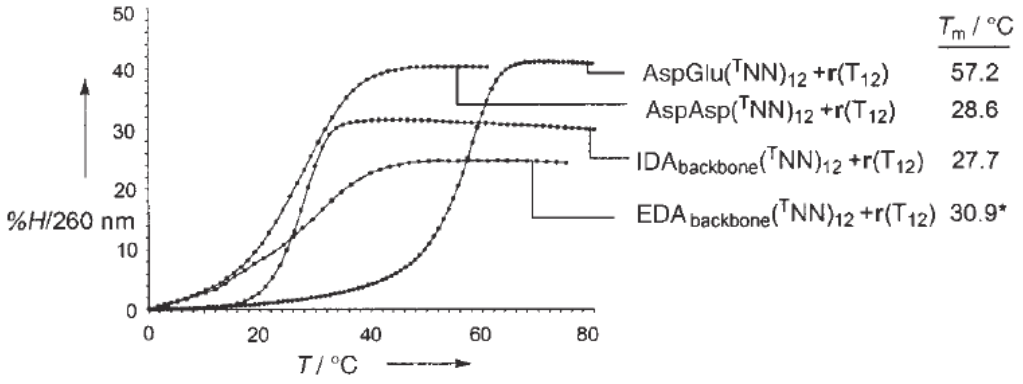


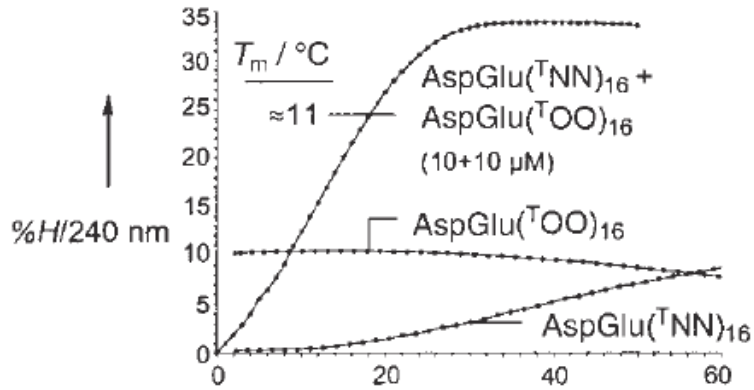
The oligomer backbone is based on natural amino acids (Asp, Glu) as well as on iminodiacetic acid and ethyldiamine

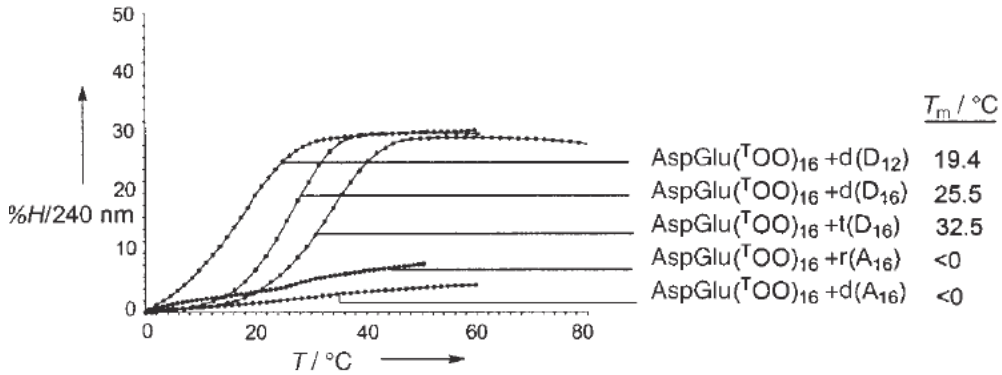
Synthesis of these macromolecules was carried out using standard peptide coupling methodology



Duplex Formation of Triazine-Tagged Oligomers

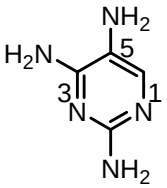




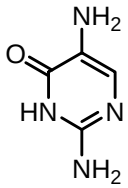


Diaminotriazine oligomer binds to RNA but, however, replacement of amino groups with OH leads to significantly lower T_m

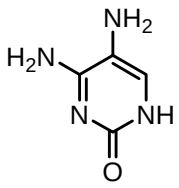
Alternative Pyrimidine Pairing



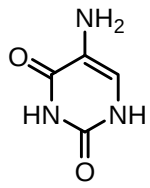
(^{AP}N,N)



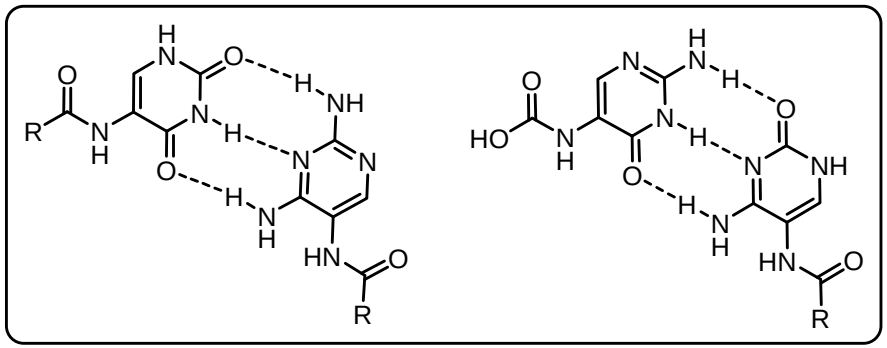
(^{AP}N,O)
or tautomer

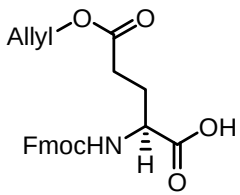


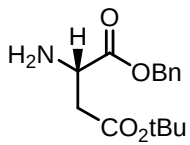
(^{AP}O,N)
or tautomer



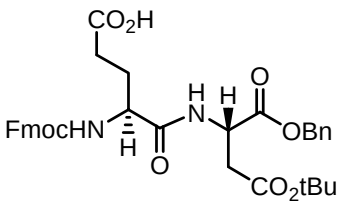
(^{AP}O,O)



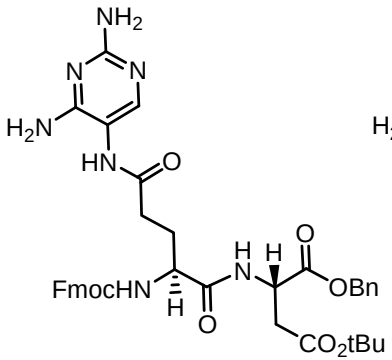




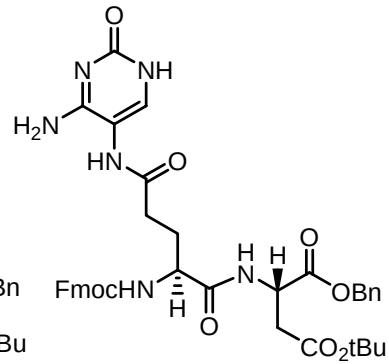
1. EDCl, HOBt, DMF, rt
2. $(PPh_3)_4Pd$, $PhSiH_3$, CH_2Cl_2, rt, 5h, 67%



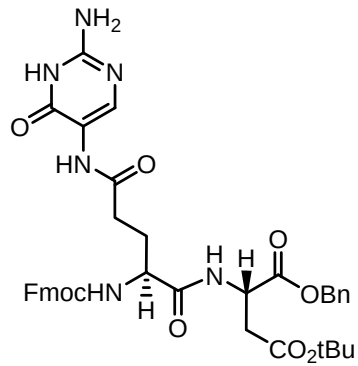
HBTU, HOBt, DMF
aminopyridine, rt



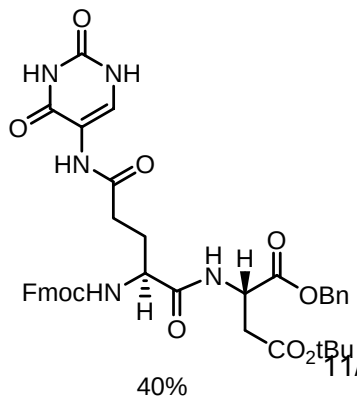
60%



32%

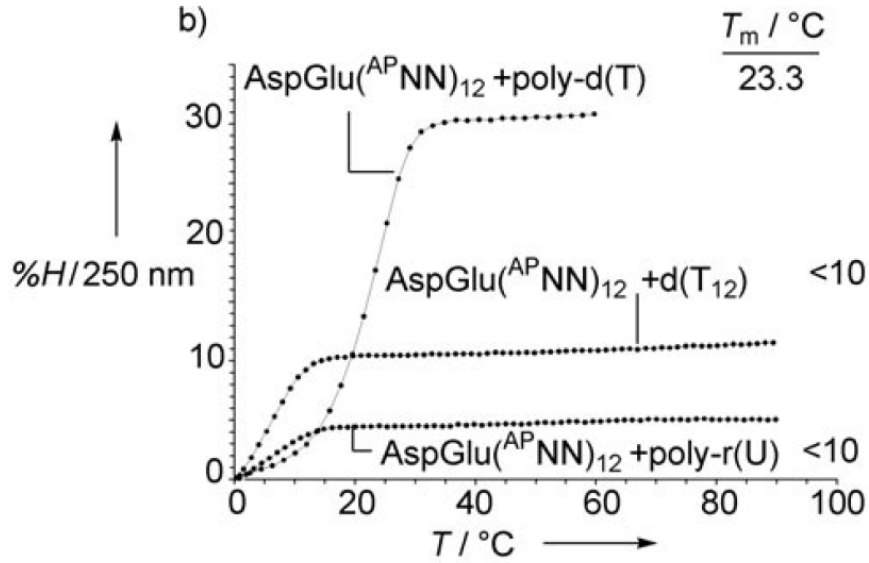


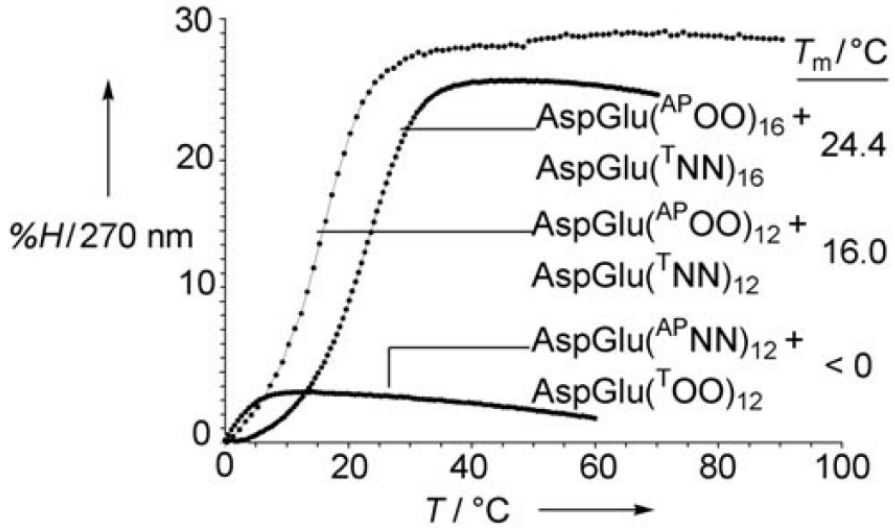
62%

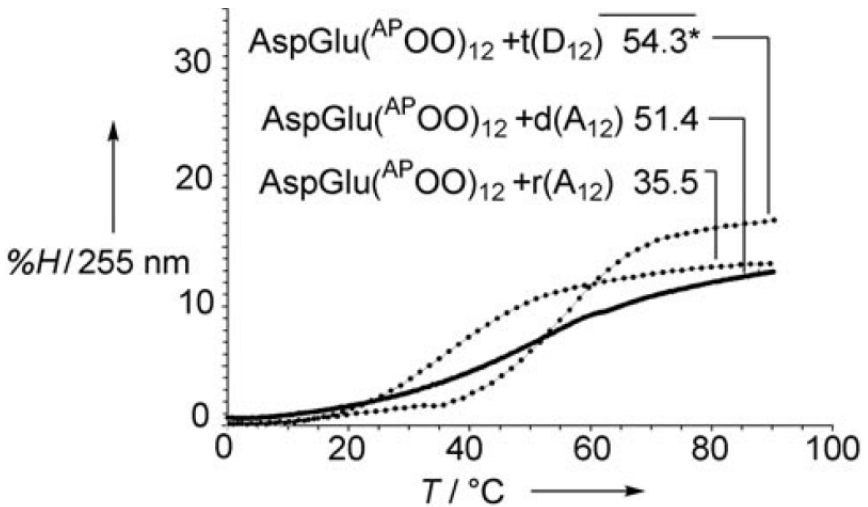


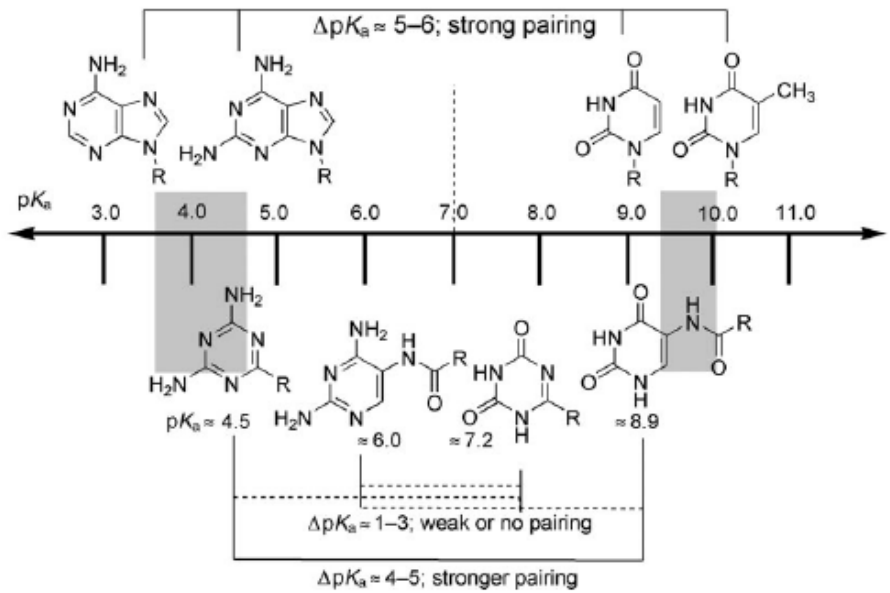
40%

Pairing Experiments









Summary

A variety of experiments shows a robustness of Watson-Crick pairing in different backbone scaffolds.

An optimal choice of pyrimidine bases (U, T, C) may be a consequence of chemical not biological selection criteria (synthetic vs. functional selection).

A comprehensive screening of potential candidates of primitive nucleic acids may not only explain why and how simple life emerged, but can establish a ground for the realization that matter can lead to life.