Nucleic Acids
Why do I care?

Nucleic Acids
Why do I care?

Proteins do everything, right?

Nucleic Acids
Why do I care?

Proteins do everything, right?

revolutions at the turn of the century

opportunities for the 21st century

In the beginning…

DNA

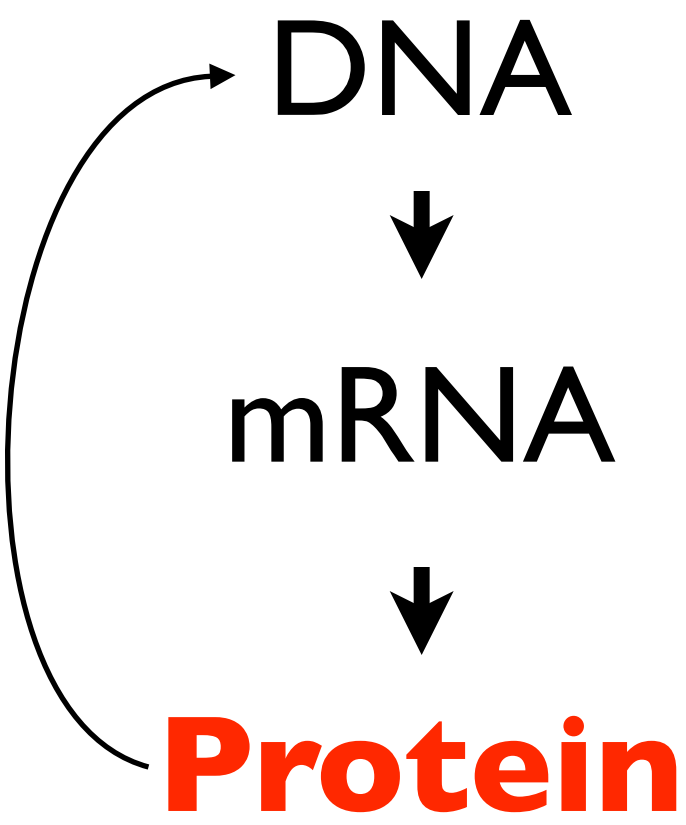
↓

mRNA

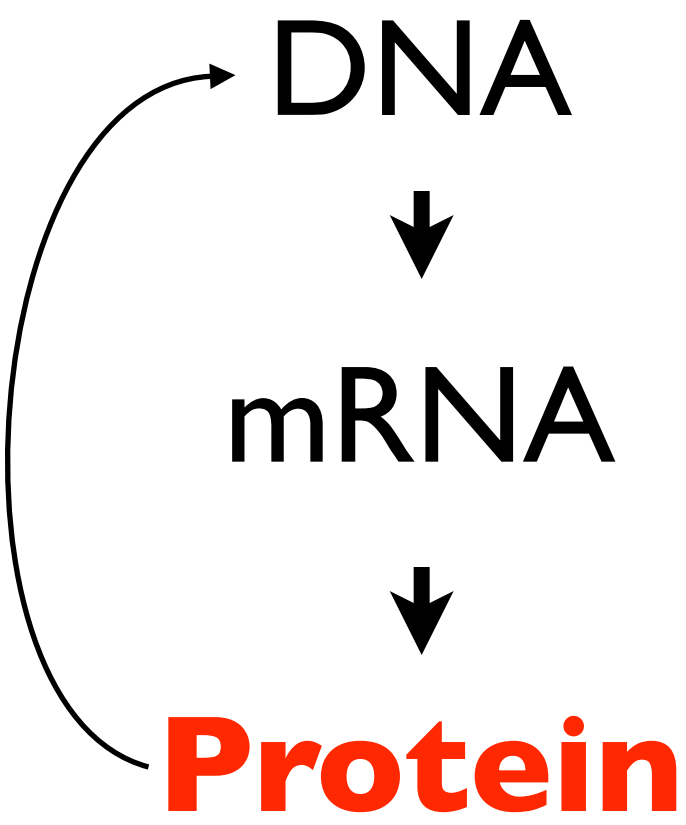
↓

Protein

In the beginning…

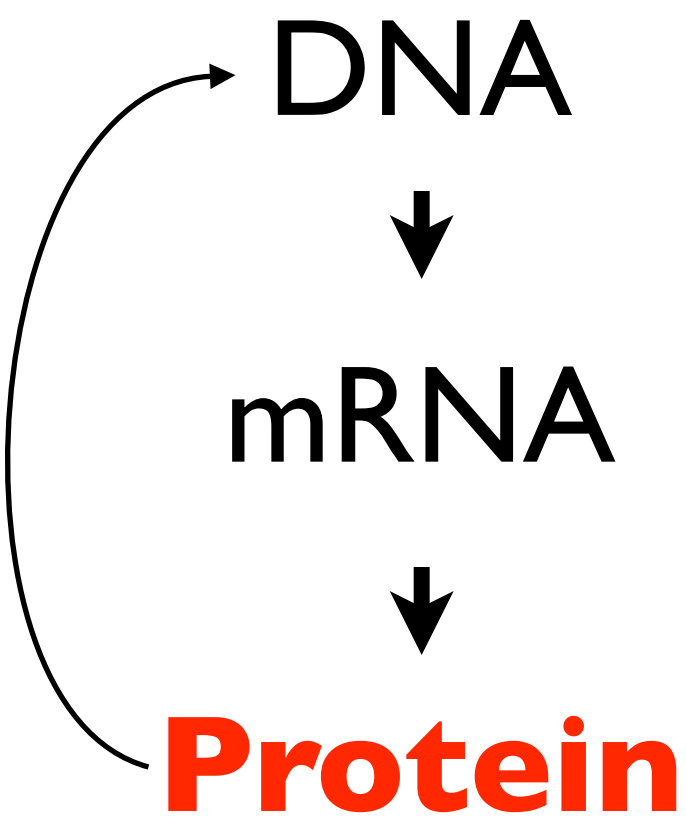


In the beginning…



Archival information storage

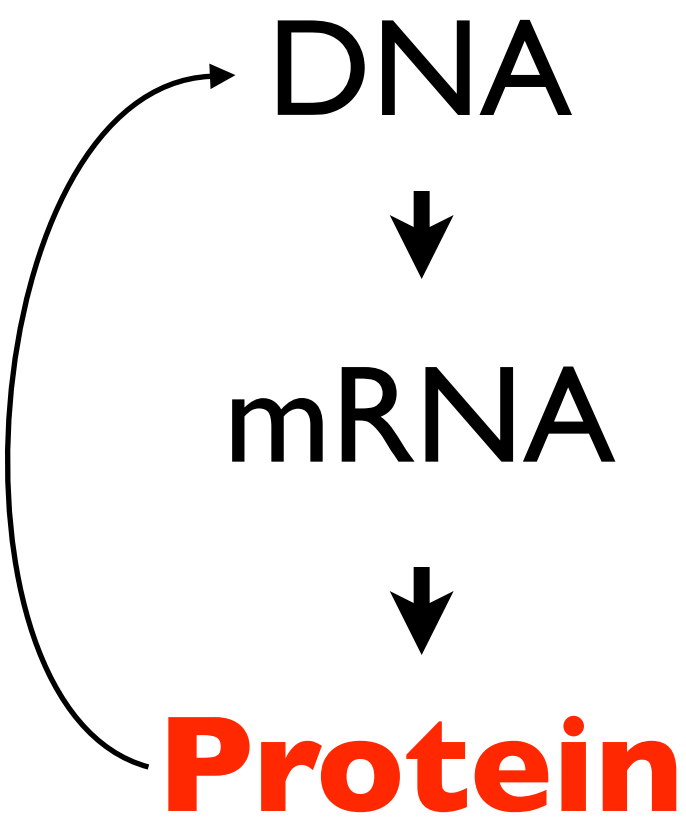
In the beginning…



Archival information storage

Transient information storage

In the beginning…

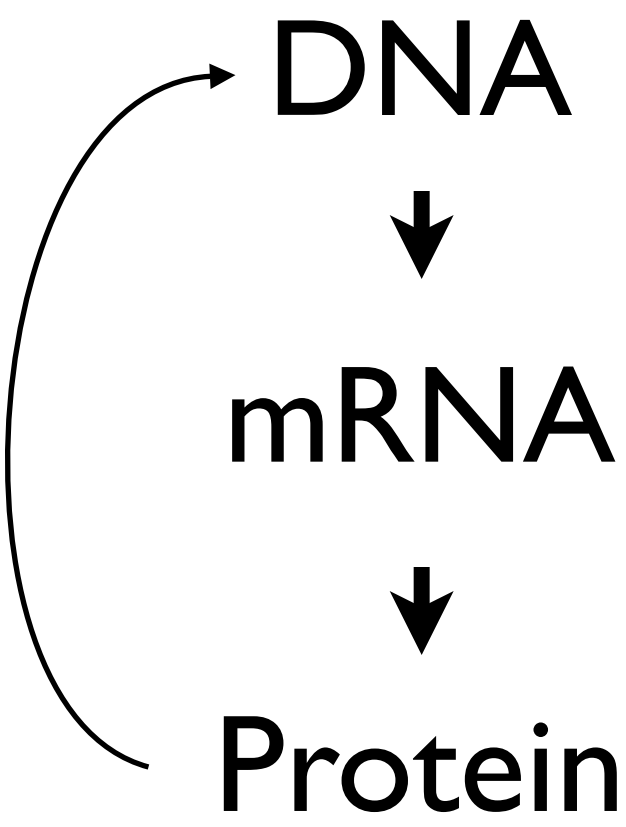


Archival information storage

Transient information storage

Catalysis, structure, regulation, et al.

Chicken & Egg?

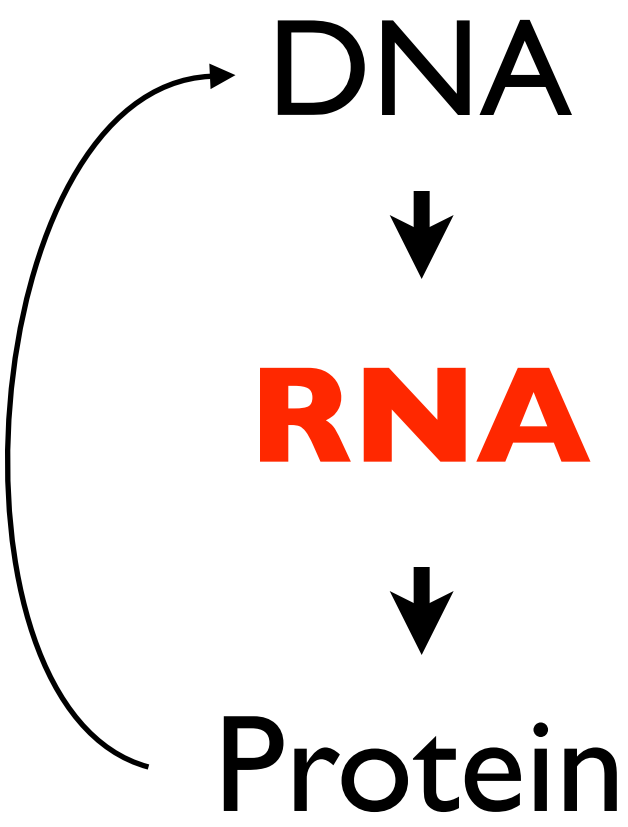


Archival information storage

Transient information storage

Catalysis, structure, regulation, et al.

RNA can do everything



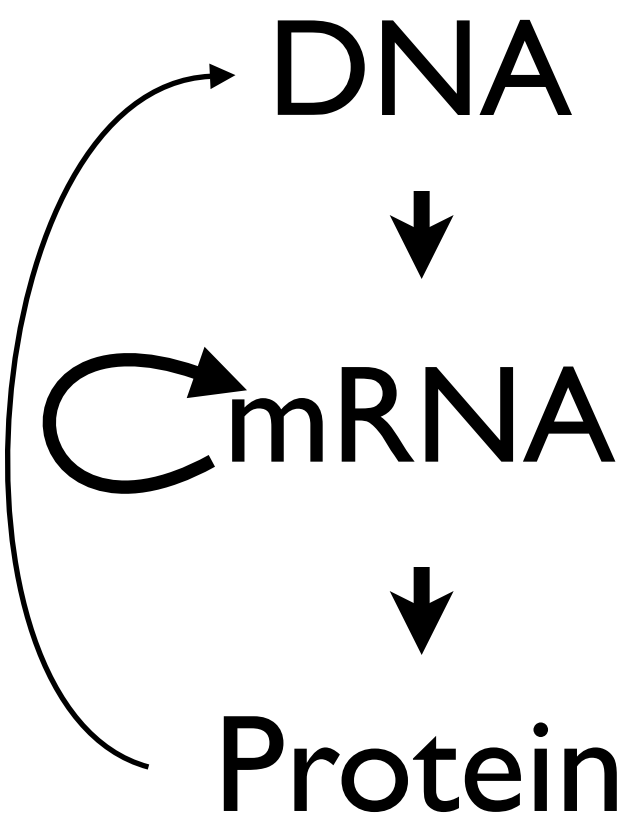
Archival information storage

Transient information storage
Catalysis!

1980-2000

Catalysis, structure, regulation, et al.

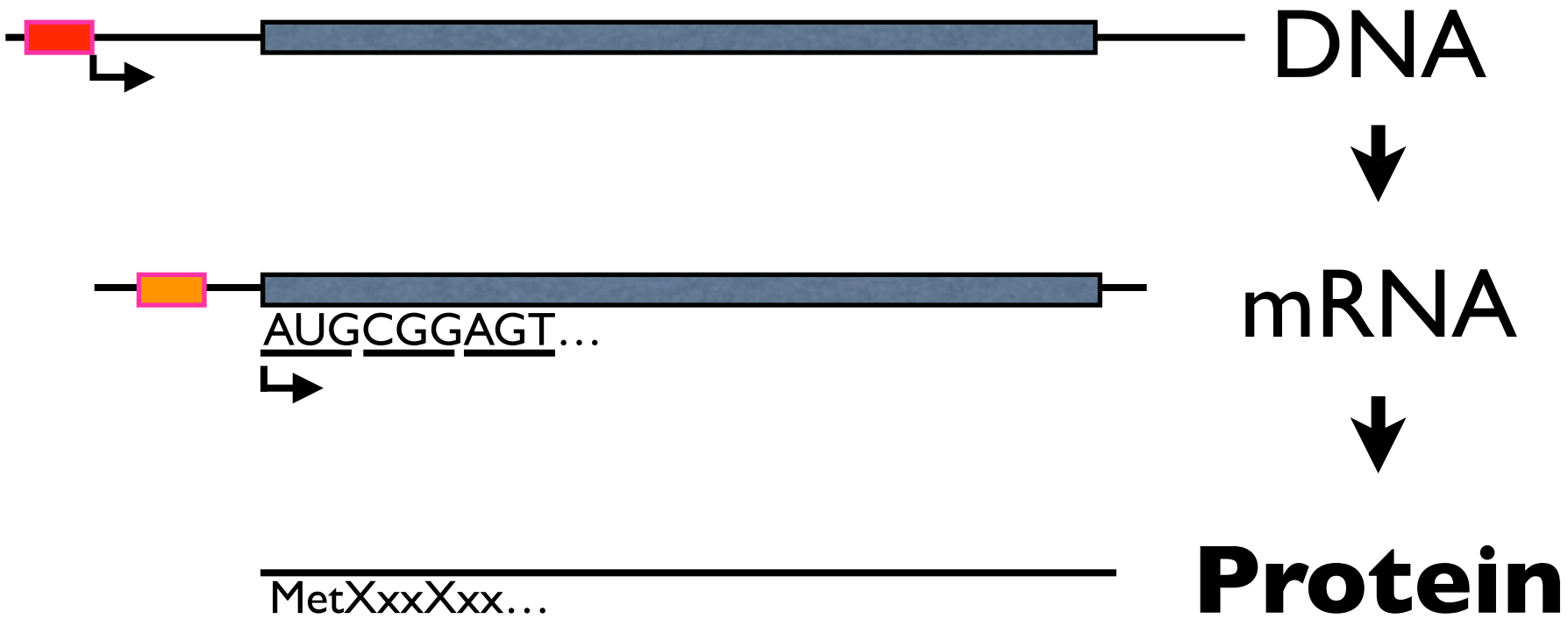
RNA - primordial molecule



So we accepted that RNA was probably the first, primitive do-everything biomolecule.

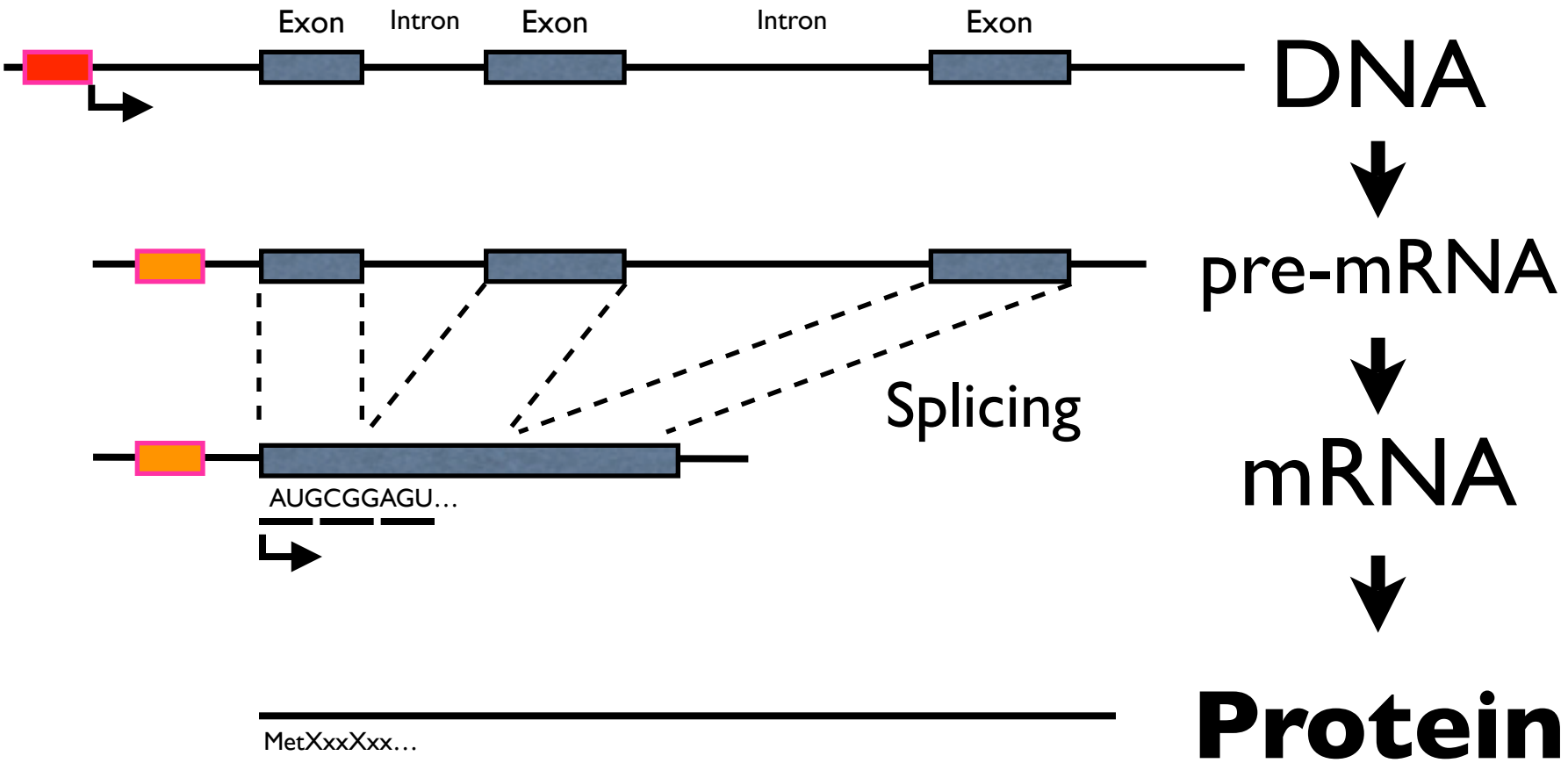
But **proteins** came along to supplant everything and make the world, evolutionarily, what it is today. All hail the protein!

Seems simple…

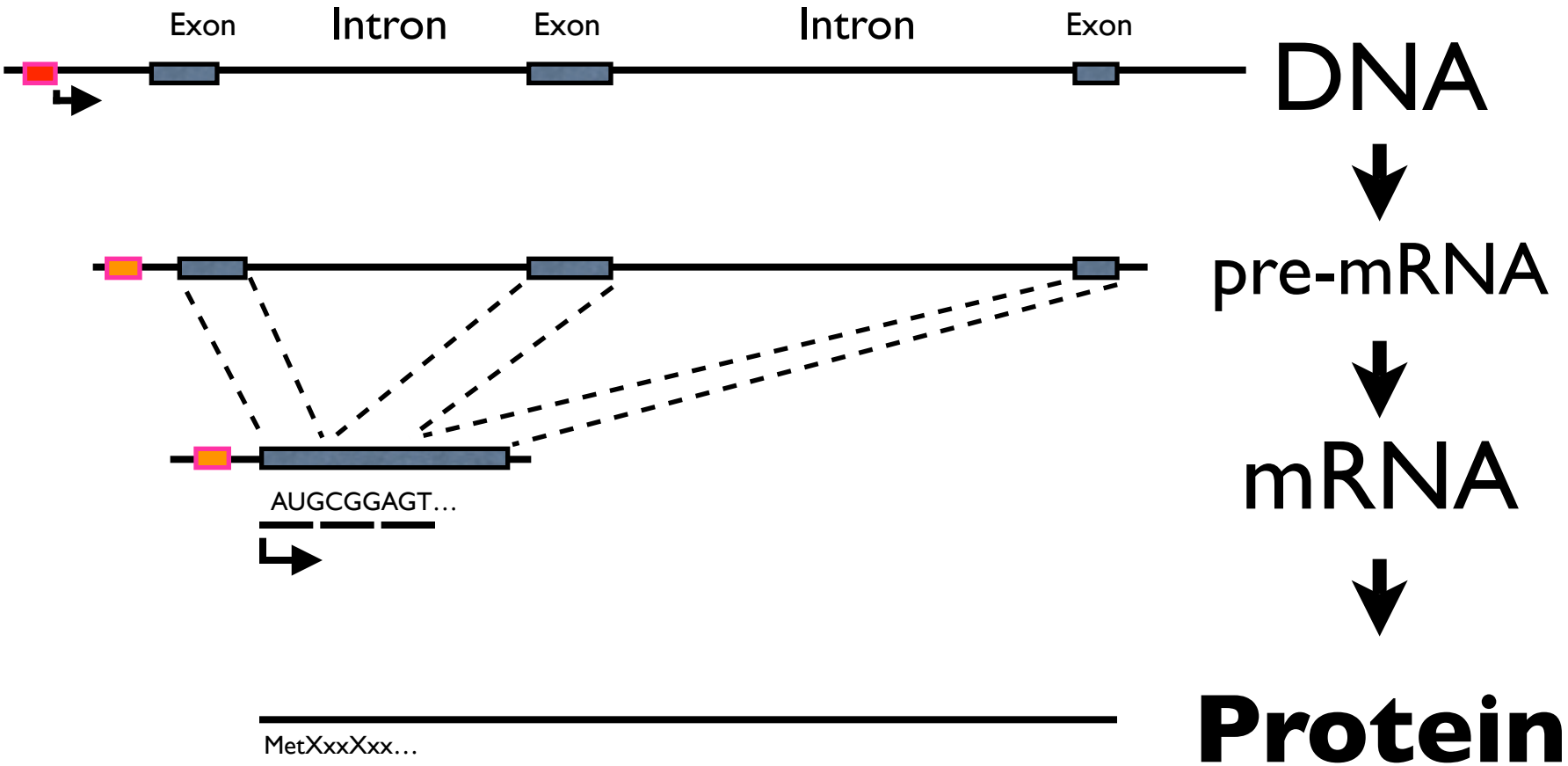


Seems simple?

Even more complicated…

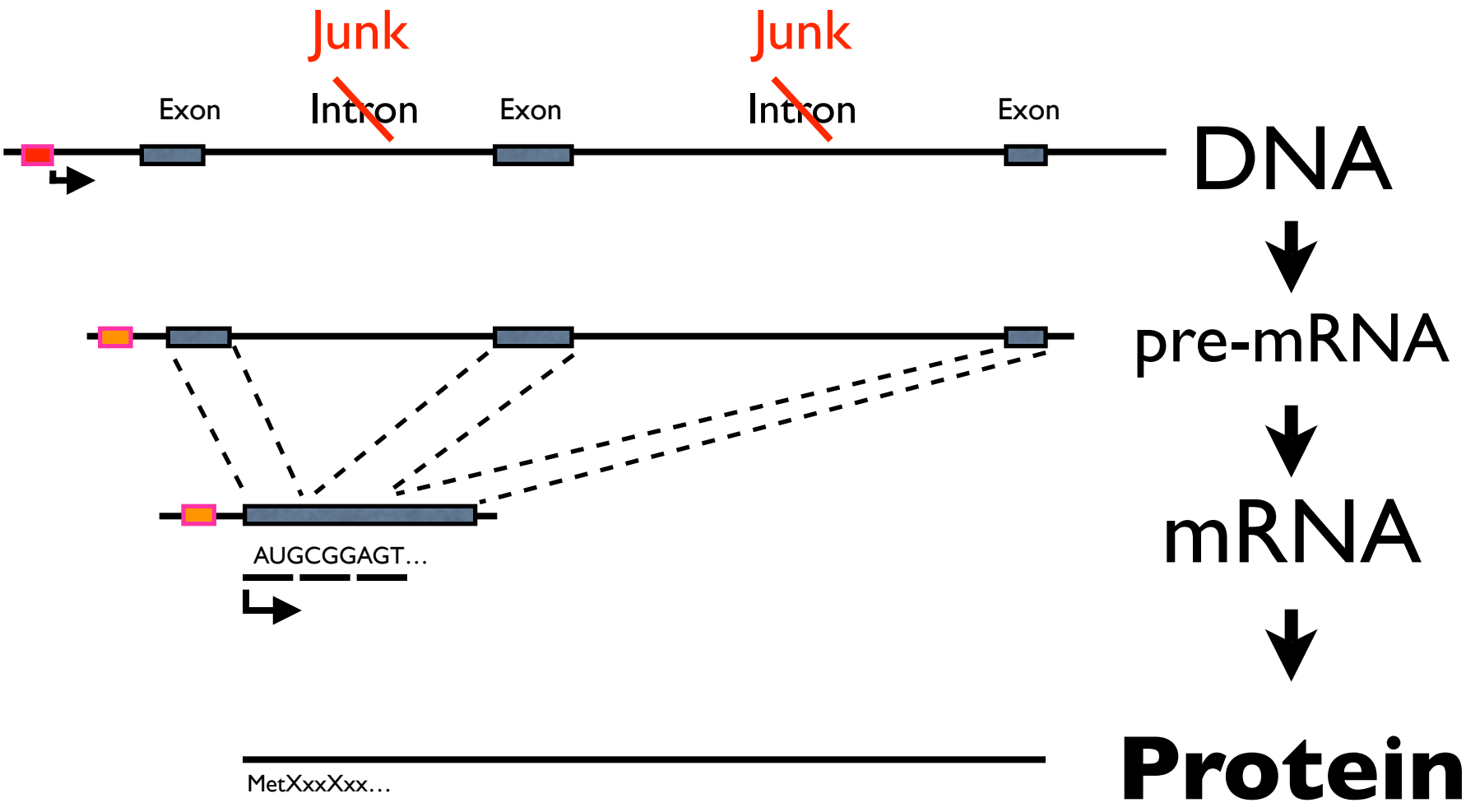


Reality…


Exon
Intron
Exon
Intron
Exon
DNA
pre-mRNA
mRNA
AUGCGGAGT…
MetXxxXxx…
Protein

Reality…

and our perception of it



Reality…

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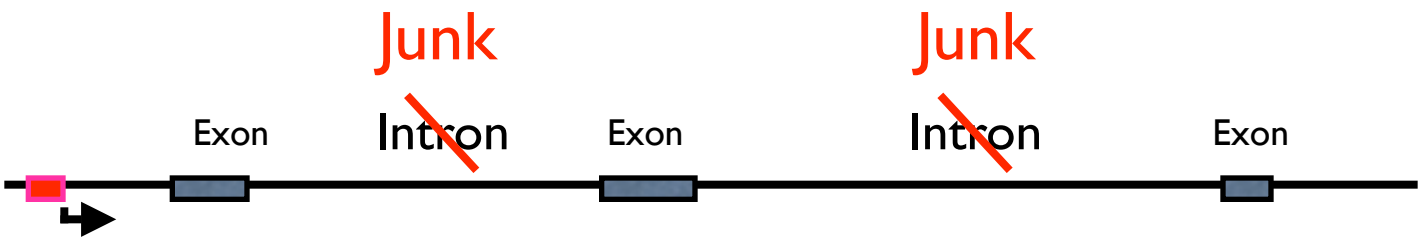
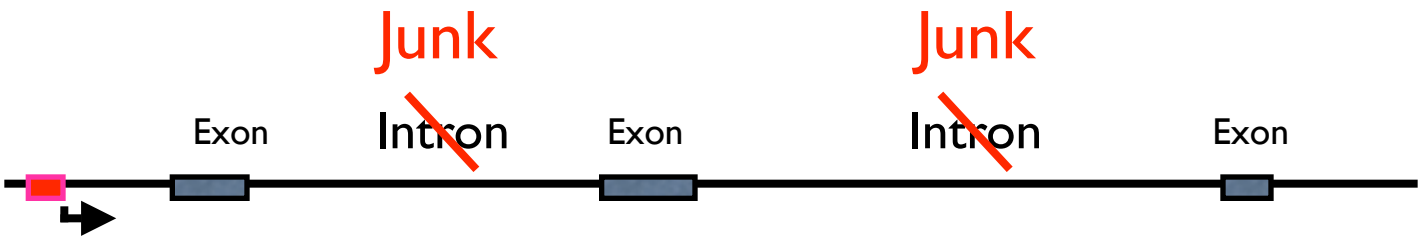


Reality…

and our perception of it



Genome project goals

Identify and characterize the proteins.
What are their structures?
What do they do?
How do they interact?

20th Century View

Polymerases

Kinases

Hydrogenases

Receptors

Oxygenases

Proteases

20th Century View

Polymerases

Kinases

Hydrogenases

Receptors

Oxygenases

Proteases

Nucleic acids → Trash

21st Century News

Genome project

Number of protein-encoding genes in the human genome: 25,000

21st Century News

Genome project

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Number of protein-encoding genes in the 1,000 cell *C elegans* genome: 19,500

21st Century News

Genome project

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Number of protein-encoding genes in the 1,000 cell *C elegans* genome: 19,500

Number of protein-encoding genes in the corn genome: 40,000

21st Century News

Genome project

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21st Century News

Genome project

Number of protein-encoding genes in the human genome: 25,000

Number of different proteins: ≫25,000

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How? RNA editing and alternative splicing

21st Century News

Genome project

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Up to 3/4 of all human genes are subject to alternative editing

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How? RNA editing and alternative splicing

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The prevalence of alternative editing appears to increase with an organism's complexity

21st Century News

Genome project

How? RNA editing and alternative splicing

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Humans have the highest number of introns per gene of any organism

21st Century News

Genome project

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21st Century News

Genome project

How? RNA editing and alternative splicing

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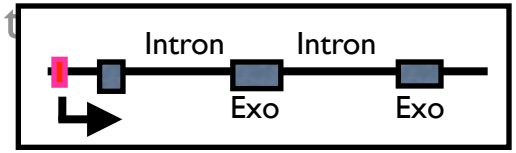

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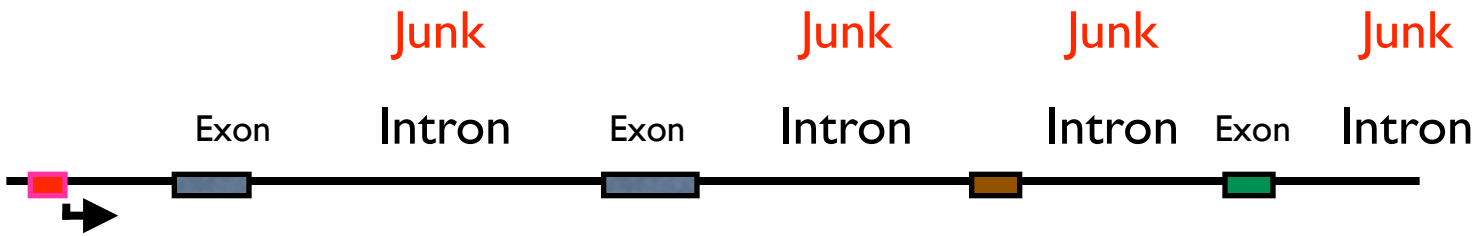
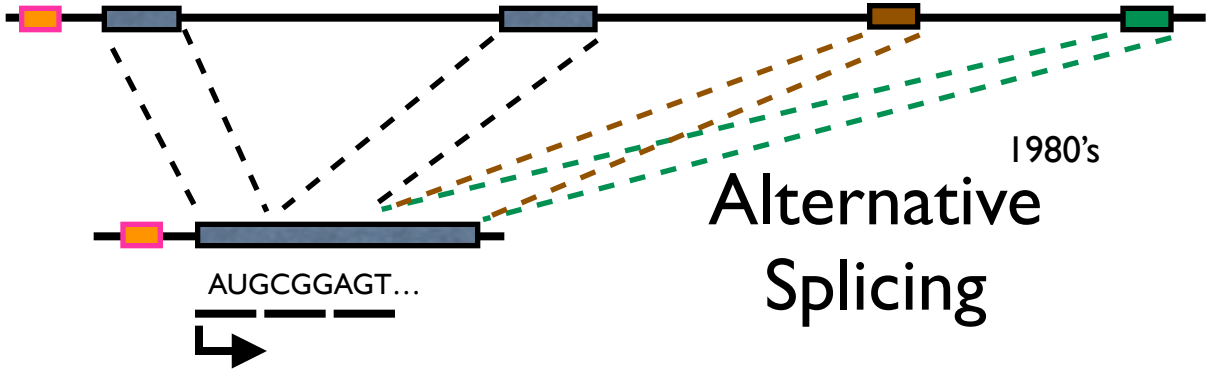
21st Century News



DNA

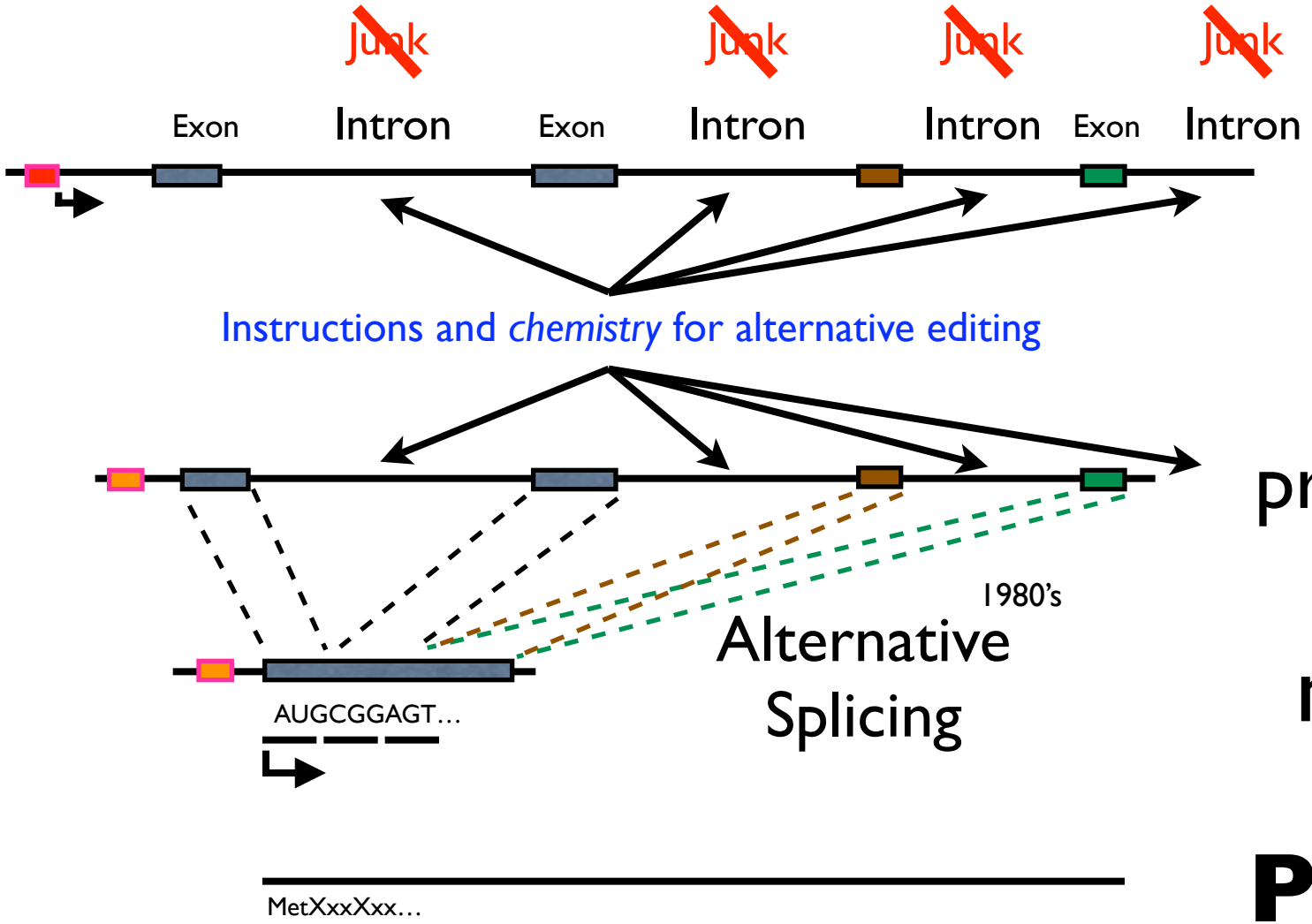


pre-mRNA

mRNA

Protein

21st Century News



Back in the lab…

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With the advent of PCR, nucleic acids have been recognized as extremely powerful combinatorial tools in the test tube

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Aptamers can be selected that bind to "your favorite molecule"

Can create riboswitches

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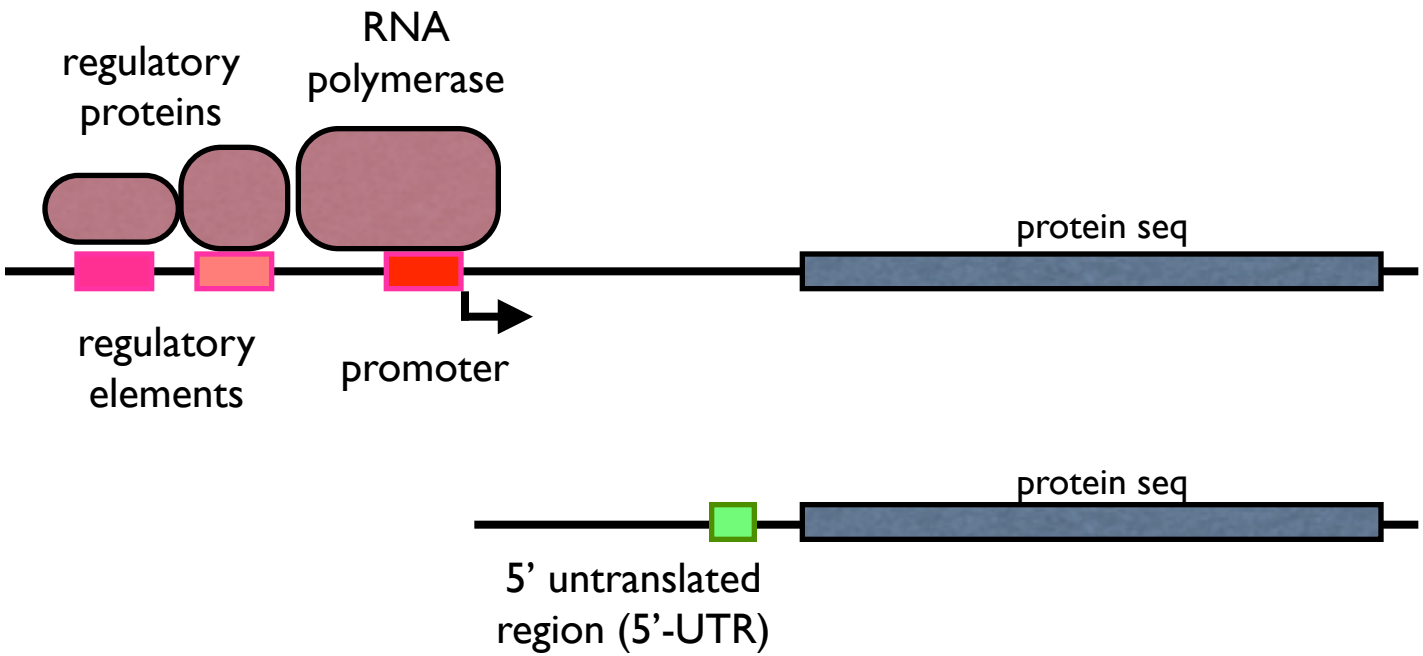
Can create riboswitches

Ron Breaker:
"if it's so easy for us, I'll bet nature exploits this"

More gene regulation



DNA

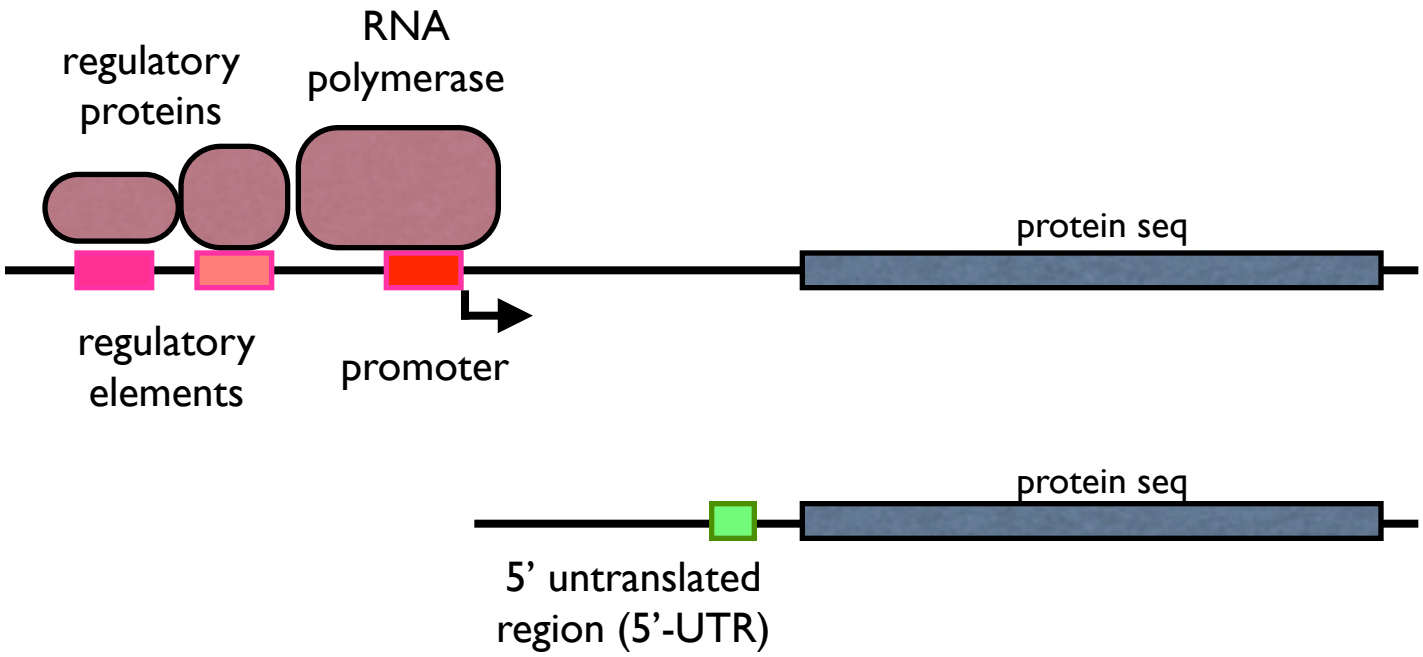
↓

mRNA

↓

Protein

More gene regulation



DNA

↓

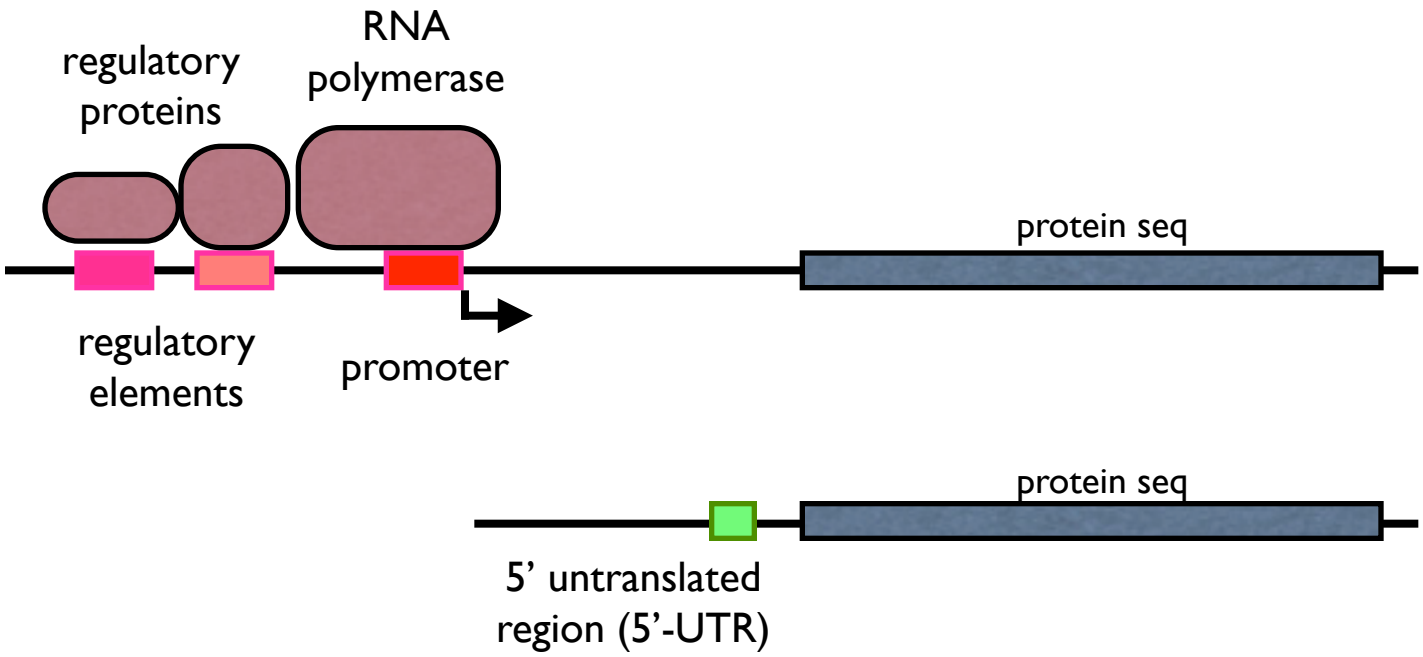
mRNA

↓

Protein

Ron: search for genes with no known protein regulator and which have a highly conserved 5' UTR

More gene regulation



DNA

↓

mRNA

↓

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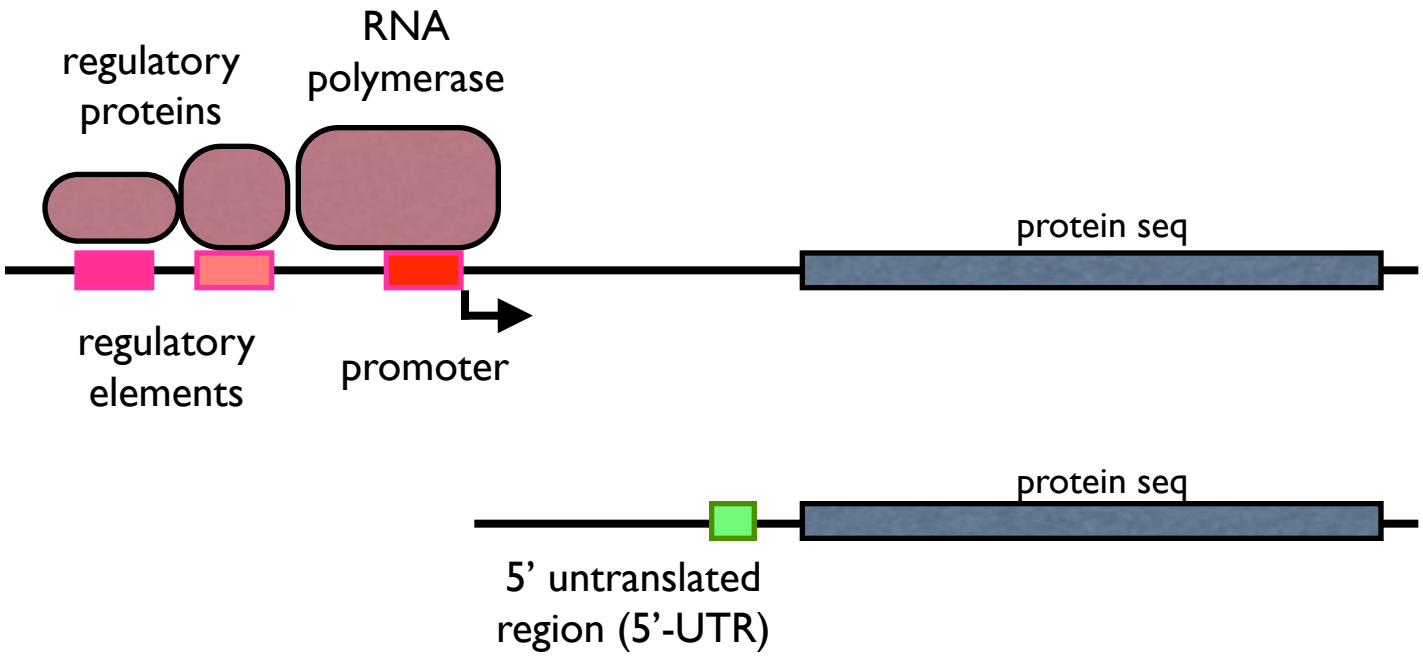
Does RNA from that conserved 5' UTR bind the product or substrate of the encoded enzyme?

More gene regulation



DNA

↓

mRNA

↓

Protein

Ron: search for genes with no known protein regulator and which have a highly conserved 5' UTR

Does RNA from that conserved 5' UTR bind the product or substrate of the encoded enzyme?

2004

↘ One week: a Nature paper!

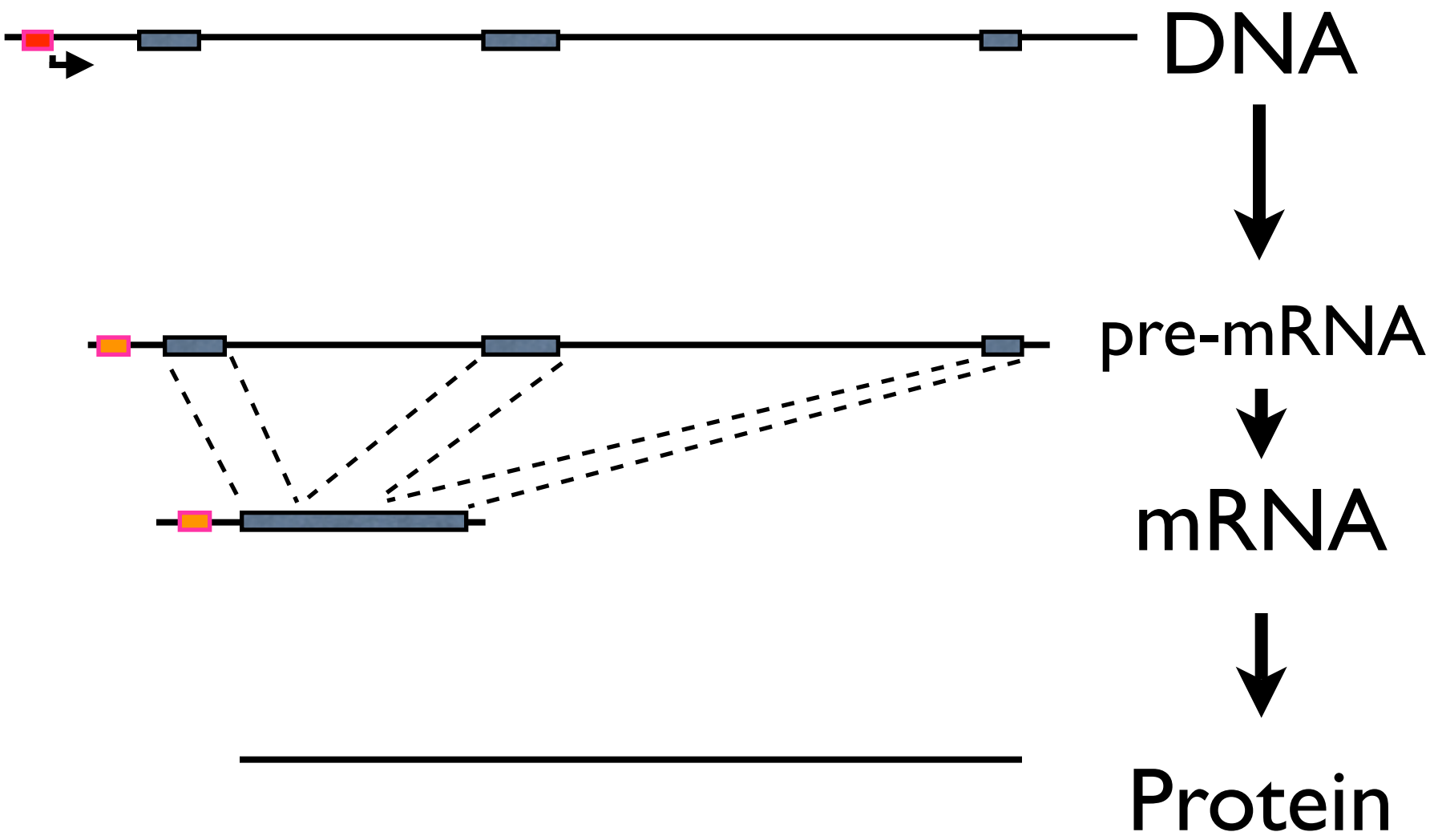
Project Encode (2007)

(More) rewriting of textbooks

June 2007, published in Nature

- Some regions of DNA far from protein-coding genes (extreme "junk?") are nevertheless highly conserved
- Most of both strands of the DNA is transcribed (far beyond that required for protein-coding genes)

21st Century Opportunities

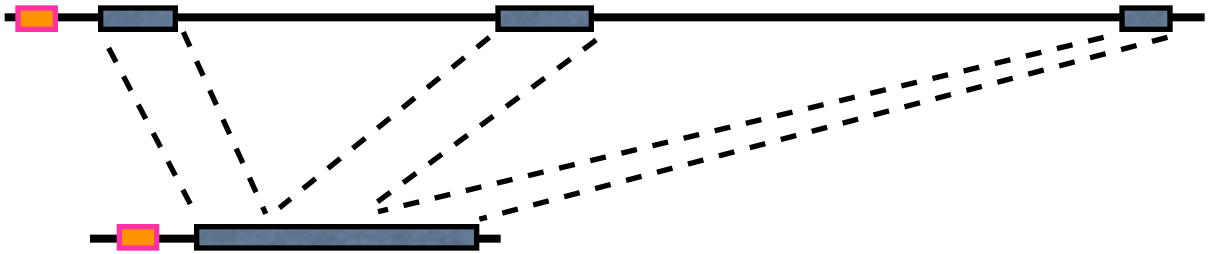


21st Century Opportunities

DNA

early '80s, but…

Alternative splicing



pre-mRNA

mRNA

Protein

21st Century Opportunities

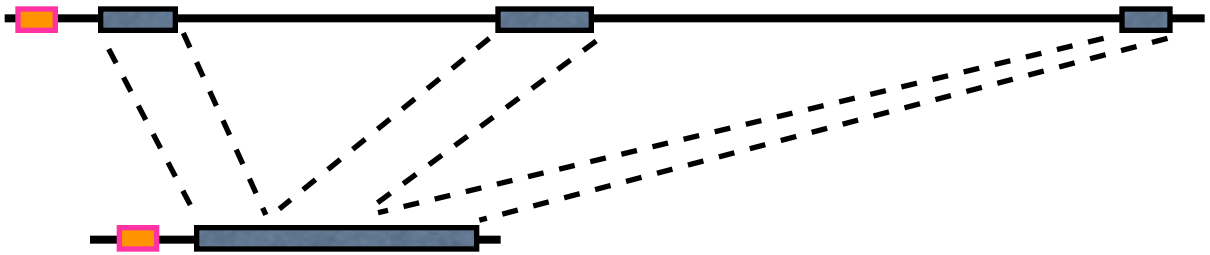
DNA

early '80s, but…

Alternative splicing

late '80s

RNA Editing



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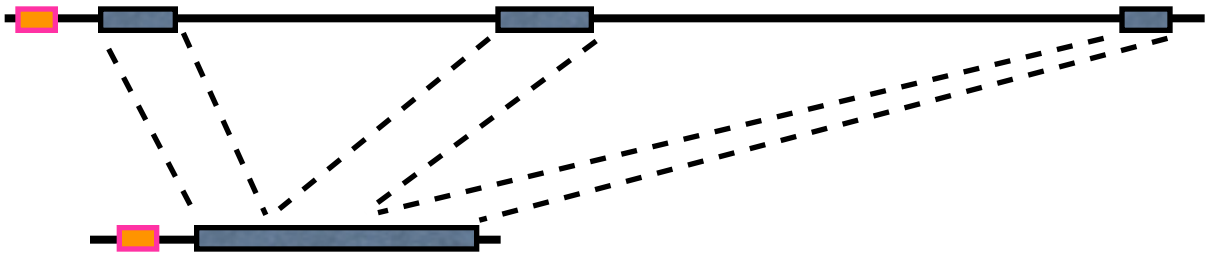


pre-mRNA

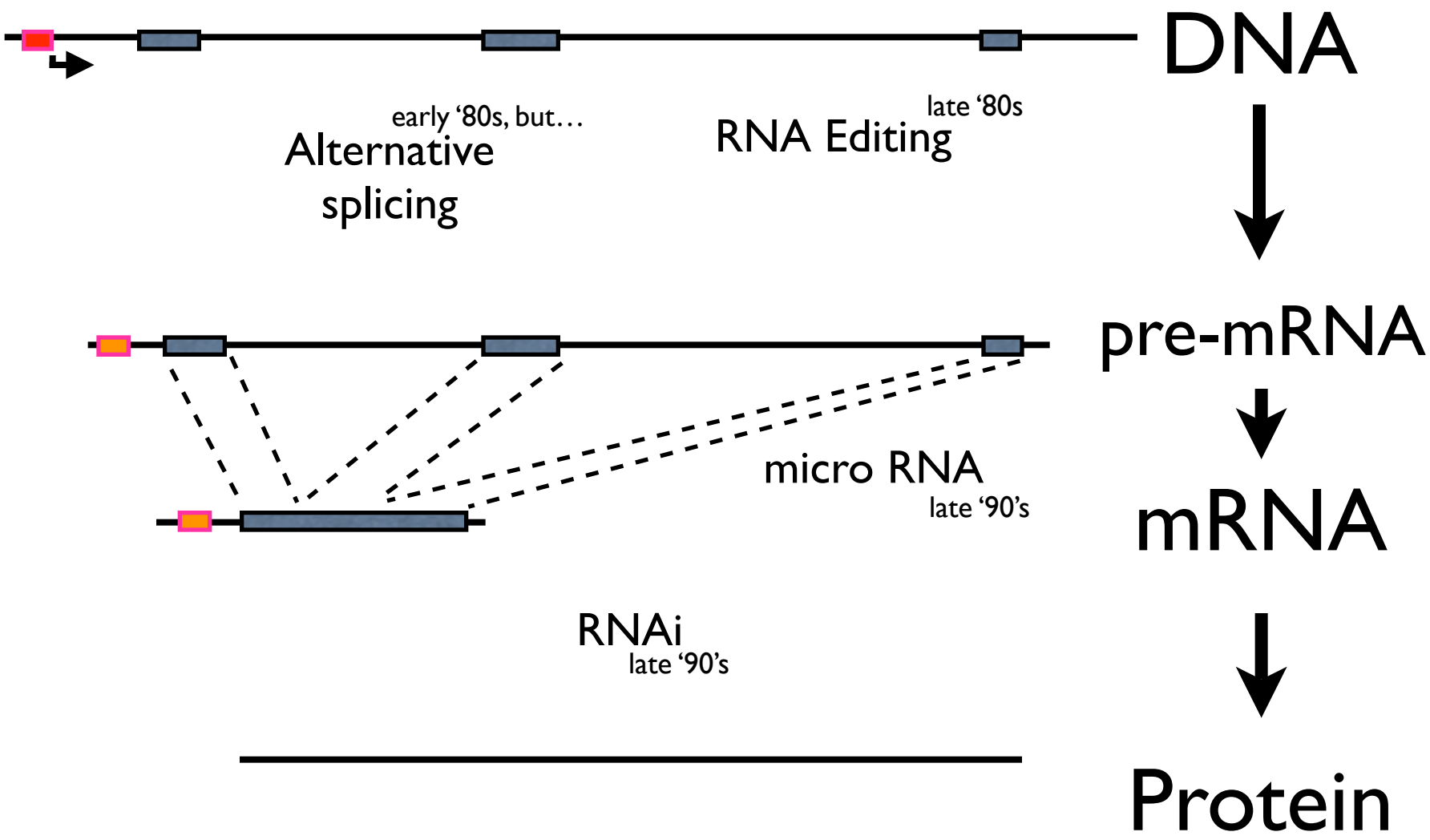
mRNA

RNAi

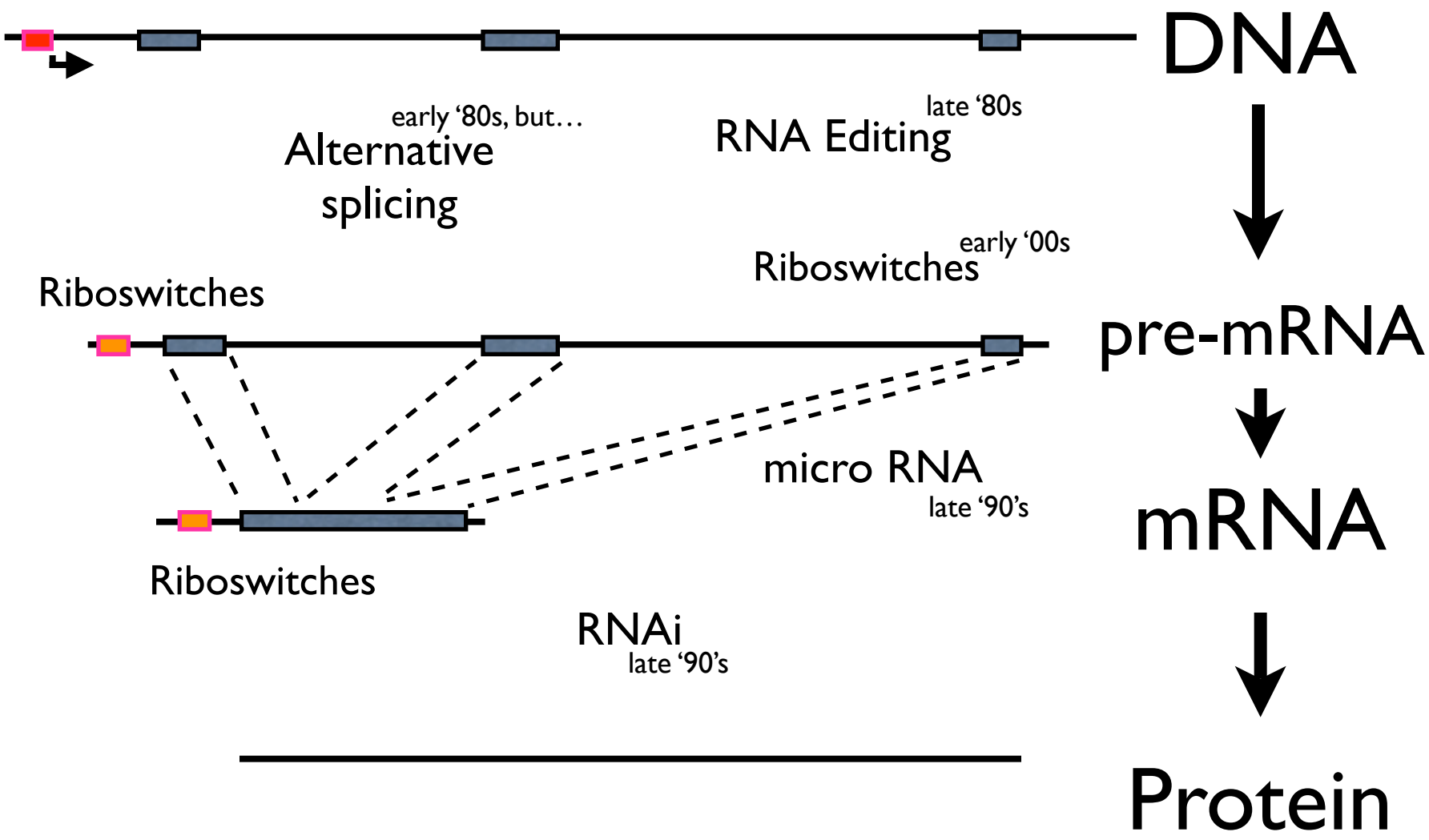
late '90's

Protein

21st Century Opportunities



21st Century Opportunities



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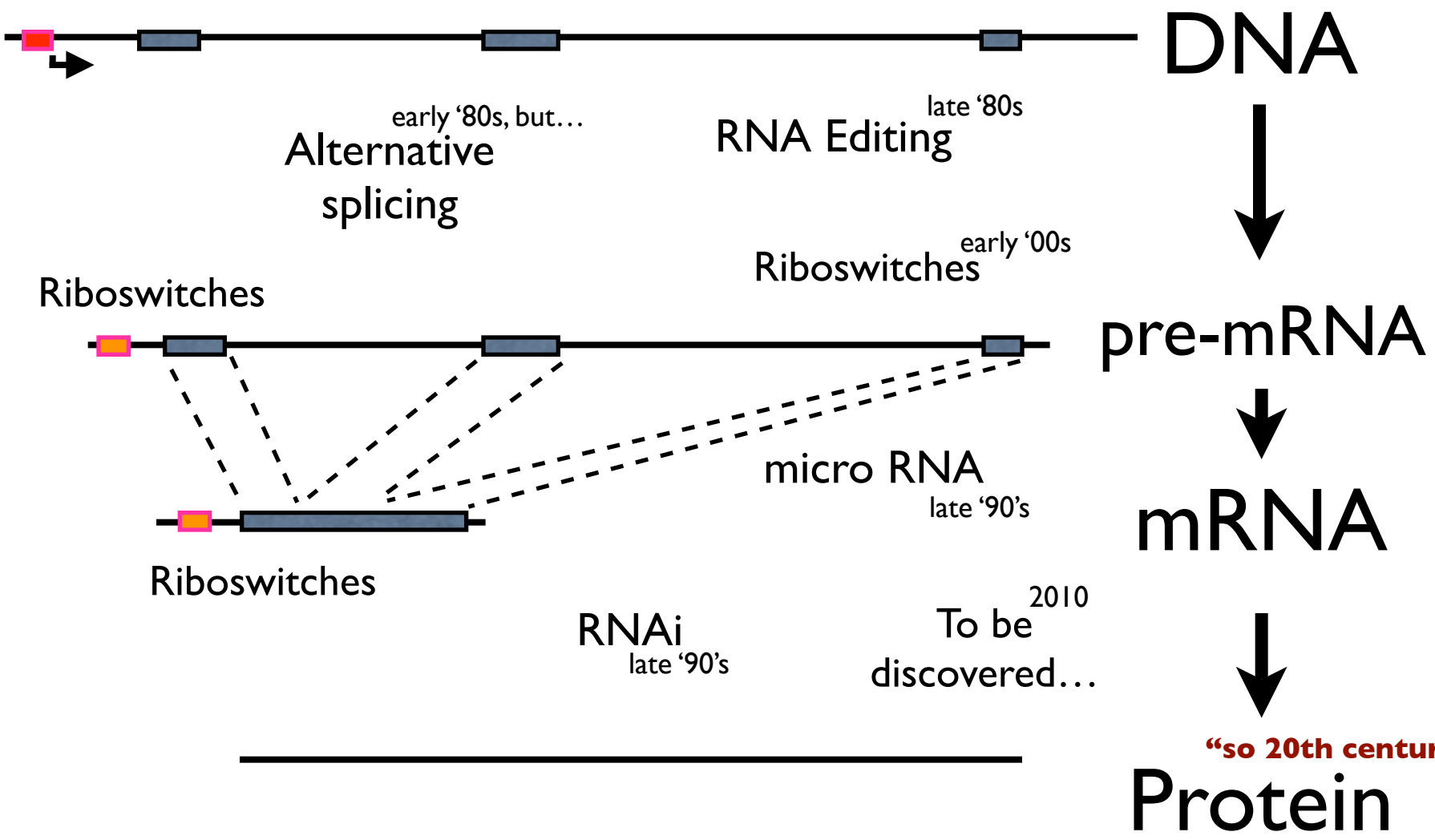
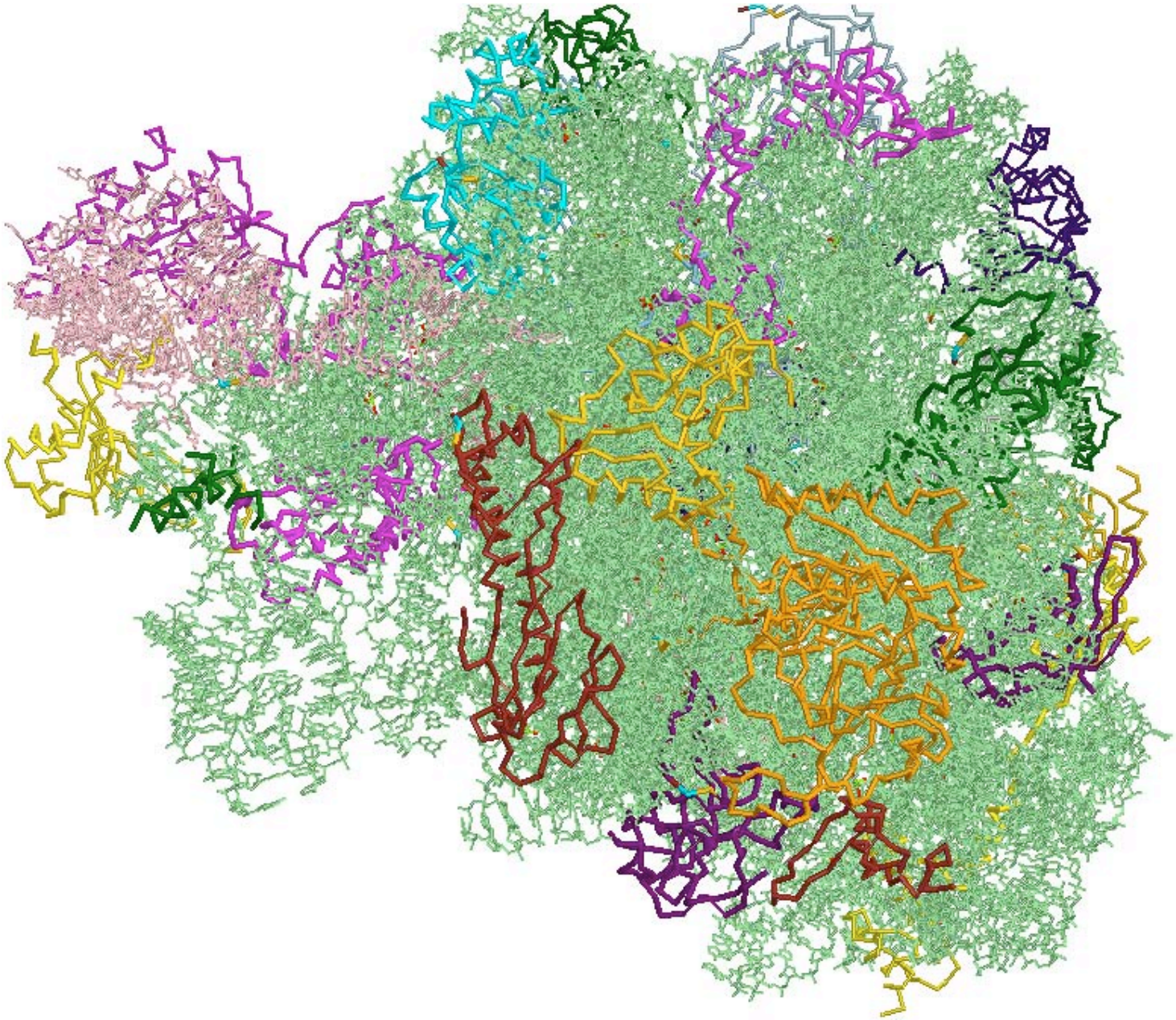


Ribosome

An RNA machine with protein cofactors



What stabilizes protein structures?

What stabilizes protein structures?

What *directs* protein structures?

The DNA Duplex

The DNA Duplex

What stabilizes the duplex?

The DNA Duplex

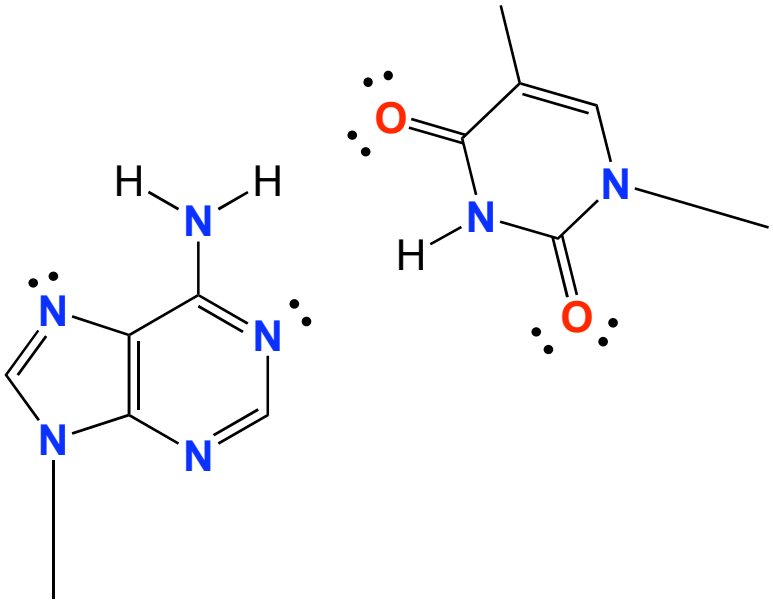
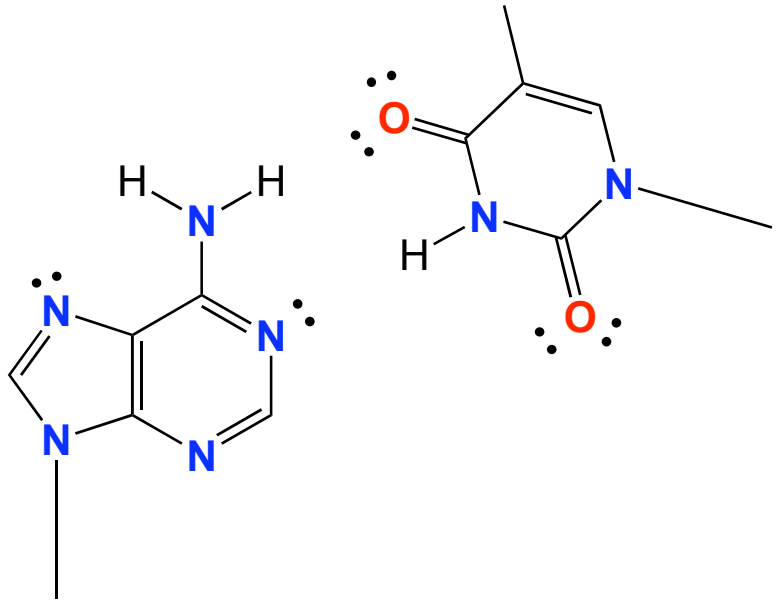
What stabilizes the duplex?

What *directs* duplex structure?

Which is most stable?

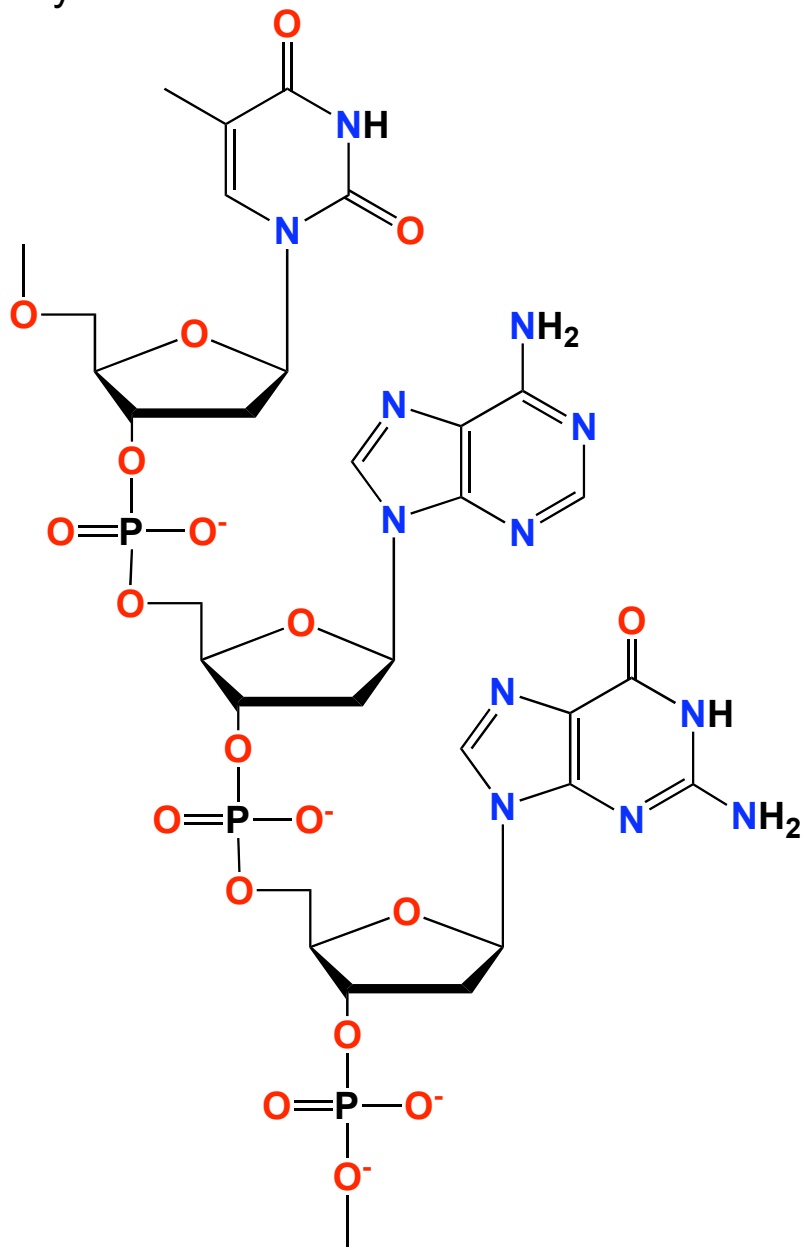
```
5′-ACCGCCGACGT-3′
3′-TGGCGGCTGCA-5′
```

```
5′-ACCGCCGACGT-3′
3′-AGGCGGCTGCC-5′
```


H
H
N
N
N
N
N
O
N
H
O

H
H
N
N
N
N
N
O
N
H
O

DNA

A look at the Chemistry



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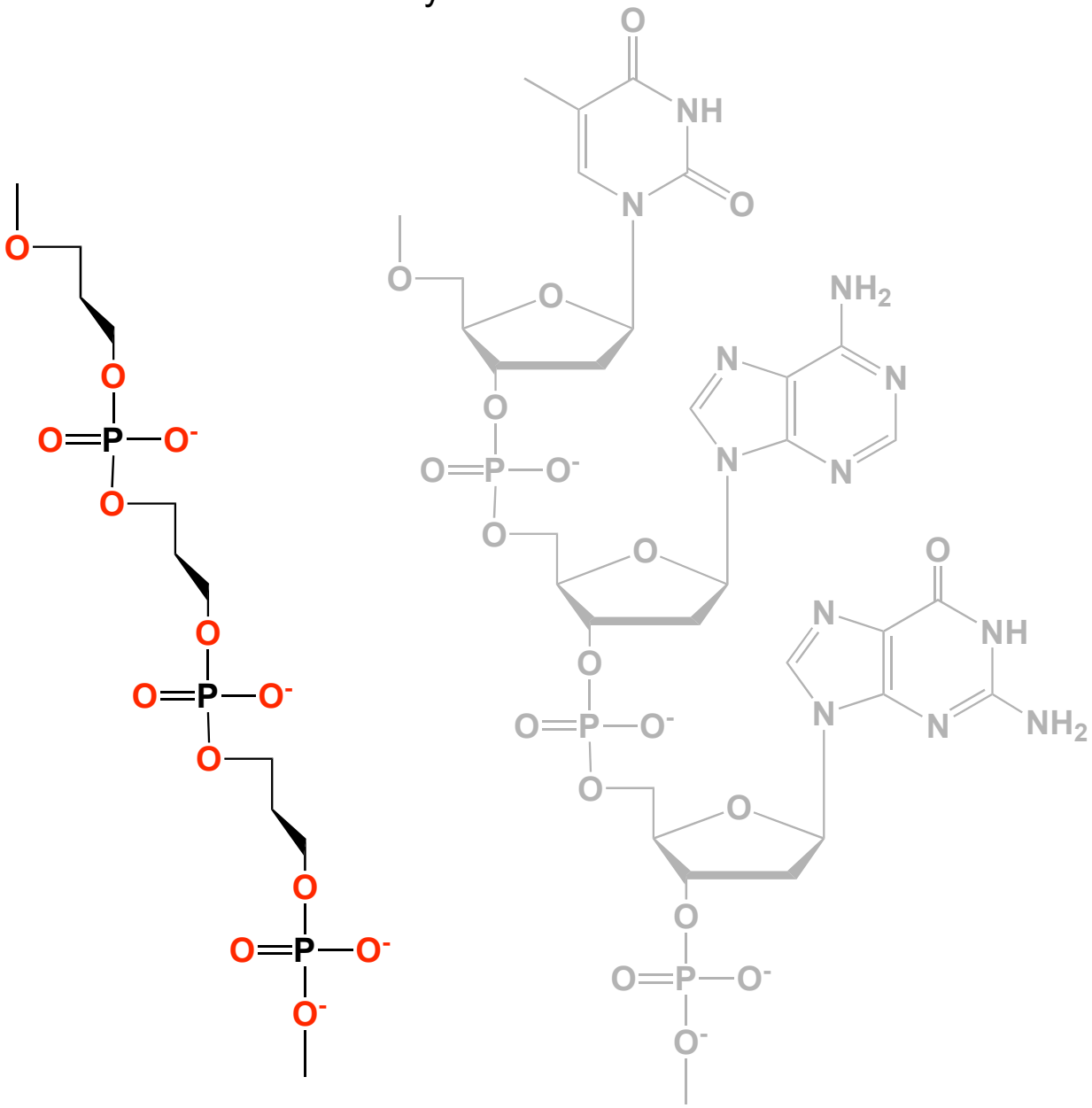
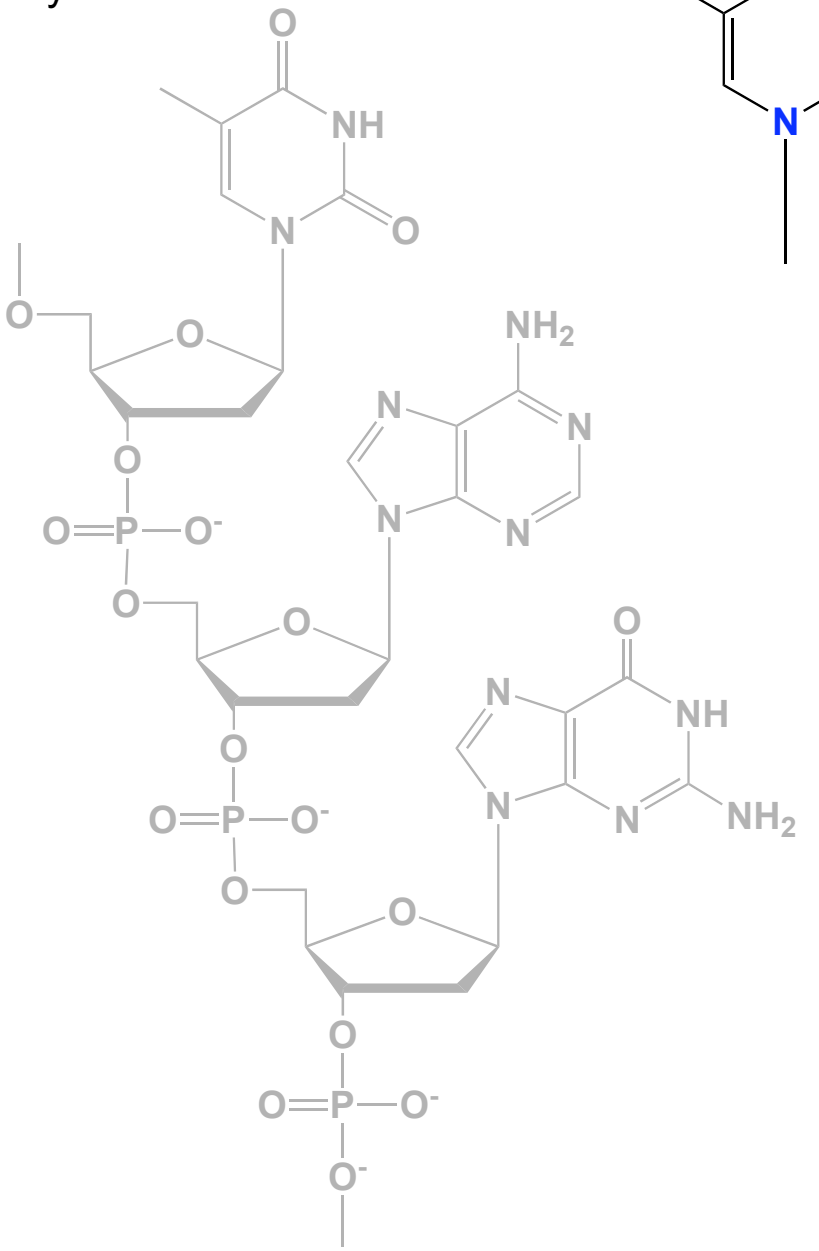
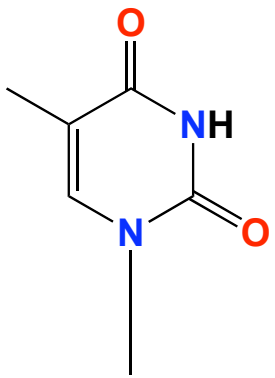
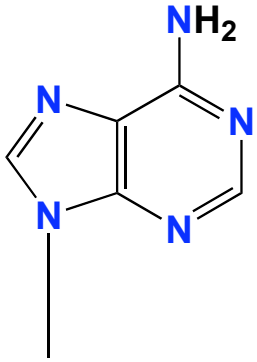

O
NH
N
O
NH2
N
N
N
N
O
O
O

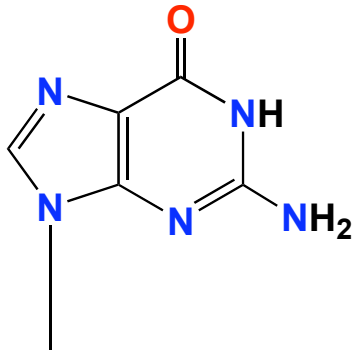
DNA

A look at the Chemistry









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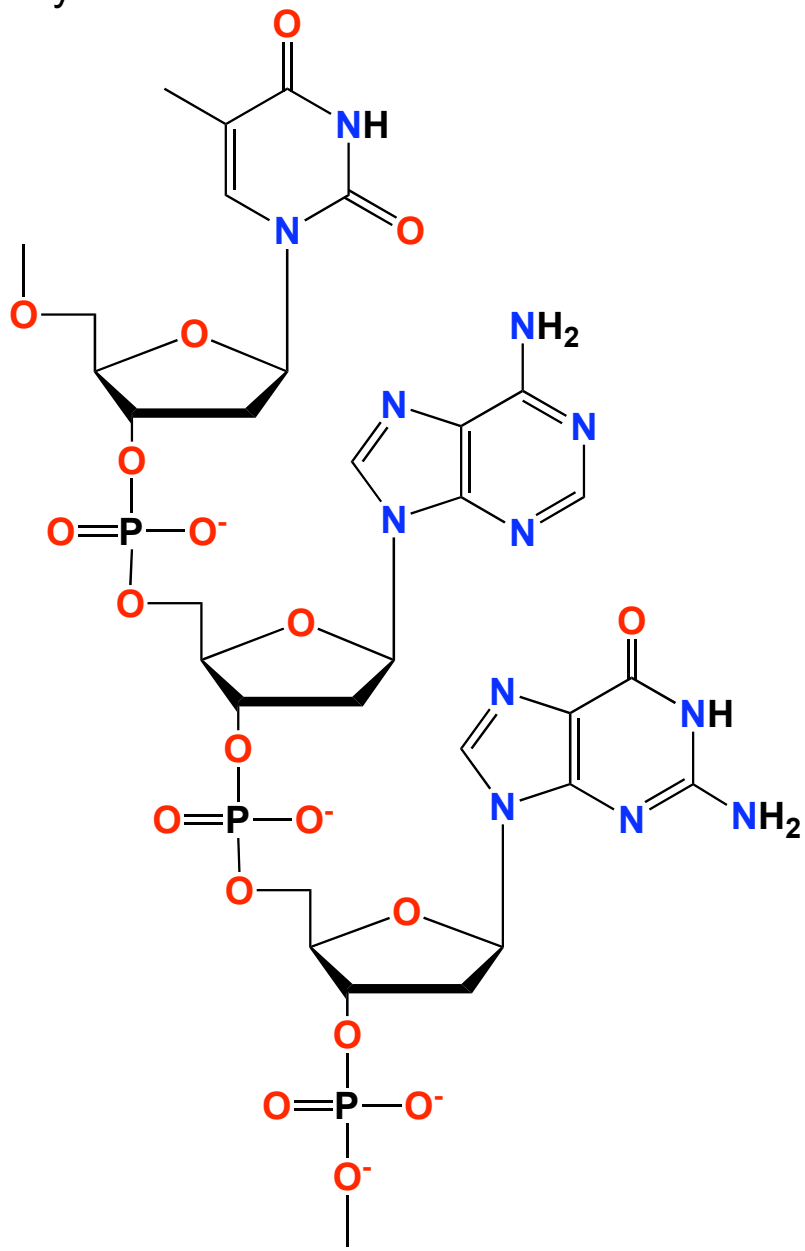

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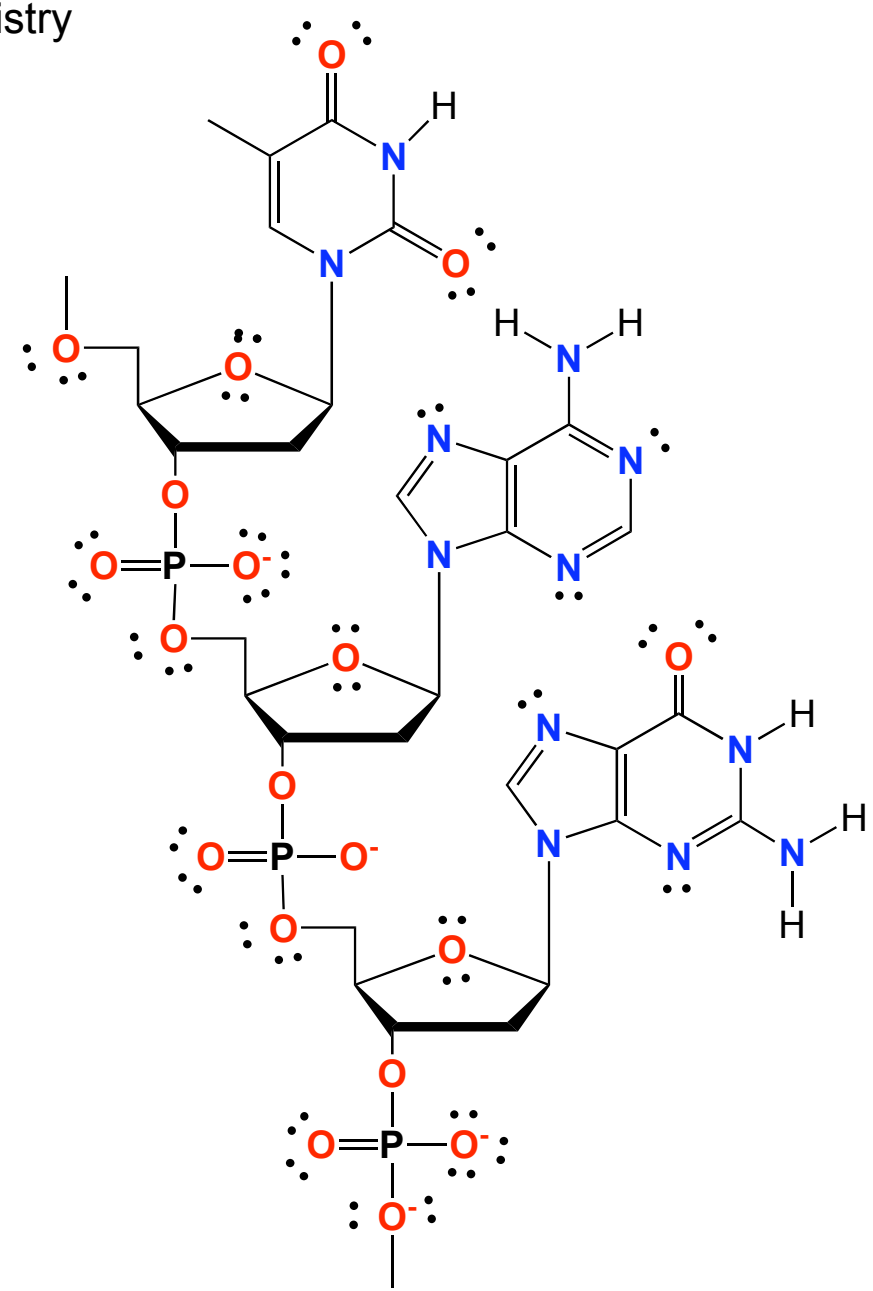

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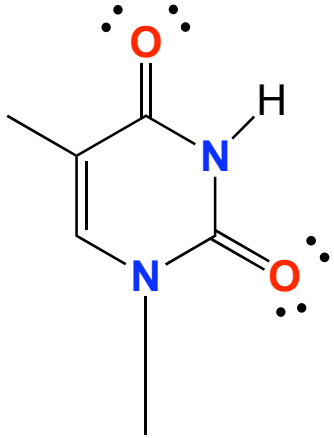
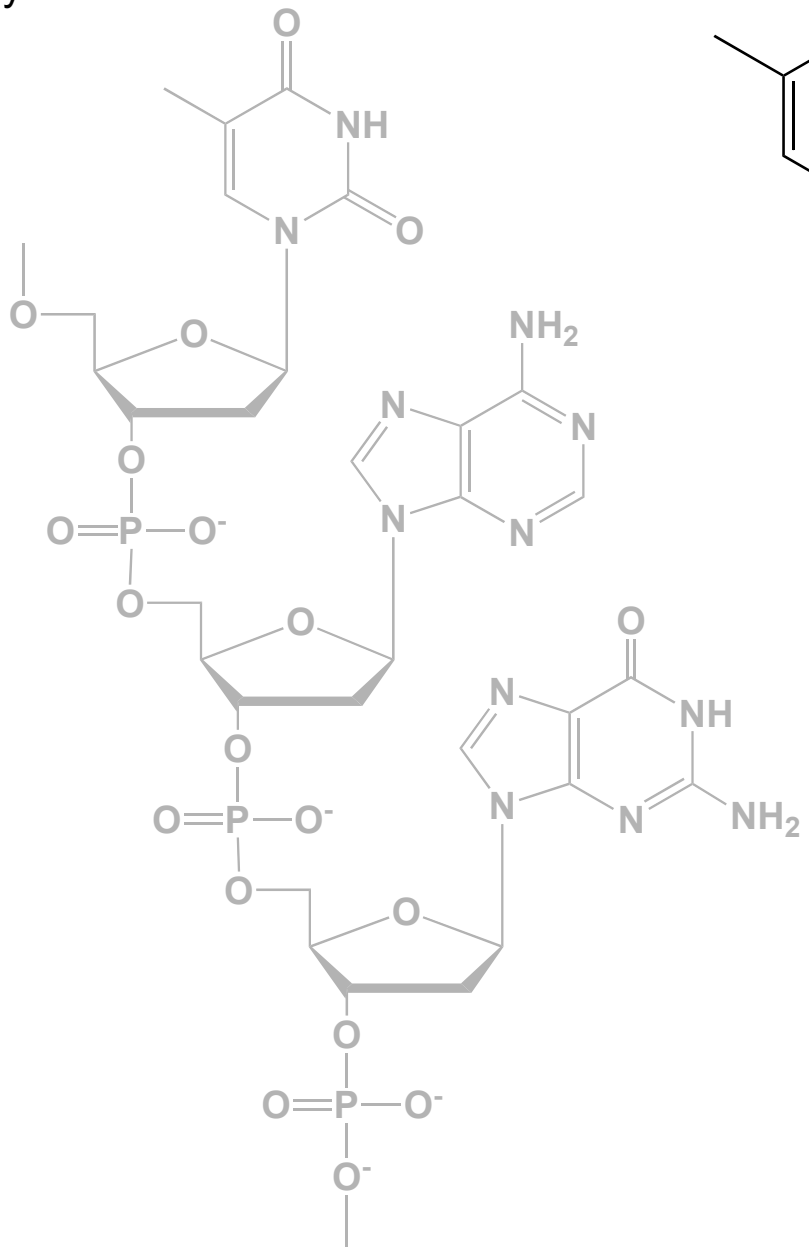
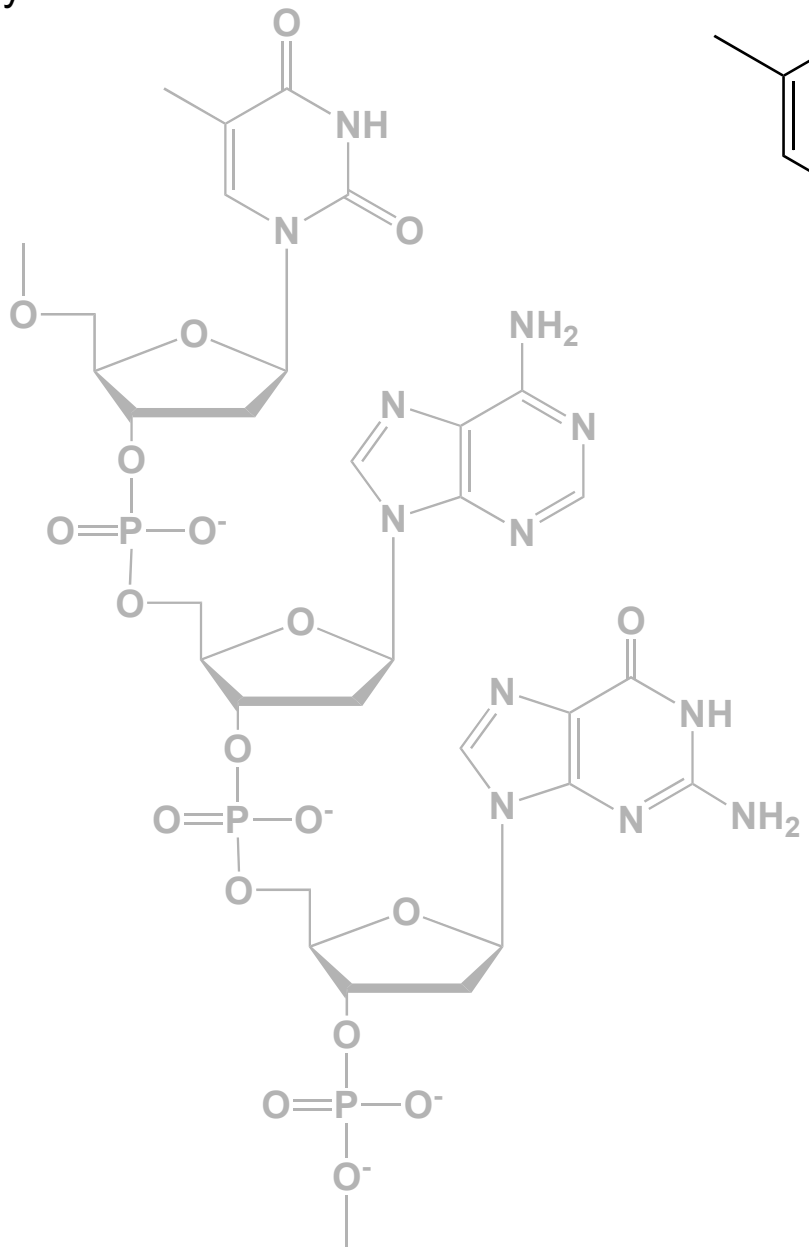
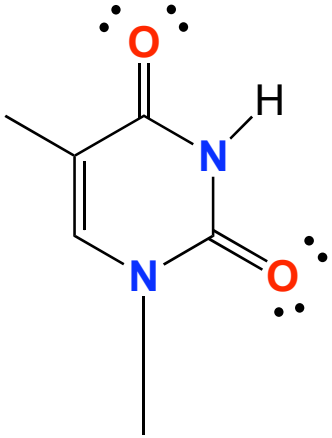


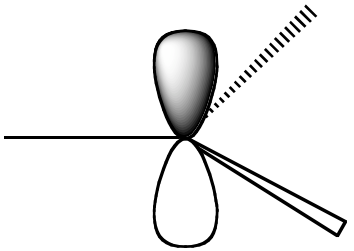


DNA

A look at the Chemistry

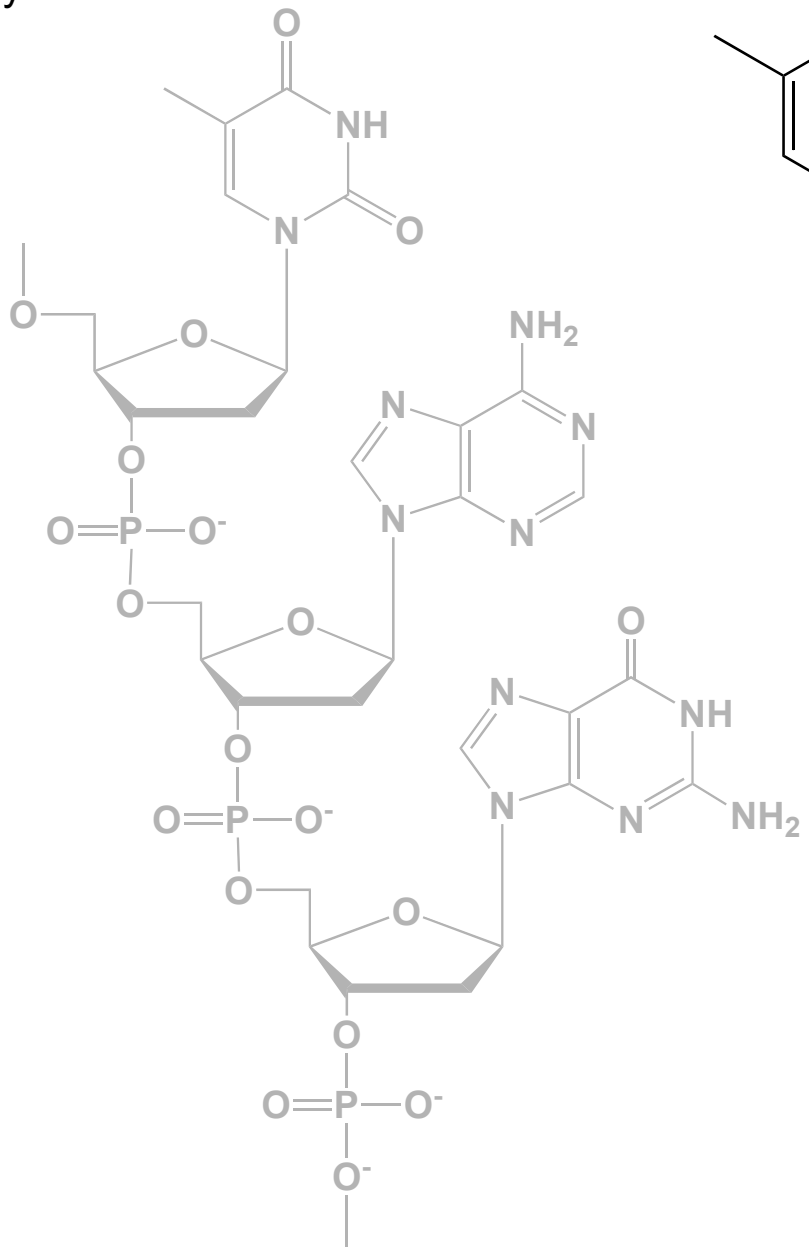


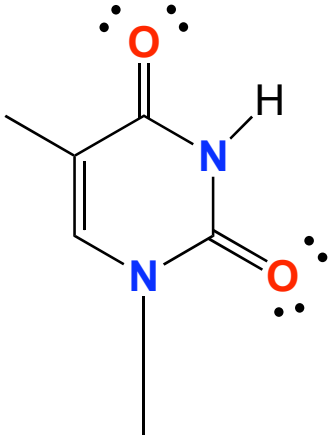


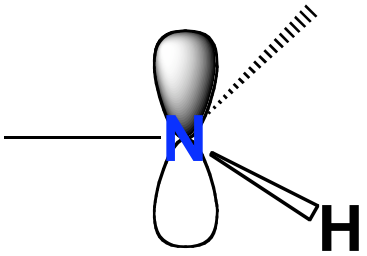


DNA

A look at the Chemistry

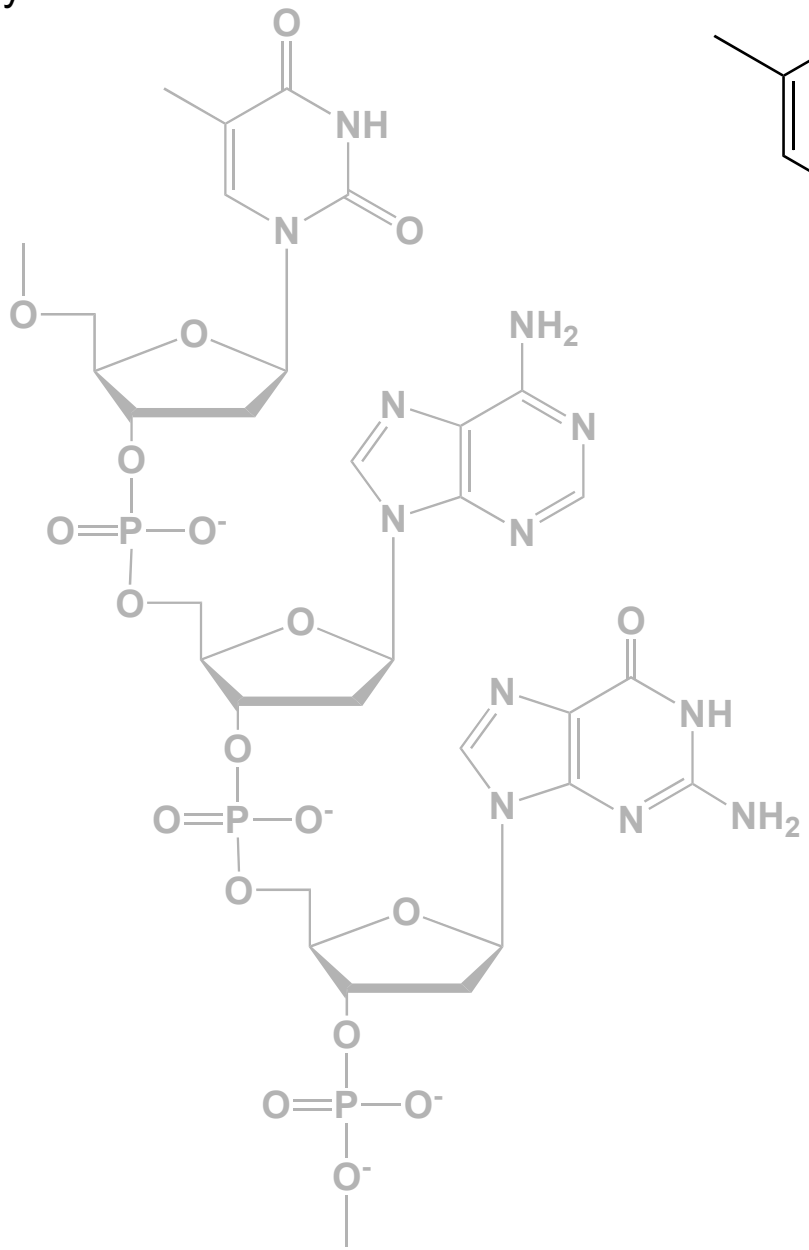


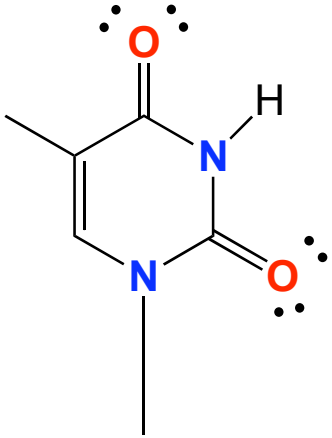


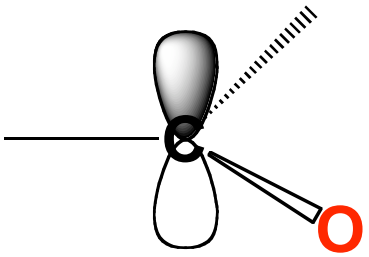


DNA

A look at the Chemistry

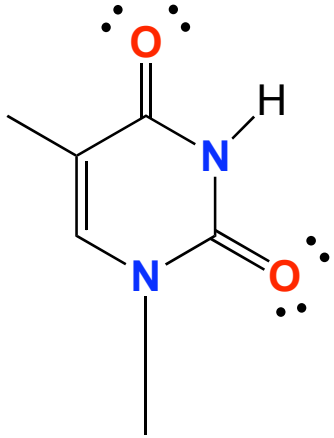


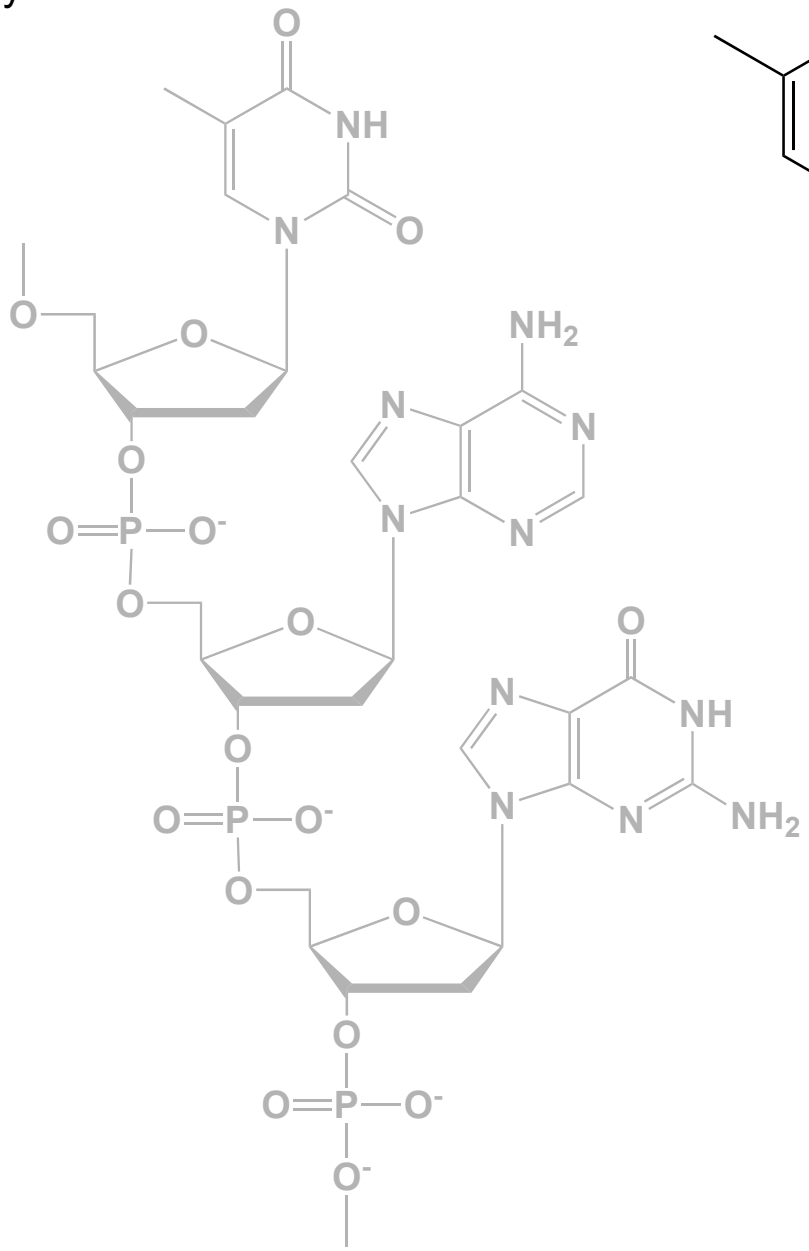




DNA

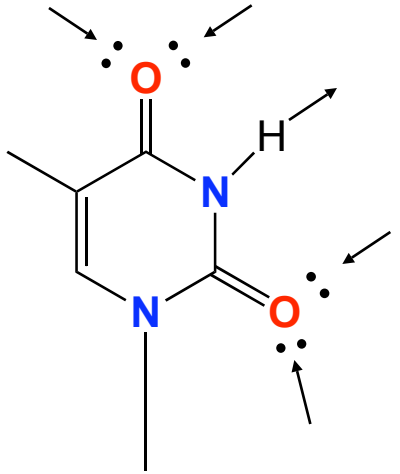
A look at the Chemistry

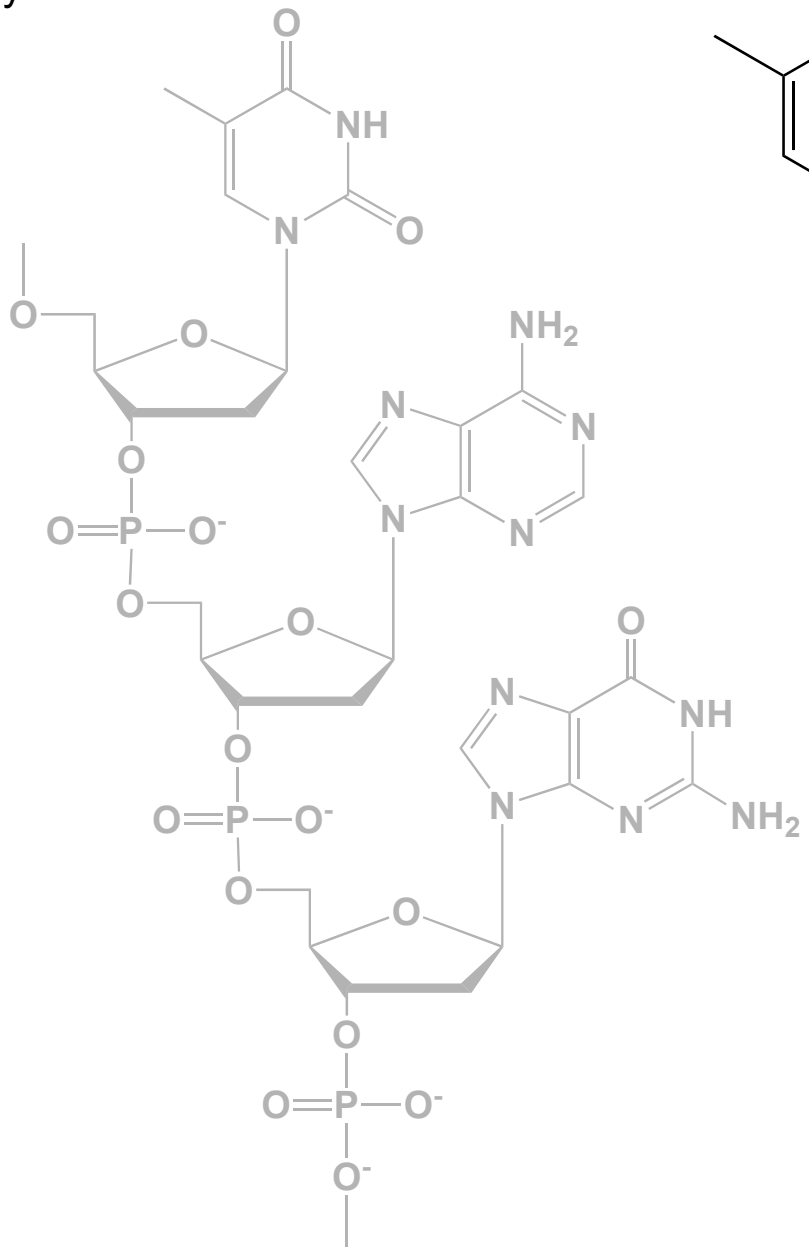




DNA

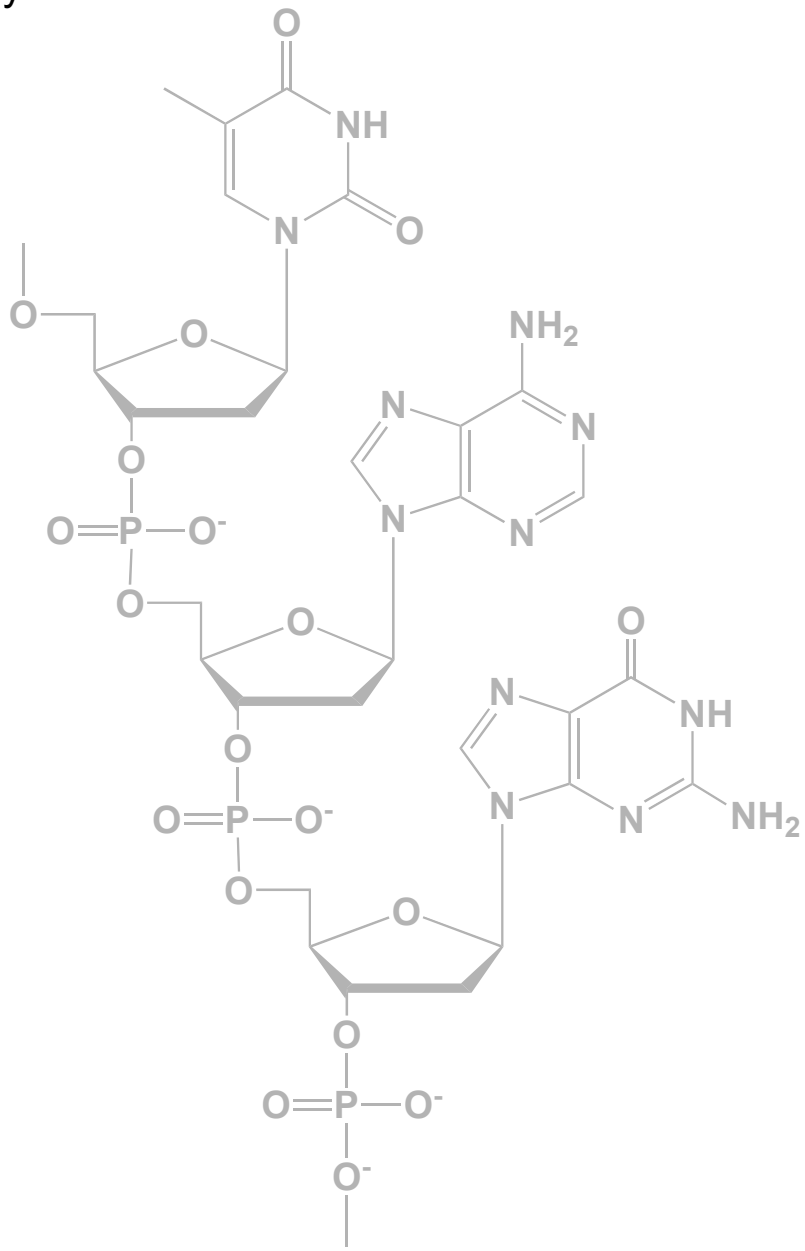
A look at the Chemistry

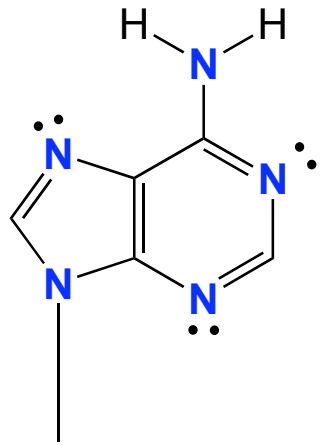




DNA

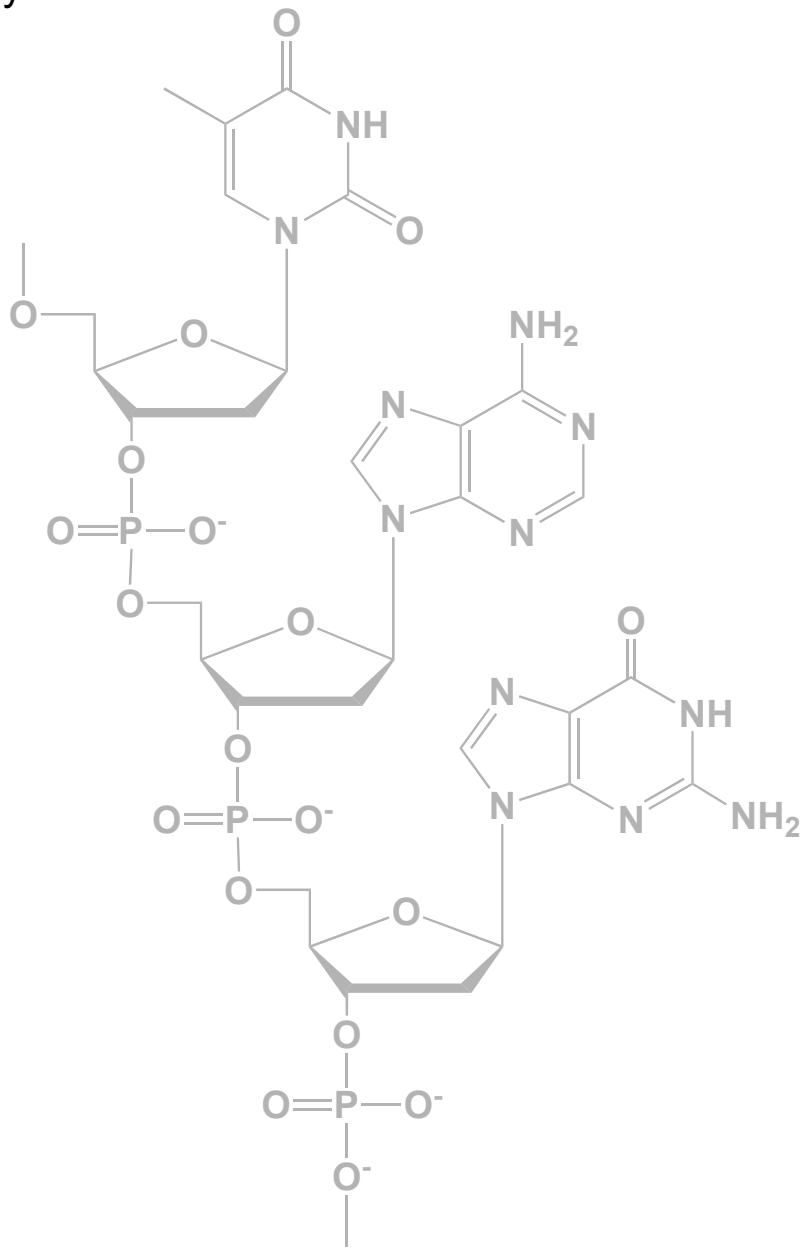
A look at the Chemistry

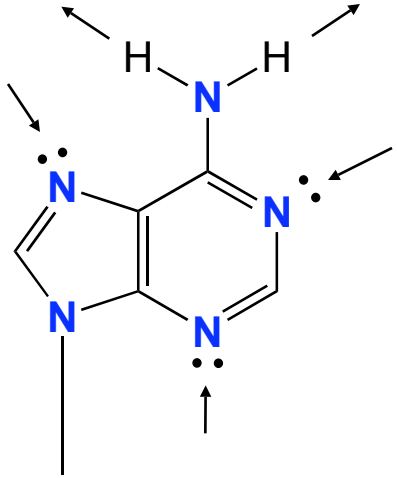




DNA

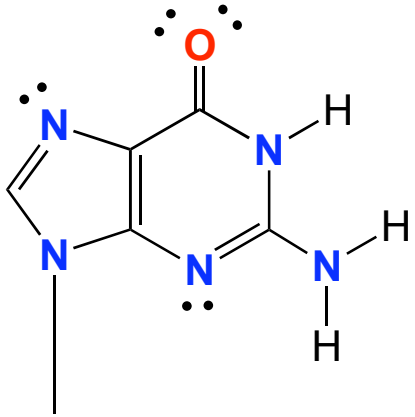
A look at the Chemistry

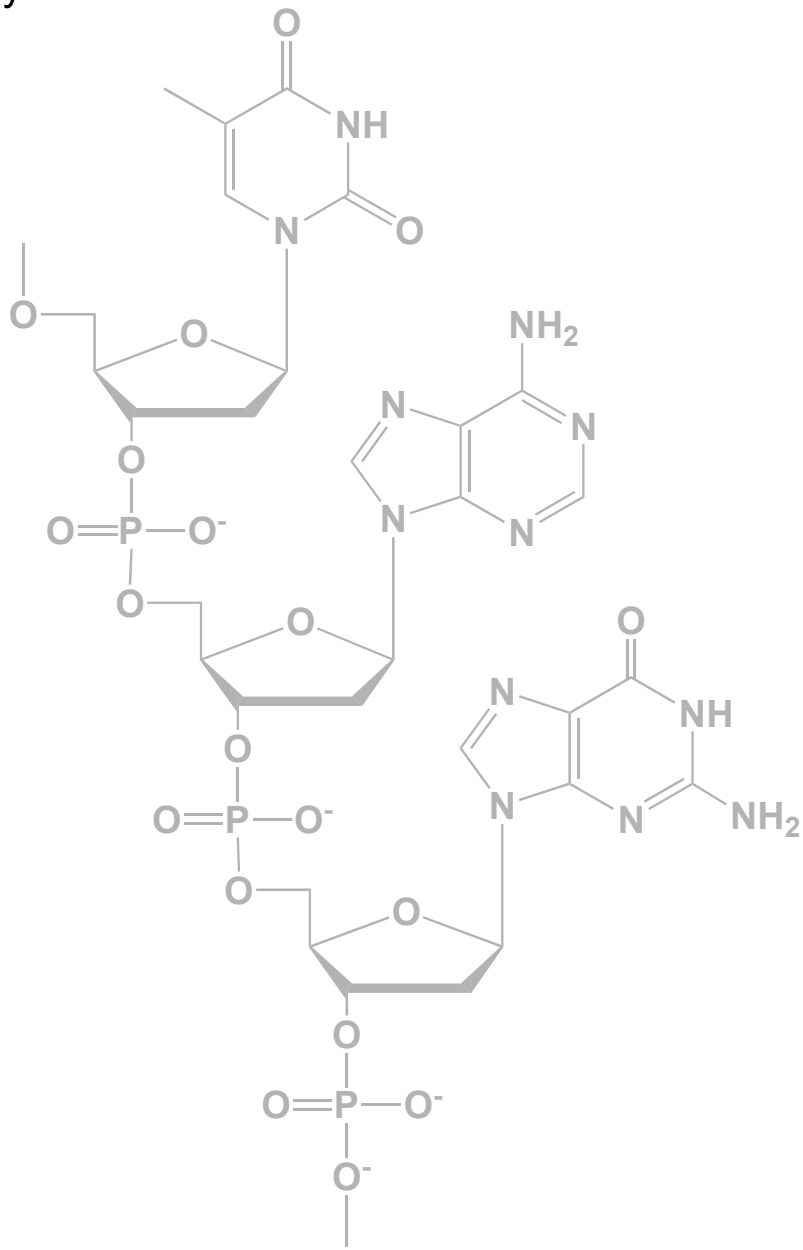




DNA

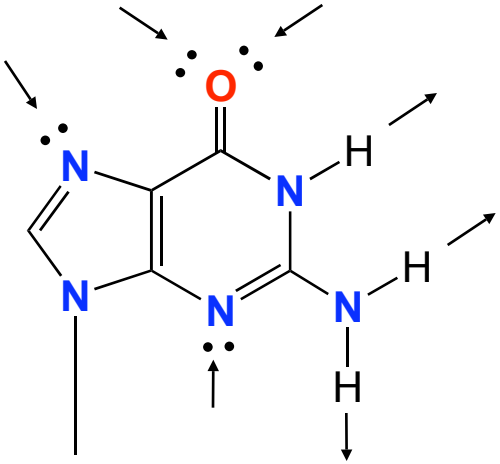
A look at the Chemistry

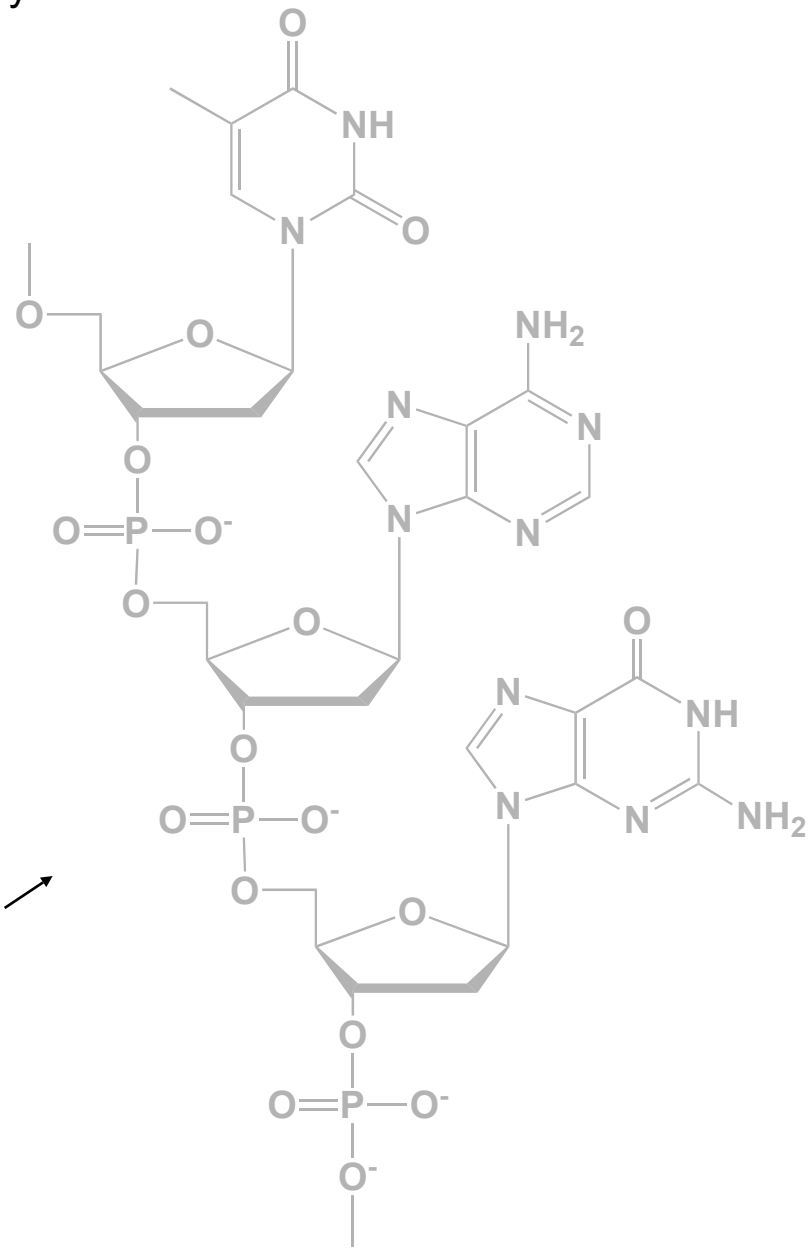




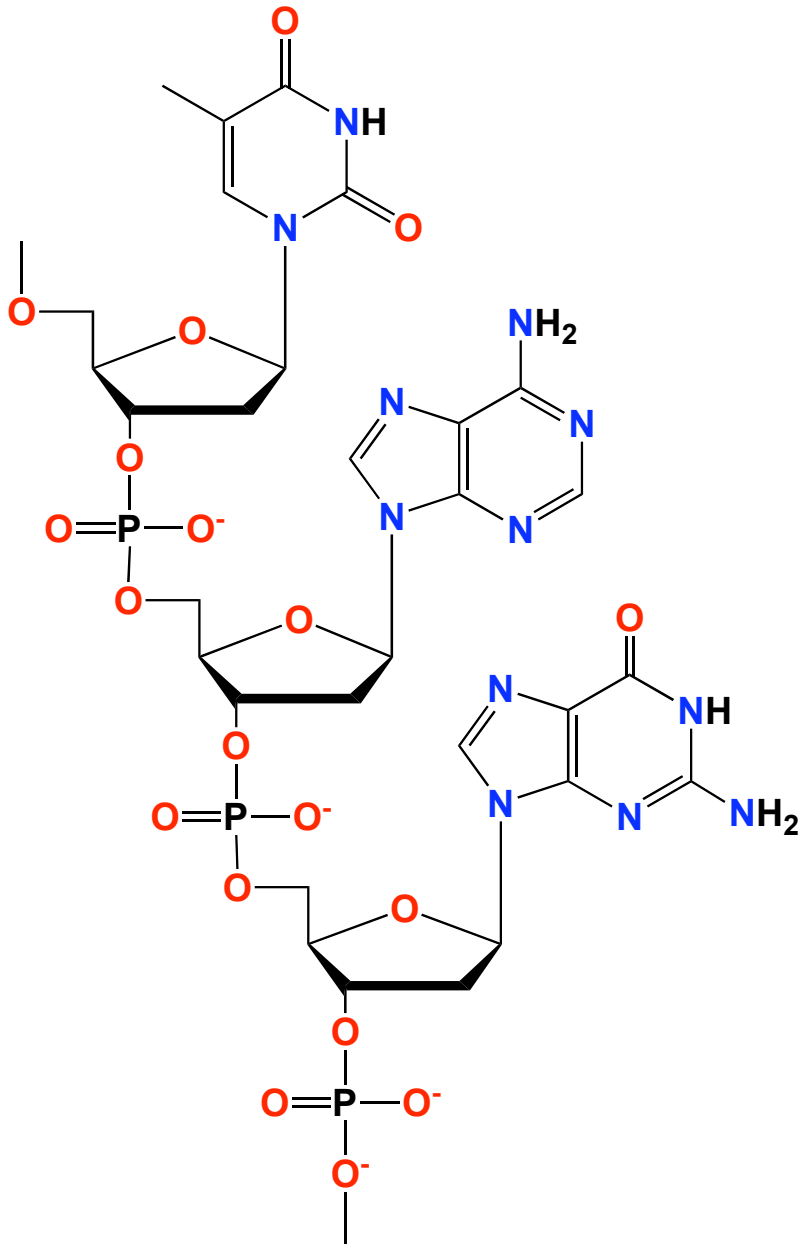
DNA

A look at the Chemistry

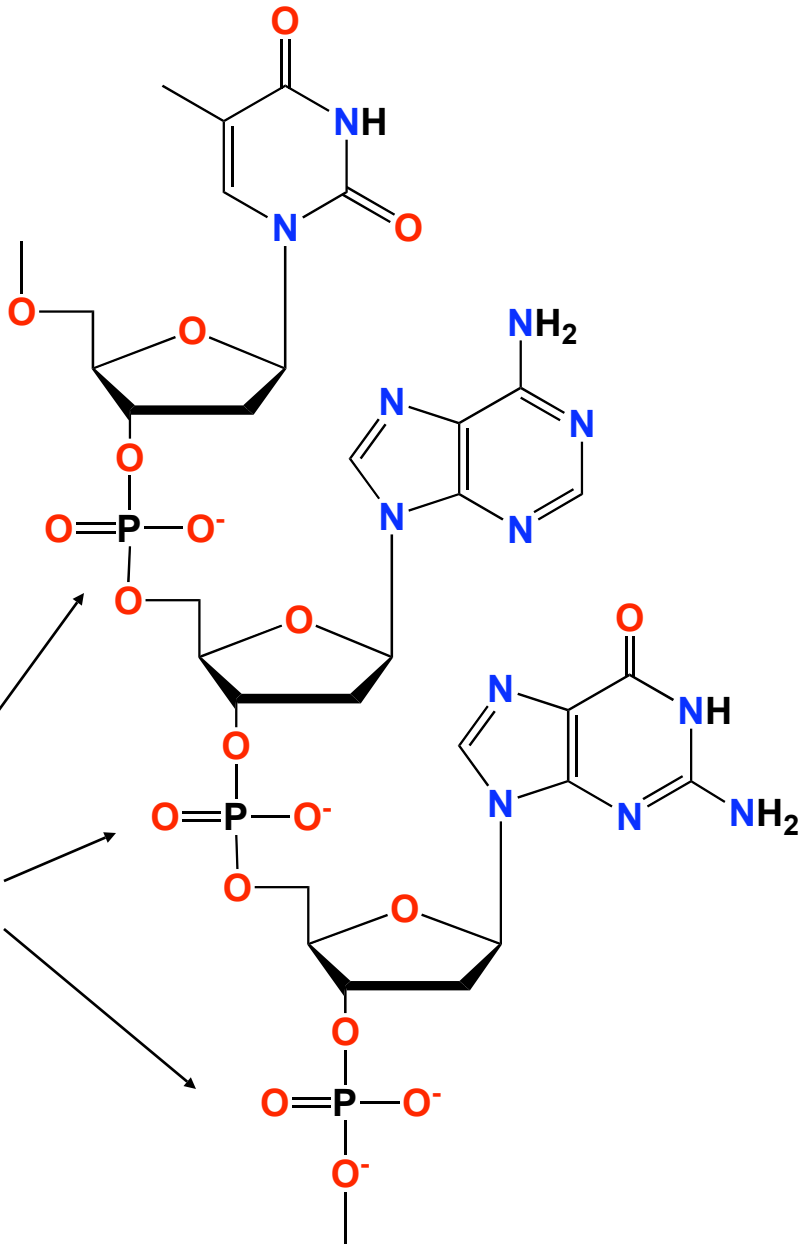




What forces are important?

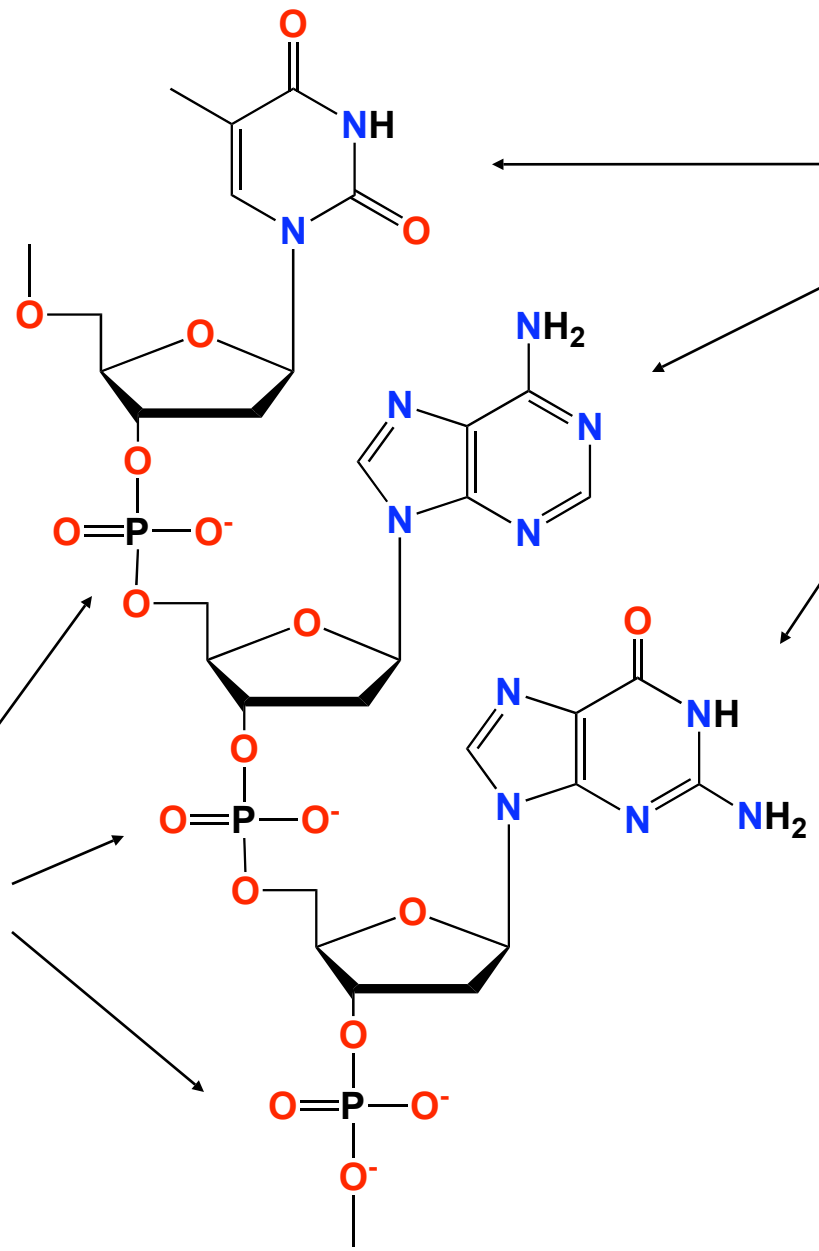


What forces are important?



Electrostatics

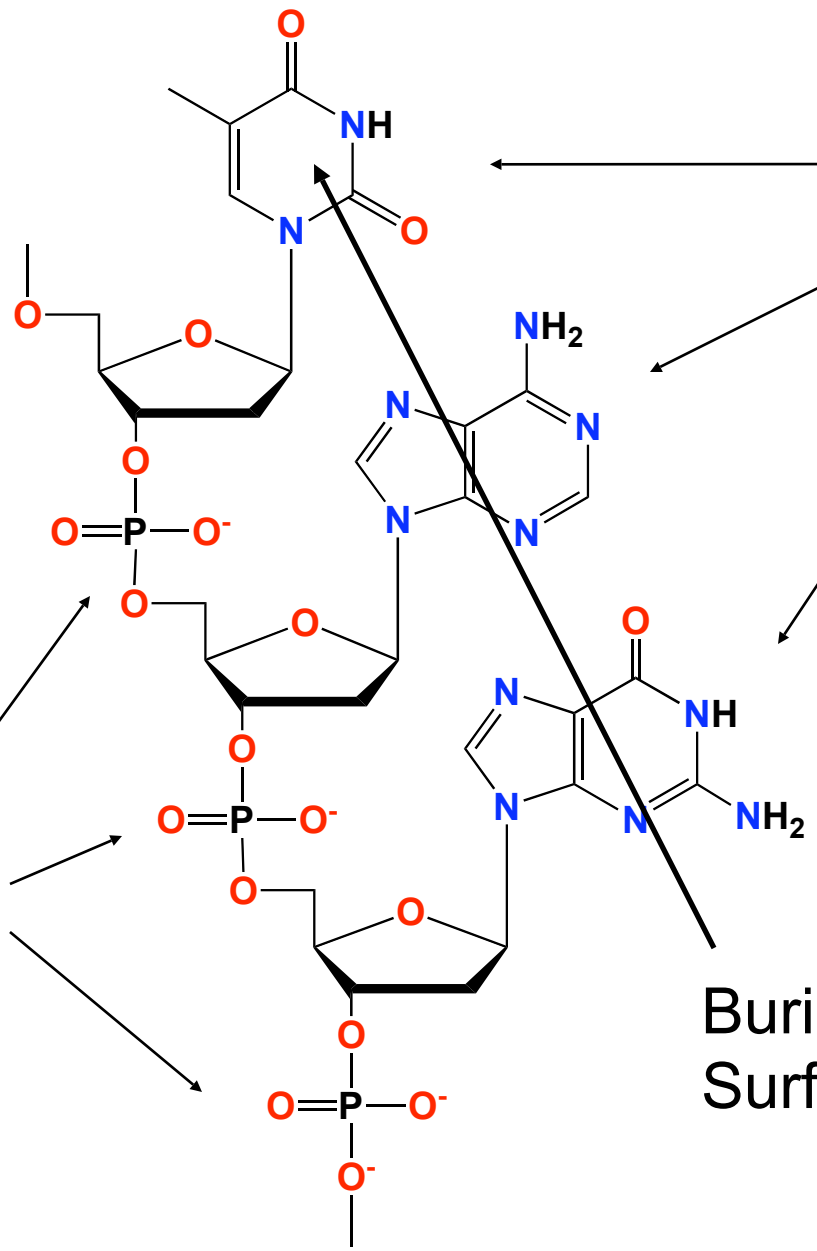
What forces are important?



Hydrogen Bonding

Electrostatics

What forces are important?



Hydrogen Bonding

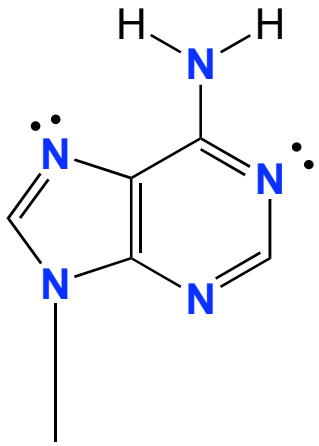
Electrostatics

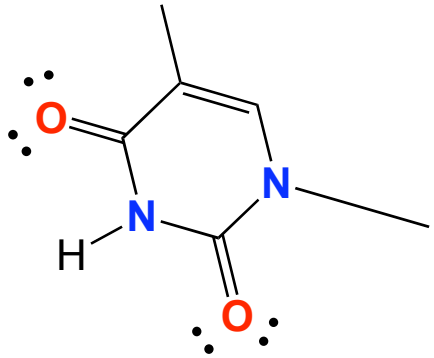
Burial of Hydrophobic Surface & Stacking

Base Pairing

(Donors matched to Acceptors)

A

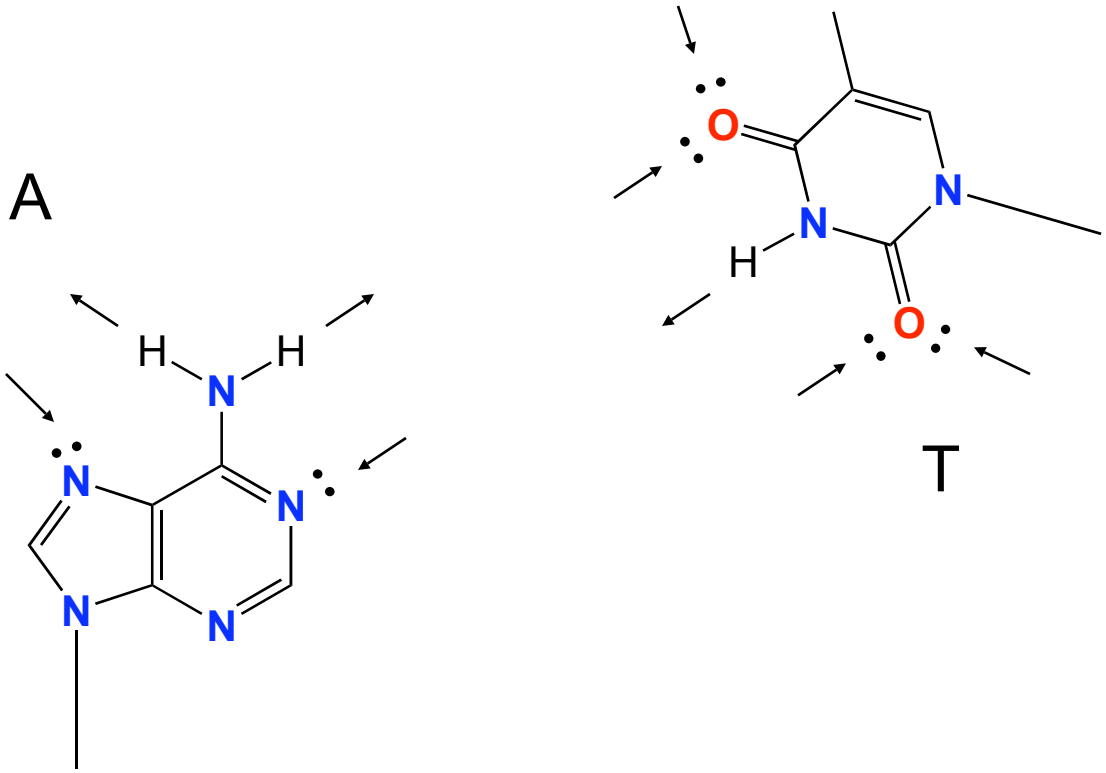




T

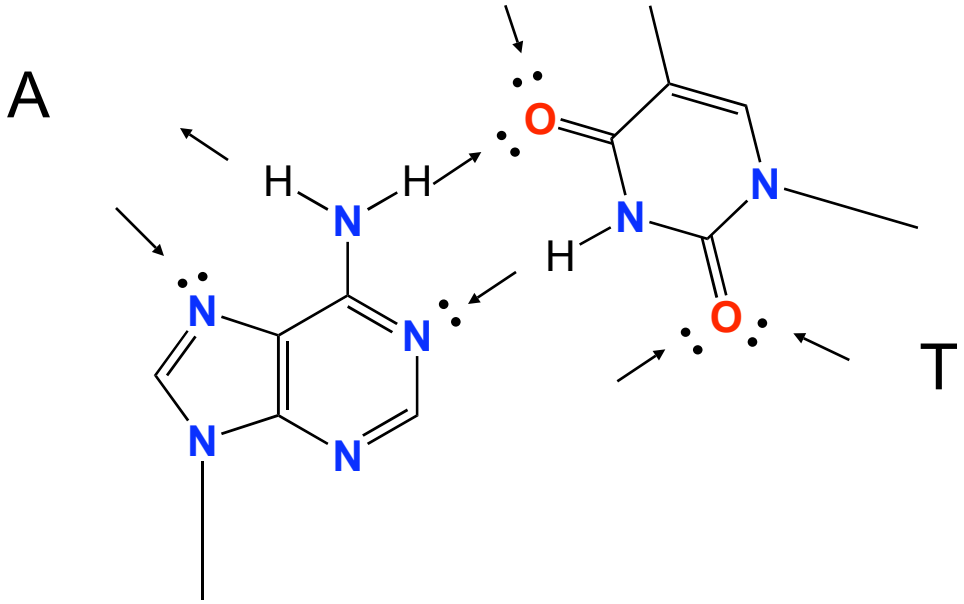
Base Pairing

(Donors matched to Acceptors)



Base Pairing

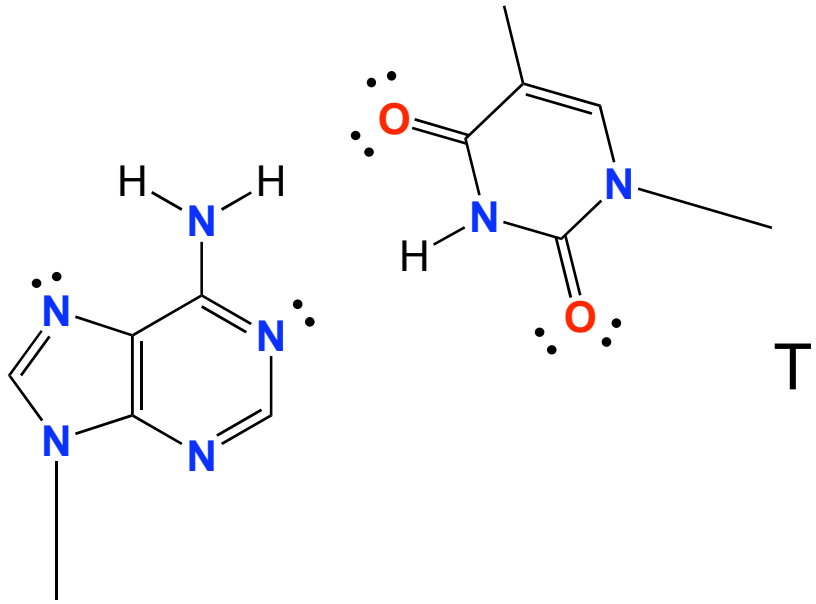
(Donors matched to Acceptors)



Base Pairing

(Donors matched to Acceptors)

A



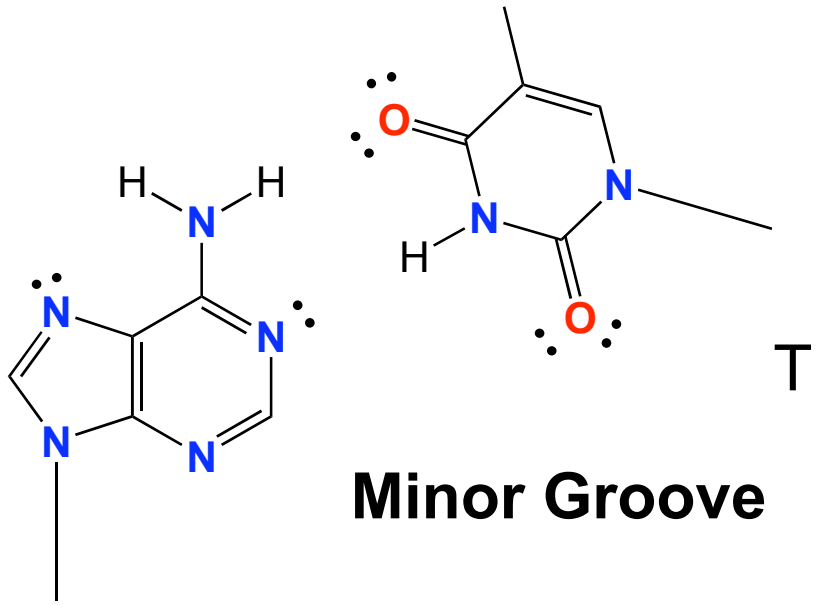
T

Base Pairing

(Donors matched to Acceptors)

Major Groove

A



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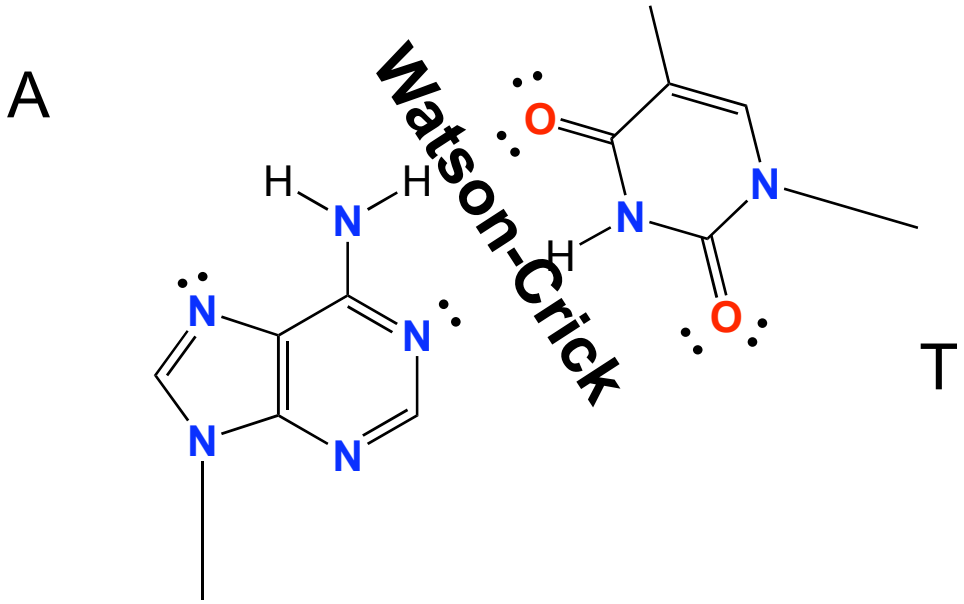
Minor Groove

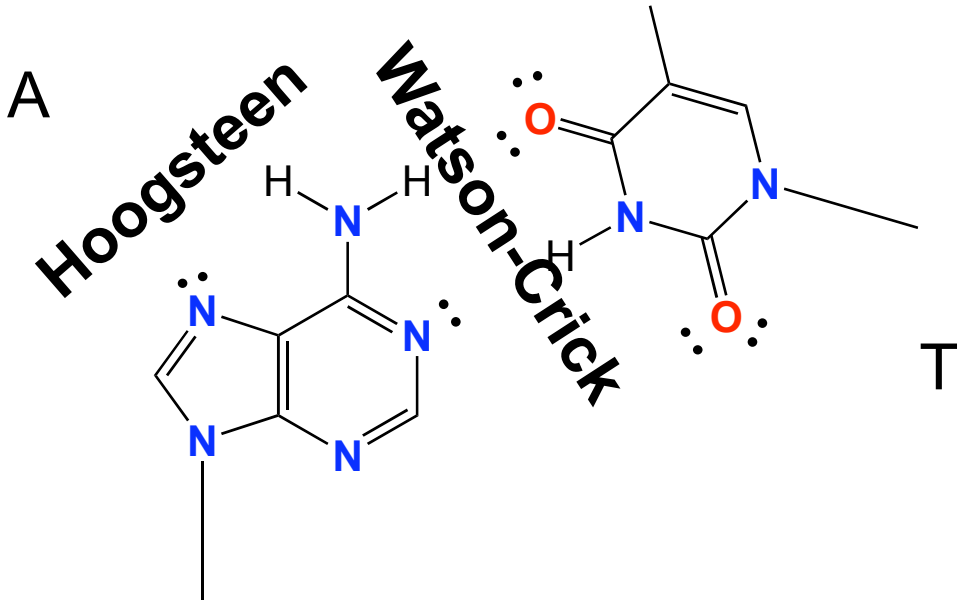
Base Pairing

(Donors matched to Acceptors)



Base Pairing

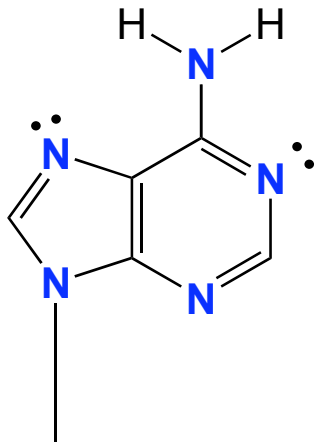
(Donors matched to Acceptors)

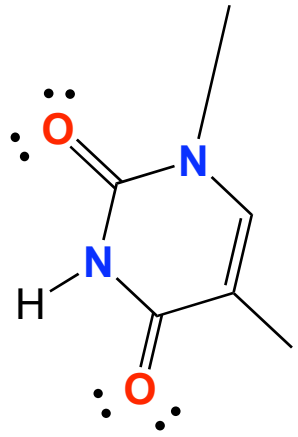


Base Pairing

(Donors matched to Acceptors)

A





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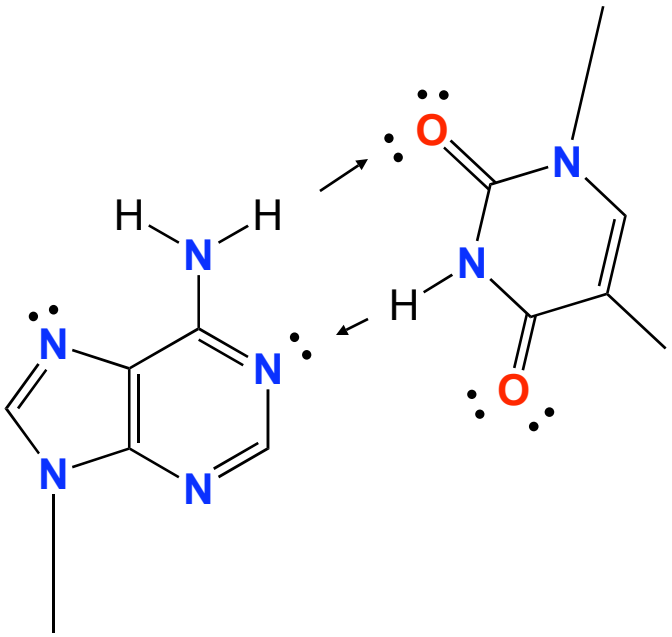
Base Pairing

(Donors matched to Acceptors)

A



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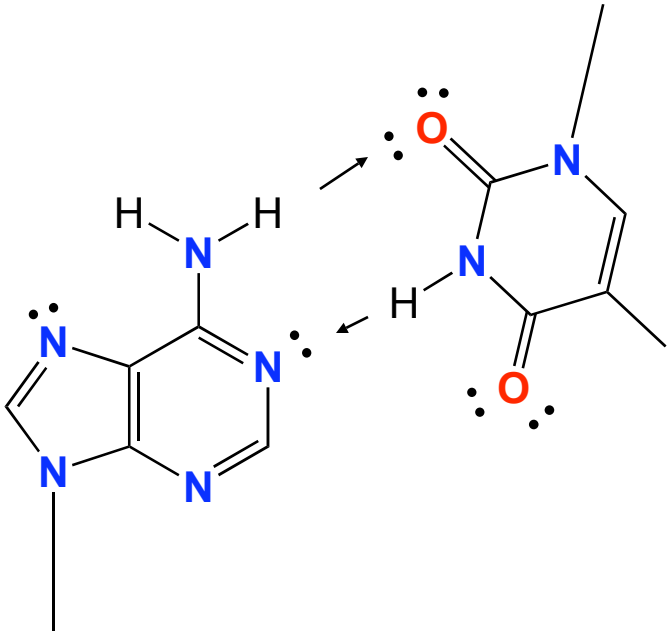
Base Pairing

(Donors matched to Acceptors)

A



T

Good base pairing

Base Pairing

(Donors matched to Acceptors)

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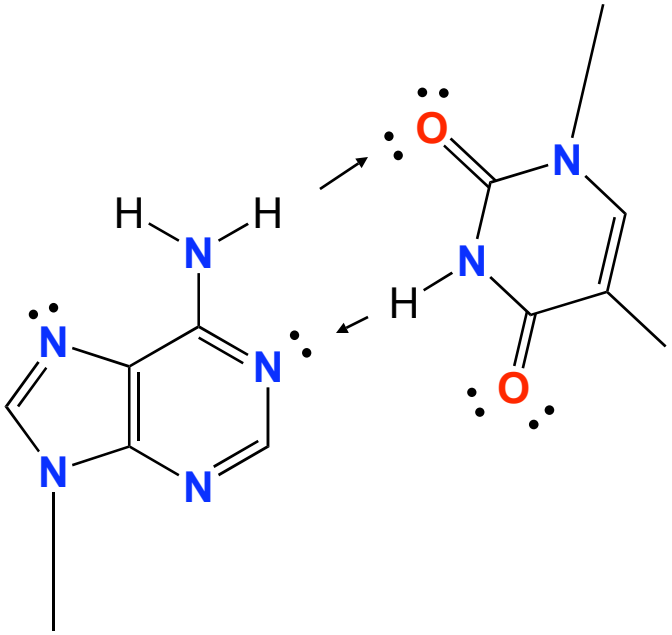
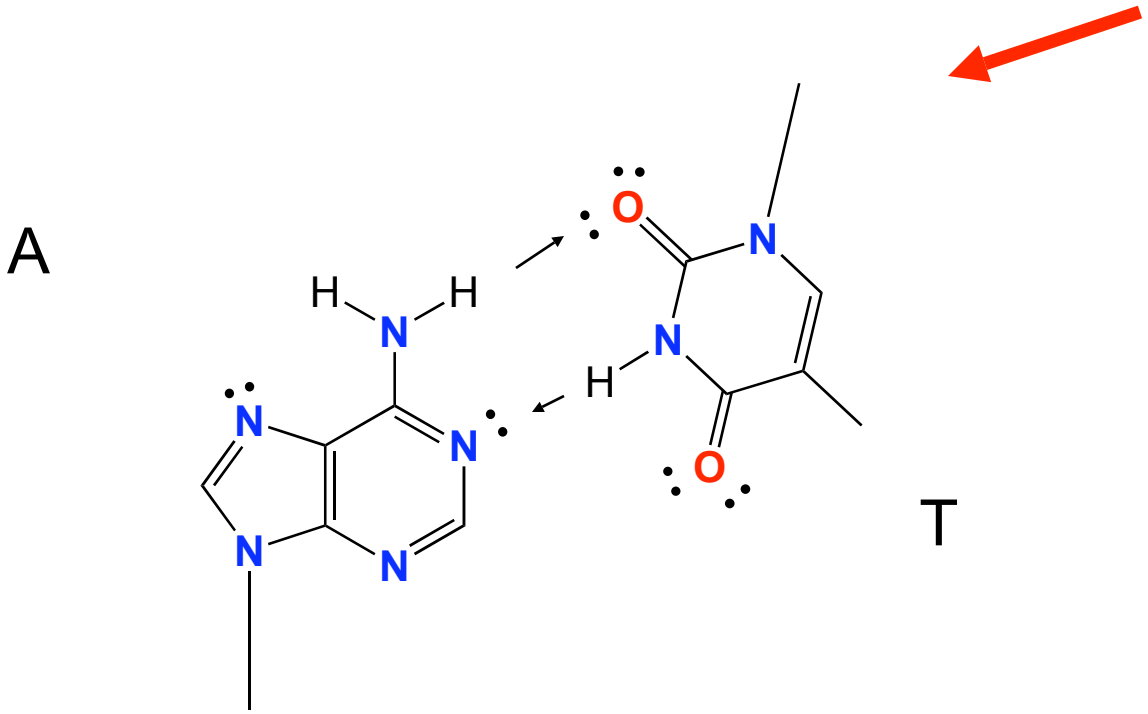


T

Good base pairing
Watson-Crick facing

Base Pairing

(Donors matched to Acceptors)

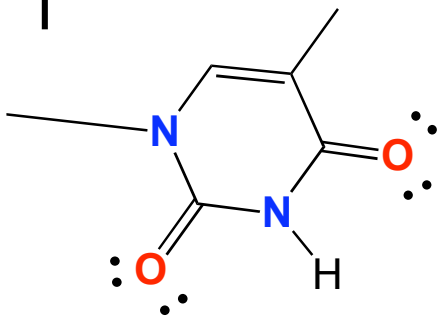


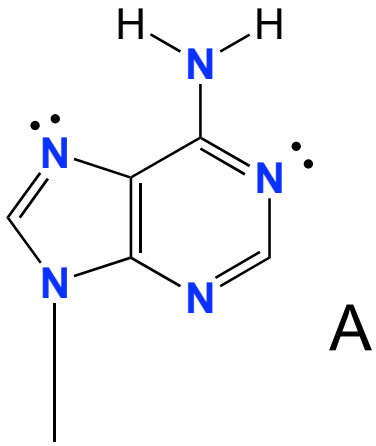
Good base pairing
Watson-Crick facing
but *Anti-Watson-Crick* orientation

Base Pairing

(Donors matched to Acceptors)

T



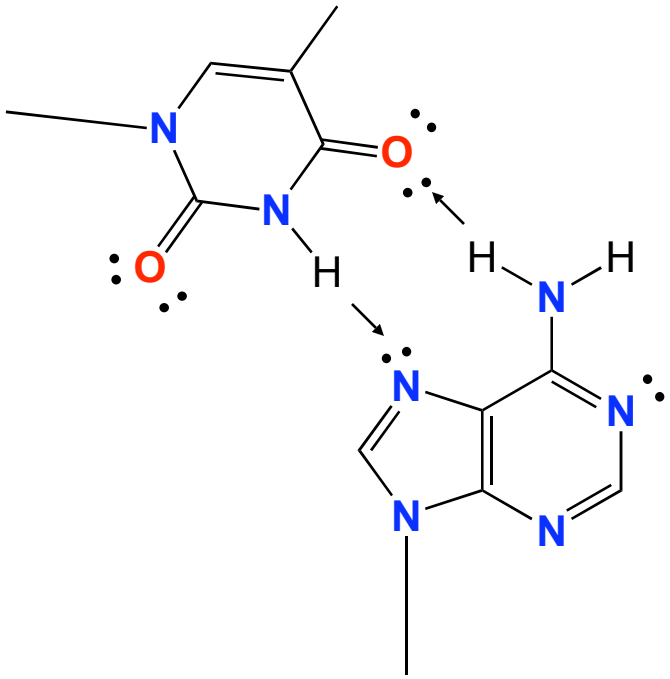


A

Base Pairing

(Donors matched to Acceptors)

T

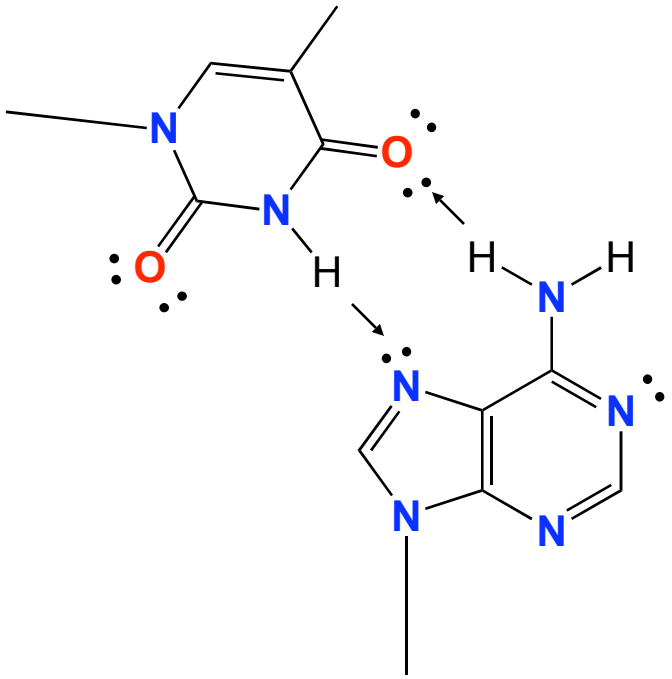


A

Base Pairing

(Donors matched to Acceptors)

T



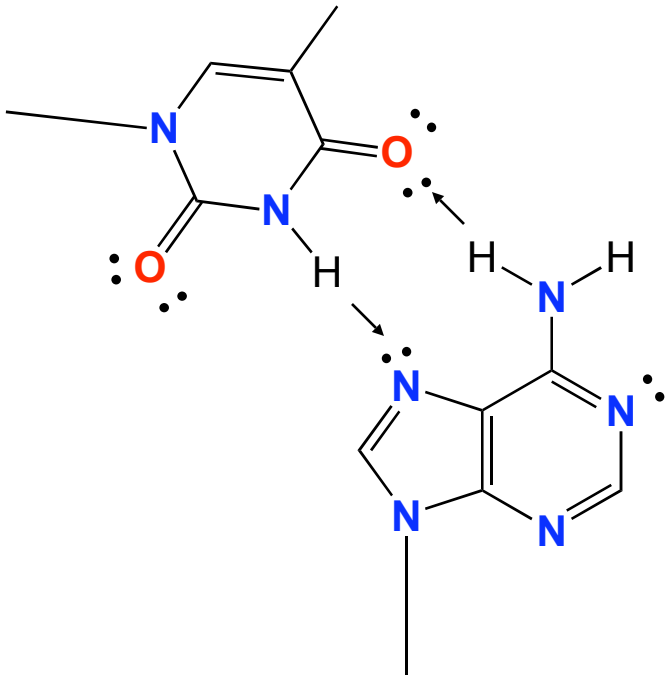
A

Good base pairing

Base Pairing

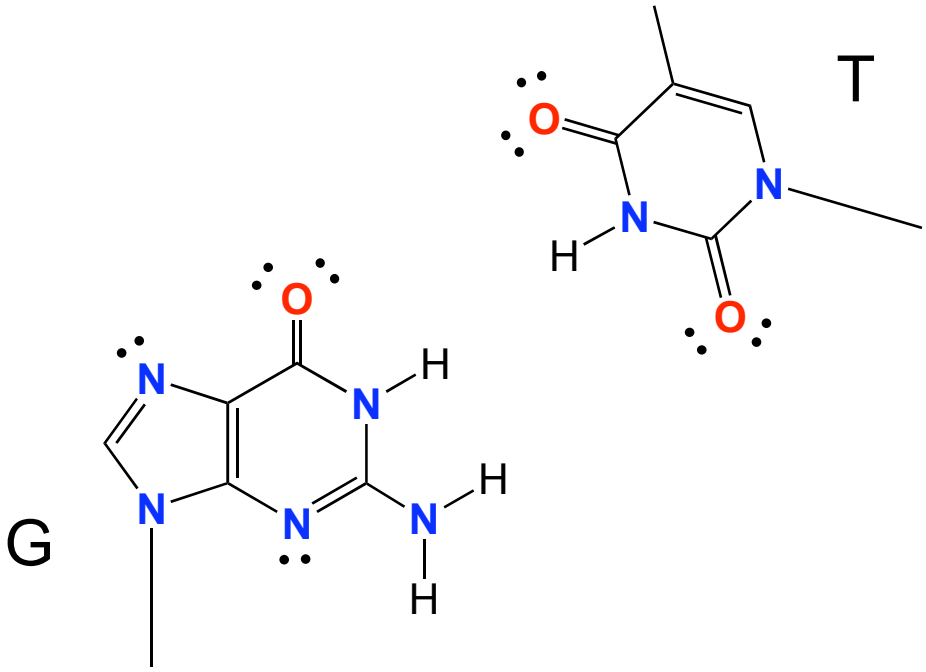
(Donors matched to Acceptors)

T



A

Good base pairing
WC-Hoogsteen facing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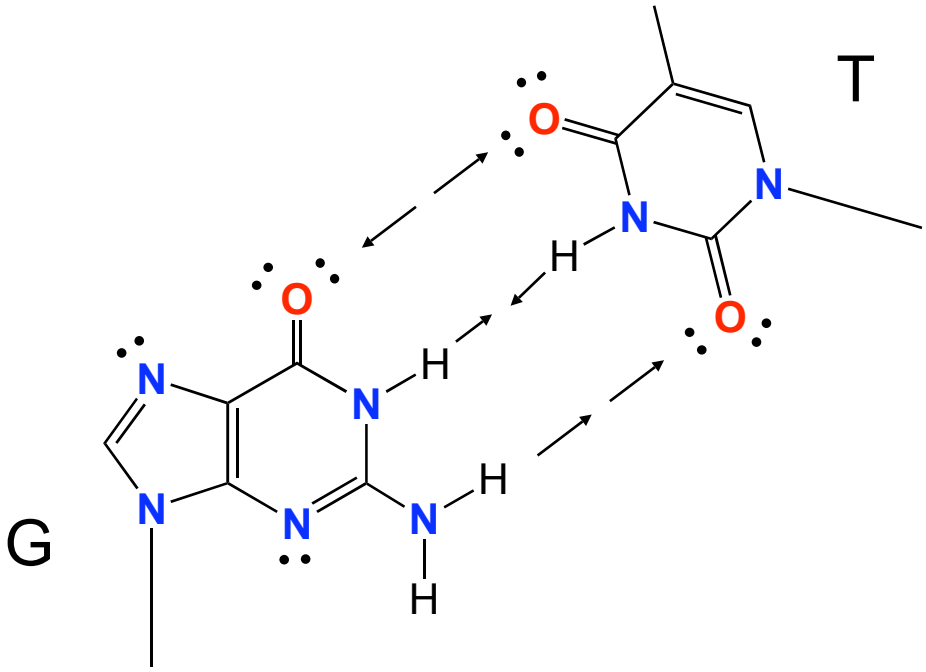
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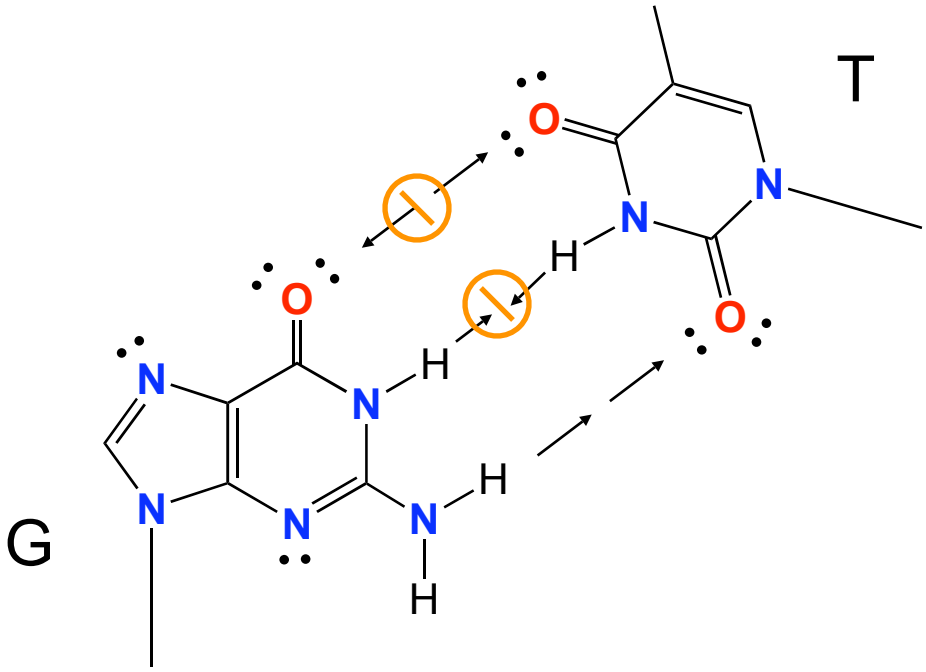
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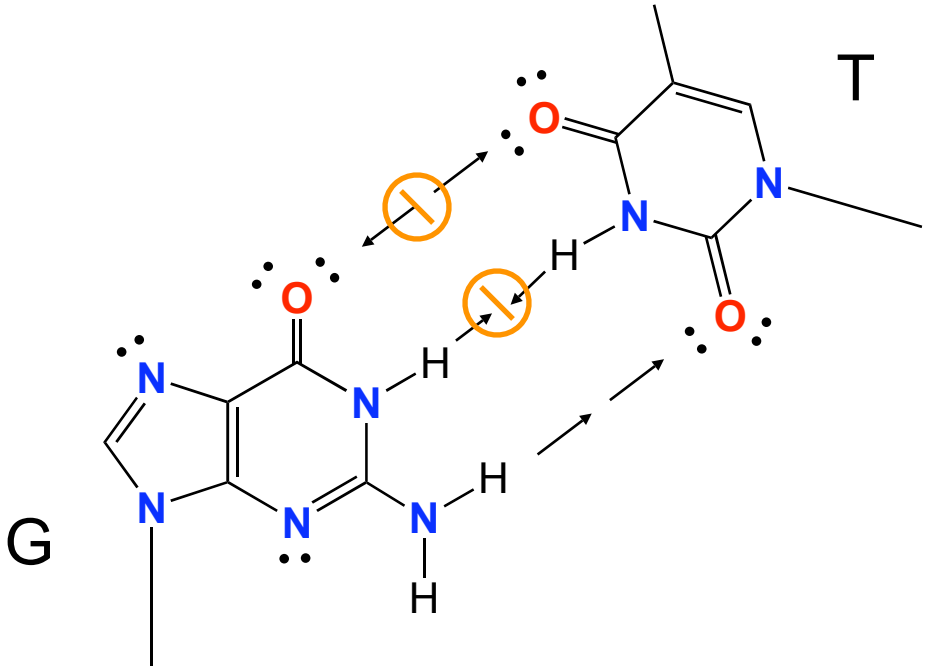
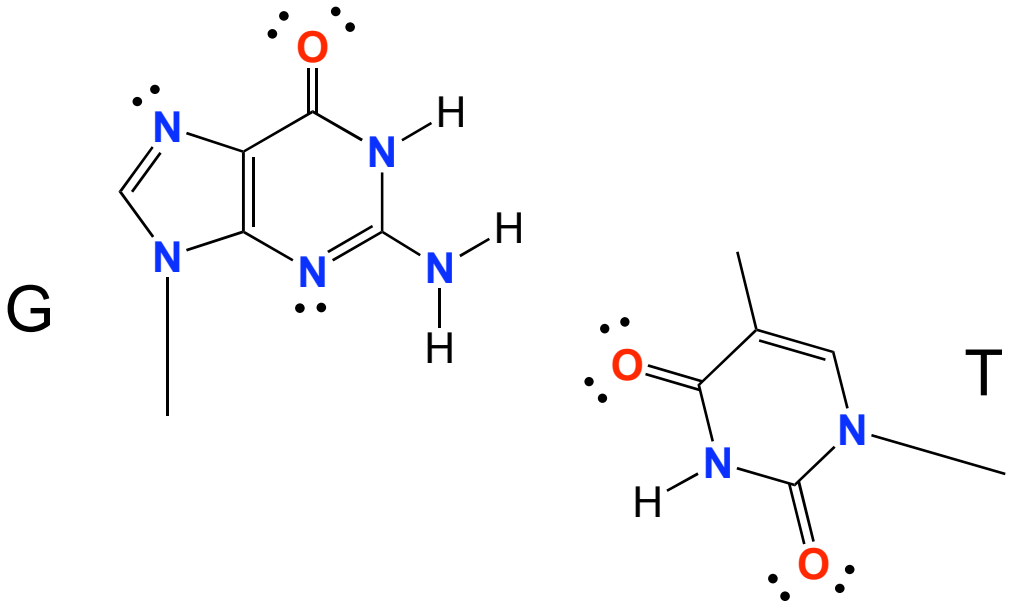
Bad Base Pairing

(Donors ***not*** matched to Acceptors)

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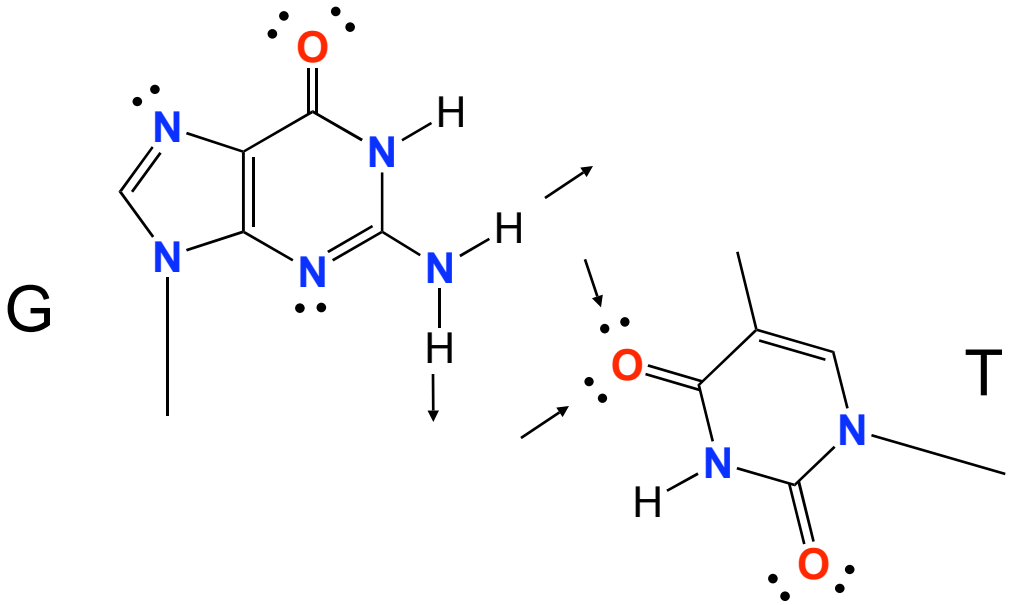
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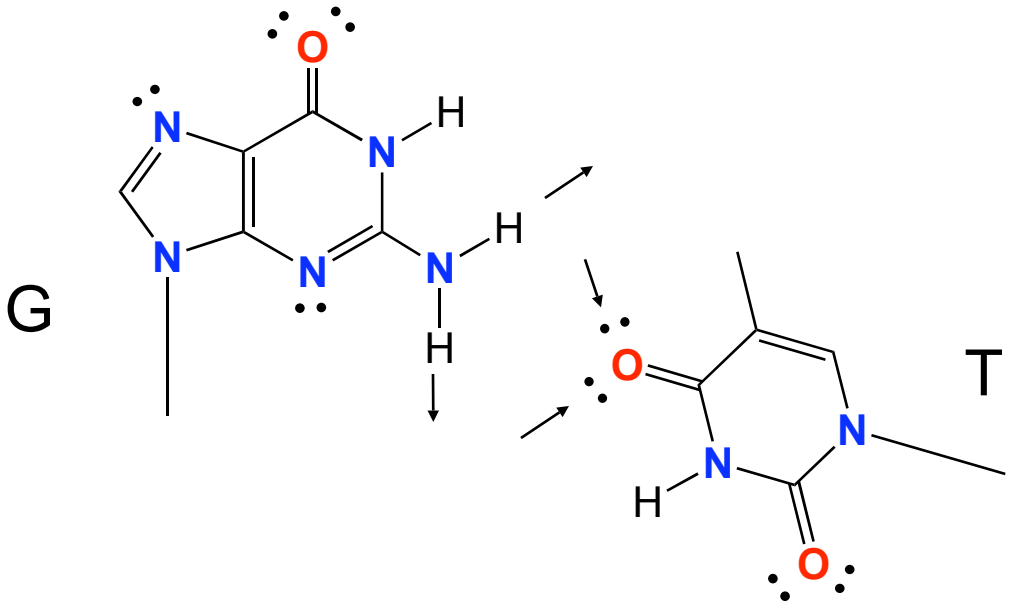
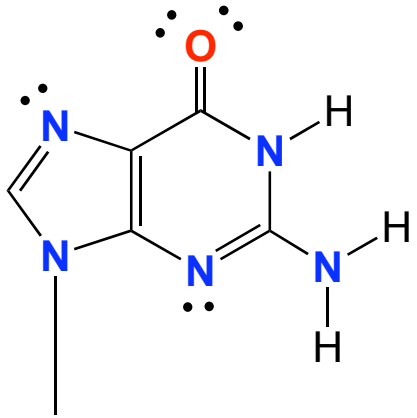
Bad Base Pairing

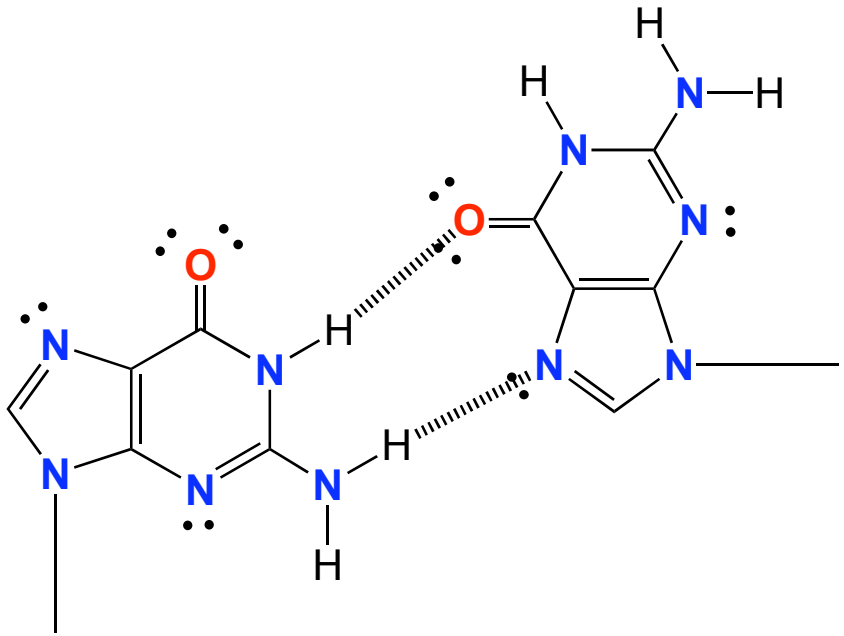
(Donors to Acceptors with ***terrible angles***)



Wild (but good) Base Pairing



Wild (but good) Base Pairing



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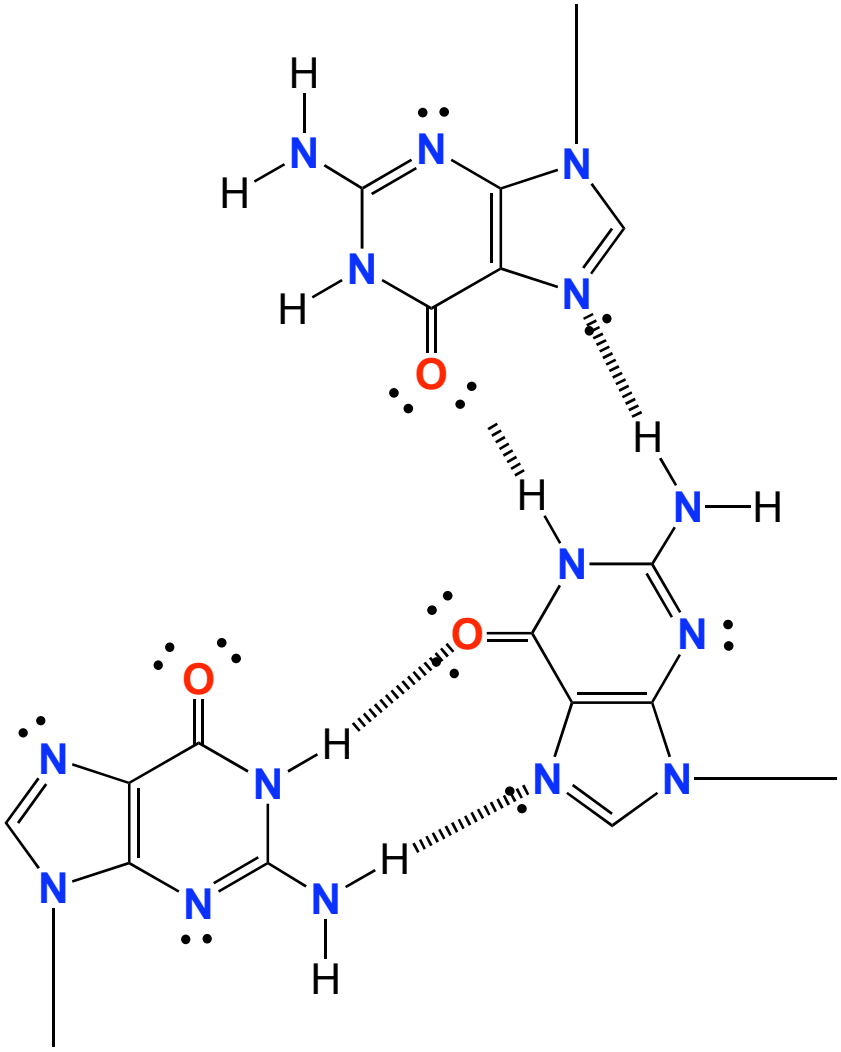

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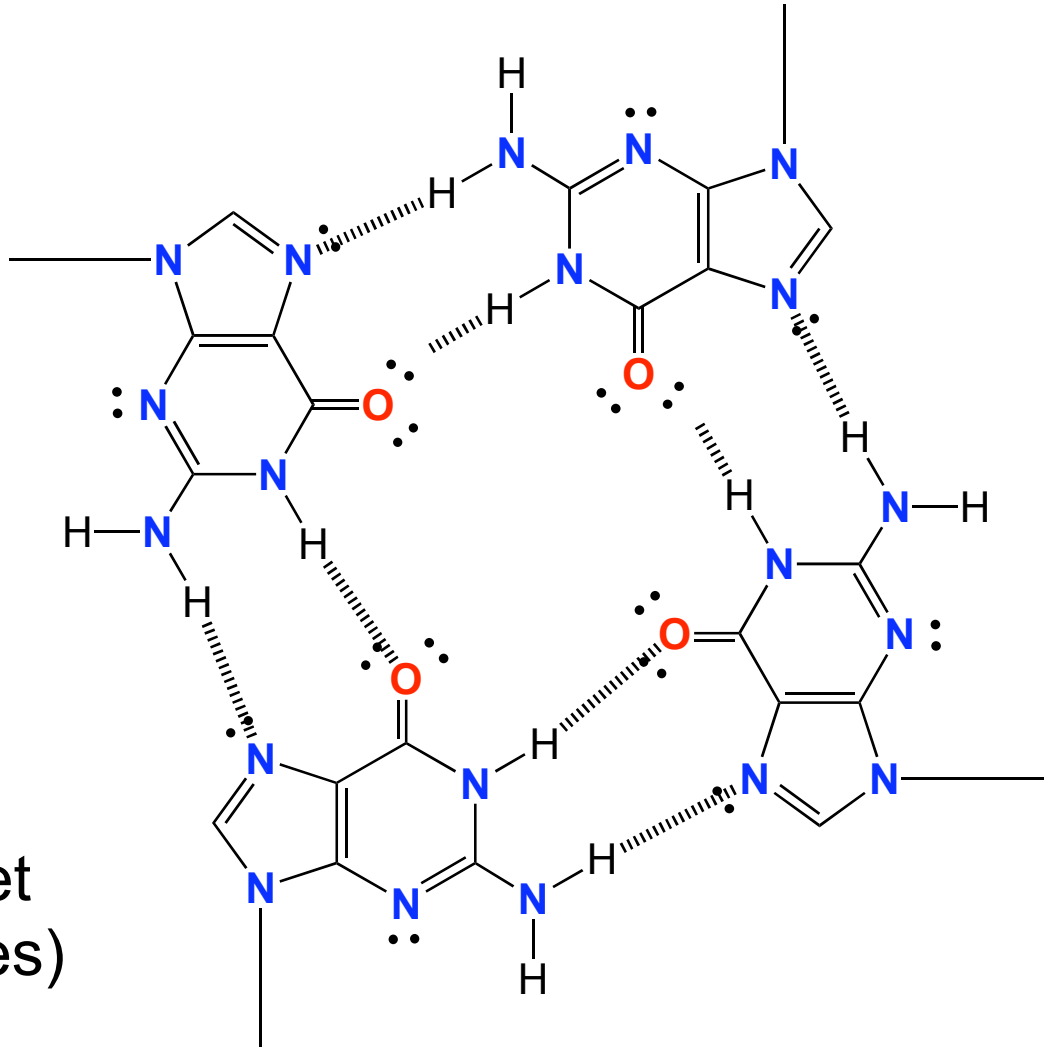
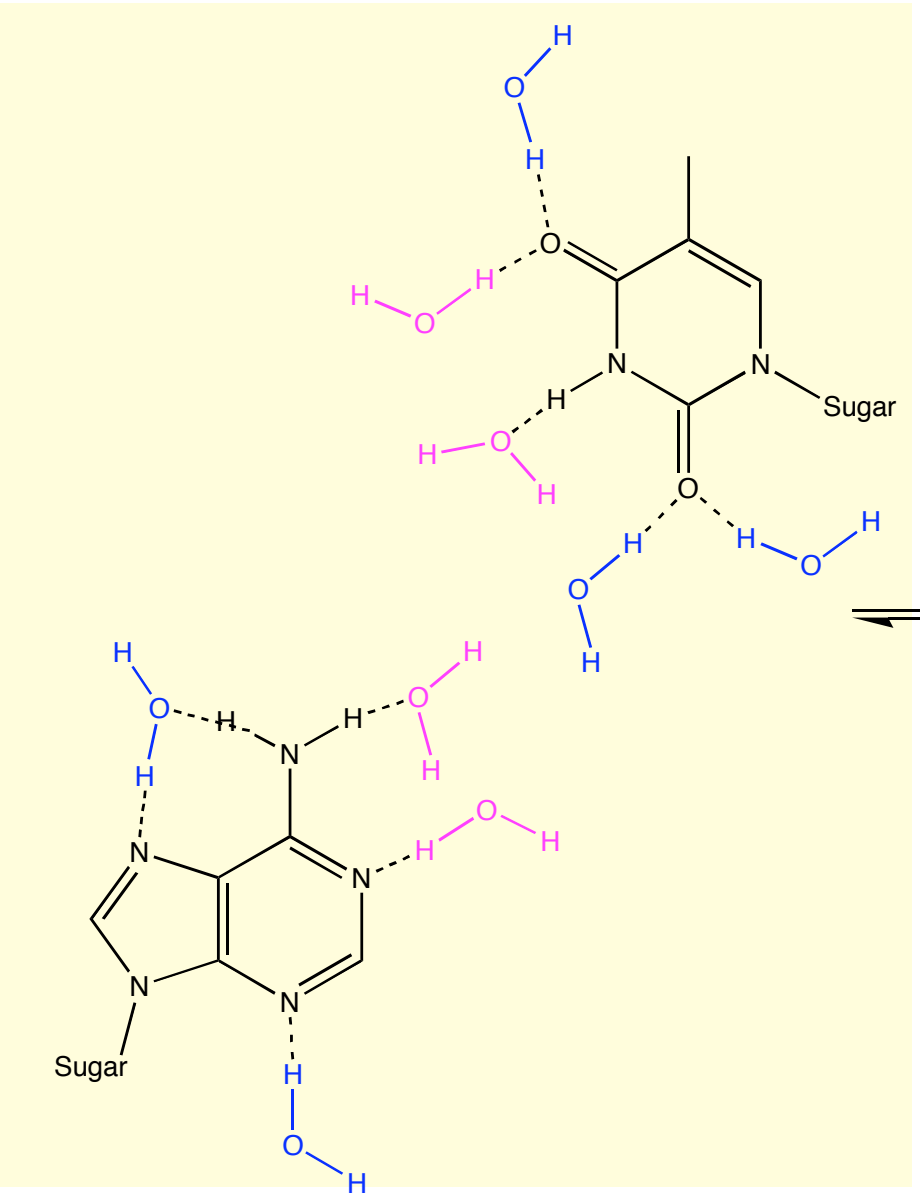


G-quartet
(Telomeres)

AT Base Pair



Ten H-Bonds

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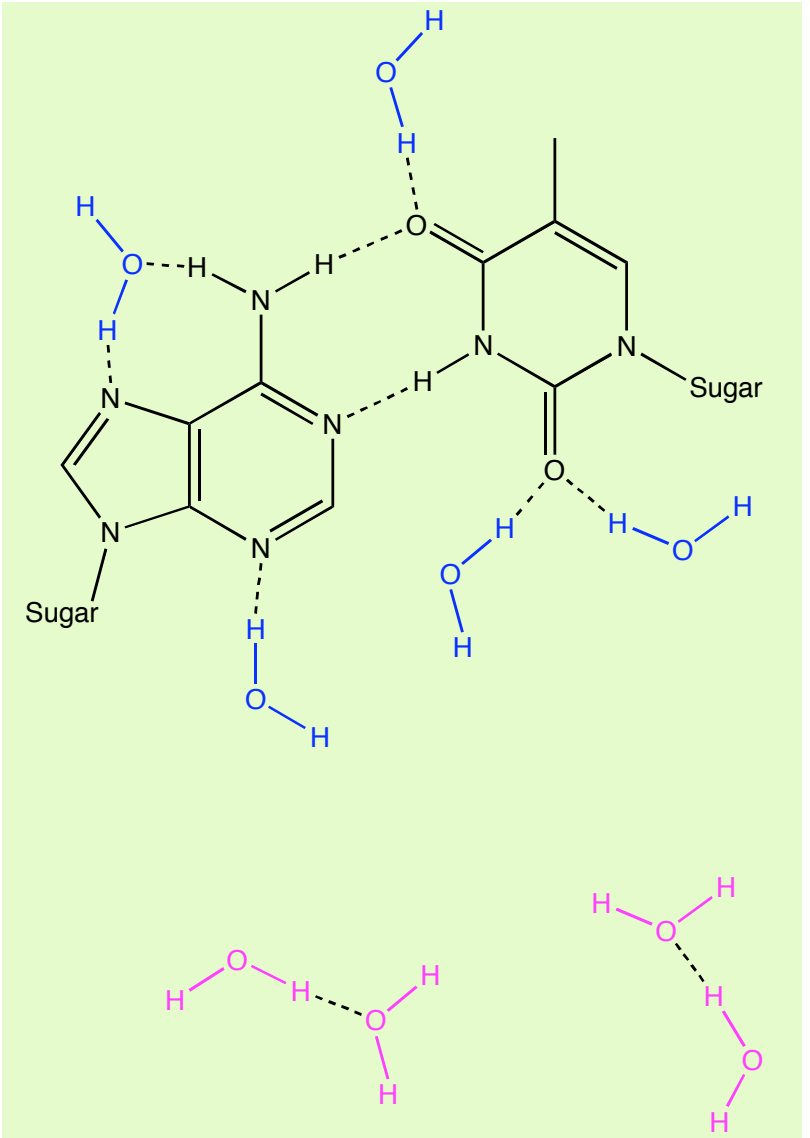
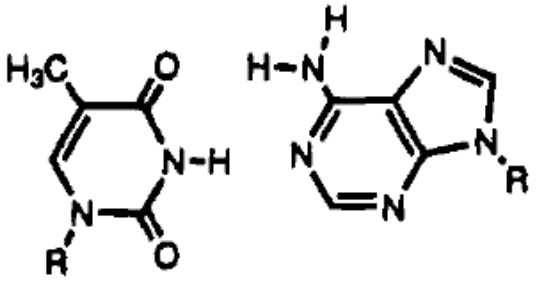
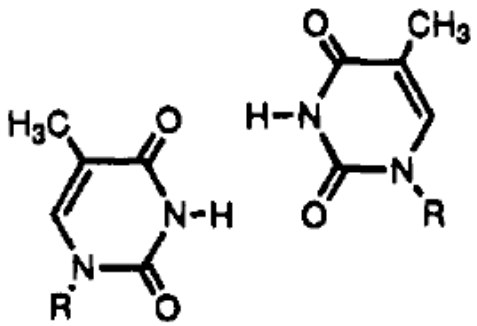


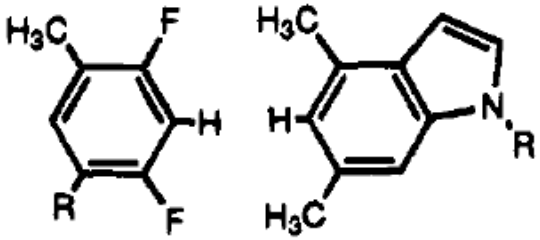
How important are H-bonds in DNA?



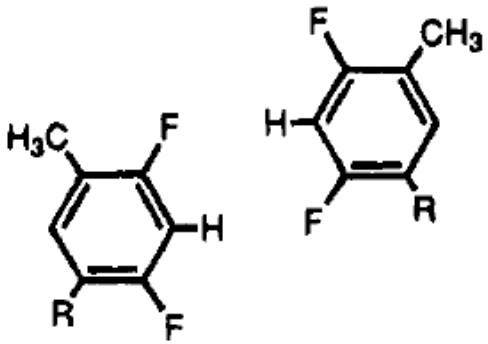
T - A



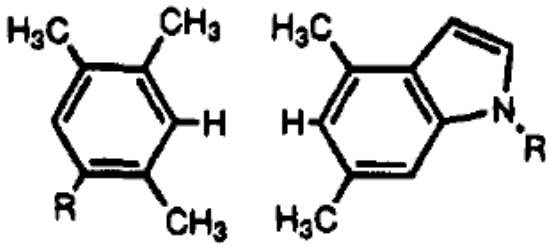
T - T



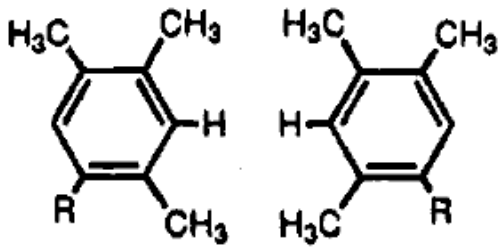
F - D



F - F



B - D



B - B

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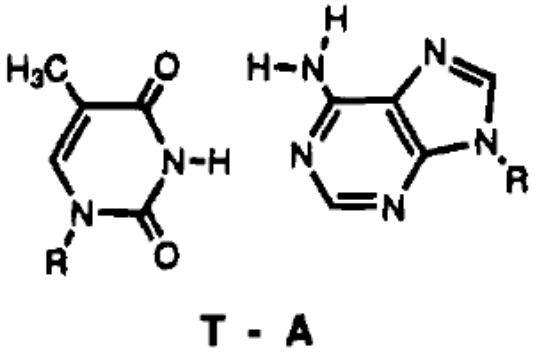
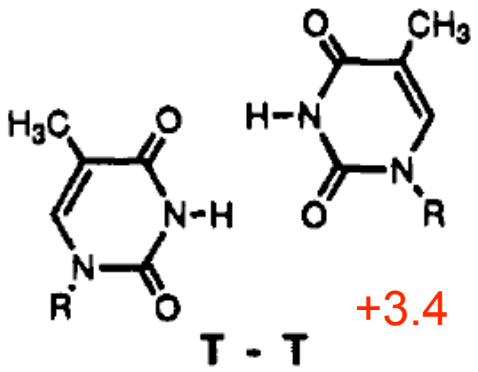
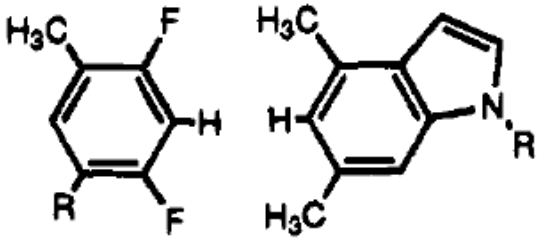


T - A

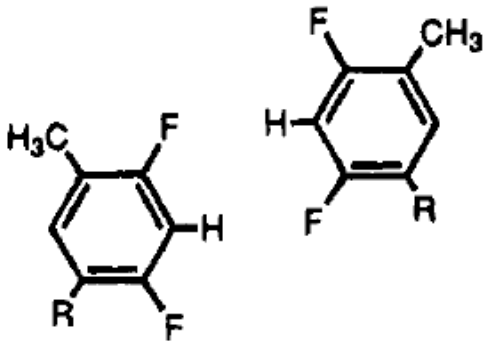


T - T

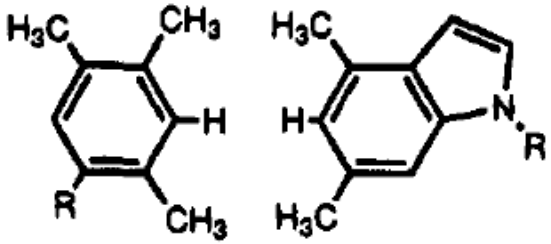
+3.4



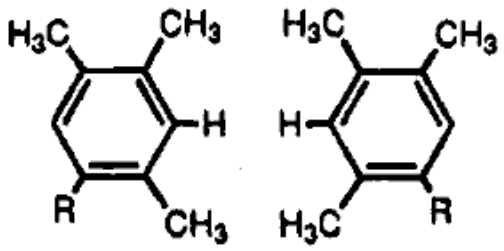
F - D



F - F



B - D



B - B

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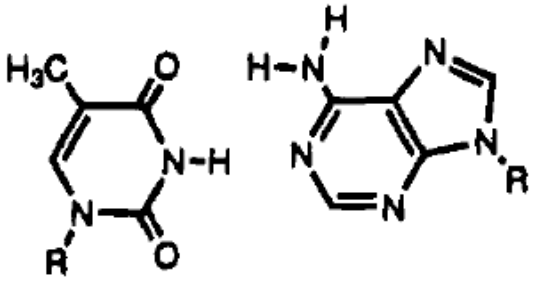
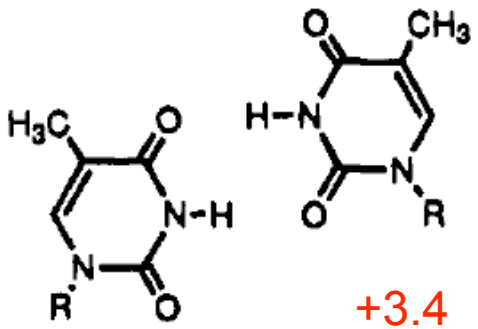
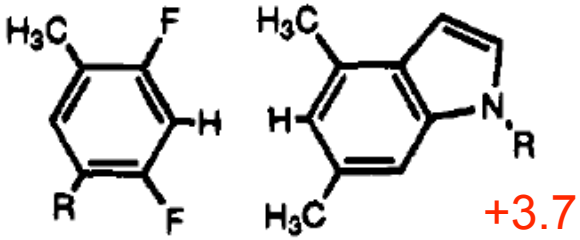


T - A



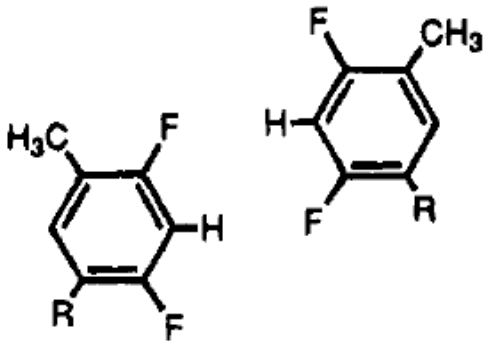
T - T

+3.4

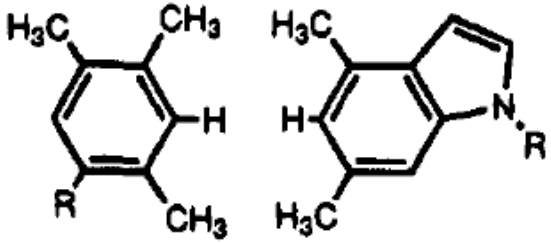


F - D

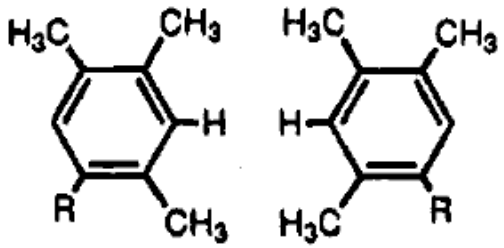
+3.7



F - F



B - D



B - B

J. Am. Chem. Soc., Vol. 117, No. 7, 1995 1867

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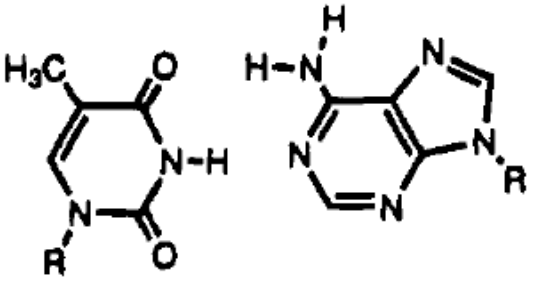
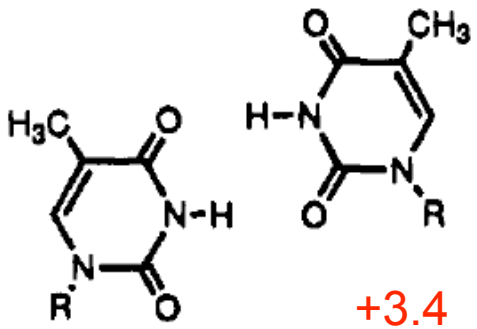
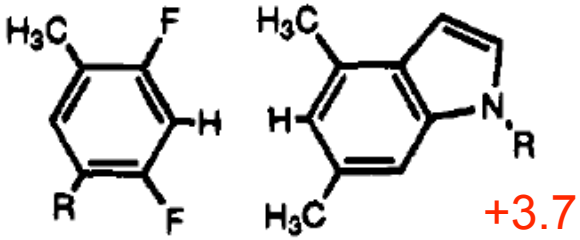


T - A



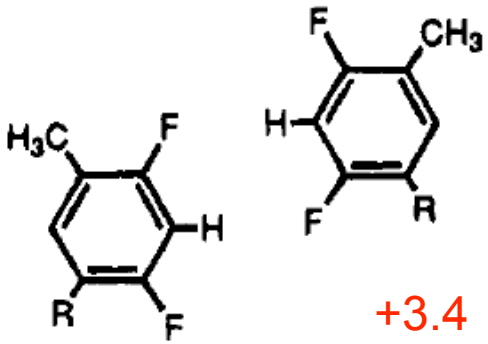
+3.4

T - T



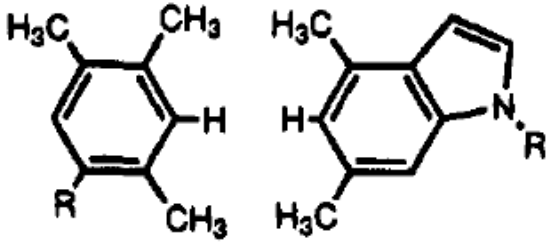
+3.7

F - D

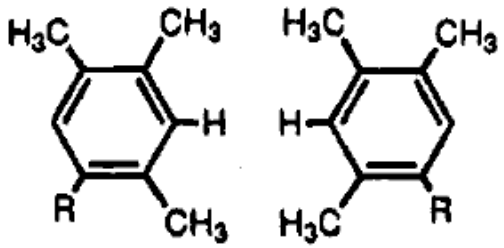


+3.4

F - F



B - D



B - B

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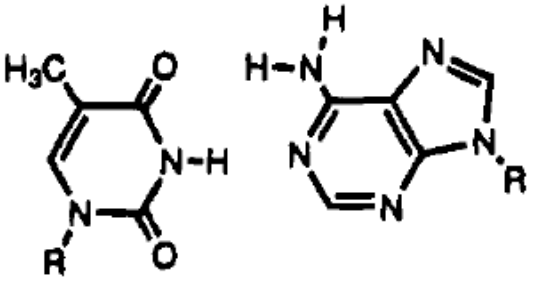
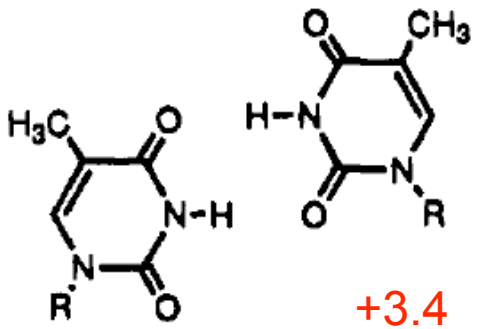
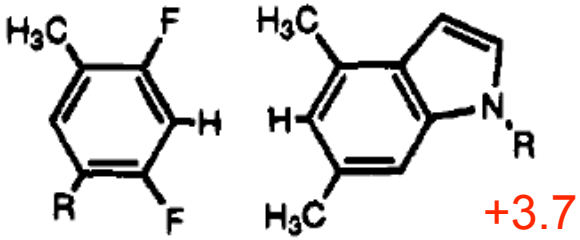


T - A



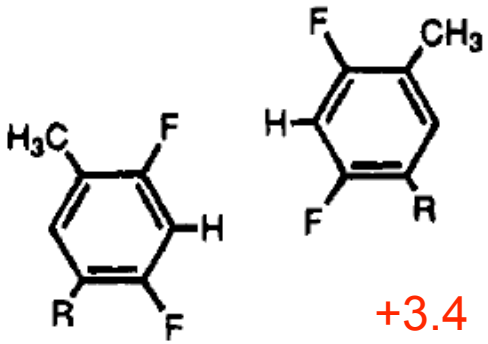
+3.4

T - T



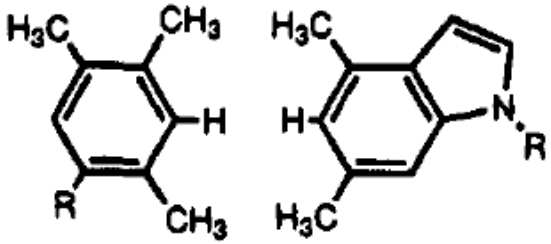
+3.7

F - D



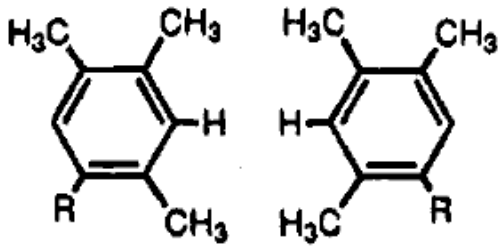
+3.4

F - F



+3.5

B - D



B - B

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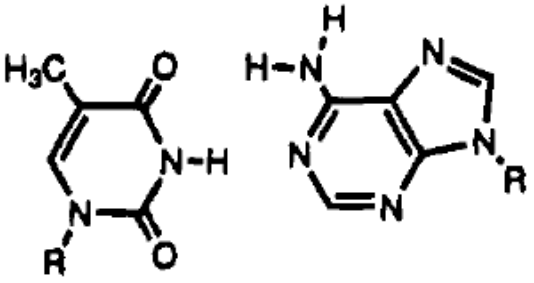
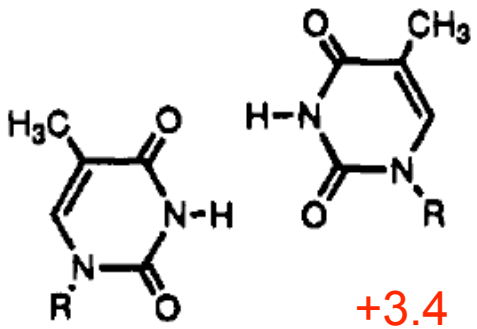
How important are H-bonds in DNA?

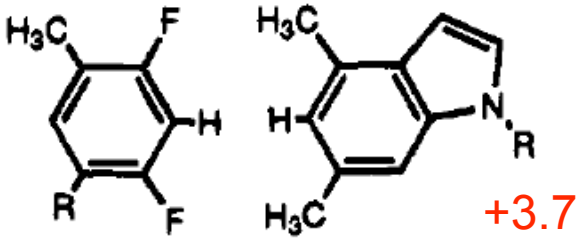


T - A



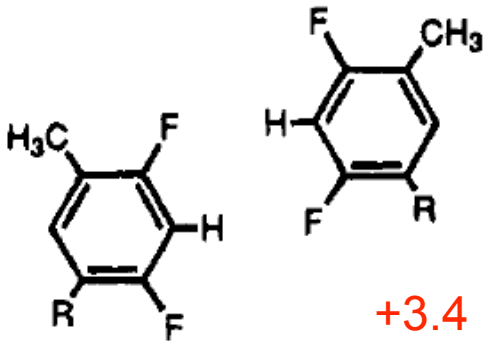
+3.4

T - T



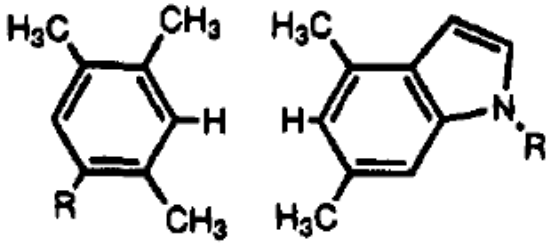
+3.7

F - D



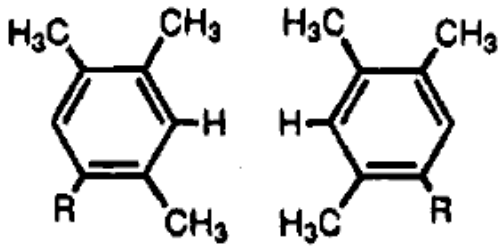
+3.4

F - F



+3.5

B - D



+3.0

B - B

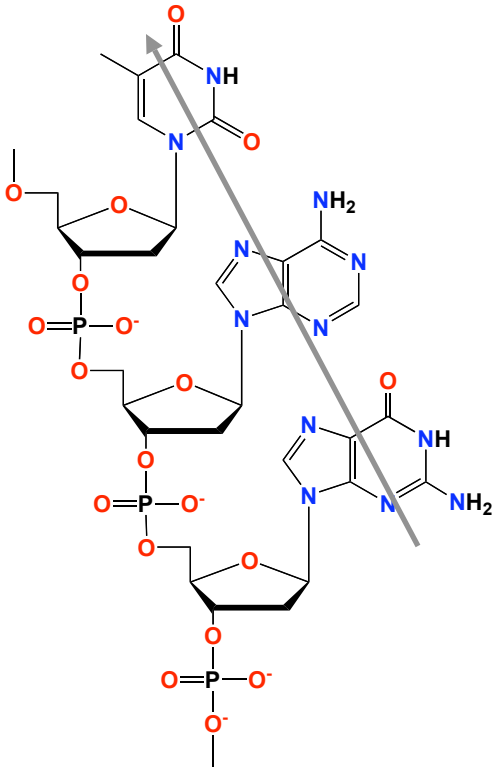
J. Am. Chem. Soc., Vol. 117, No. 7, 1995 1867

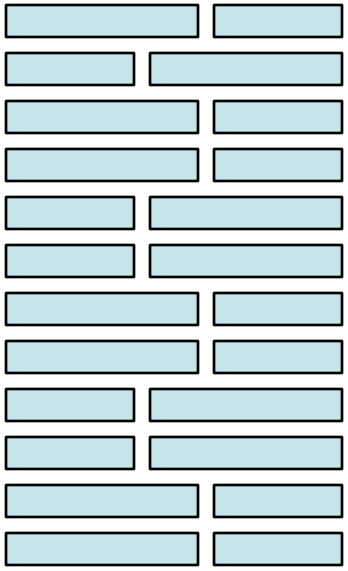
Table 1. Free Energies and Melting Temperatures for Dodecamer Duplexes Containing a Variable T−X, F−X, B−X, or D−X Base Pair (X = A, T, C, G)

duplex	T_m (°C) [a]	$-\Delta G°_{25}$ (kcal)
5'-CTTTTGTTTCTT 3'-GAAAACAAAGAA	39.4	12.3
5'-CTTTTGTTTCTT 3'-GAAAACGAAGAA	26.4	8.7
5'-CTTTTGTTTCTT 3'-GAAAAGGAAGAA	30.7	9.3
5'-CTTTTGTTTCTT 3'-GAAAAGTAAGAA	27.1	8.9
5'-CTTTTGFTTCTT 3'-GAAAACAAAGAA	21.4	7.4
5'-CTTTTGFTTCTT 3'-GAAAACGAAGAA	25.0	8.2
5'-CTTTTGFTTCTT 3'-GAAAAGGAAGAA	23.0	8.0
5'-CTTTTGFTTCTT 3'-GAAAAGTAAGAA	20.2	7.3
5'-CTTTTGBTTCTT 3'-GAAAACAAAGAA	21.0	7.5
5'-CTTTTGBTTCTT 3'-GAAAACGAAGAA	22.9	7.8
5'-CTTTTGBTTCTT 3'-GAAAAGGAAGAA	20.1	7.6
5'-CTTTTGBTTCTT 3'-GAAAAGTAAGAA	20.3	6.7
5'-CTTTTGDTTCTT 3'-GAAAACAAAGAA	20.8	7.4
5'-CTTTTGDTTCTT 3'-GAAAACGAAGAA	22.2	7.6
5'-CTTTTGDTTCTT 3'-GAAAAGGAAGAA	19.7	7.4
5'-CTTTTGDTTCTT 3'-GAAAAGTAAGAA	17.6	6.9

[a] Conditions: 100 mM NaCl, 10 mM $MgCl_2$, 10 mM Na·PIPES, pH 7.0, 1.6 μM each strand.

Burial of hydrophobic surface drives helix formation (hydrophobic core / stacking interactions)





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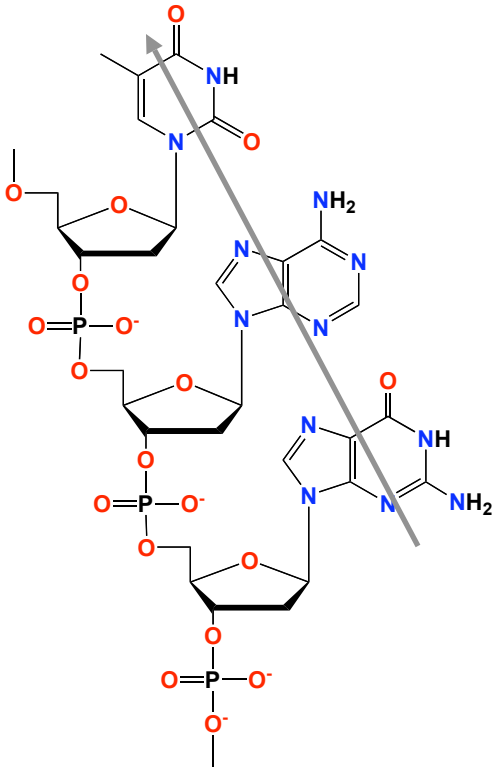
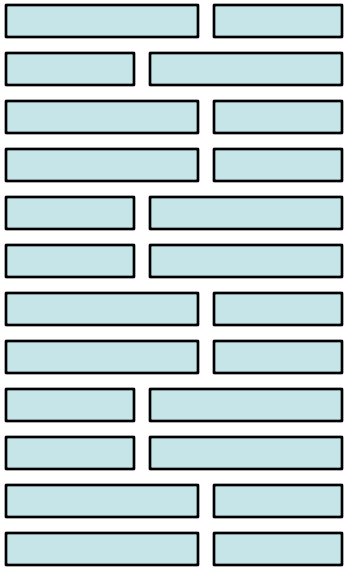
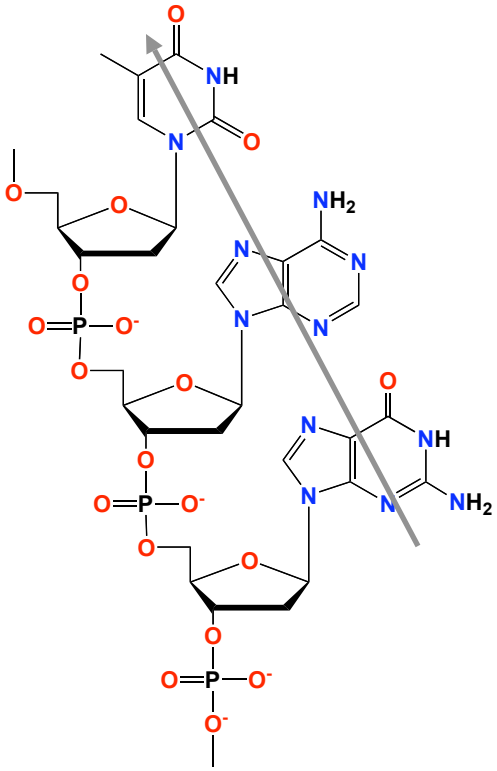
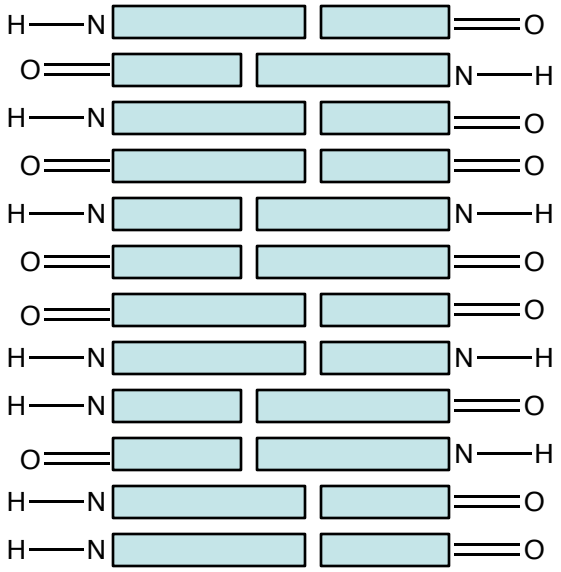




Flat faces are nonpolar

Burial of hydrophobic surface drives helix formation (hydrophobic core / stacking interactions)

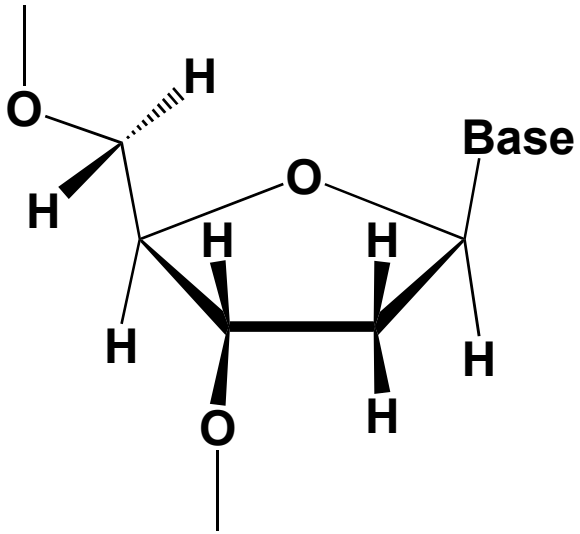


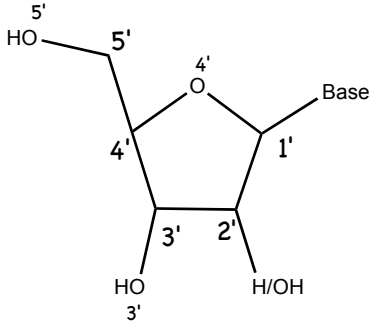


Flat faces are nonpolar
Edges are very polar (can H-bond)

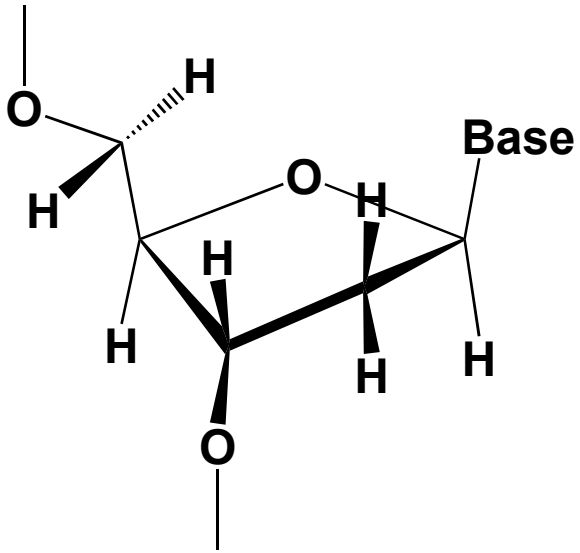
Other chemical constraints

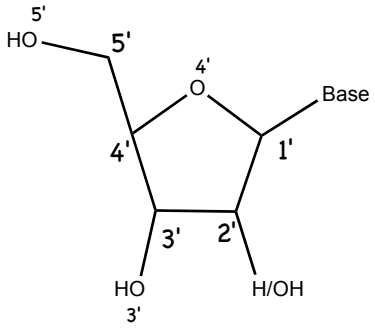
Furanose Sugar Ring



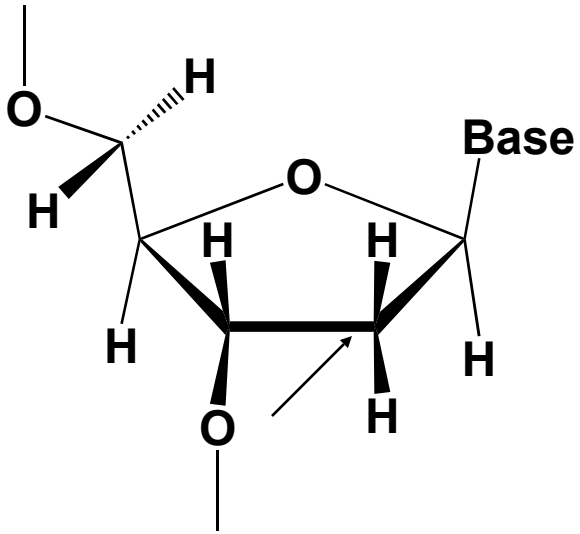


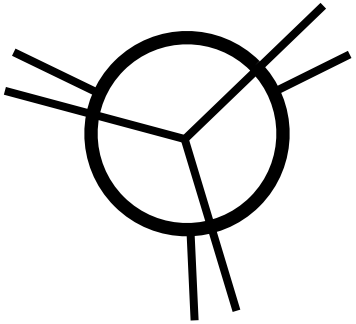
Furanose Sugar Ring

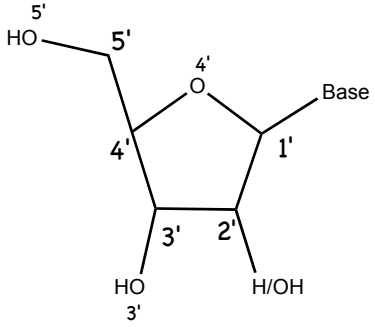




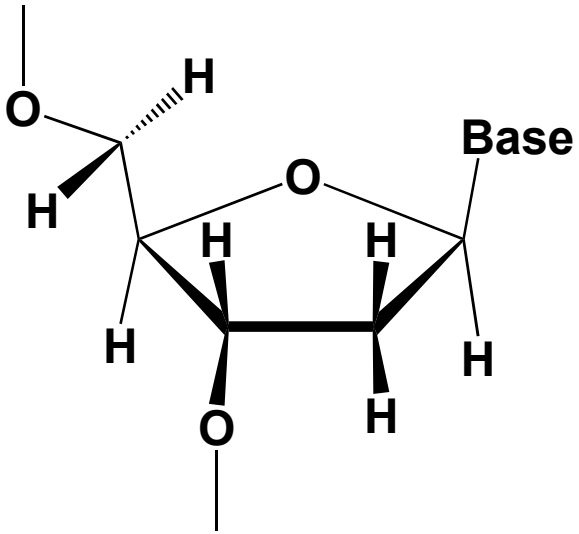
Furanose Sugar Ring

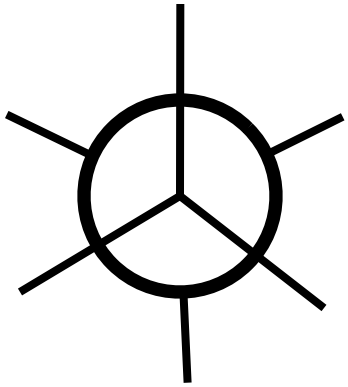


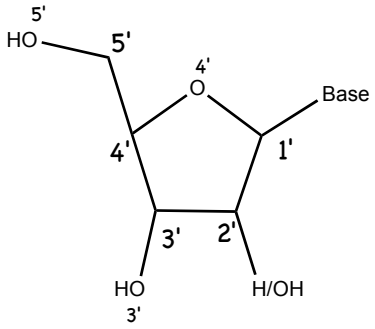




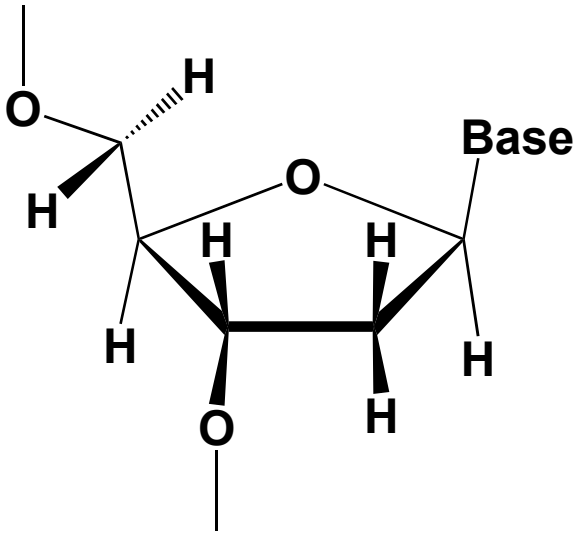
Furanose Sugar Ring

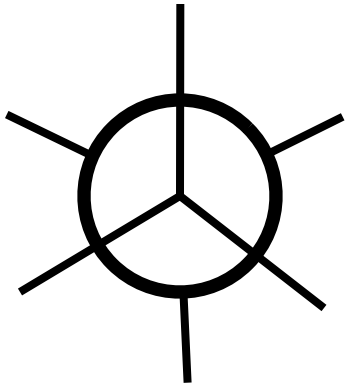


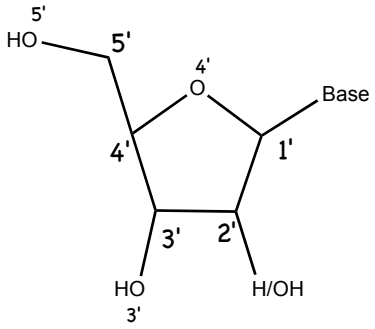


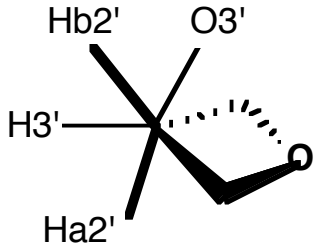


Furanose Sugar Ring

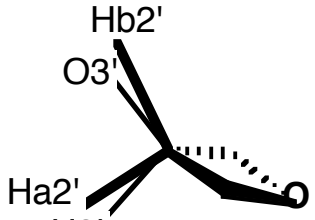






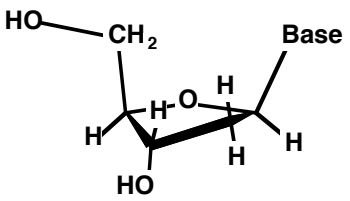


Staggered
Puckered

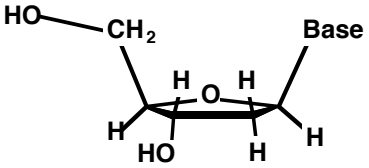


Eclipsed
Planar

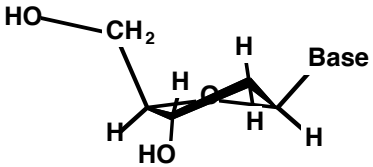
Furanose Sugar Ring



C3' exo



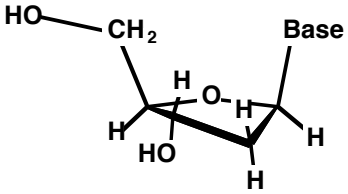
Unpuckered



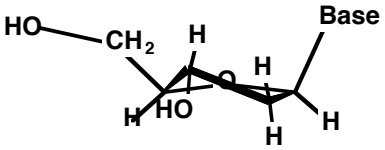
C2' endo

endo

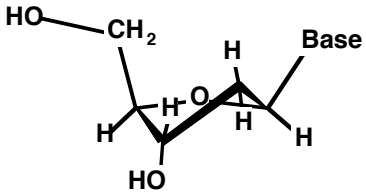
exo



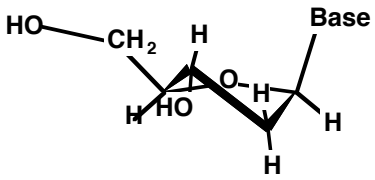
C2' exo



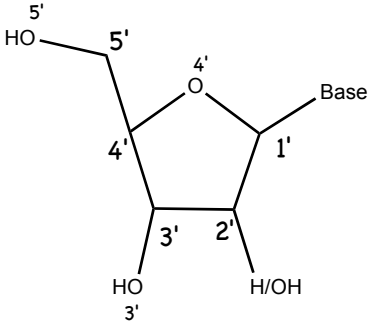
C3' endo

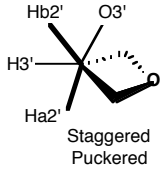


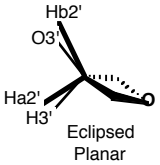
C2' endo - C3' exo



C2' exo - C3' endo







Hoogsteen vindicated

Letters to Nature

Nature **430**, 377-380 (15 July 2004) | doi: 10.1038/nature02692

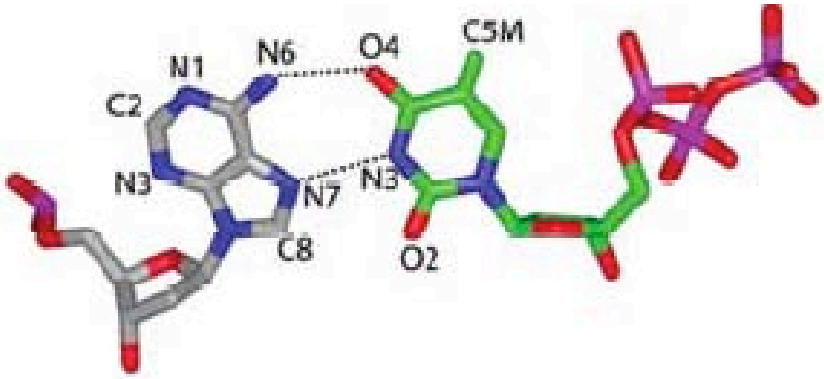
Replication by human DNA polymerase-ι occurs by Hoogsteen base-pairing

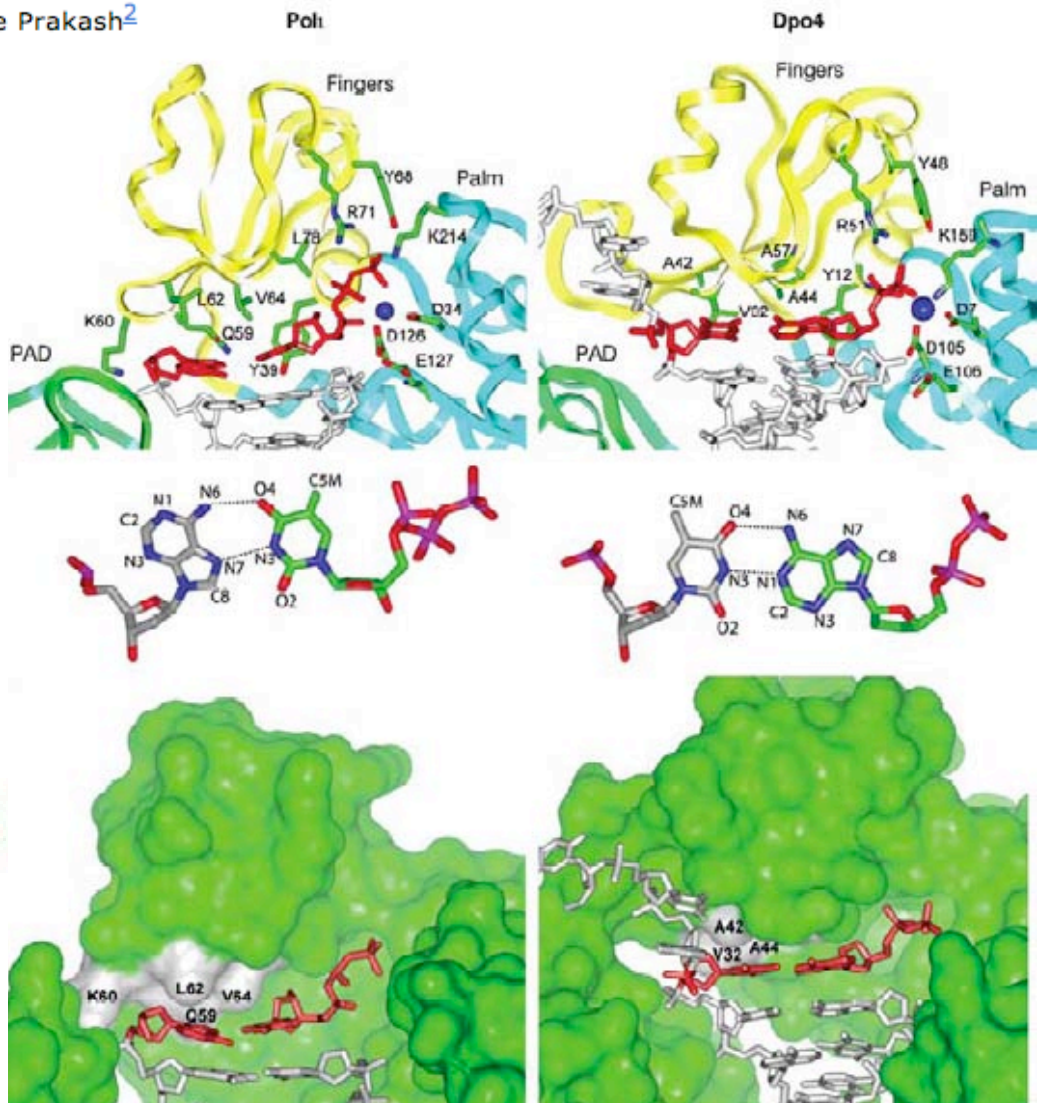
Deepak T. Nair[1], Robert E. Johnson[2], Satya Prakash[2], Louise Prakash[2] and Aneel K. Aggarwal[1]

A crystal structure from from July 2004 shows that an error correcting (and error-prone) DNA polymerase uses Hoogsteen-WC base pairing to recognize the incoming substrate dNTP.

This supports biochemical studies that had been suggesting such a pairing.

This polymerase is good at bypassing lesions in the DNA (eg, damaged Watson-Crick face of G).





Hoogsteen vindicated

But… perhaps not…

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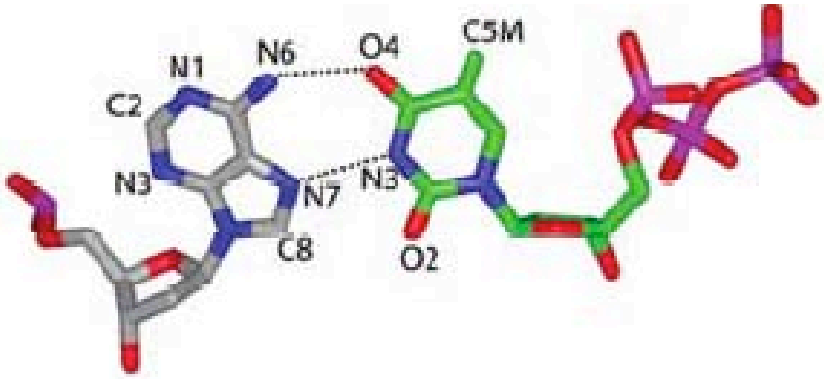
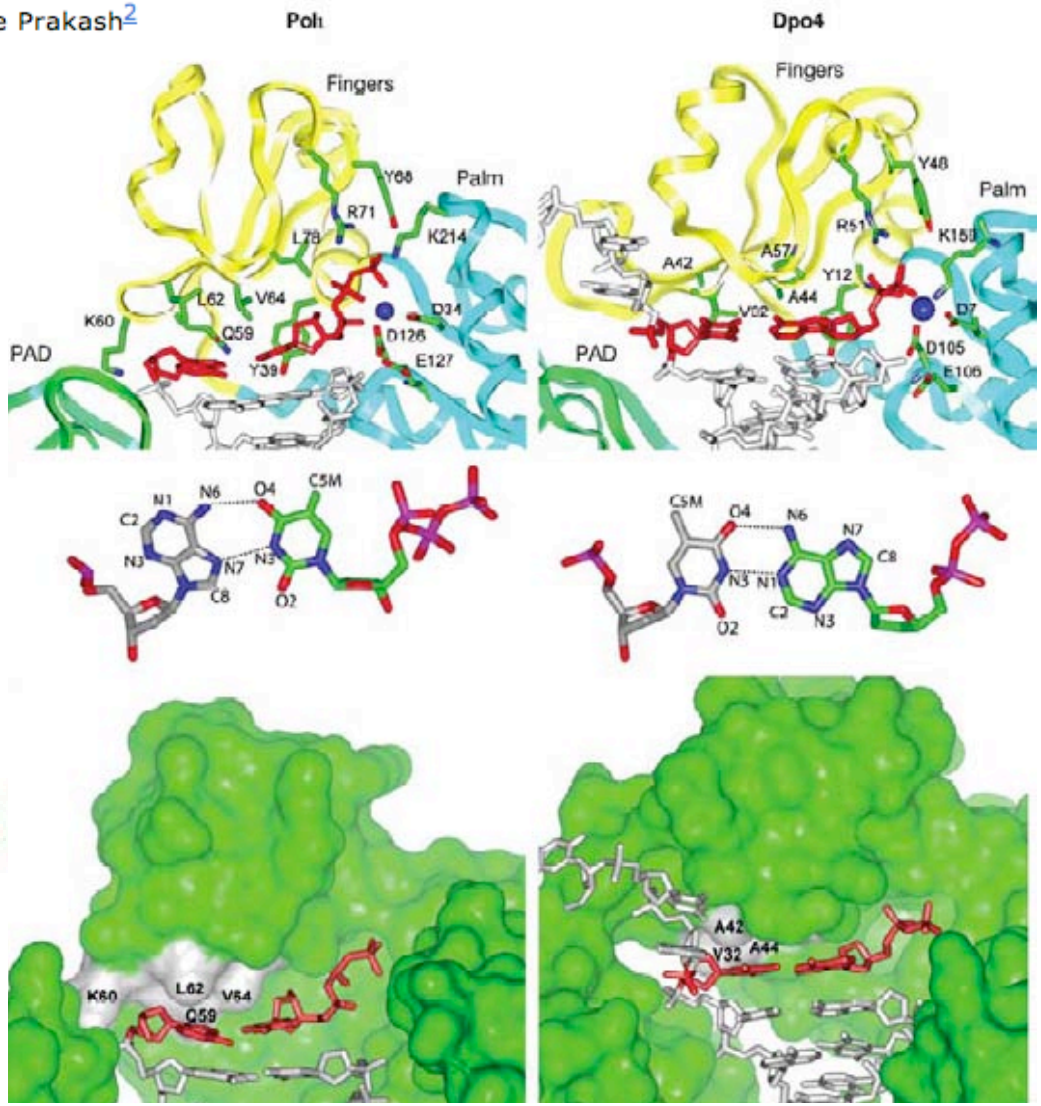
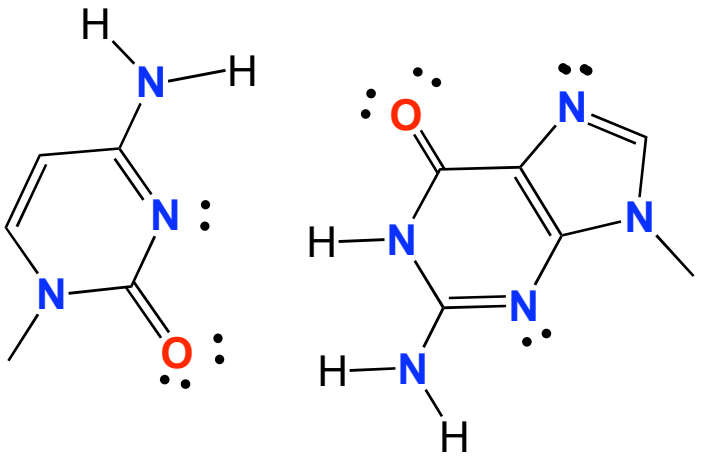




Why is Watson-Crick so good?

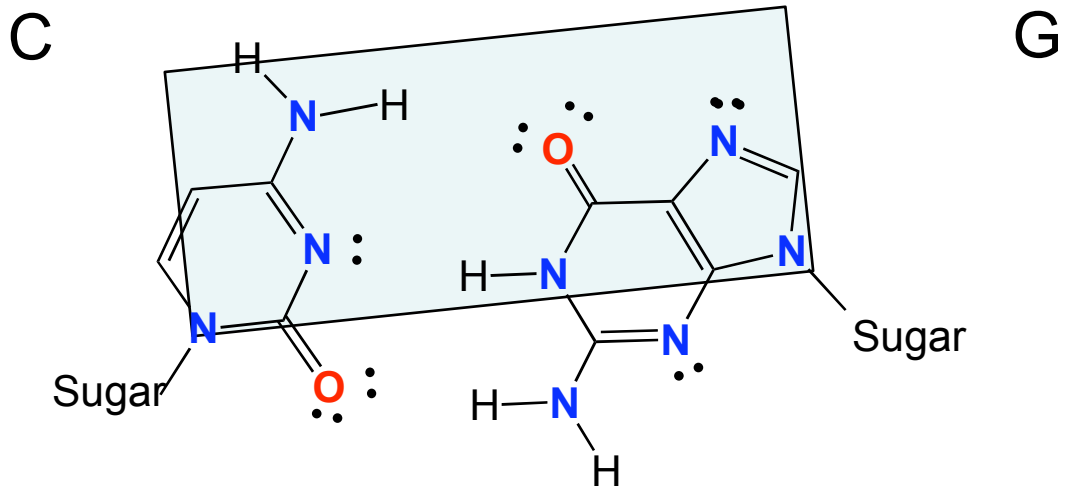
C



G

All four WC base pairs
are
isosteric

Why is Watson-Crick so good?



All four WC base pairs
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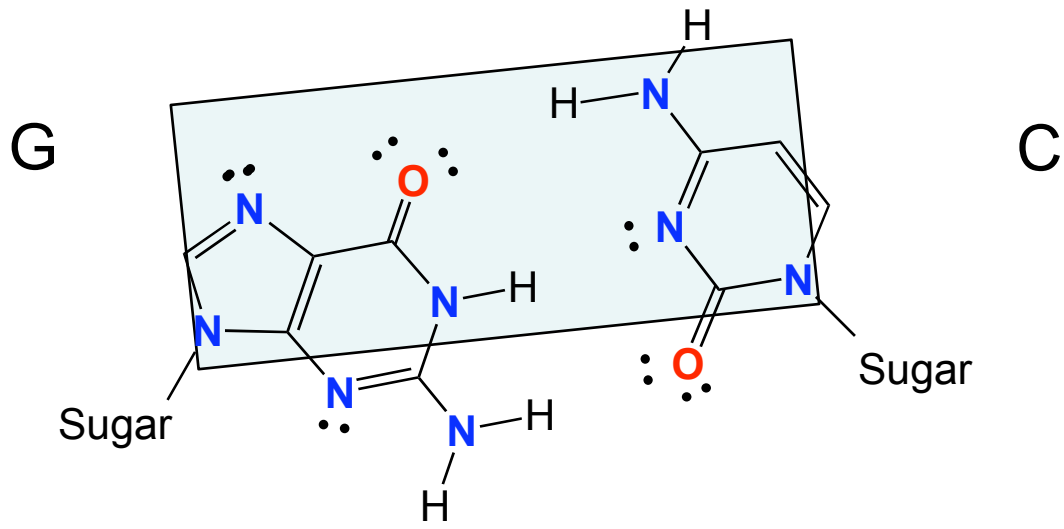

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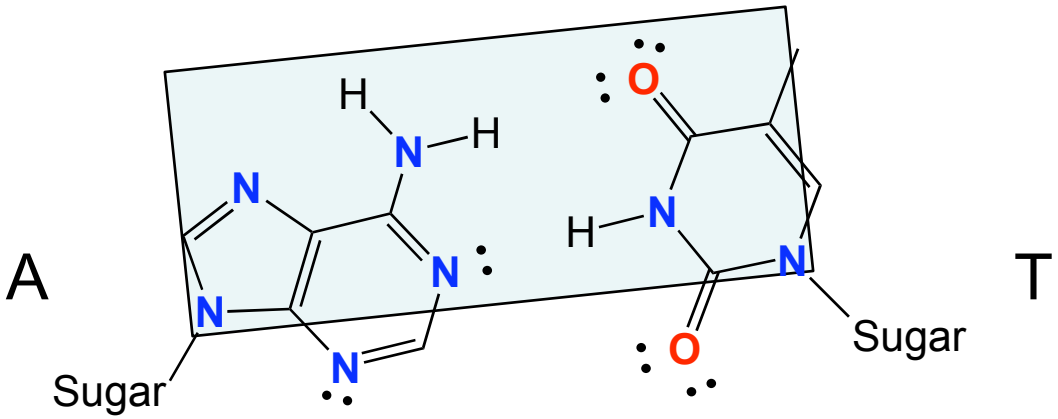

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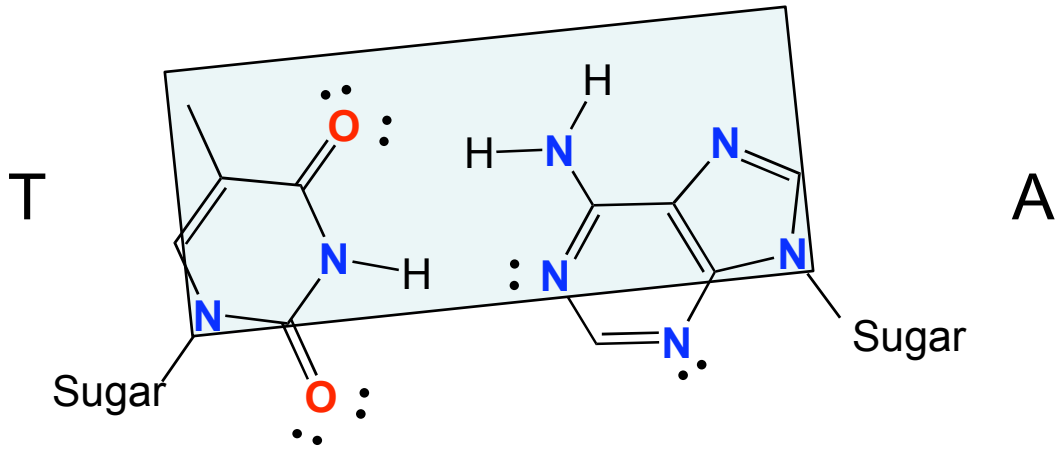

All four WC base pairs
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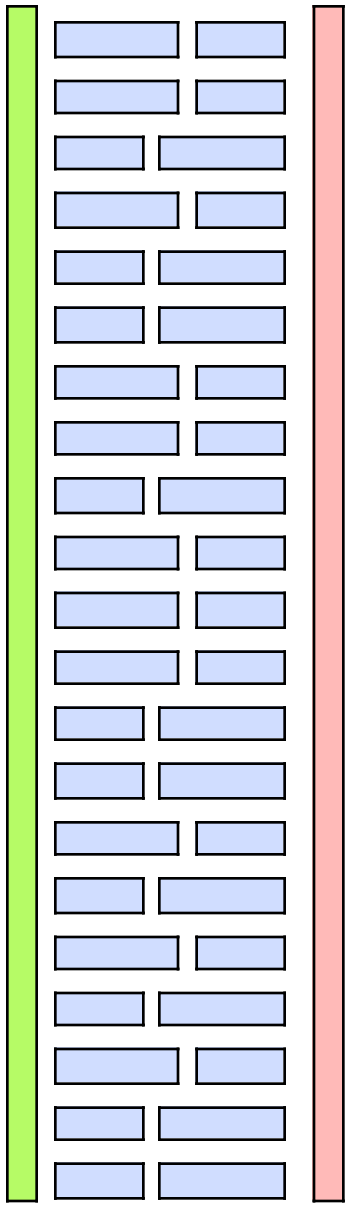
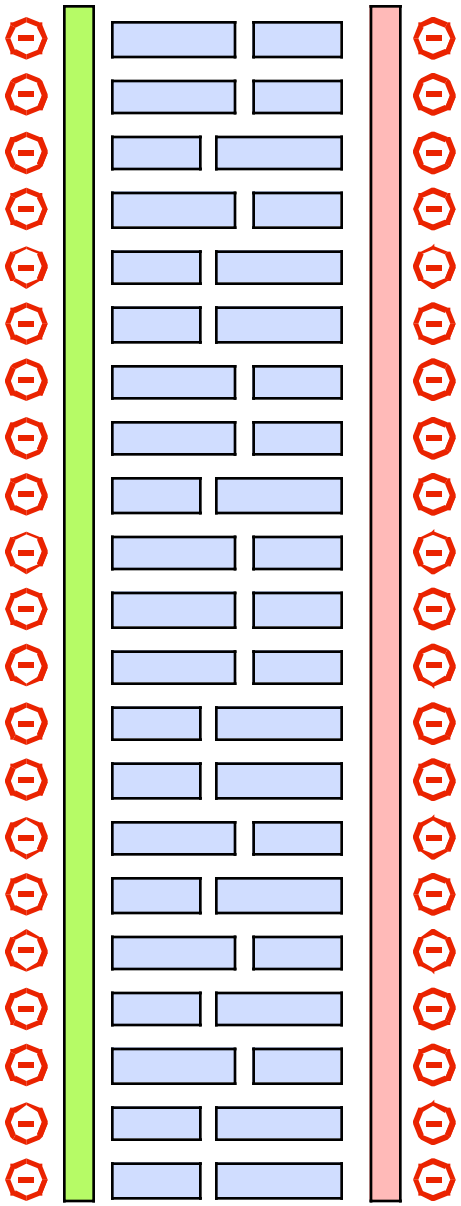
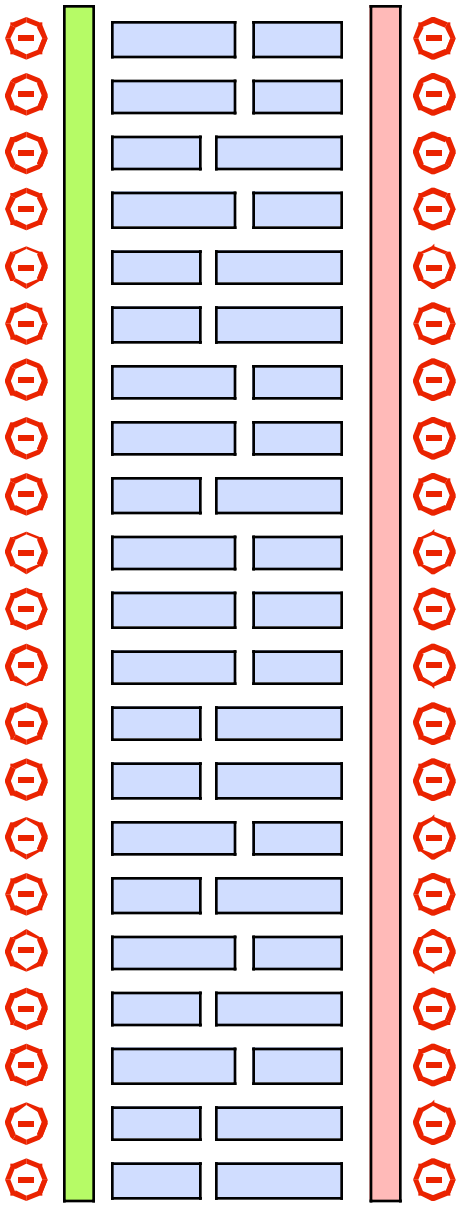
Why ***a helix***?

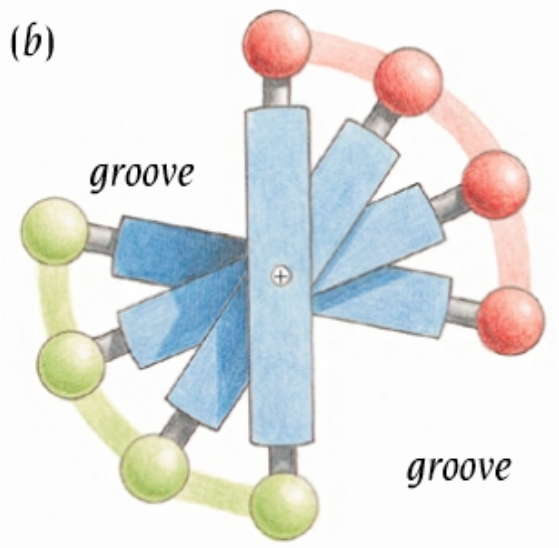




Why ***a helix***?



Why ***a helix***?



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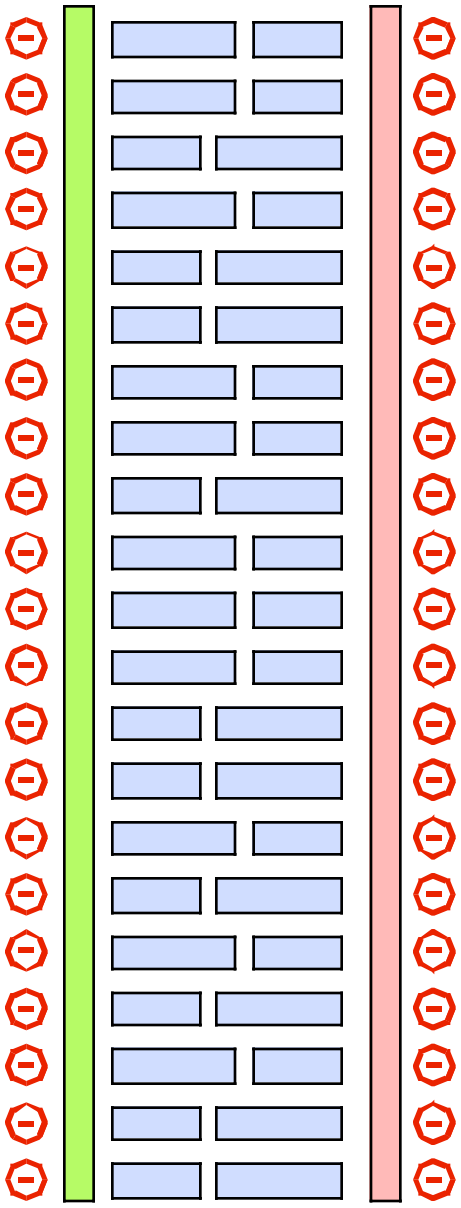
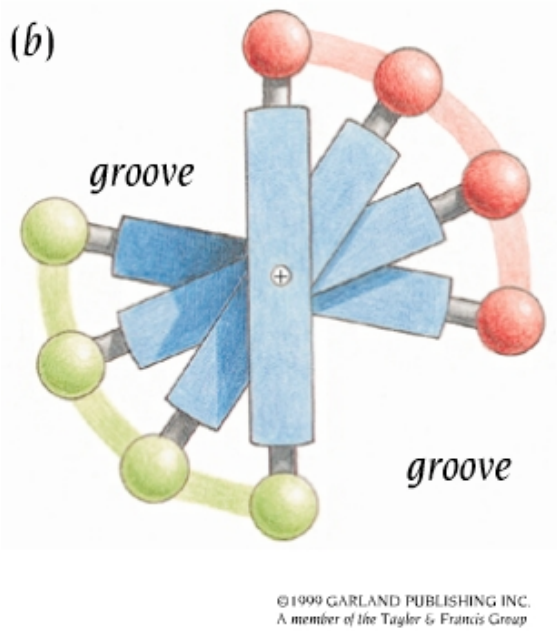


Why ***a helix***?



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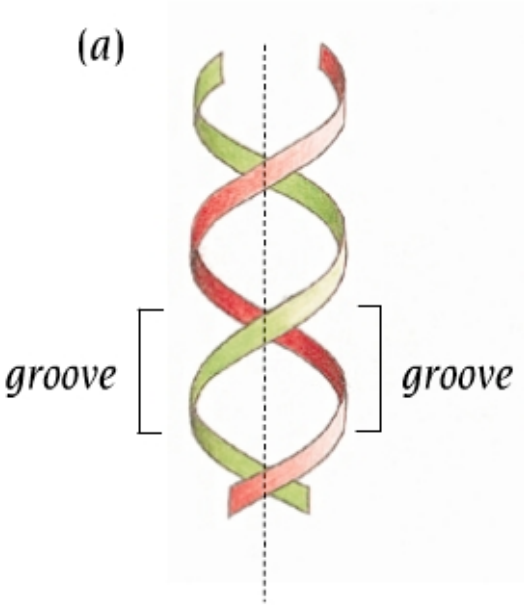
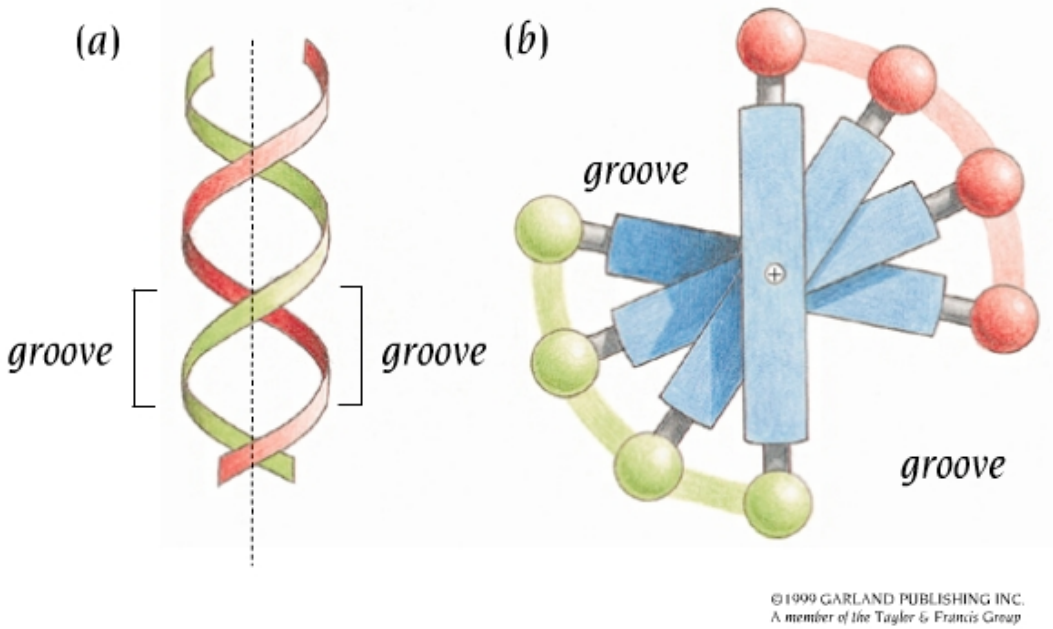


Why ***major*** and ***minor*** grooves?



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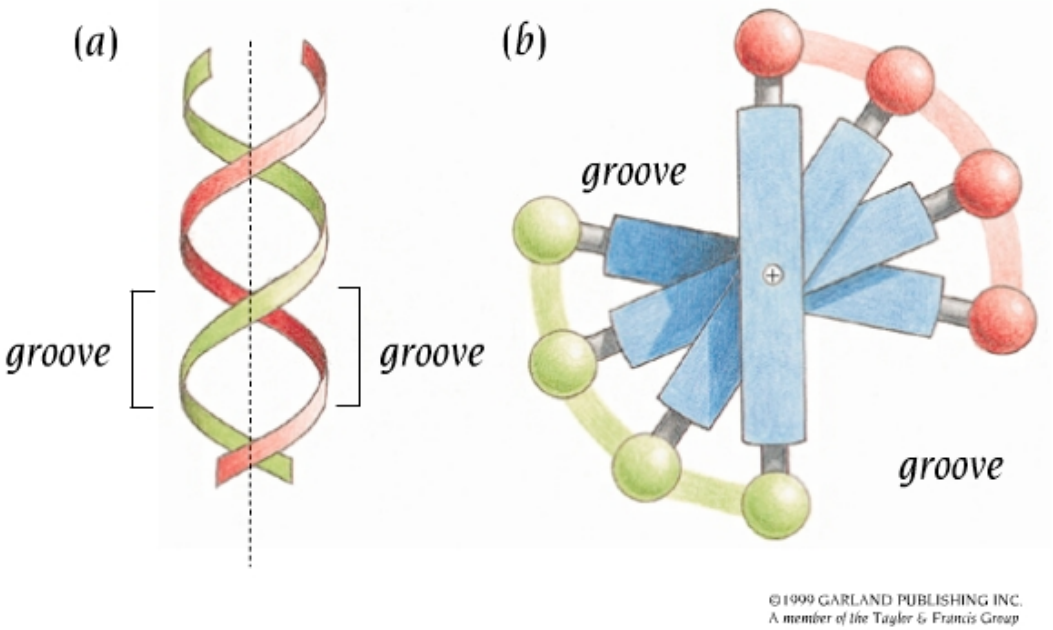
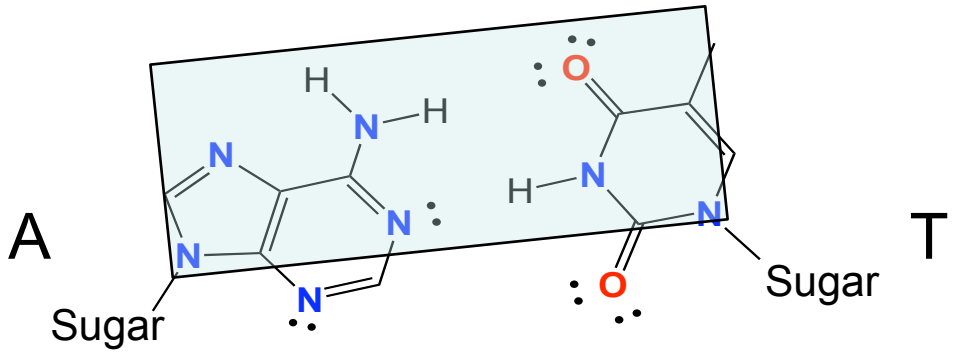
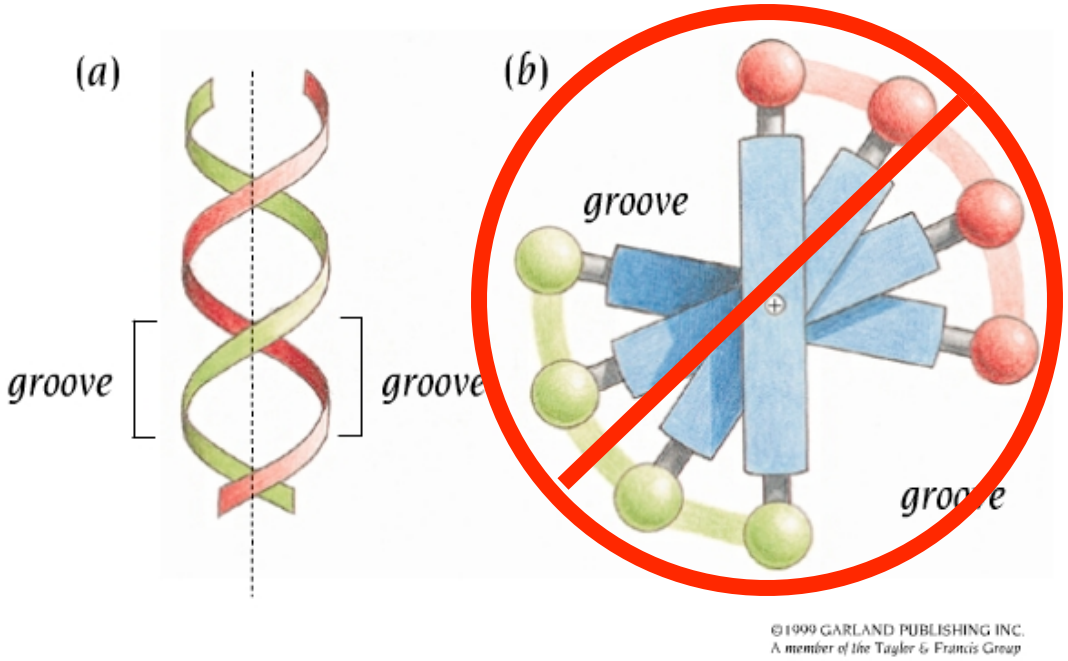
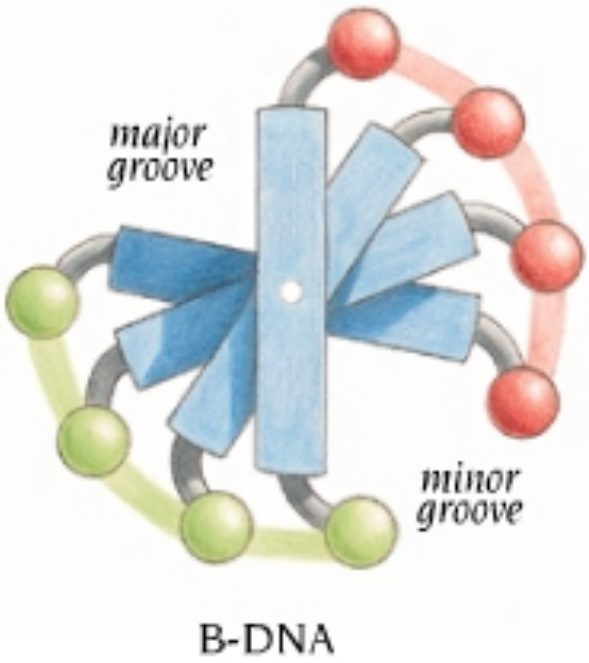
Why ***major*** and ***minor*** grooves?

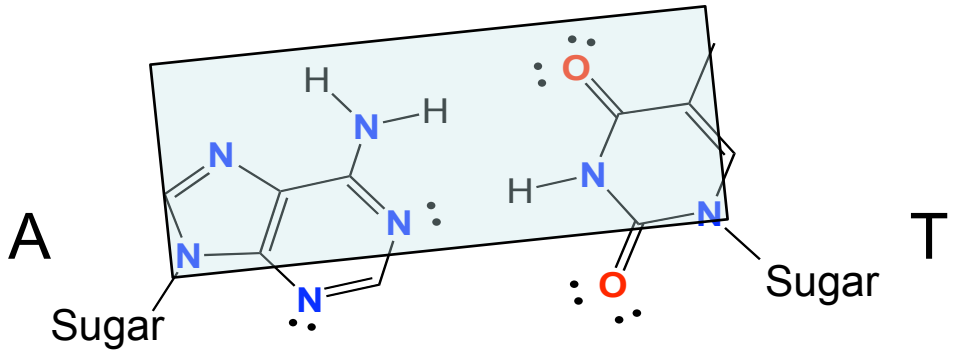




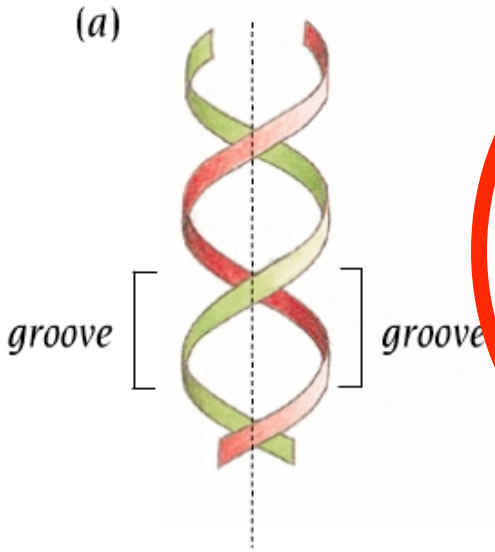
Why ***major*** and ***minor*** grooves?

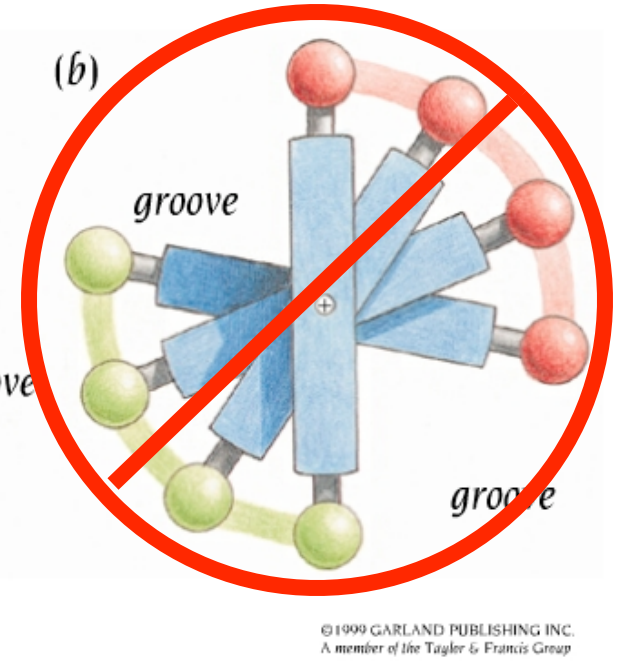






Why ***major*** and ***minor*** grooves?





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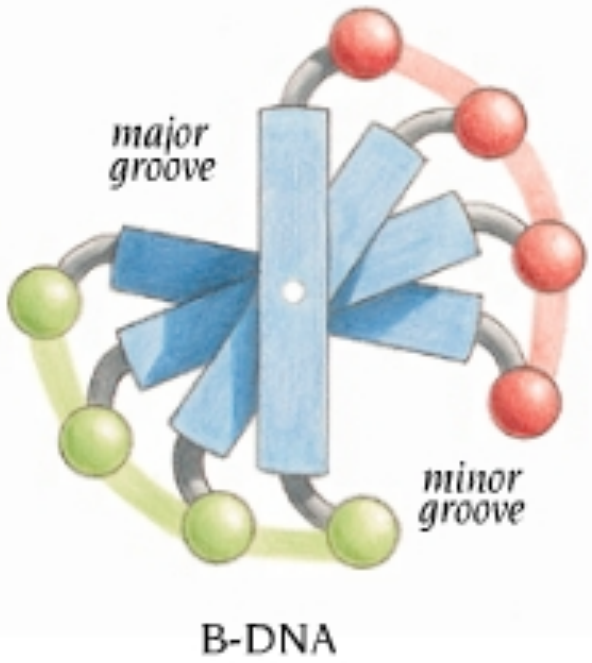
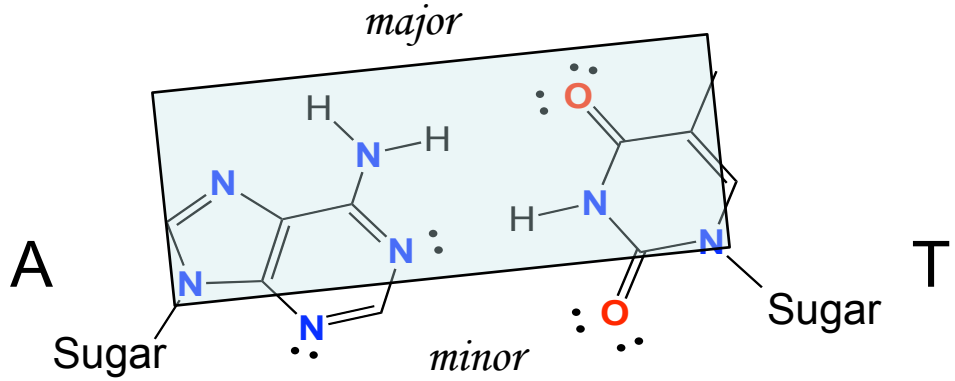
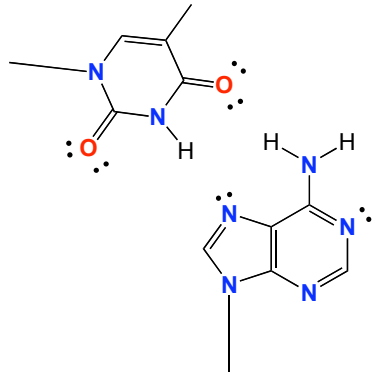
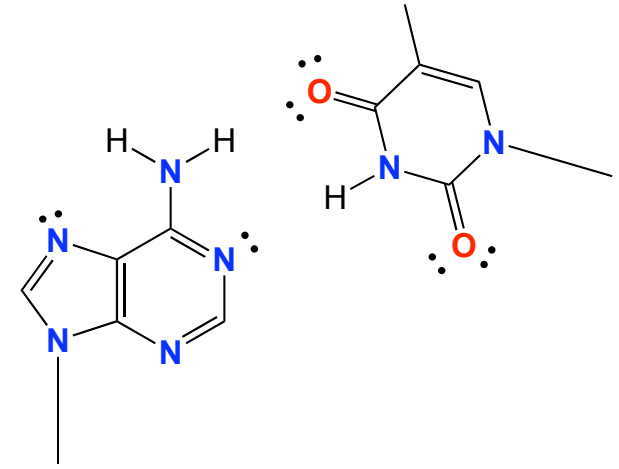


B-DNA

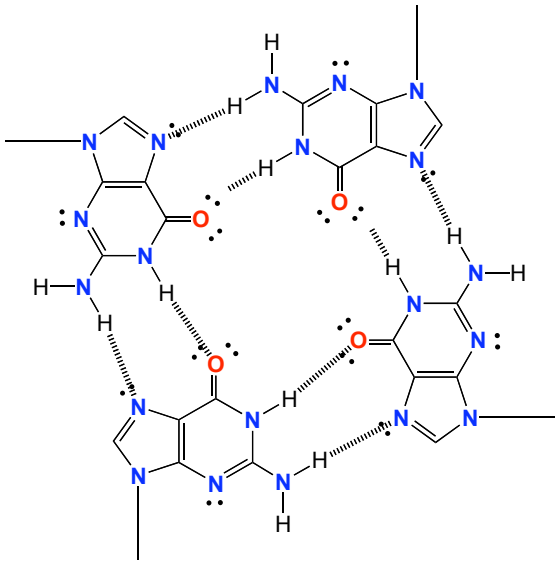


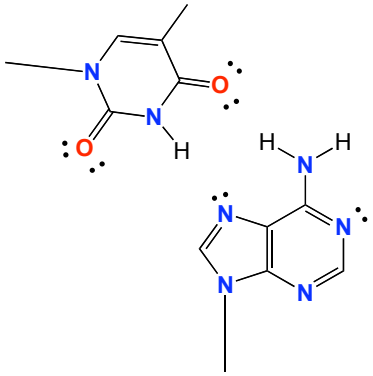
Nucleic Acid - Nucleic Acid Recognition

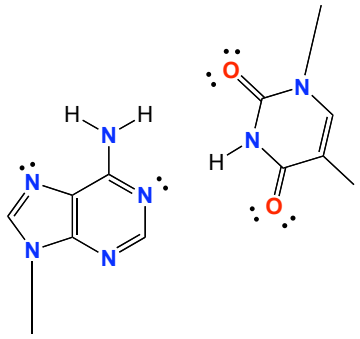


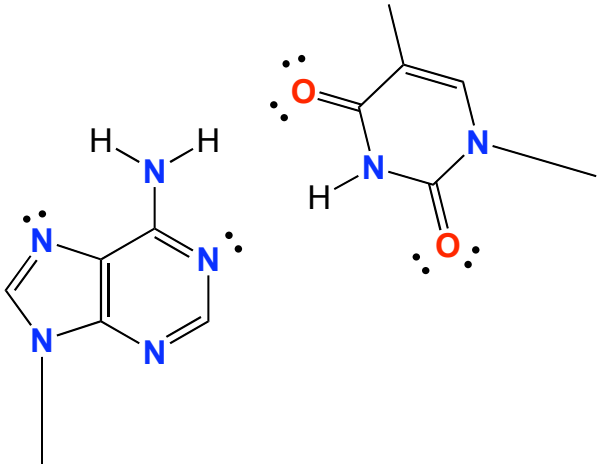


Nucleic Acid - Nucleic Acid Recognition





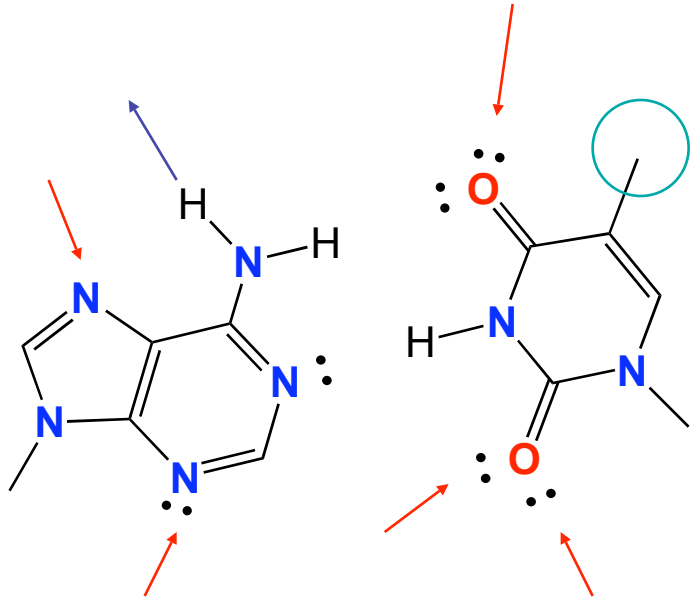




Why is the major groove so good?

Major Groove

A



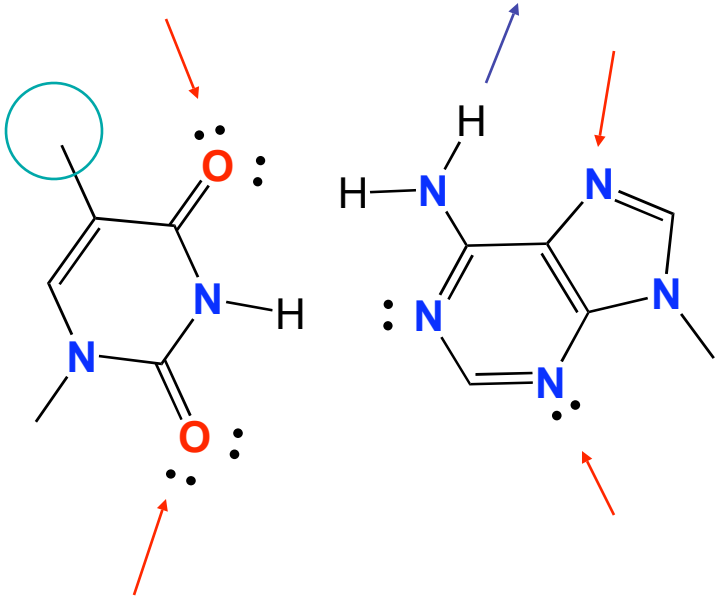
T

Minor Groove

Why is the major groove so good?

Major Groove

T



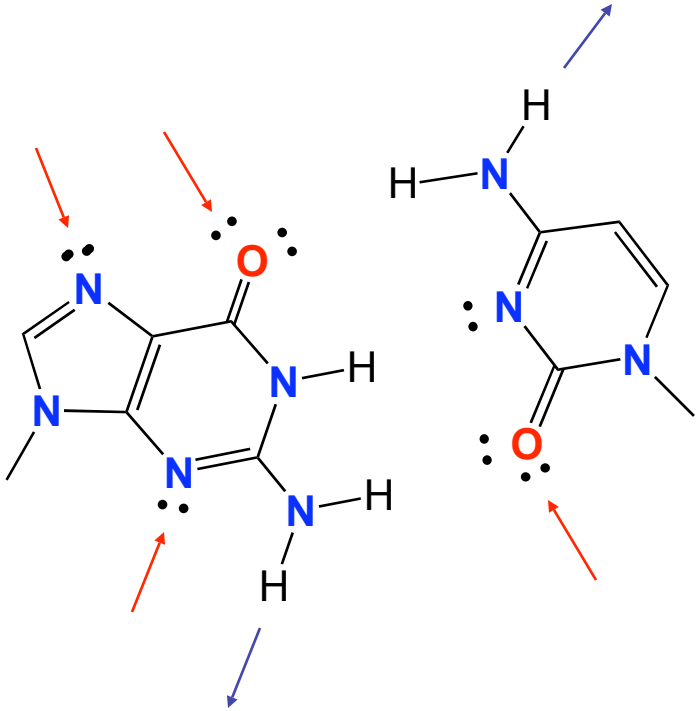
A

Minor Groove

Why is the major groove so good?

Major Groove

G

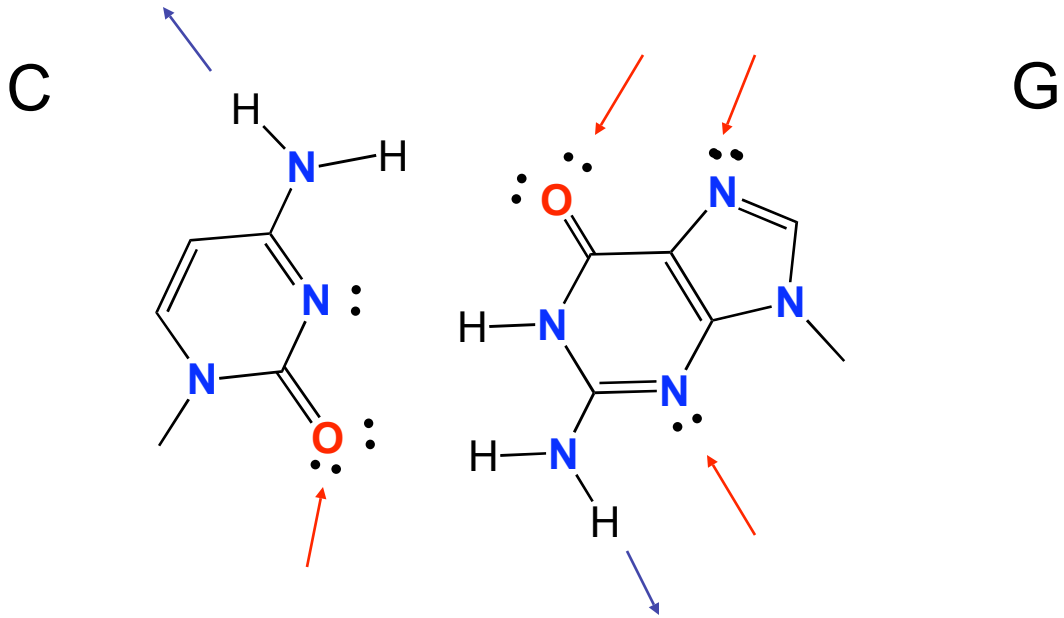


C

Minor Groove

Why is the major groove so good?

Major Groove



Minor Groove

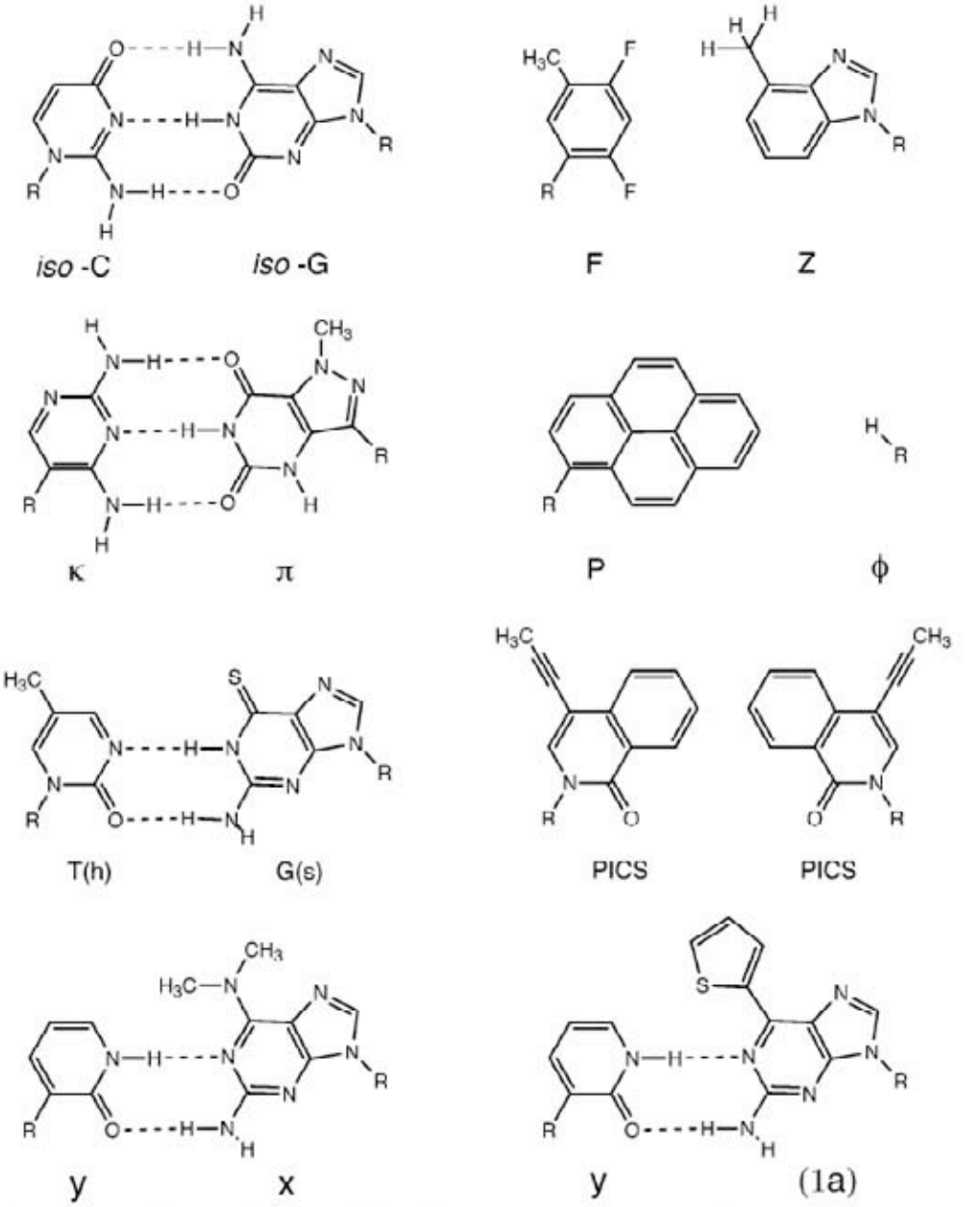
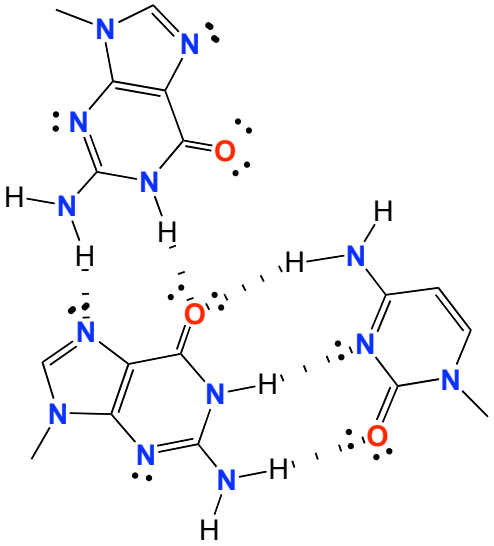
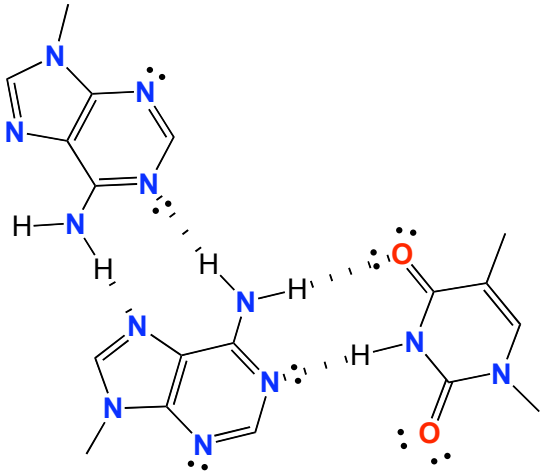


FIGURE 7. Examples of DNA base replacements designed to form stable pairs and/or to be replicated selectively by DNA polymerase enzymes.[17,23,24,49,54,55]

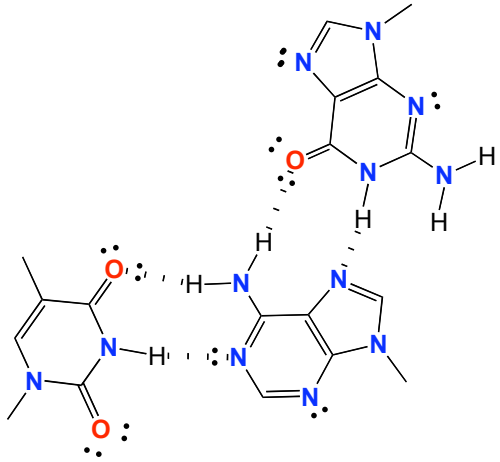
Bases that polymerases like

Nucleic Acid “Triples / Platforms”

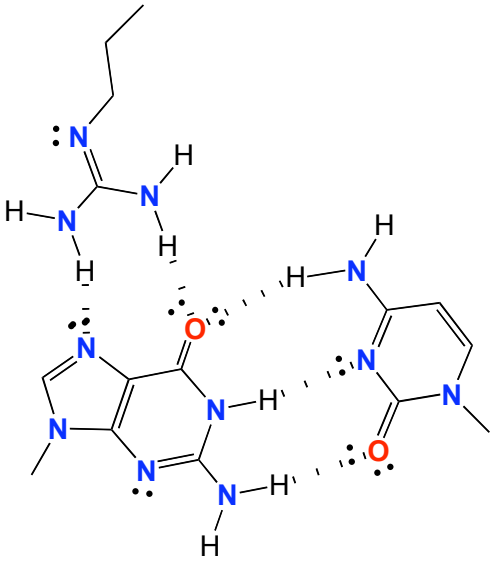


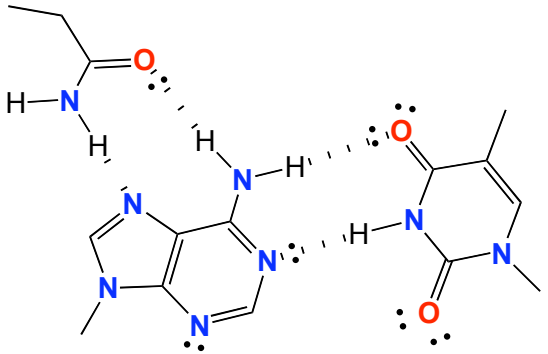


Major Groove Interactions

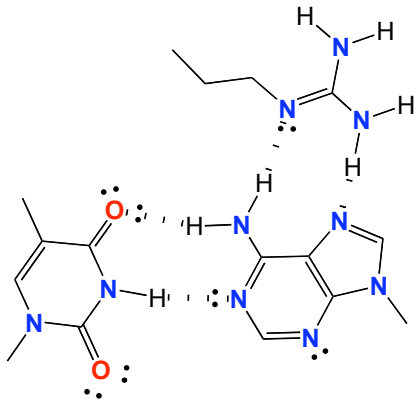


Protein - Nucleic Acid Interactions





Major Groove Interactions

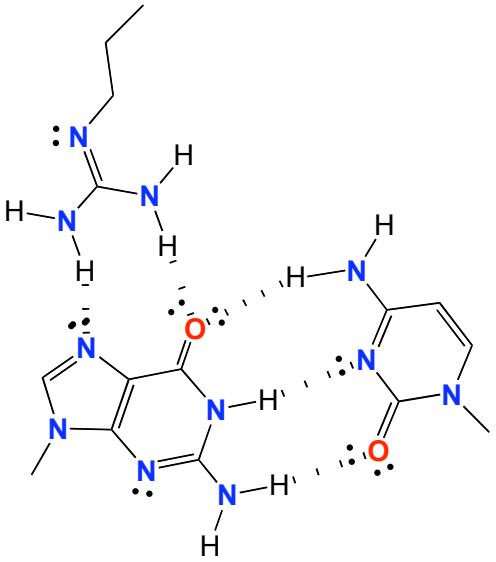


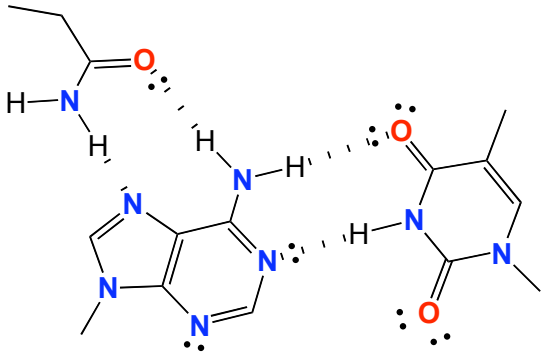
Protein - Nucleic Acid Interactions

Gln

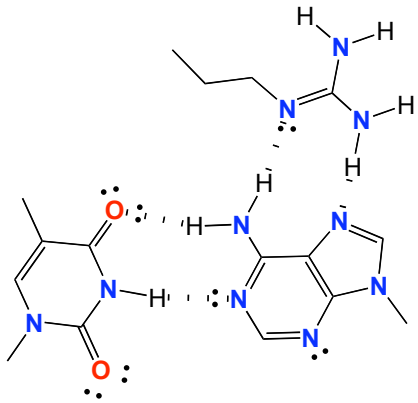
Asn

Arg





Major Groove Interactions



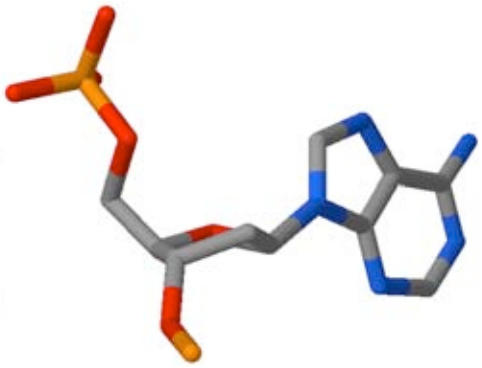
B-form DNA

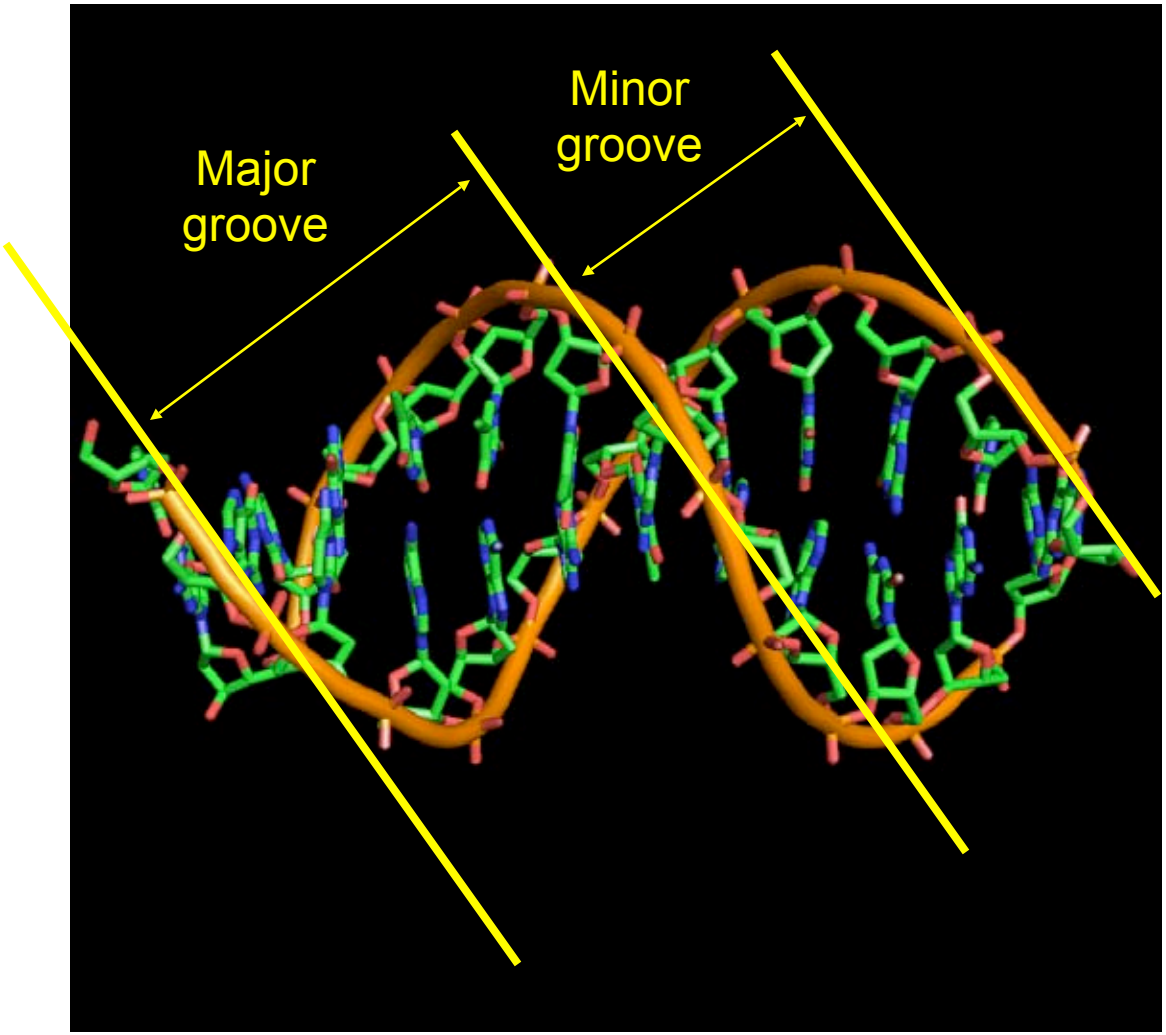
B-form

Residues per turn =10
Twist per base pair = 36°
Rise per pair = 3.4Å
c2'-endo

Minor groove width = 5.7Å
Major groove width = 11.7Å

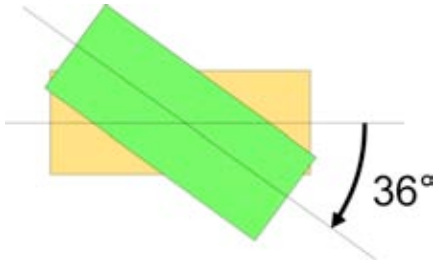
Minor groove depth = 7.5Å
Major groove depth = 8.8Å





B-form DNA

Residues per turn =10
Twist per base pair = 36°



Rise per pair = 3.4Å
c2'-endo

Minor groove width = 5.7Å
Major groove width = 11.7Å

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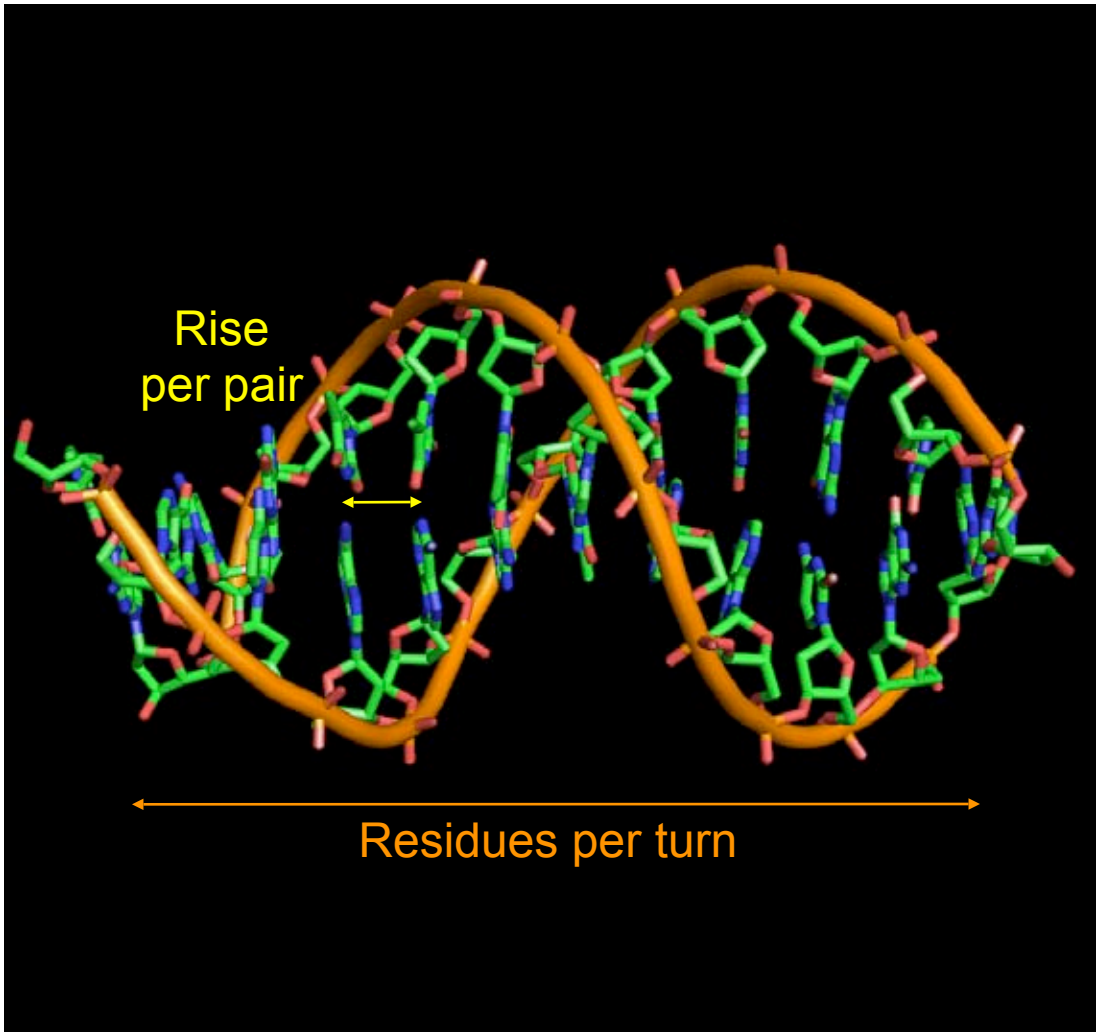
Major groove depth = 8.8Å

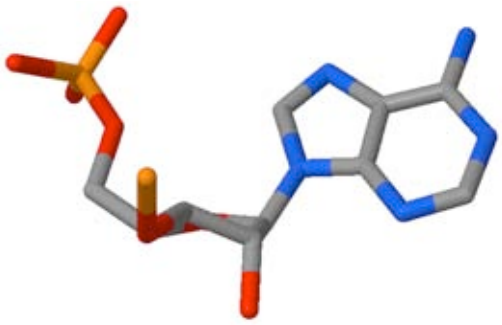


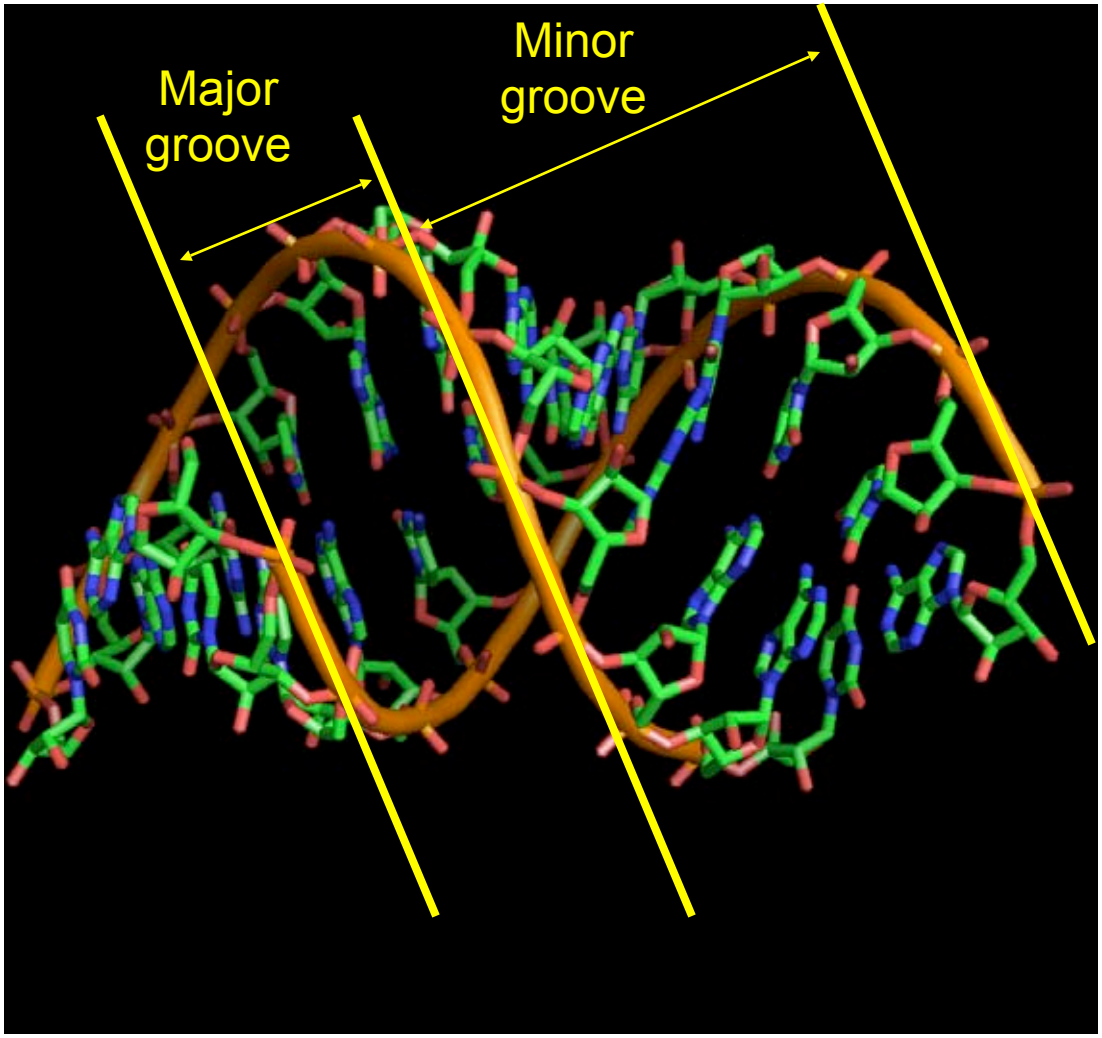
A-form RNA

Residues per turn =11
Twist per base pair = 33°
Rise per pair = 2.9Å
c3'-endo

Minor groove width = 11Å
Major groove width = 2.7Å

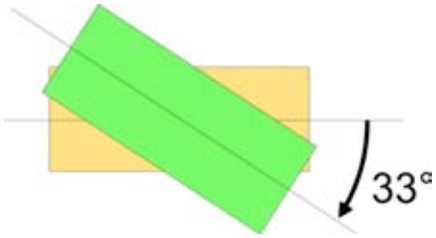
Minor groove depth = 2.8Å
Major groove depth = 13.5Å





A-form RNA

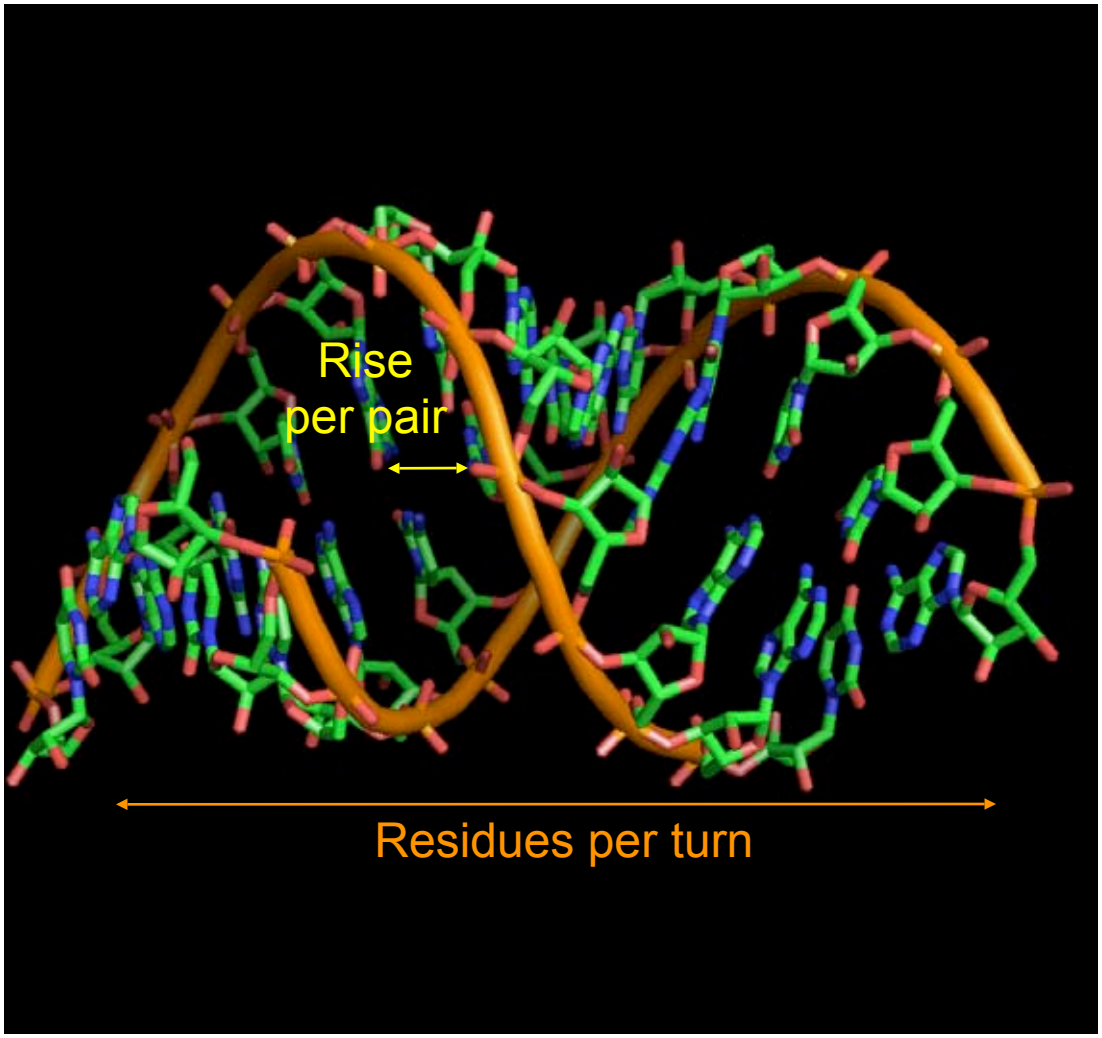
Residues per turn =11
Twist per base pair = 33°



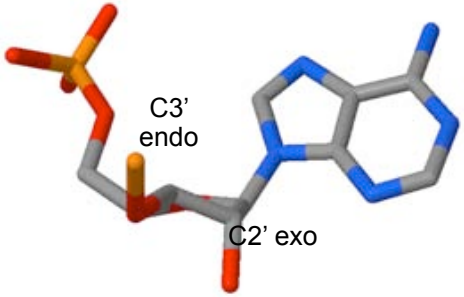
Rise per pair = 2.9Å
c3'-endo

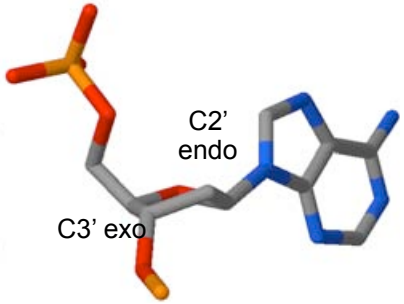
Minor groove width = 11Å
Major groove width = 2.7Å

Minor groove depth = 2.8Å
Major groove depth = 13.5Å



Compare





A-form (RNA)

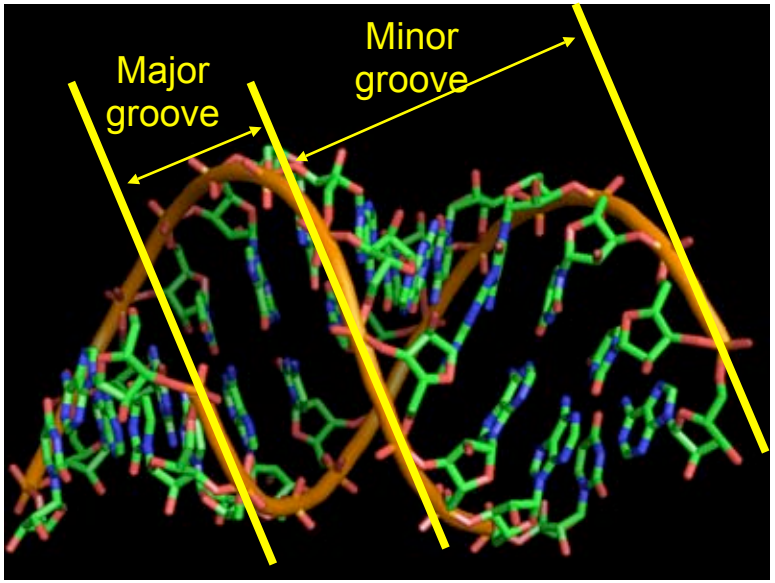
Minor groove width = 11Å
Major groove width = 2.7Å

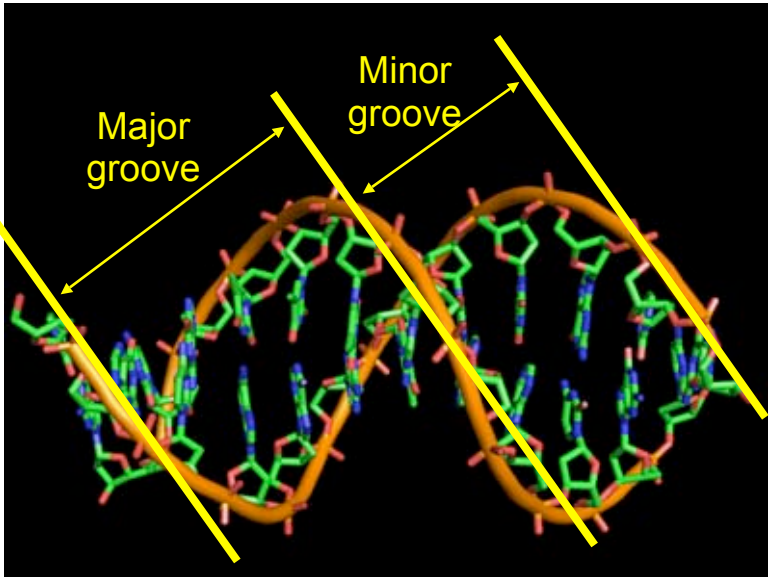
Minor groove depth = 2.8Å
Major groove depth = 13.5Å

B-form (DNA)

Minor groove width = 5.7Å
Major groove width = 11.7Å

Minor groove depth = 7.5Å
Major groove depth = 8.8Å





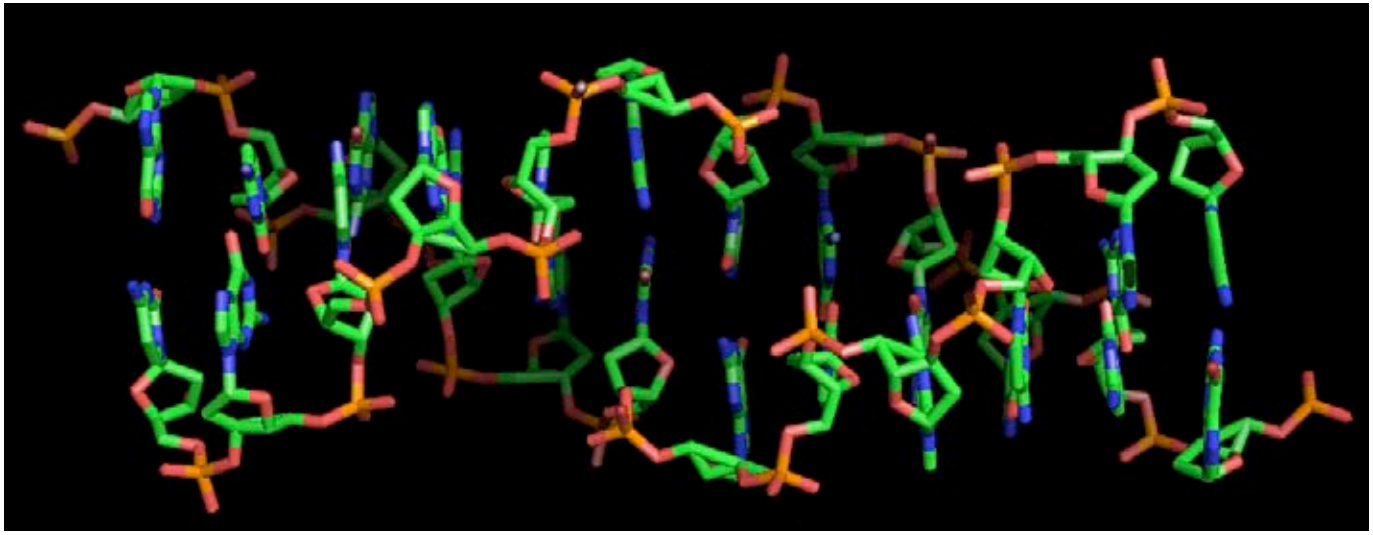
Z-DNA

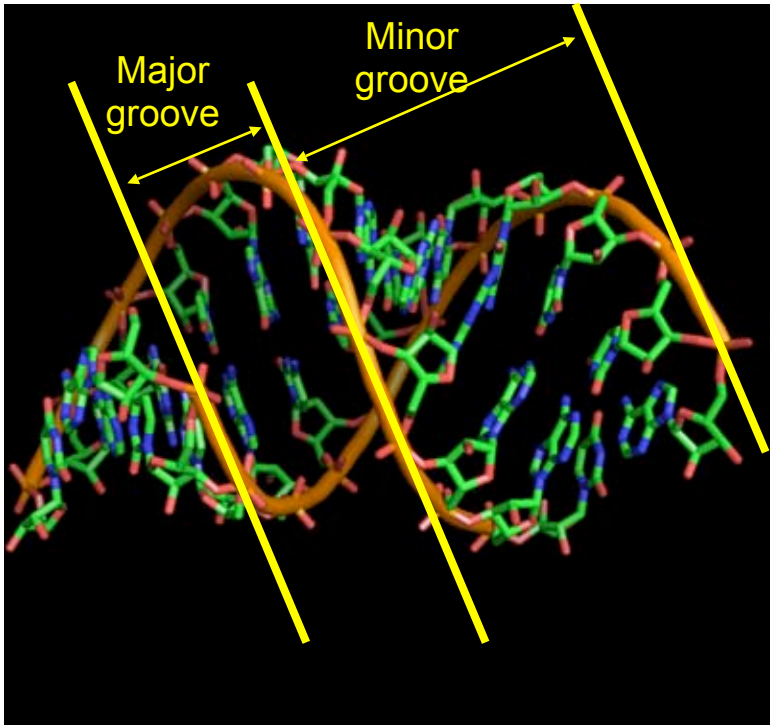
Residues per turn =12
Twist per base pair = -9 / -51°

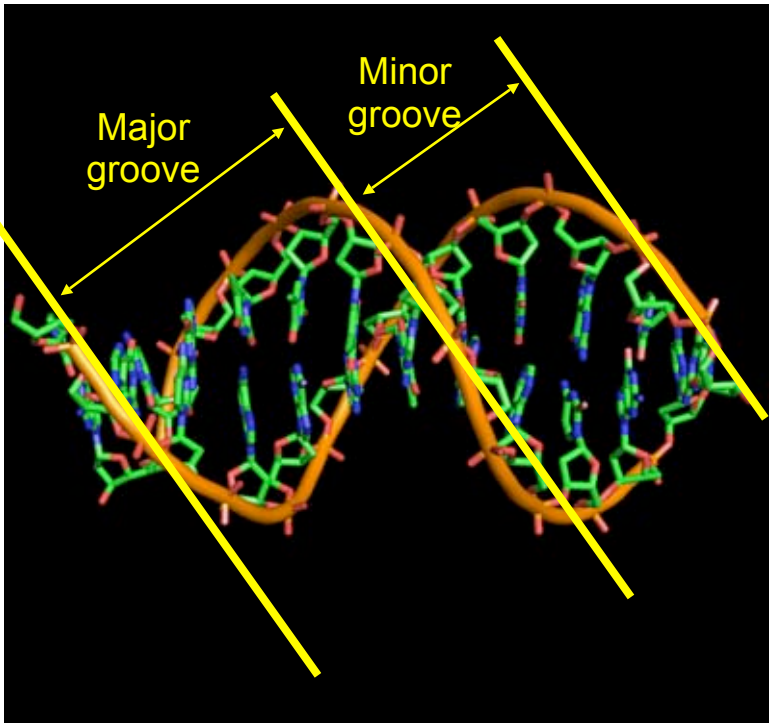
Rise per pair = 3.7Å
c3'-endo(syn) / c2'-endo

Minor groove width = 2.0Å
Major groove width = 8.8Å

Minor groove depth = 13.8Å
Major groove depth = 3.7Å

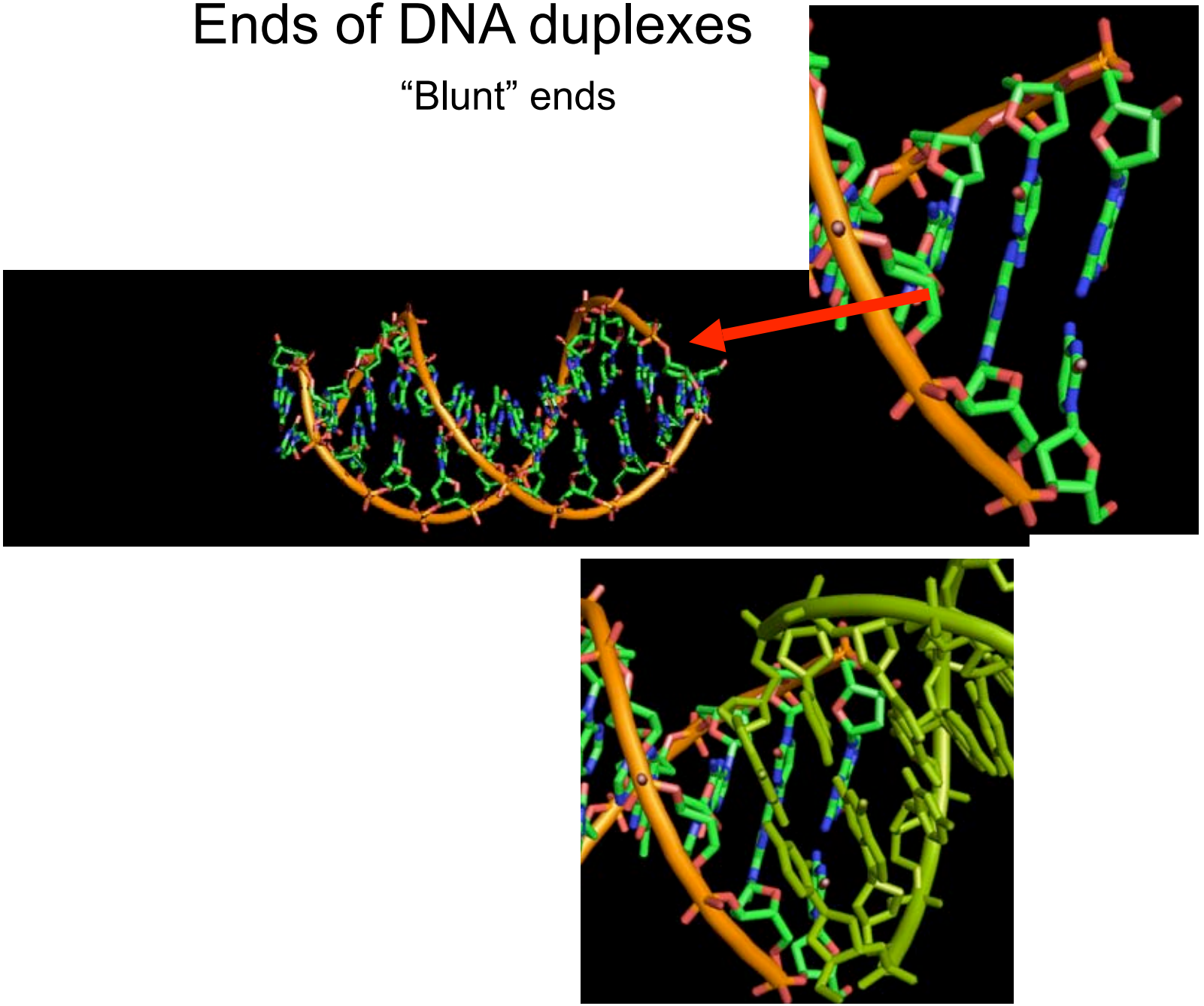






Ends of DNA duplexes

"Blunt" ends



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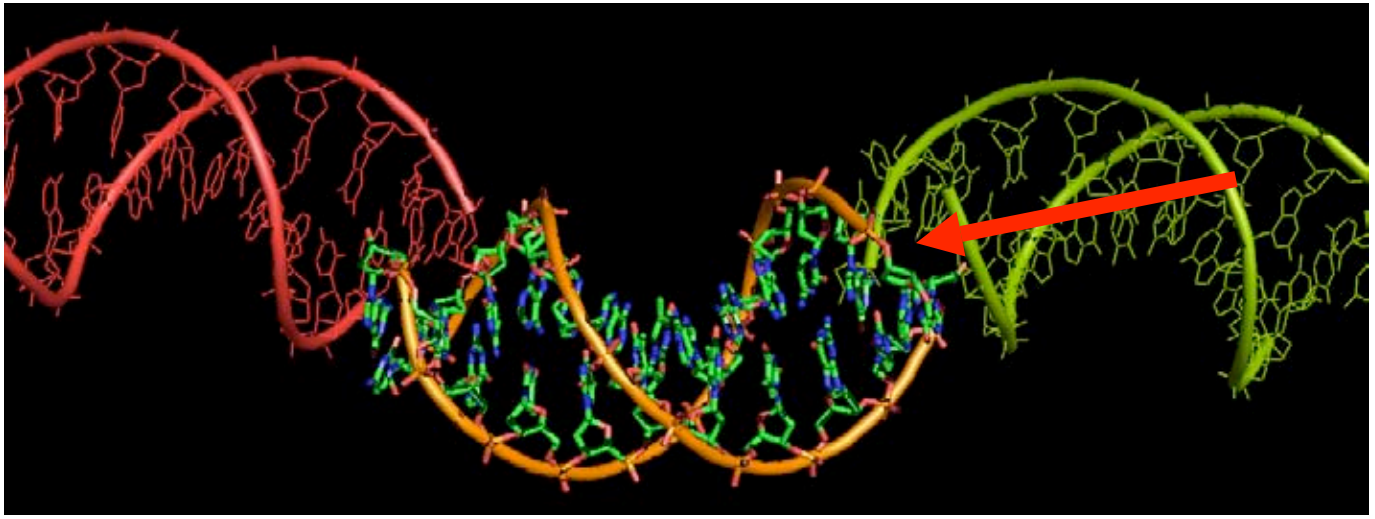
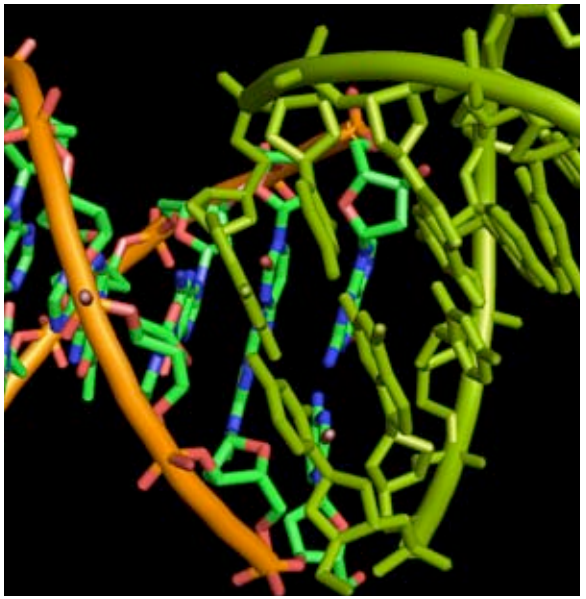
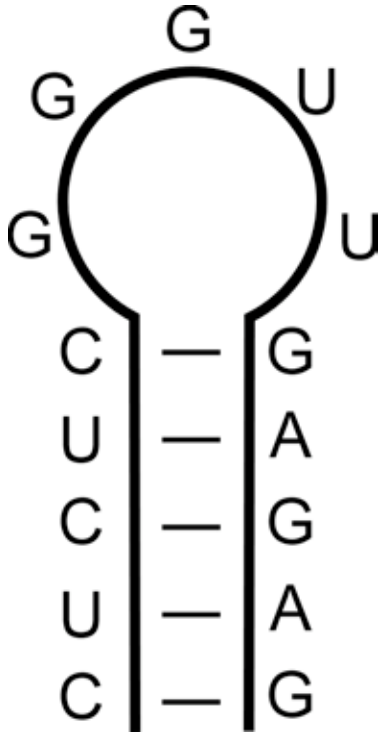
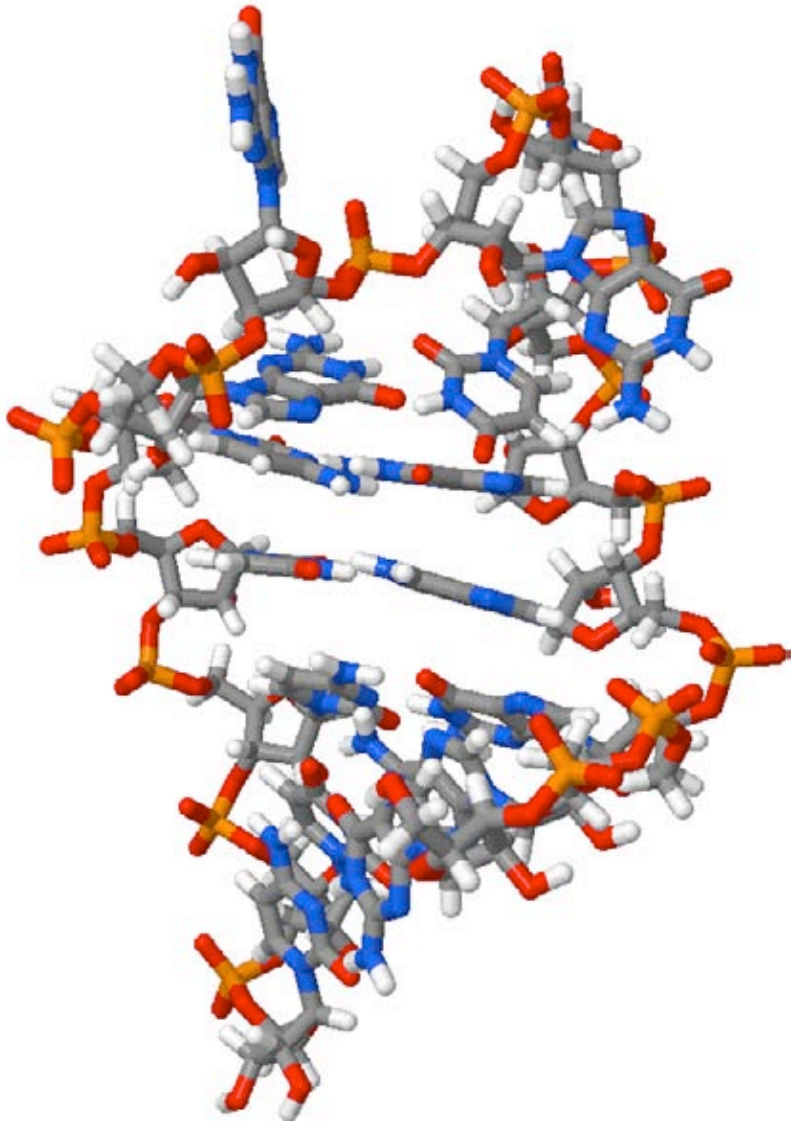


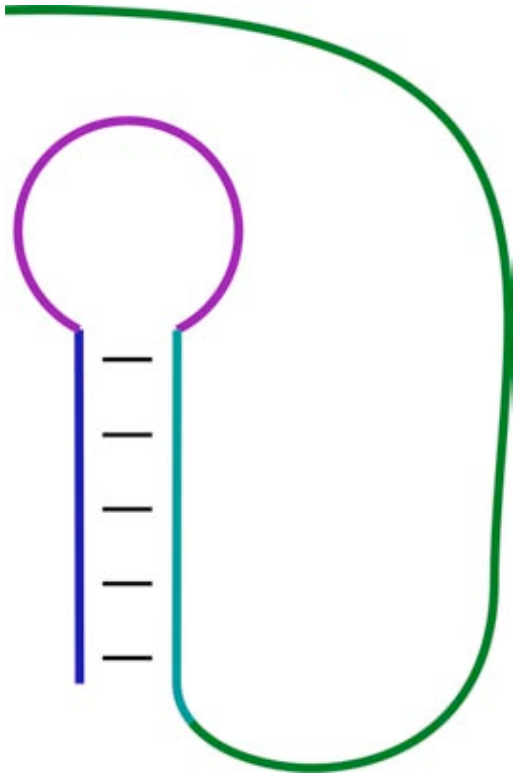


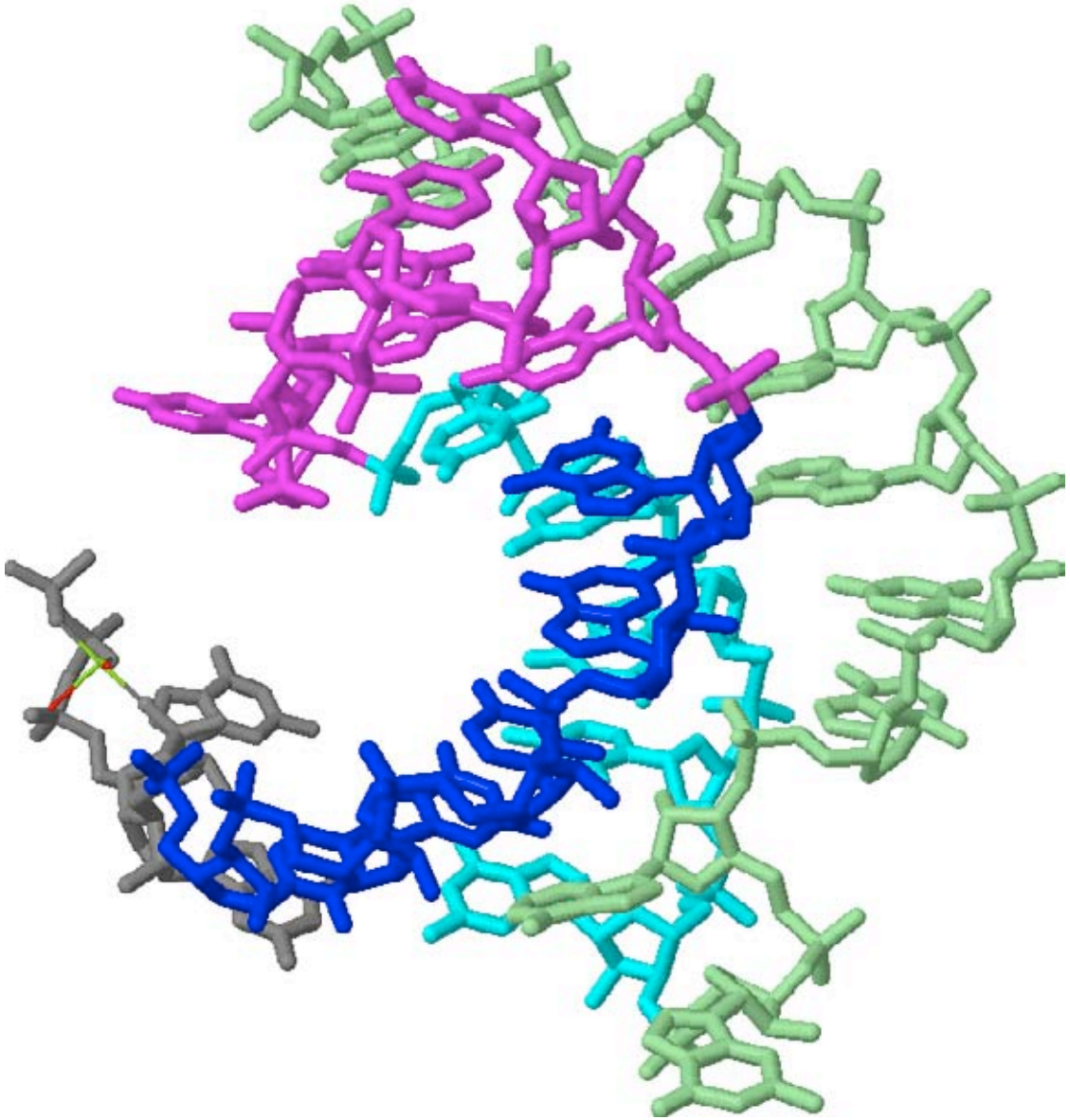
Simple Structure - Hairpin



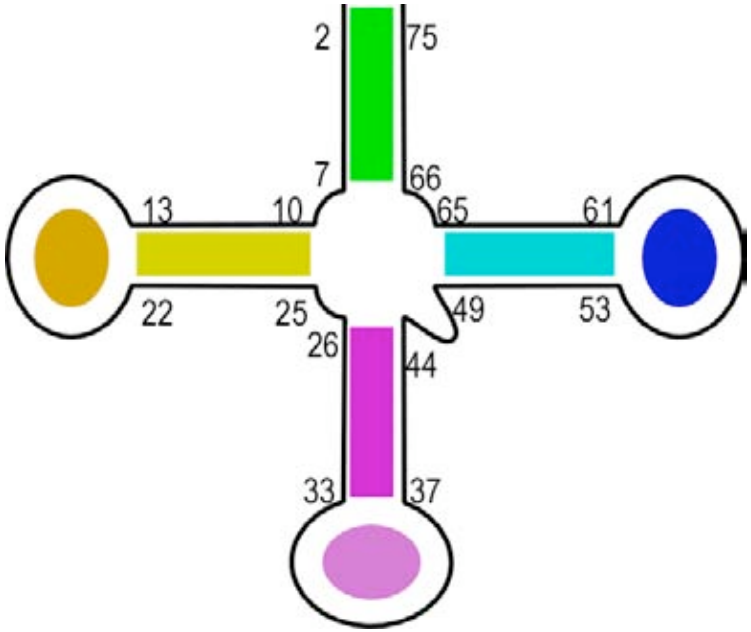


Classic Structure - Pseudoknot





tRNA



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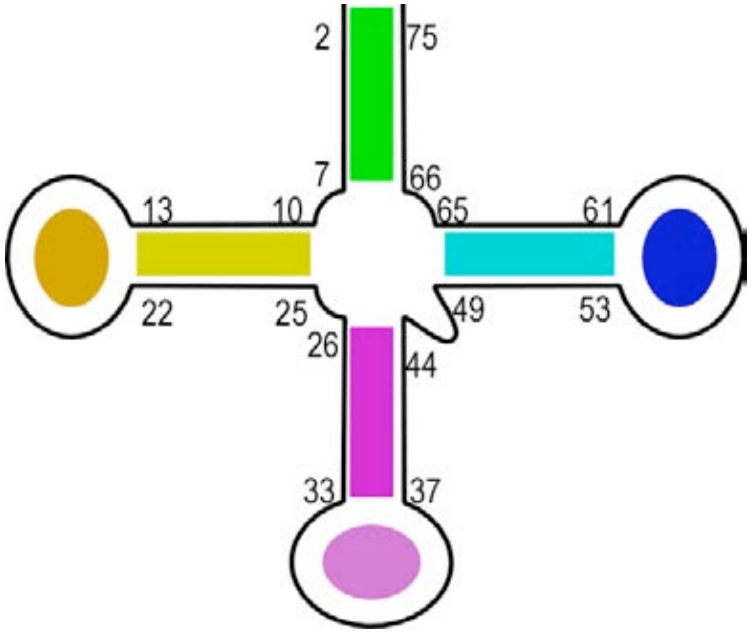
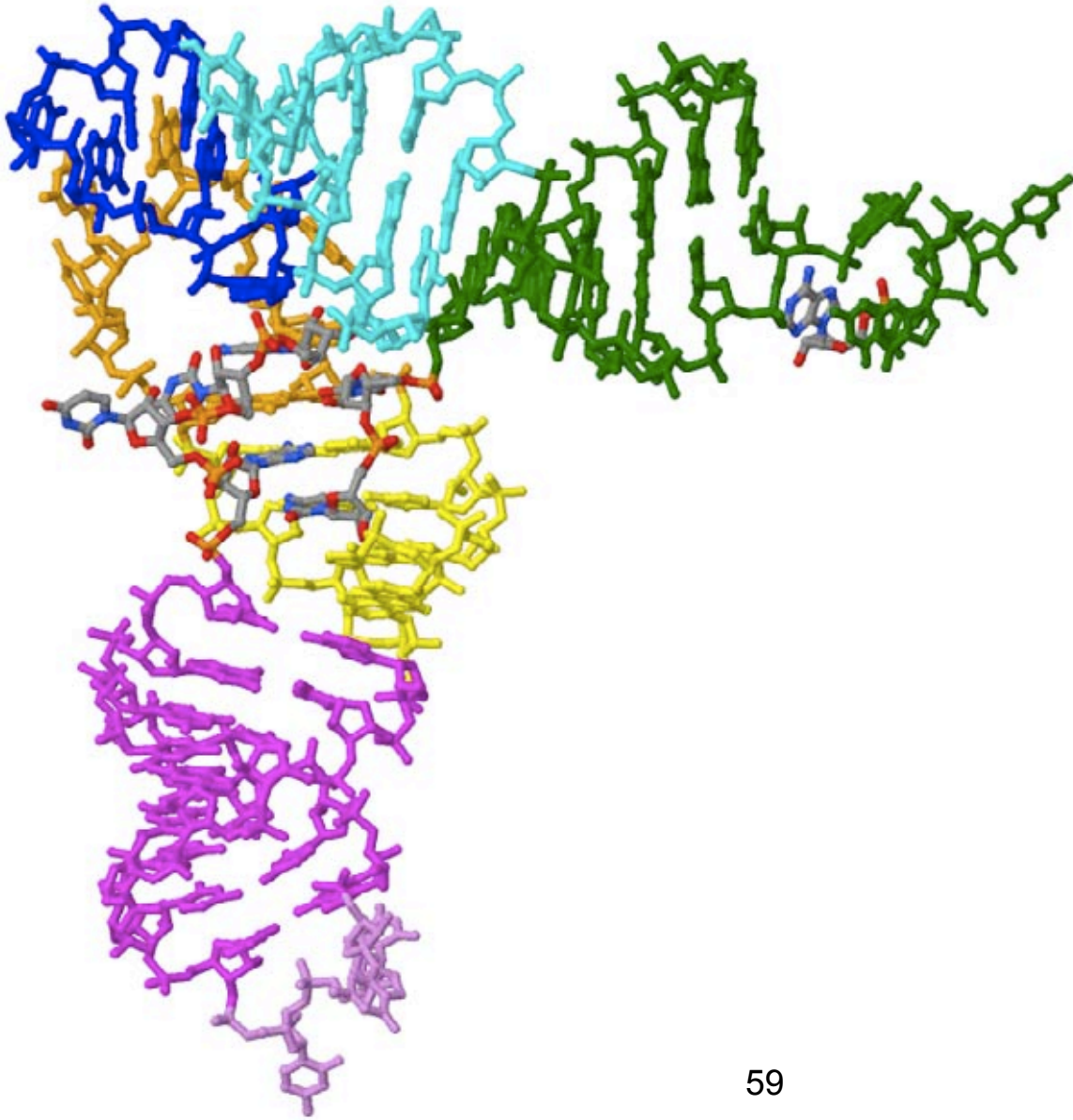
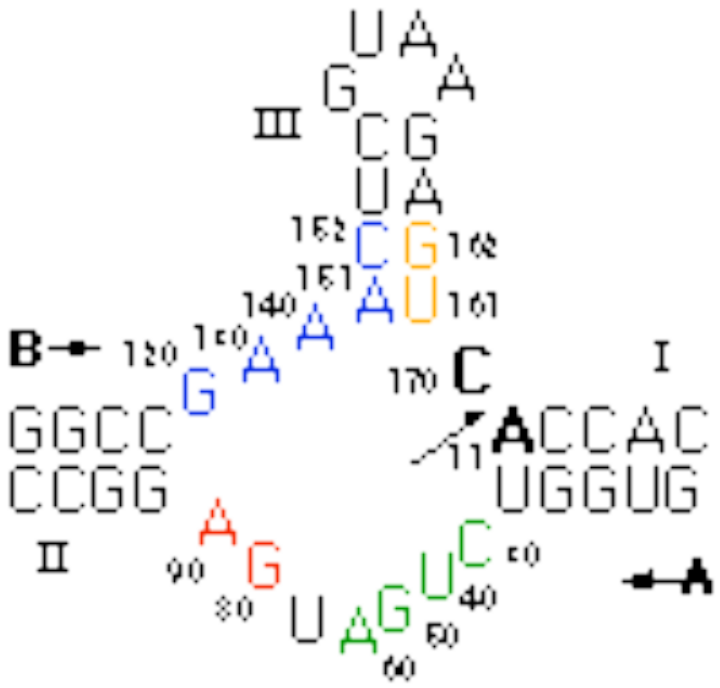
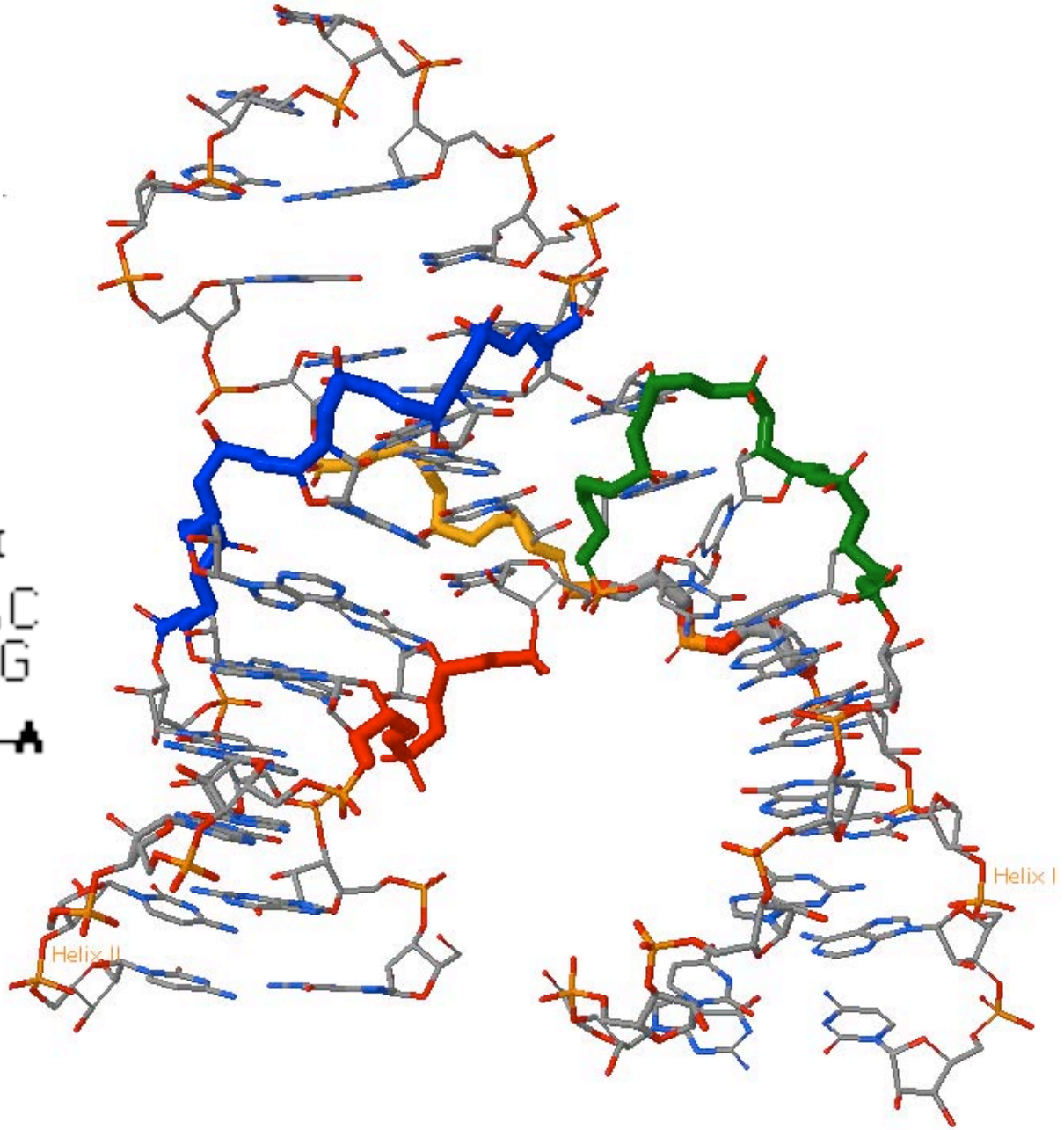


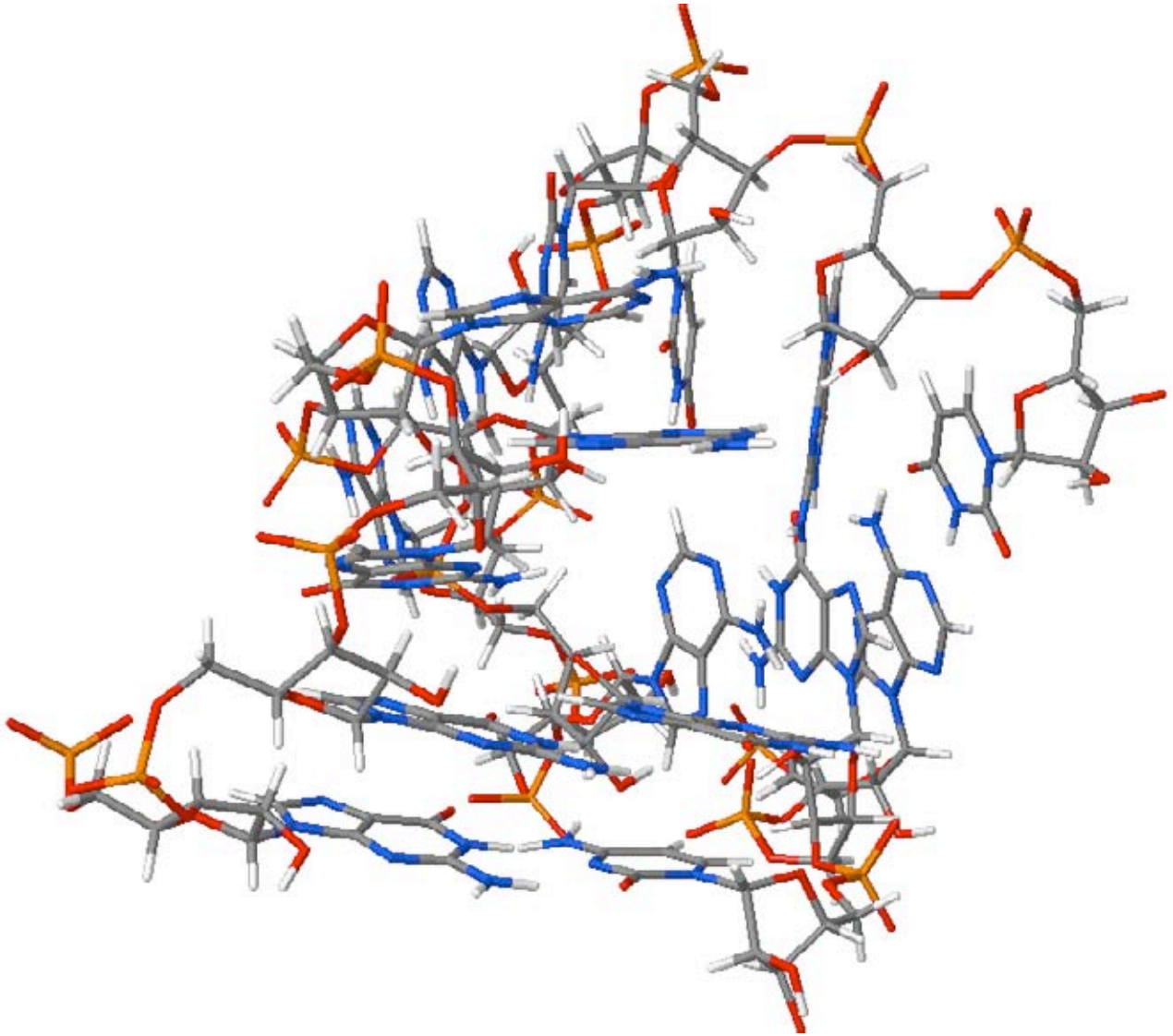


Hammerhead Ribozyme





AMP Aptamer



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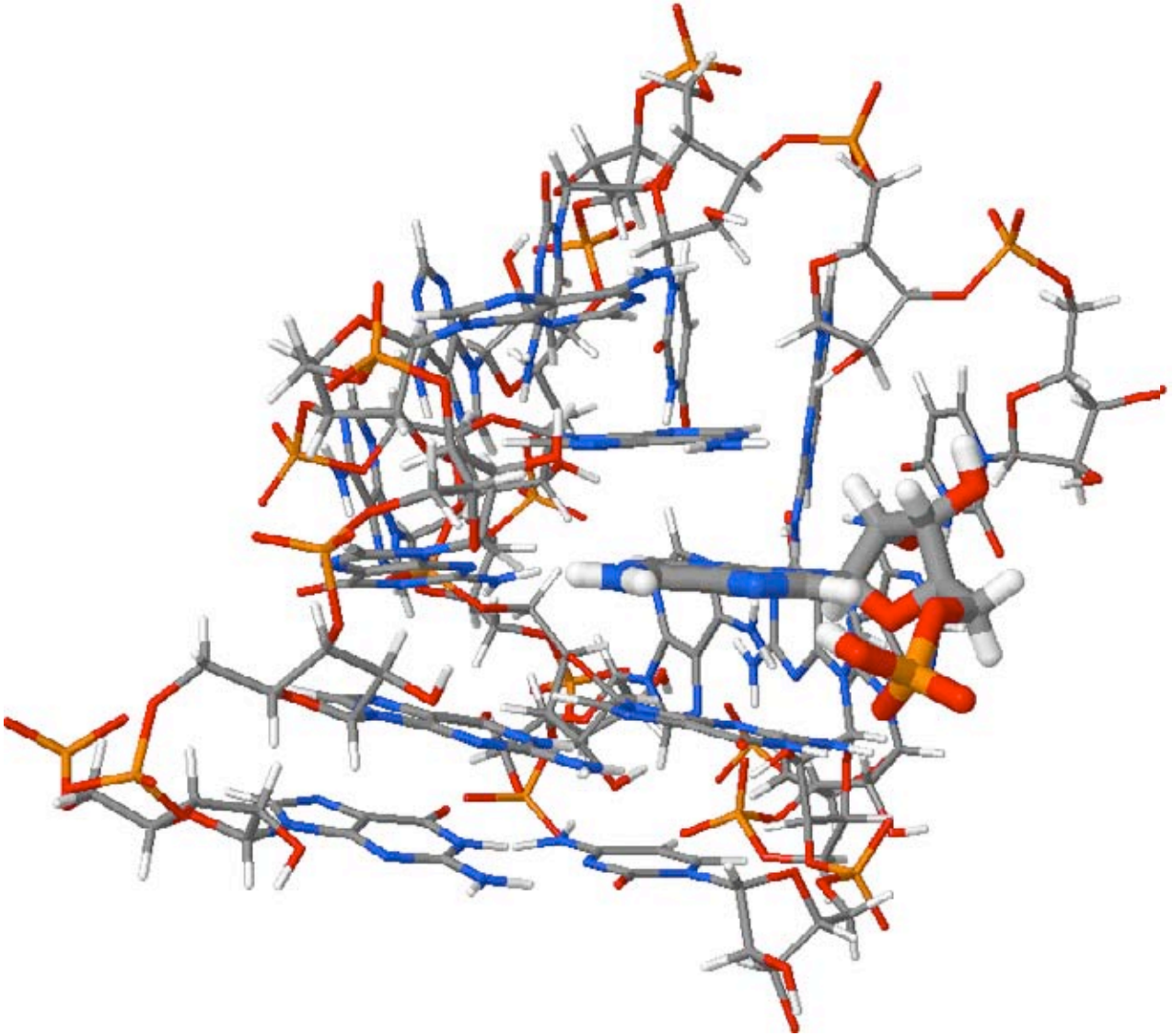
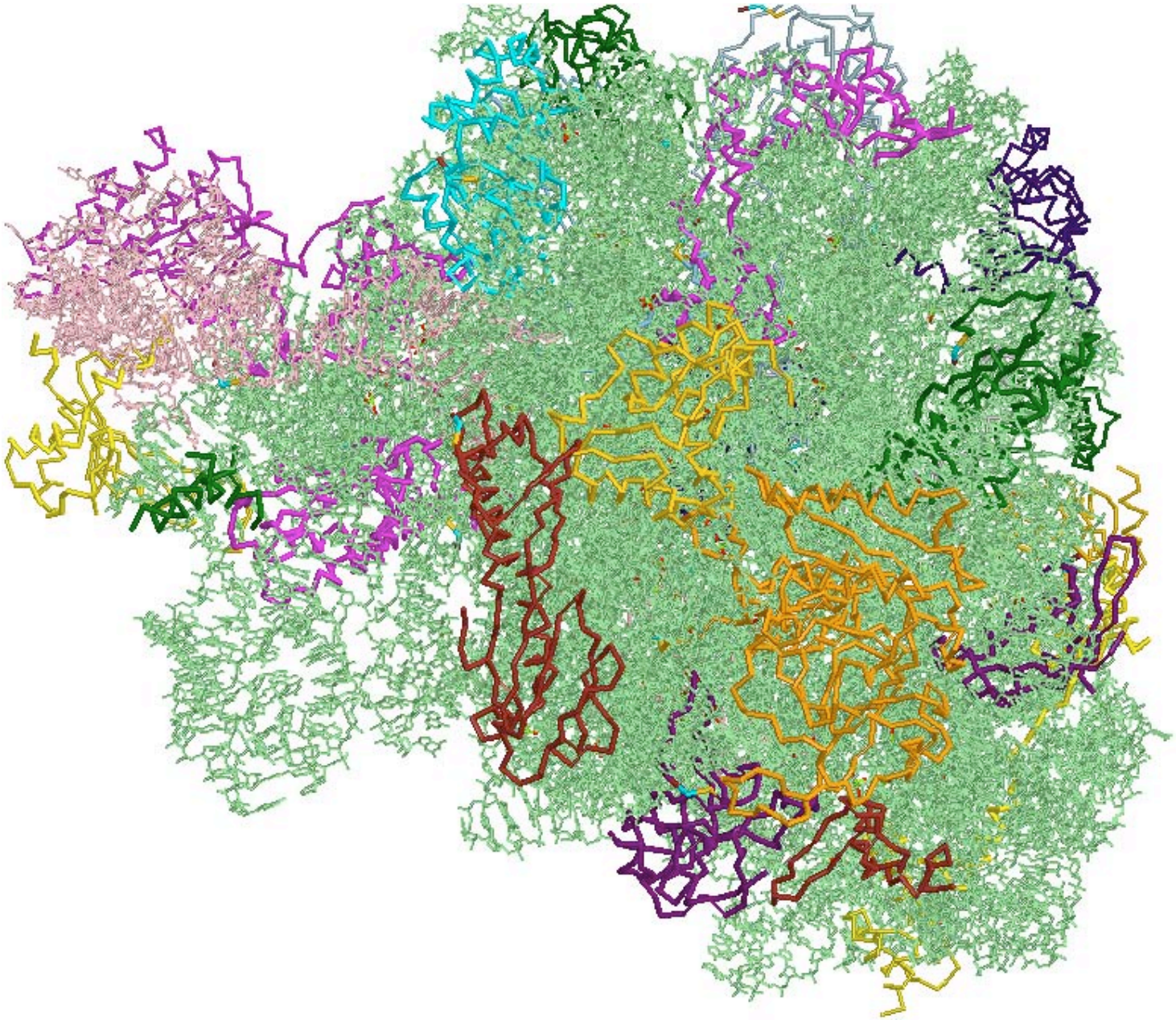


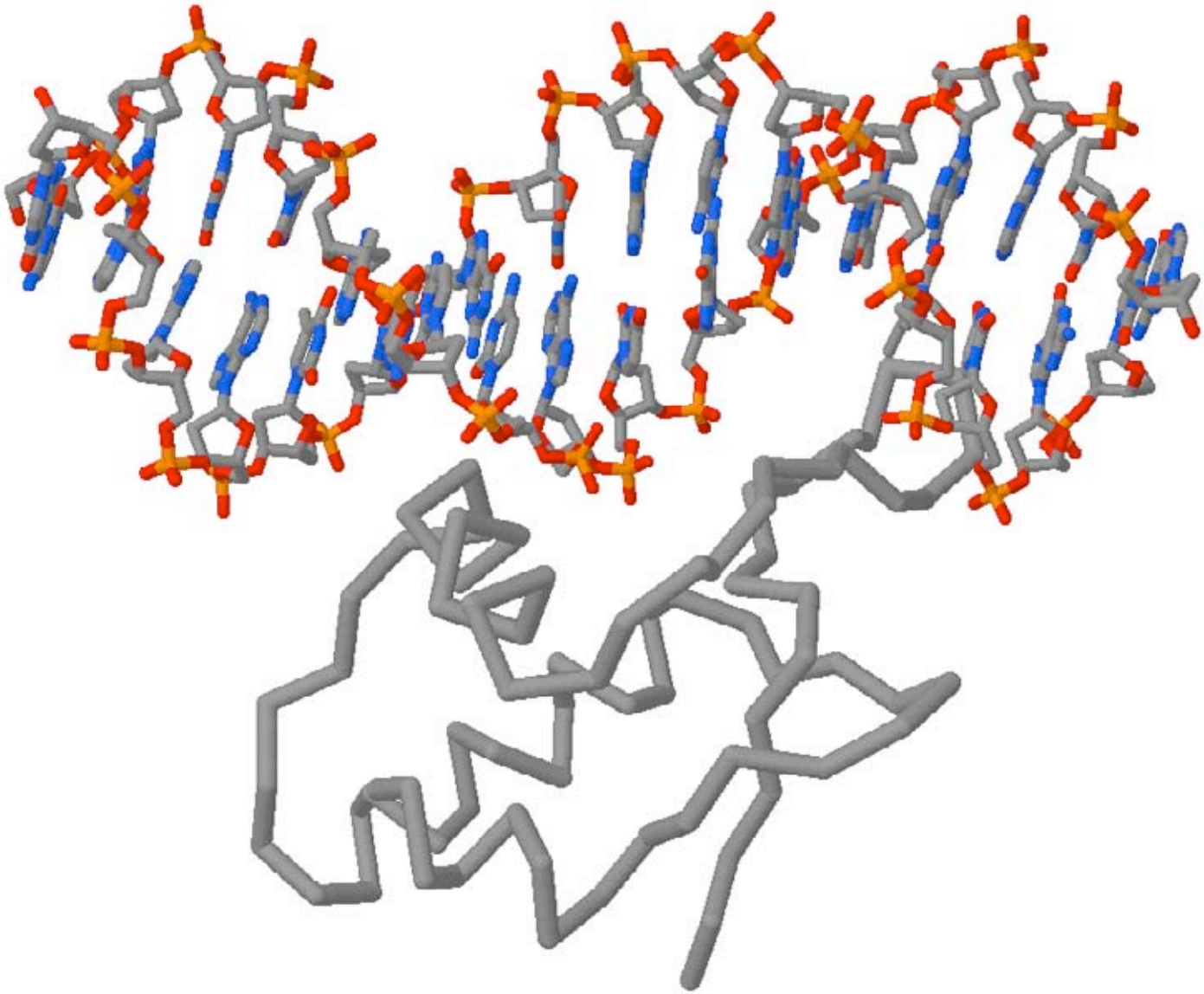
Ribosome

An RNA machine with protein cofactors



Winged Helix DNA Binding Domain

Classic helix-turn-helix



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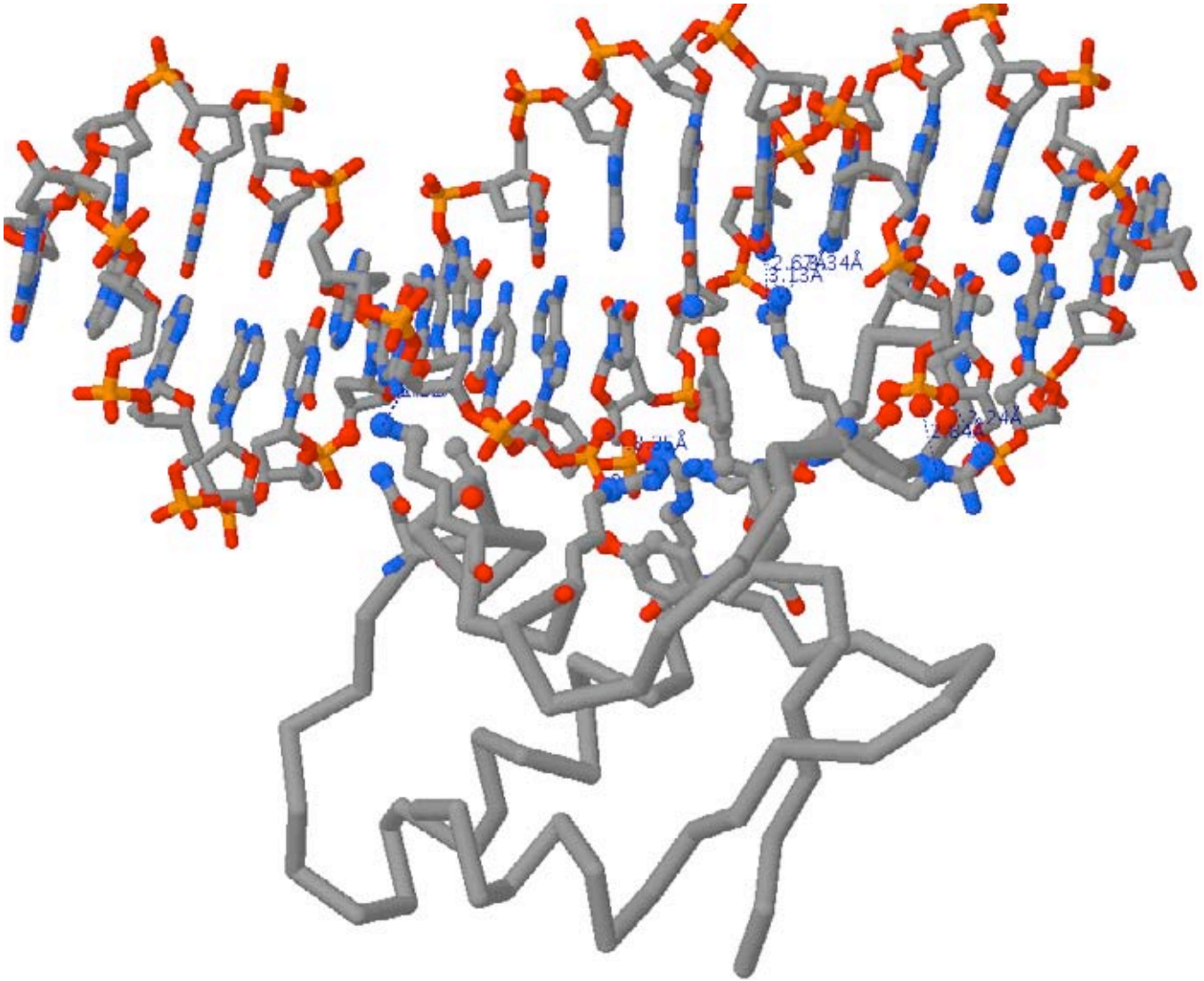

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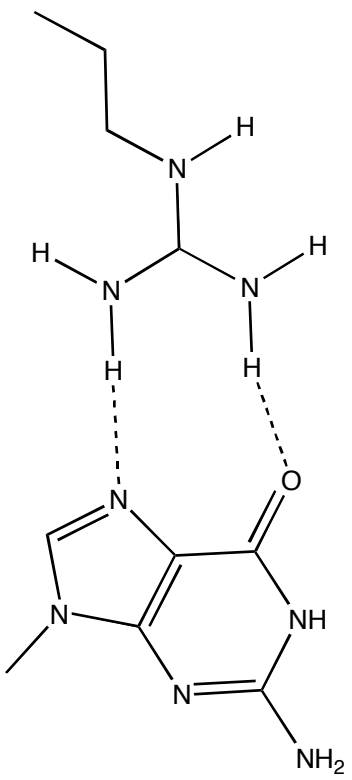

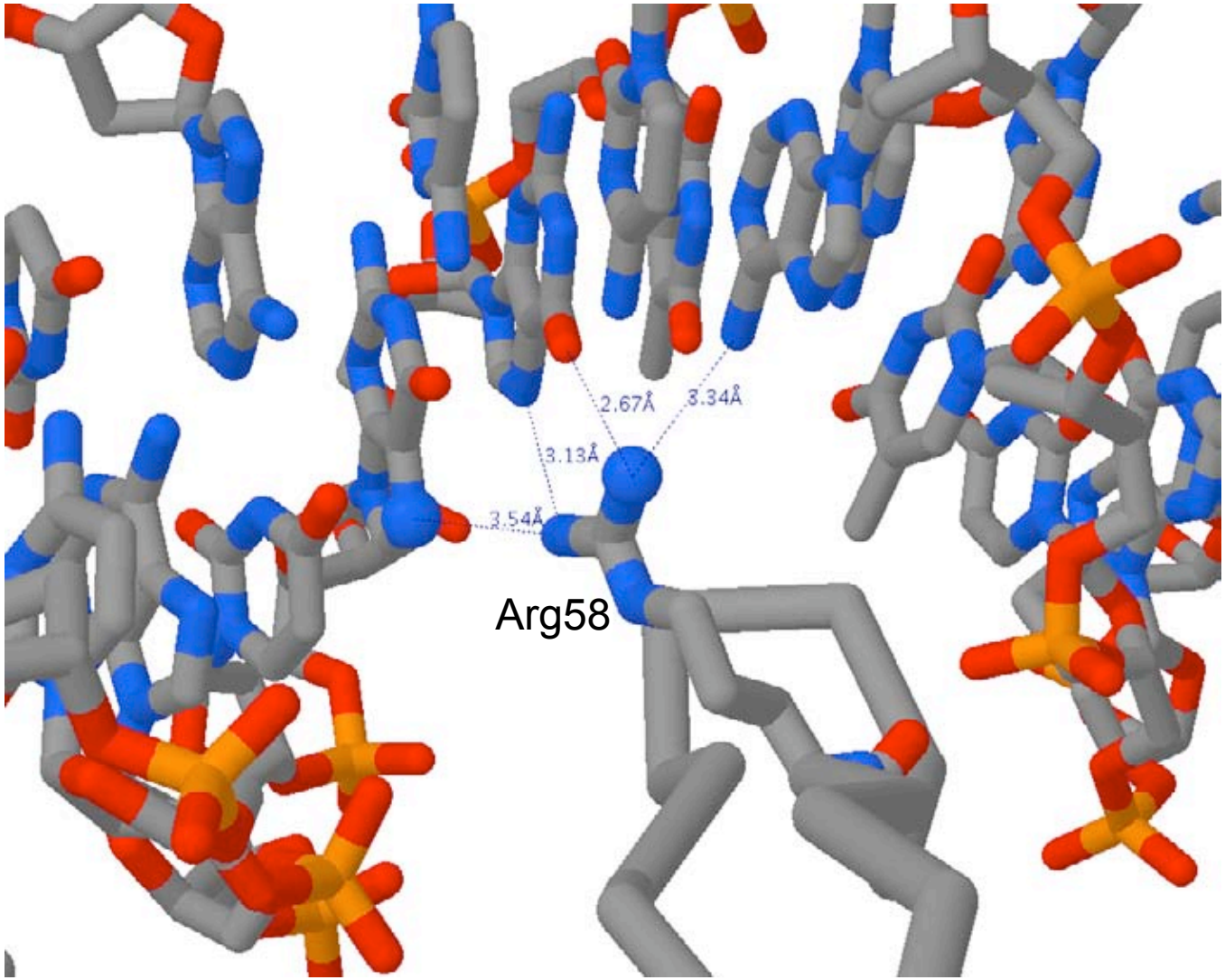

Hrfx1 bound to its X-box binding site