

Today's class:

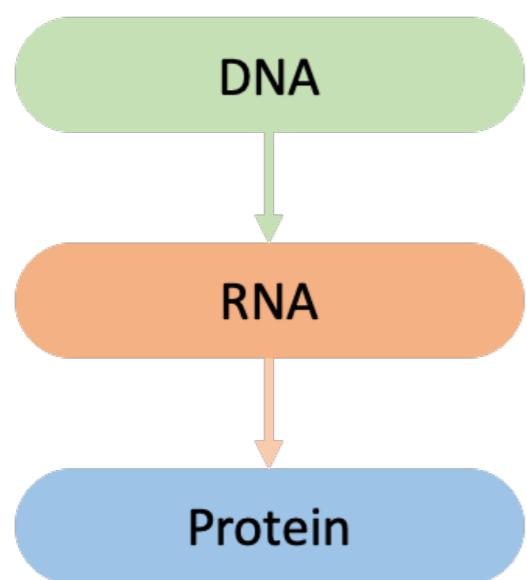
Nucleic acids - structure and function

*This lecture mostly follows the chapter 2 and parts of chapter 19 in the book
‘The Molecules of Life’ by Kuriyan, Konforti & Wemmer, 1st Ed, 2013*

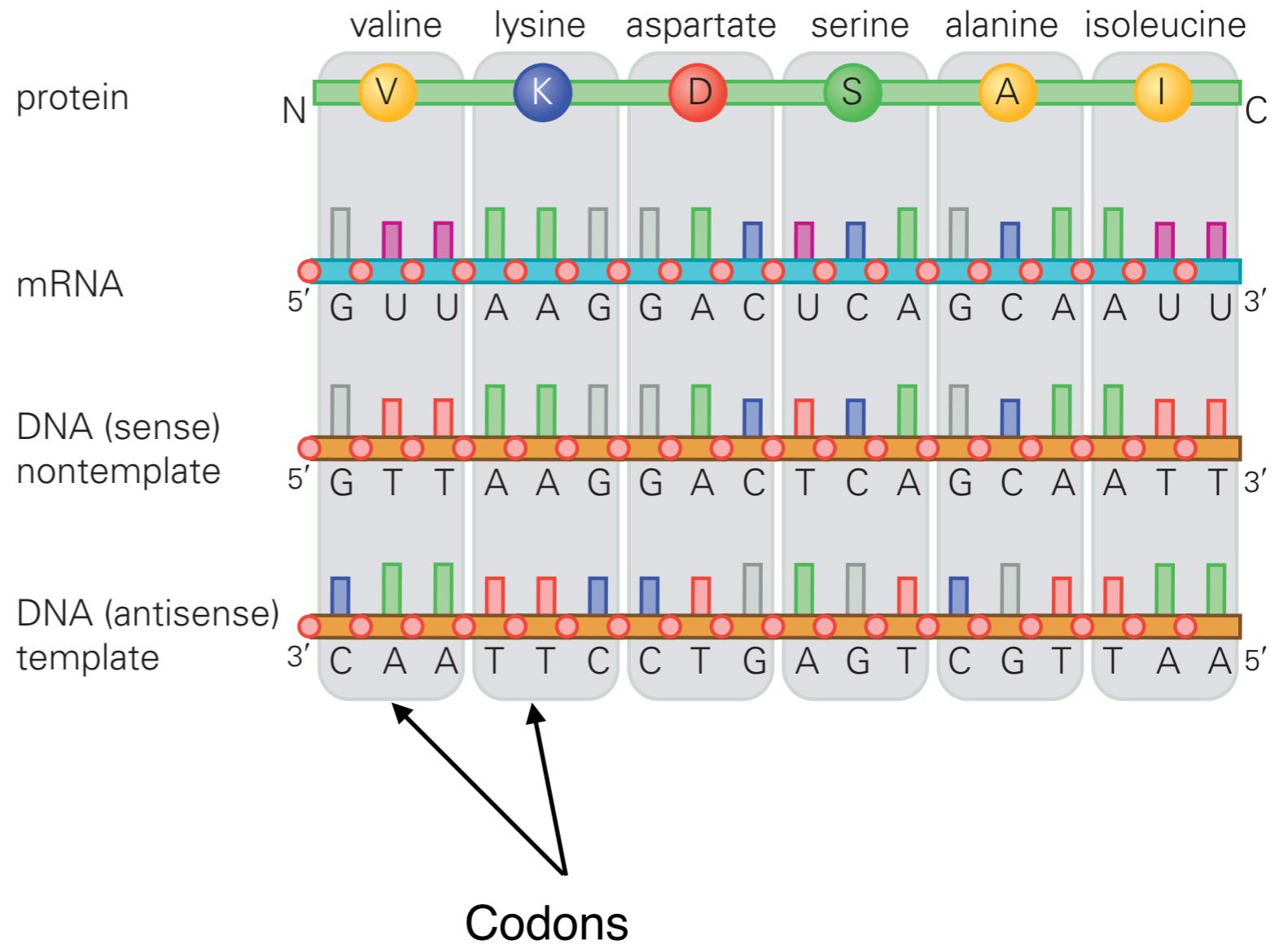
The curious case of central dogma

Francis Crick 1970

Central dogma of molecular biology



Complementary base pairing and genetic code



Alternative representation of central dogma

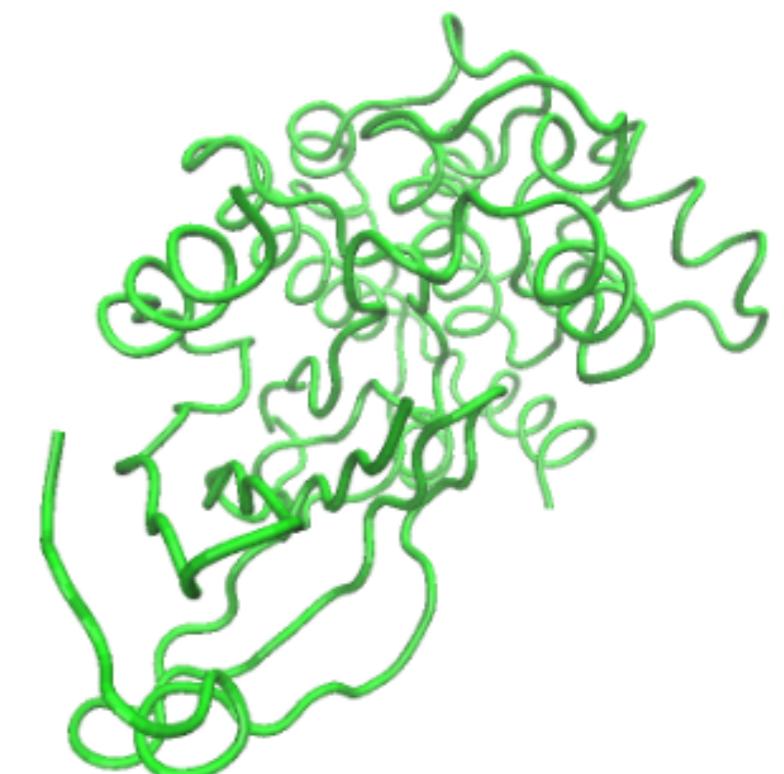
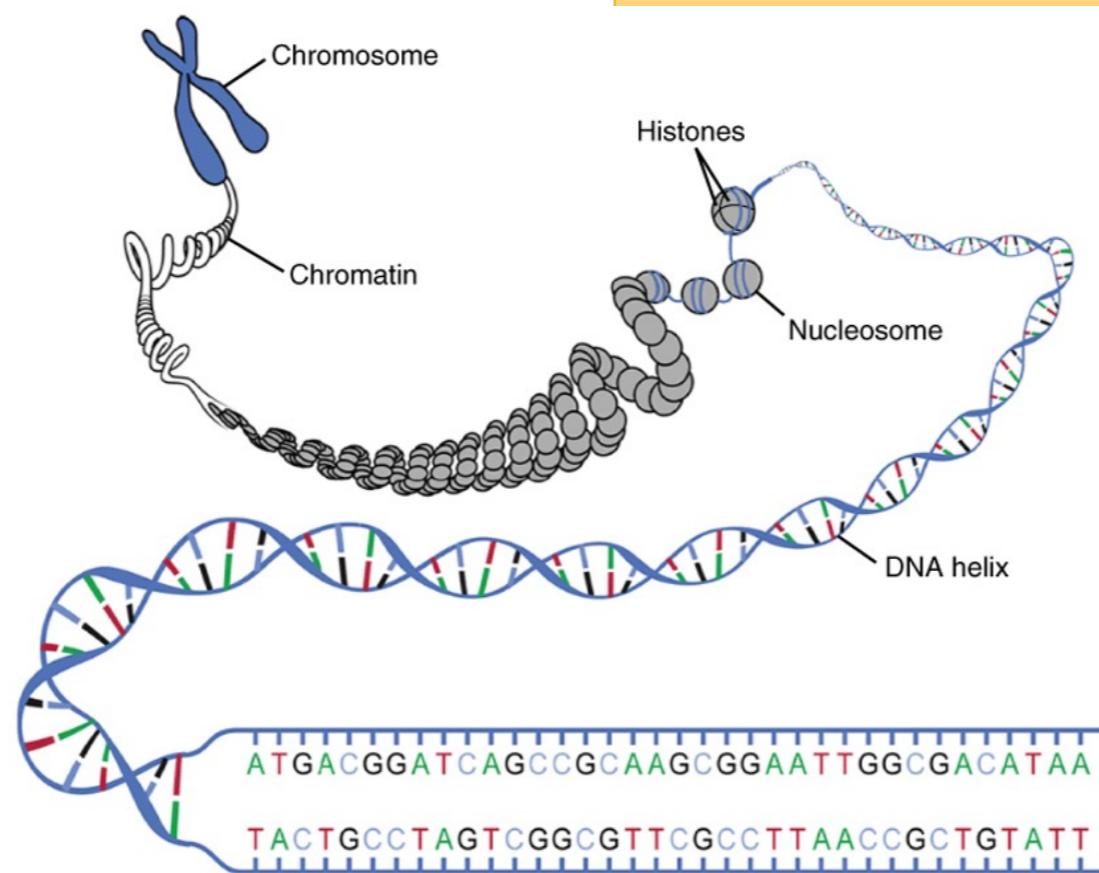
Petsko & Ringe 2004

Sequence

Structure

Function

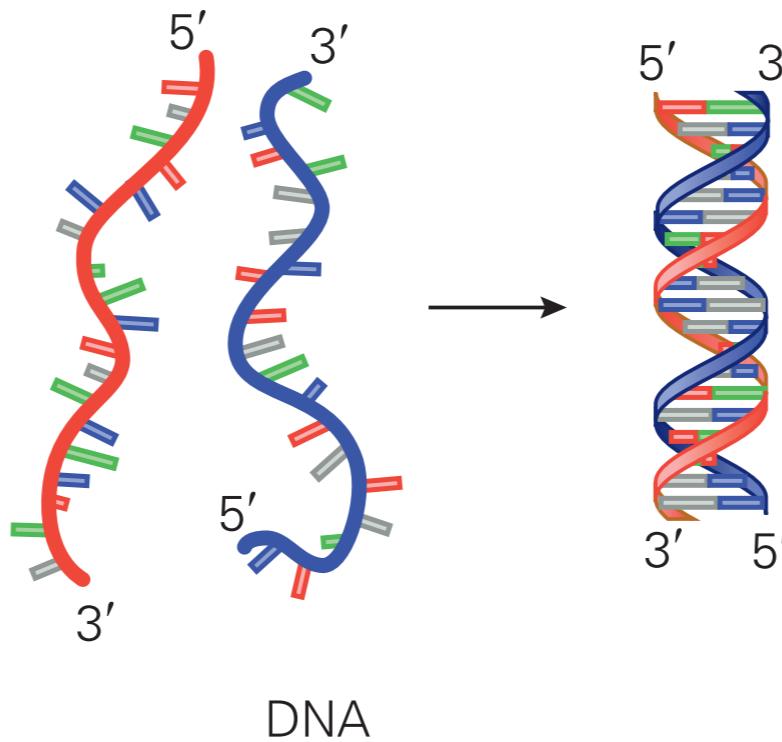
Structure ----> Function
hierarchical and contextual



The double helical structure of DNA and RNA

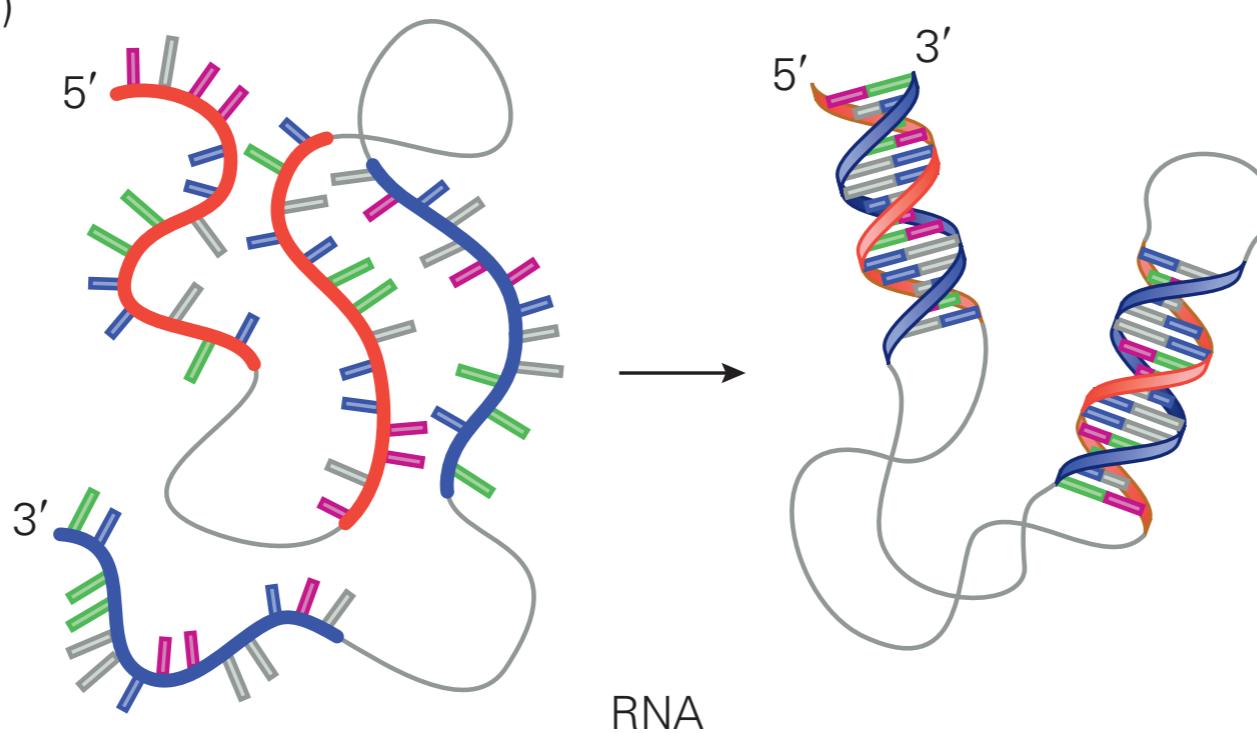
Here red and blue are complementary for both examples

(A)



DNA

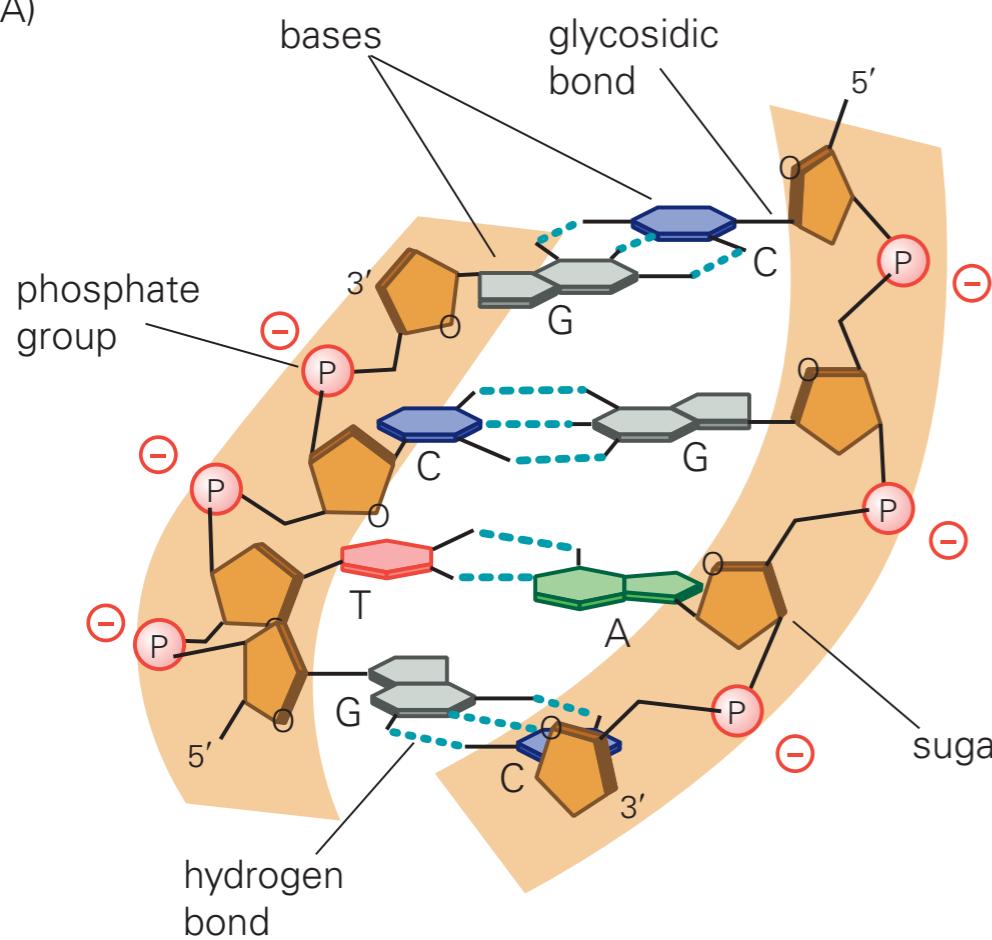
(B)



RNA molecules do not exist in pairs, but structured RNA molecules usually contain internal regions that are self-complementary. The RNA molecule folds up to form two double helices.

Formation of base pairs in DNA

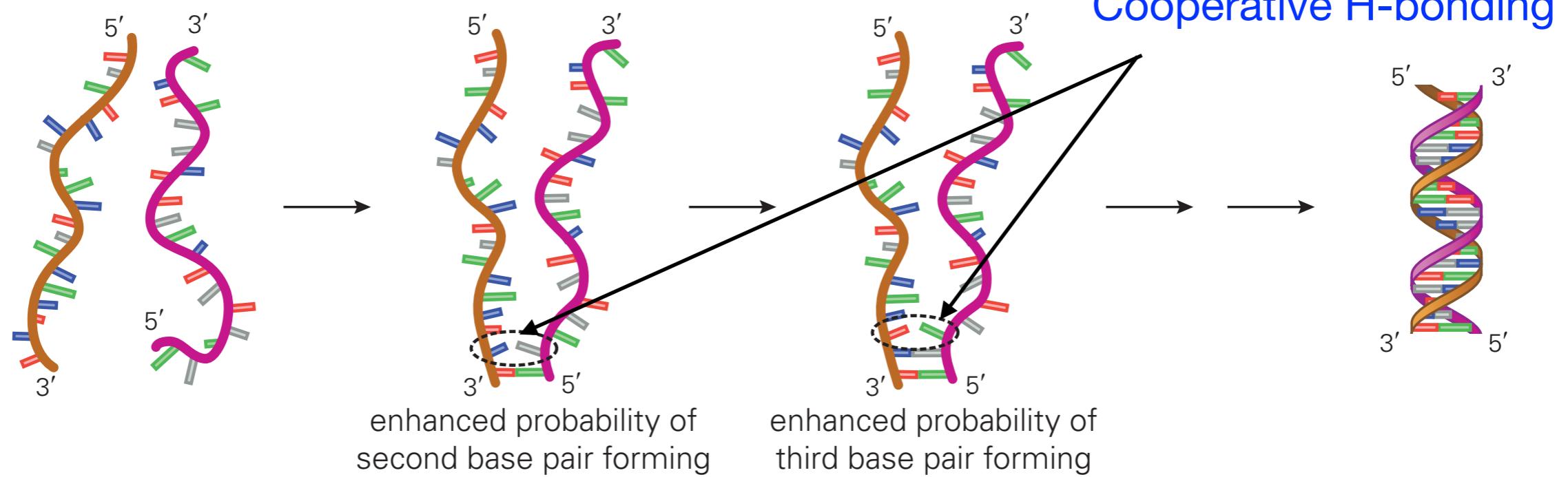
(A)



Specific arrangement of all the glycosidic bonds with respect to the sugar-phosphate backbone allows formation of base pairs

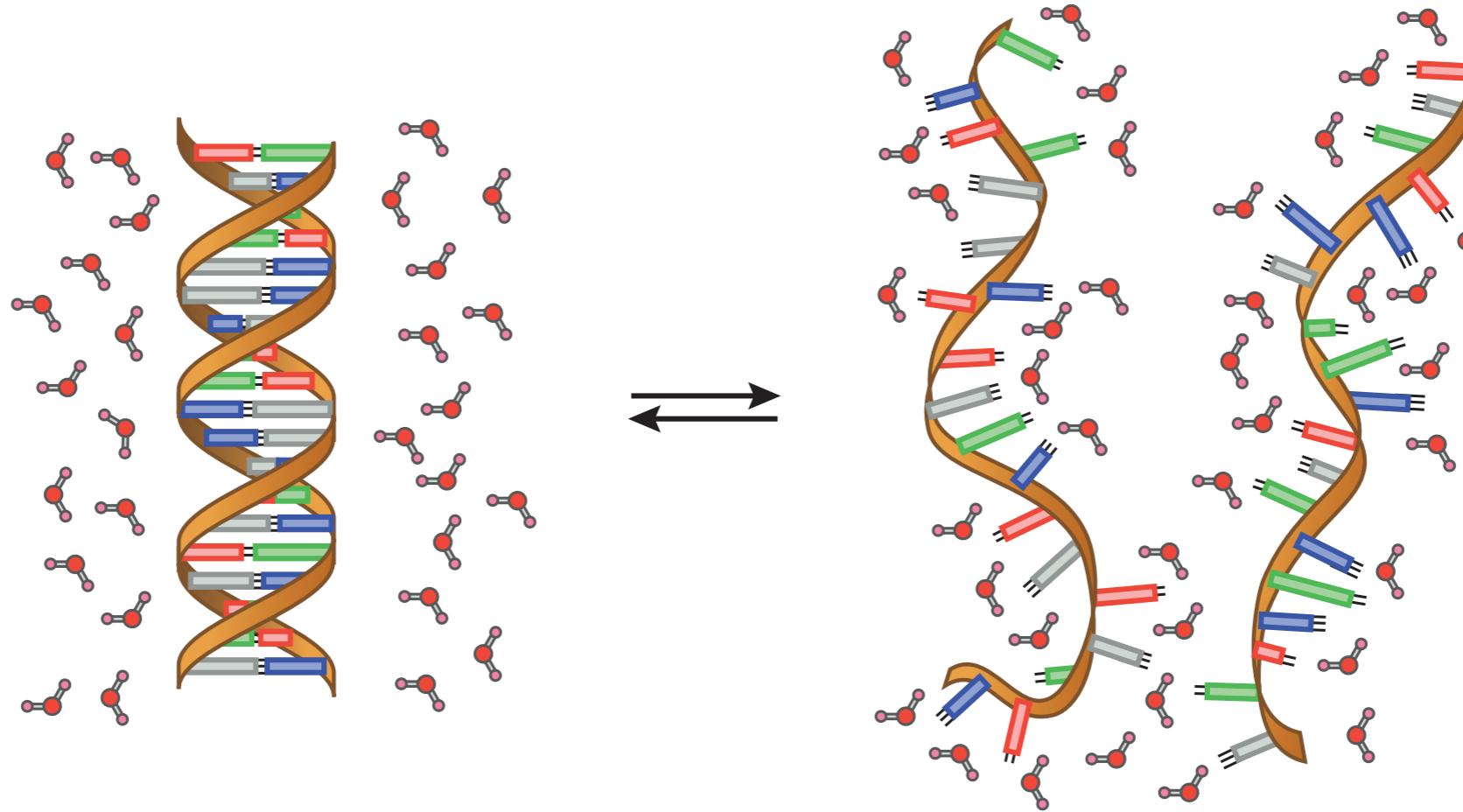
All Watson-Crick base-pairs are of the same shape so all DNA can be double helix that is unlike proteins that have complicated secondary and tertiary structures. RNA is in the middle.

(A)



H-bonding of base pairs has to compete against water

Competition with base-water H-bonding reduces the effects of base-base H-bonding on the stability of DNA



base-base H-bonding between matched base-pair compensates the energy penalty associated with the loss of base-water H-bonds

Base stacking is more important than H-bonding for DNA stability

Base stacking interaction

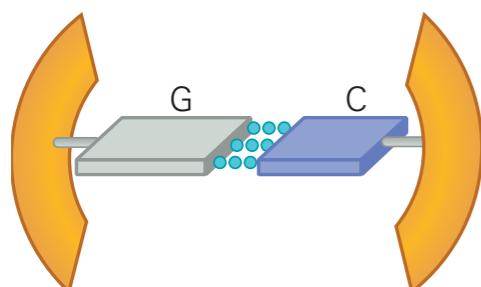
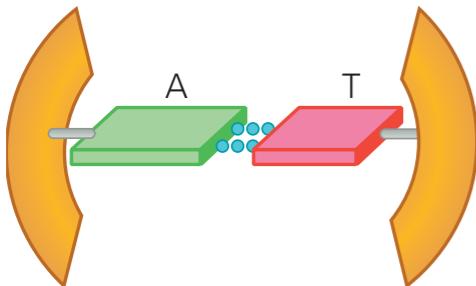


van der Waals interaction
Polarizability of aromatic rings
electrostatic interaction
Partial charges on N and O atoms

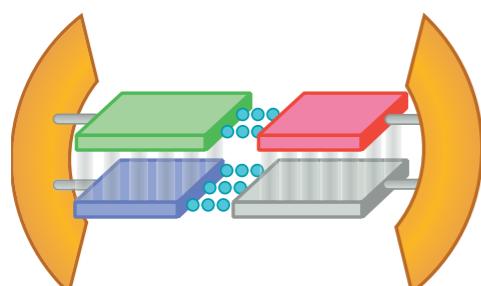
Table 19.2 Changes in enthalpy, entropy, and free energy in 1 M NaCl solution (at 37°C) for stacked DNA base pairs.

Base stack energy	5' GC 3' 3' CG 5'	5' GG 3' 3' CC 5'	5' CG 3' 3' GC 5'	5' GA 3' 3' CT 5'	5' GT 3' 3' CA 5'	5' CA 3' 3' GT 5'	5' CT 3' 3' GA 5'	5' TA 3' 3' AT 5'	5' AT 3' 3' TA 5'	5' AA 3' 3' TT 5'
ΔH^0 (kJ•mol ⁻¹)	-41.0	-33.5	-44.3	-34.3	-35.1	-35.6	-32.6	-30.1	-30.1	-33.1
ΔS^0 (J•mol ⁻¹ •K ⁻¹)	-102.1	-83.3	-114	-92.9	-93.7	-95.0	-87.9	-89.1	-85.4	-92.9
ΔG^0 (37°C; kJ•mol ⁻¹)	-9.37	-7.70	-9.08	-5.44	-6.03	-6.07	-5.36	-2.43	-3.68	-4.18

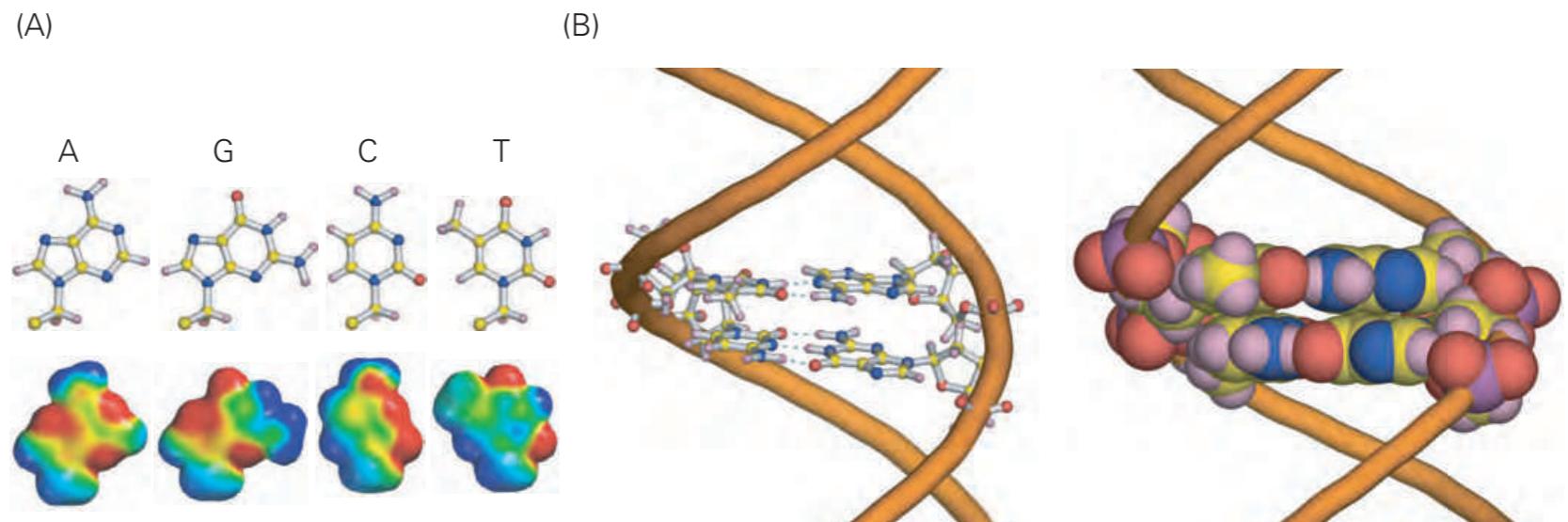
(A) base pairs



(B) a stack of base pairs



When bases stack, the partial charges interact favorably for electrostatic complementarity



Base-base H-bonding only contributes 2-6 kJ mol⁻¹ per H-bond

3 such contributions for a G-C pair
2 such contributions for A-T pair

Base stacking is observed in RNA as well

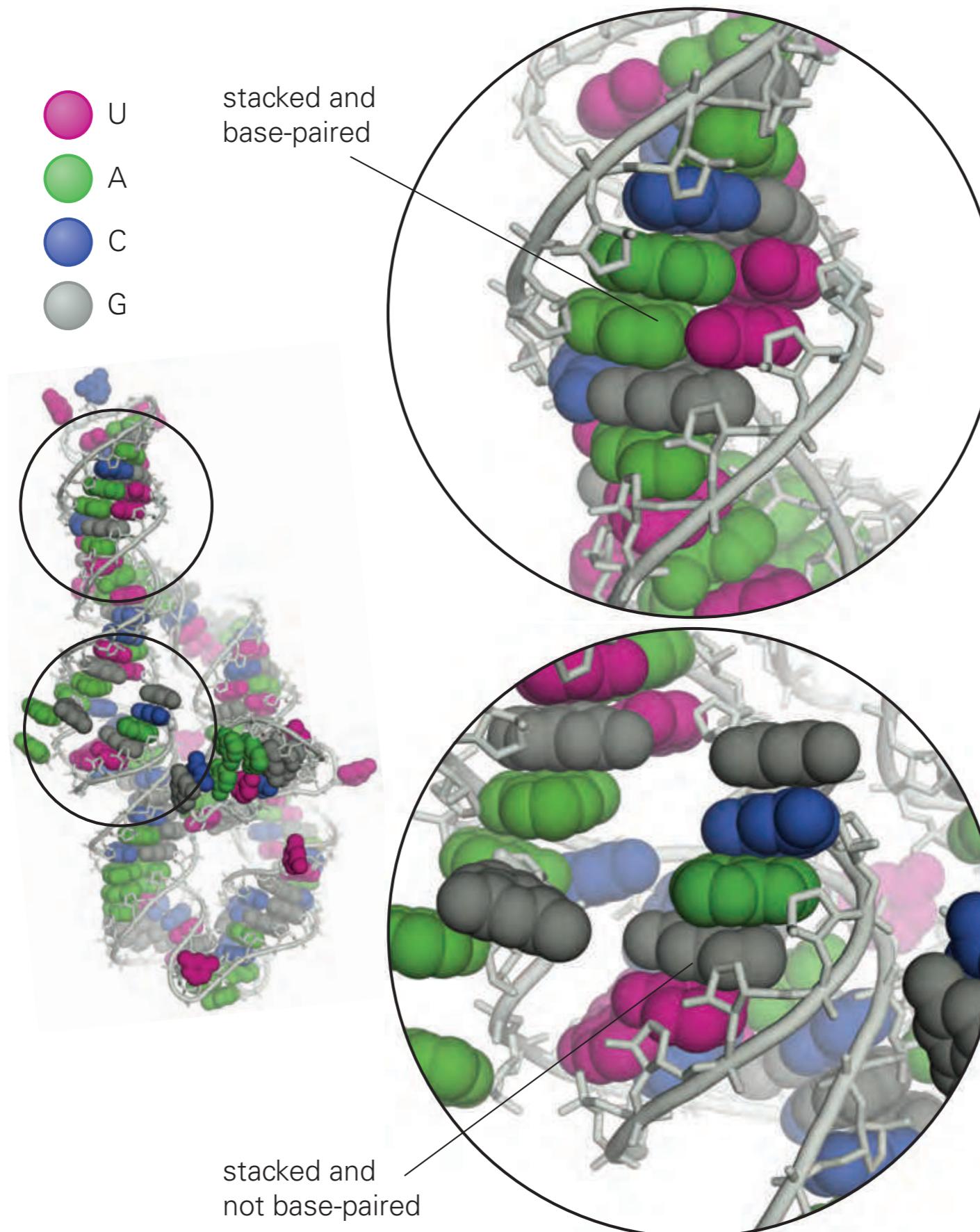
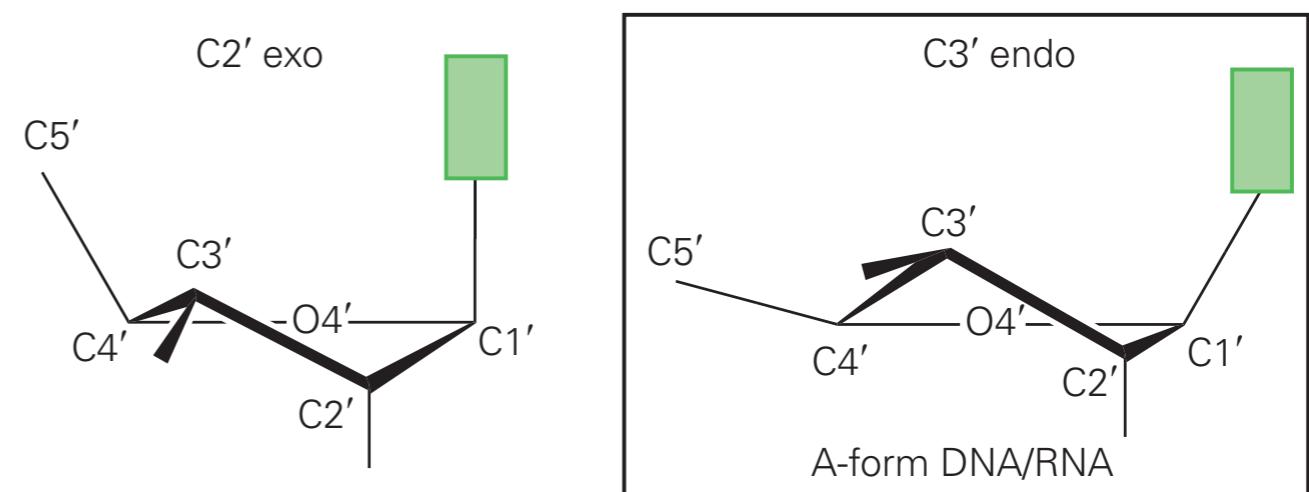
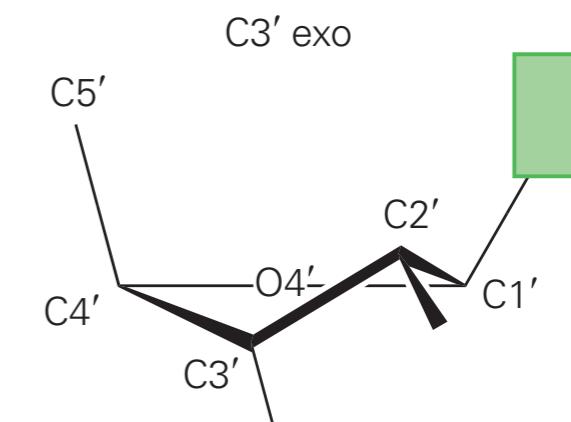
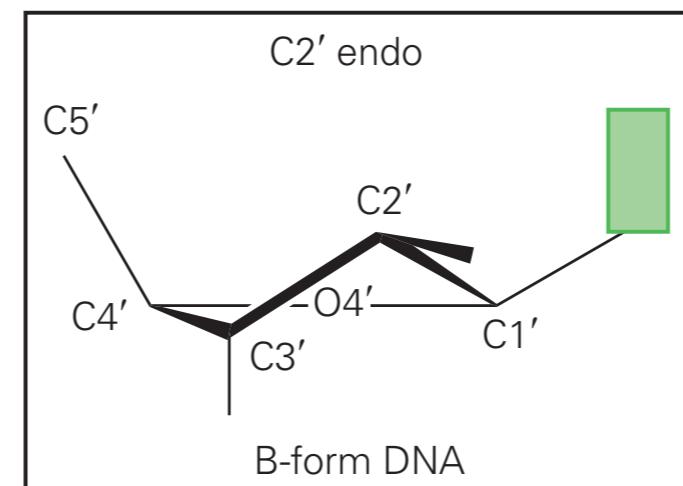
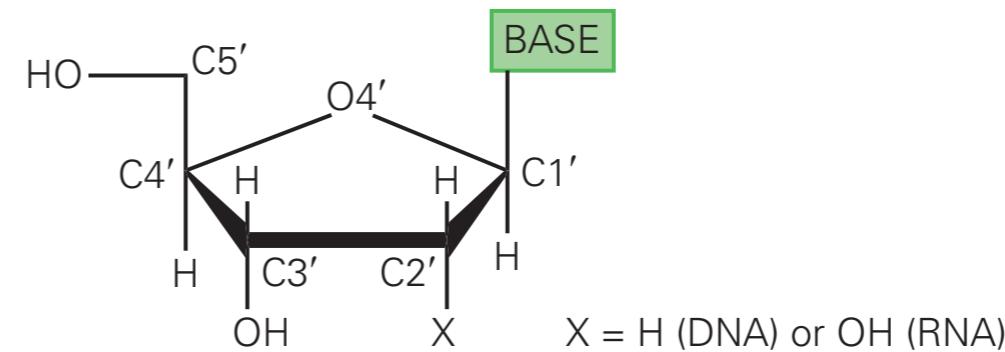


Figure 2.5 Base stacking in a noncoding RNA molecule. The favorable energetics of stacking is demonstrated by the fact that even nonbase-paired regions of RNA are often found to be well-stacked, as shown in this example. (PDB code: 1HR2.)

Sugar pucker distortions in DNA and RNA conformations

Sugar pucker

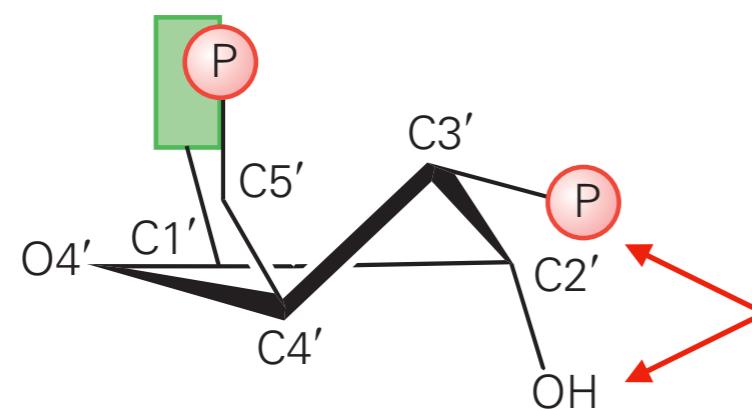
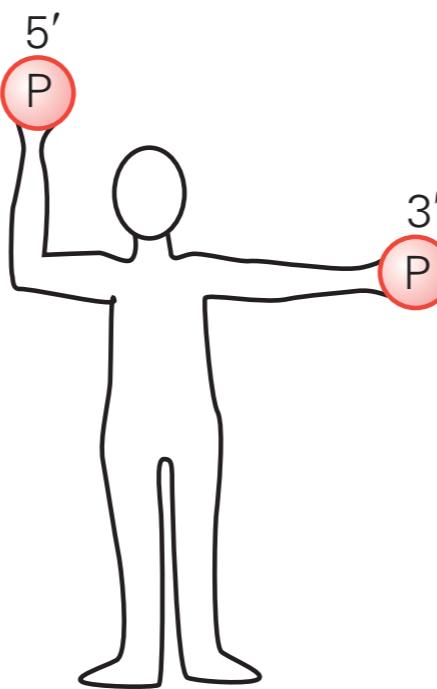
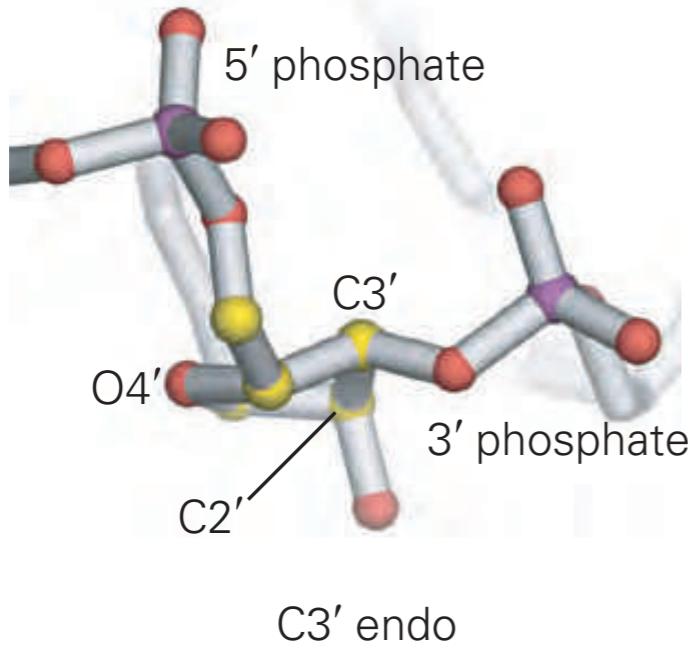
The sugar ring in polynucleotides is generally nonplanar and it displays a preferred puckering mode, C3' endo, found in A-form helices, or C2' endo, found in B-form helices. The terms endo and exo specify the nature of the out-of-plane atom of the sugar ring, with endo indicating displacement toward the side with the C5' carbon and exo indicating displacement toward the opposite side.



Commonly observed sugar pucksers in DNA and RNA

(A)

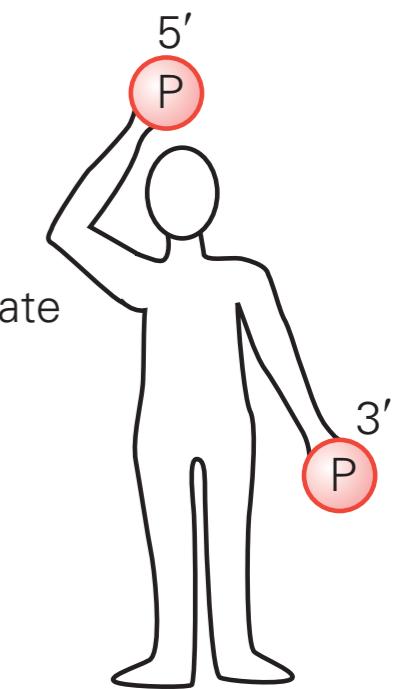
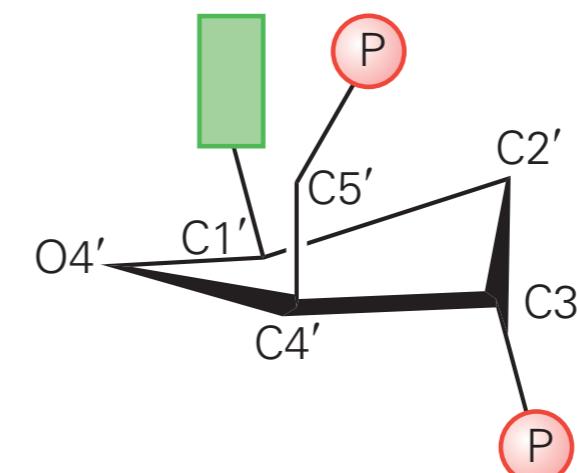
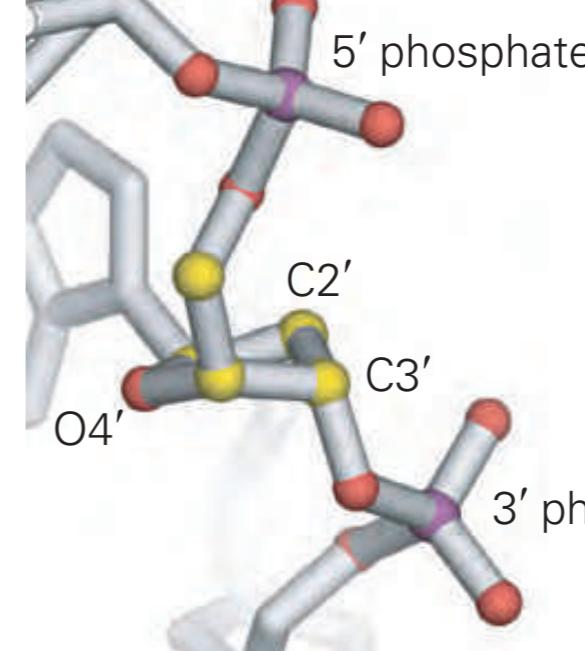
RNA



These two groups would overlap in *C2'* endo form, so it is not possible for RNA

(B)

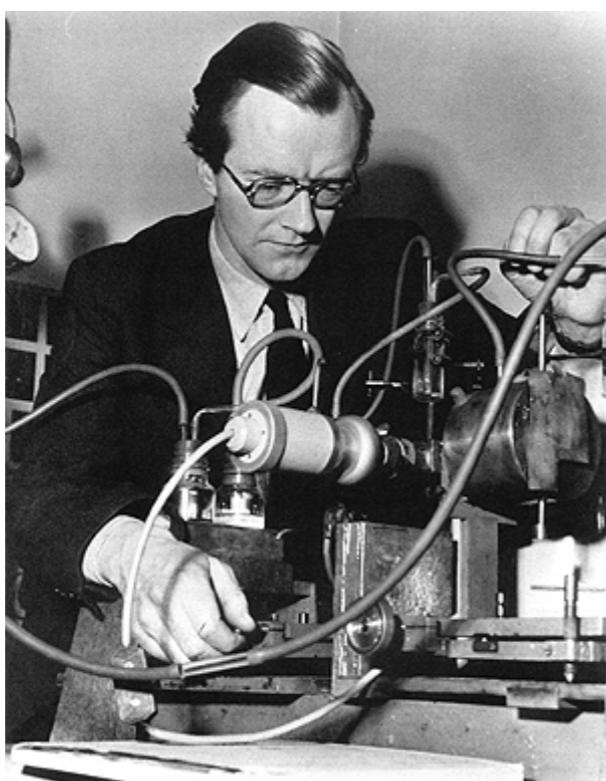
DNA



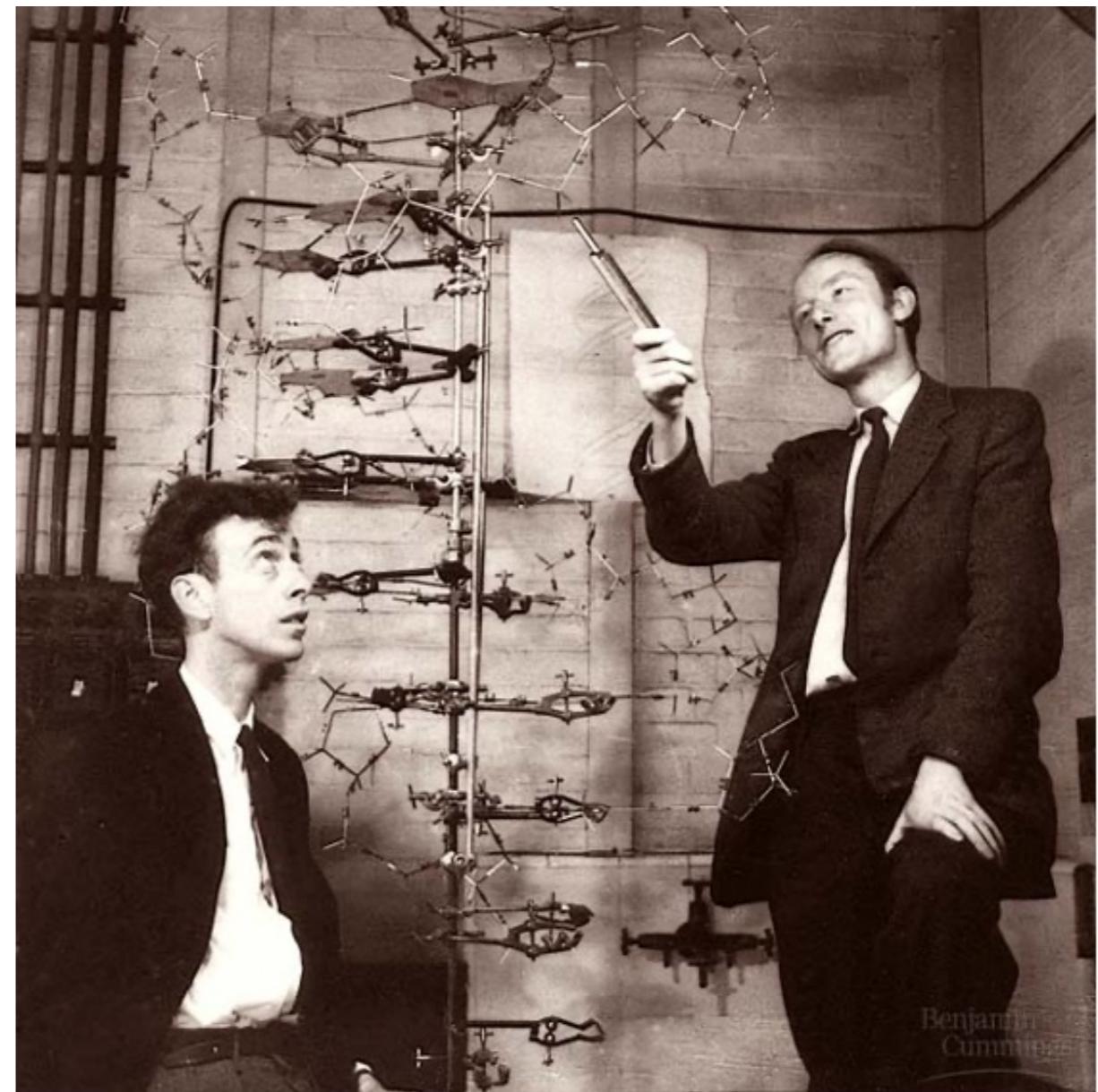
Let's now talk about the helical structure of DNA

History behind the structure of DNA

Franklin & Wilkins (1952): structure of DNA using X-ray crystallography @ Kings College, London



Watson-Crick model of DNA (1953)



At Cavendish Laboratories

The two pairs of scientists announced the structure of DNA in two different articles that appeared together in the same issue of *Nature*!

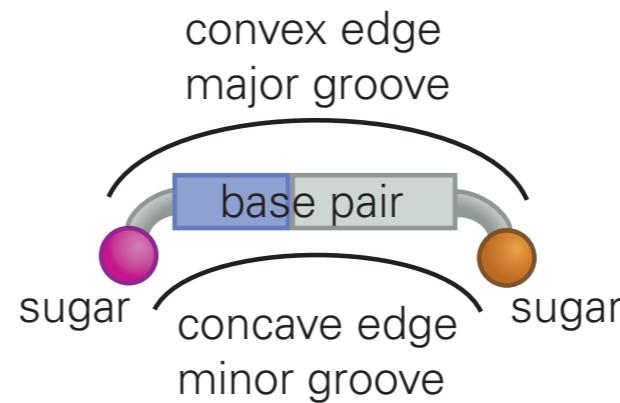
Watson, Crick and Wilkins won Nobel prize in 1962

The Watson-Crick model of B-DNA

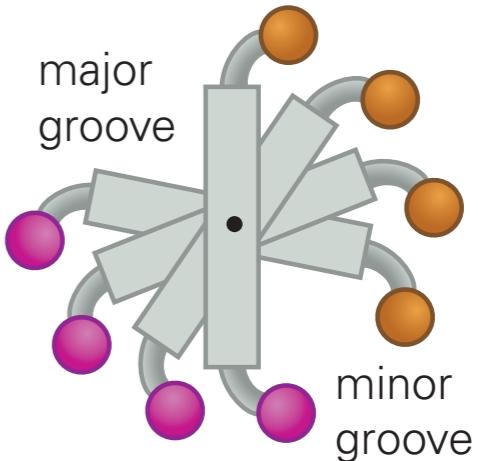
B-form DNA

B-form DNA is the standard conformation of double-helical DNA. The sugar pucker is C^{2'} endo, which is inaccessible to RNA. The base is in the anti conformation with respect to the sugar.

(A)



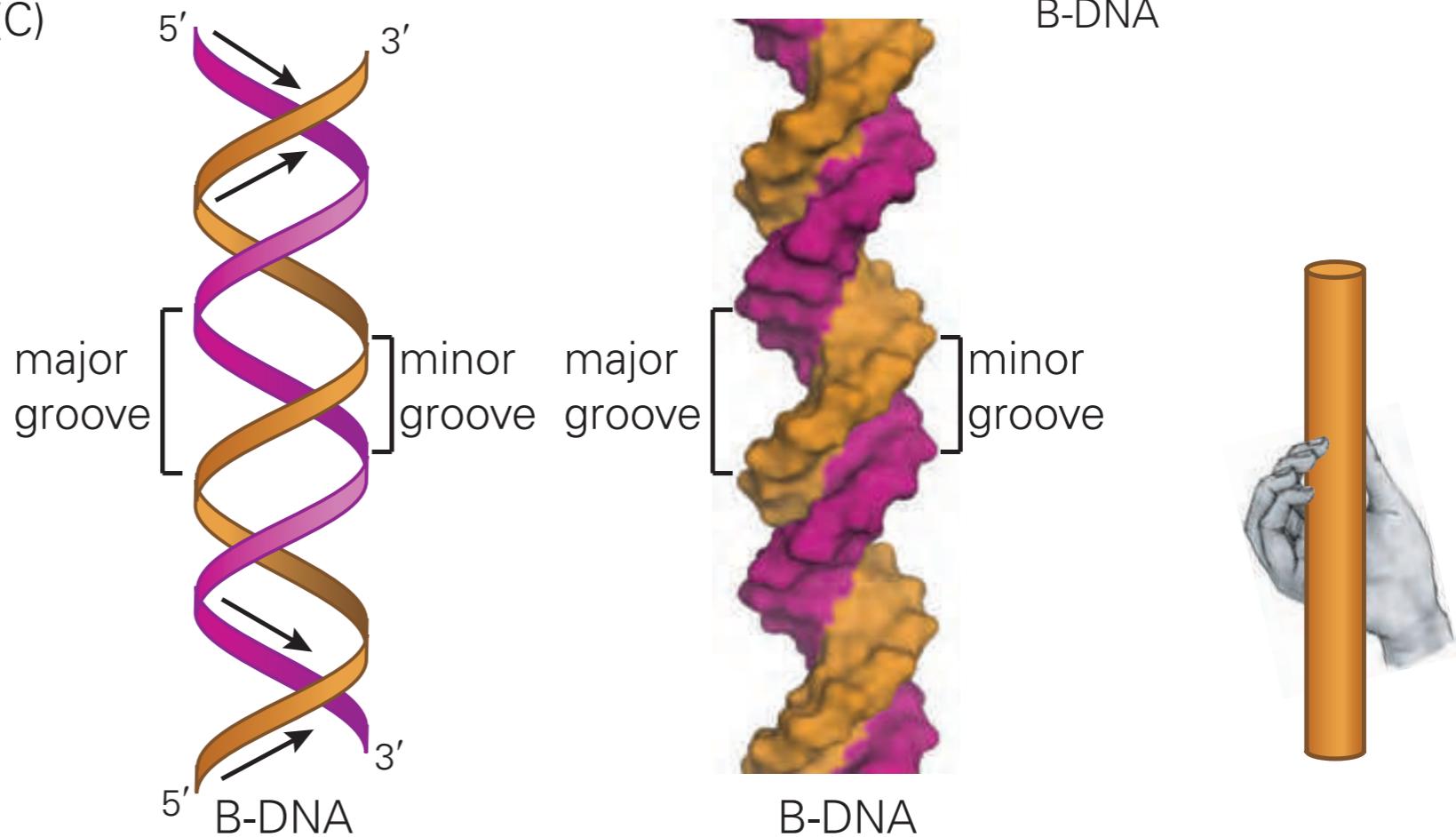
(B)



Major and minor grooves

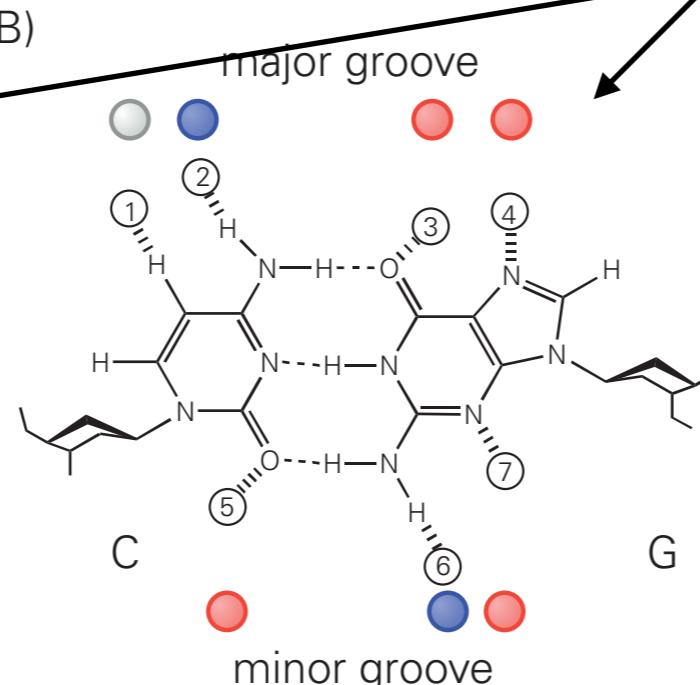
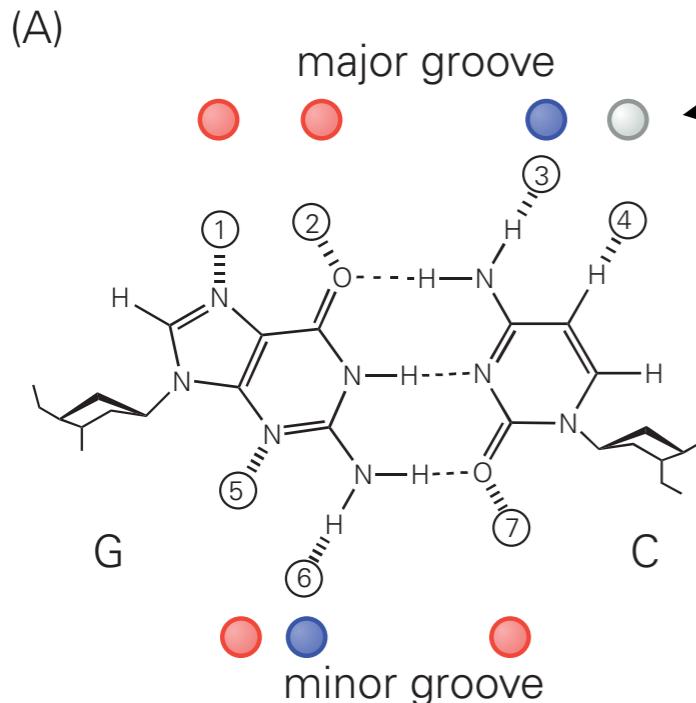
DNA and RNA double helices have two characteristic grooves, denoted the major and minor grooves. In B-form DNA, the major groove is wide and can accommodate α helices, which is important for the sequence-specific recognition of DNA by proteins. The major and minor grooves can be identified by looking at the connections of the base pairs to the sugars. The major groove is at the convex edge of the base pair, while the minor groove is at the concave edge, as shown in Figure 2.10.

(C)



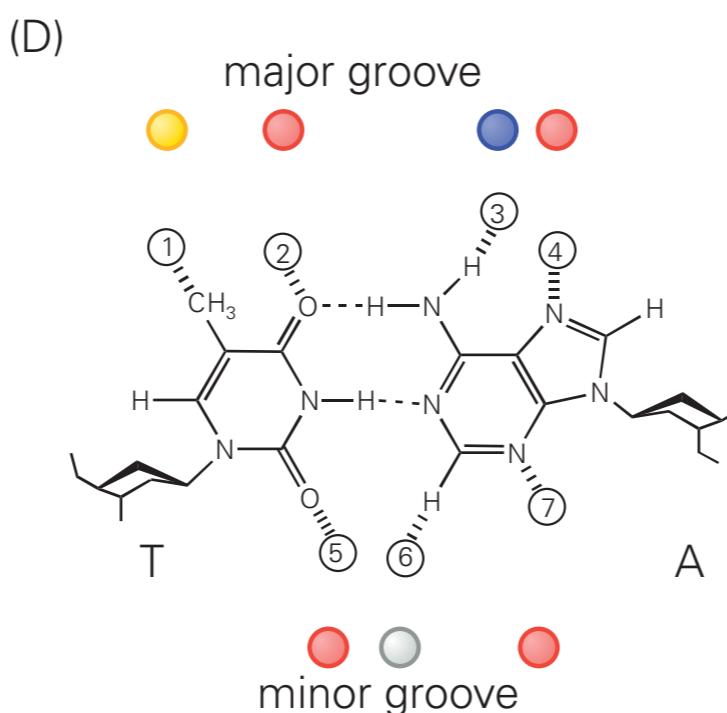
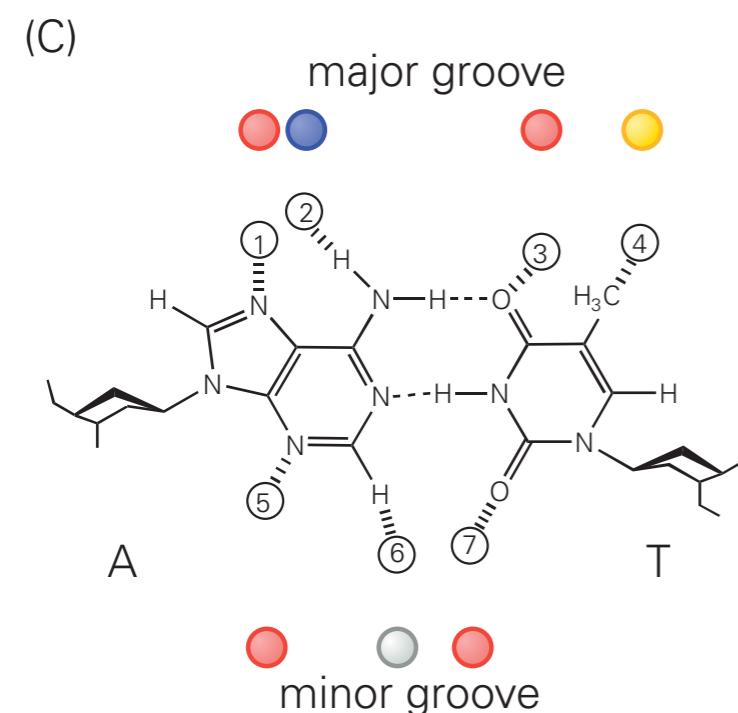
B-DNA allows sequence specific recognition of major groove

Potential interaction sites at the edges of WC base pairs



Major groove patterns change with seq reversal while minor groove does not

This makes major groove more apt for recognition



● H-bond acceptor

● H-bond donor

● Hydrogen atom

● Methyl group

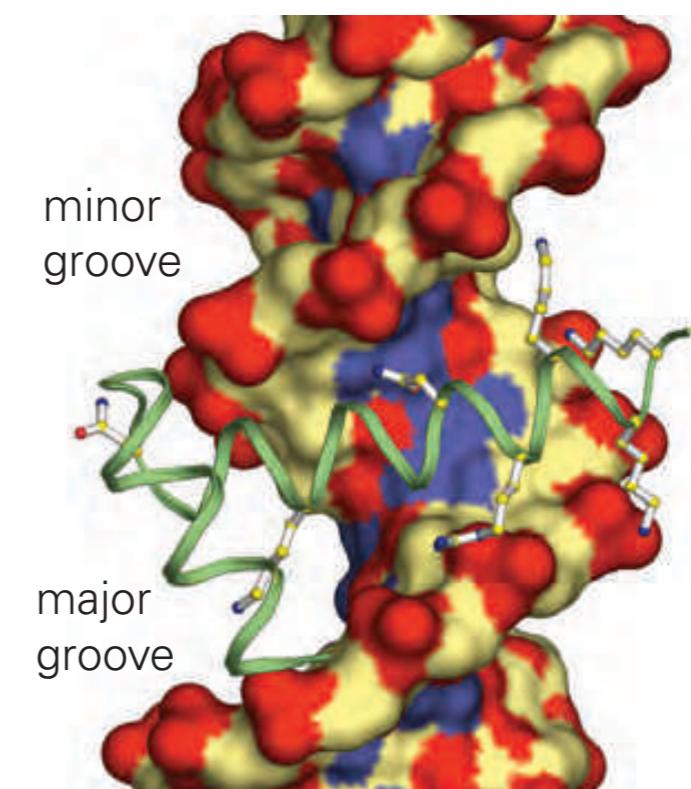
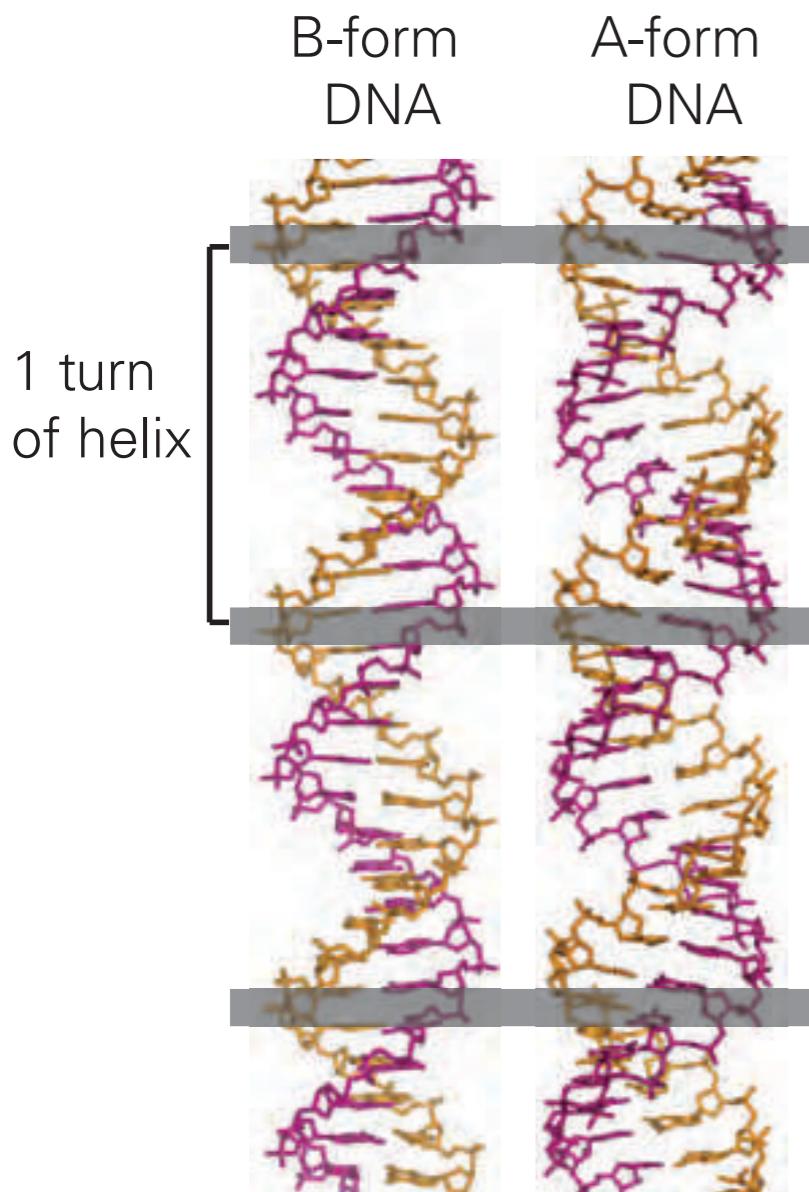
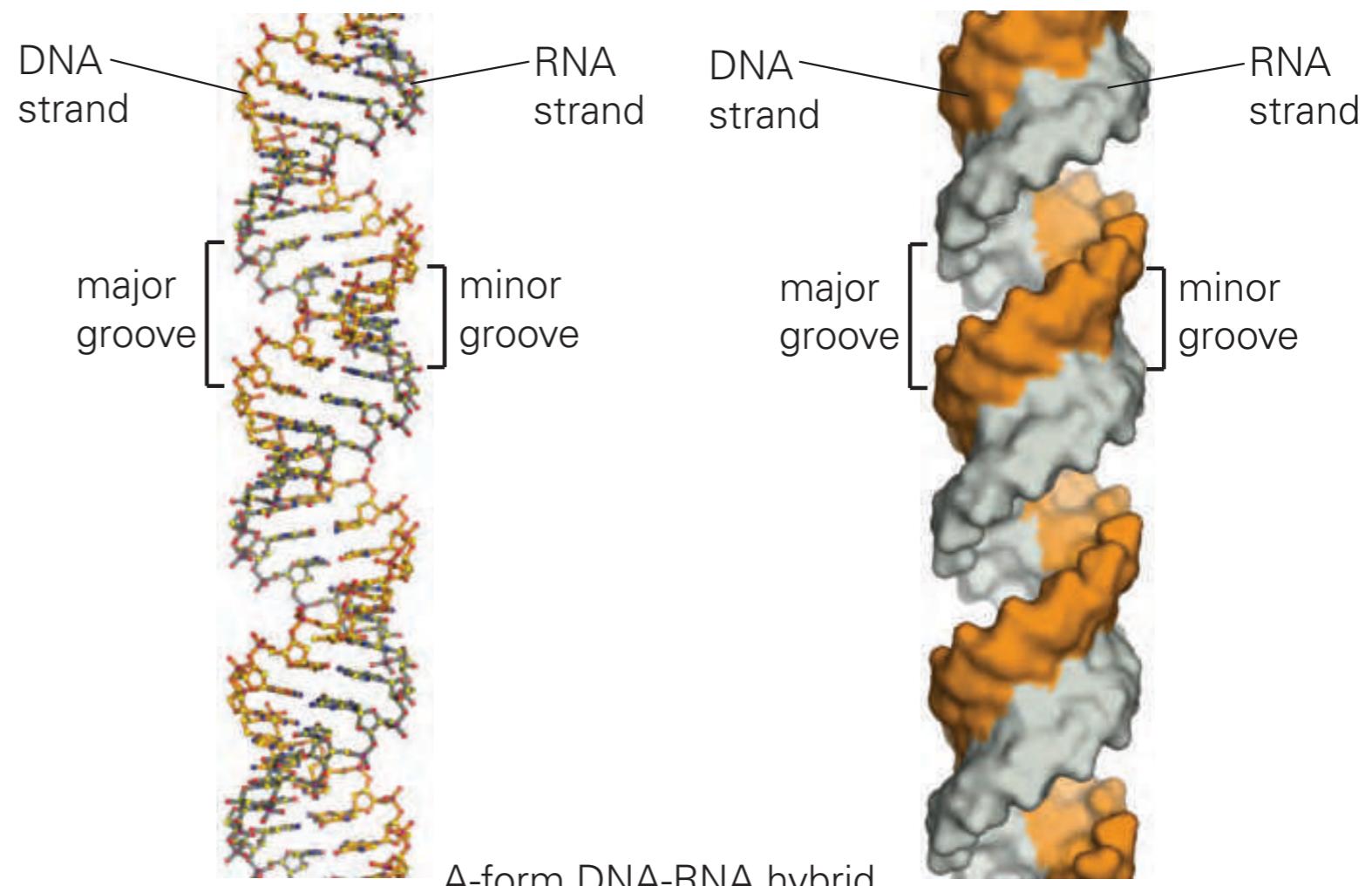


Figure 2.14 Interaction between a protein and the major groove of DNA. The molecular surface of DNA is shown. The surface is colored according to the nature of the underlying atoms, with nitrogens blue, oxygens red, and carbons yellow. (PDB code: 1DU0.)

A-DNA is the only helical structure for RNA



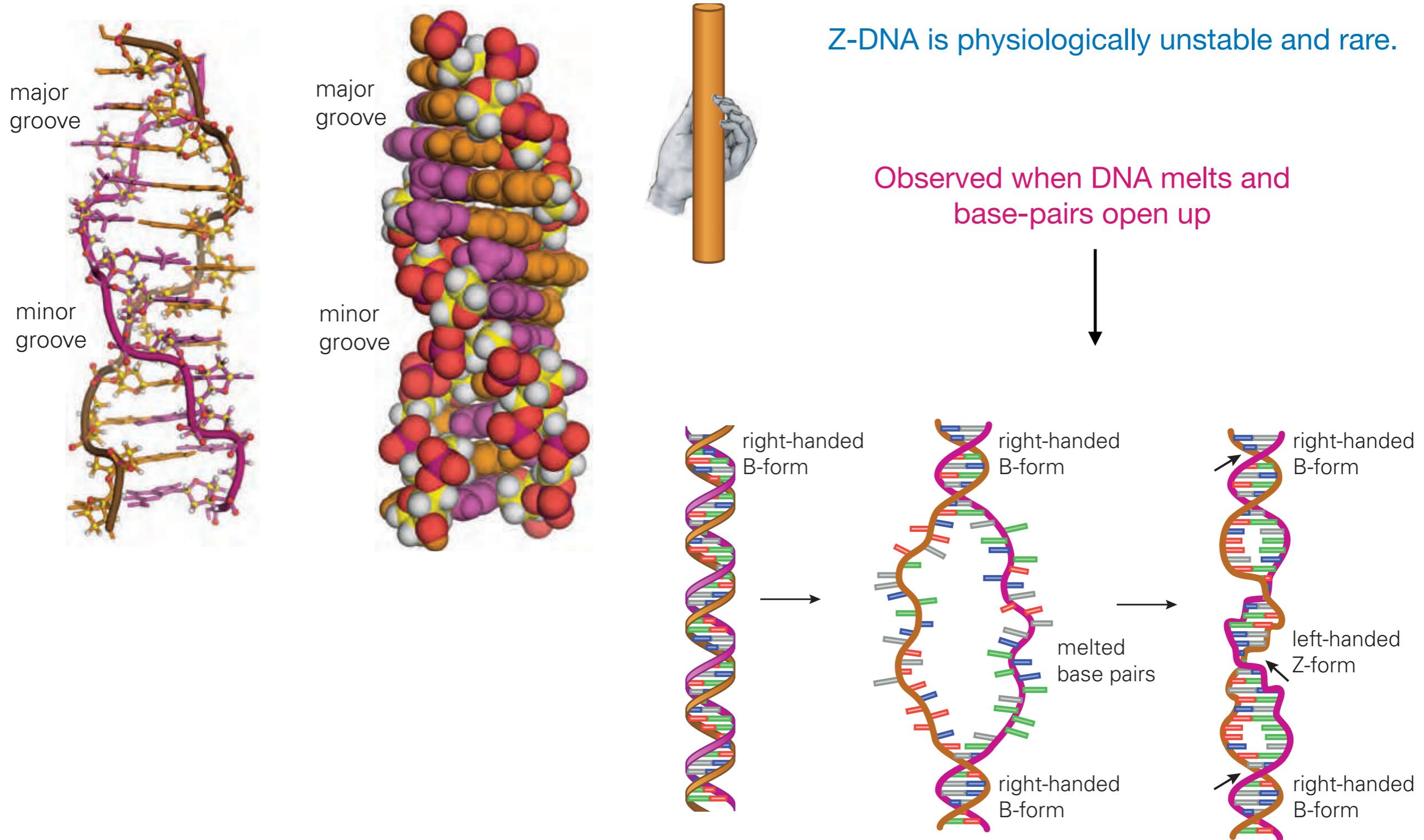
Here the sugar pucker is *C3'* endo, the major groove is deeper and narrower and the minor groove is shallower than in B-form



A-form of DNA is observed when limited water is available, B-DNA spontaneously switches to A-DNA

When RNA forms double helix it is always in the A-form because of the restriction of the sugar pucker.

Z-DNA is a left-handed helical structure for DNA



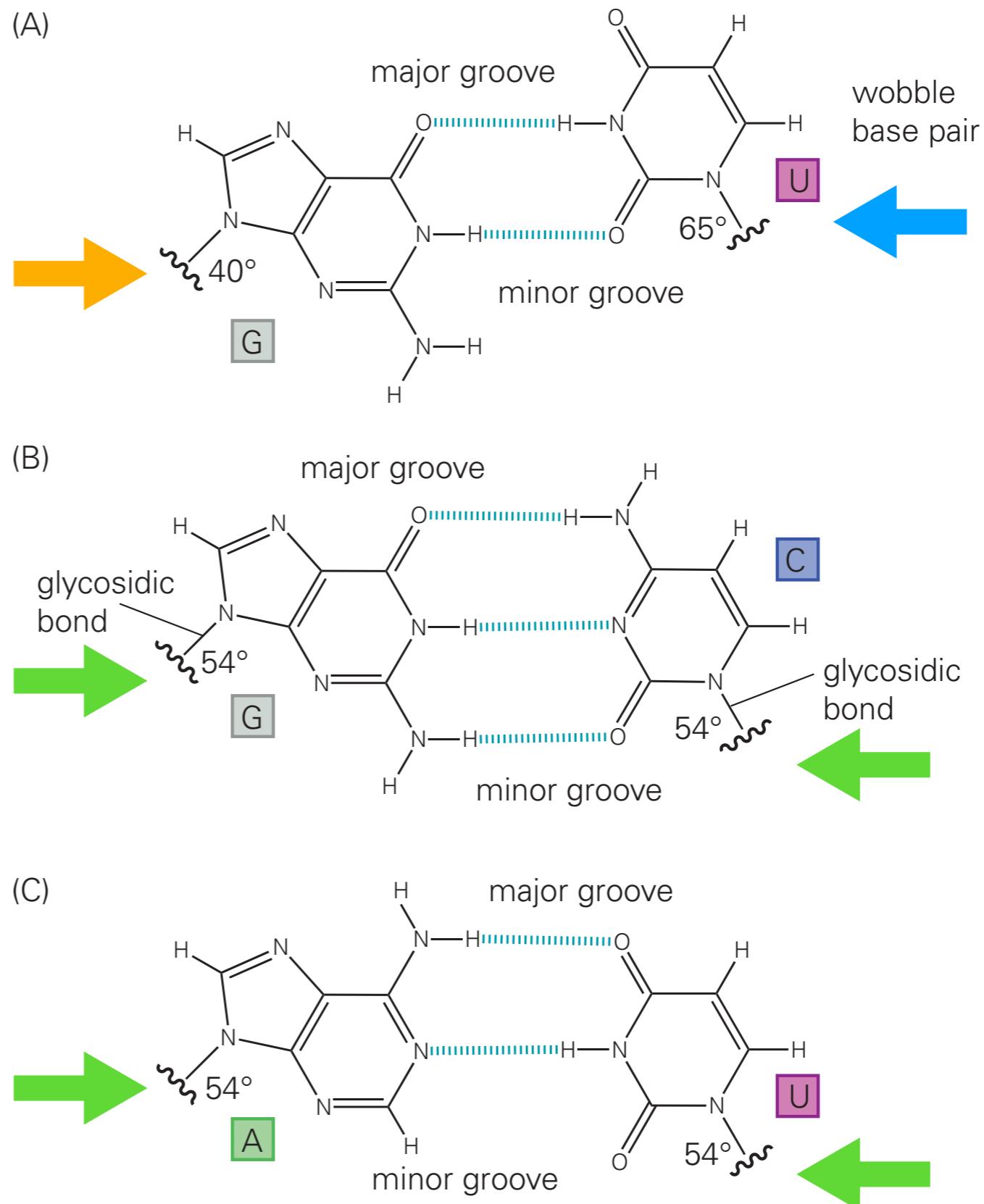
Non-canonical base pairing in RNA

Standard base pairs and nonstandard base pairs

The standard base pairs, or Watson-Crick base pairs, are A-T and C-G in DNA and A-U and C-G in RNA. Folded RNA structures often contain alternative base pairs (for example, G-U), which are referred to as nonstandard.

Wobble base pair

A nonstandard base pair, first identified in codon–anticodon interactions. The base pair involves two hydrogen bonds (between G and U, as illustrated in Figure 2.32), but the geometry of the base pair is different from that of a standard base pair.

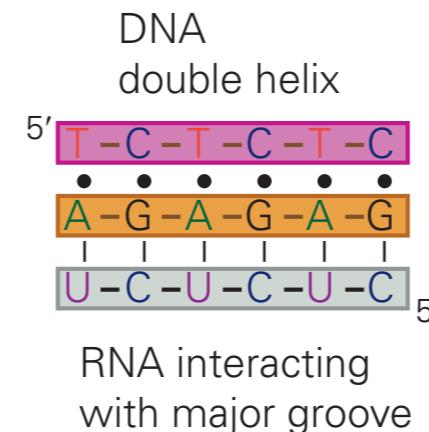


Non-canonical base pairing in RNA ... *contd*

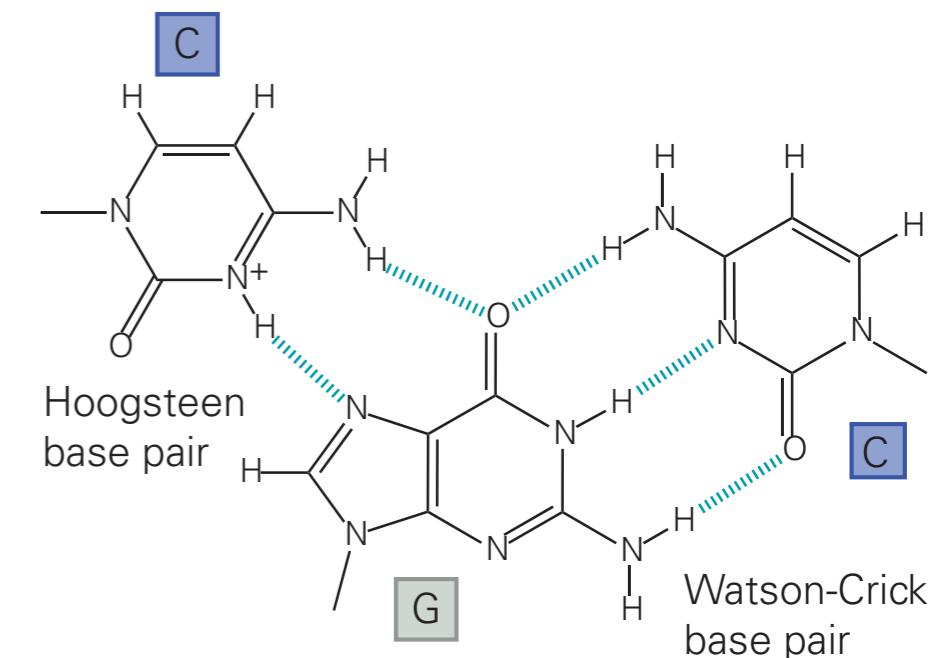
Hoogsteen base pair

A nonstandard base pair in which the hydrogen-bonding interactions utilize the Watson-Crick base-pairing edge on one base and the edge corresponding to the major groove in the other (see Figure 2.37).

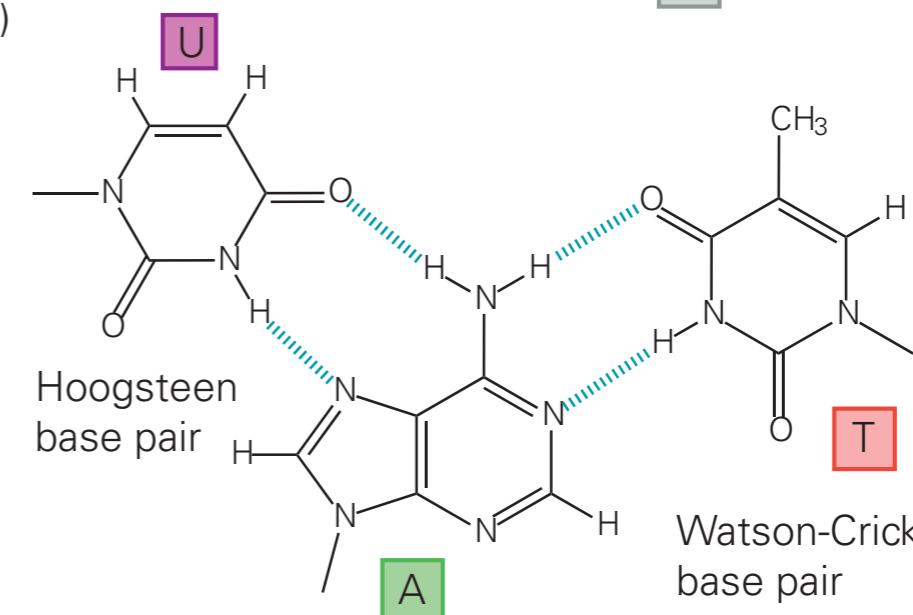
(A)



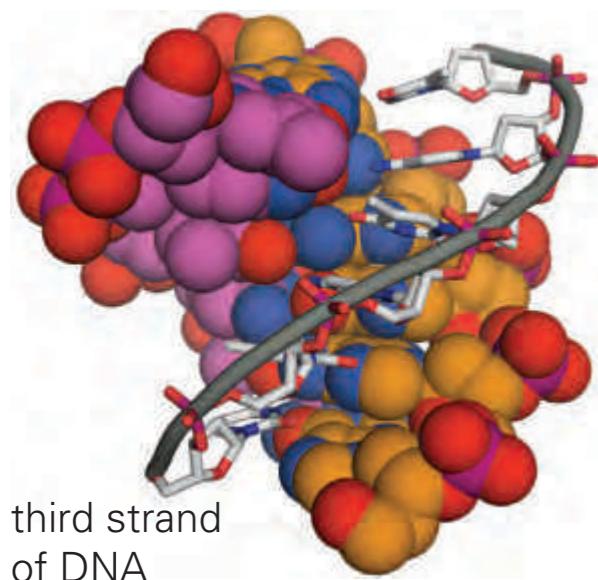
(B)



(C)

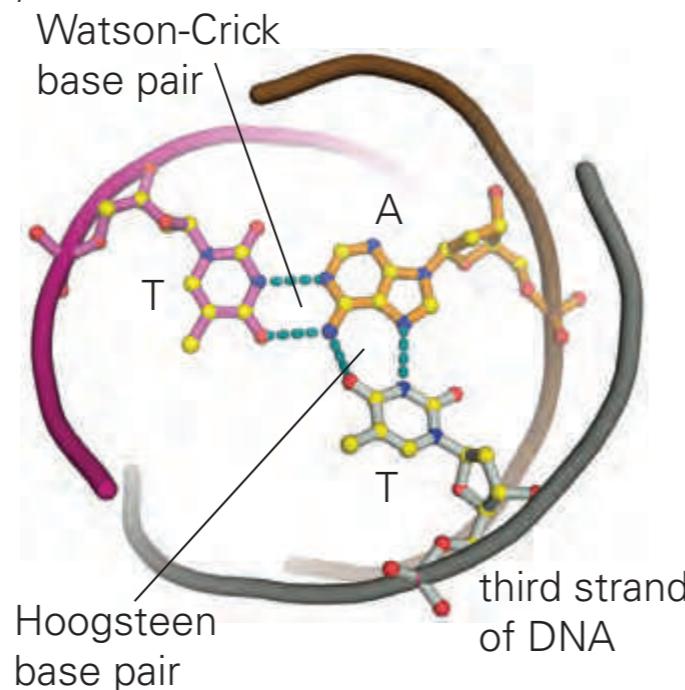


(C)



third strand of DNA

(D)



These kinds of interactions can be used to detect specific sequences in DNA and, for tasks like, shutting down transcription of certain genes.

DNA double helix is quite deformable

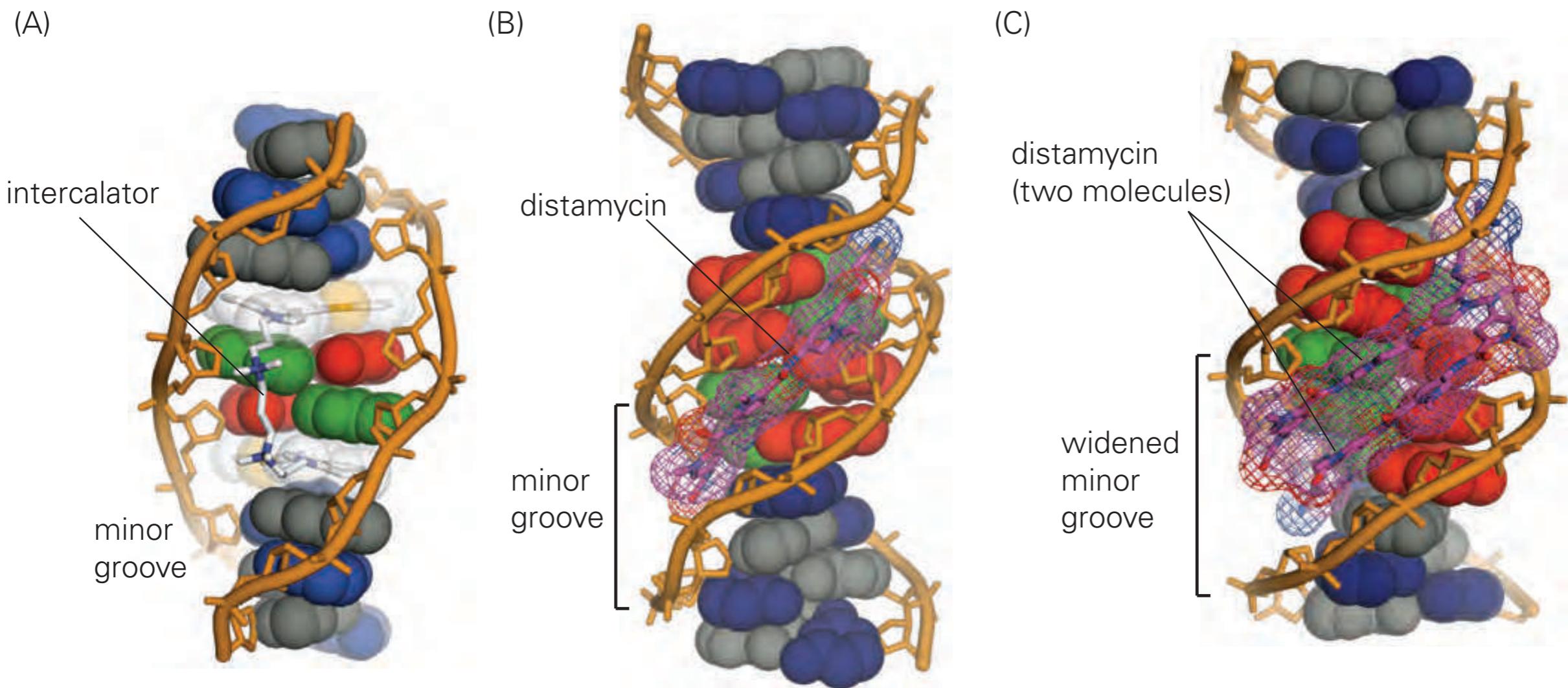


Figure 2.22 Small molecules that distort DNA. (A) An intercalator DNA complex. The intercalator TOTO (bis-thiazole orange) is shown bound to DNA. The aromatic parts of the intercalator stack with DNA bases both above and below it. The increased separation of the base pairs causes local unwinding of the DNA.

Some DNA sequences, rich in A-T base pairs, will accommodate either one (B) or two (C) minor groove ligands (such as distamycin in this case). The width of the minor groove must increase substantially for the second ligand to bind. (A, PDB code: 108D; B and C, courtesy of the laboratory of David Wemmer.)

DNA double helix is quite deformable ...*contd*

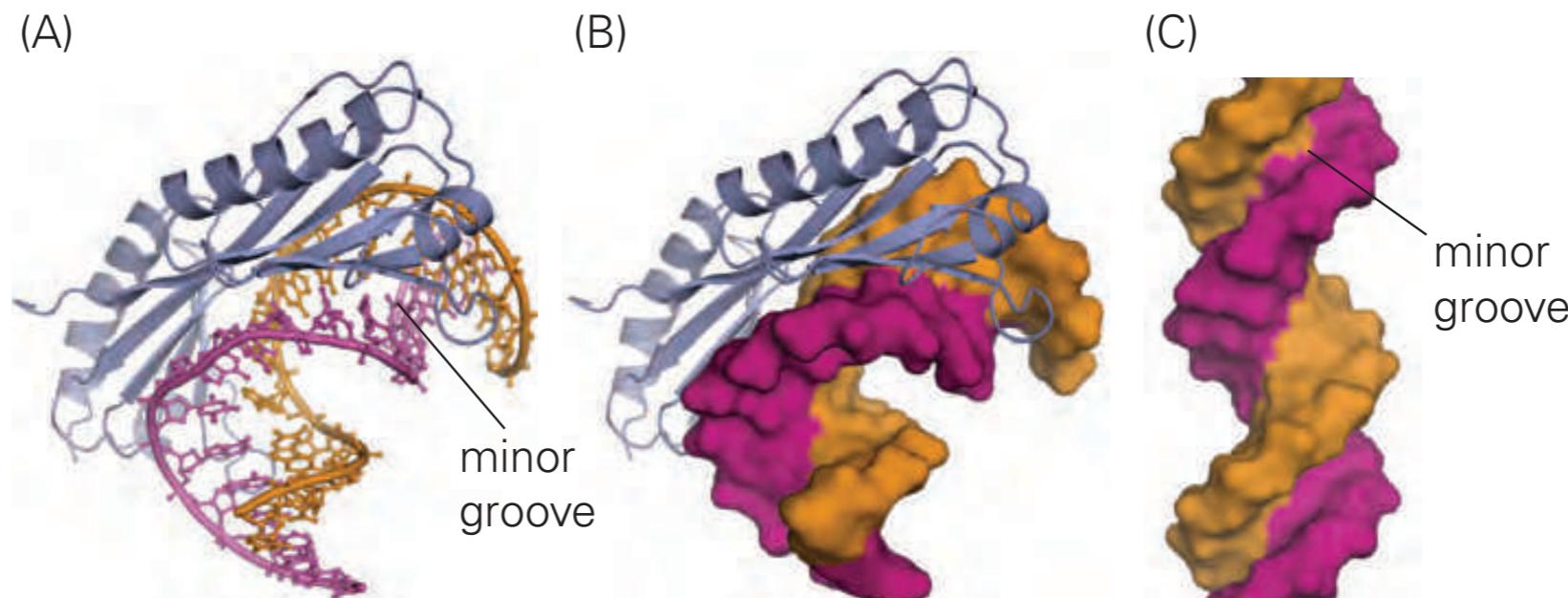


Figure 2.24 TBP deforming DNA.

(A) and (B) The TATA-box binding protein (TBP) induces a sharp bend in the double helix and drastically widens the minor groove. (C) Standard B-DNA, included here for comparison.
(A and B, PDB code: 1CDW.)

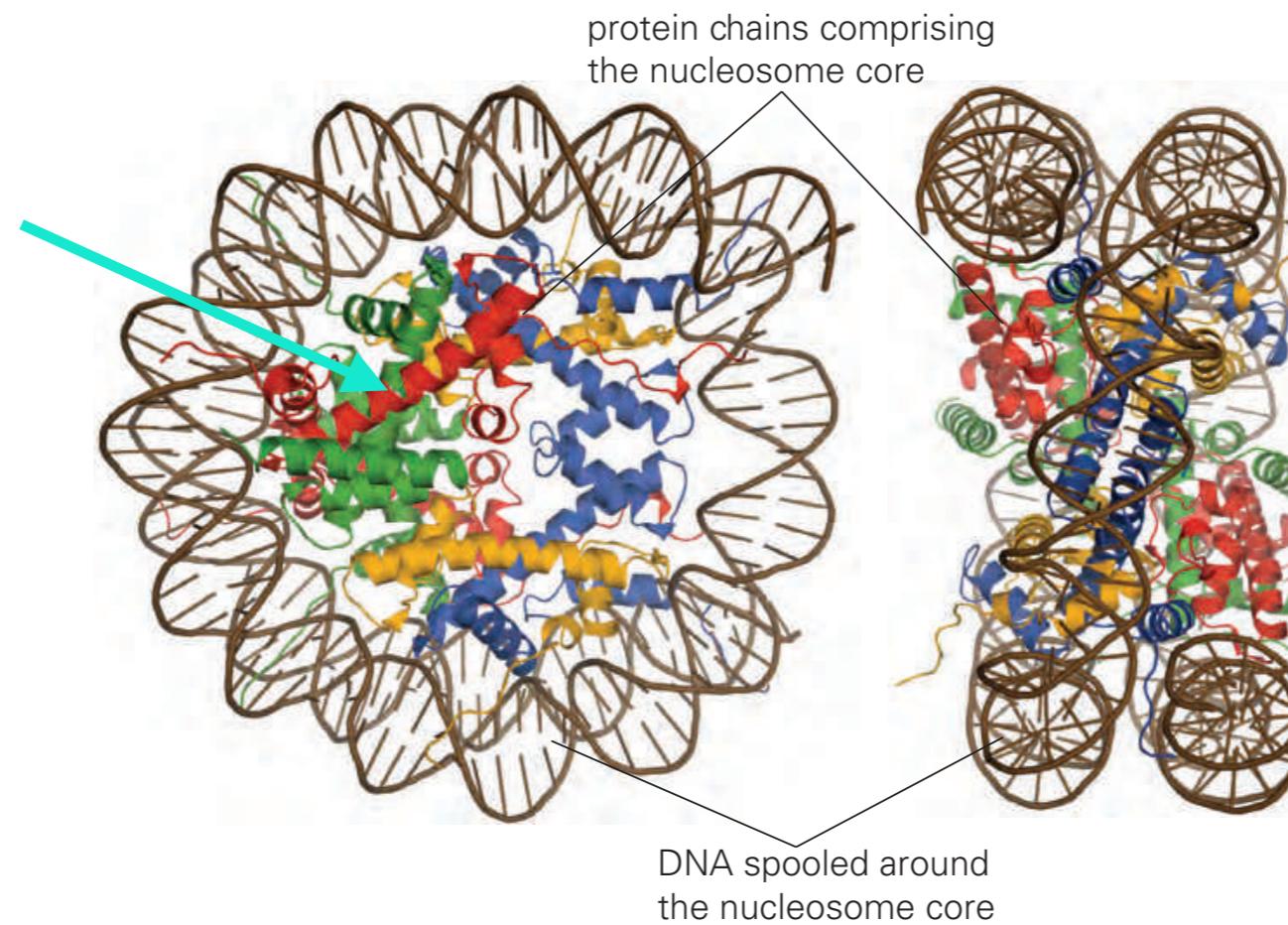
Such deformability is the key to packaging of DNA in nucleus

The packaging of DNA in chromatin

8 Histone chains called a histone octamer

~ 150 base pairs of DNA spooled around the nucleosome core

~ 50 base pairs of linker DNA between nucleosomes



Energy cost of coiling
DNA like this is compensated by strong electrostatic interactions between DNA and histones rich in basic residues

Such packaging allows transcription of active genes and insulation of inactive genes

