Forces stabilizing DNA

Van der Waals Interactions

-Electrostatic interaction between two mutually induced dipoles

Lennard-Jones Potential

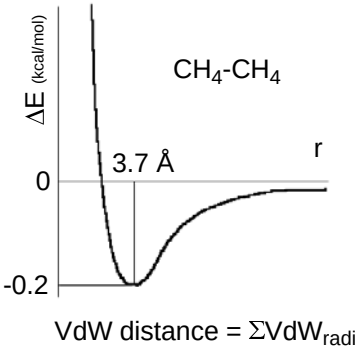
$$\Delta E = \frac{-B}{r^6} + \frac{A}{r^{12}}$$

B is a function of polarizability

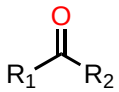
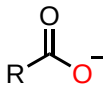
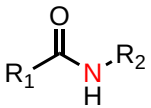
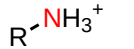
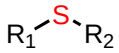
Benzene crystal VdW Energy
-9.9 kcal/mol

Atom	B (A^6·kcal/mol)
H	46
—O—	220
—OH	470
—CH_2—	1160
—S—	3760
—SH	4560

Van der Waals radius



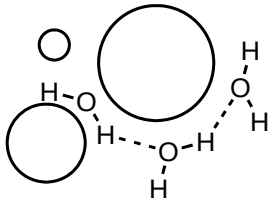
VdW distance = ΣVdW_{radii}

Atom	VdW radii (Å)
RO—H	1.5
	1.5
	1.5
	1.55
	1.65
CH (tet)	1.85
CH (tri)	1.7
	1.8

Forces stabilizing DNA

Hydrophobic Effect

-Describes tendency of hydrophobic molecules to transfer from aqueous phase to organic phase



(1) Iceberg-like structure of water around organic solute: All four hydrogen bonds formed/ high order-entropic rerdty

(In liquid water:
roughly 1/2 hydrogen bonds formed)

(2) poor polarizability of oxygen

↓

decreased VdW interaction between water and organic solute

↓

also drives hydrophobic effect

organic molecule tends to aggregate in water to minimize hydrophobic effect

-Measurement of hydrophobicity is partitioning of molecule between n-octanol and H_2O

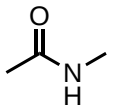
$$S\text{—}H \Rightarrow \frac{\text{Solubility in octanol}}{\text{Solubility in water}} = P_0$$

$$S\text{—}R \Rightarrow \frac{\text{Solubility in octanol}}{\text{Solubility in water}} = P$$

ΔG = transfer from n-octanol to water

$\Delta G = RT \log P/P_0$

-Energetic contribution due to substituent
-R groups have a constant additive effect on hydrophobicity of parent compound in absence of strong resonance/inductive effects

Group	ΔG (kcal/mol)	Group	ΔG (kcal/mol)
$-CH_4$	0.68	-benzyl	3.6
-Et	1.36	-OH	-1.58
-propyl	2.05		-1.65
-isopropyl	1.77		

1 A^2 of hydrophobic surface ca. 24 cal/mol stabilization when removed from H_2O

-Hydrophobic Effect can be relatively non-specific when molecules bind to protein or DNA

Lecture 2- Nucleic Acid Structure

Forces stabilizing DNA

Electrostatic Interaction

-Proportional to 1/r; Long distance interaction compared to VdW

$$E = \frac{e_1 e_2}{D r}$$

$H^+ \longleftrightarrow e^-$ 3.3 Å

D is dielectric constant

-Point charge induces dipoles in solvent which together with counterions induce field to neutralize charge

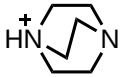
D water ~ 80 ⇒ -1.3 kcal/mol (very small)

D pentane ~ 2 ⇒ --50 kcal/mol

-So electrostatic interactions are far more important in organic solvent than water.

pK_{a1} ~ 8.8

pK_{a2} ~ 3

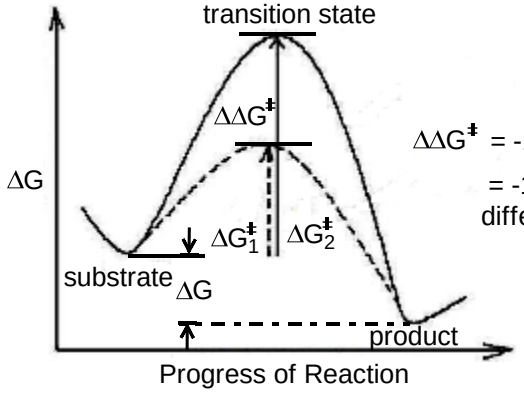


ΔpKa ~ 6 ⇒ ΔG = -RT logK

ΔG ca. 8.4 kcal/mol

ΔG = -RT logK = -1.4 logK kcal/mol (room temp)

= -1.4 kcal/mol for Product/Substrate = 10



$\Delta\Delta G^{\ddagger}$ = -1.4 log(K_2/K_1) at room temp

= -1.4 kcal/mol for a 10 fold difference in rate

Environmental Effect on pK_as

	pKa: % dioxane in H_2O			
	0	20	45	70
acetic acid (CH_3CO_2H)	4.76	5.29	6.31	8.34
glycine (NH_3^+)	9.8	9.3	8.5	7.42

-Leveling Effect

Metal ion coordination stabilizes DNA

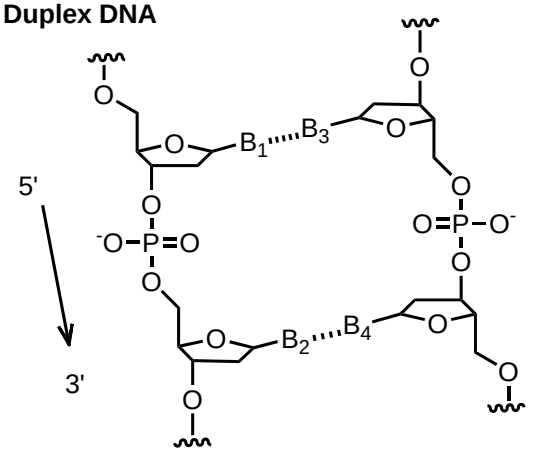
Mg^{2+} Co^{2+} Ni^{2+} Mn^{2+} Zn^{2+} Cd^{2+} Cu^{2+}

(Hard) ⟶ (Soft)

Bind -OH/-PO_4^-

Bind Bases

Duplex DNA

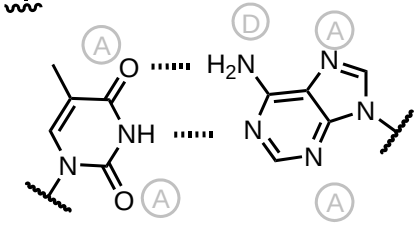


5'-GCAT⋯⋯

3'-CGTA⋯⋯

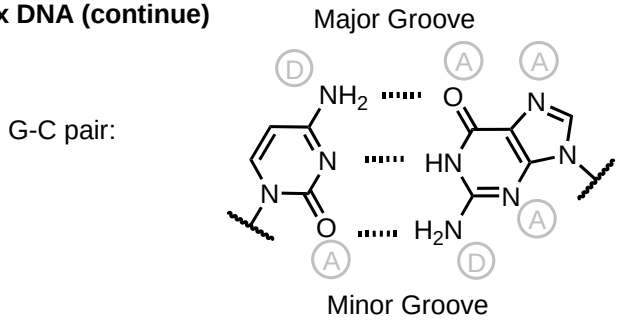
Always specify directionality of DNA sequence

A-T pair:



Lecture 2- Nucleic Acid Structure

Duplex DNA (continue)



B form DNA (dominant form)

-Right handed under physiological conditions
-10 bp/turn
-3.3 Å/bp
-helix axis through center of bp
-anti
-C2' endo
-wide major groove - binds peptides
-narrow minor groove - binds planar molecules

A form DNA

-Right handed (more contact)
-11 bp/turn
-2.3 Å/bp (short/broader)
-24 Å/turn
-major groove (deep narrow)/minor groove (broad shallow)
-anti
-C3' endo

Z form DNA

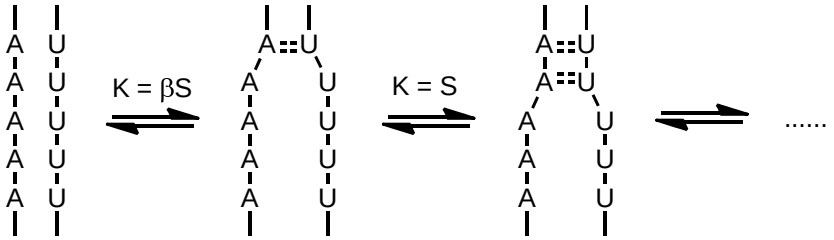
-Left handed
-12 bp/turn
-3.8 Å/bp
-anti C/Syn G
-no major groove/minor groove (deep narrow)

A form RNA

-C3' endo
-RNA can adapt more distinct structures than DNA

Single-stranded RNA	**A form**
DNA-RNA duplexes	**A form**
DNA duplexes	**A form**

Helix formation is cooperative



$\beta = 10^{-3}\ M^{-1}$ at 0 °C
S = 10 at 0 °C

-Helix coil transition is highly cooporative and nucleates by 3 bps

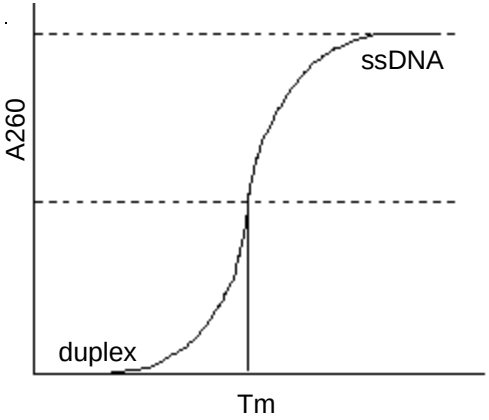
Melting Temperature Tm

-Tm characterizes the stability of double helix

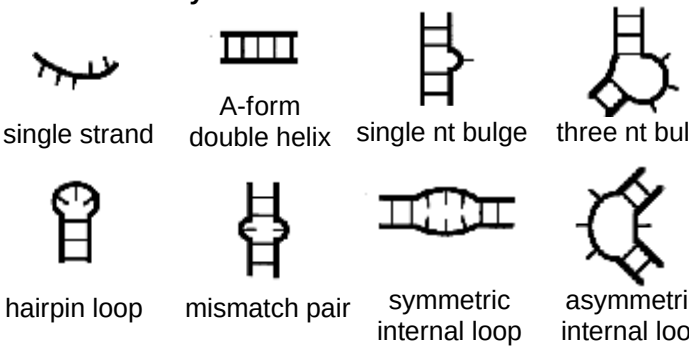
-Melting duplex to single-stranded is accompanied by an increase in absorbance

-Tm depends on length, ionic strength and GC/AT ratio

Tm calculator: + 2 °C A-T pair
+ 4 °C A-T pair



RNA secondary structure



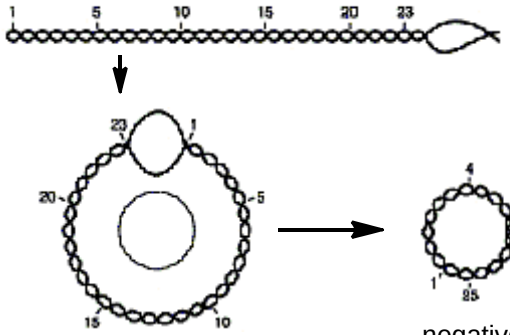
-Secondary RNA structure can be predicted

-tertiary RNA structure is hard to be predicted

Lecture 2- Nucleic Acid Structure

Higher order of DNA structure

-Supercoiling



-2 supercoil (neg) ~ 2 linear base

Enzymes to control winding and unwinding of DNA

-Topoisomerase (wind and unwind DNA)
target for cancer drug

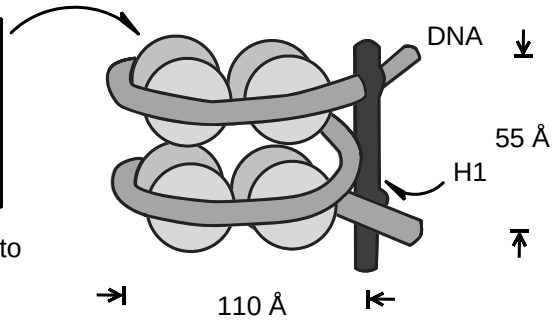
Packing of chromosomal DNA

-DNA is packaged into chromatin in mammalian cells

-duplex DNA tightly binds to 5 histones

packing ratio is 10^4 in human genome

H2A X 2
H2B X 2
H3 X 2
H4 X 2
10-20 kDa



680 Å into ~110 Å leads to packing ratio of 7

-Modulate duplex DNA and histone Interaction

-acetylation of lysine (positive charge of histone proteins~ neutralized)

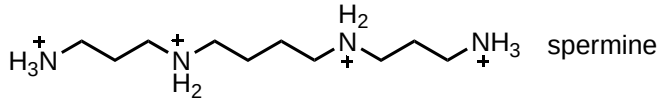
-other post-translational modifications (PTMs) exist for modulating histone/DNA interaction

-DNA is a popular target for cancer drugs as rapidly proliferating cells need to replicate DNA faster

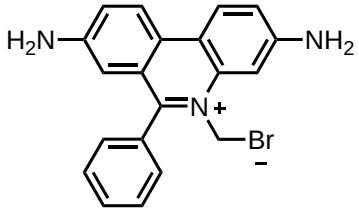
DNA-binding small molecules

Electrostatic Interaction

-target phosphated sugar backbone



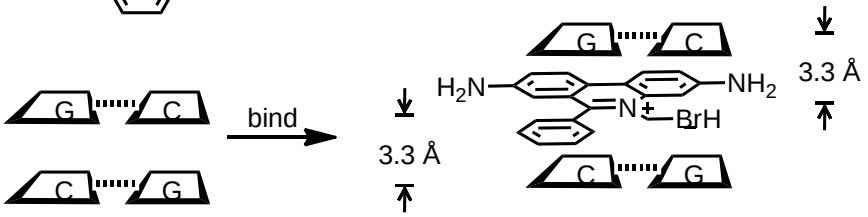
Intercalation



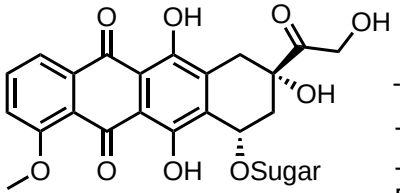
-targets G-C rich regions

-Kd 10^{-6} M^{-1}

-binds DNA from the narrow groove



Cancer drug - Doxorubicin



Doxorubicin

-binds DNA from minor groove

-cancer drug

-when Topo unwinds DNA, dox stablizes single strand DNA intermediate