

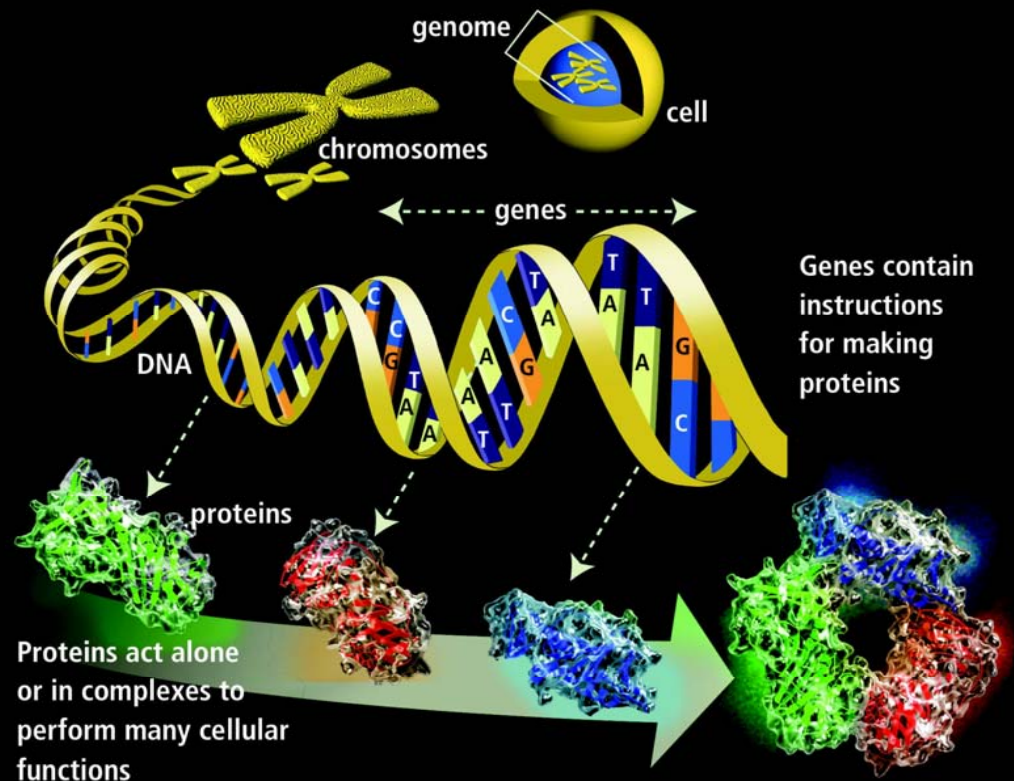


Macromoléculas Biológicas

ACIDOS NUCLEICOS
nucleotidos

PROTEINAS
aminoácidos

POLISACARIDOS
monosacáridos

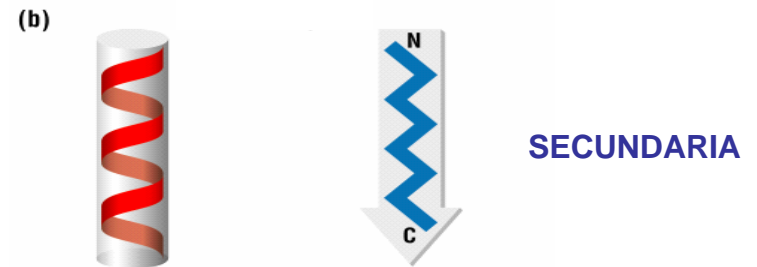
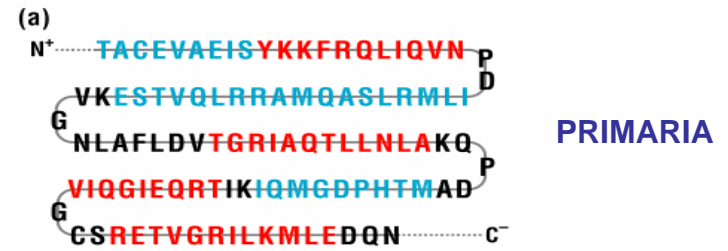
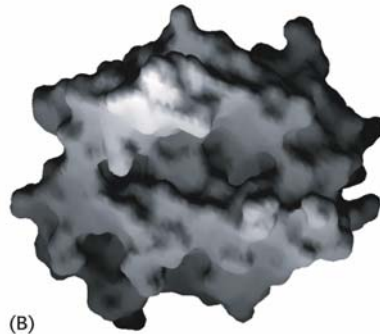
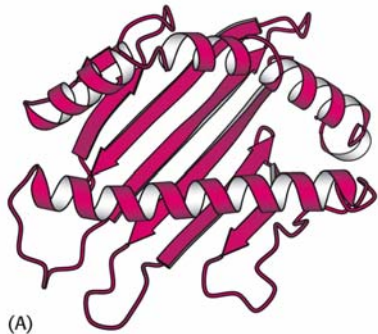


ESTRUCTURA DE PROTEÍNAS: POLÍMEROS DE AMINOÁCIDOS

NIVELES ESTRUCTURALES

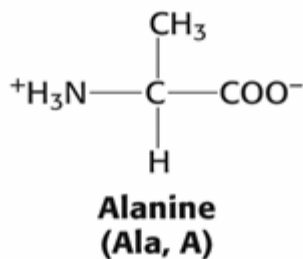
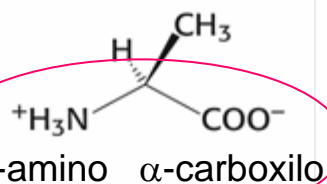
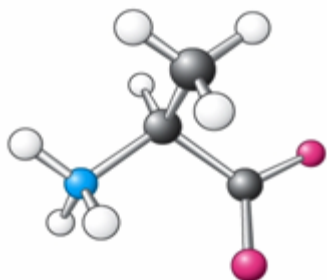


Formas de representación de proteínas

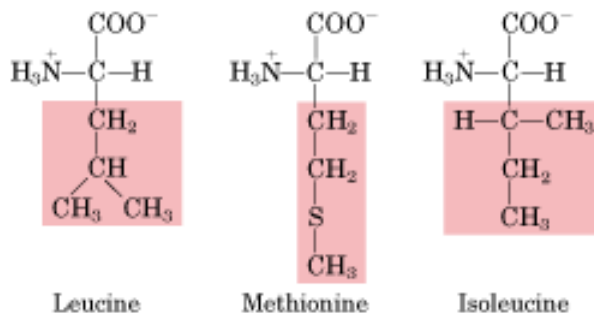
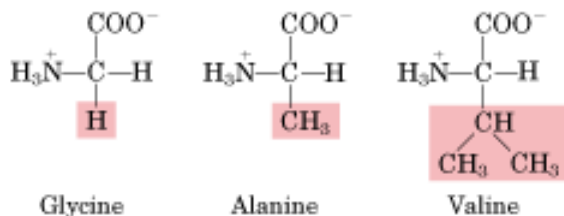


Aminoácidos proteicos

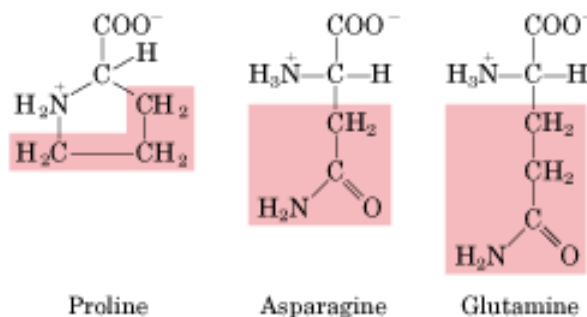
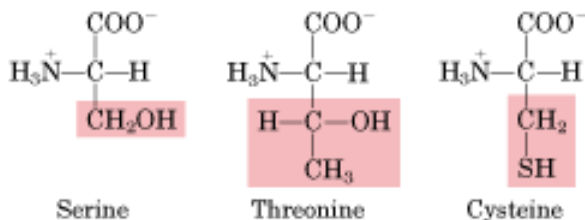
Alanine (Ala, A)



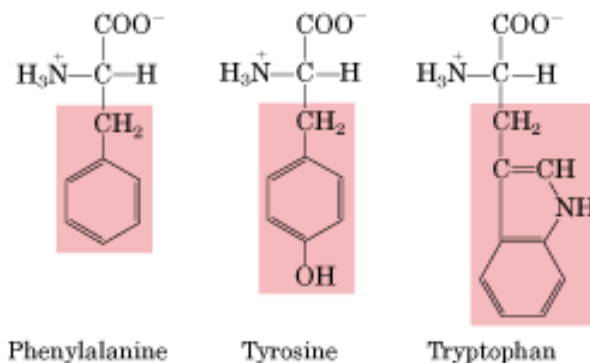
Nonpolar, aliphatic R groups



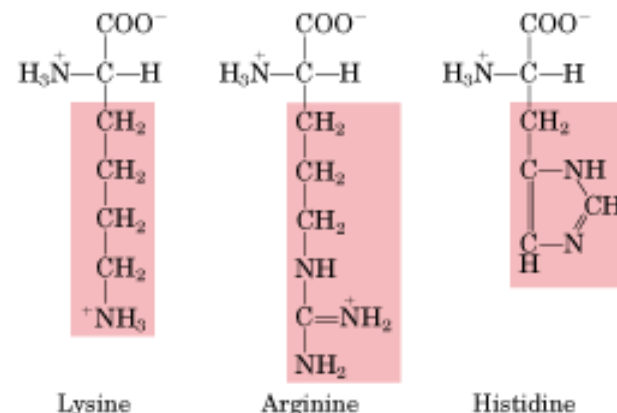
Polar, uncharged R groups



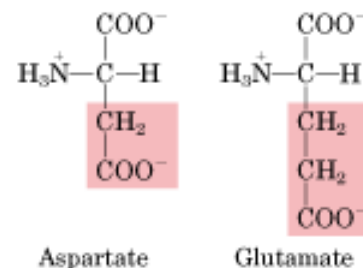
Aromatic R groups



Positively charged R groups



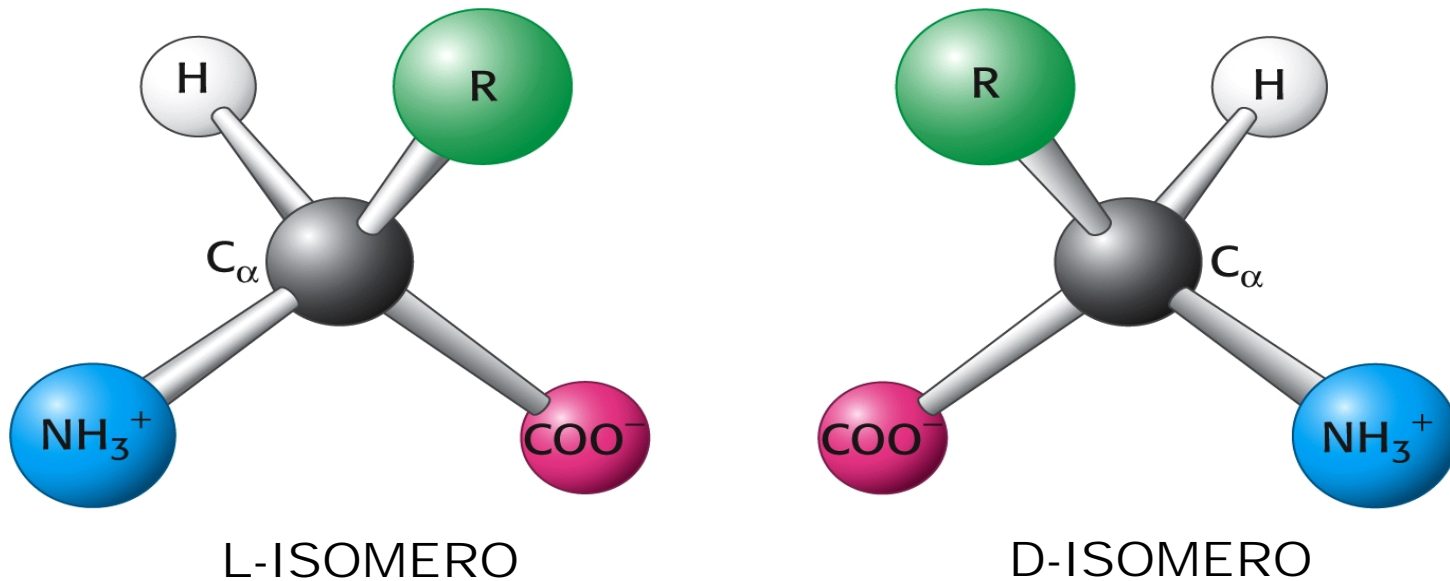
Negatively charged R groups



PROPIEDADES DE LOS AMINOÁCIDOS

Esteroisomería
Propiedades ácido-base
Propiedades espectroscópicas

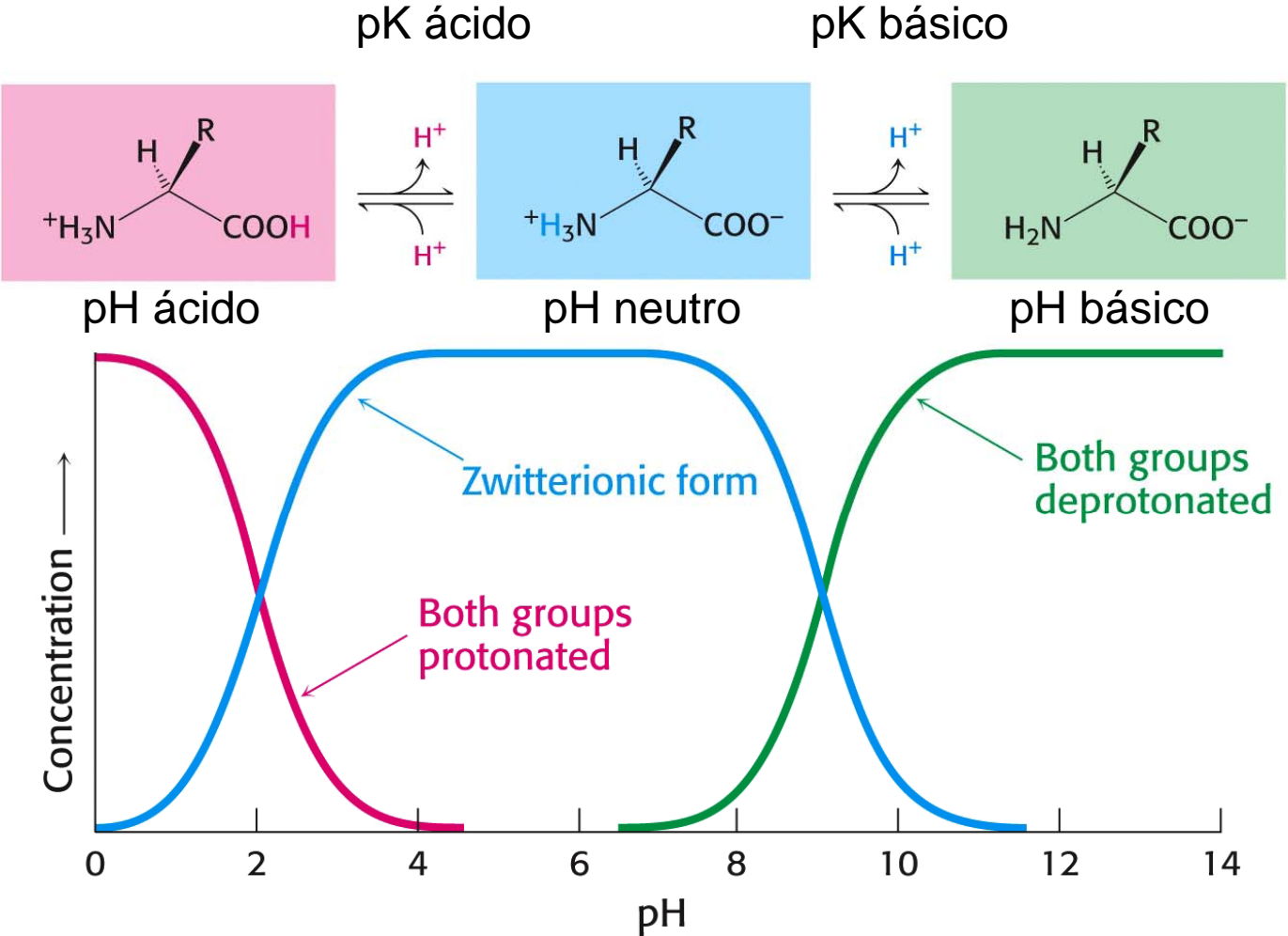
ESTEROISOMERÍA DE LOS AMINOÁCIDOS



Proteínas: L-aminoácidos

Excepciones: péptidos de paredes bacterianas (D-Ala y D-Glu)

CARÁCTER ACIDO-BASE DE LOS AMINOÁCIDOS

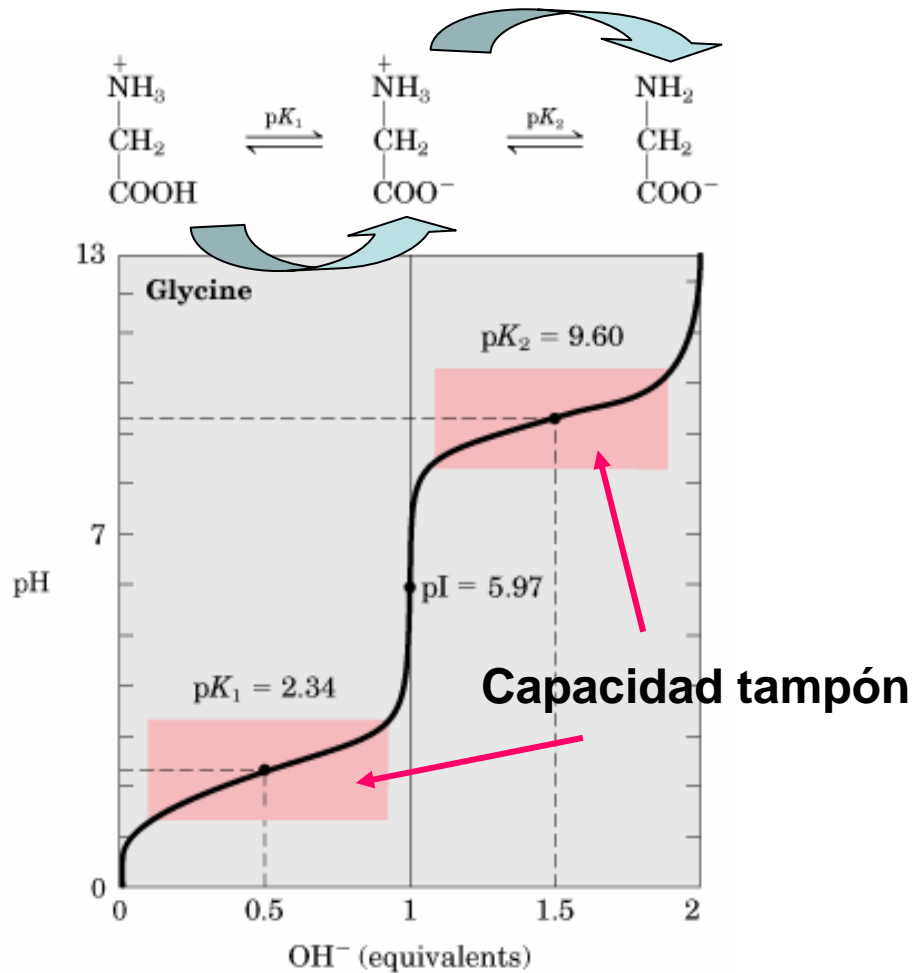


TITULACIÓN DE AMINOÁCIDOS

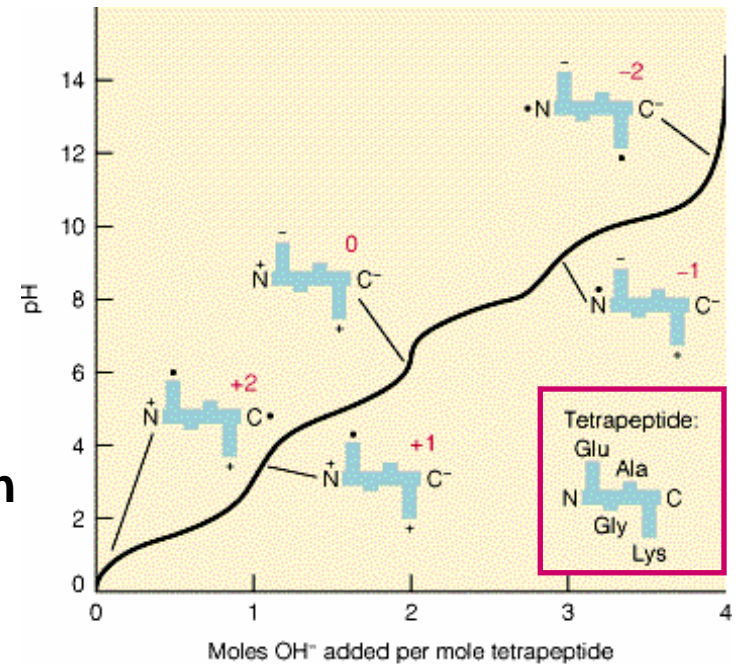
<i>Grupo/aminoácido</i>	<i>ácido</i> \longleftrightarrow <i>base</i> + H^+	<i>pK Típico</i> *
Carboxilo terminal	$\text{—C} \begin{array}{l} \text{O} \\ \parallel \\ \text{OH} \end{array} \longleftrightarrow \text{—C} \begin{array}{l} \text{O} \\ \parallel \\ \text{O}^- \end{array} + H^+$	3.1
Aspartico y Glutámico	$\text{—C} \begin{array}{l} \text{O} \\ \parallel \\ \text{OH} \end{array} \longleftrightarrow \text{—C} \begin{array}{l} \text{O} \\ \parallel \\ \text{O}^- \end{array} + H^+$	4.4
Histidina	$\text{—CH}_2 \begin{array}{c} \diagup \text{HN} \diagdown \\ \diagdown \text{NH}^+ \diagup \end{array} \longleftrightarrow \text{—CH}_2 \begin{array}{c} \diagup \text{HN} \diagdown \\ \diagdown \text{N} \diagup \end{array} + H^+$	6.5
Amino terminal	$\text{—NH}_3^+ \longleftrightarrow \text{—NH}_2 + H^+$	8.0
Cisteína	$\text{—SH} \longleftrightarrow \text{—S}^- + H^+$	8.5
Tirosina	$\text{—C}_6\text{H}_4\text{—OH} \longleftrightarrow \text{—C}_6\text{H}_4\text{—O}^- + H^+$	10.0
Lisina	$\text{—NH}_3^+ \longleftrightarrow \text{—NH}_2 + H^+$	10.0
Arginina	$\text{—N} \begin{array}{l} \diagup \text{C} \text{NH}_2^+ \\ \diagdown \text{H} \end{array} \longleftrightarrow \text{—N} \begin{array}{l} \diagup \text{C} \text{NH} \\ \diagdown \text{H} \end{array} \text{NH}_2 + H^+$	12.5

DEPENDENCIA DEL ESTADO IONICO DE AMINOÁCIDO/PEPTIDO CON EL pH

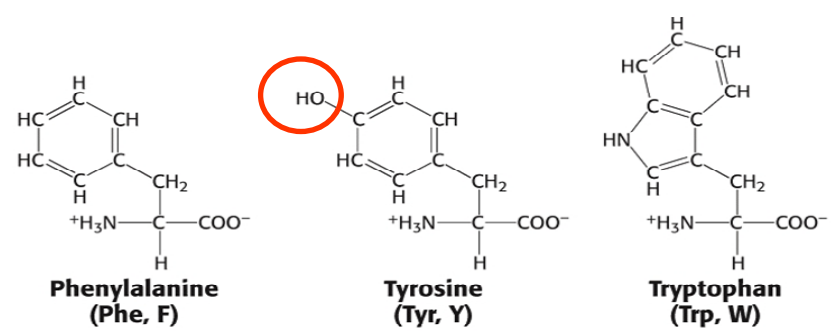
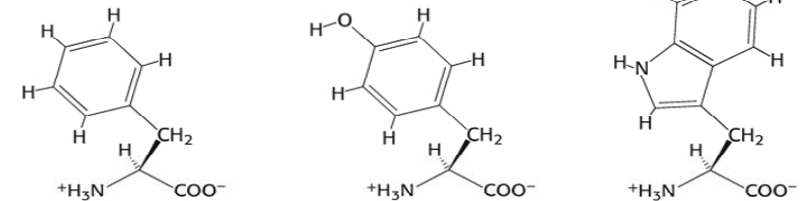
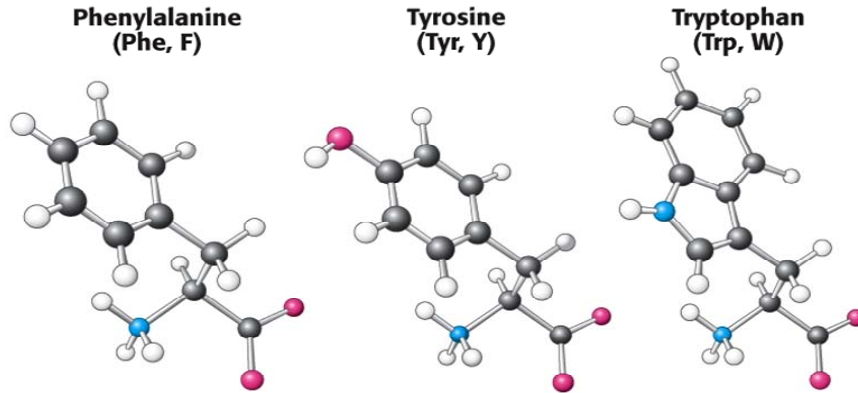
Aminoácido neutro



Péptido

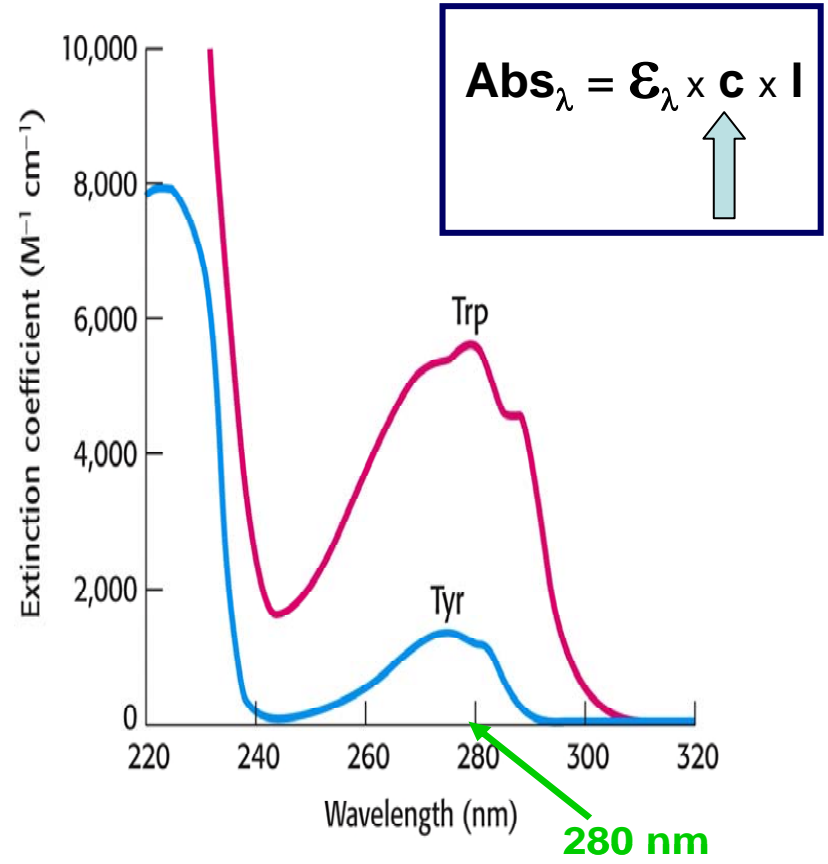


AMINOACIDOS AROMATICOS: PROPIEDADES ESPECTROSCOPICAS



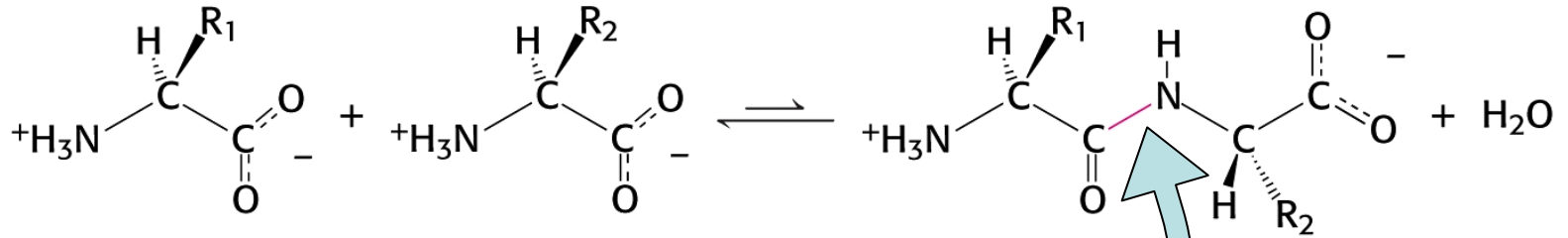
Anillo indol

Absorción de los aminoácidos aromáticos

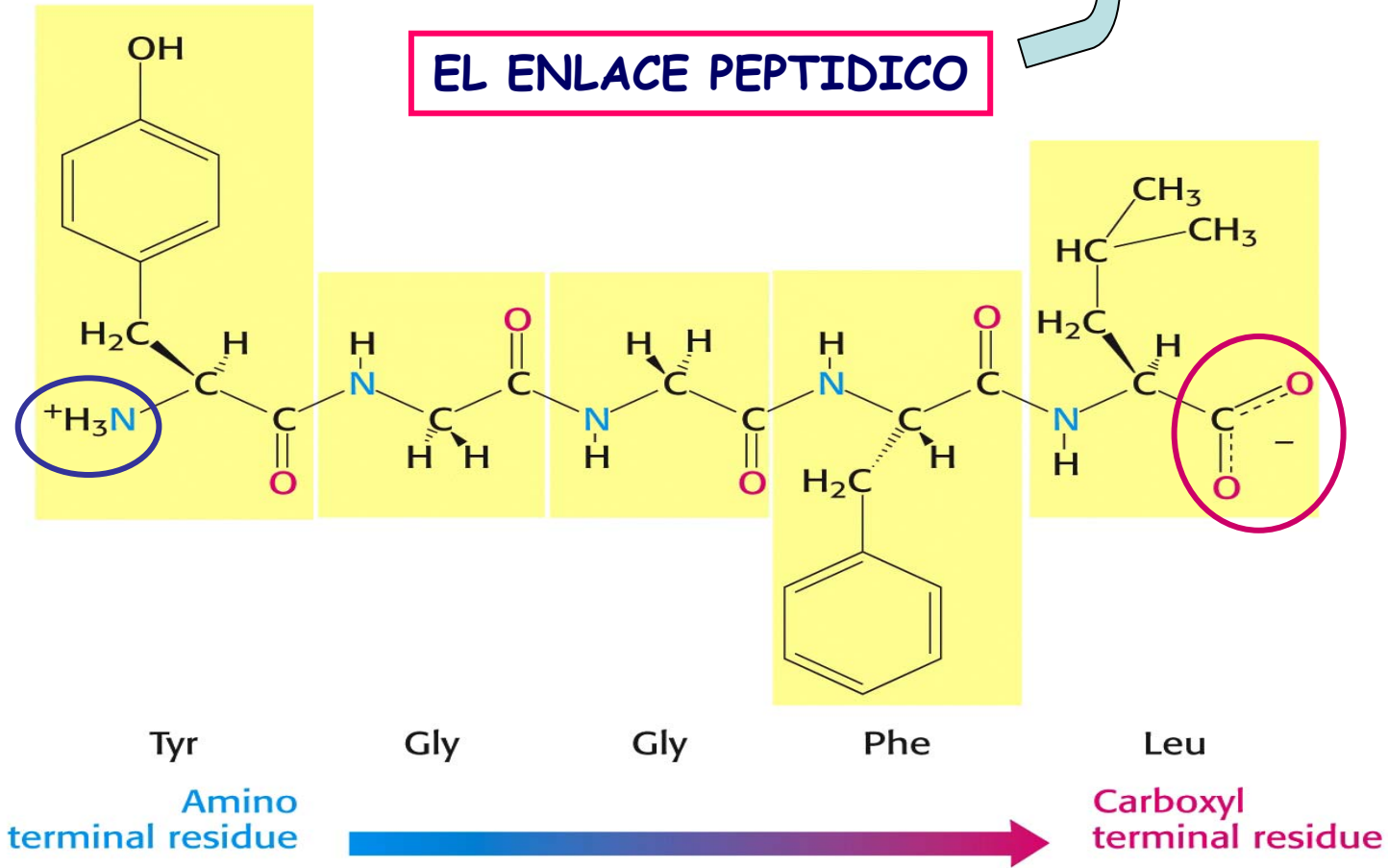


Espectro de absorción

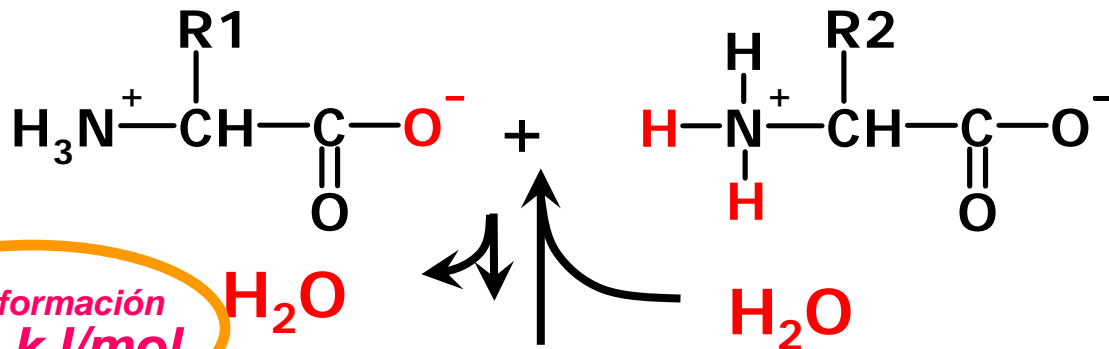
Formación del enlace peptídico



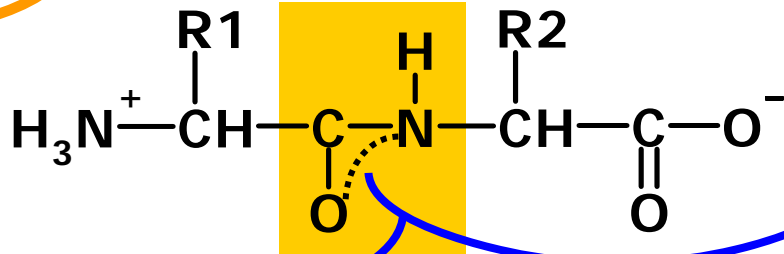
EL ENLACE PEPTIDICO



NATURALEZA QUÍMICA DEL ENLACE PEPTÍDICO

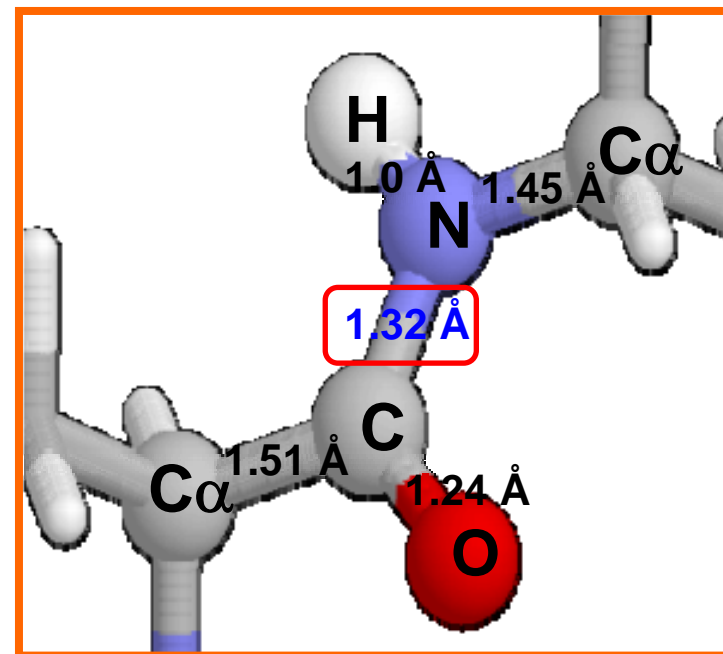
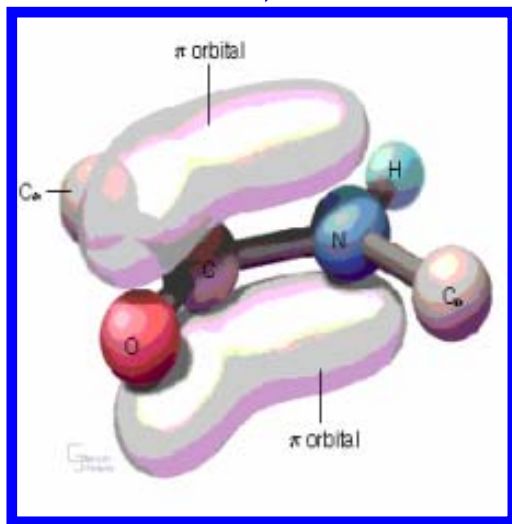


$\Delta G_{\text{formación}}$
 $+10 \text{ kJ/mol}$

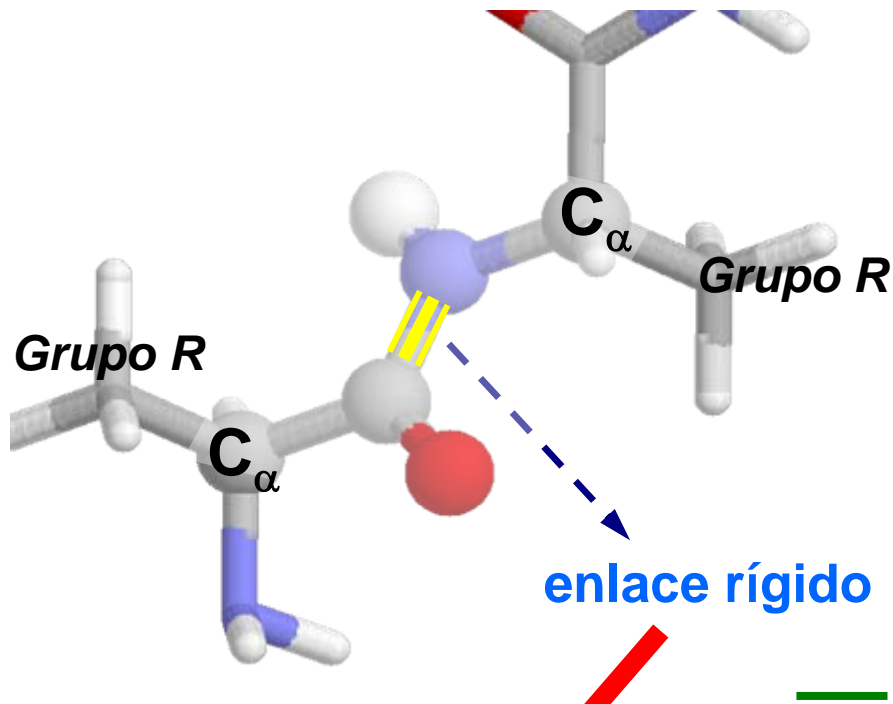


Enlace metaestable

Híbrido de resonancia

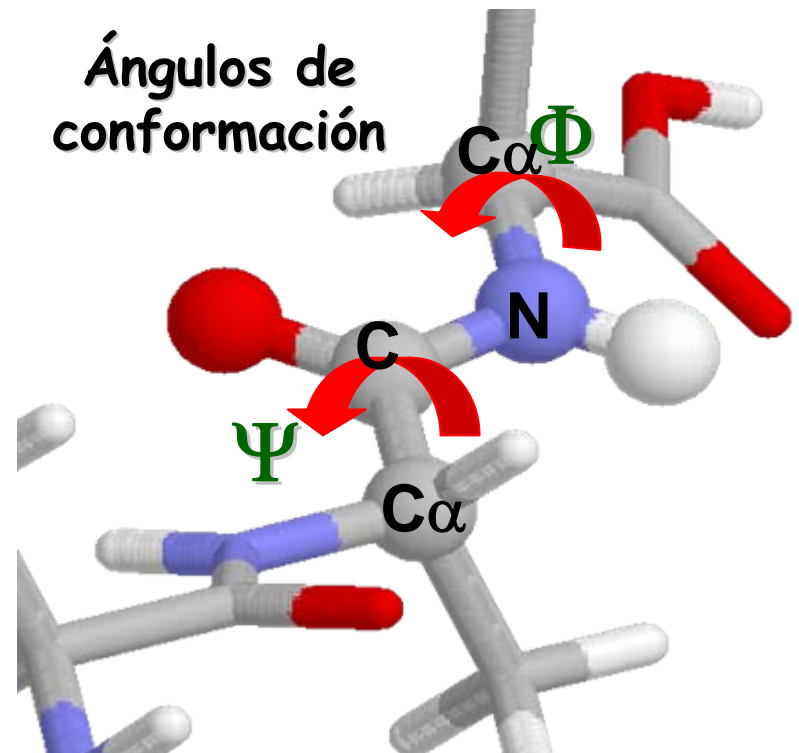


CARACTERÍSTICAS ESTRUCTURALES DEL ENLACE PEPTÍDICO

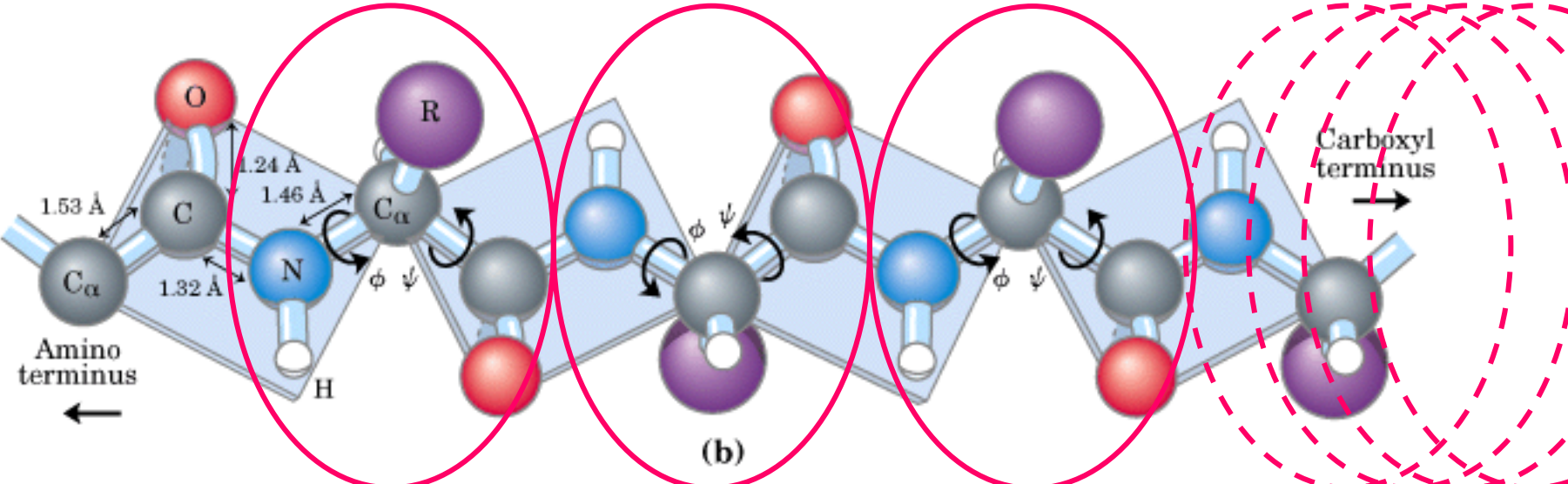
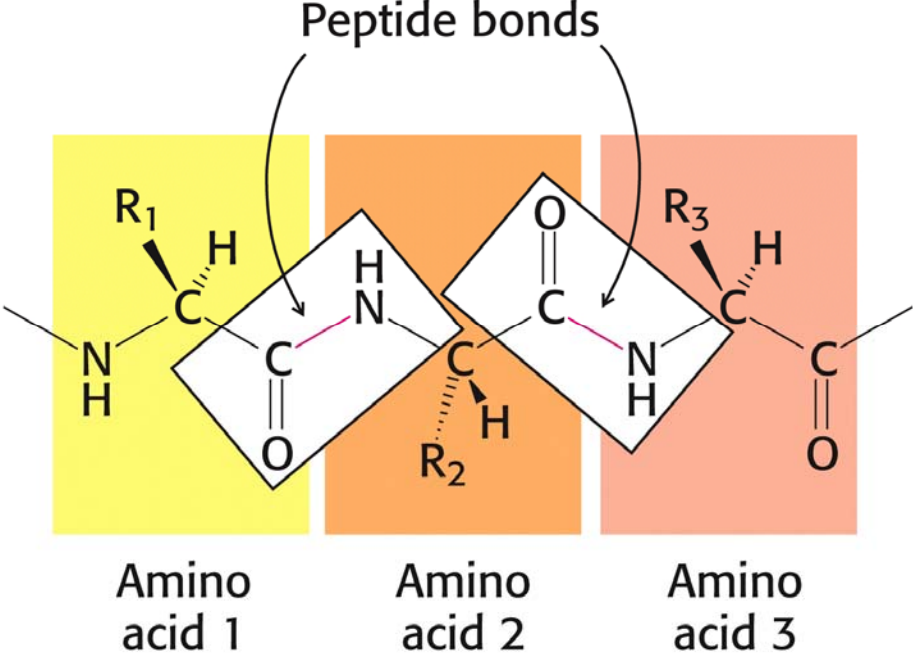


Configuración trans

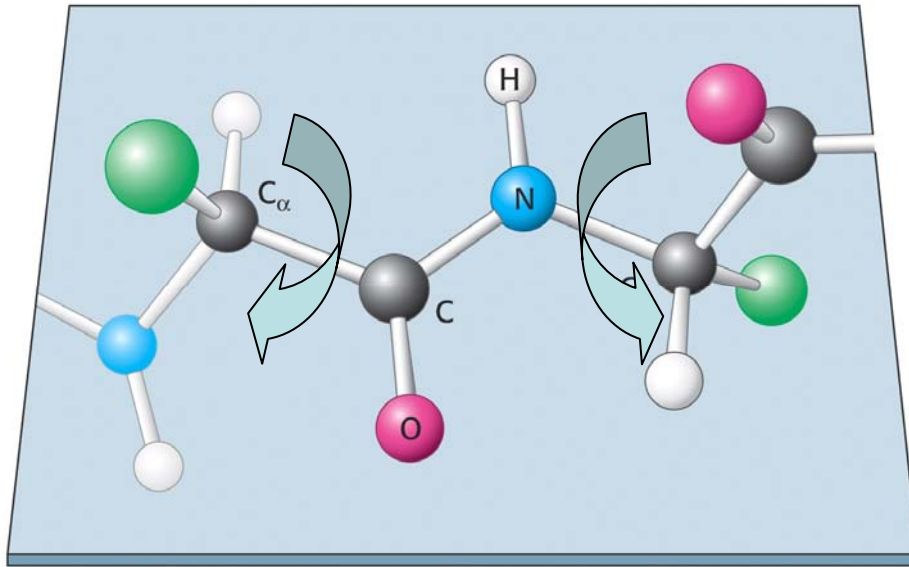
El enlace peptídico forma una estructura plana



Conformación de proteínas: Planaridad del enlace peptídico

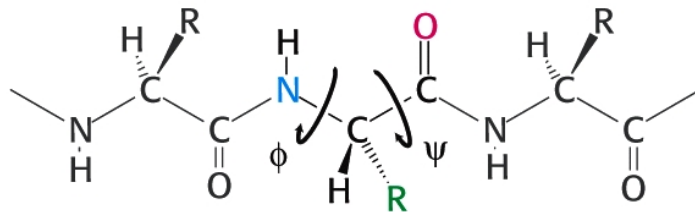


Nomenclatura de los ángulos alrededor del carbono α

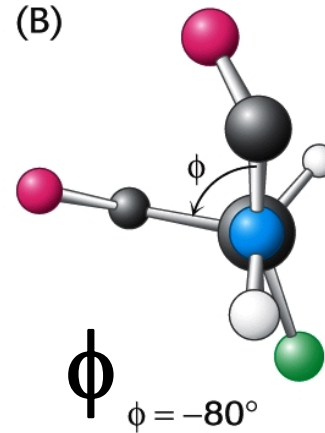


Estructuras
Ordenadas/repetitivas

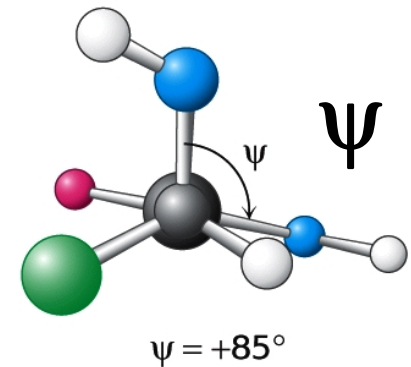
(A)



(B)

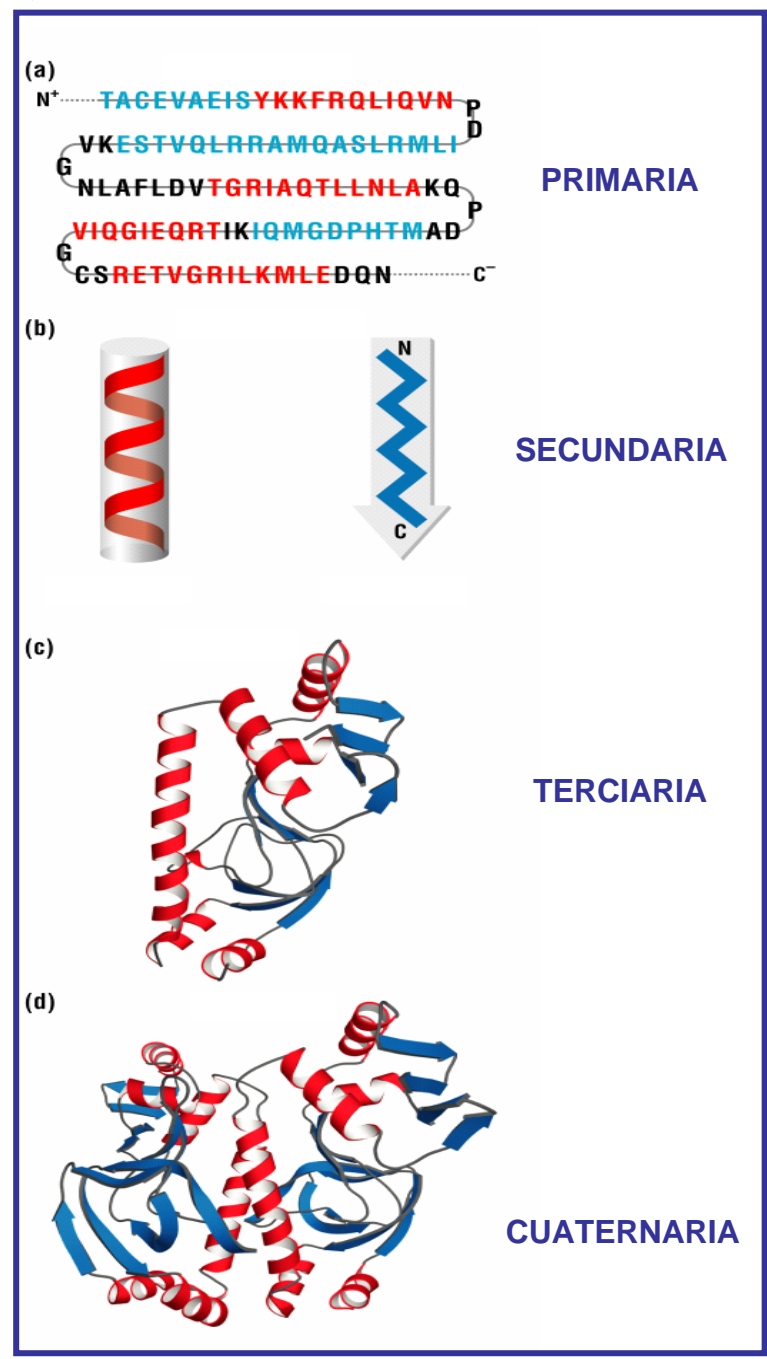
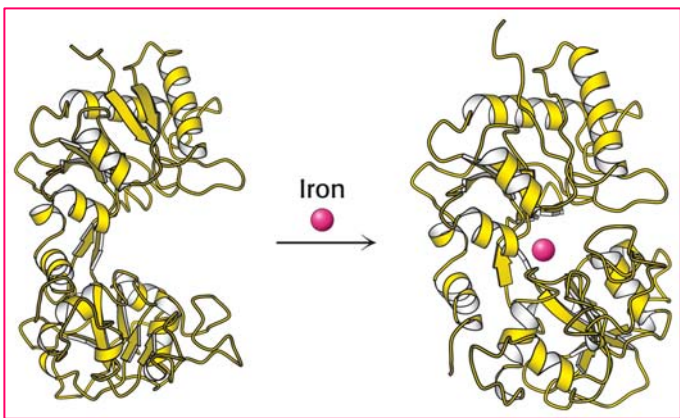


(C)



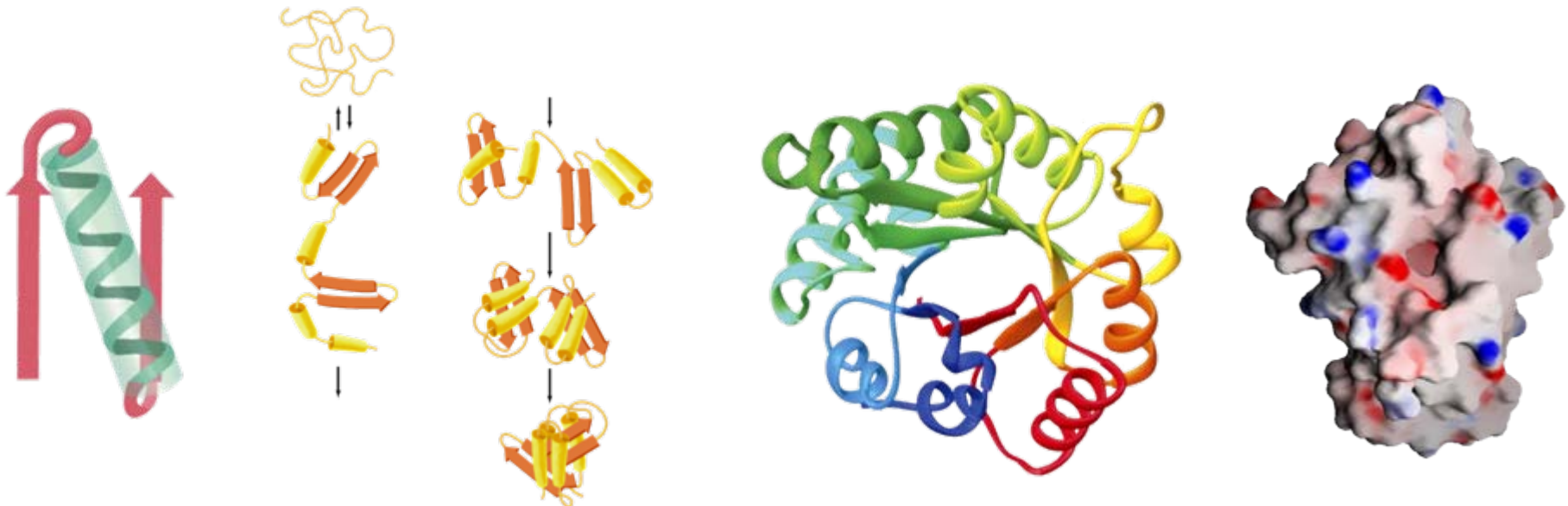
Estructura tridimensional de proteínas: niveles estructurales

Asociación covalente lineal de aminoácidos:
cadena polipeptídica que se pliega sobre sí misma.
Puede contener grupos no peptídicos:
Heteroproteínas



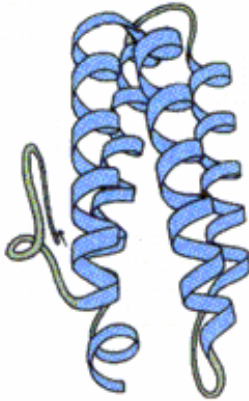
ESTRUCTURA PRIMARIA

1 MSVENVLSLIQENEVKFVDLRFTDTKGKEQHISIPSHQIDADFFEDGKMFDGSSVAGWKG
61 INESDMVMMPDASSAVLDPFTEEATLNIRCDILEPATMQGYDRDPRSIKRAEEYMRSTG
121 LADTVLVGPEPEFFLFDDVKFATDMSGSSFFKIDDVEAAWNTGSDYENGNKGHRPGVKGGY
181 FPVAPVDSSQDLRSAMCLVMEEMGLVVEAHHHEVATAGQNEIATRFNTLTTKADEIQIYK
241 YVVHNVAHAFGKTATFMPKPLVGDNGSGMHVHQS LAKDGVNLFAGDKYGG LSEMALYYIG
301 GIIKHARALNALTNPSTNSYKRLVPHYEAPVMLAYSARNRSASIRIPVVPSPKARRIEVR
361 FPDPAANPYLAFAAML MAGLDGIKNKIHPGEAMDKDLYDLP AEEAAEIPKVAESLKQALE
421 YLDNDREFLTAGGVFSDDFIDSYIELKTKEVERVNVAVHPLEFELYYSV

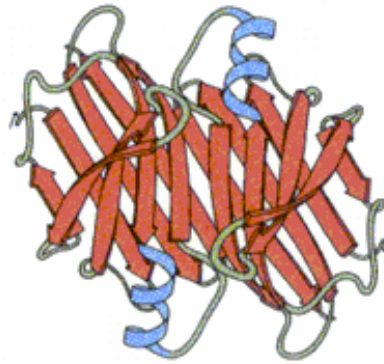


PLEGAMIENTO DE PROTEÍNAS

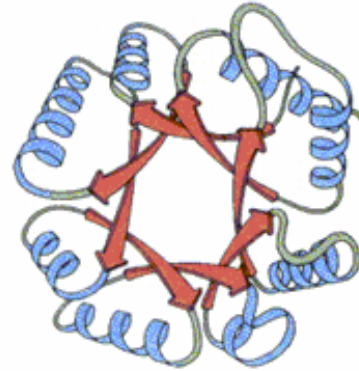
Estructura secundaria



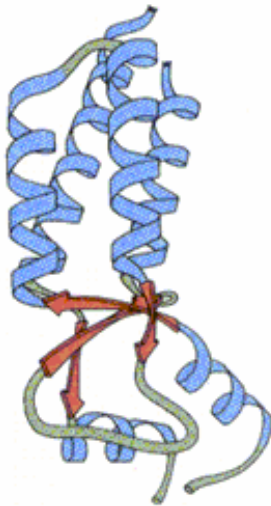
Myohemerythrin



Prealbumin

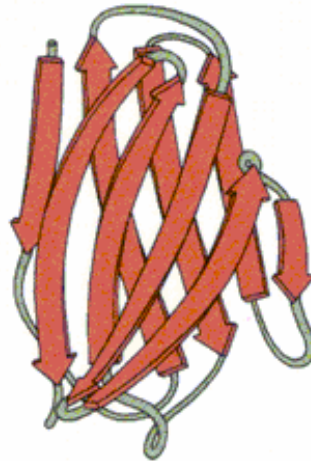


Pyruvate kinase, domain 1



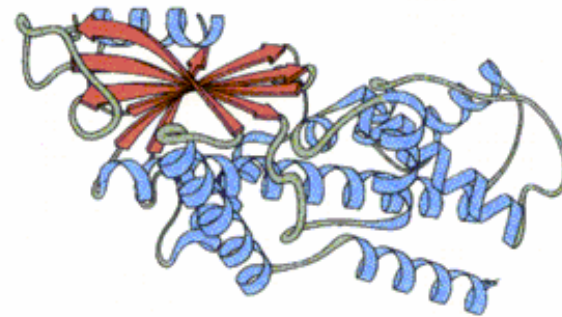
Tobacco mosaic coat protein

(a) Predominantly α helix



Immunoglobulin, V₂ domain

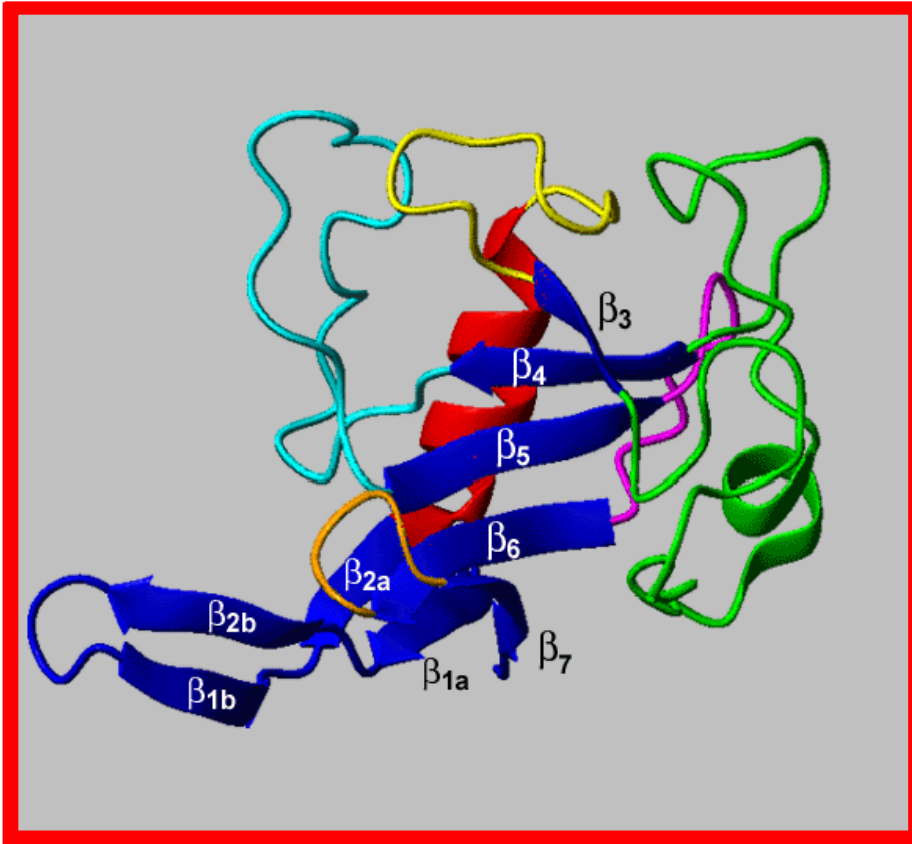
(b) Predominantly β sheet



Hexokinase, domain 2

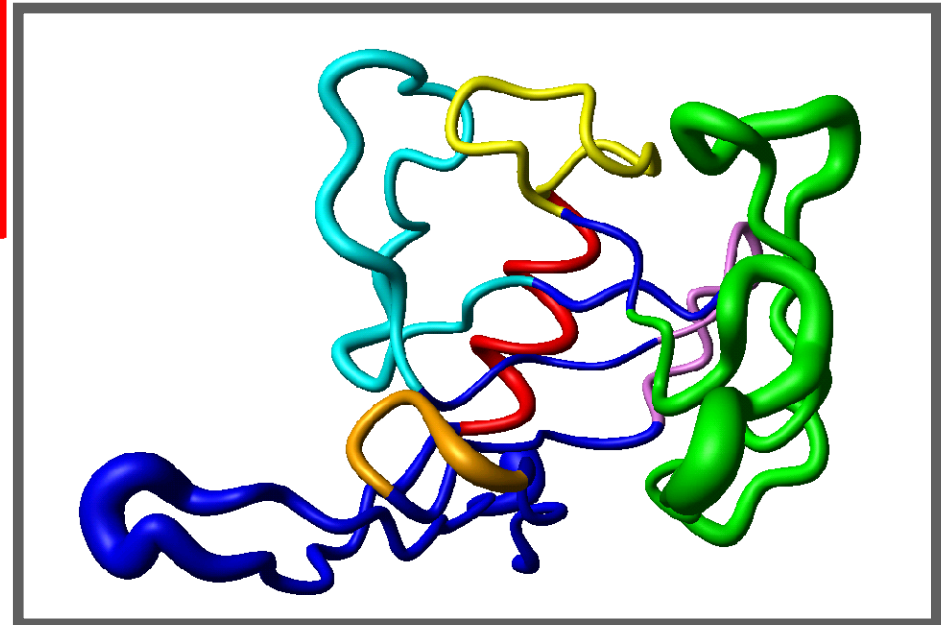
(c) Mixed α helix and β sheet

ESTRUCTURA SECUNDARIA



Estructura Ordenada

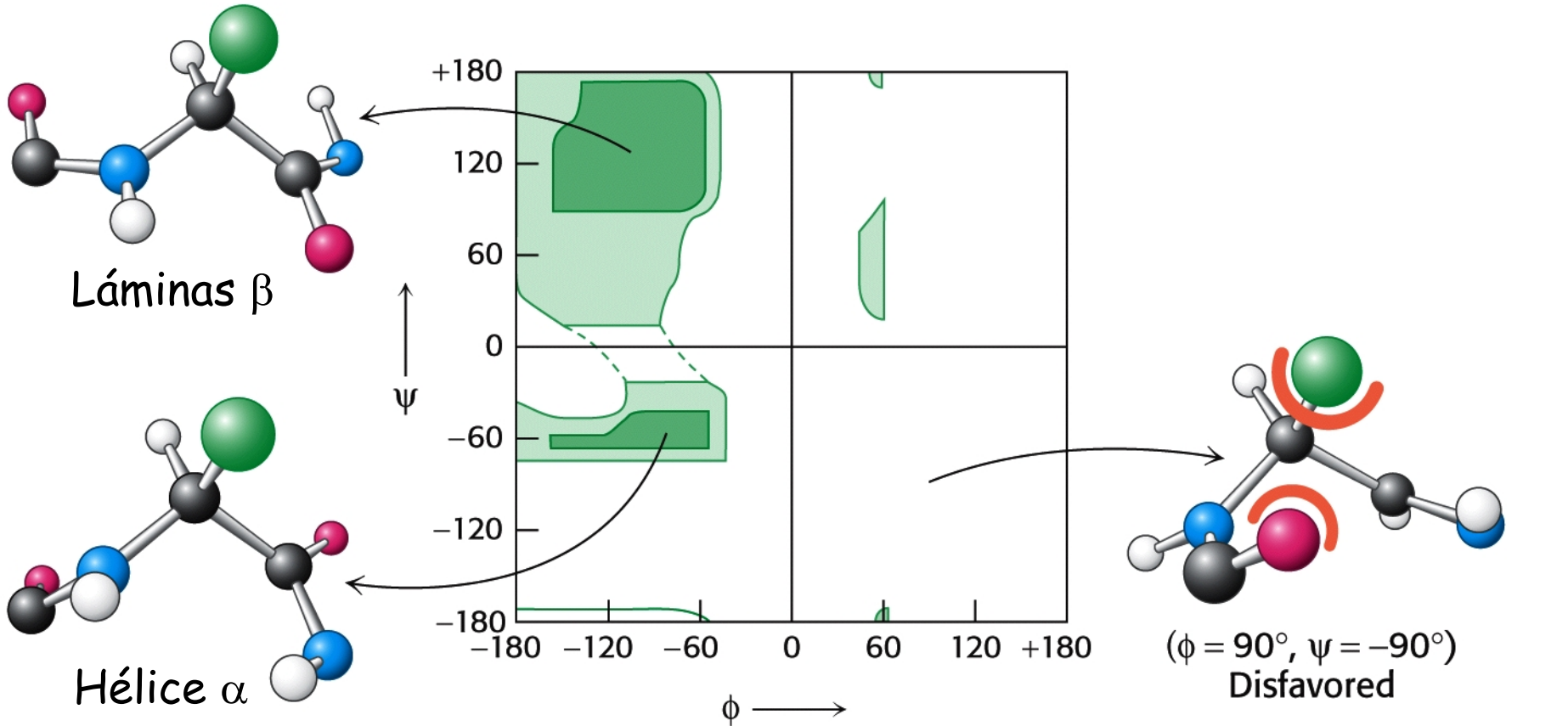
Núcleo estructural
Rigidez
Repetición valores ϕ y ψ



Estructura No Ordenada

Zonas expuestas
Flexibilidad
Variación valores ϕ y ψ

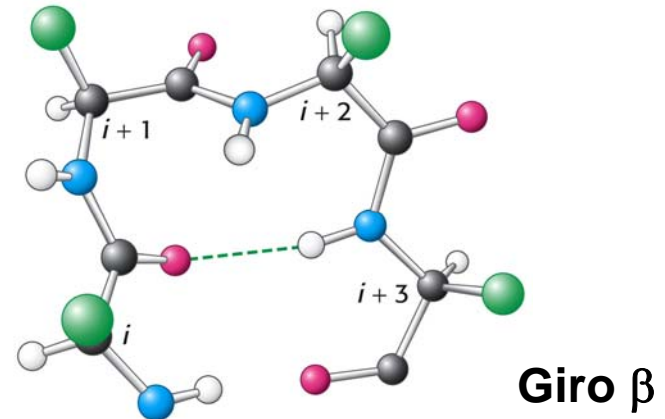
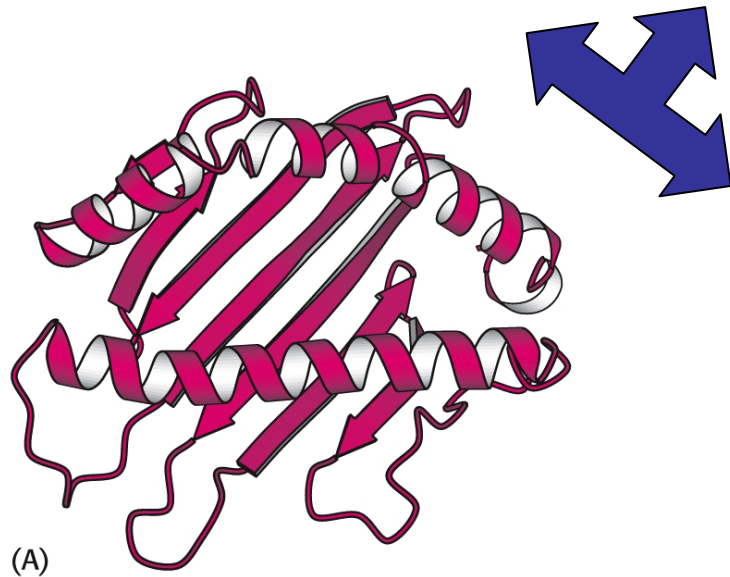
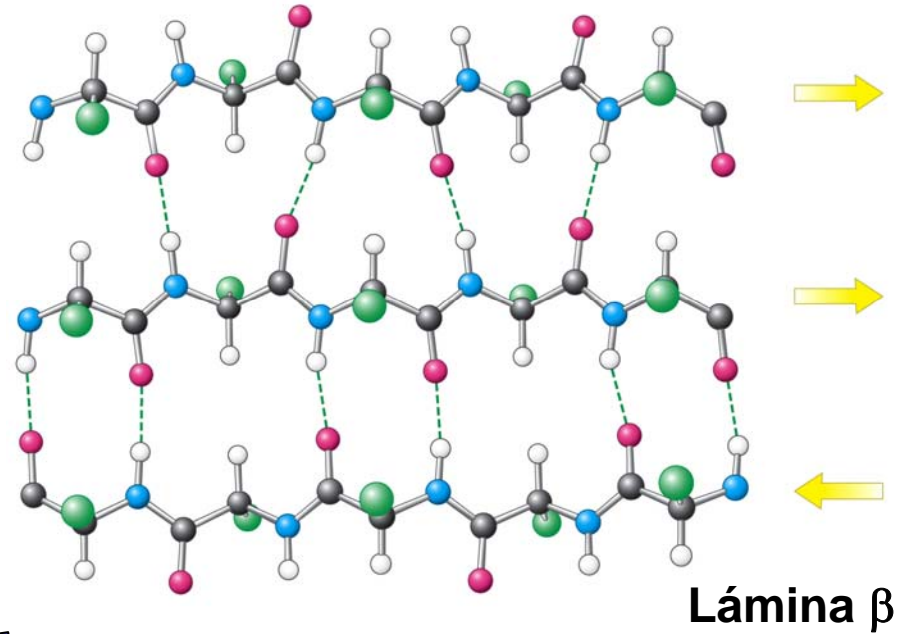
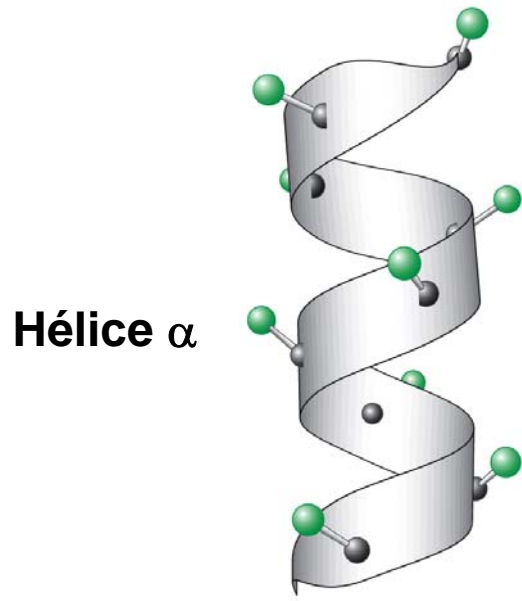
Representación de Ramachandran



Estructuras favorecidas

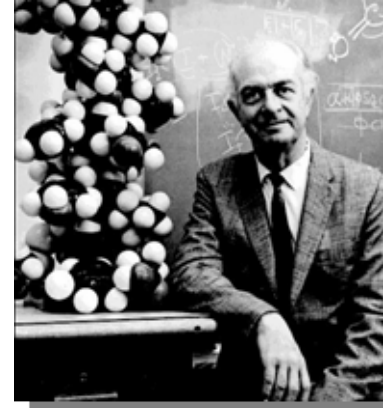
Estructuras desfavorecidas

Elementos de estructura secundaria



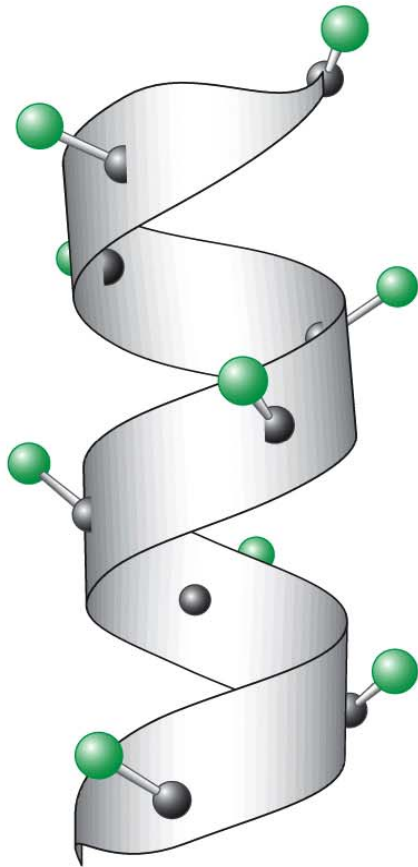
ESTRUCTURA SECUNDARIA DE PROTEÍNAS:

Hélice α

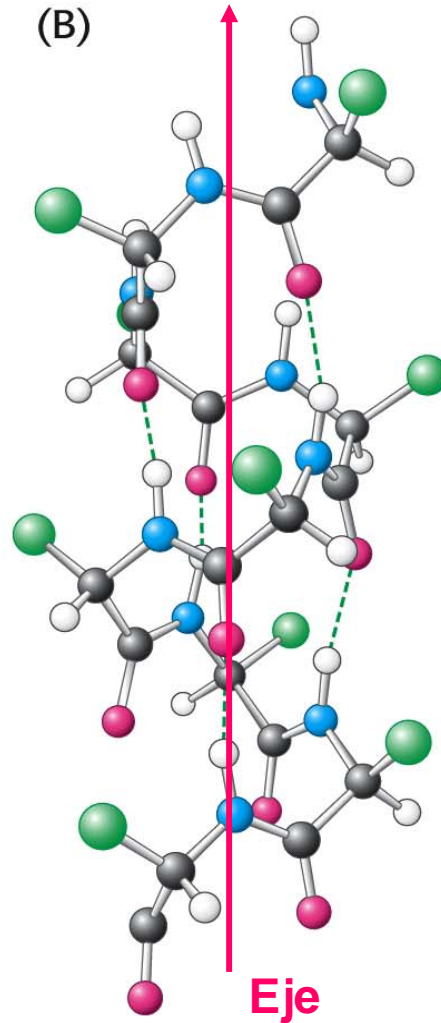


Linus Pauling

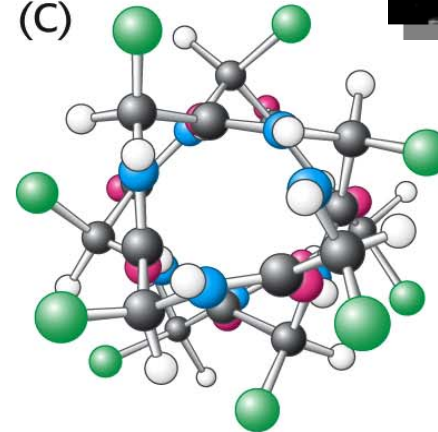
(A)



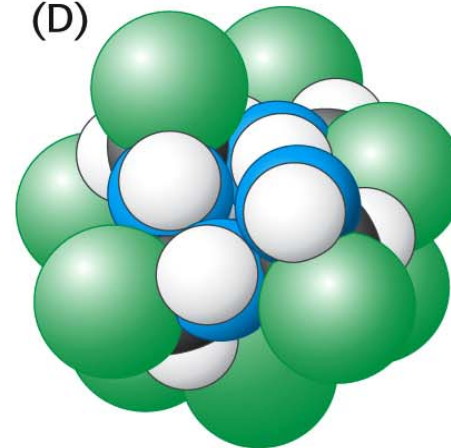
(B)



(C)

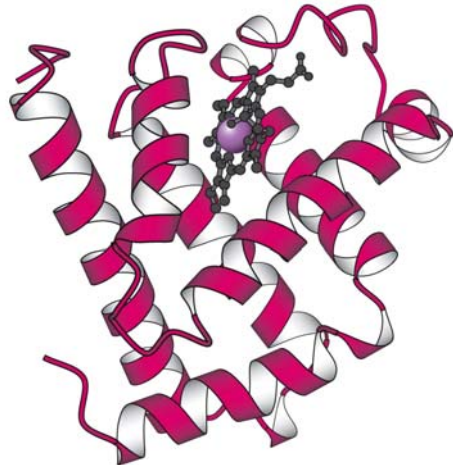


(D)

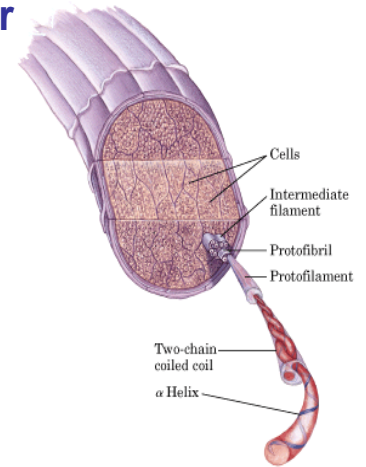


PROTEÍNAS RICAS EN HÉLICE α : queratina α

Tropomiosina
Mioglobina
Ferritina



Sección y organización molecular de un pelo



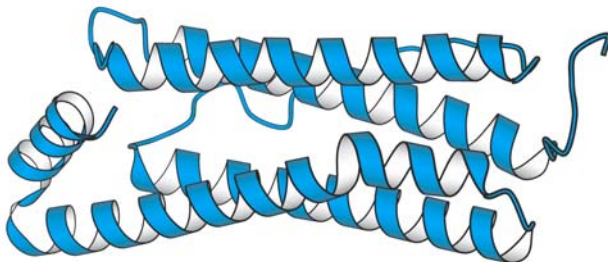
Keratin α helix —

Two-chain coiled coil —

Protofilament { } 20–30 Å

Protofibril { } 40–50 Å

(a)



Estructura del colágeno

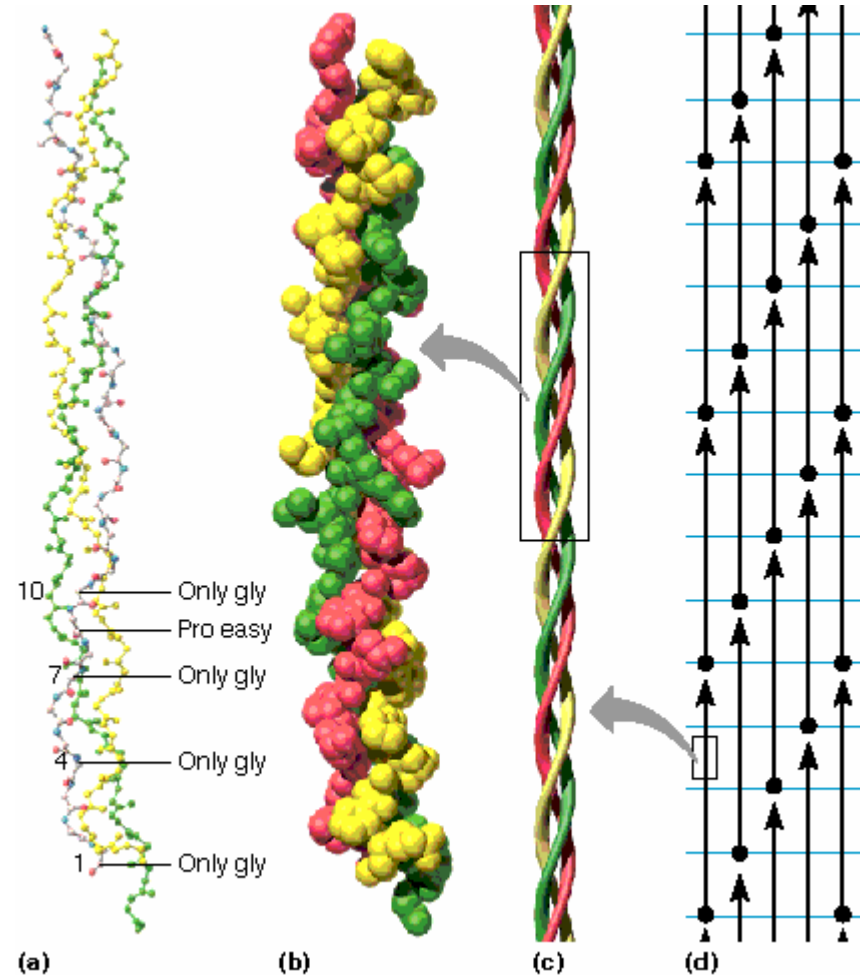
Aminoácidos más abundantes:
Gly, Pro, OH-Pro, OH-Lys

Tripéptido repetido:
Gly-X-Y

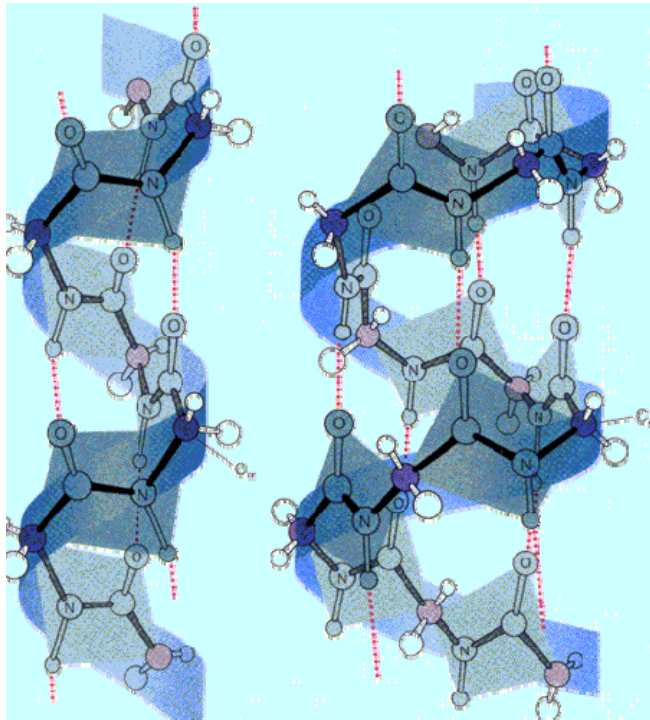
Tres cadenas polipeptídicas

Asociación longitudinal y lateral

Enlaces por puentes de hidrógeno

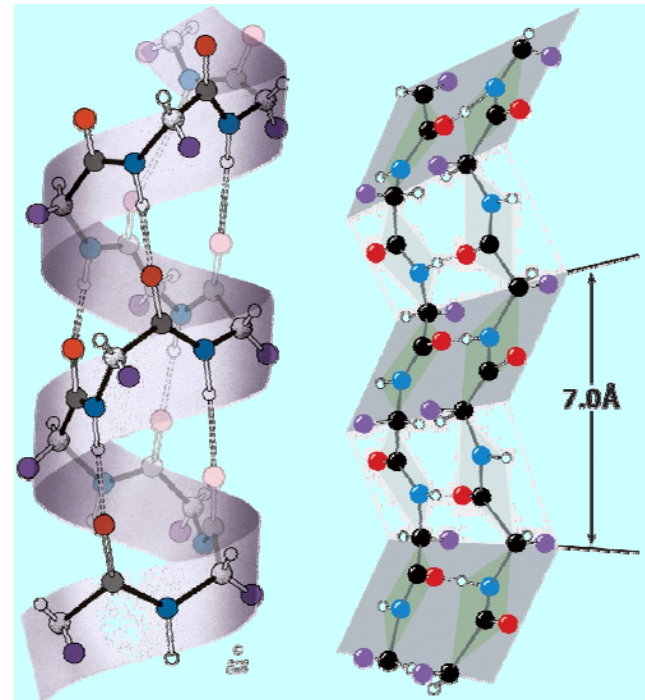


OTRAS ESTRUCTURAS HELICOIDALES



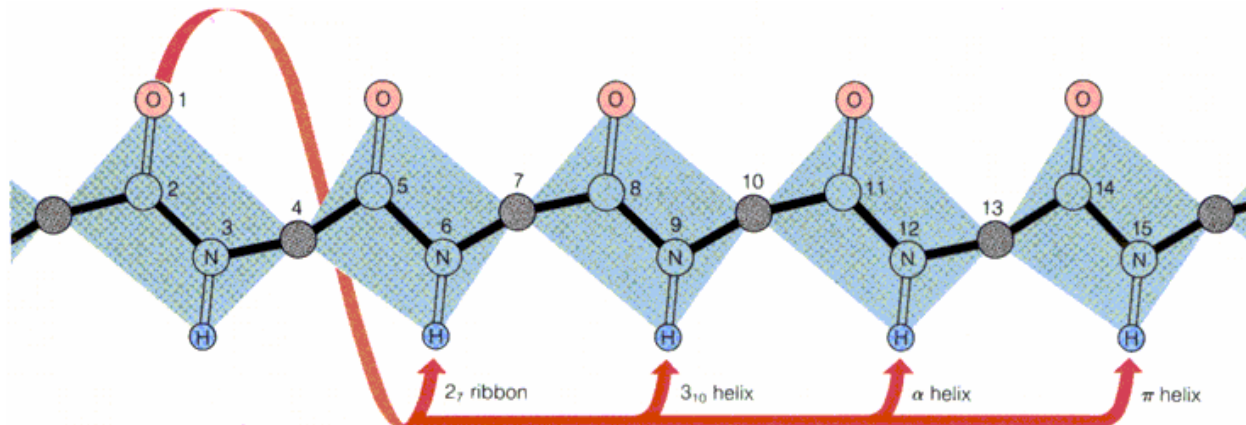
3_{10}

π

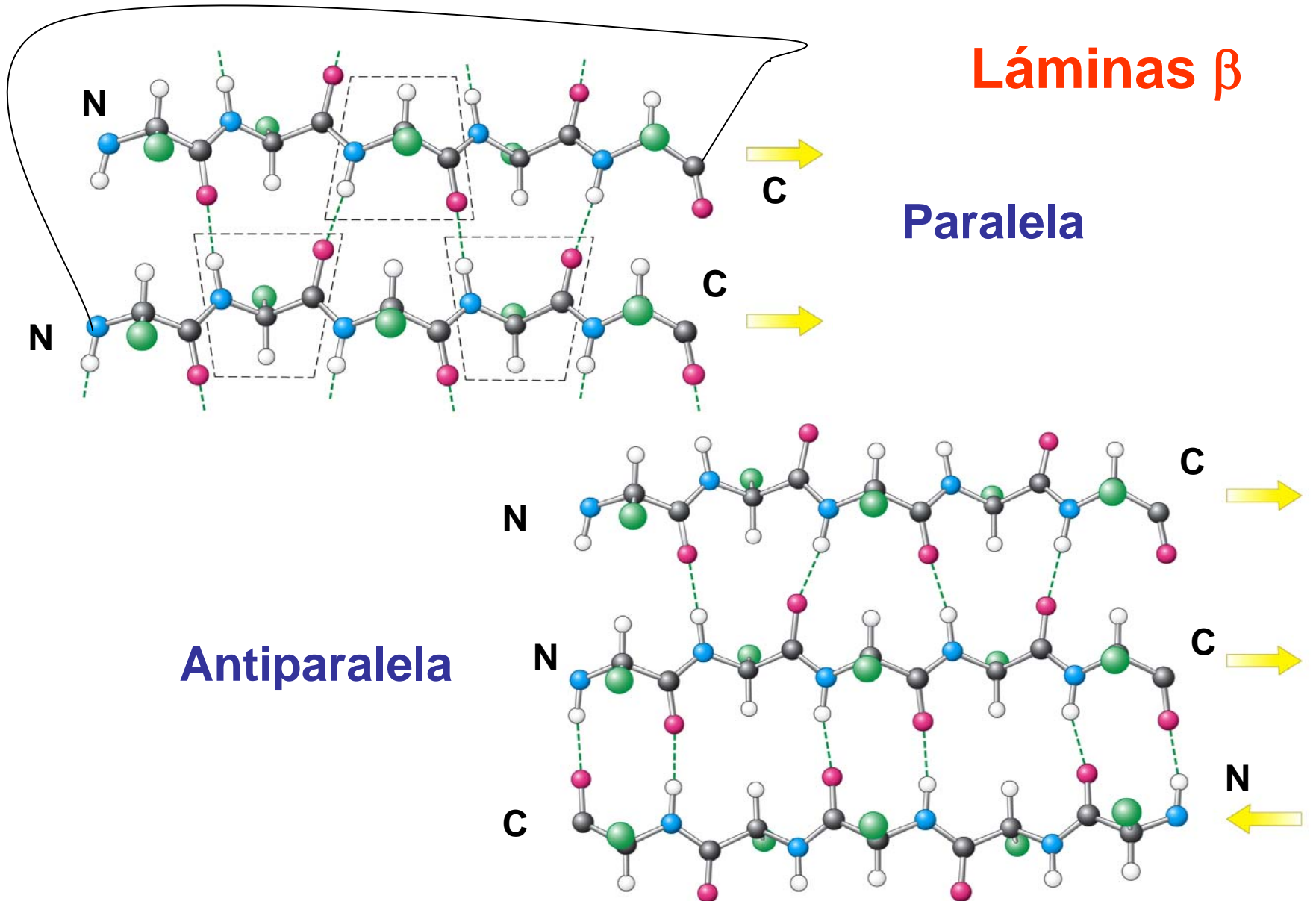


Hélice α

Cinta

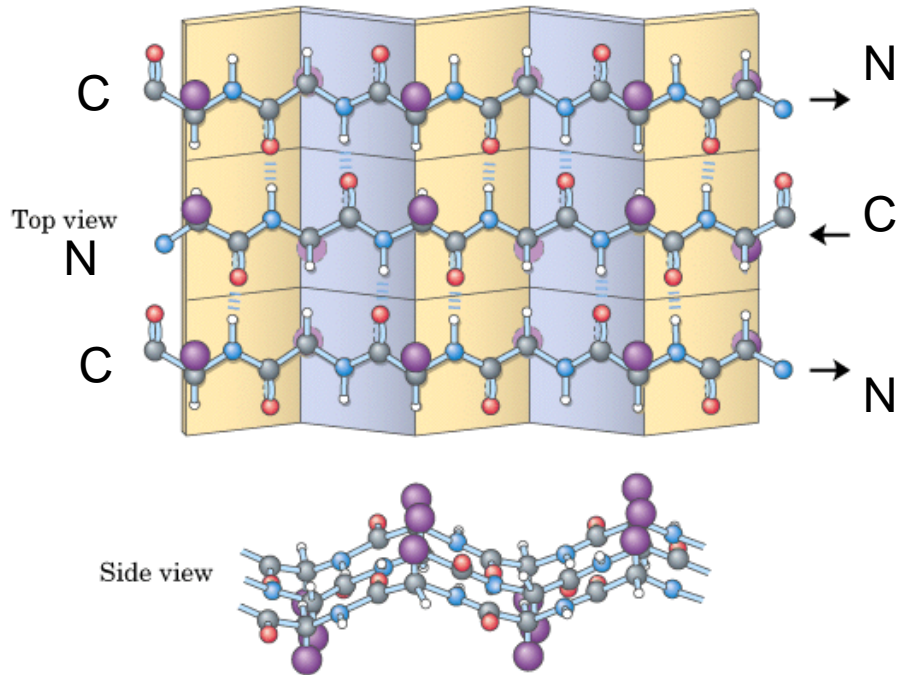


ESTRUCTURA SECUNDARIA DE PROTEÍNAS:

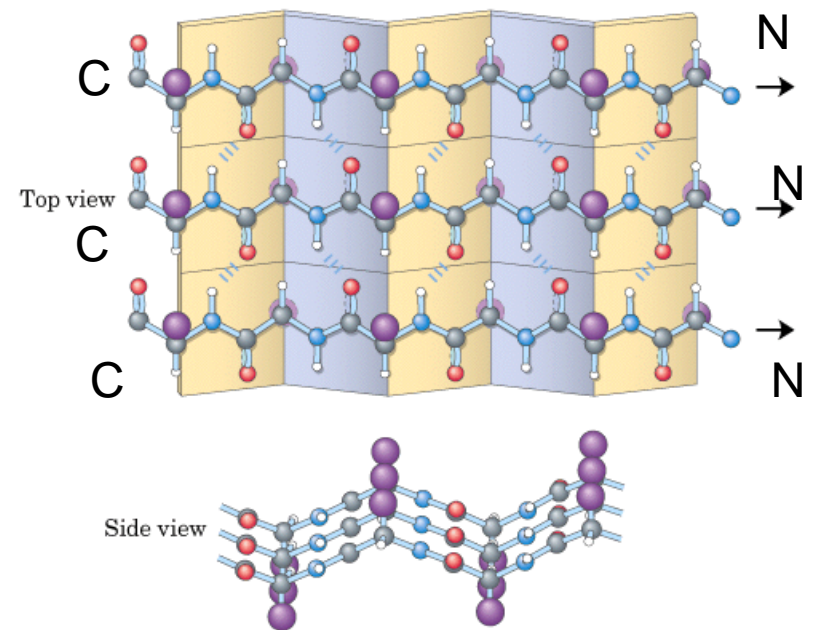


Arquitectura de las láminas β : vista superior y vista lateral

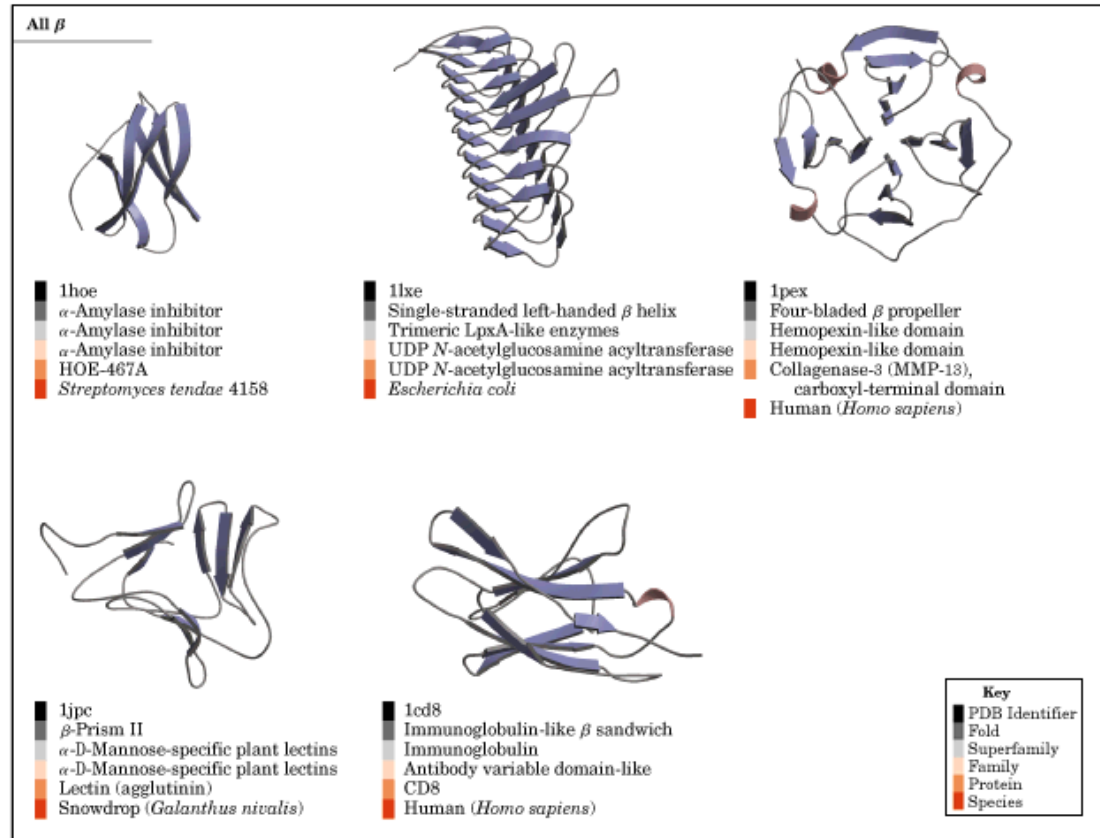
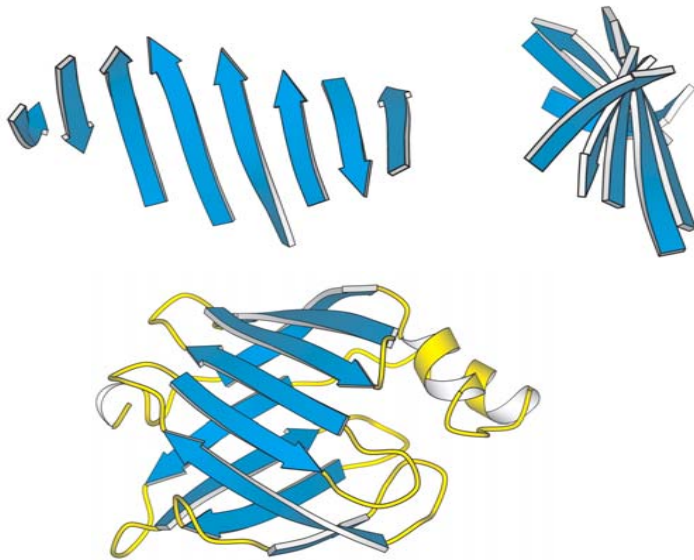
(a) Antiparalelo



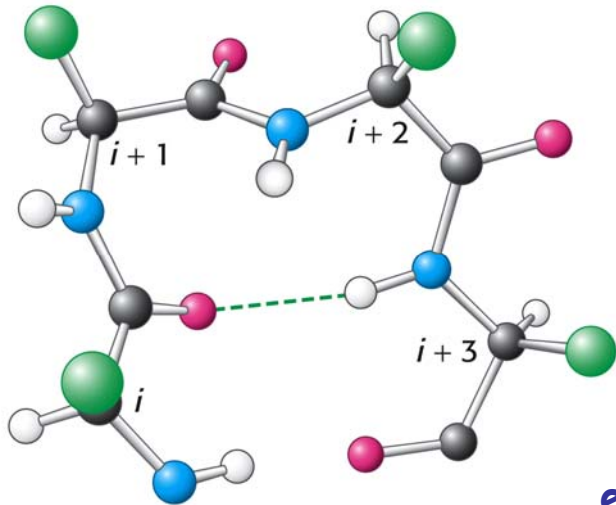
(b) Paralelo



Asociación de láminas β y proteínas ricas en lámina β



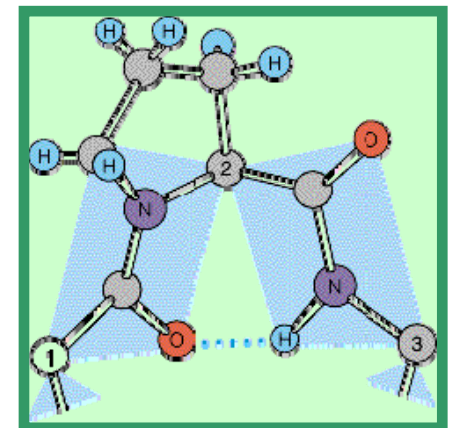
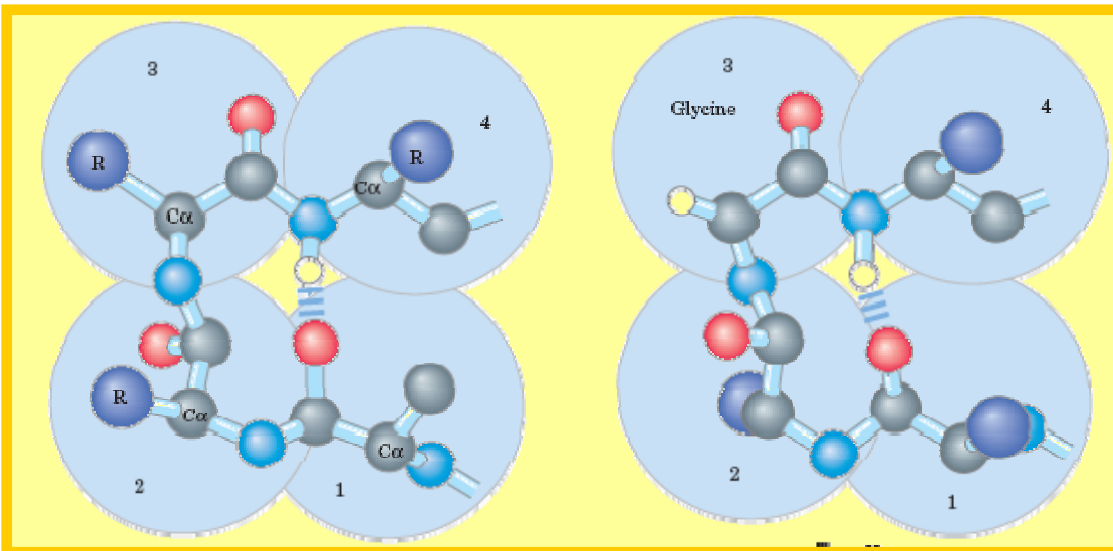
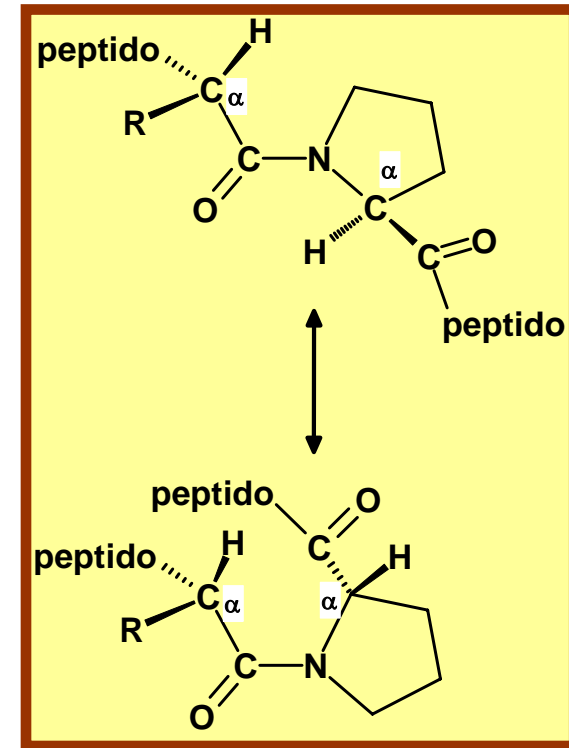
Estructura de los Giros β



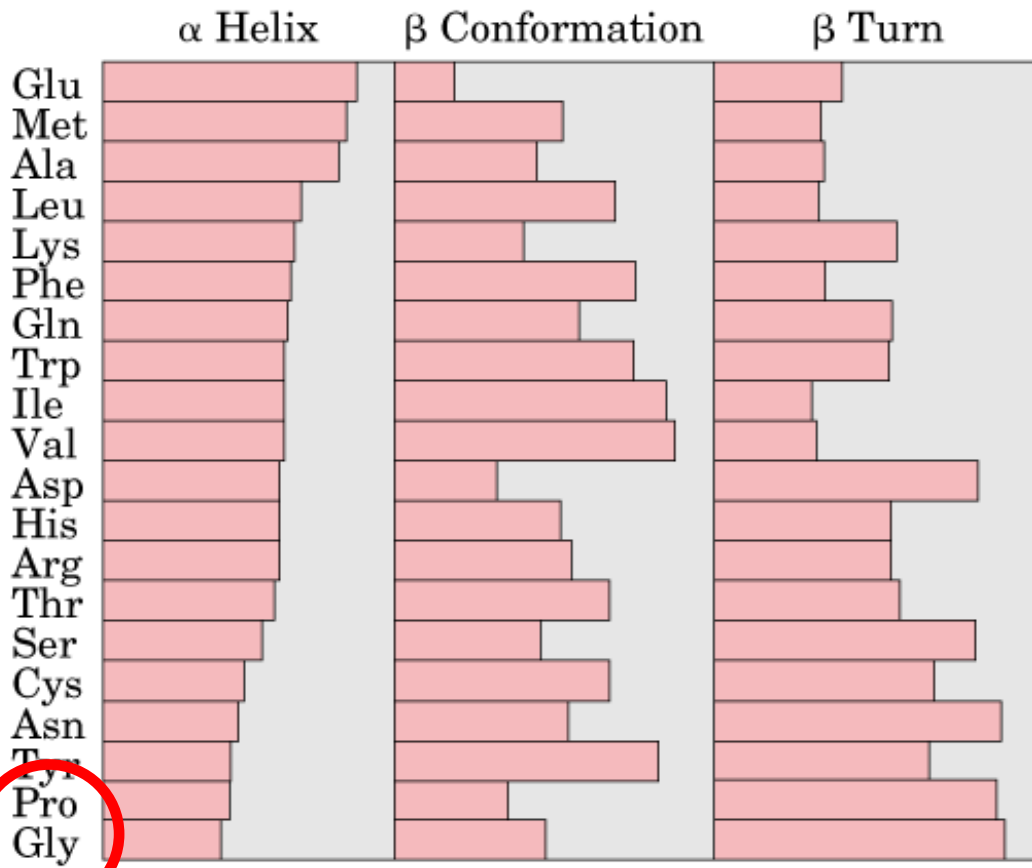
Localización de los giros β en la estructura de proteínas

Tipo I

Tipo II

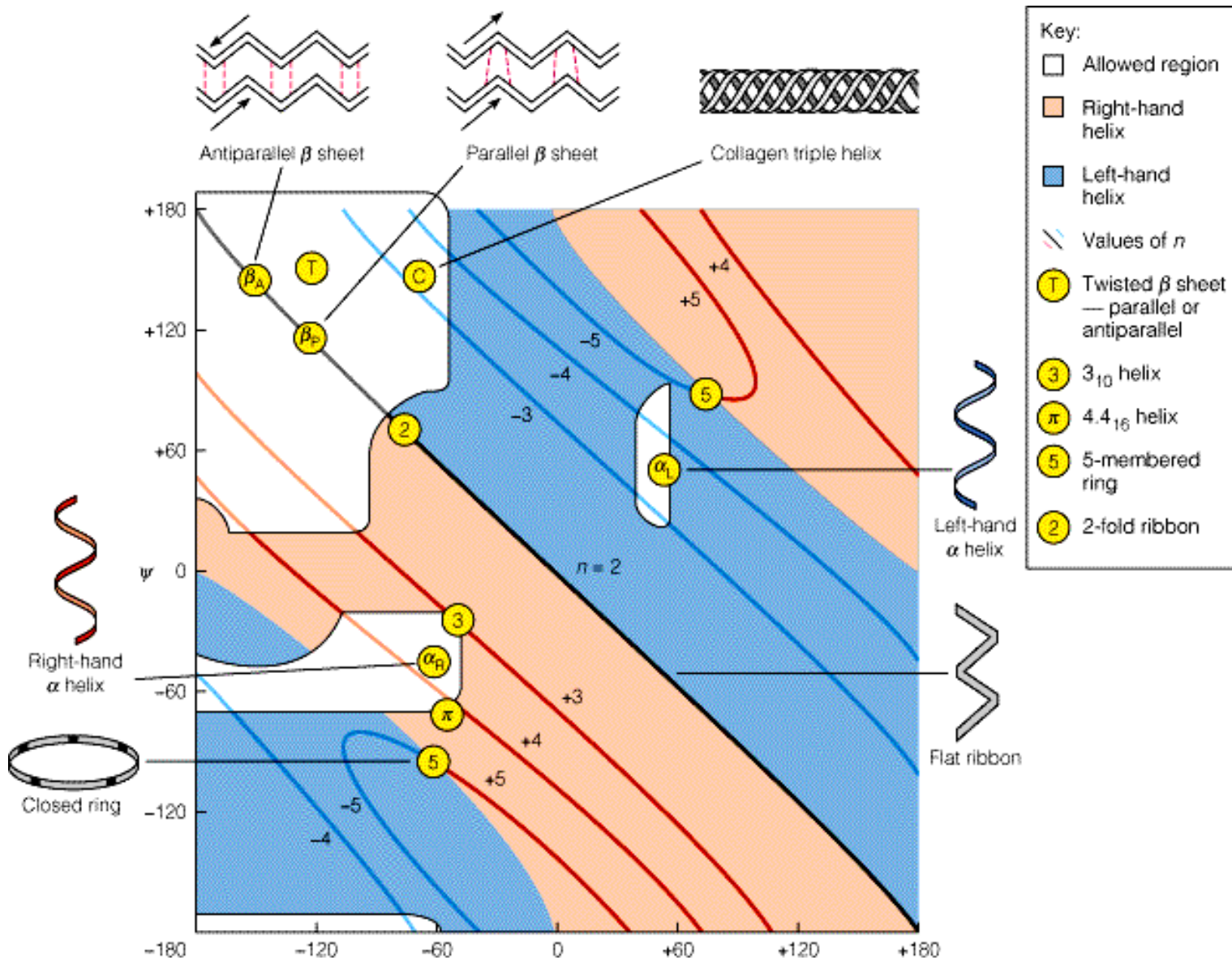


TENDENCIA DE LOS AMINOÁCIDOS ELEMENTOS ESTRUCTURA SECUNDARIA ORDENADA



Residue	P_{α}	P_{β}
Ala	1.42	0.83
Arg	0.98	0.93
Asn	0.67	0.89
Asp	1.01	0.54
Cys	0.70	1.19
Gln	1.11	1.10
Glu	1.51	0.37
Gly	0.57	0.75
His	1.00	0.87
Ile	1.08	1.60
Leu	1.21	1.30
Lys	1.16	0.74
Met	1.45	1.05
Phe	1.13	1.38
Pro	0.57	0.55
Ser	0.77	0.75
Thr	0.83	1.19
Trp	1.08	1.37
Tyr	0.69	1.47
Val	1.06	1.70

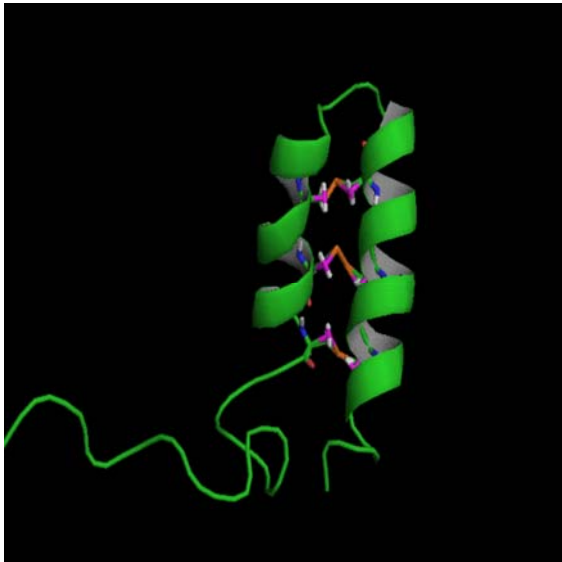
Source: Chou, P.Y. and Fasman, G.D., *Annu. Rev. Biochem.* **47**, 258 (1978).



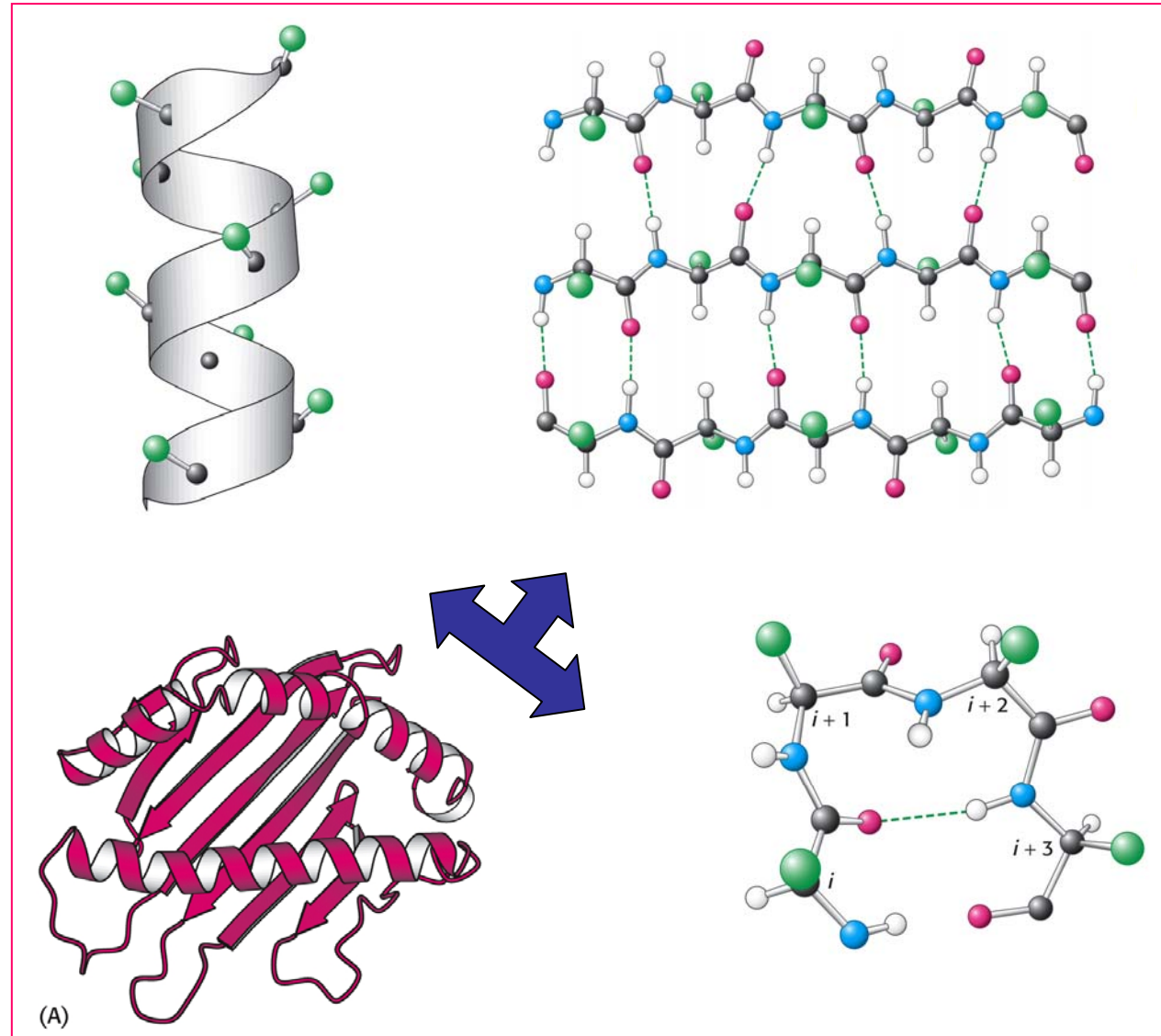
Plegamiento tridimensional de proteínas: ESTRUCTURA TERCIARIA

combinación de estructuras secundarias y regiones sin ordenamiento periódico

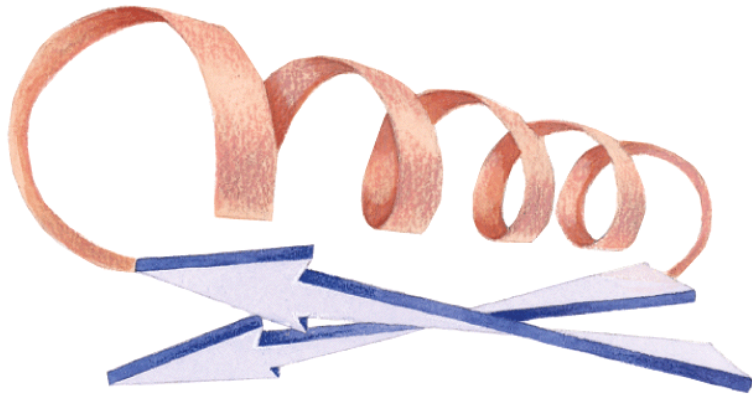
Una única cadena polipeptídica



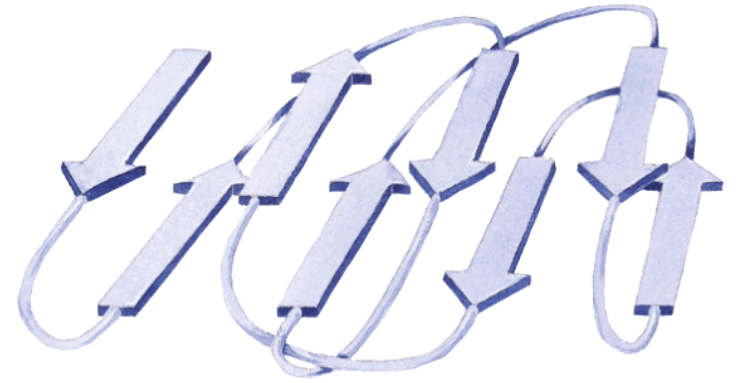
Ole e 6
Alergeno del
Polen de olivo



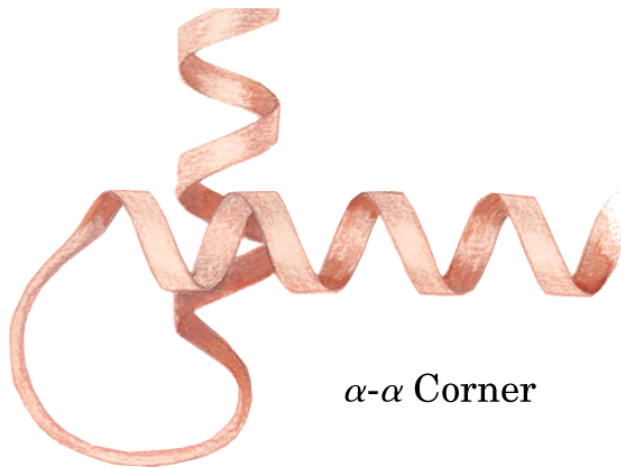
Asociaciones de elementos de estructura secundaria



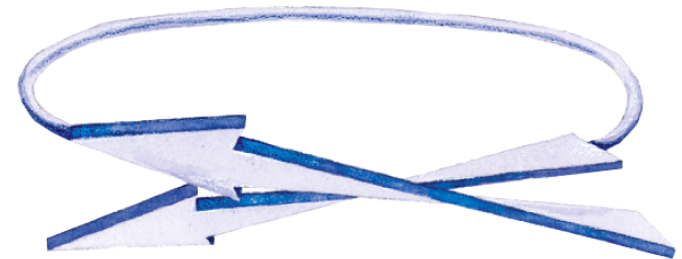
(a) β - α - β Loop



Crossover connection
(not observed)

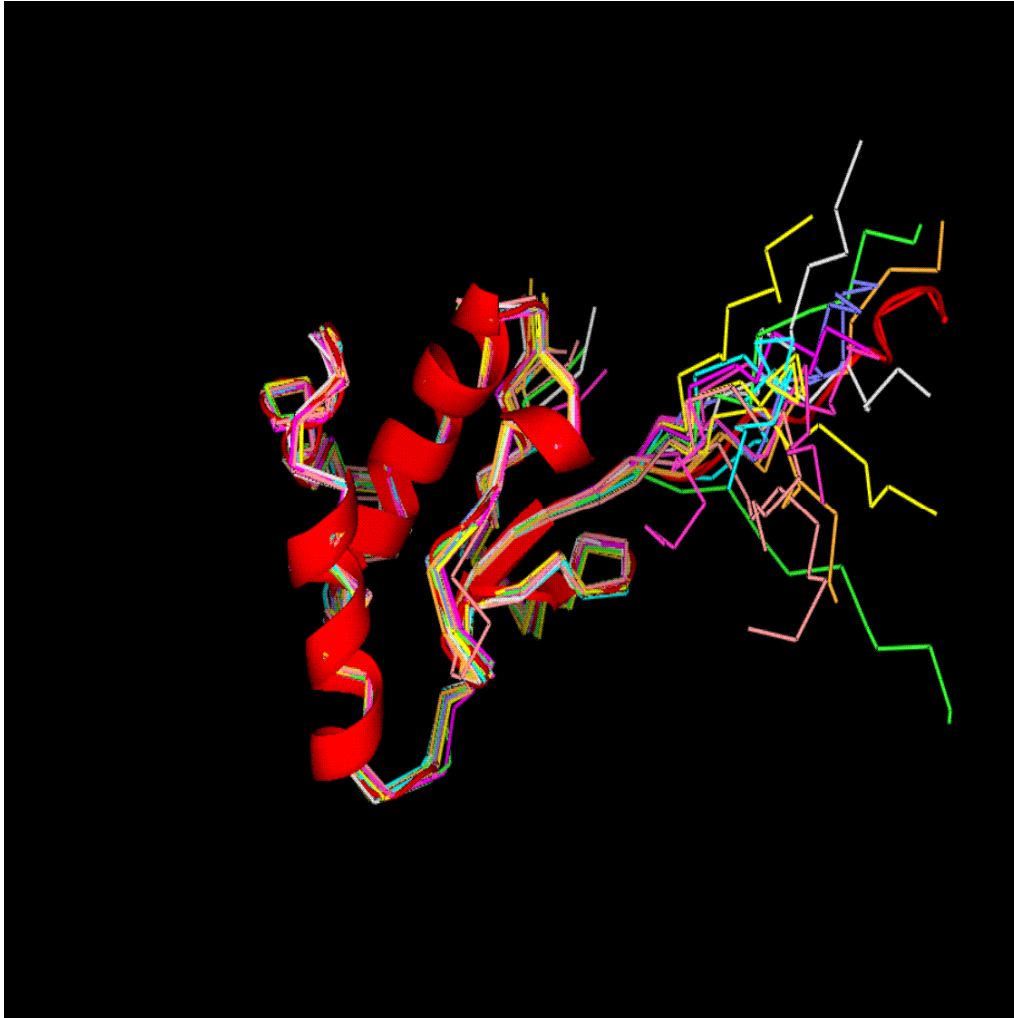


α - α Corner

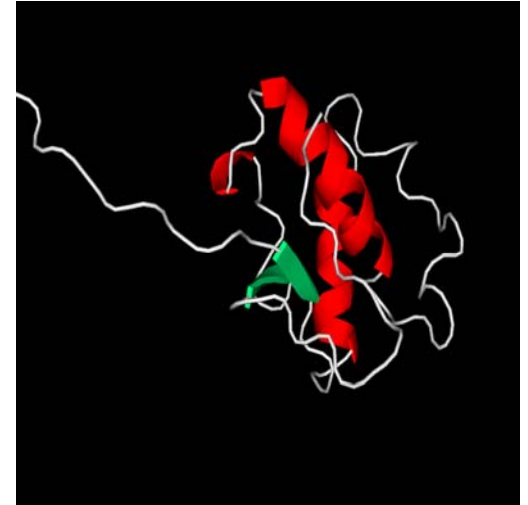


(c) Right-handed connection
between β strands

Estructura aperiódica y estructura al azar

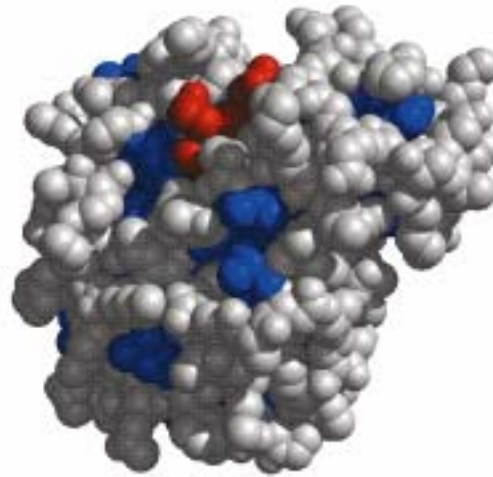
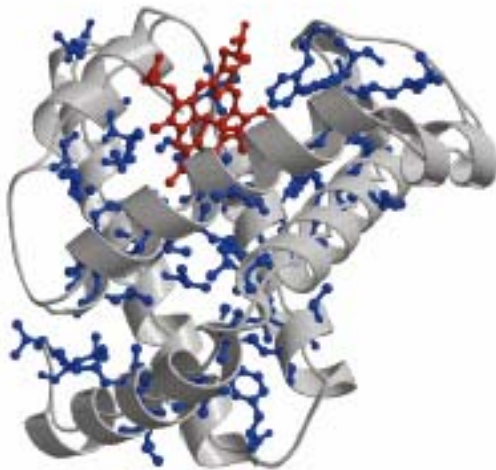
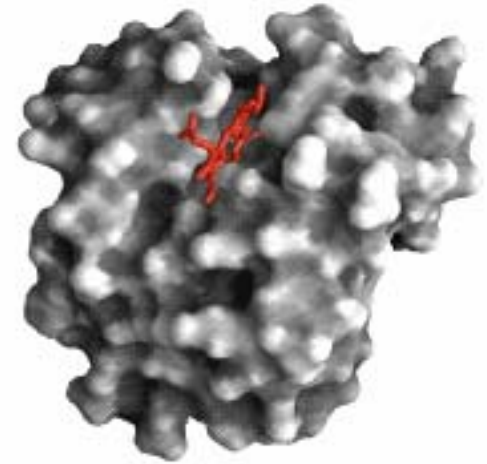
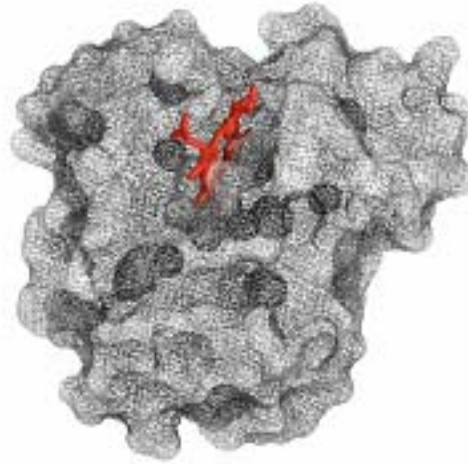
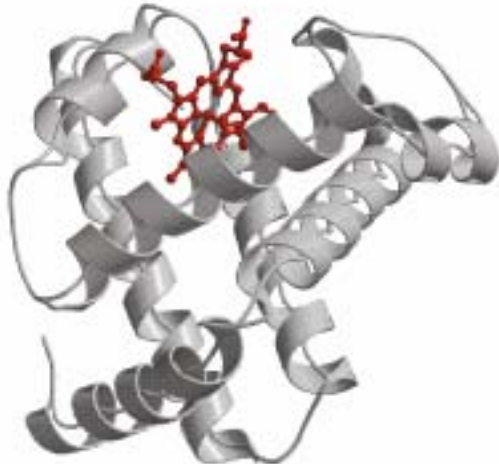


M. Bruix y col.



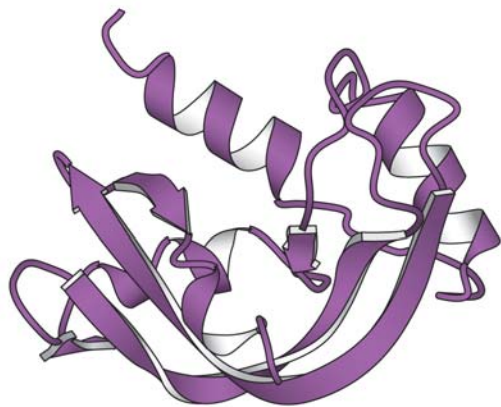
Estructura 3D del alergeno
del polen de olivo Ole e 9:
Dominio ligante de carbohidratos

Diversas formas de representación de proteínas

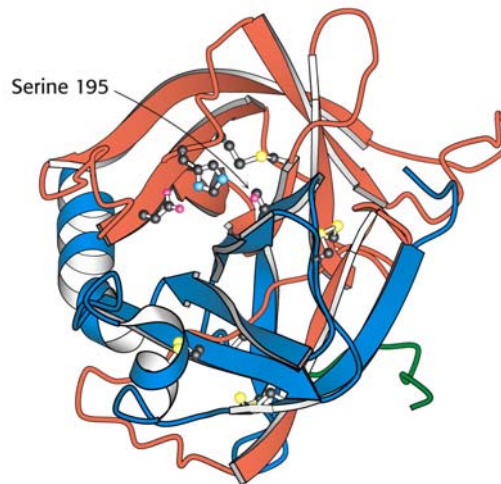


Plegamiento de
la cadena
de aminoácidos

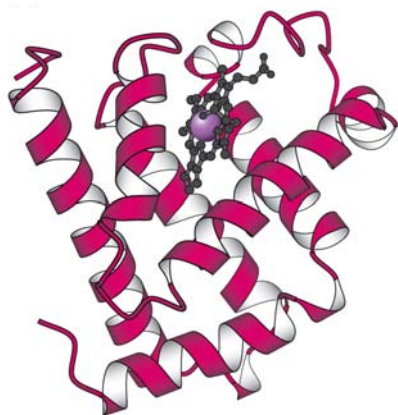
Asociación de diferentes estructuras secundarias: Ejemplos en proteínas concretas



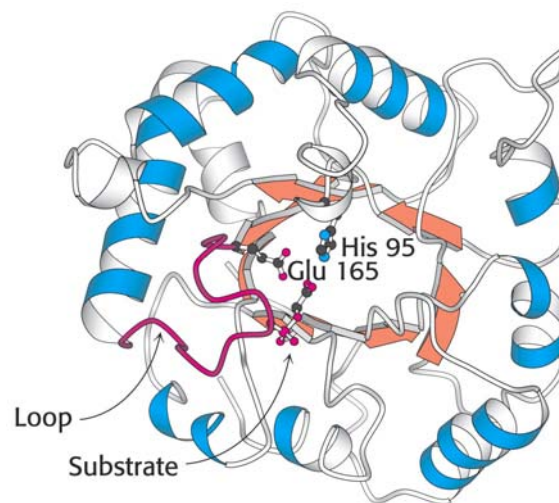
Angiogenina



Quimotripsina

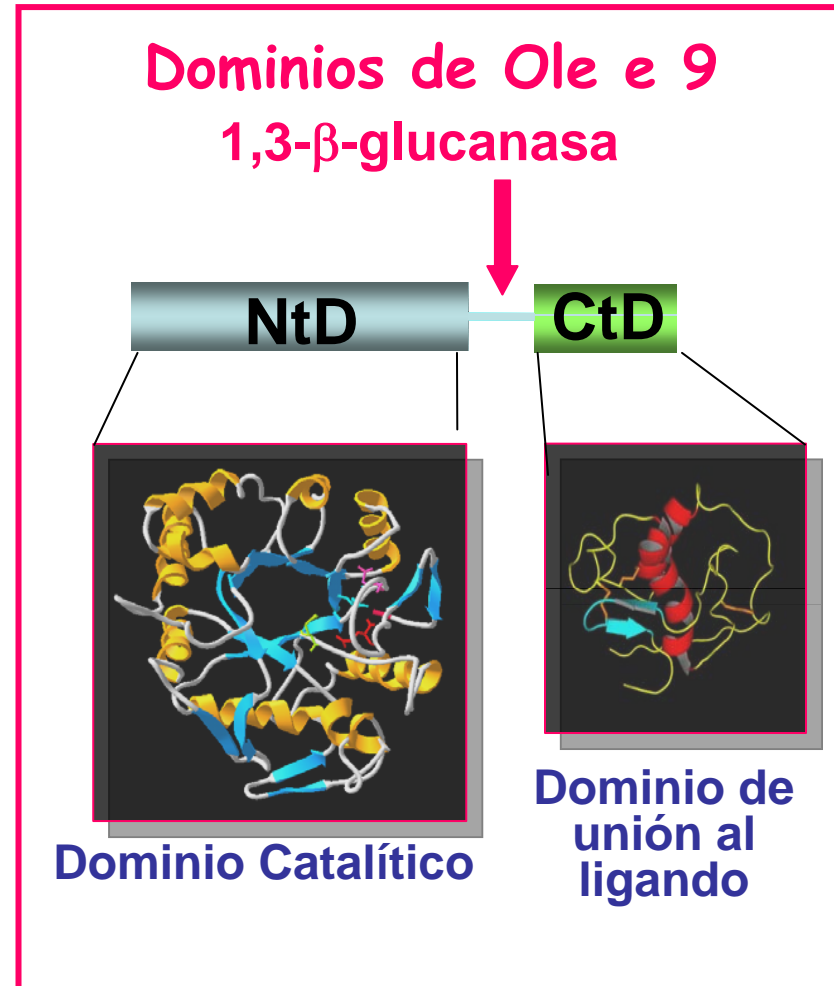
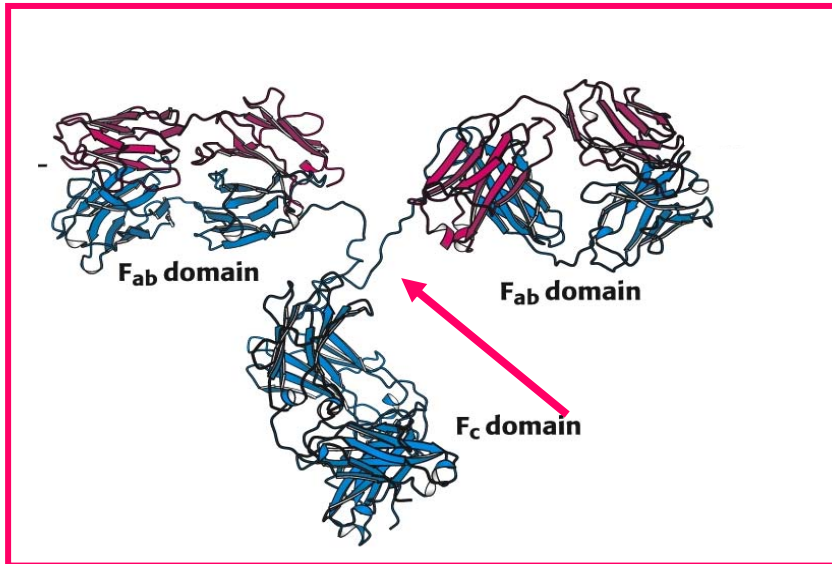
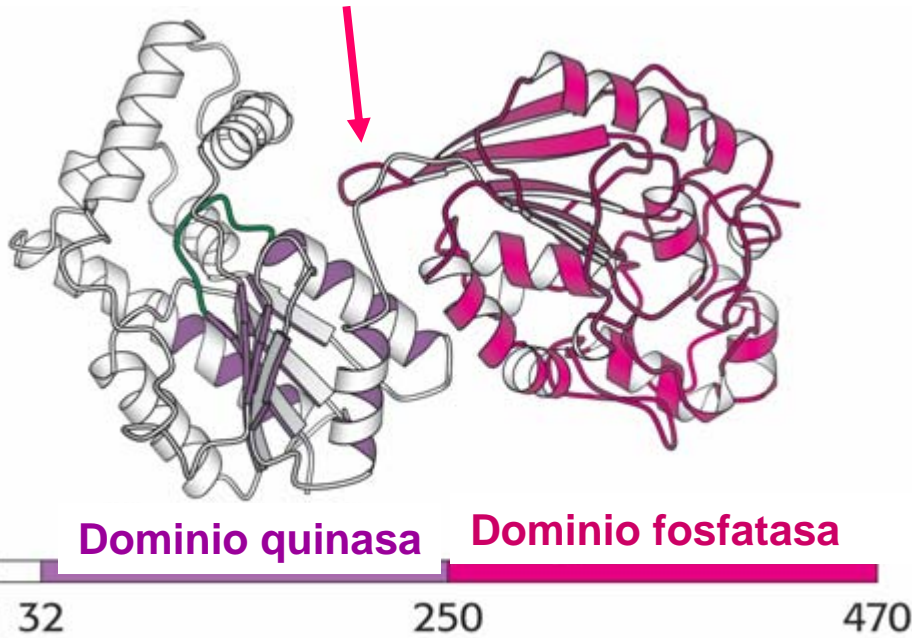


Mioglobina

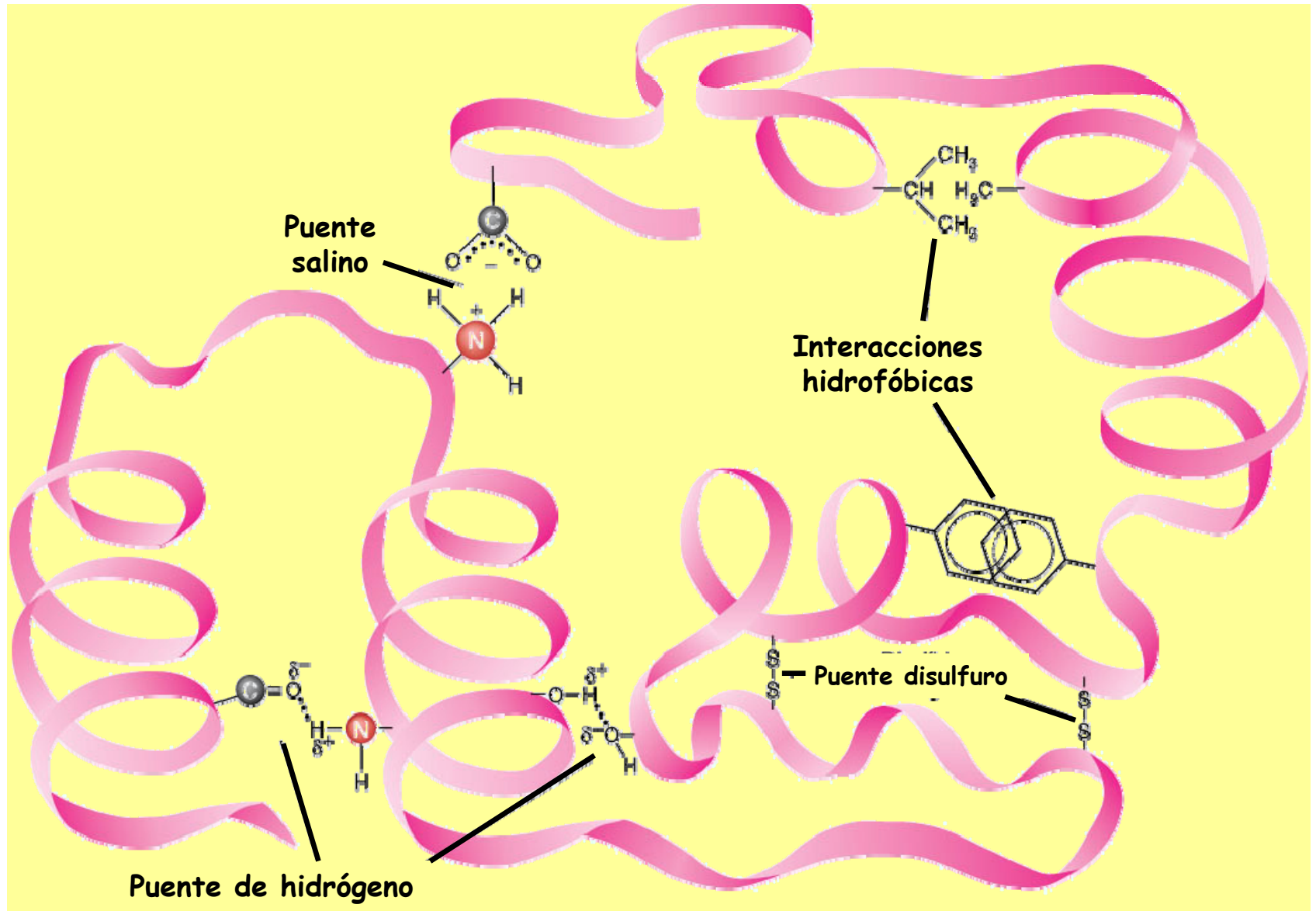


Triosafosfato isomerasa

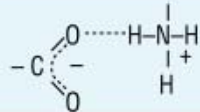
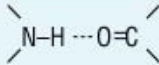
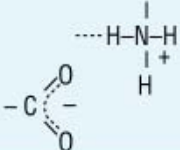
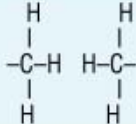
Existencia de DOMINIOS en la estructura terciaria de proteínas



Tipos de fuerzas que estabilizan la estructura terciaria

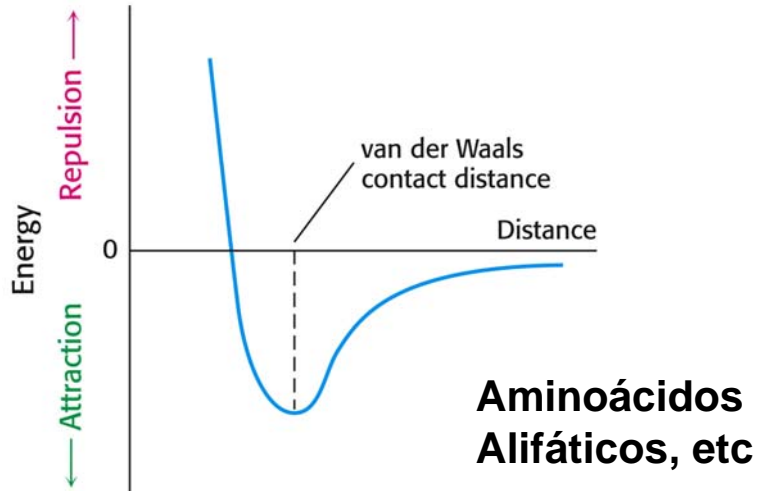


Tipos de enlaces que estabilizan la estructura terciaria

Chemical Interactions that Stabilize Polypeptides				
Interaction	Example	Distance dependence	Typical distance	Free energy (bond dissociation enthalpies for the covalent bonds)
Covalent bond	$-C_{\alpha}-C-$	-	1.5 Å	356 kJ/mole (610 kJ/mole for a C=C bond)
Disulfide bond	$-Cys-S-S-Cys-$	-	2.2 Å	167 kJ/mole
Salt bridge		Donor (here N), and acceptor (here O) atoms <3.5 Å	2.8 Å	12.5–17 kJ/mole; may be as high as 30 kJ/mole for fully or partially buried salt bridges (see text), less if the salt bridge is external
Hydrogen bond		Donor (here N), and acceptor (here O) atoms <3.5 Å	3.0 Å	2–6 kJ/mole in water; 12.5–21 kJ/mole if either donor or acceptor is charged
Long-range electrostatic interaction		Depends on dielectric constant of medium. Screened by water. $1/r$ dependence	Variable	Depends on distance and environment. Can be very strong in nonpolar region but very weak in water
Van der Waals interaction		Short range. Falls off rapidly beyond 4 Å separation. $1/r^6$ dependence	3.5 Å	4 kJ/mole (4–17 in protein interior) depending on the size of the group (for comparison, the average thermal energy of molecules at room temperature is 2.5 kJ/mole)

ALGUNOS ENLACES QUE ESTABILIZAN LA ESTRUCTURA 3ª

Interacciones de Van der Waals



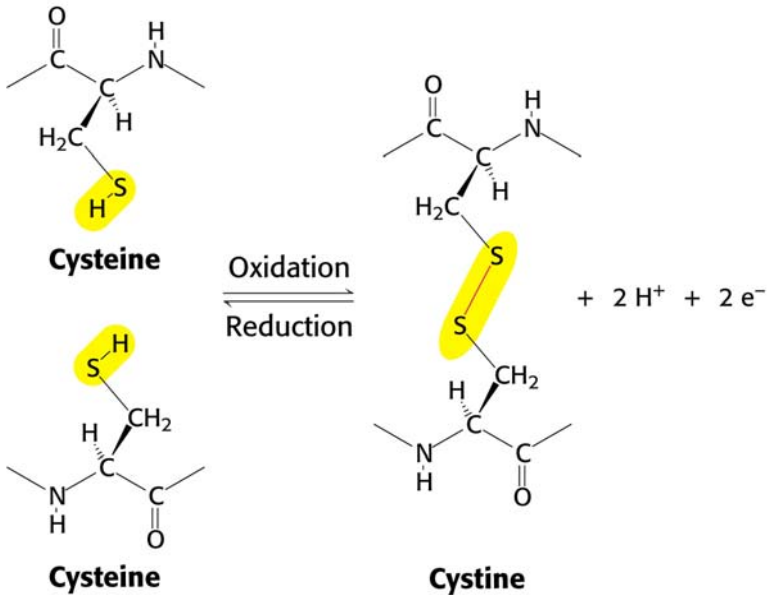
Enlace por puente de hidrógeno

Donador de H

Aceptor de H

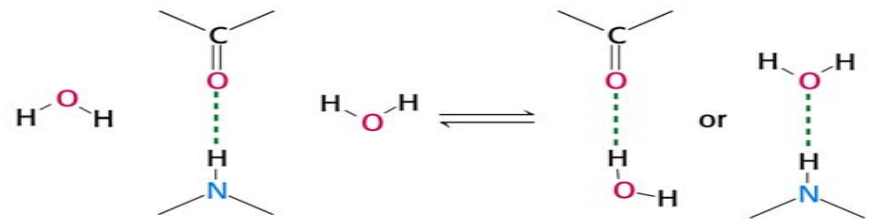


Enlace covalente



Aminoácidos:

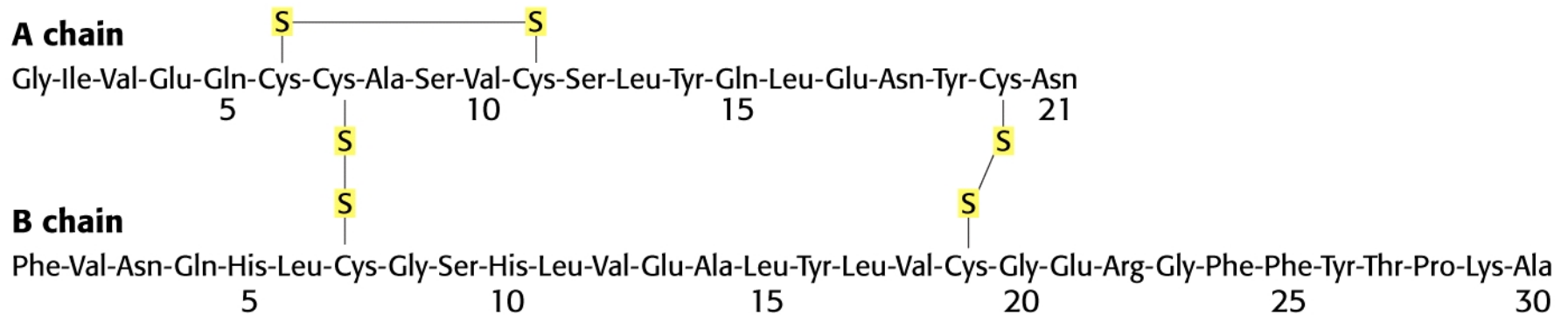
Arg, His, Asn, Gln, Ser, Thr, Tyr, Lys, Glu, Asp, etc



Tipos de puentes disulfuro

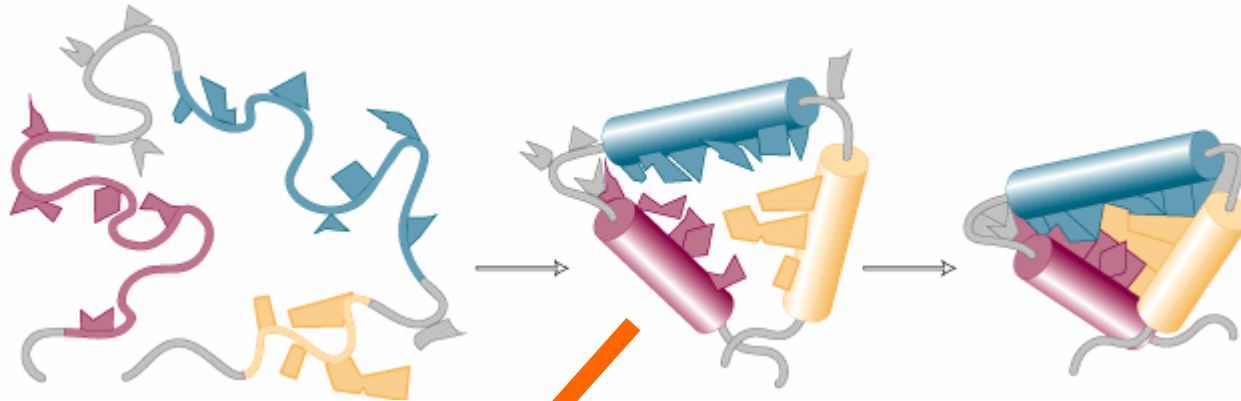
INSULINA: hormona polipeptídica

Intracatenario



Intercatenarios

CONFORMACIÓN NATIVA DE UNA PROTEÍNA

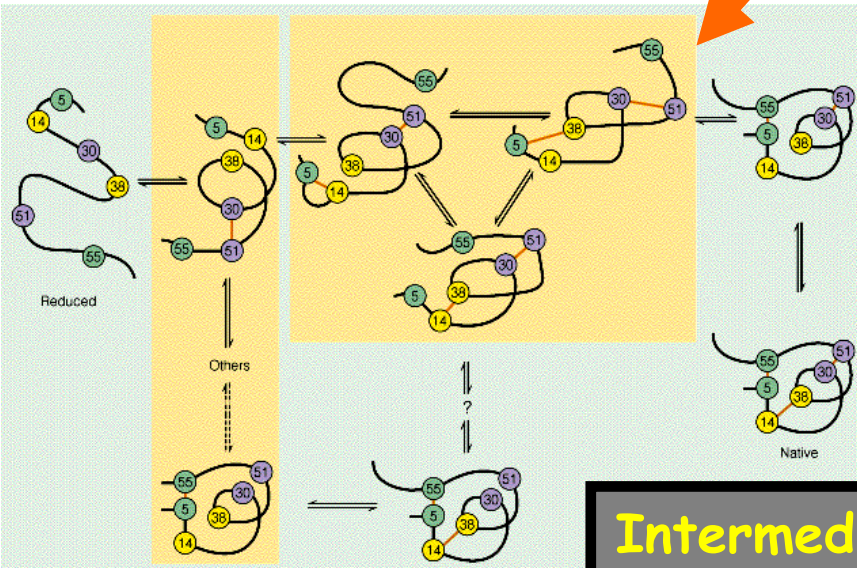


Estructura primaria

Conformación nativa

Más estable termodinámicamente

Permite desempeñar función

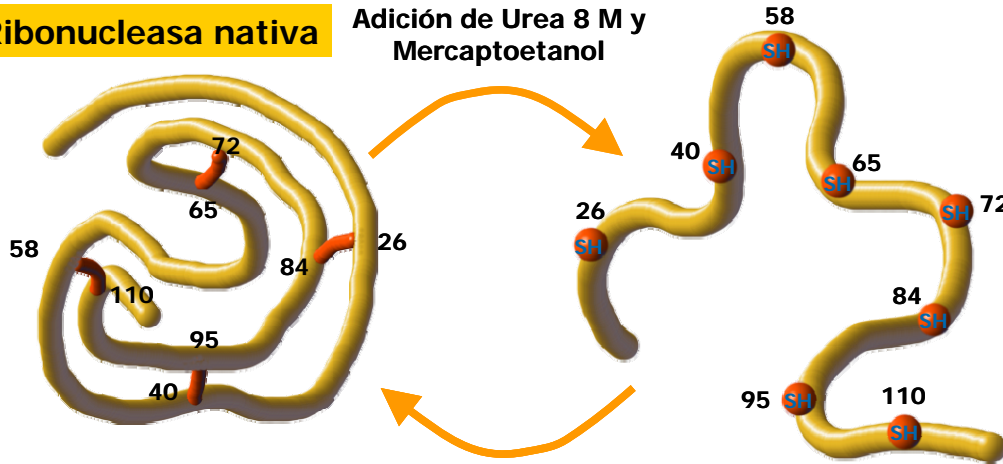


Intermedios de plegamiento
INESTABLES
NO FUNCIONALES

Desnaturalización de proteínas

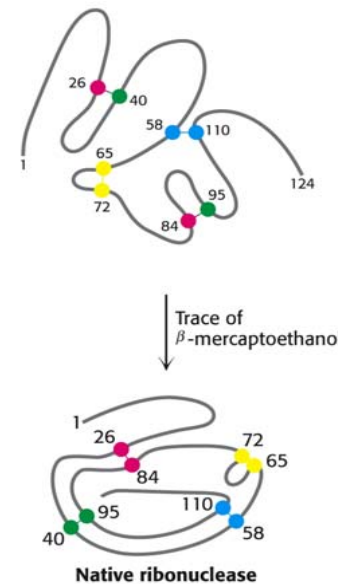
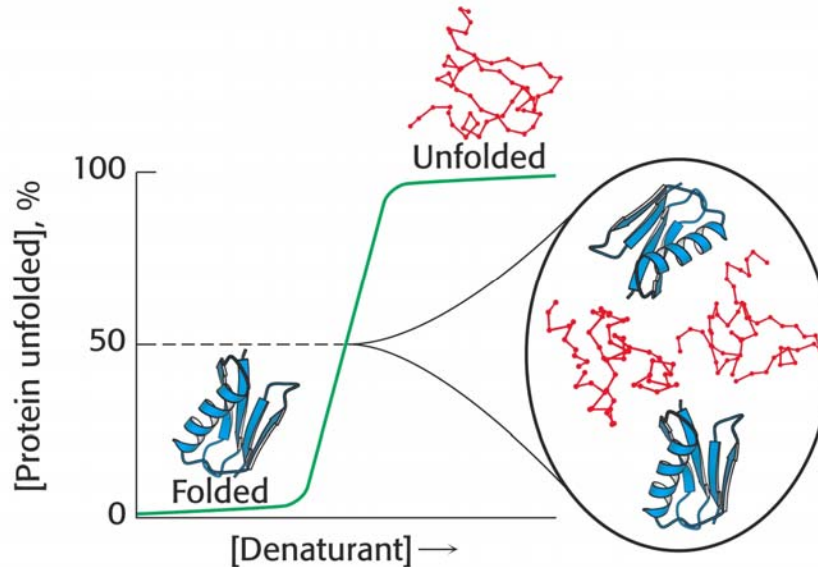
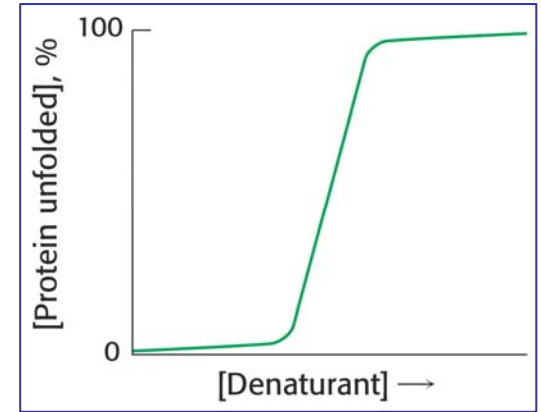
Ribonucleasa nativa

Adición de Urea 8 M y Mercaptoetanol

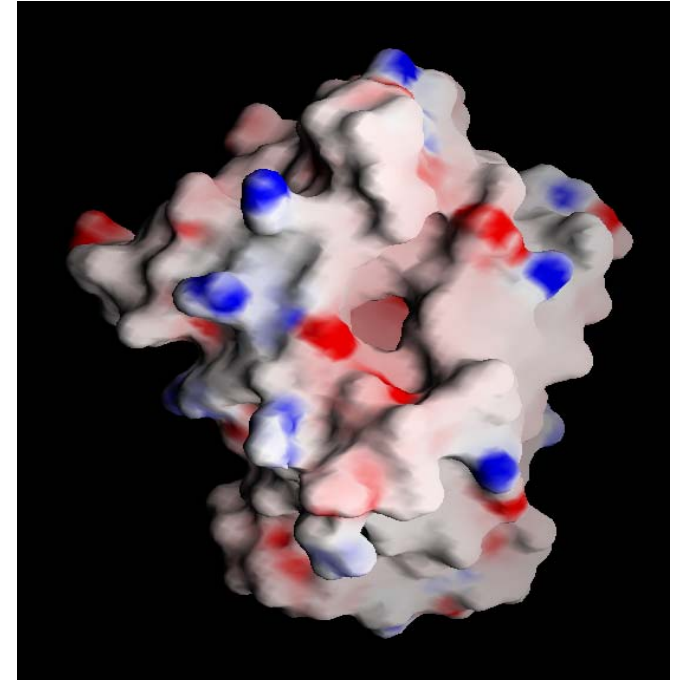
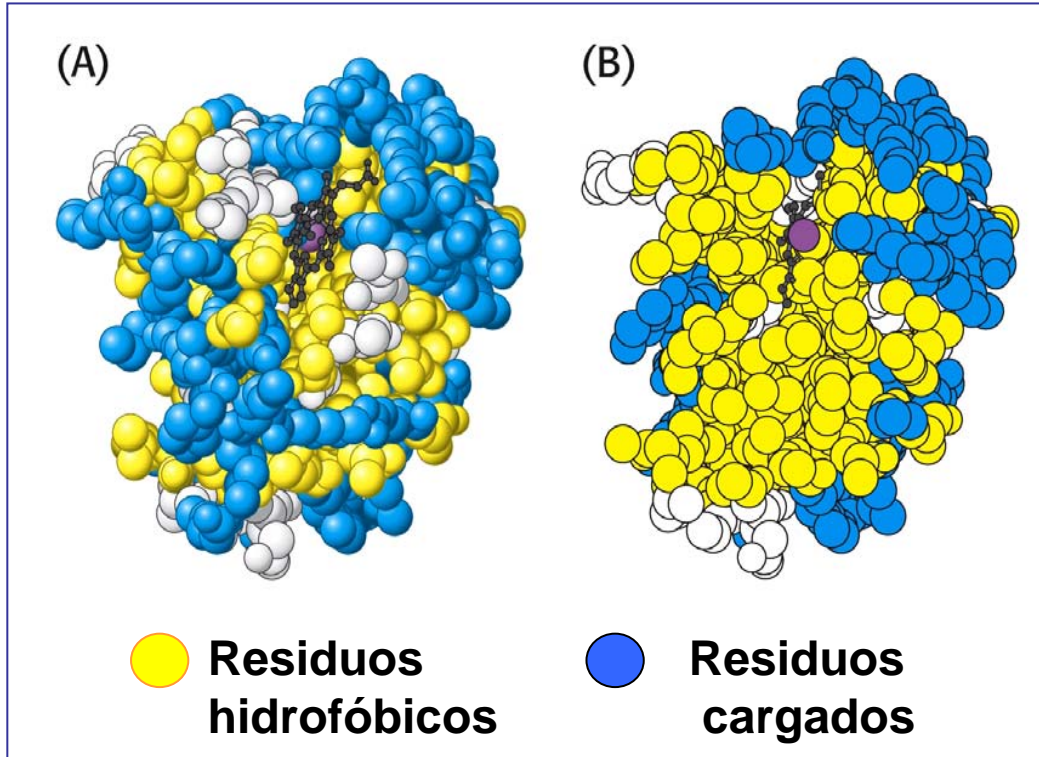


Eliminación de la Urea y el Mercaptoetanol

Ribonucleasa desnaturalizada (inactiva)

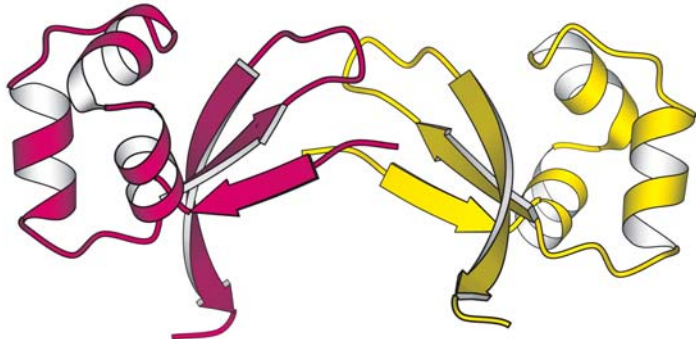


Disposición de los aminoácidos en la estructura 3D de una proteína

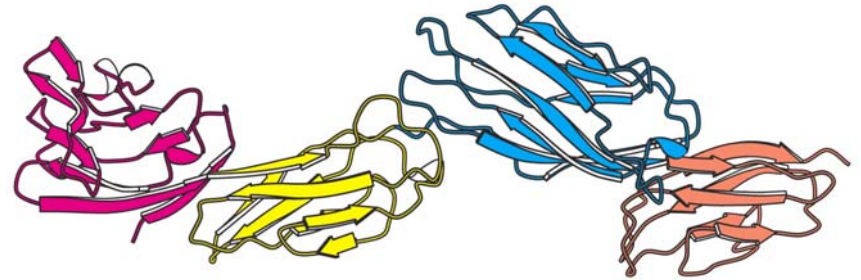


Los residuos localizados en posiciones externas ofrecen mayor variabilidad que los que ocupan situaciones internas

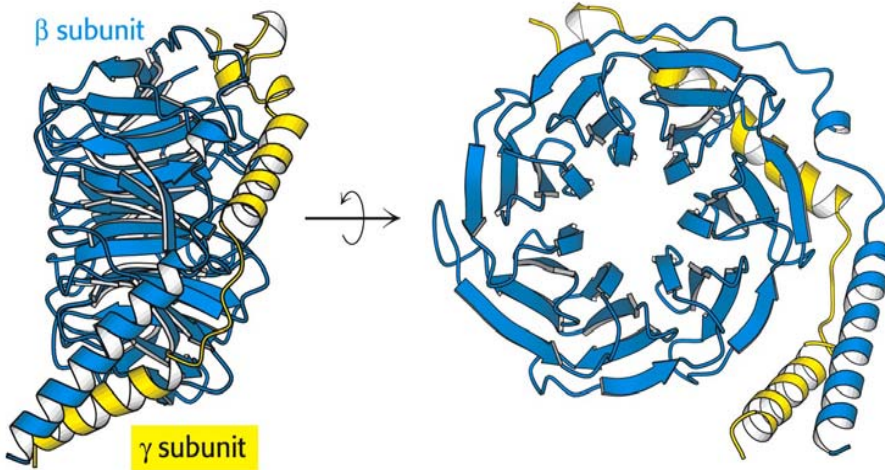
Estructura cuaternaria de proteínas



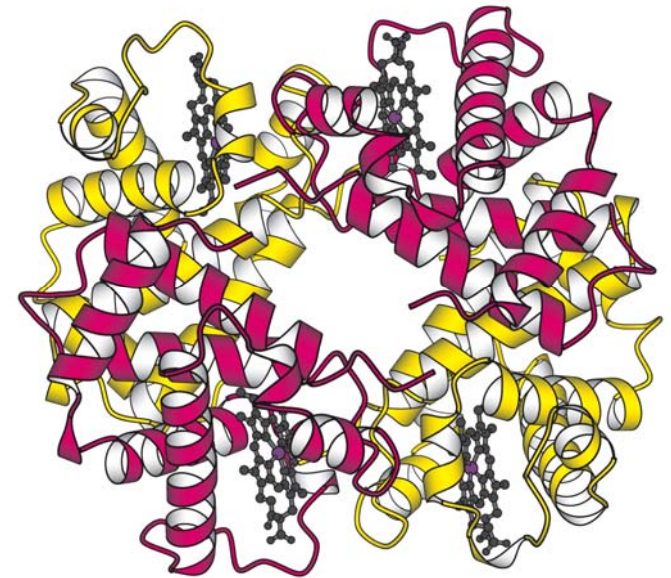
Proteína Cro: HOMODÍMERO (α_2)



Proteína CD4: HOMOTETRÁMERO (α_4)



Proteína G: HETERODÍMERO ($\alpha\beta$)



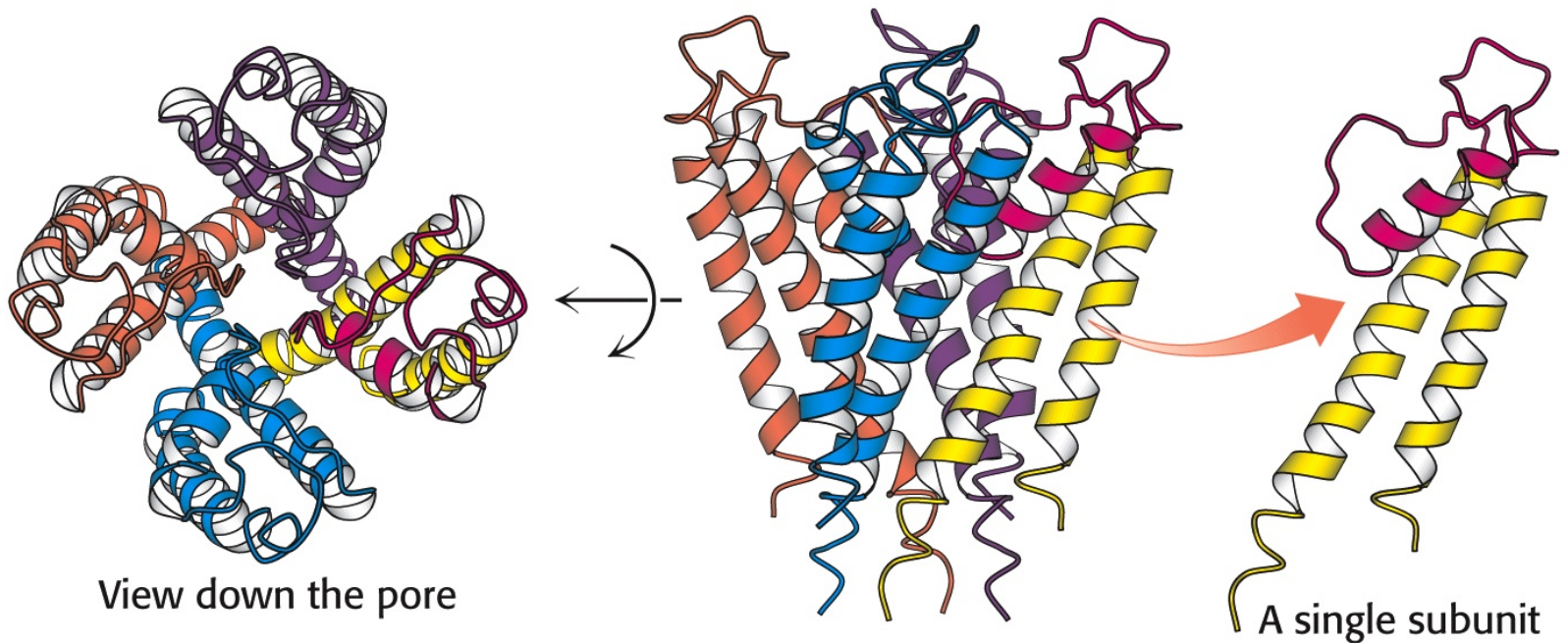
Hemoglobina: HETEROTETRÁMERO ($\alpha_2\beta_2$)

Estructura cuaternaria de proteínas

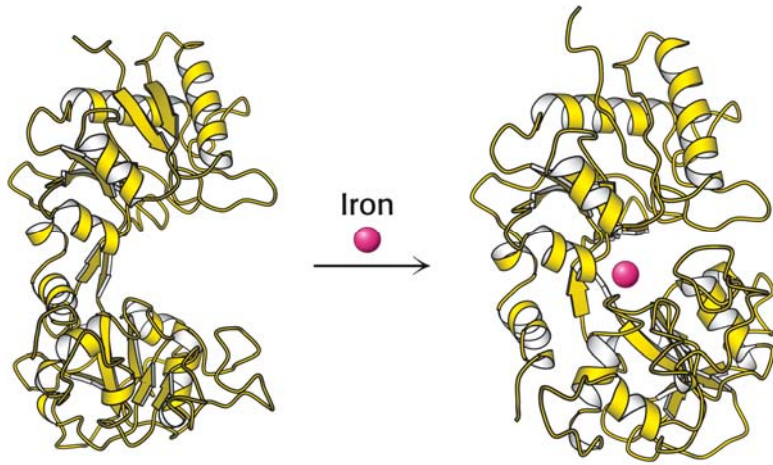
Fibrinógeno



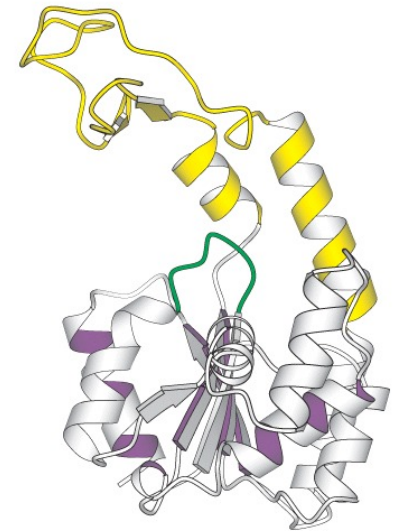
Canal de potasio



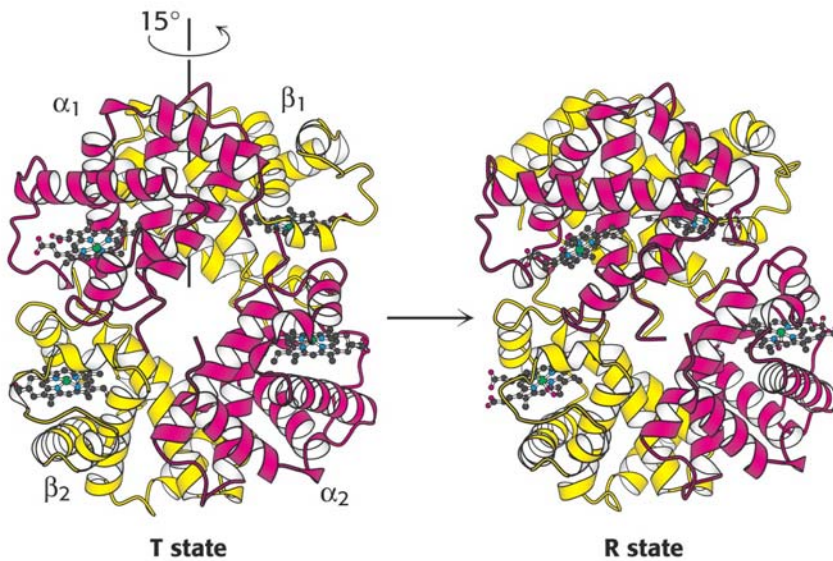
Flexibilidad de las proteínas



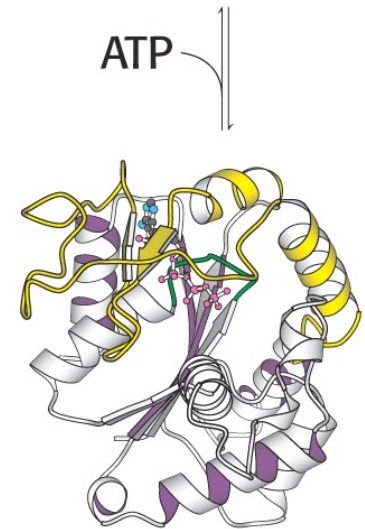
Adaptación a un cofactor



ATP

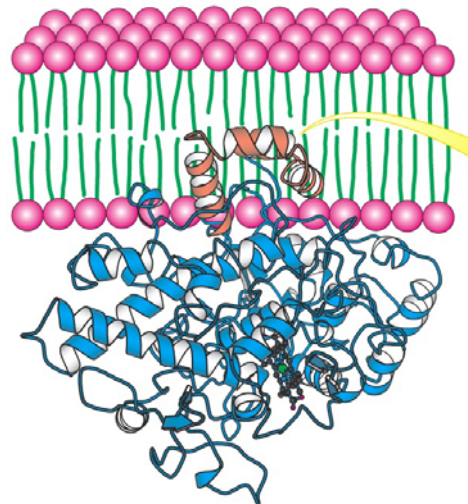
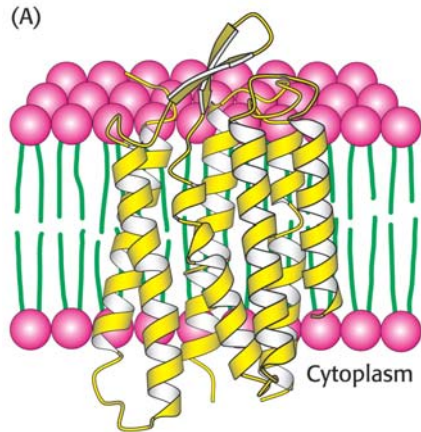
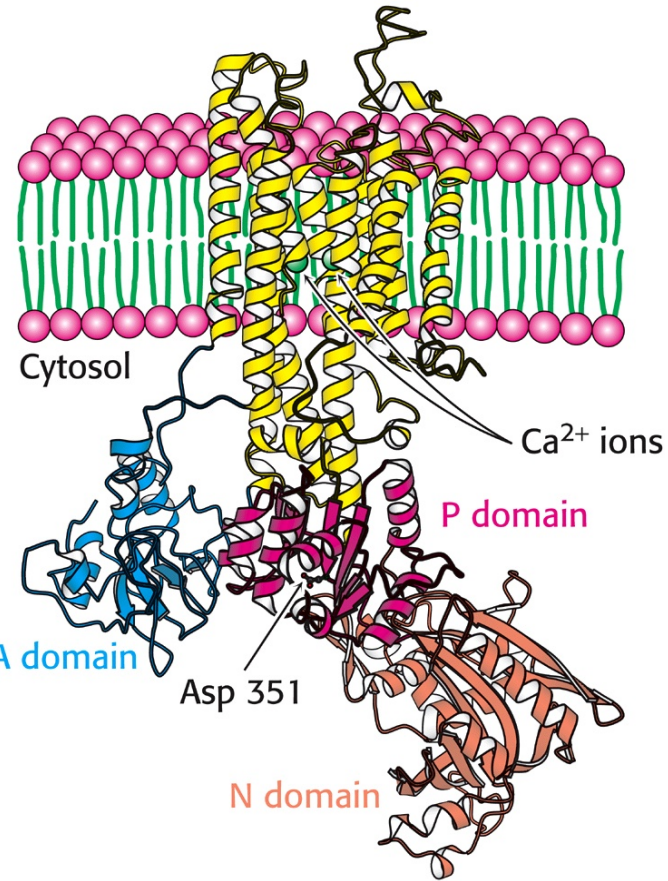
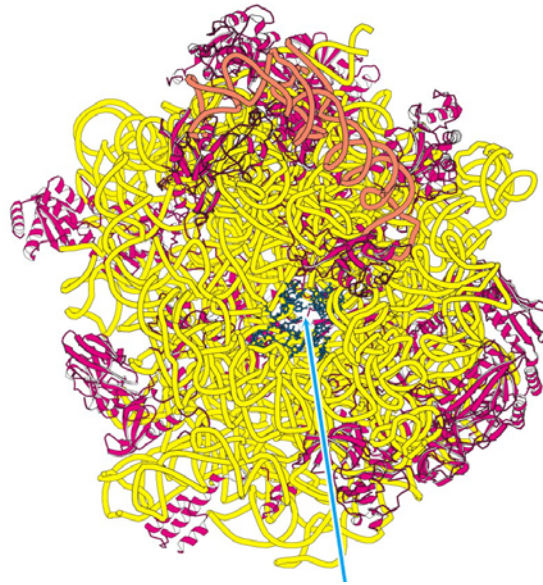
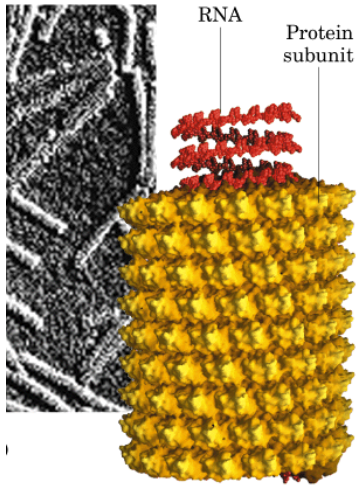


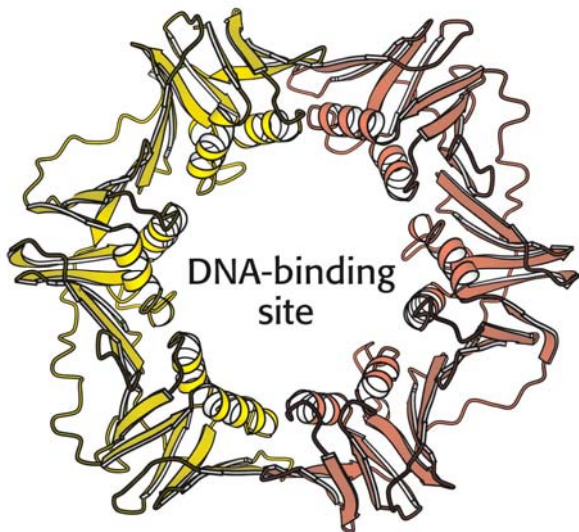
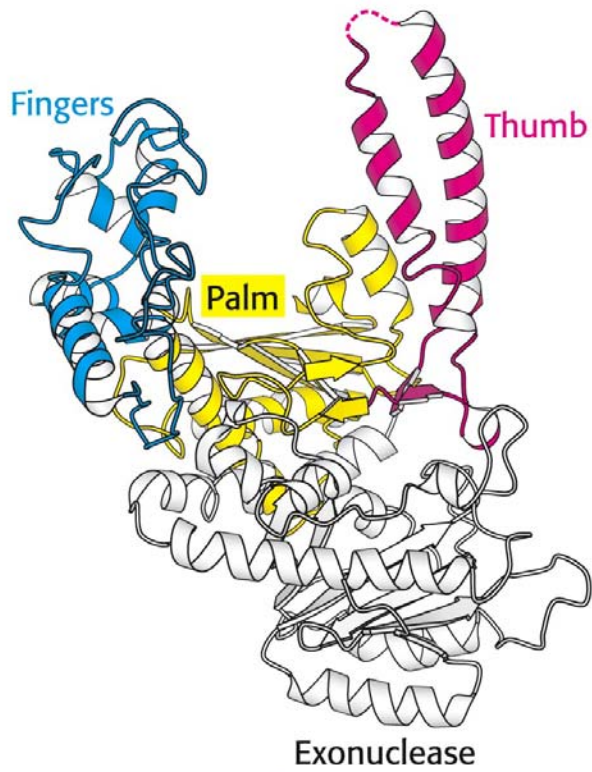
Adaptación a un ligando



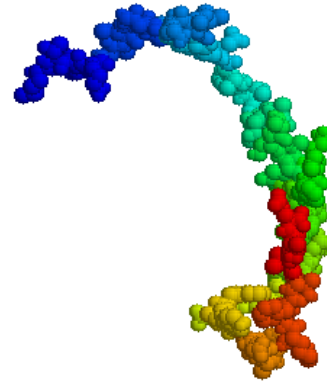
Adaptación a un sustrato

Asociación de proteínas a grandes estructuras: ácidos nucleicos (virus, biosíntesis de proteínas), lípidos (membranas)

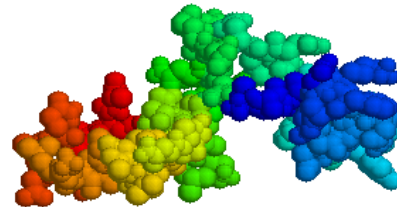
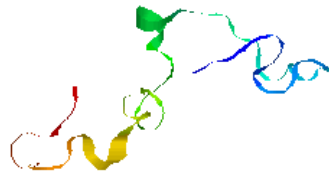




¿Cómo se pliegan las proteínas?



Proteína G



Proteína A

Energética del plegamiento de una proteína

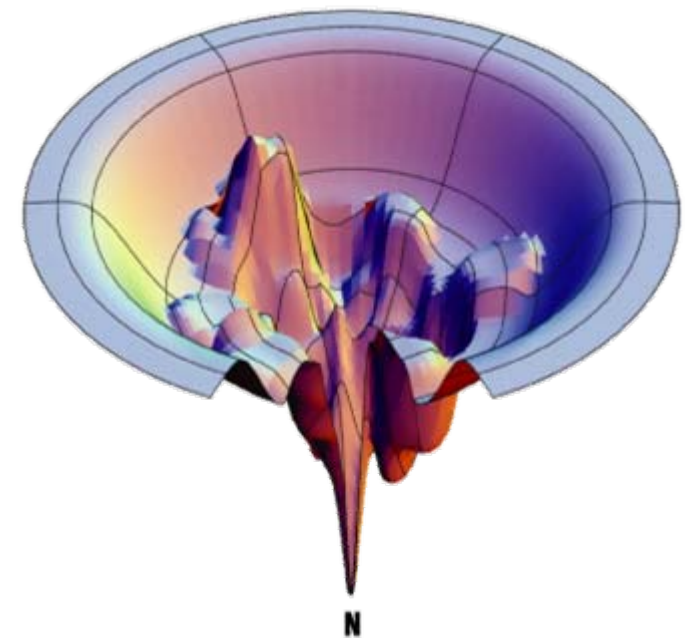
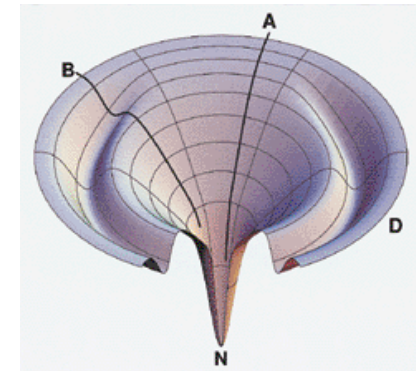
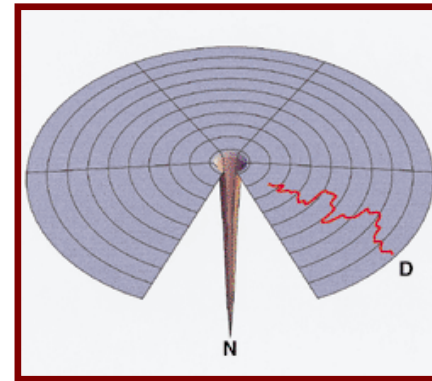
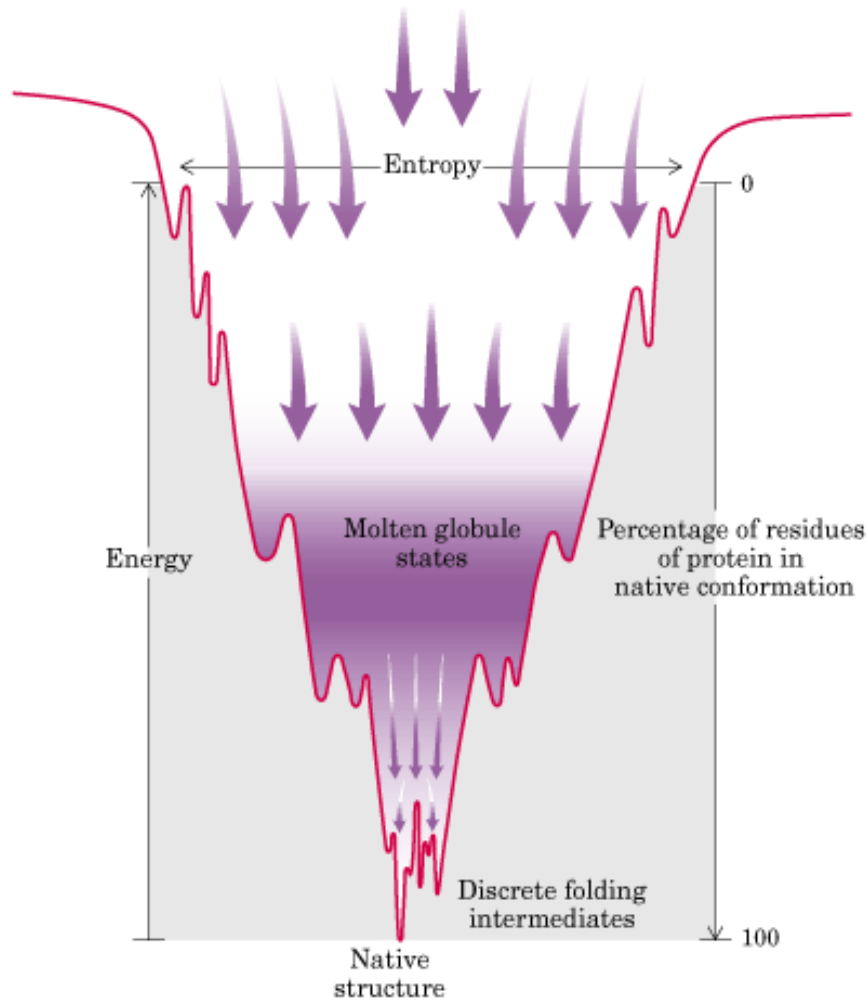


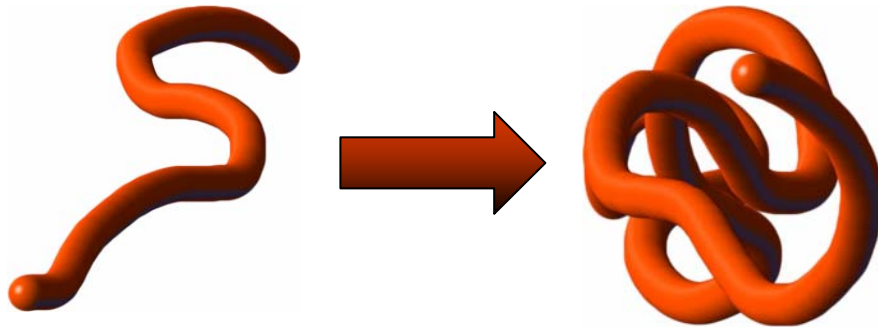
Diagrama energía-entropía para el plegamiento proteico

Mecanismo de plegamiento de una proteína

Búsqueda aleatoria estricta
Paradoja de Levinthal

vs

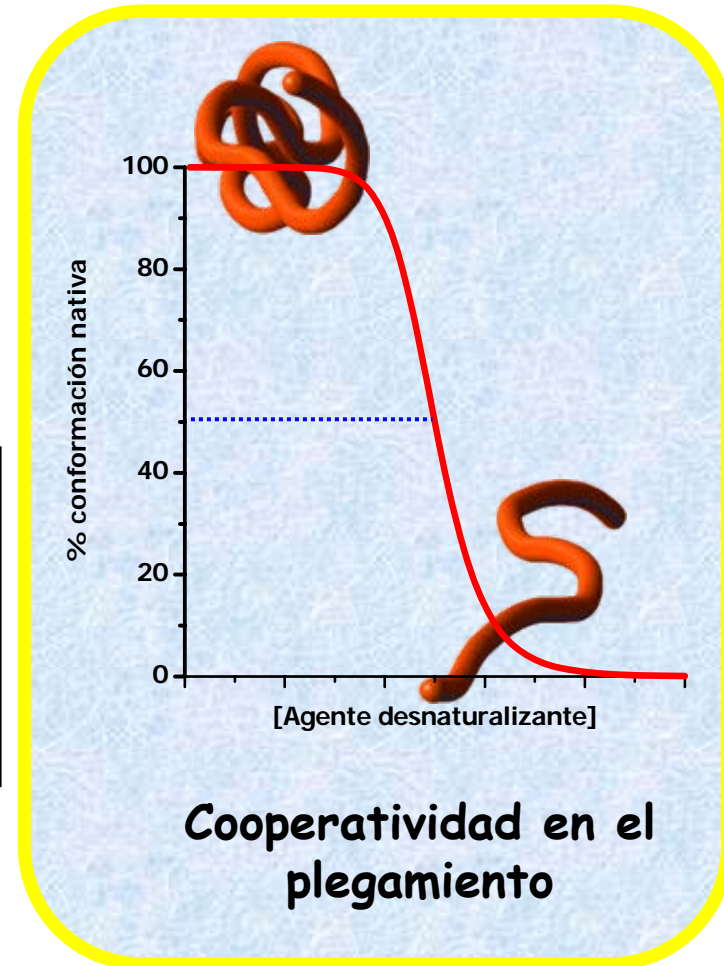
Búsqueda Cooperativa
Estabilización estados intermedios



- Entropía conformacional
- Puentes de hidrógeno con el agua
- $G = -190$ kcal/mol

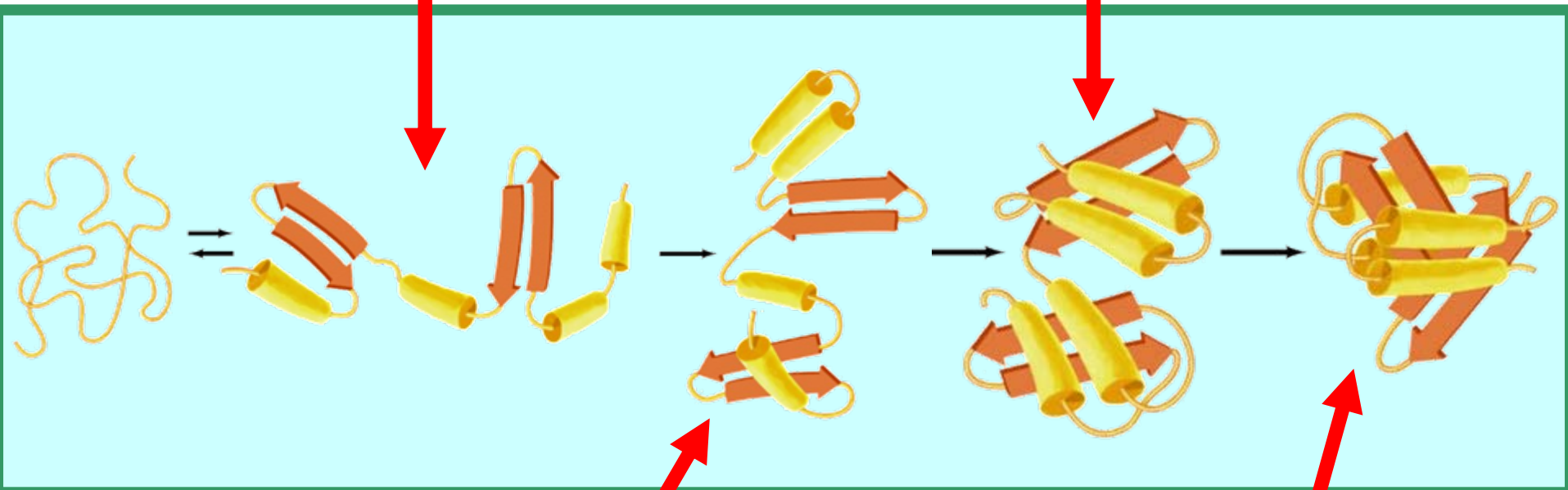
- "Colapso hidrofóbico"
- Puentes de hidrógeno intramoleculares
- Interacciones de Van der Waals
- $G = -200$ kcal/mol

$$\Delta G_{D \rightarrow P} = -10 \text{ Kcal/mol}$$



Formación pequeños
elementos estructura
2ª

Estabilización
mediante
interacciones
hidrofóbicas



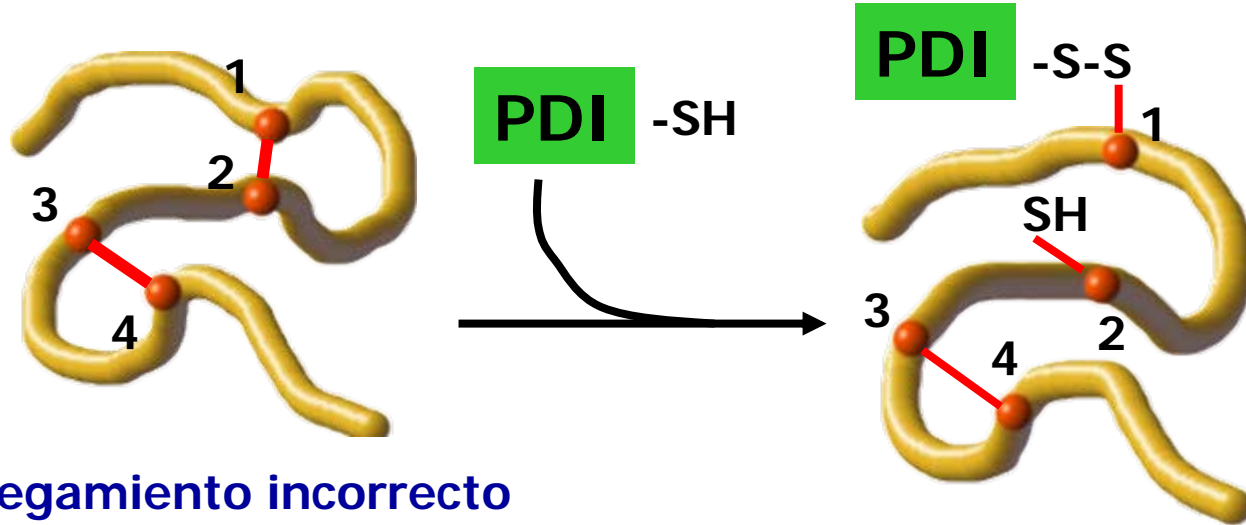
Nucleación alrededor
de los dominios

Evolución hasta
conformación nativa

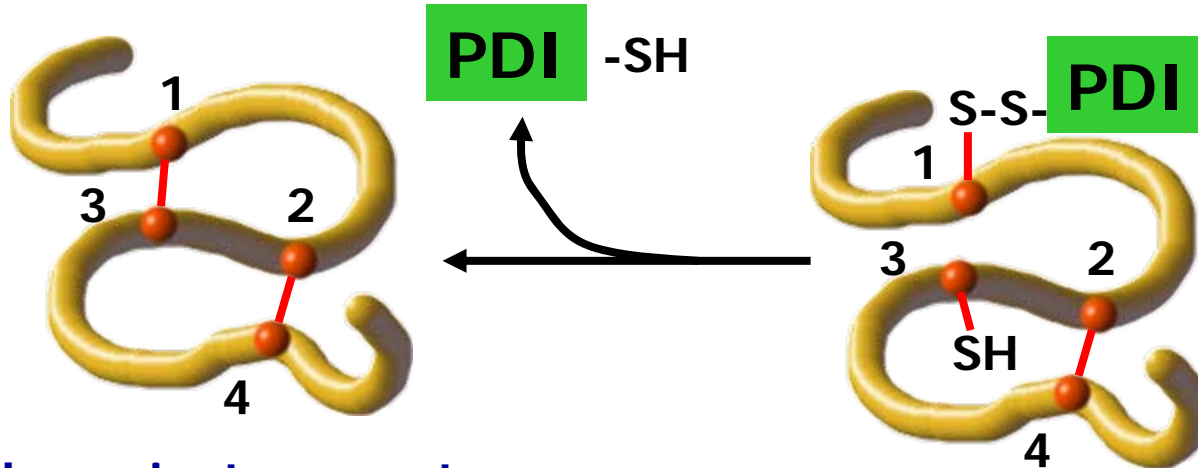
PROTEÍNAS QUE FACILITAN EL PLEGAMIENTO

Conversiones entre diferentes configuraciones

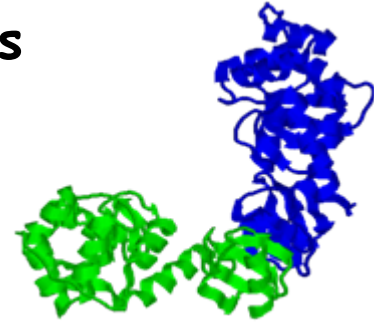
Proteína Disulfuro Isomerasa



Plegamiento incorrecto



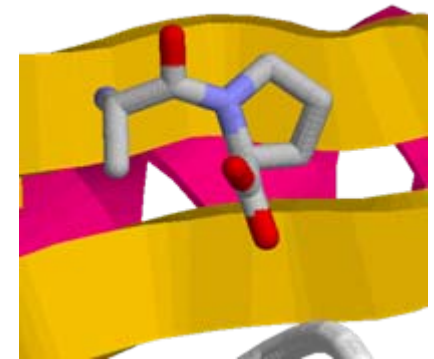
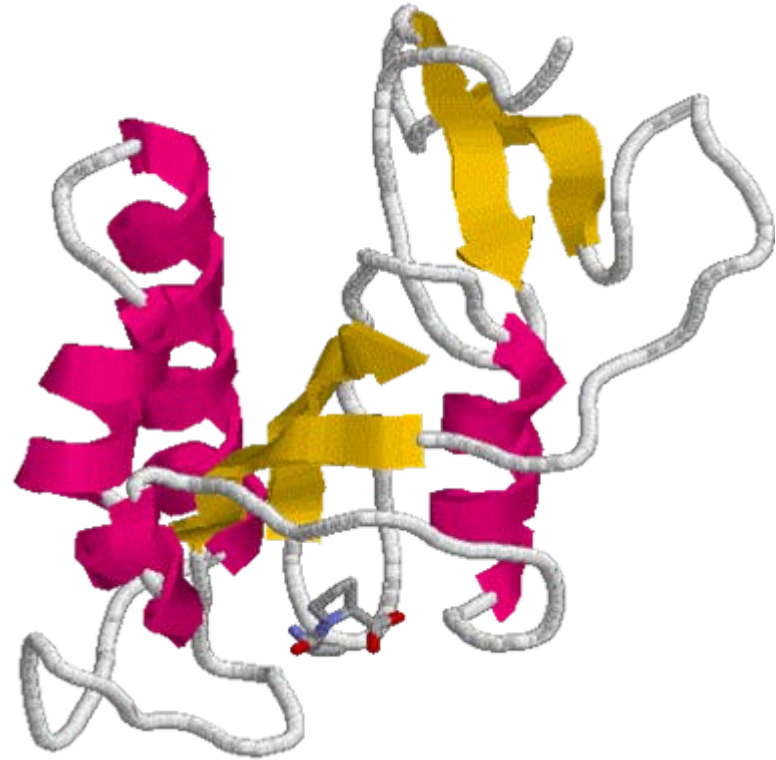
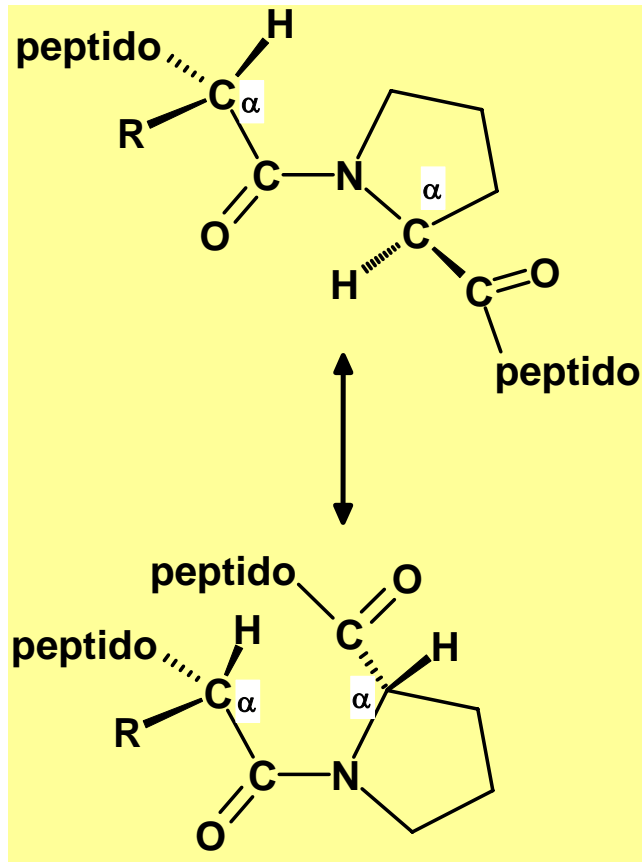
Plegamiento correcto



PROTEÍNAS QUE FACILITAN EL PLEGAMIENTO

Conversiones entre diferentes configuraciones

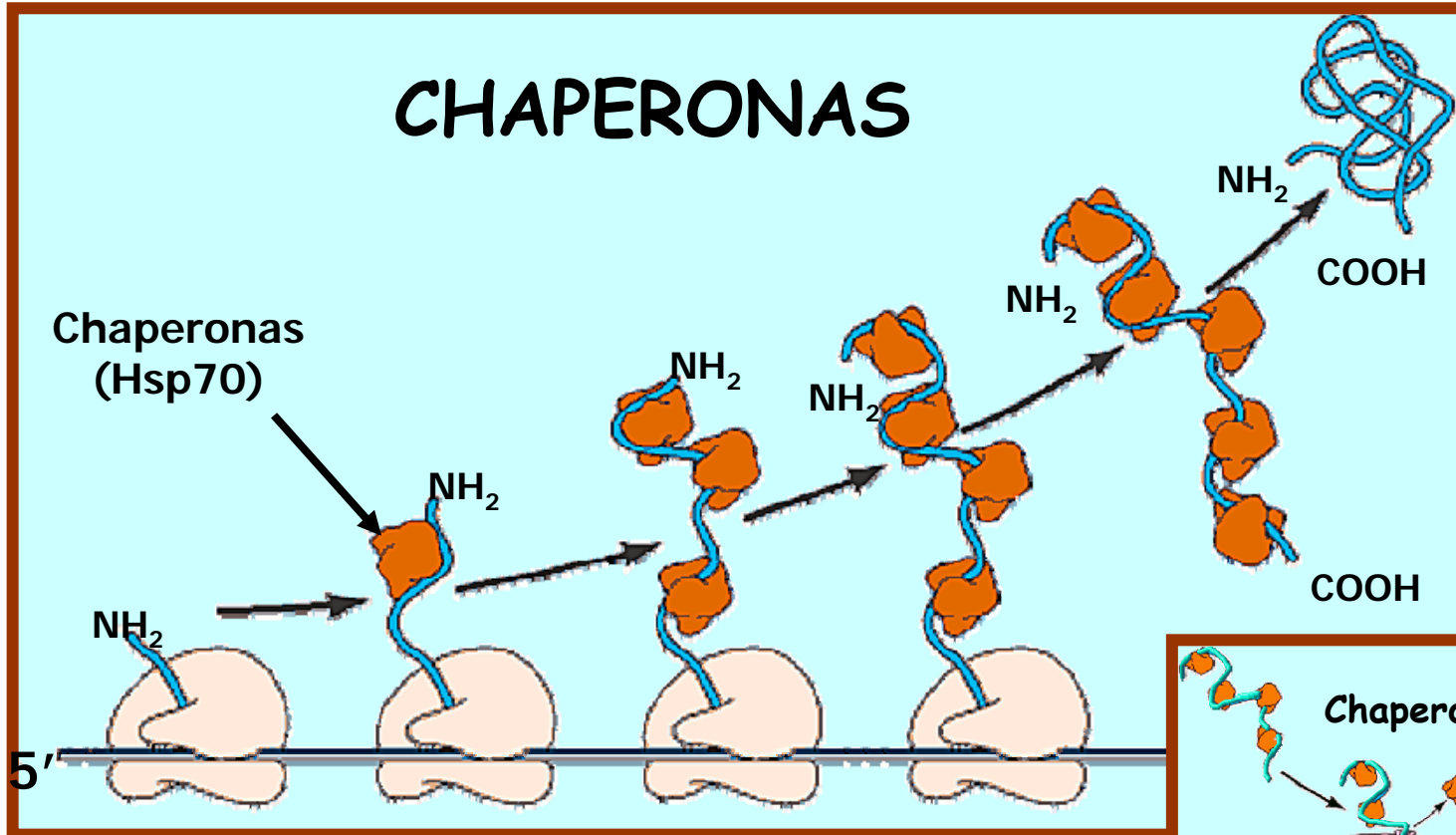
Péptido prolin *cis-trans* isomerasa (PPI)



PROTEÍNAS QUE FACILITAN EL PLEGAMIENTO

Favorecen plegamiento correcto

CHAPERONAS



Chaperonas
(Hsp70)

NH₂

NH₂

NH₂

NH₂

NH₂

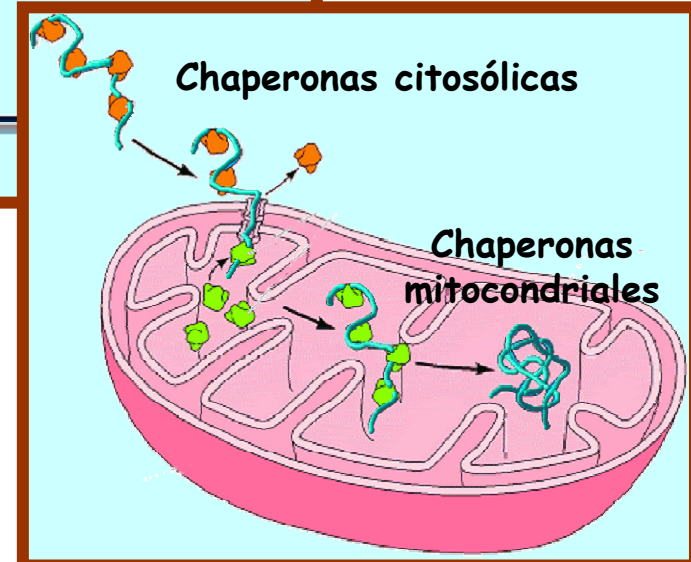
NH₂

COOH

COOH

5'

Impiden plegamientos prematuros



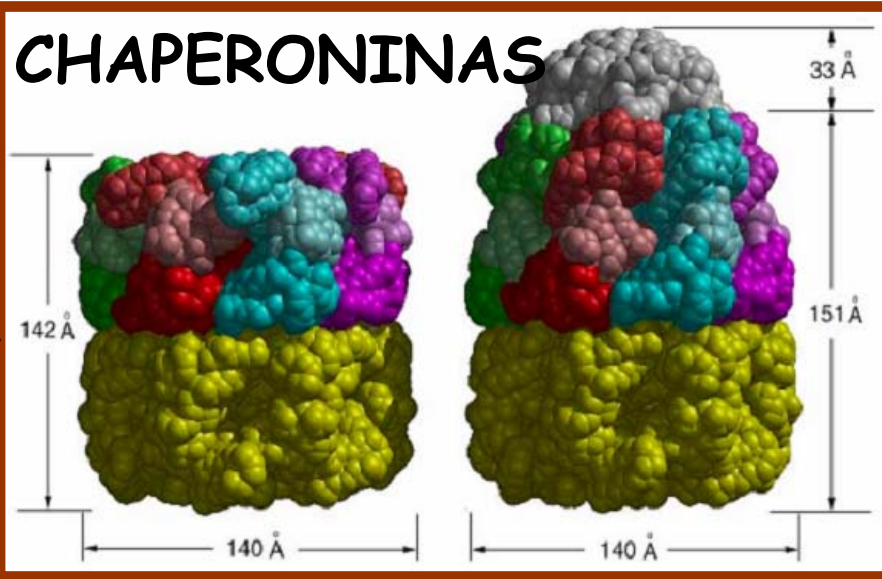
Chaperonas citosólicas

Chaperonas
mitocondriales

PROTEÍNAS QUE FACILITAN EL PLEGAMIENTO

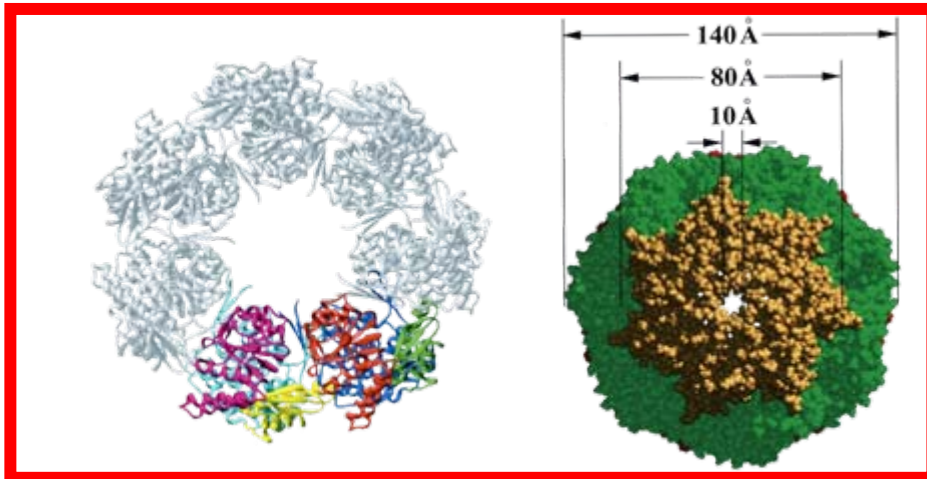
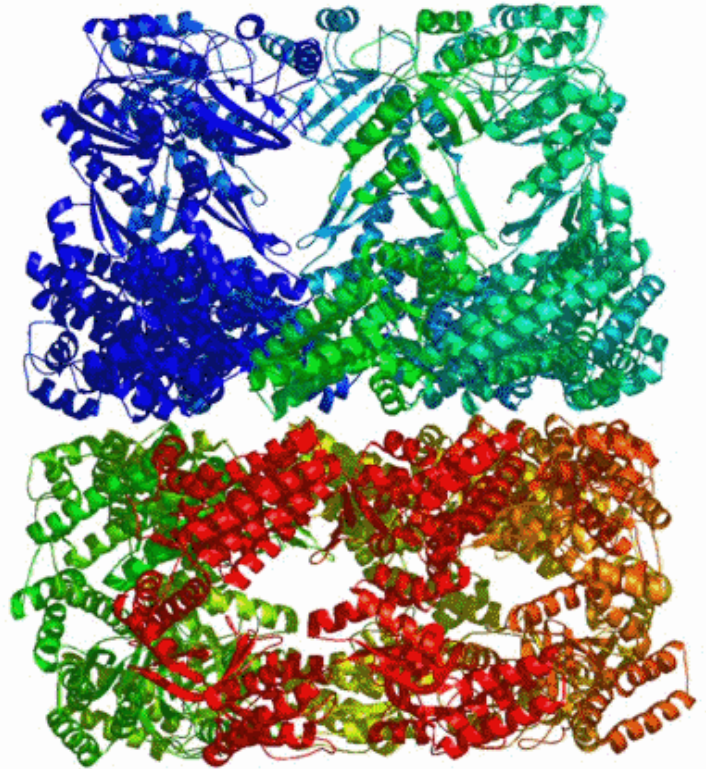
Favorecen plegamiento correcto

CHAPERONINAS



GroES

GroEL



La hidrólisis de ATP reduce la cavidad de GroEL favoreciendo el plegamiento

Posible mecanismo de actuación de GroEL-GroES

