

1 H																	2 He	
3 Li	4 Be												5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg												13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr	
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe	
55 Cs	56 Ba		72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn	
87 Fr	88 Ra		Lanthanides Actinides															

Figure 1-12

Lehninger Principles of Biochemistry, Fifth Edition

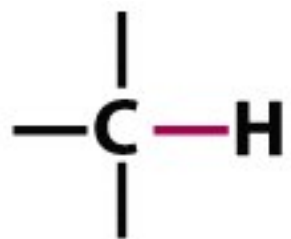
© 2008 W. H. Freeman and Company

Prevalence of Elements by Weight		
Elements	Human Body	Earth's Crust
Oxygen	65%	49%
Carbon	18%	<1%
Hydrogen	10%	<1%
Nitrogen	3%	trace
Calcium	2%	3%
Iron	<0.05%	5%
Aluminum	<0.001%	8%
Silicon	trace	26%

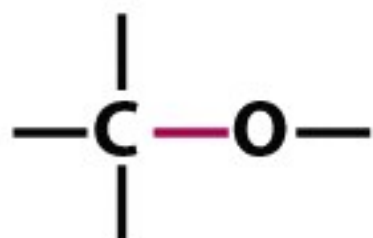
>95%

Créditos: HarvardX

O átomo de carbono é versátil, pode construir moléculas estruturalmente diversas



hibridização



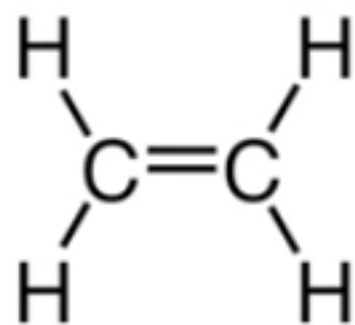
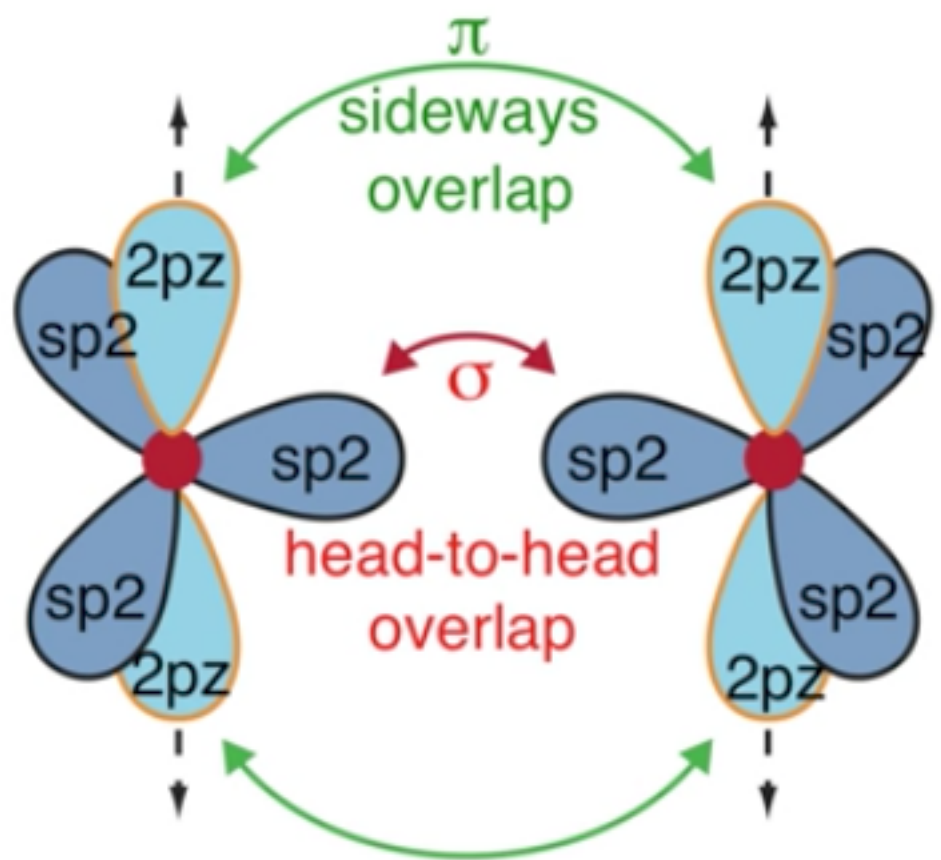
sp³



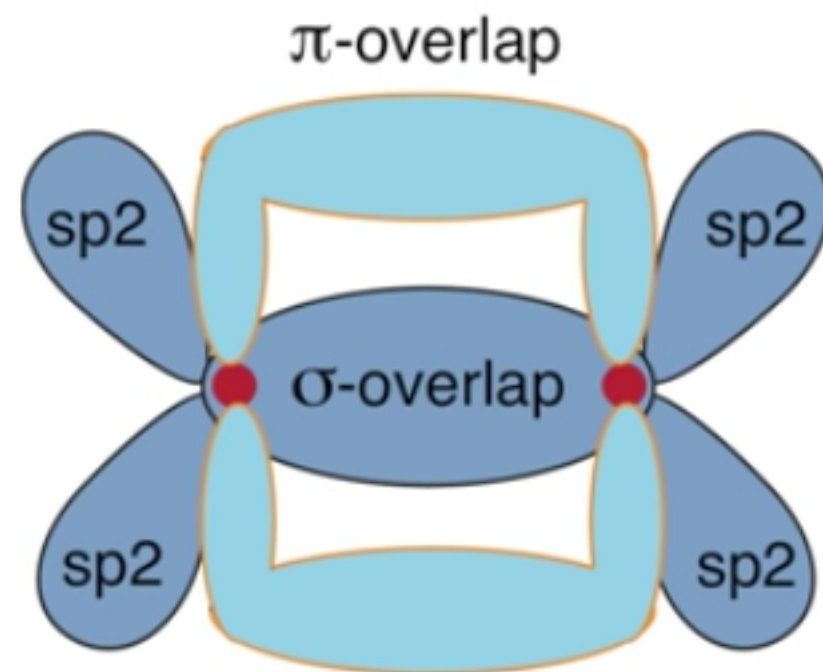
sp²



sp



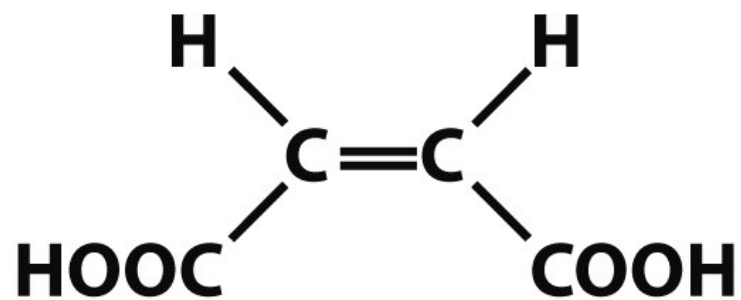
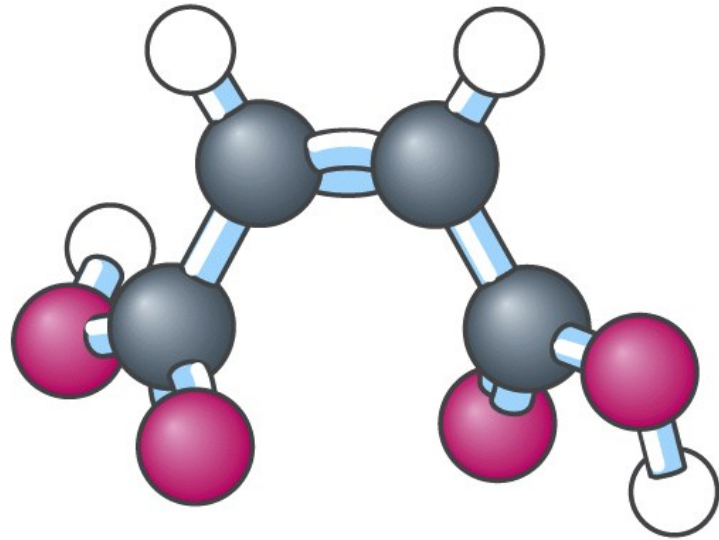
Ethylene
(C_2H_4)



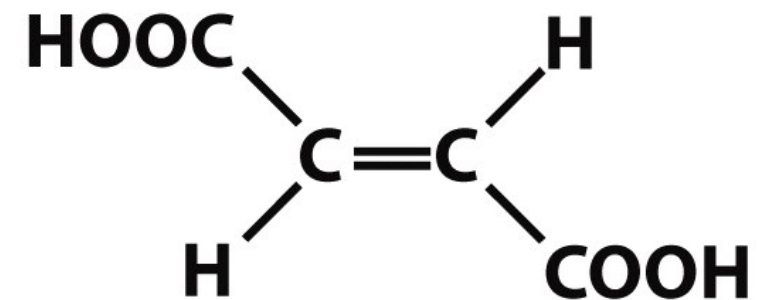
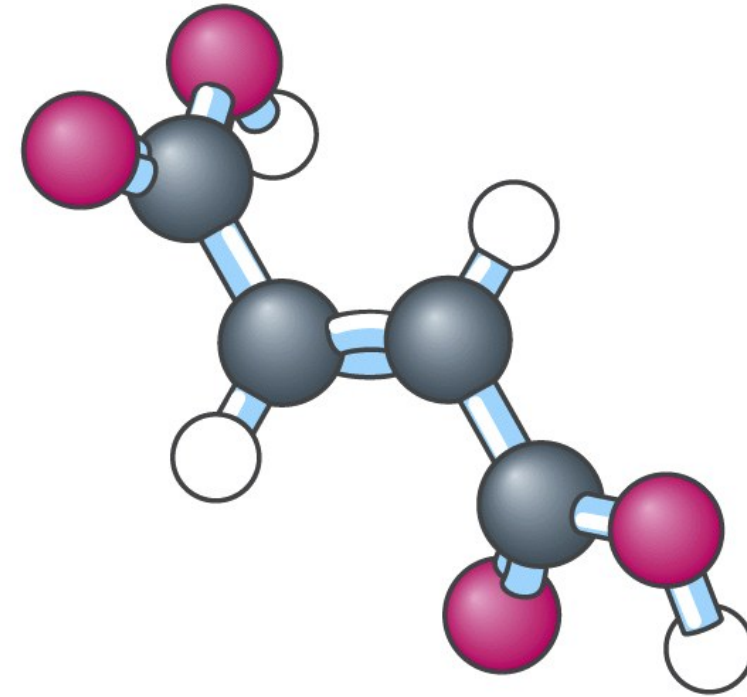
Bond	Length (Å)	Bond strength (kcal/mol)	ΔEN
C—H	1.09	99	0.4
O—H	0.96	110	1.4
N—H	1.02	84	0.9
C=O	1.23	174	1
C—C	1.54	88	0
C=C	1.34	147	0

Créditos: HarvardX

Ácido malêico e ácido fumárico possuem a mesma composição, mas diferentes estruturas



Maleic acid (cis)

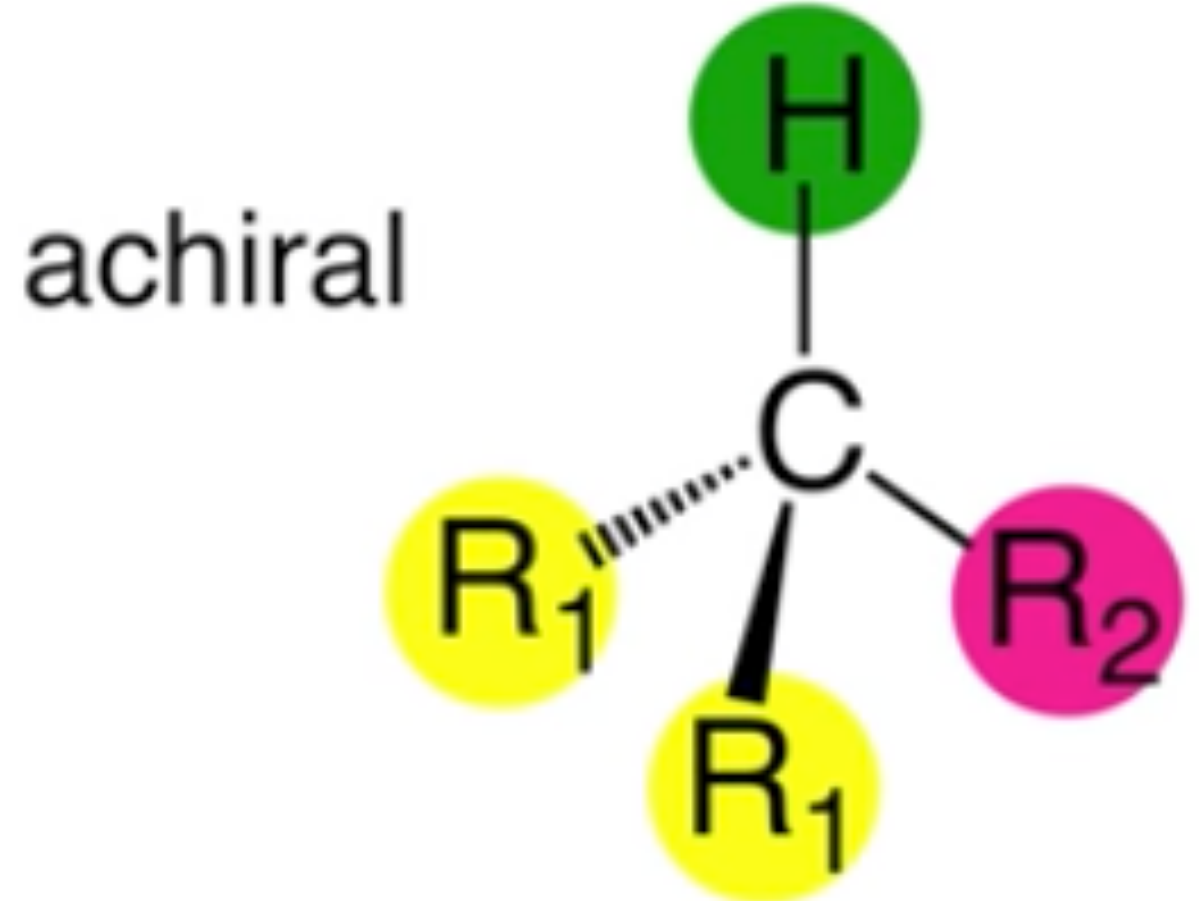
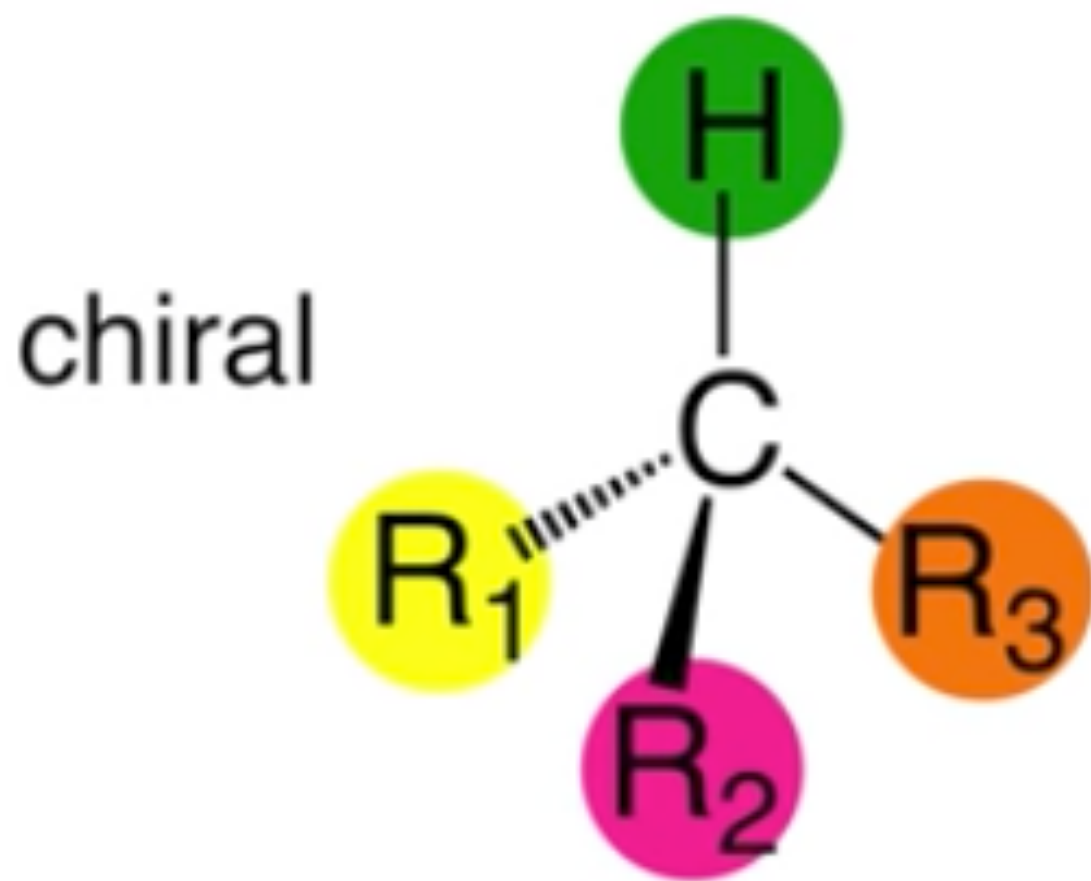


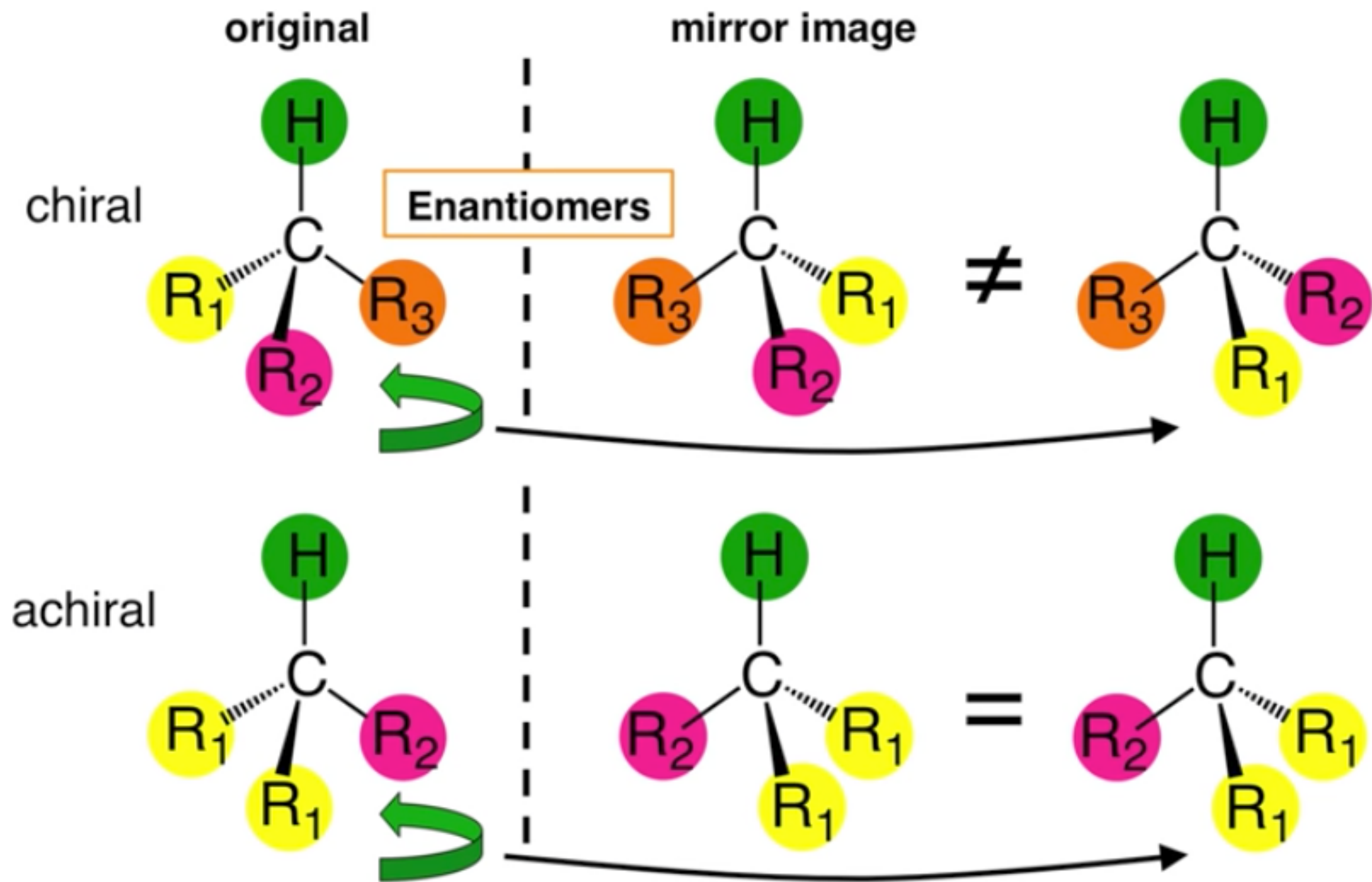
Fumaric acid (trans)

Figure 1-18a
Lehninger Principles of Biochemistry, Fifth Edition
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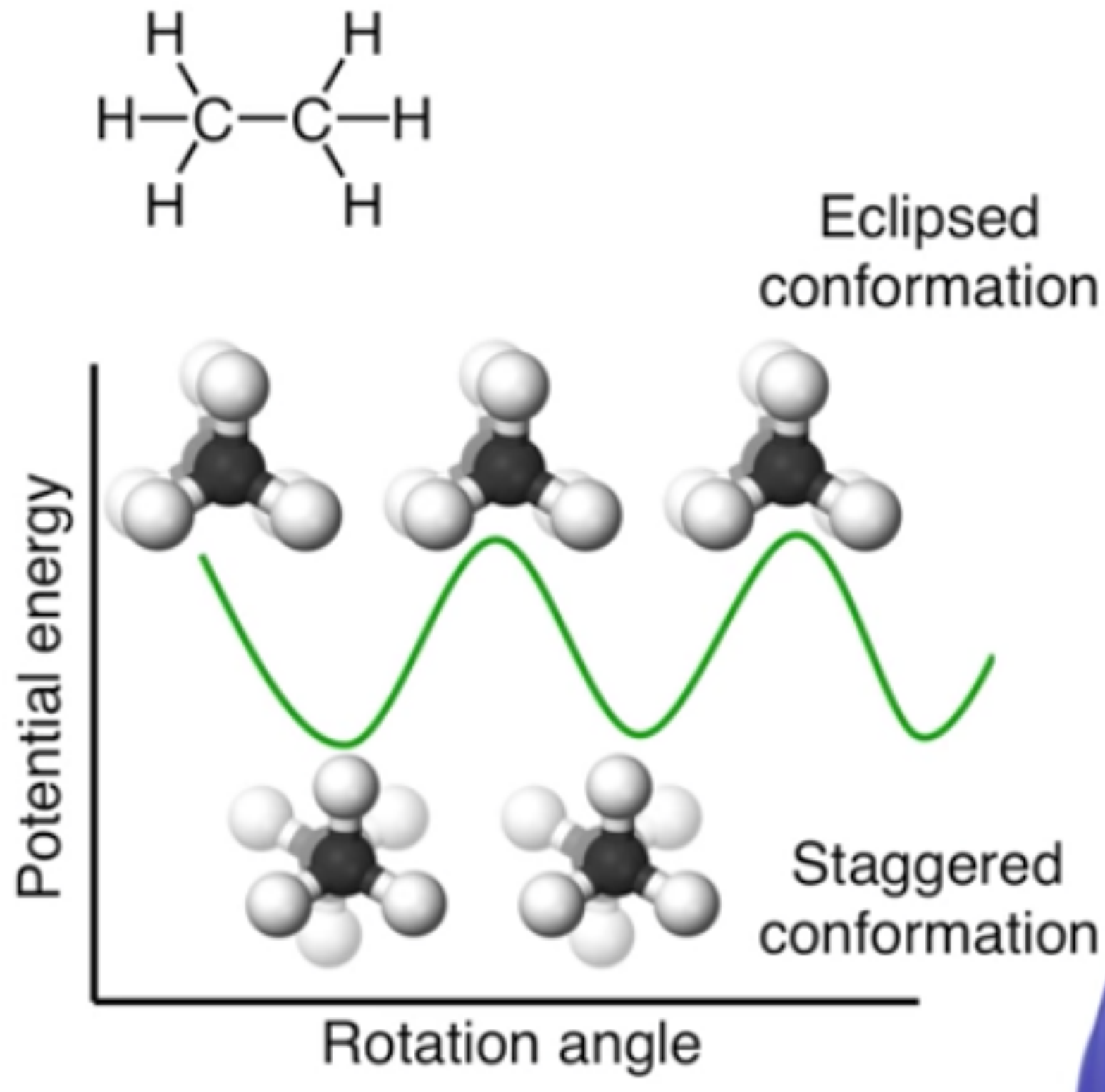
A ligação dupla impede rotação ao redor do eixo C-C
Configuração diferente Estereoisômeros

Moléculas com a mesma composição, mas com um centro quiral, também existem em configurações diferentes

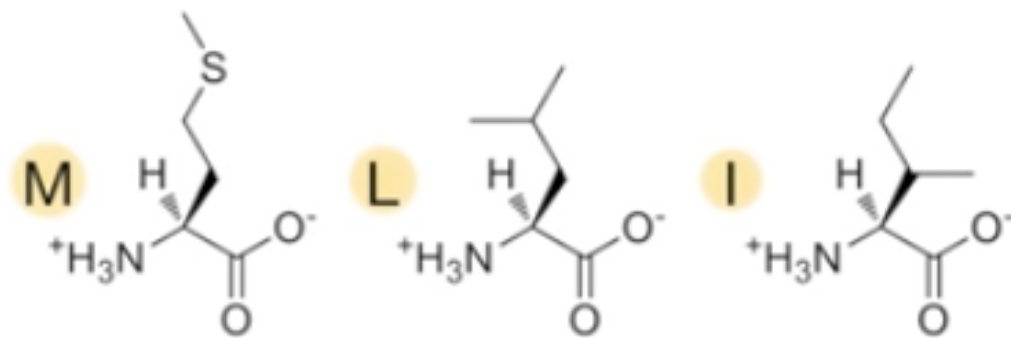
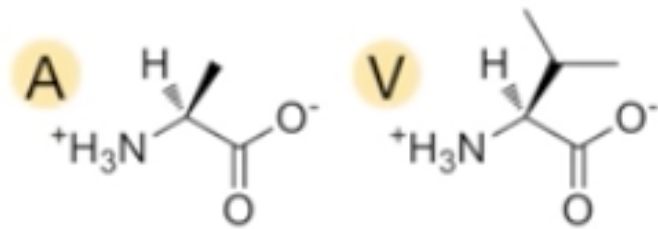




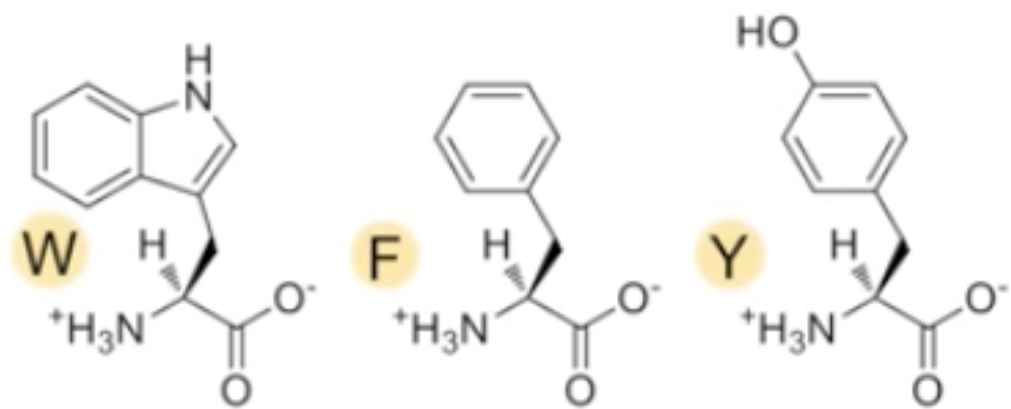
Moléculas podem assumir diferentes estruturas a partir de rotações ao redor de ligações simples: conformação



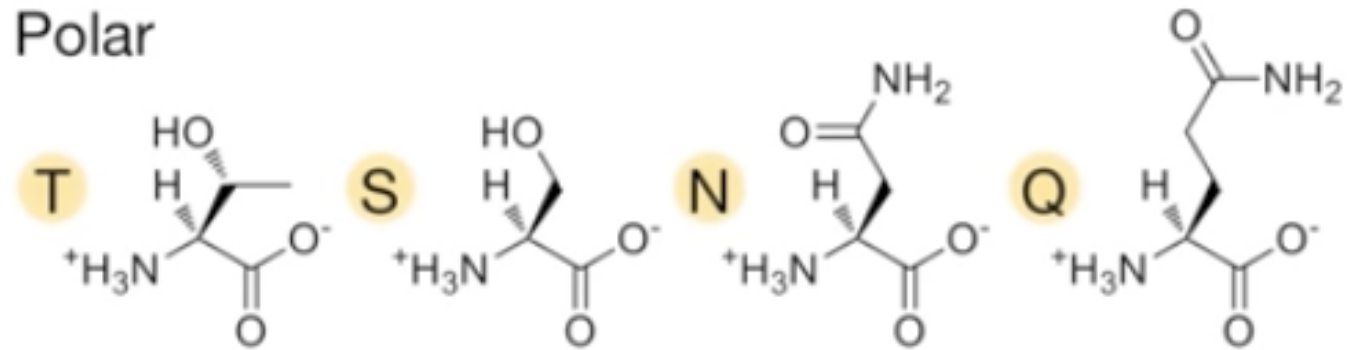
Aliphatic



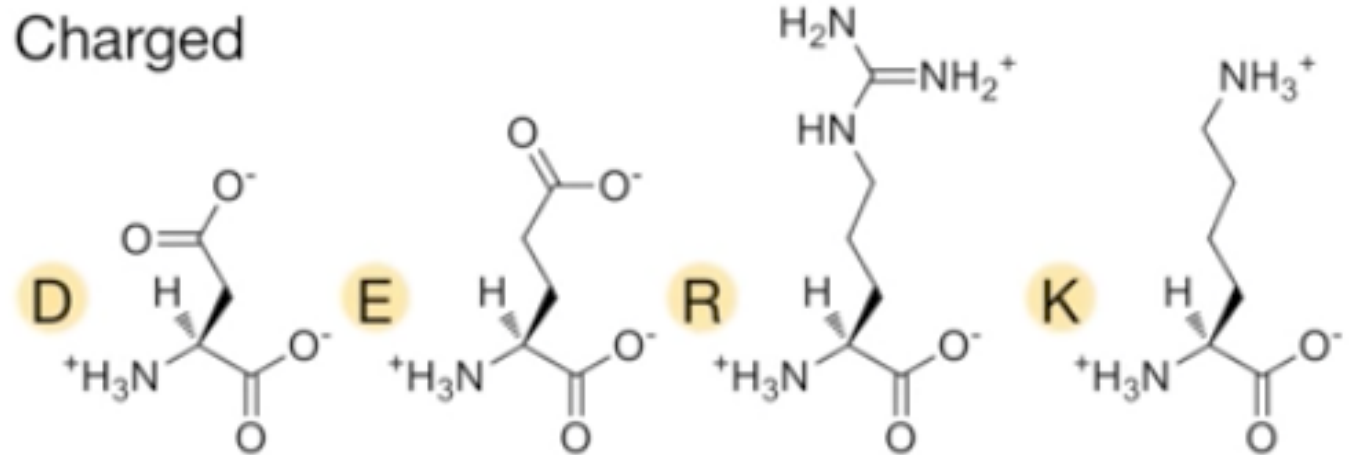
Aromatic



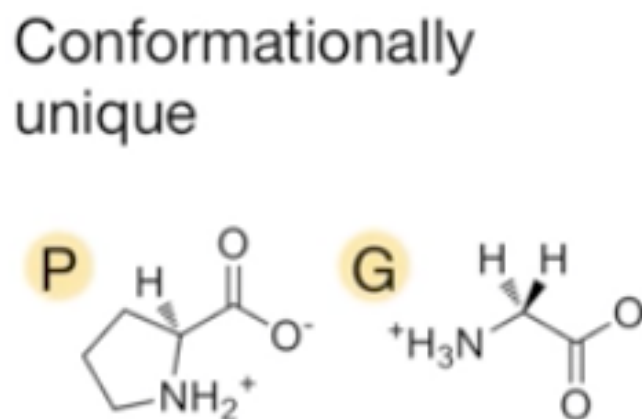
Polar



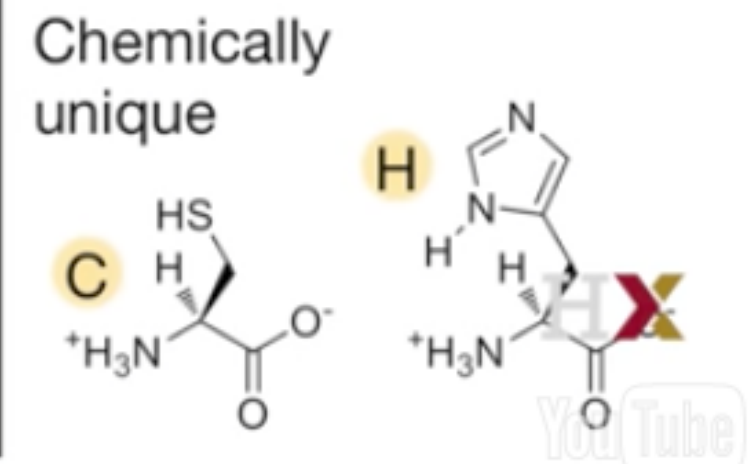
Charged

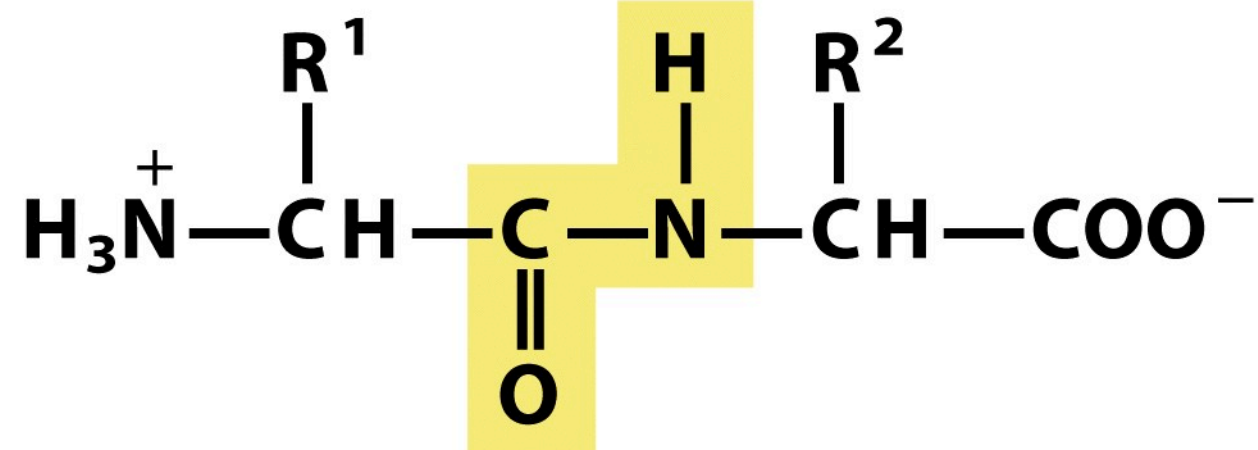
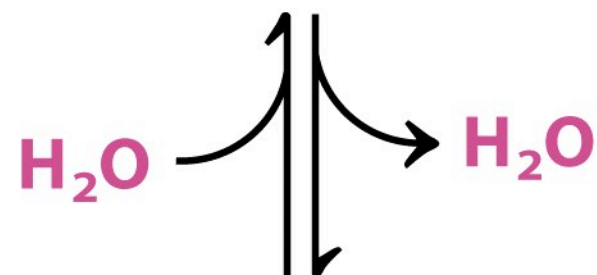
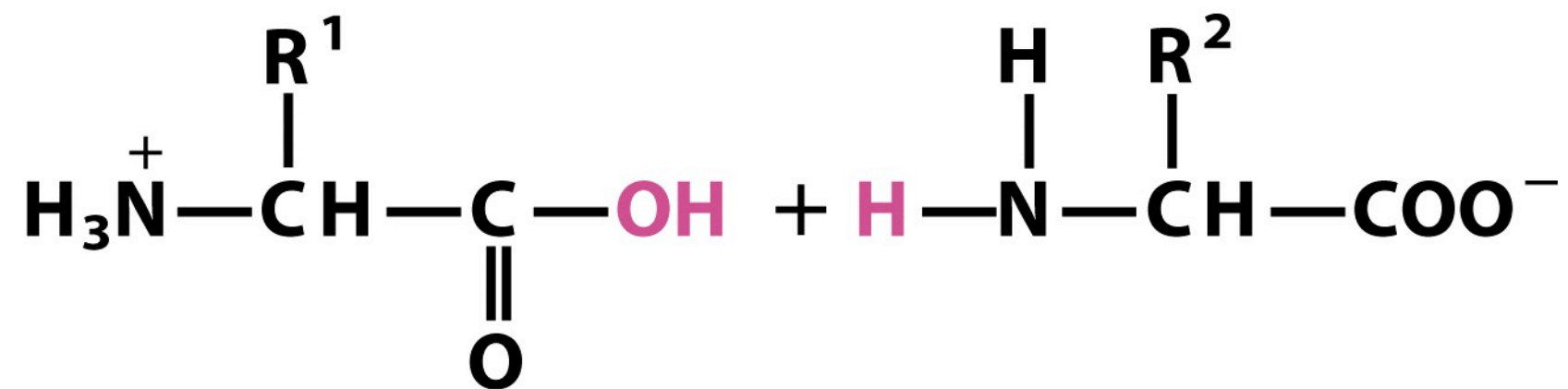


Conformationally unique

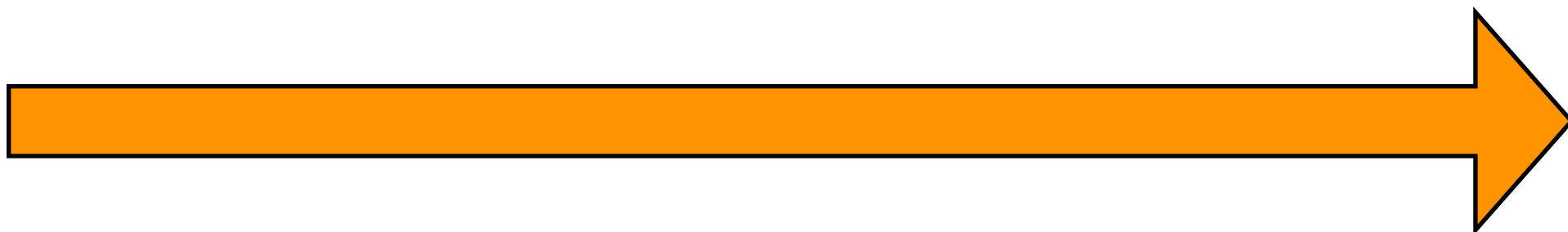
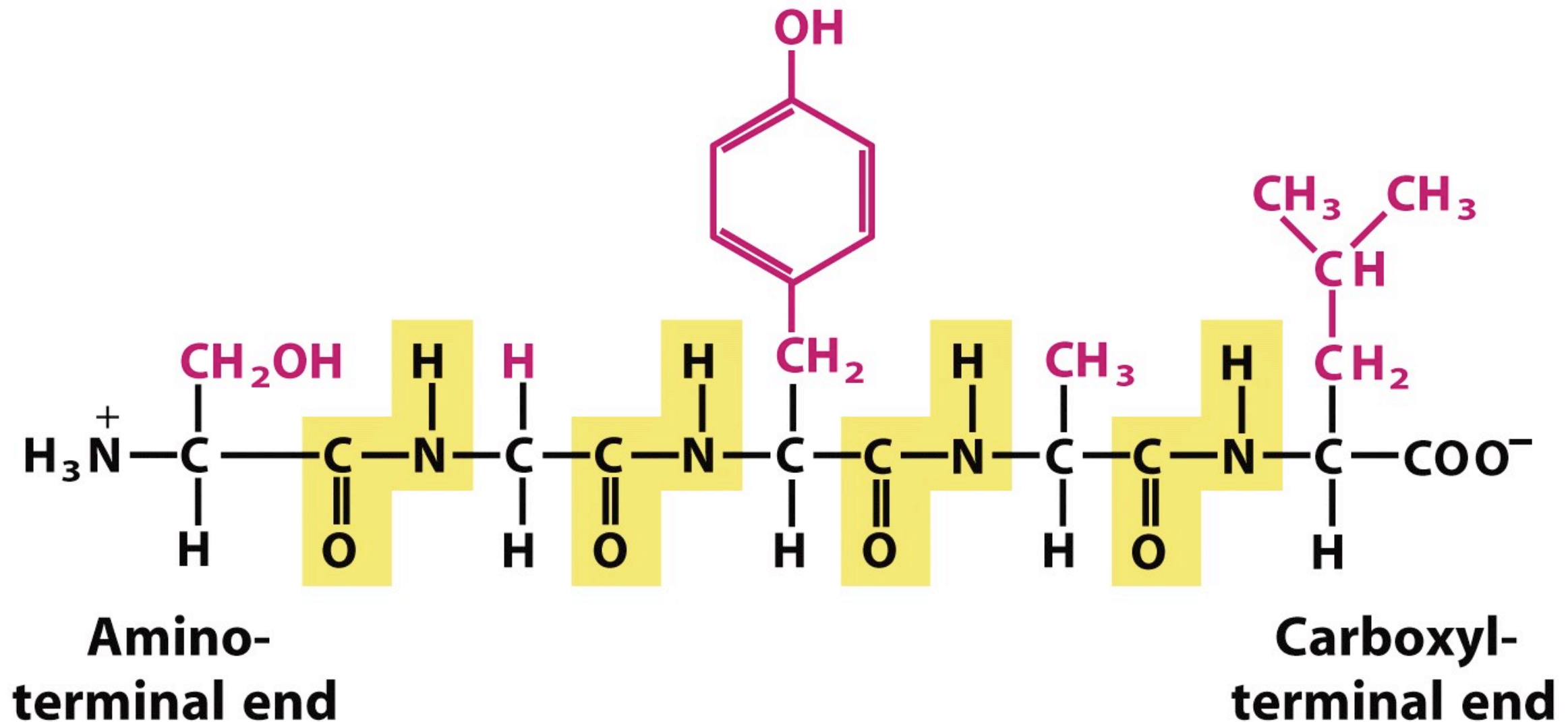


Chemically unique





Estrutura primária é a sequência de aminoácidos da proteína:



Polaridade: da extremidade NH_3^+ -terminal à extremidade COO^- -terminal

Pauling e Corey analisaram dados de difração de raios-X de peptídeos para propor modelos conformacionais para o esqueleto polipeptídico

VOL. 37, 1951

CHEMISTRY: PAULING AND COREY

251

THE PLEATED SHEET, A NEW LAYER CONFIGURATION OF POLYPEPTIDE CHAINS

BY LINUS PAULING AND ROBERT B. COREY

GATES AND CRELLIN LABORATORIES OF CHEMISTRY,* CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, CALIFORNIA

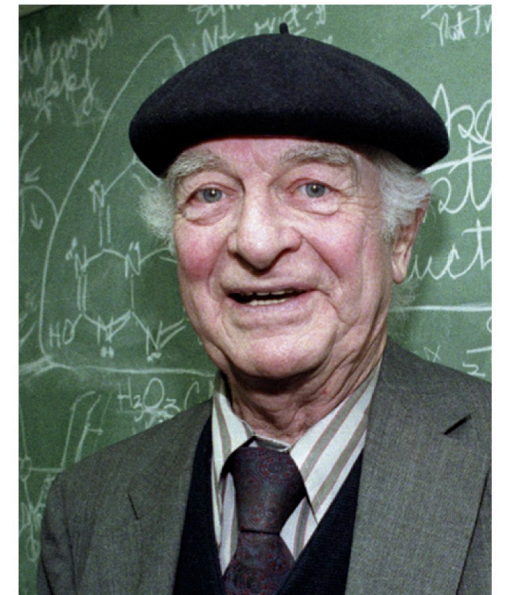
Communicated March 31, 1951

THE STRUCTURE OF PROTEINS: TWO HYDROGEN-BONDED HELICAL CONFIGURATIONS OF THE POLYPEPTIDE CHAIN

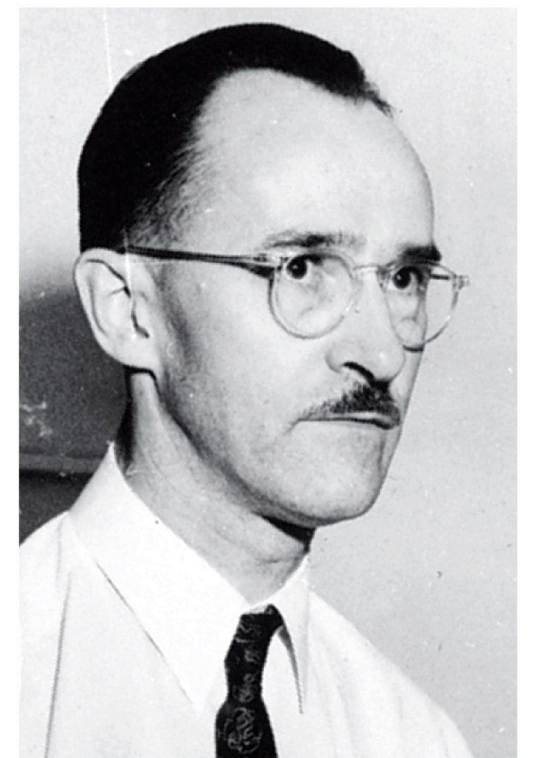
BY LINUS PAULING, ROBERT B. COREY, AND H. R. BRANSON*

GATES AND CRELLIN LABORATORIES OF CHEMISTRY,
CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, CALIFORNIA†

Communicated February 28, 1951

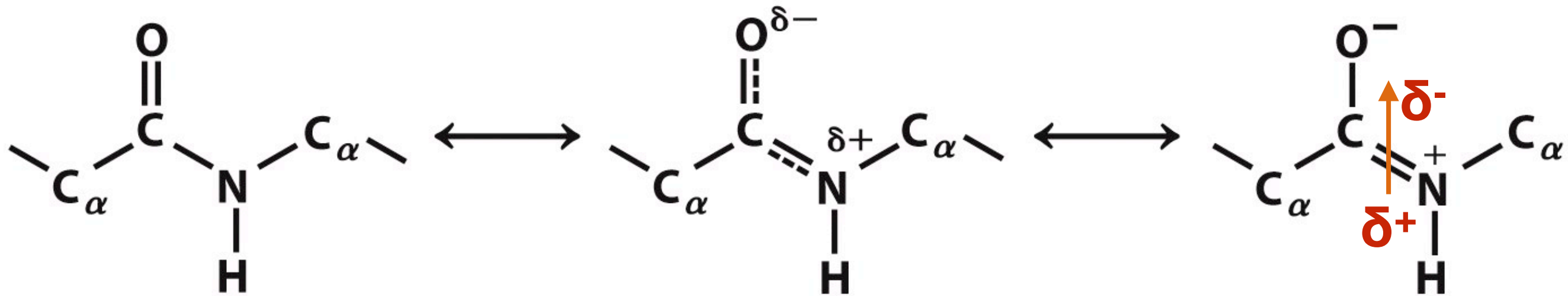


Linus Pauling, 1901–1994



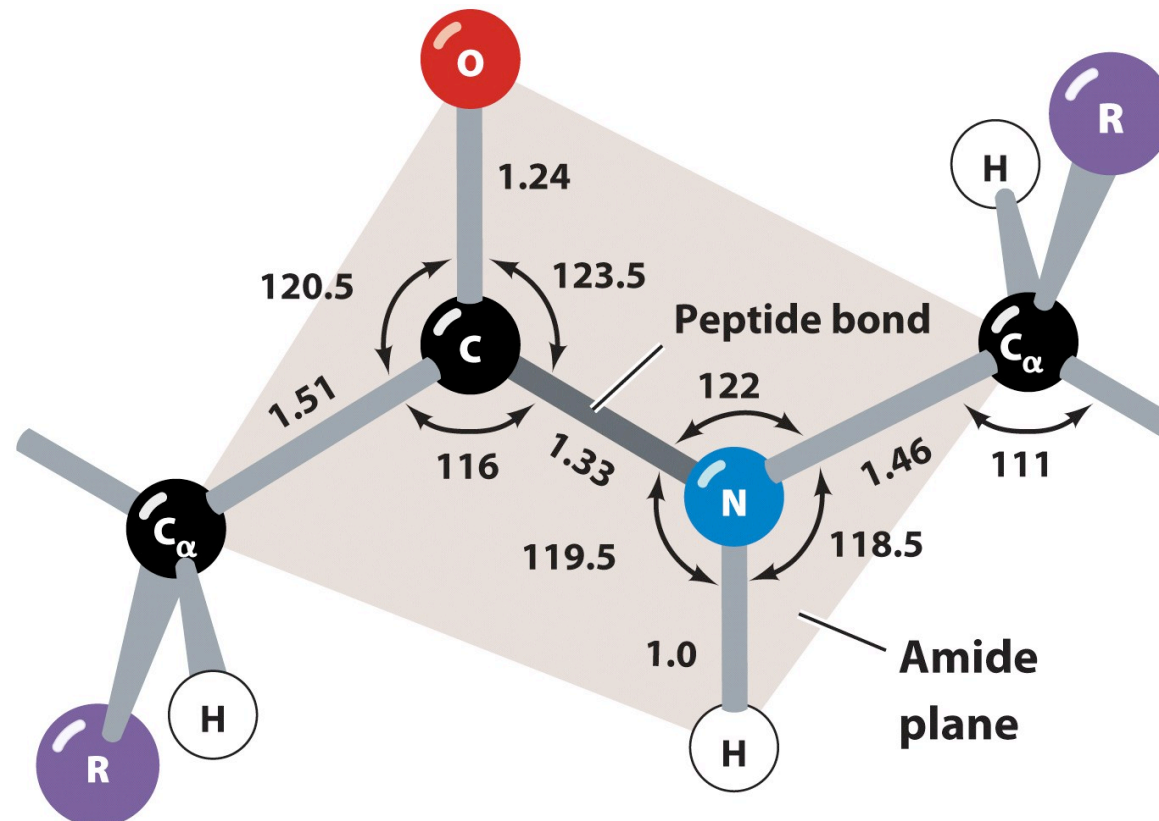
Robert Corey, 1897–1971

A ligação peptídica é rígida

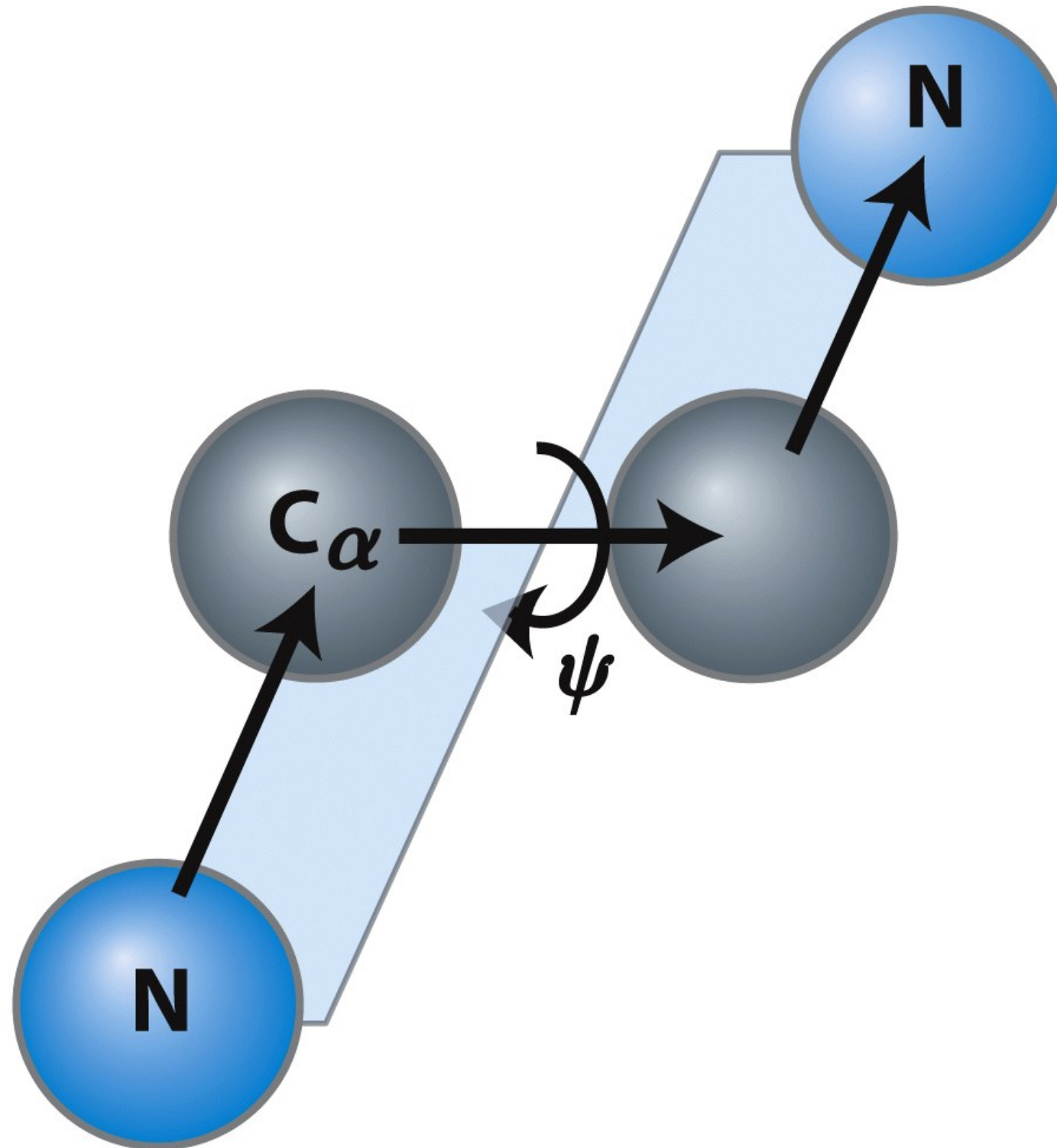


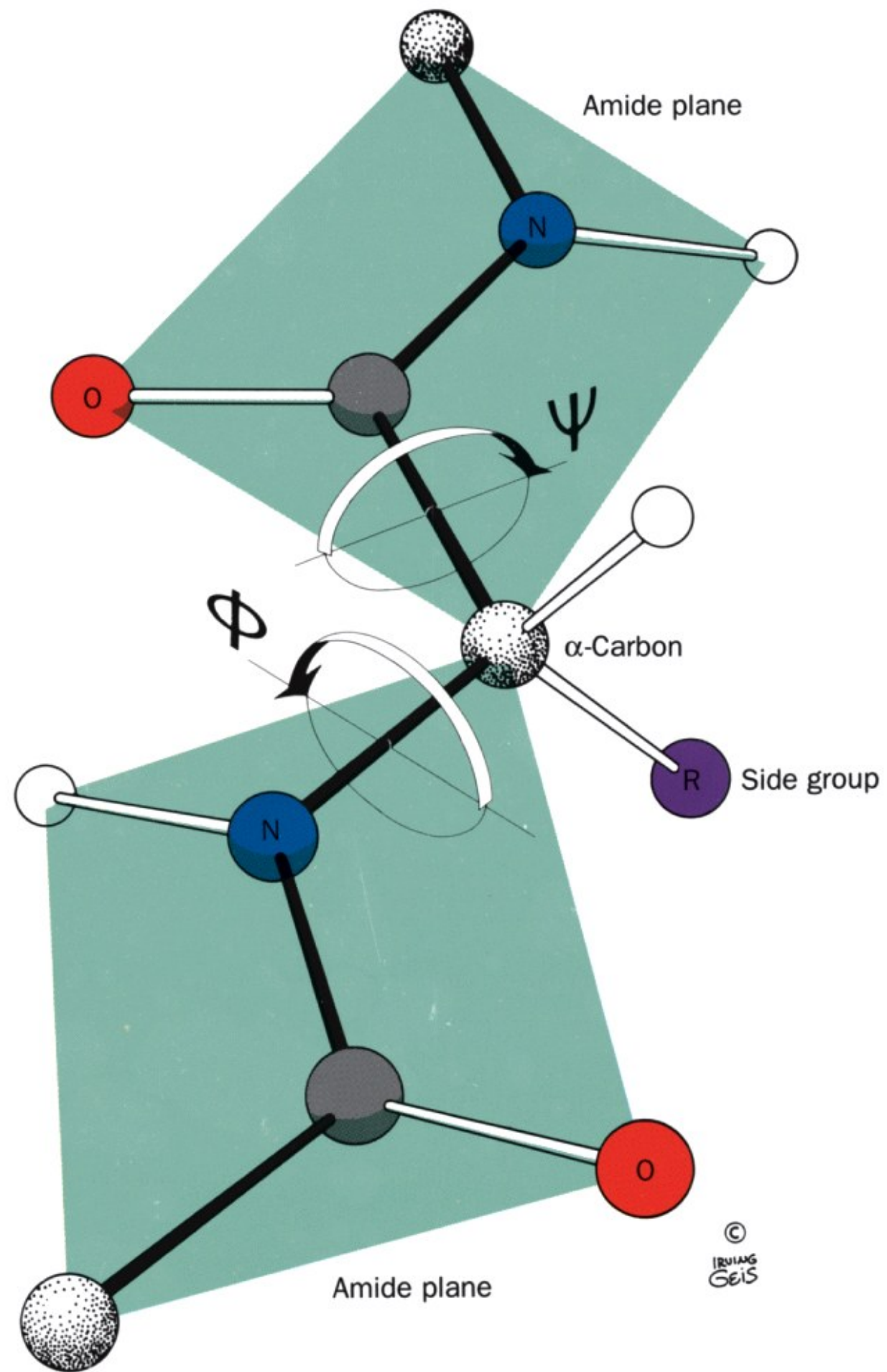
Obs.: Note o dipolo elétrico da ligação peptídica

...e planar

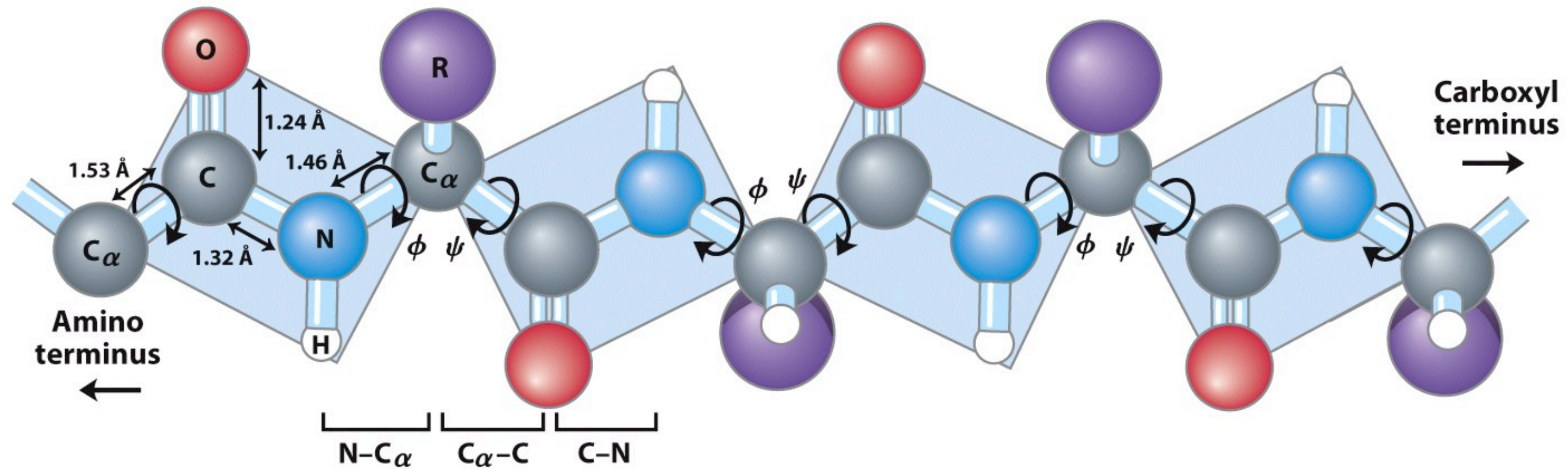


Ângulo diedral

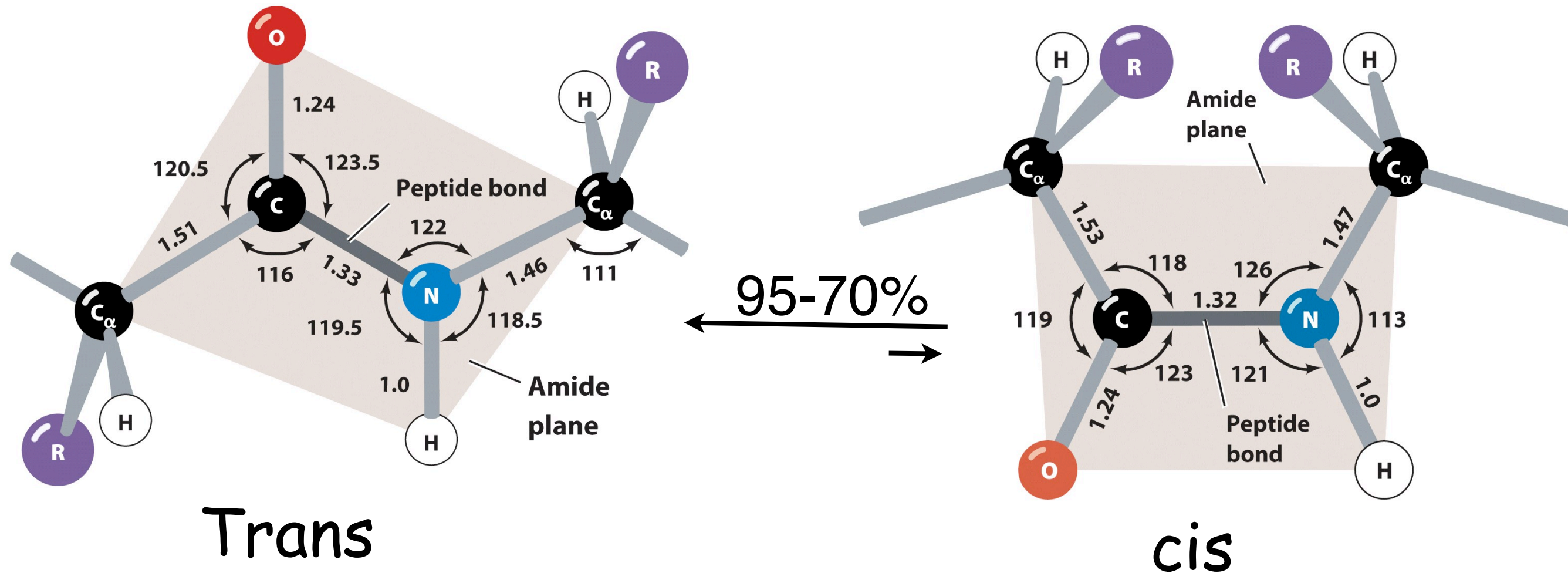




A conformação do esqueleto polipeptídico é descrita por três ângulos: ϕ , ψ , e ω

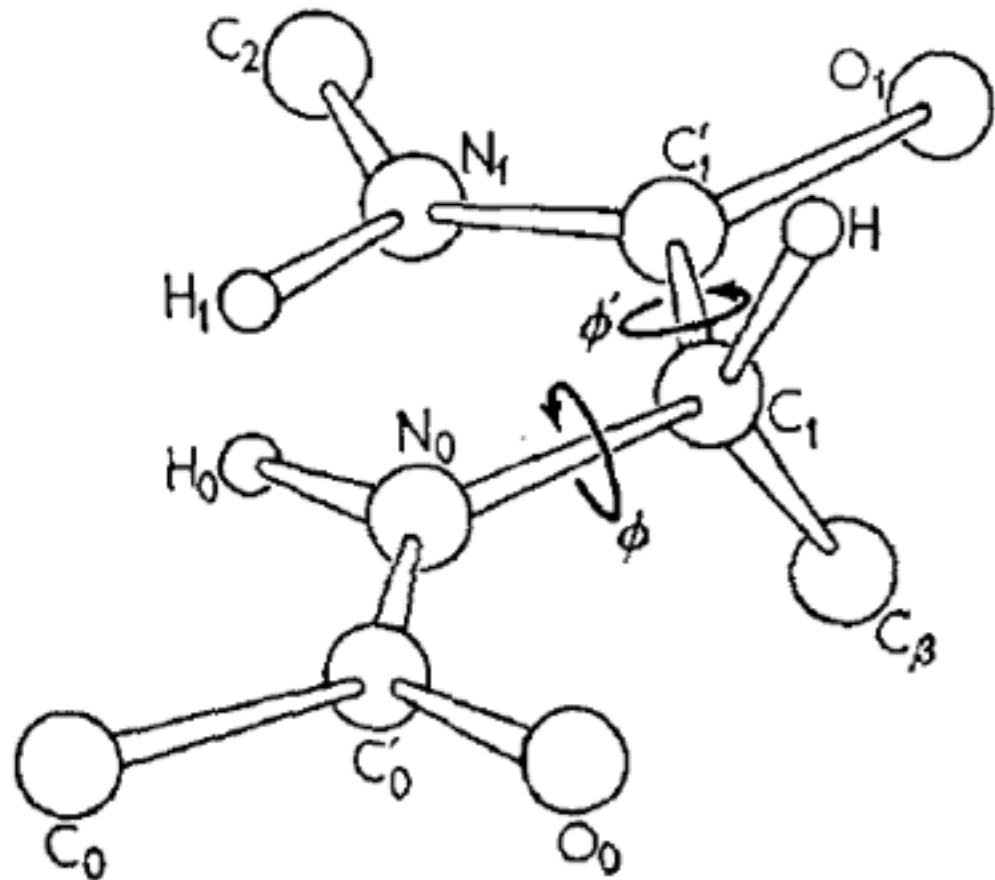


A ligação peptídica sempre assume conformação *trans* ($\omega=180^\circ$). Prolinas podem, eventualmente, assumir conformação *cis* ($\omega = 0^\circ$)

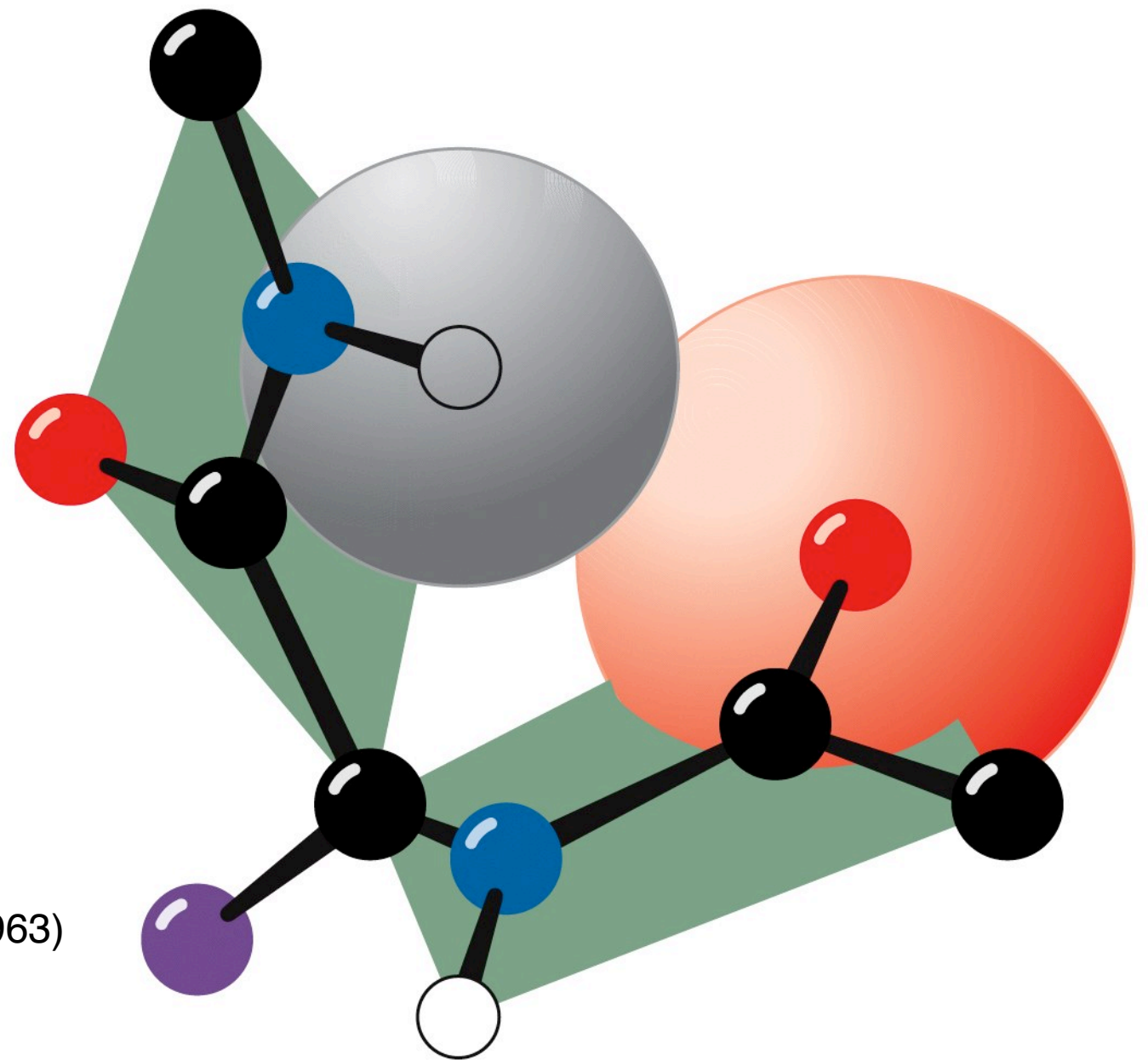


A lenta isomerização *cis-trans* das prolinas retarda o enovelamento de proteínas

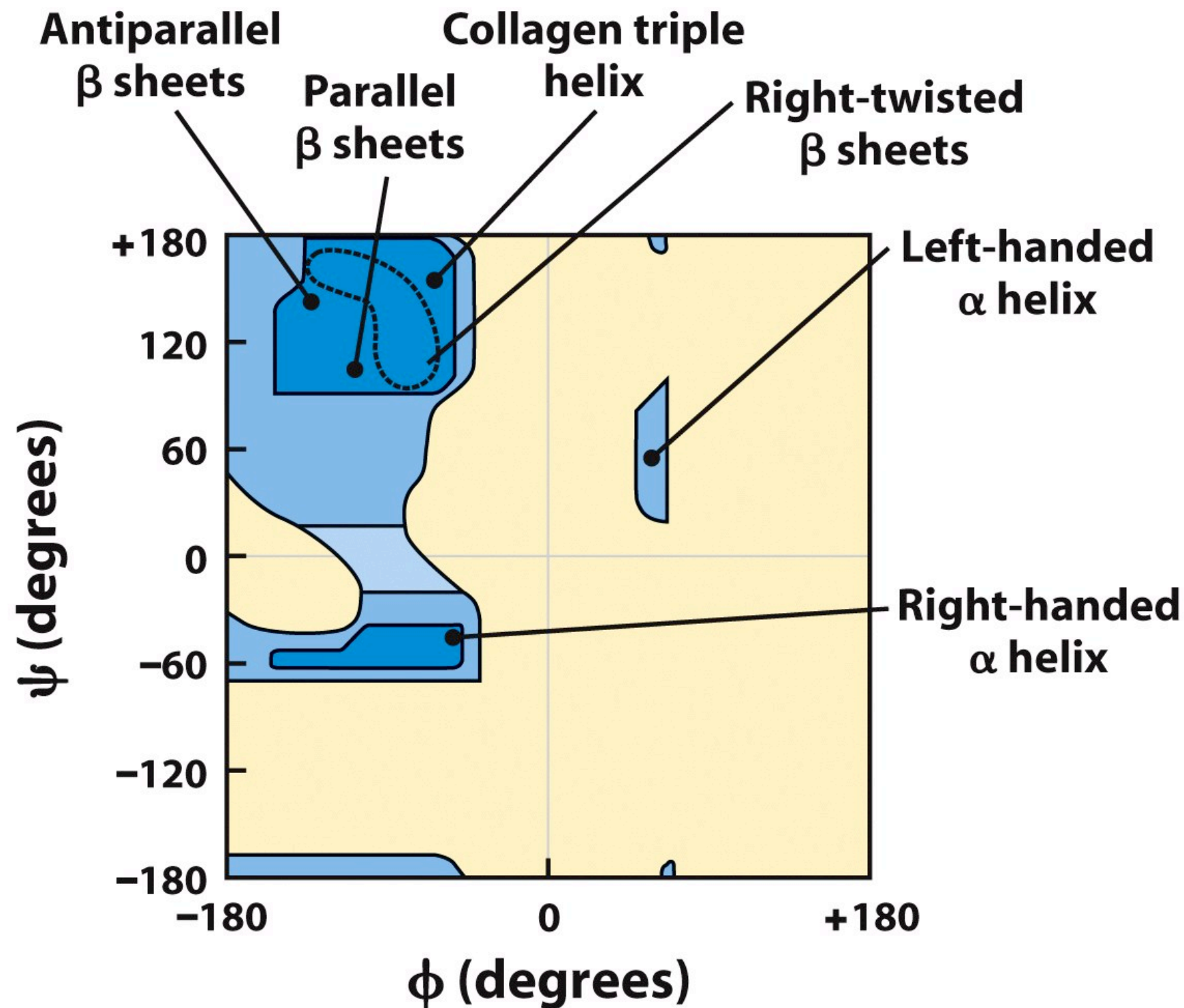
Gráfico de Ramachandran: nem todas as combinações de ϕ e ψ são permitidas



Stereochemistry of polypeptide chain configurations (1963)
J. Mol. Biol. 7, 95-99



Estruturas secundárias possuem valores ϕ e ψ muito bem definidos



Glicina permite conformações pouco usuais

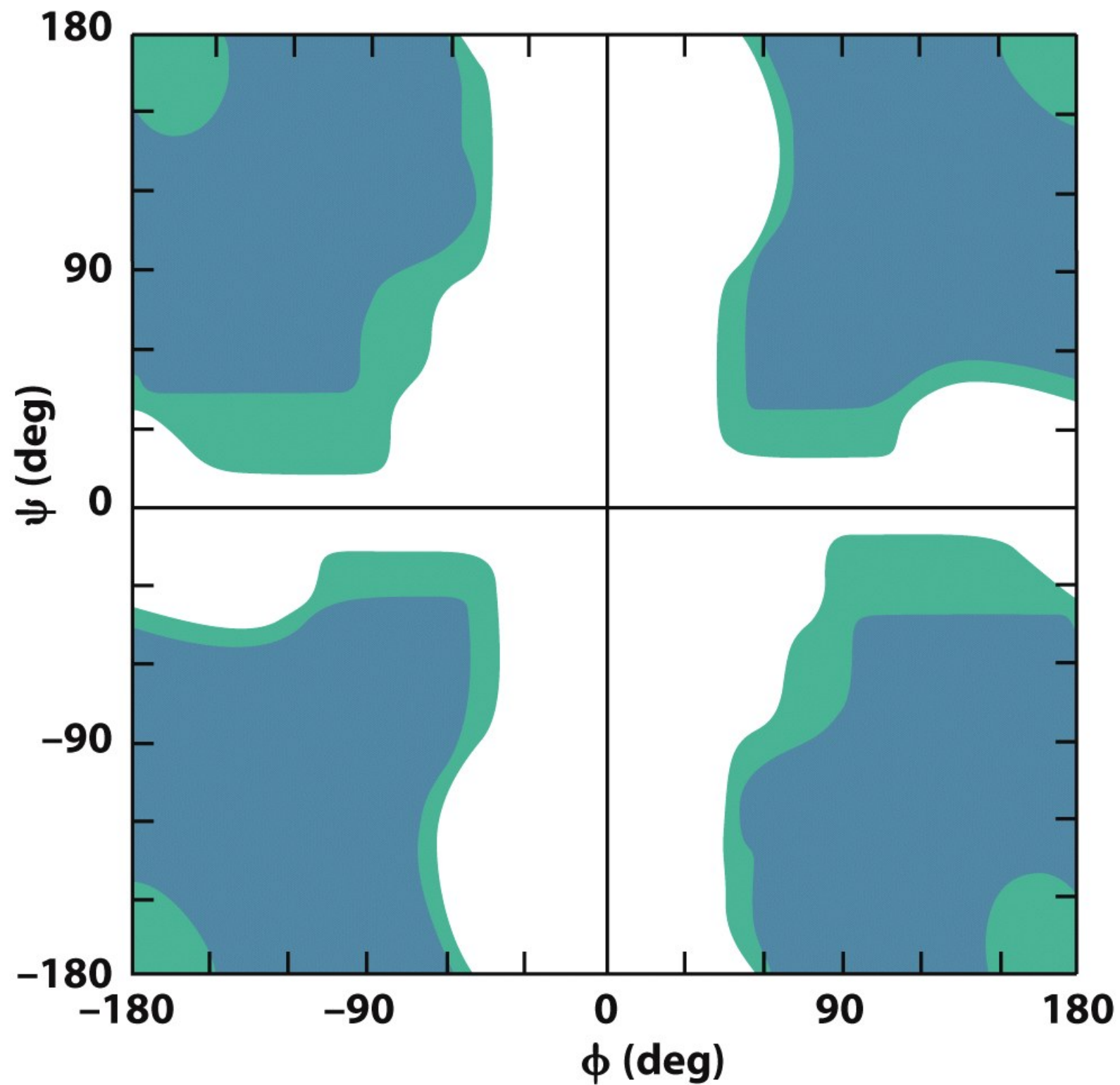
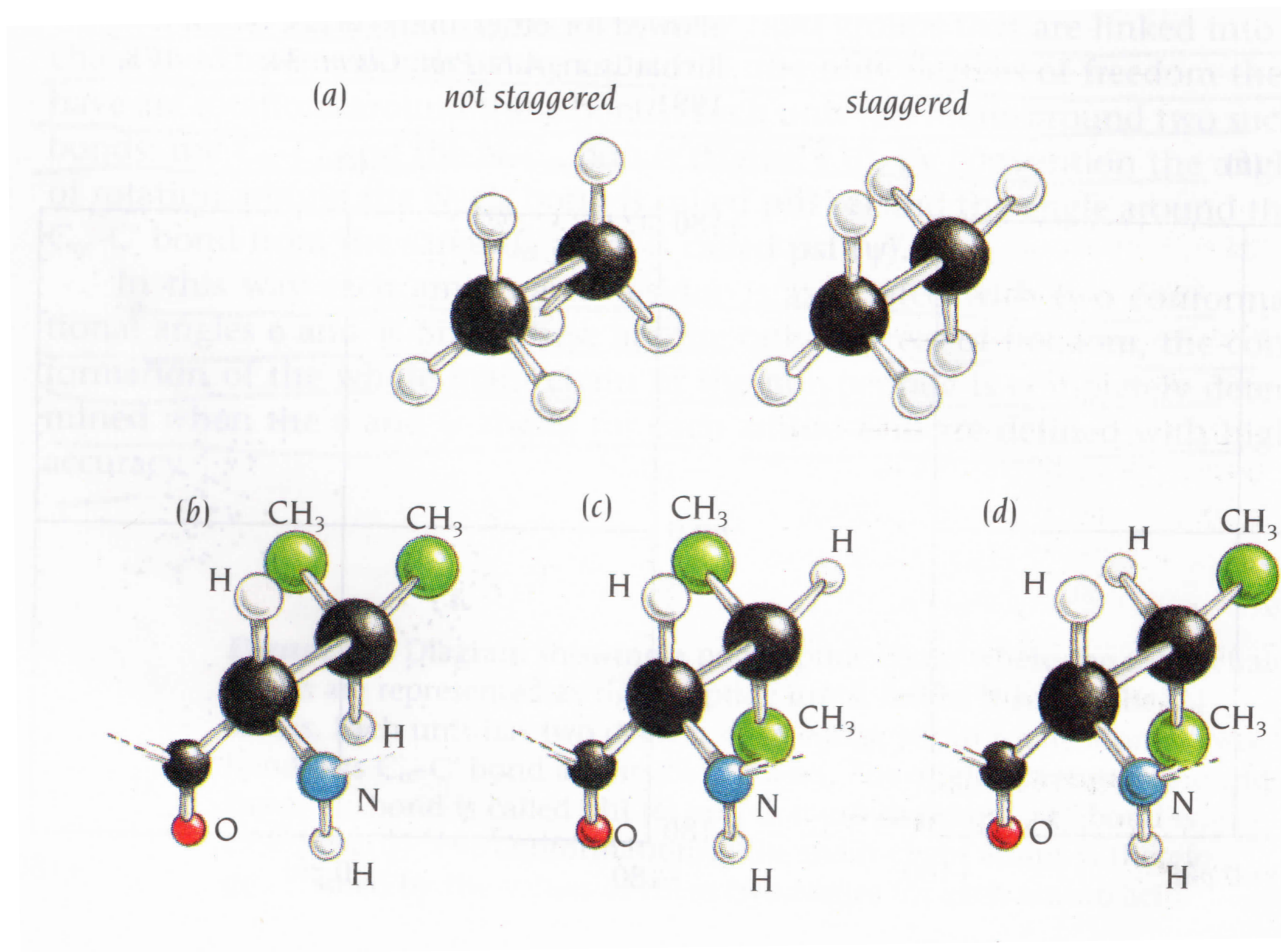
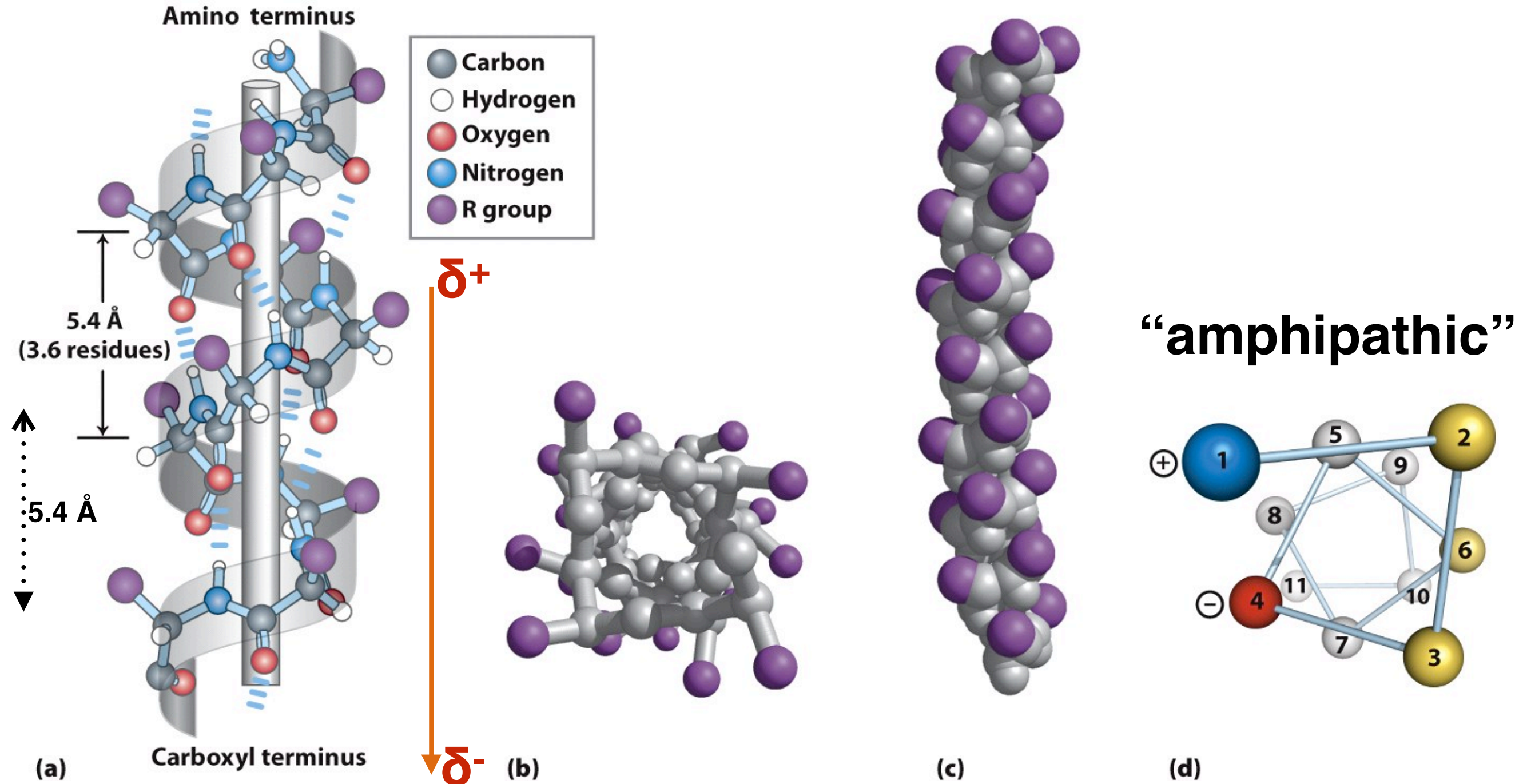


Figure 8-9
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Nem todas as conformações das cadeias laterais são igualmente prováveis



α -hélice



Ligações de hidrogênio entre $\text{HN}_{(i+4)}$ e $\text{CO}_{(i)}$ estabilizam a hélice
Os primeiros 4 e os últimos 4 amino ácidos não formam ligações de hidrogênio (“helix fraying”)

Alguns aminoácidos estabilizam hélices, enquanto que outros destabilizam

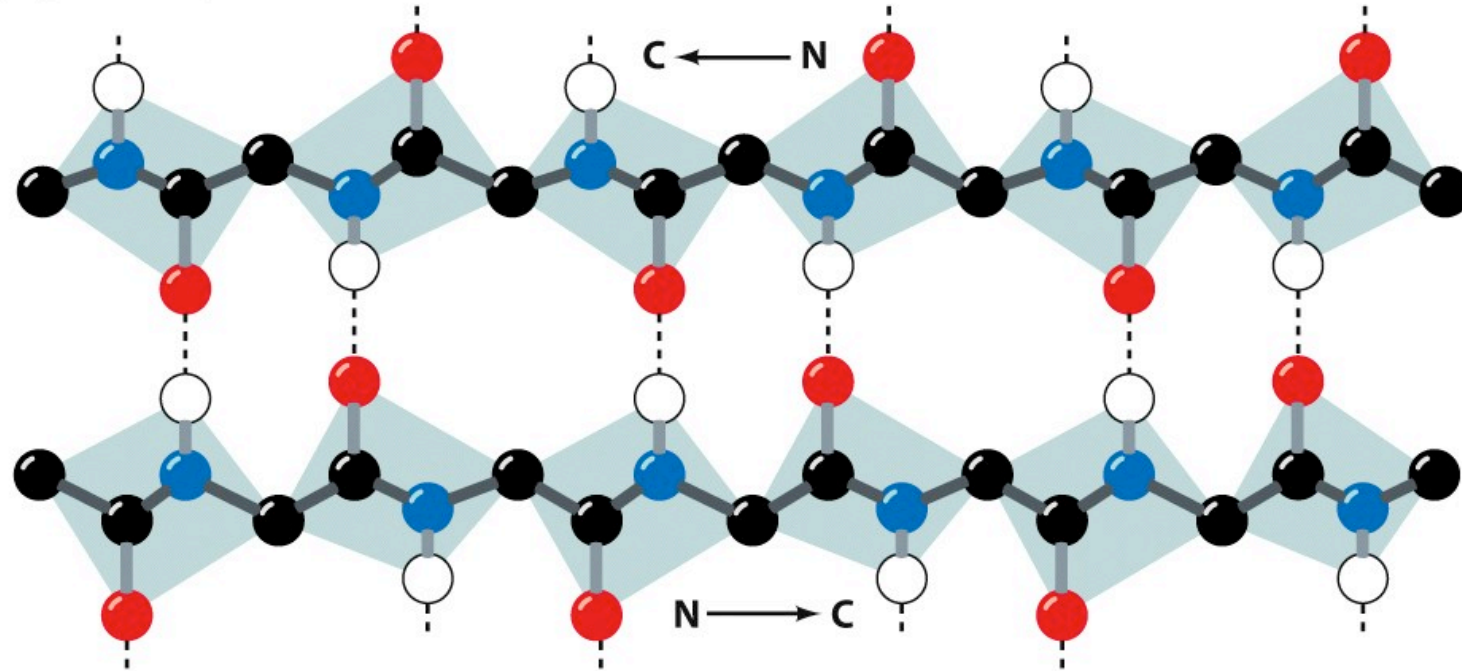
TABLE 4–1		Propensity of Amino Acids to Take Up an α -Helical Conformation	
Amino acid	$\Delta\Delta G^\circ$ (kJ/mol)*	Amino acid	$\Delta\Delta G^\circ$ (kJ/mol)*
Ala	0	Leu	0.79
Arg	0.3	Lys	0.63
Asn	3	Met	0.88
Asp	2.5	Phe	2.0
Cys	3	Pro	>4
Gln	1.3	Ser	2.2
Glu	1.4	Thr	2.4
Gly	4.6	Tyr	2.0
His	2.6	Trp	2.0
Ile	1.4	Val	2.1

Sources: Data (except proline) from Bryson, J.W., Betz, S.F., Lu, H.S., Suich, D.J., Zhou, H.X., O'Neil, K.T., & DeGrado, W.F. (1995) Protein design: a hierarchic approach. *Science* 270, 935. Proline data from Myers, J.K., Pace, C.N., & Scholtz, J.M. (1997) Helix propensities are identical in proteins and peptides. *Biochemistry* 36, 10,926.

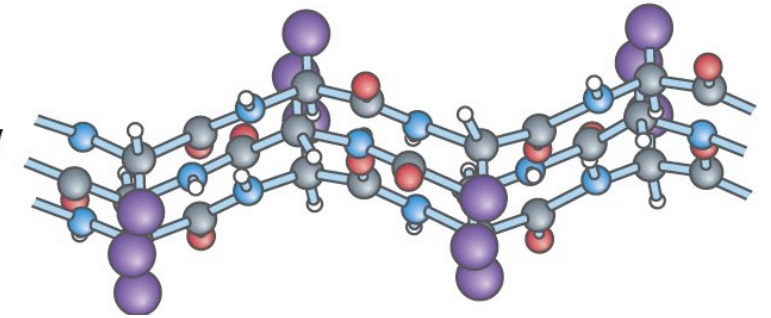
* $\Delta\Delta G^\circ$ is the difference in free-energy change, relative to that for alanine, required for the amino acid residue to take up the α -helical conformation. Larger numbers reflect greater difficulty taking up the α -helical structure. Data are a composite derived from multiple experiments and experimental systems.

Folha- β antiparalela e paralela

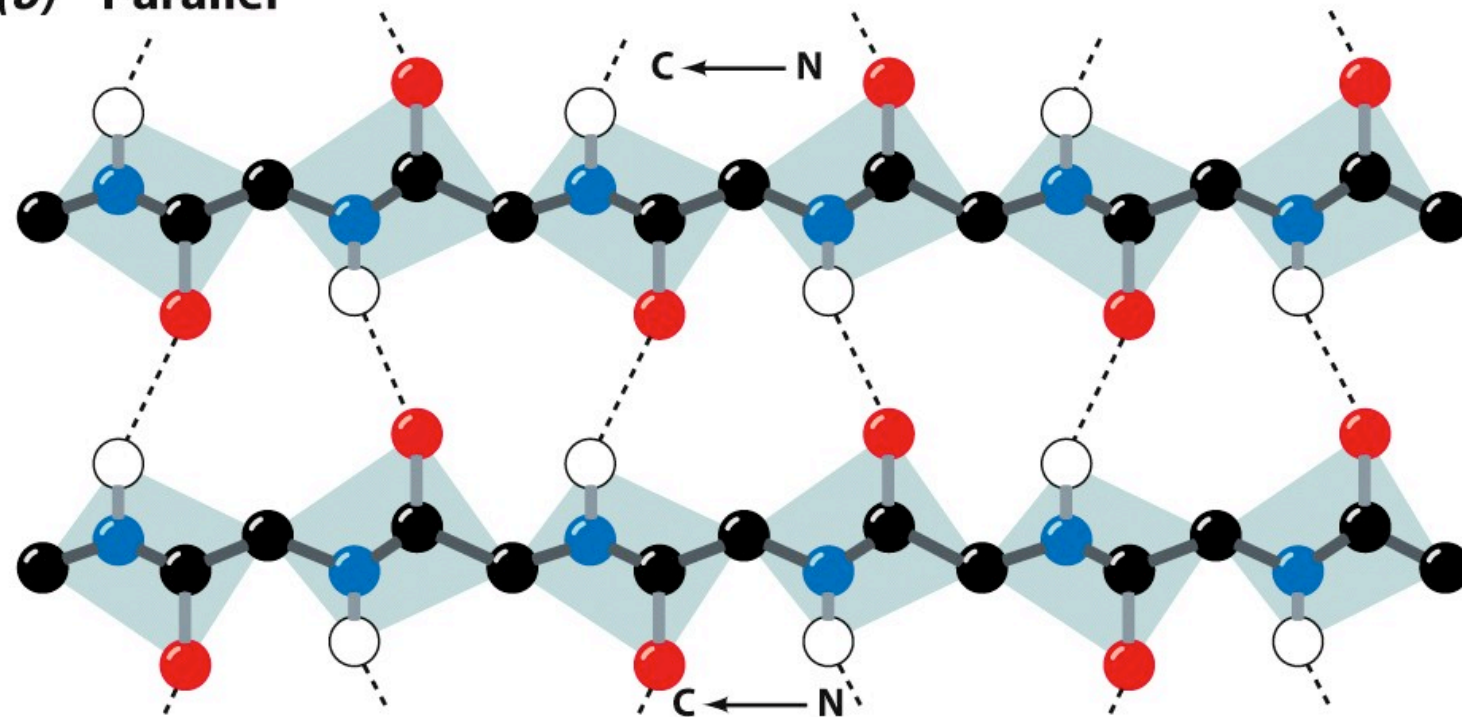
(a) Antiparallel



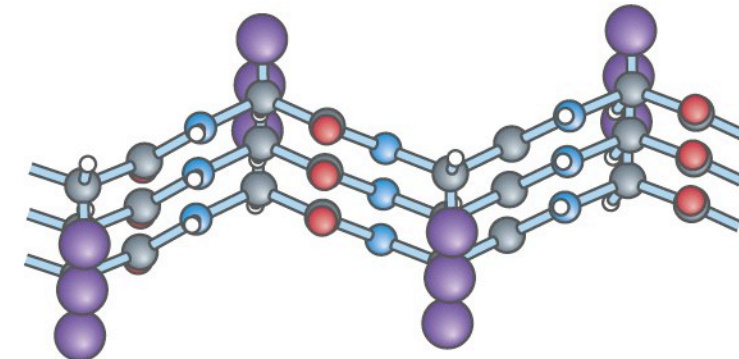
Side view



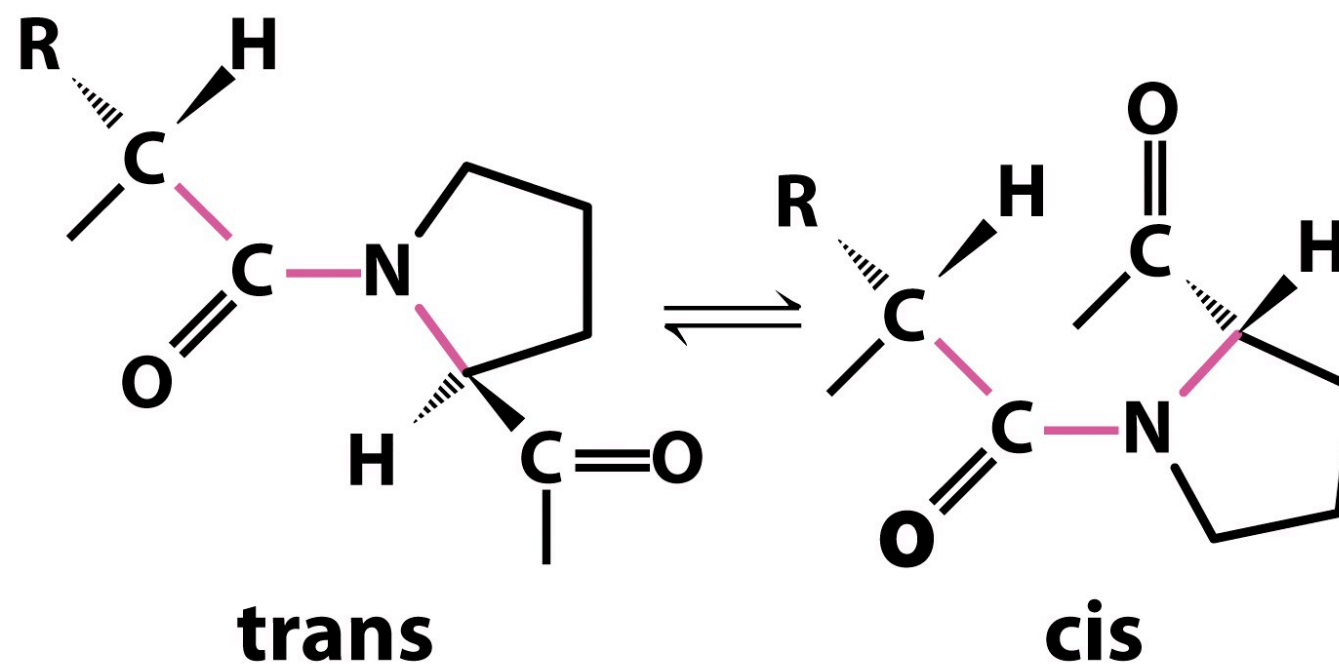
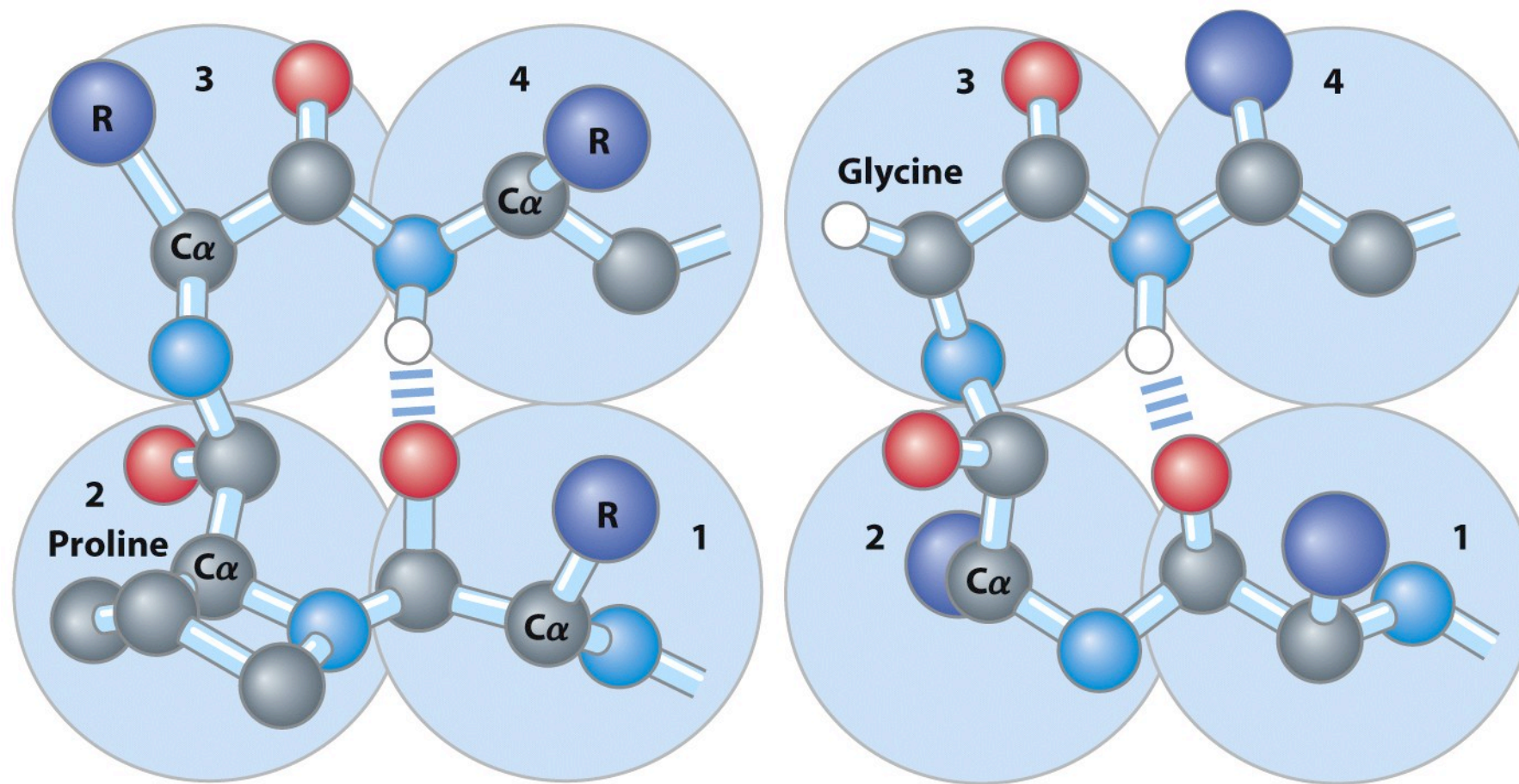
(b) Parallel



Side view



Dobras- β



Torsion angles for regular polypeptide conformations

Estrutura	ϕ	ψ
Hypothetically fully extended	+180°	+180°
Antiparallel β -sheet	-139°	+135°
Parallel β -sheet	-119°	+113°
Right-handed α -helix	-57°	-47°
Left-handed α -helix	+60°	+60°
3_{10} helix	-49°	-26°

Representação esquemática de estrutura secundária

Computer-Generated Schematic Diagrams of Protein Structures

Abstract. Computer-generated pictures are essential for studying and comparing the structures of proteins that have been solved by x-ray crystallography. Stereoscopic pairs produced by a computer program are particularly useful in providing an intelligible portrayal of the molecular topology.

ARTHUR M. LESK*

*Fairleigh Dickinson University,
Teaneck, New Jersey 07666*

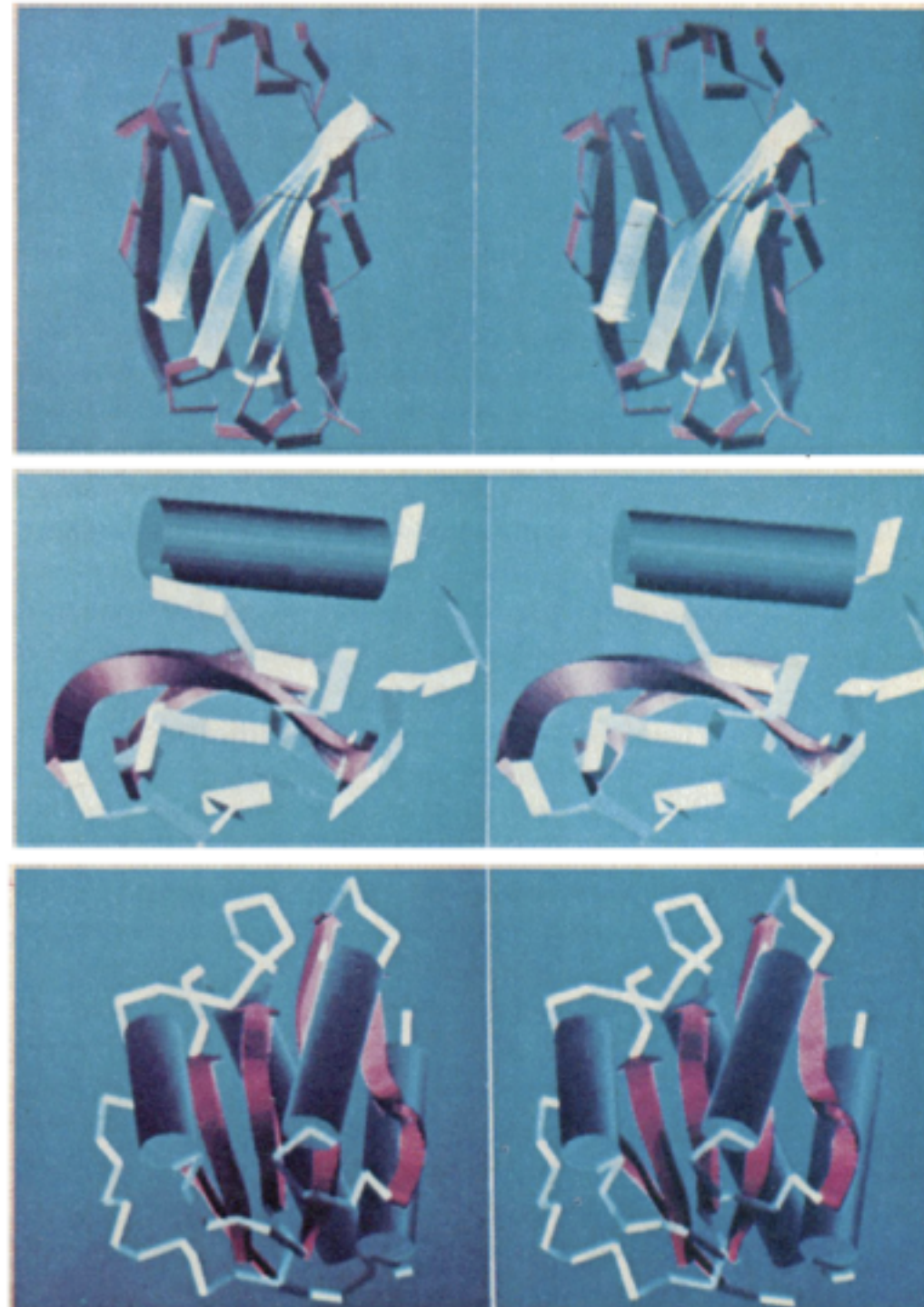
KARL D. HARDMANT†

*Thomas J. Watson Research Center,
IBM Corporation, P.O. Box 218,
Yorktown Heights, New York 10598*

SCIENCE, VOL. 216, 30 APRIL 1982



Arthur Lesk

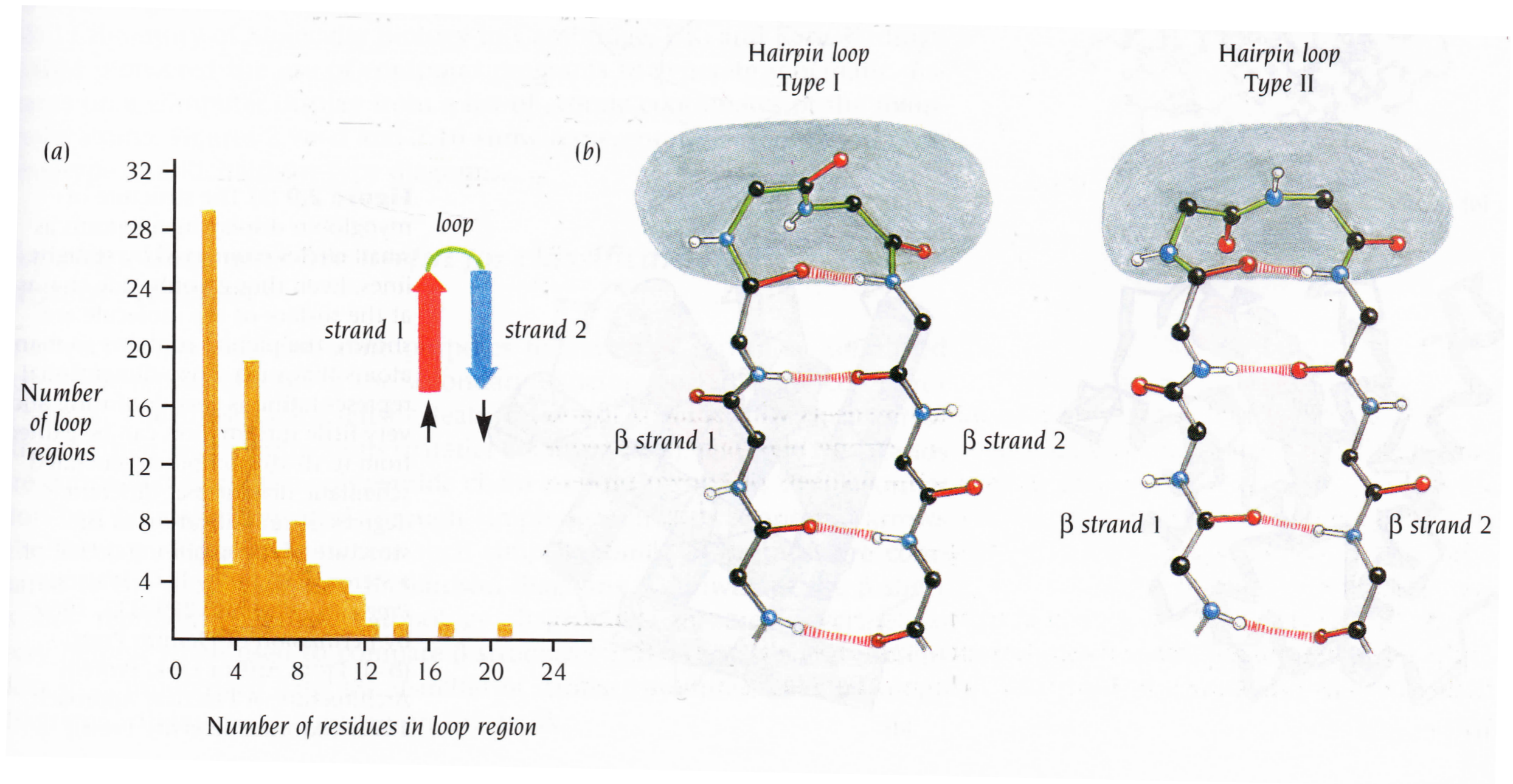


Visualização de uma alfa-hélice

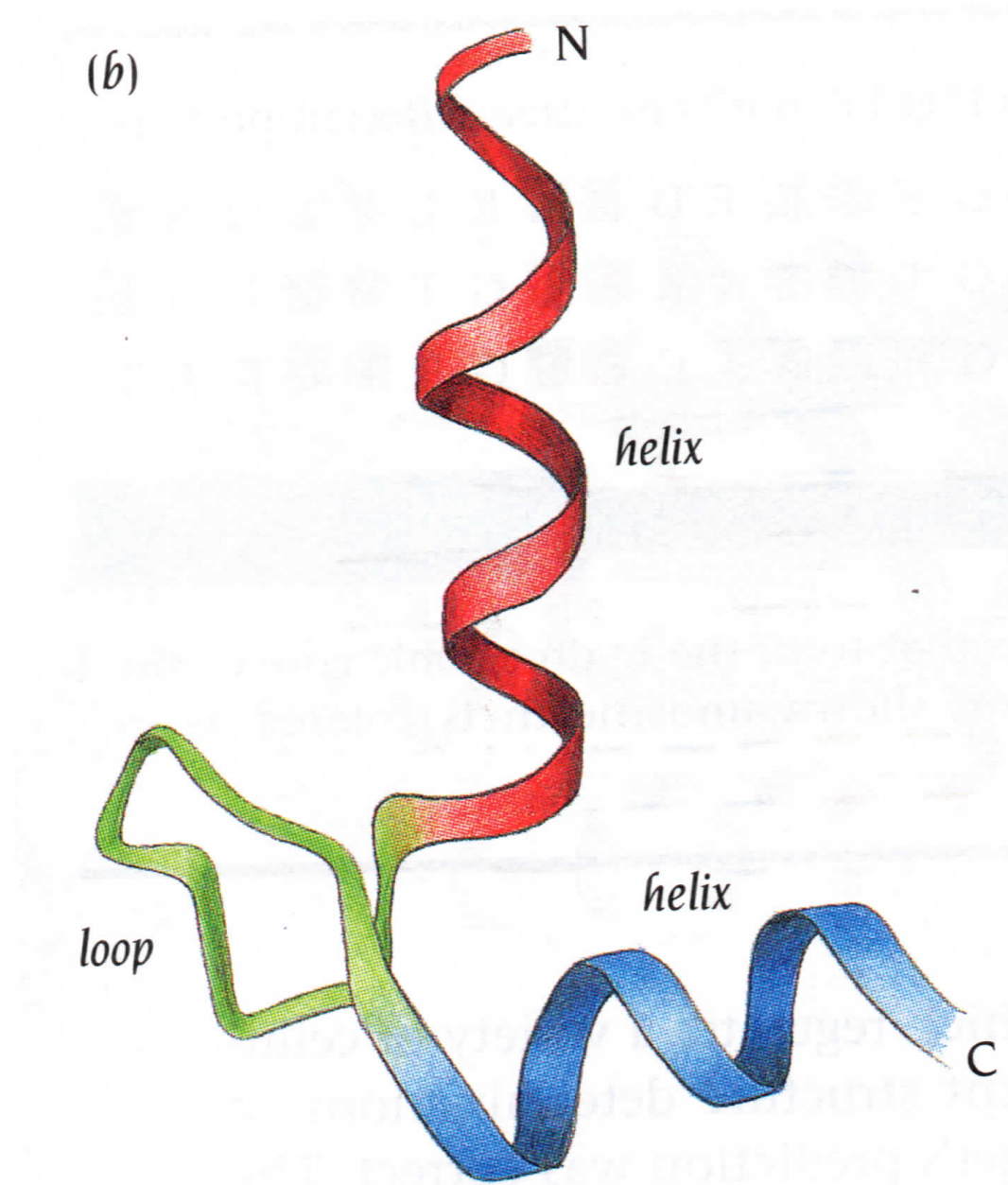
http://www.iq.usp.br/roberto/aulas_2014/qbq4010/pratica/pratica_validacao.html

Motivos

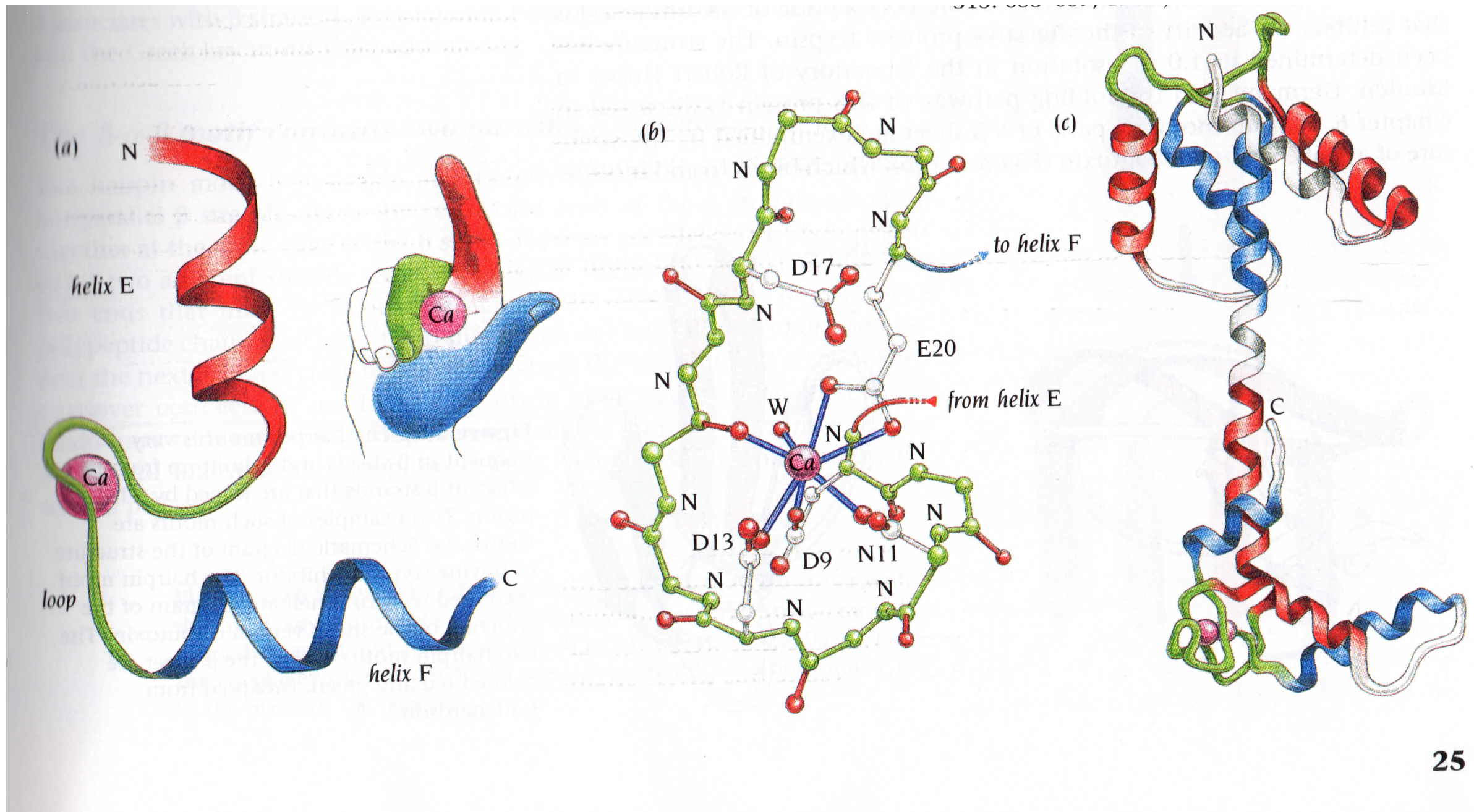
β -hairpin



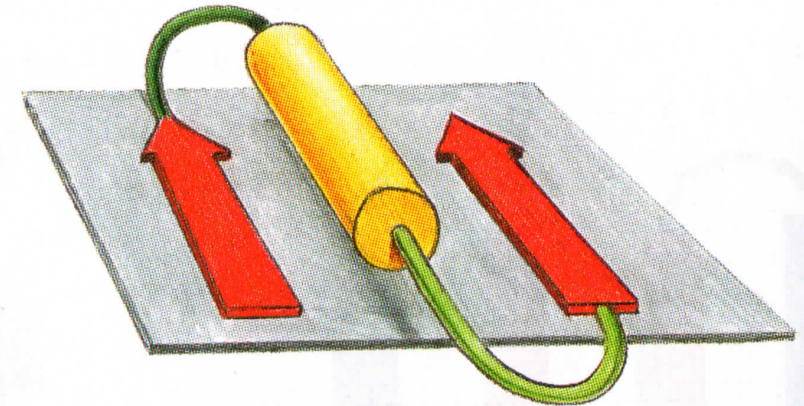
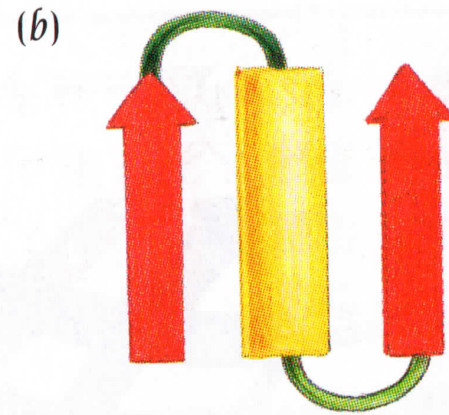
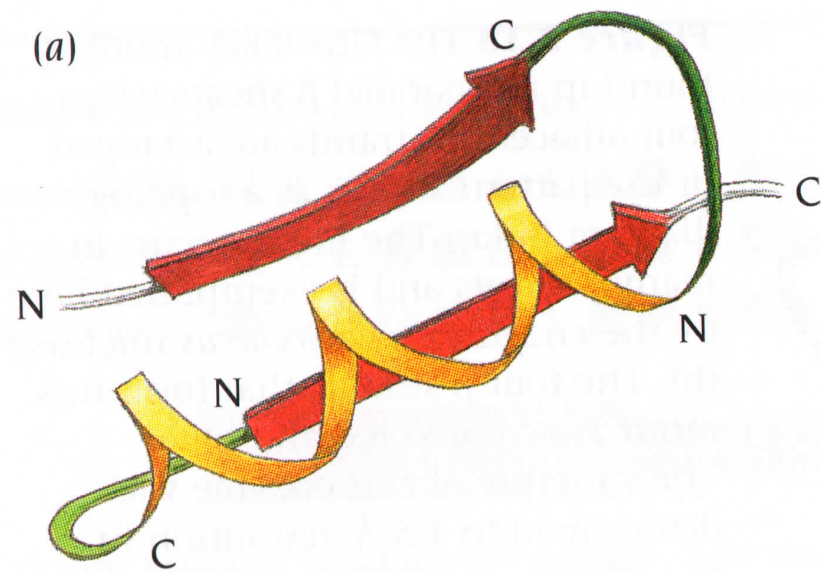
Helix-loop-helix Ca^{2+} -binding motif



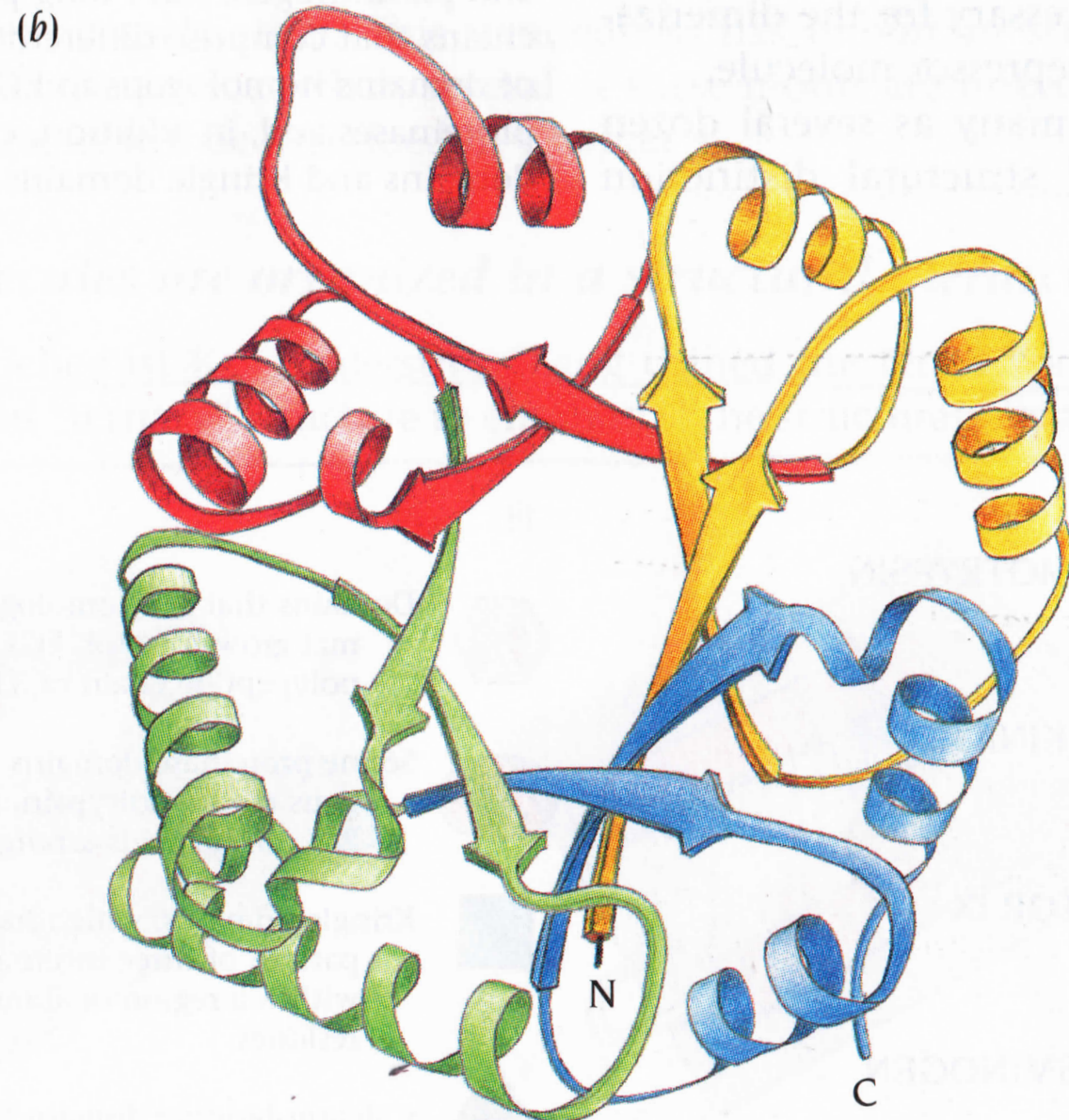
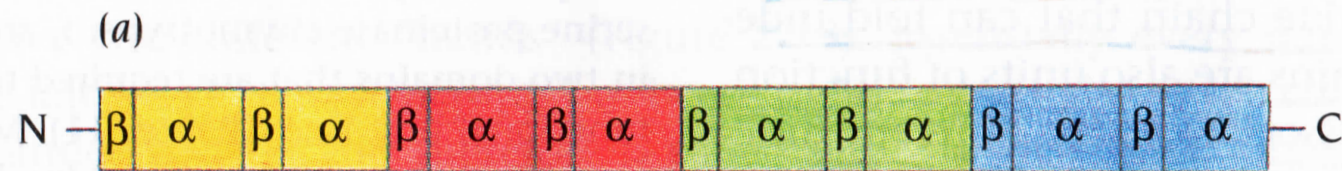
Helix-loop-helix Ca^{2+} -binding motif in calmodulin



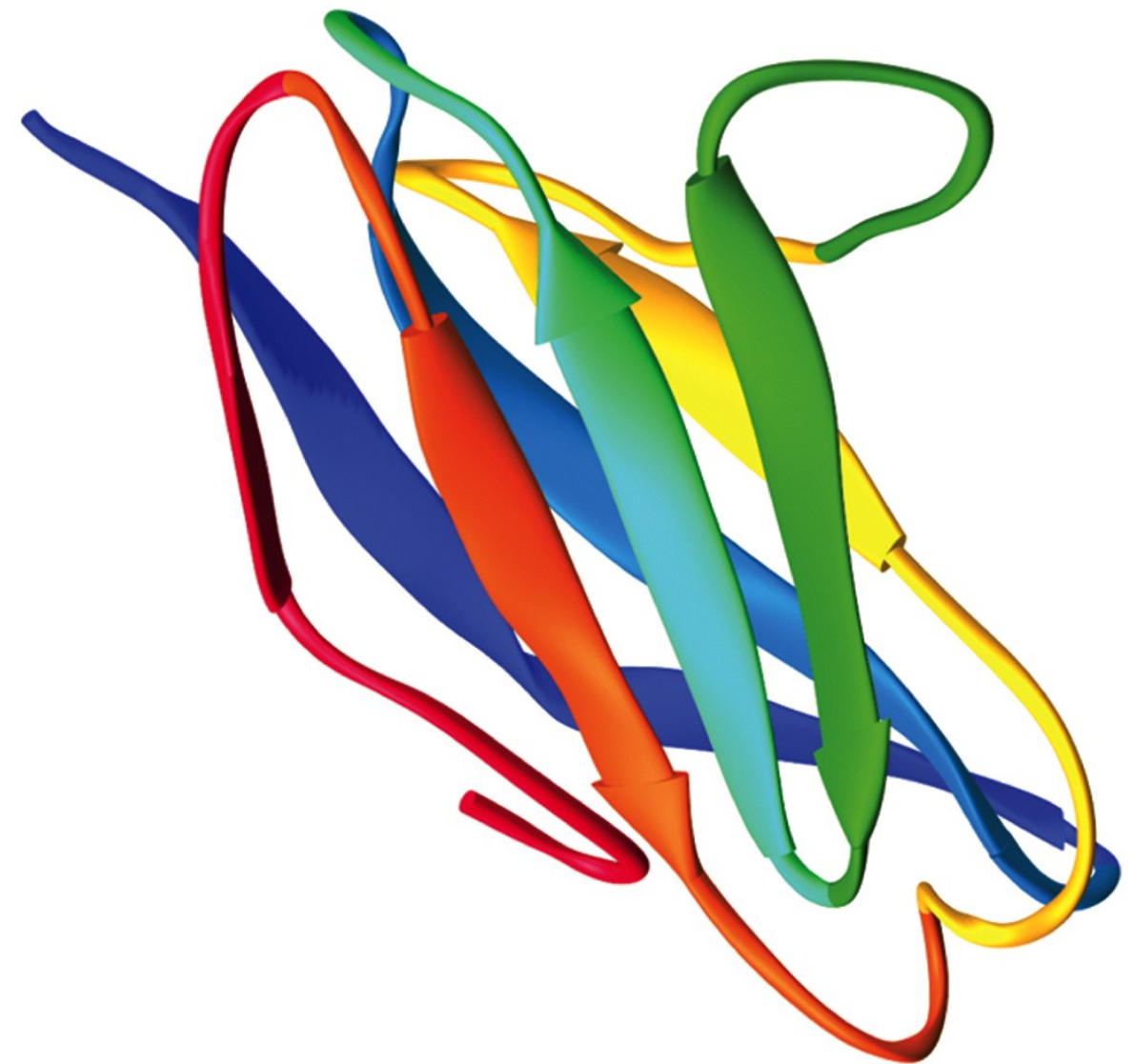
α - β - α motif



Domínios são formados a partir da combinação de motivos estruturais

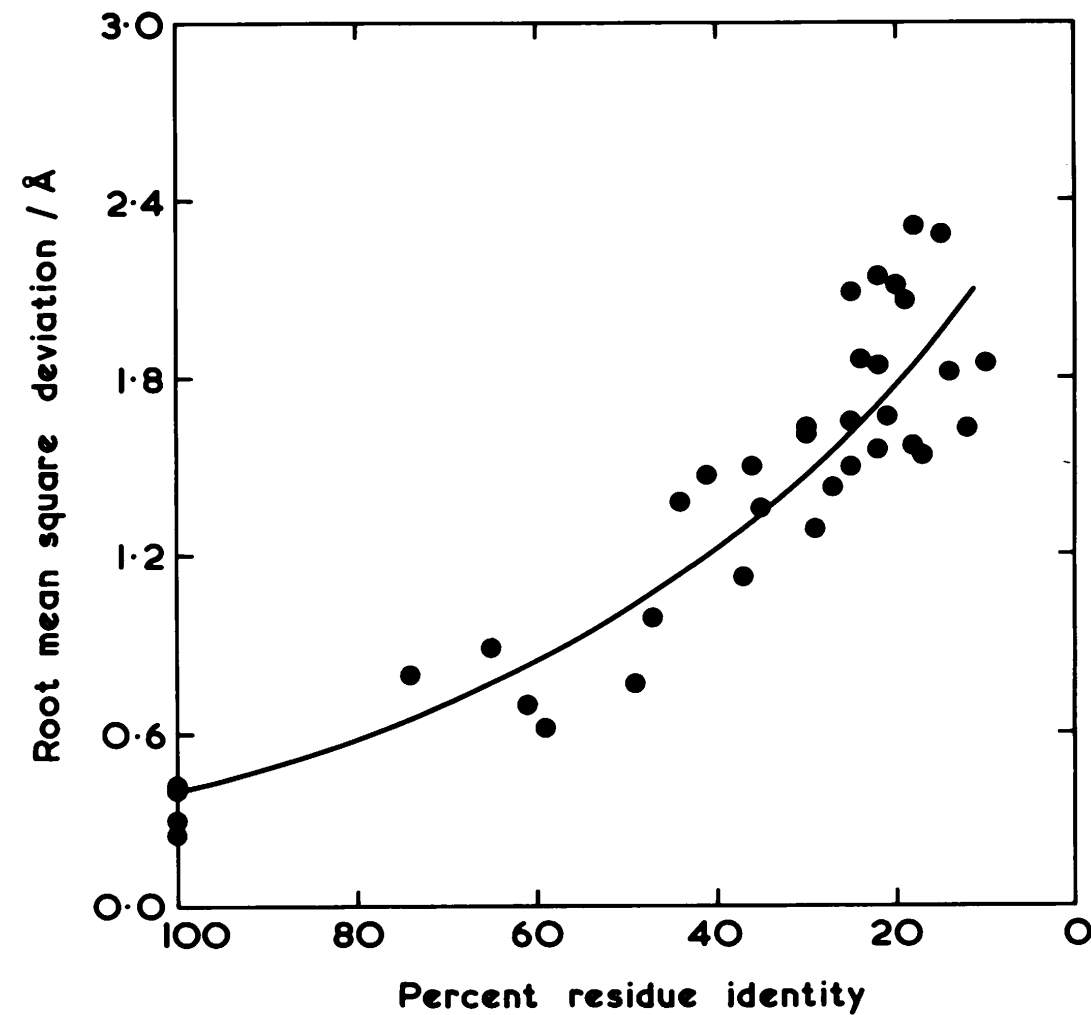


Triose-fosfato-isomerase (TIM)



Imunoglobulina

Em geral, um grau de identidade maior que 30 % indica estrutura similar



Clothia and Lesk (1986) *EMBO J.* **5**: 823

Estabilidade

● A hipótese termodinâmica de Anfinsen

A sequência de aminoácidos determina a estrutura tridimensional

The studies on the renaturation of fully denatured ribonuclease required many supporting investigations (6–8) to establish, finally, the generality which we have occasionally called (9) the “thermodynamic hypothesis.” This hypothesis states that the three-dimensional structure of a native protein in its normal physiological milieu (solvent, pH, ionic strength, presence of other components such as metal ions or prosthetic groups, temperature, and other) is the one in which the Gibbs free energy of the whole system is lowest; that is, that the native conformation is determined by the totality of interatomic interactions and hence by the amino acid sequence, in a given environment. In terms of natural selection

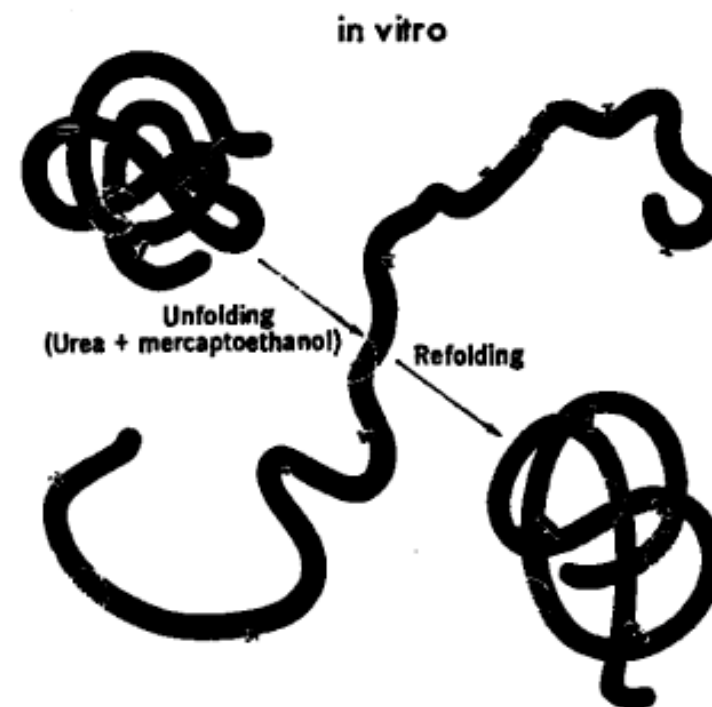


Fig. 2. Schematic representation of the reductive denaturation, in 8M urea solution containing 2-mercaptoethanol, of a disulfide-cross-linked protein. The conversion of the extended, denatured form to a randomly cross-linked, “scrambled” set of isomers is depicted at the lower right.

Interações que estabilizam a estrutura 3D

Não covalentes

Interações de van der Waals

Interações eletrostáticas

Ligações de hidrogênio

Covalente

Ligação dissulfeto

**Proteínas enovelam-se em consequência do efeito
hidrofóbico**

Ligações de disulfeto

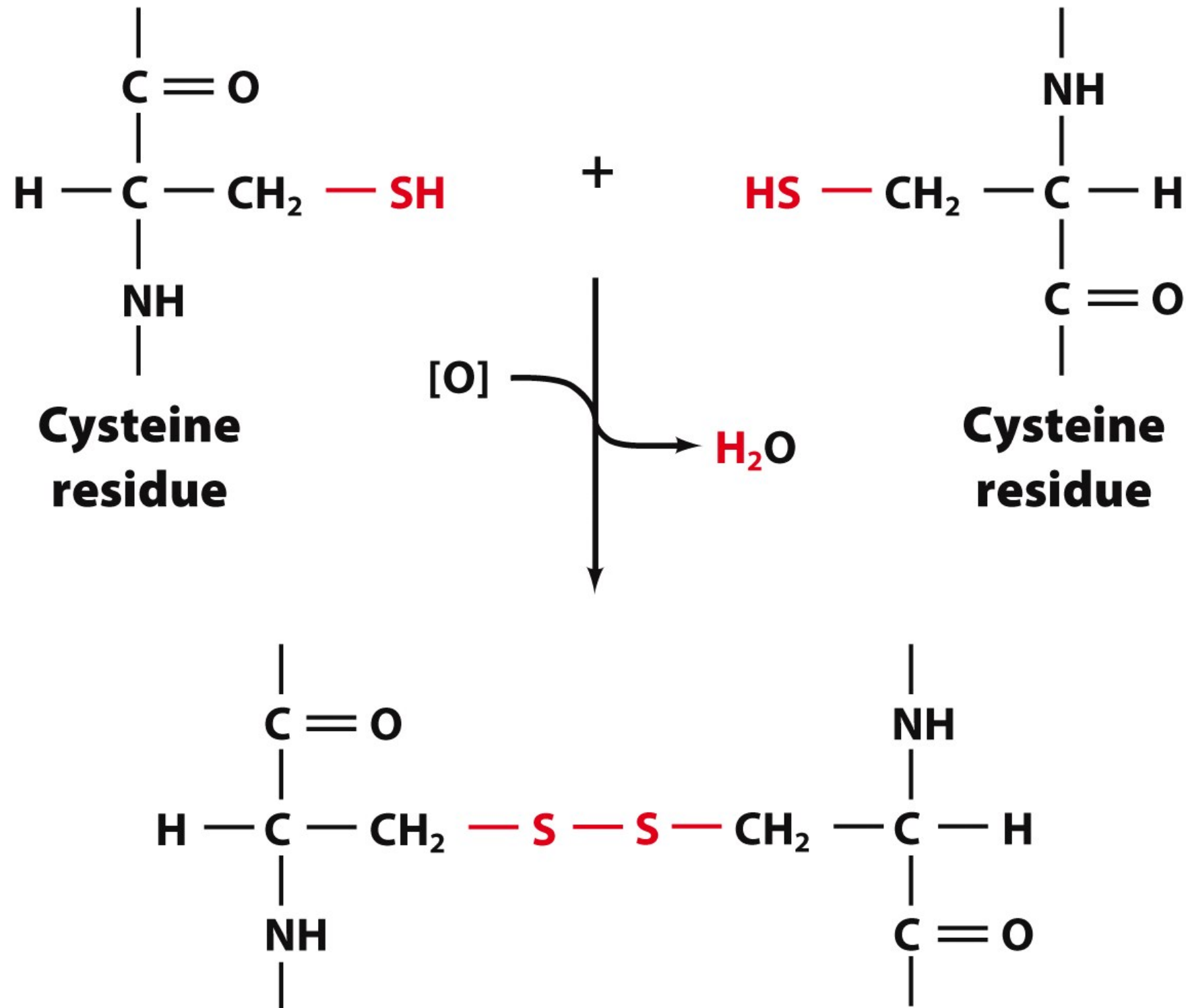


Figure 4-5
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Interações de van der Waals

$U_{\text{london}}(r) = -14.54 \times 10^{-21} \text{ J}$ para duas moléculas de HCl ($r=3 \text{ \AA}$) a 300K

$$U_{\text{dipolo-dipolo}}(r) = -2.5 \times 10^{-21} \text{ J}$$

$$U_{\text{dipolo-dipolo induzido}}(r) = -0.77 \times 10^{-21} \text{ J}$$

$$k_B T = 4.1 \times 10^{-21} \text{ J a 300K}$$

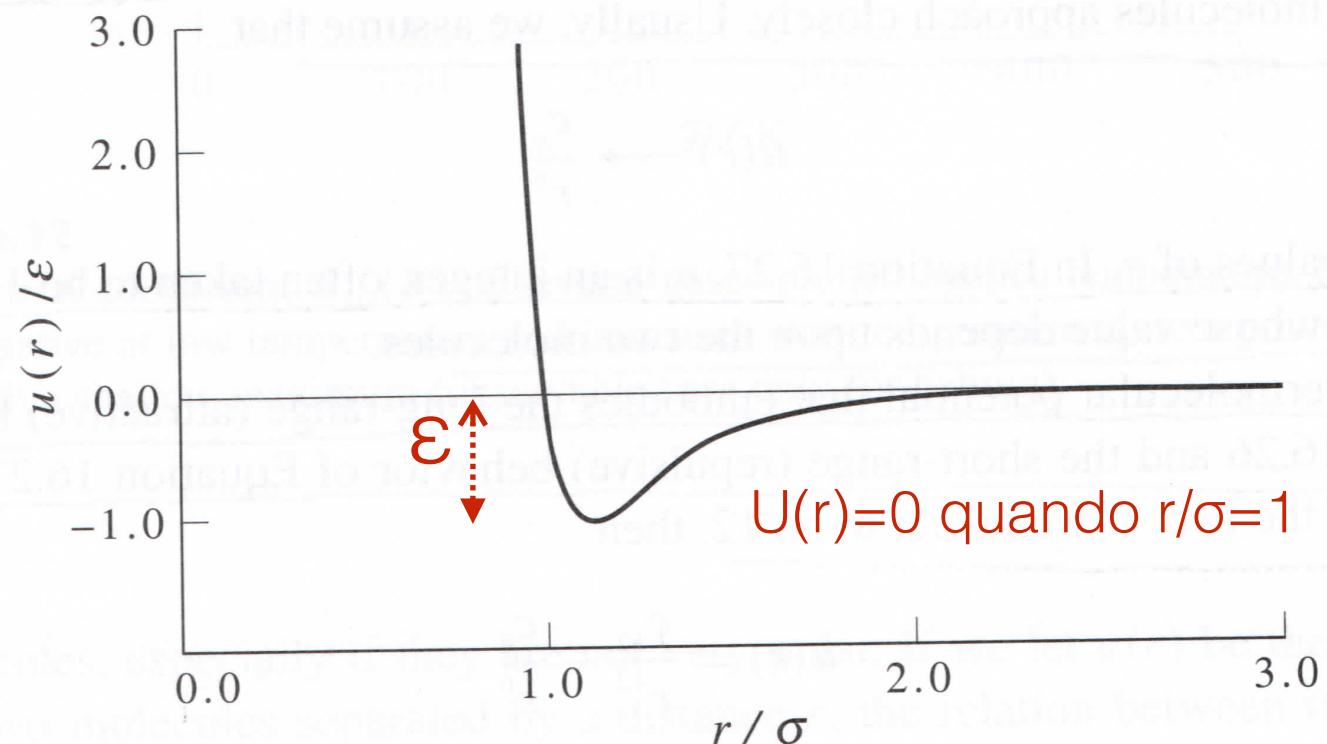
$$C_6 = U_{\text{london}} + U_{\text{dipolo-dipolo}} + U_{\text{dipolo-dipolo induzido}} \quad \textbf{(moléculas polares)}$$

$$C_6 = U_{\text{london}} \quad \textbf{(moléculas apolares)}$$

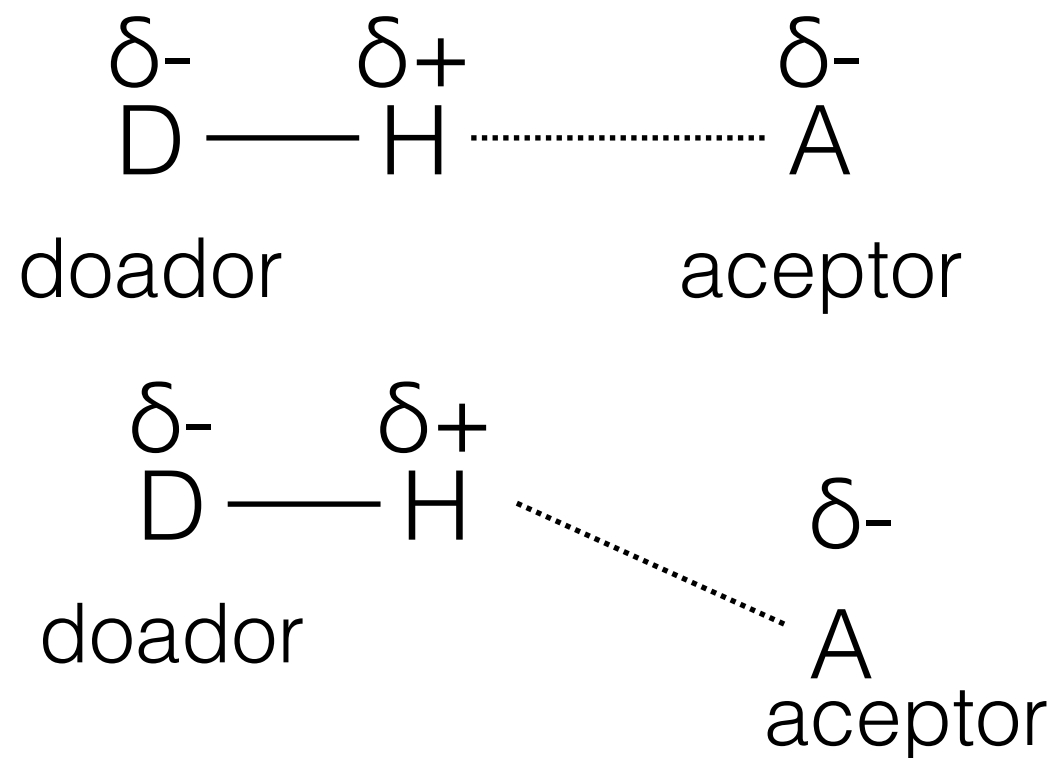
$$U(r) = \frac{C_{12}}{r^{12}} - \frac{C_6}{r^6}$$

$$U(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$$

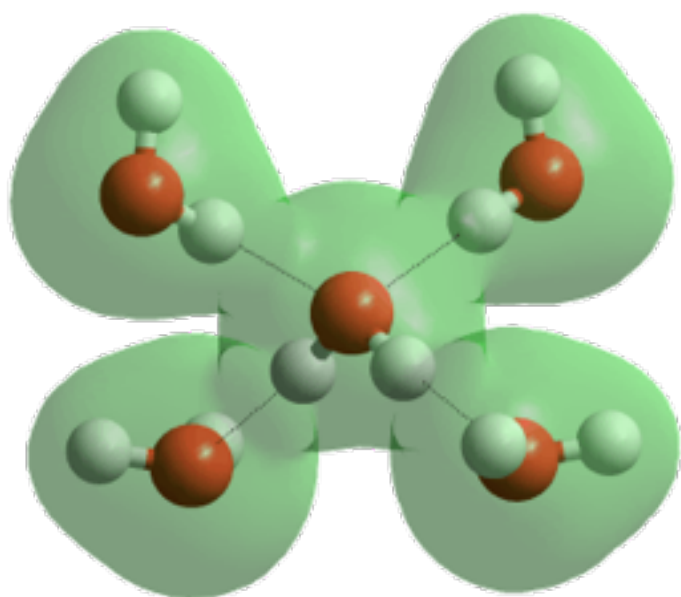
↑ ↑
repulsão atração



Ligações de hidrogênio



Caráter de ligação é 90% eletrostático e 10% covalente



Energia de ligações covalentes

Ligação	u (kcal/mol)
H—C	80.6
C—C	98.3

Ligação de hidrogênio:

Interação	Energia (kcal/mol)
Água/Água	5.5
Dipolo-dipolo	0.5
dipolo-dipolo induzido	0.012

Dill, K. et al. Molecular Driving Forces, Garland Science, 1ª. ed., 2003, Madison

Como as ligações de hidrogênio são muito mais fracas do que ligações covalentes o tempo de vida das ligações de hidrogênio é muito curto

Energias envolvidas na formação de interações não covalentes vs. covalentes

$$u(r) = (\text{constant})r^{-p}$$

Diferentes tipos de energia $u(r)$

Tipo	u (kcal/mol)	Dependência em r
iônica	66	$1/r$
íon/dipolo	4	$1/r^2$
dipolo/dipolo	0.5	$1/r^3$
dipolo/dipolo induzido	0.012	$1/r^6$

Energia de ligações covalentes

Ligação	u (kcal/mol)
H—C	80.6
C—C	98.3

Ponte de hidrogênio:

Água/Água	5.5 kcal/mol
-----------	--------------

A estabilidade da proteína é da mesma ordem de grandeza que 4-5 ligações de hidrogênio

Termodinâmica de enovelamento de proteínas

Proteína	ΔG^0 (kcal/mol)	ΔH^0 (kcal/mol)	$T\Delta S^0$ (kcal/mol)
CI2	-6.62	-32.26	-25.64
EglinC	-8.82	-27.48	-18.66
RNAse T1	-8.96	-67.16	-58.22
Citocromo c	-8.87	-21.27	-12.40
Barnase	-11.69	-73.37	-61.71

Fonte: Lesk, A. *Introduction to protein science*. Oxford University Press, 2ª edição, p. 352 (2010)

• Proteínas são marginalmente estáveis

1. Estabilidade está intimamente conectada com enovelamento, proteínas precisam ser estáveis no estado enovelado (nativo)
2. Estado desnaturado (D) não é necessariamente o mesmo que desenovelado (U)
3. $\Delta G = \Delta H - T\Delta S$
4. A energia livre de enovelamento é a soma de termos entálpicos e entrópicos, resultando em um valor ΔG pequeno (tipicamente -5 a -15 kcal/mol), portanto **proteínas são marginalmente estáveis**
5. Durante o enovelamento, os ganhos entálpicos (pontes de hidrogênio, pontes salinas) são compensados por uma grande perda de entropia conformacional
6. Mas também existe um grande ganho de entropia do solvente (efeito hidrofóbico)
7. Para uma proteína de 100aa:
 - +167 kcal/mol = perda de entropia conformacional
 - 95 kcal/mol = efeito hidrofóbico
 - 83 kcal/mol = efeitos entálpicos (p. exemplo: pontes de hidrogênio)

- 11 kcal/mol

Table 8.3 Folding of mutants of Arg96 in T4 lysozyme.

Protein	ΔT_m (°C)	$\Delta\Delta G^\ominus$ (kJ mol ⁻¹)	Crystal structure?
WT	0.0	0.0	Yes
Arg96Lys	-0.2	0.0	Yes
Arg96Gln	-1.4	-1.3	Yes
Arg96Ala	-5.1	-8.4	Yes
Arg96Val	-6.4	-10.0	Yes
Arg96Ser	-7.0	-10.9	Yes
Arg96Glu	-7.0	-10.5	Yes
Arg96Gly	-7.1	-10.9	Yes
Arg96Met	-7.1	-11.3	Yes
Arg96Thr	-7.6	-11.7	No
Arg96Cys	-7.7	-12.1	No
Arg96Ile	-7.9	-12.1	No
Arg96Asn	-8.0	-12.6	Yes
Arg96His	-8.3	-13.0	Yes
Arg96Leu	-8.6	-13.4	No
Arg96Asp	-9.5	-14.6	Yes
Arg96Phe	-11.5	-17.6	No
Arg96Trp	-12.8	-18.8	Yes
Arg96Tyr	-13.2	-19.7	Yes
Arg96Pro	-15.5	-23.0	Yes

From: Mooers, H.M., Baase, W.A., Wray, J.W., and Matthews, B.W. (2009). Contributions of all 20 amino acids at site 96 to the stability and structure of T4 lysozyme. *Prot. Sci.*, **18**, 871–880.

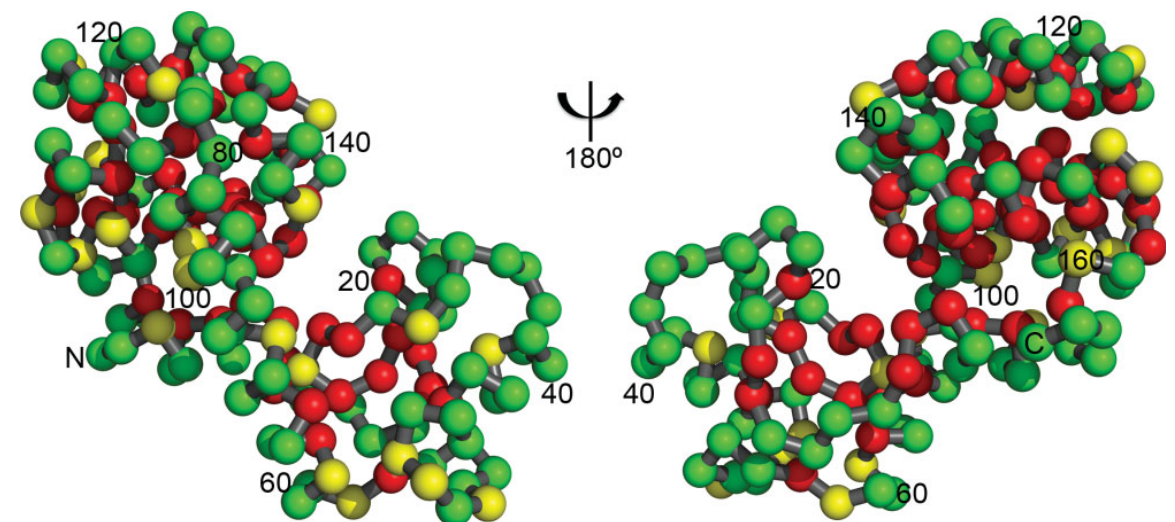


Figure 2. Figure illustrating the tolerance of T4 lysozyme to point mutation (following Ref. ⁴). Substitutions at the green-colored sites have little if any effect on folding or activity. One or more substitutions at the red sites compromise folding and/or activity. These locations, typically in the core or the active site cleft, are the least tolerant sites. The yellow sites are tolerant, but less so than the green ones (see text for details).

Fonte: Baase *et al.* (2010) *Protein Science* **19**:631

Estrutura quaternária

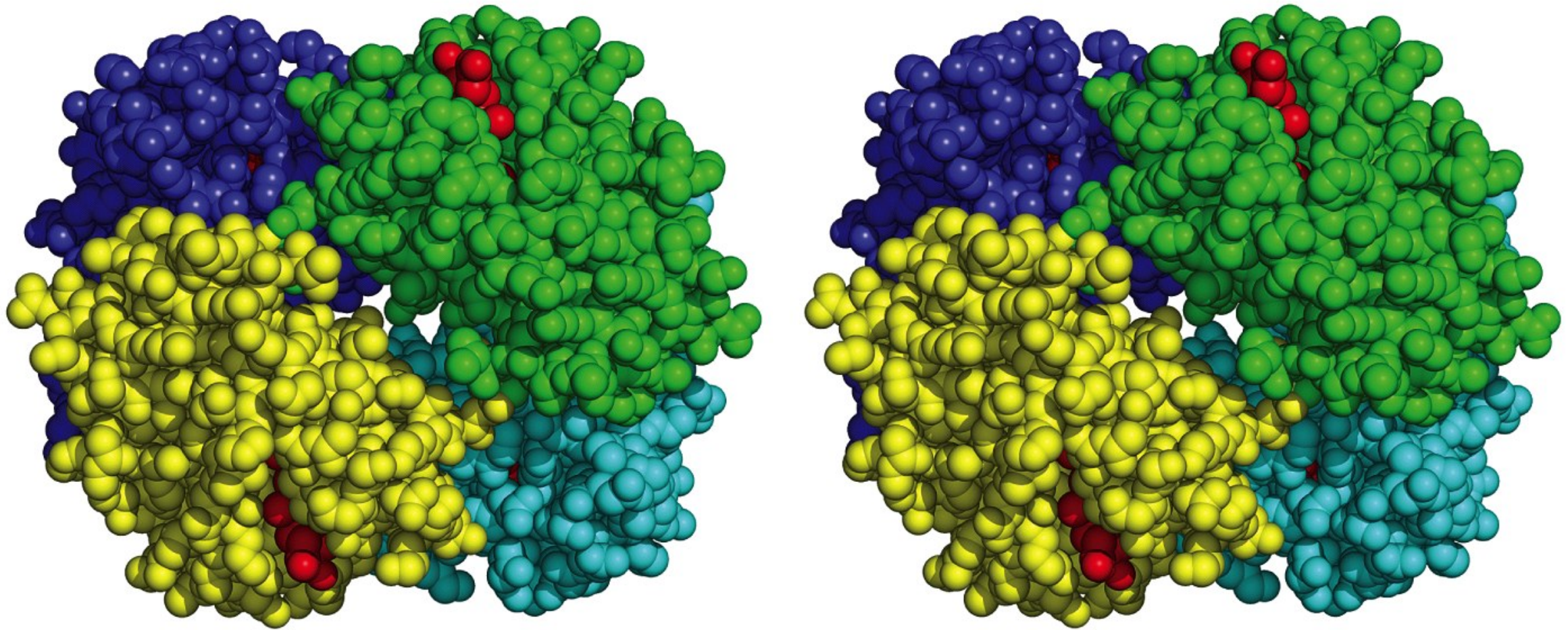
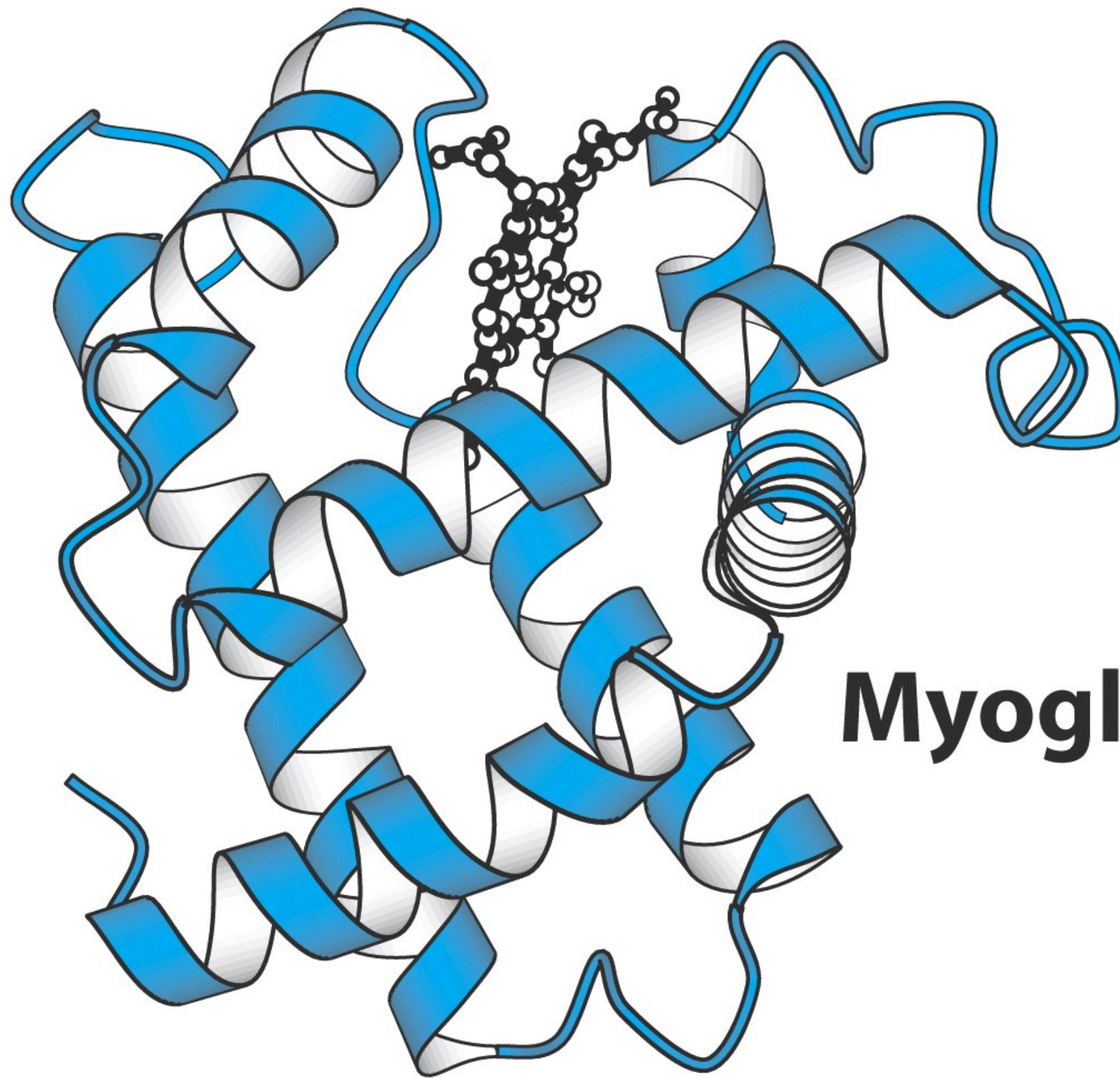
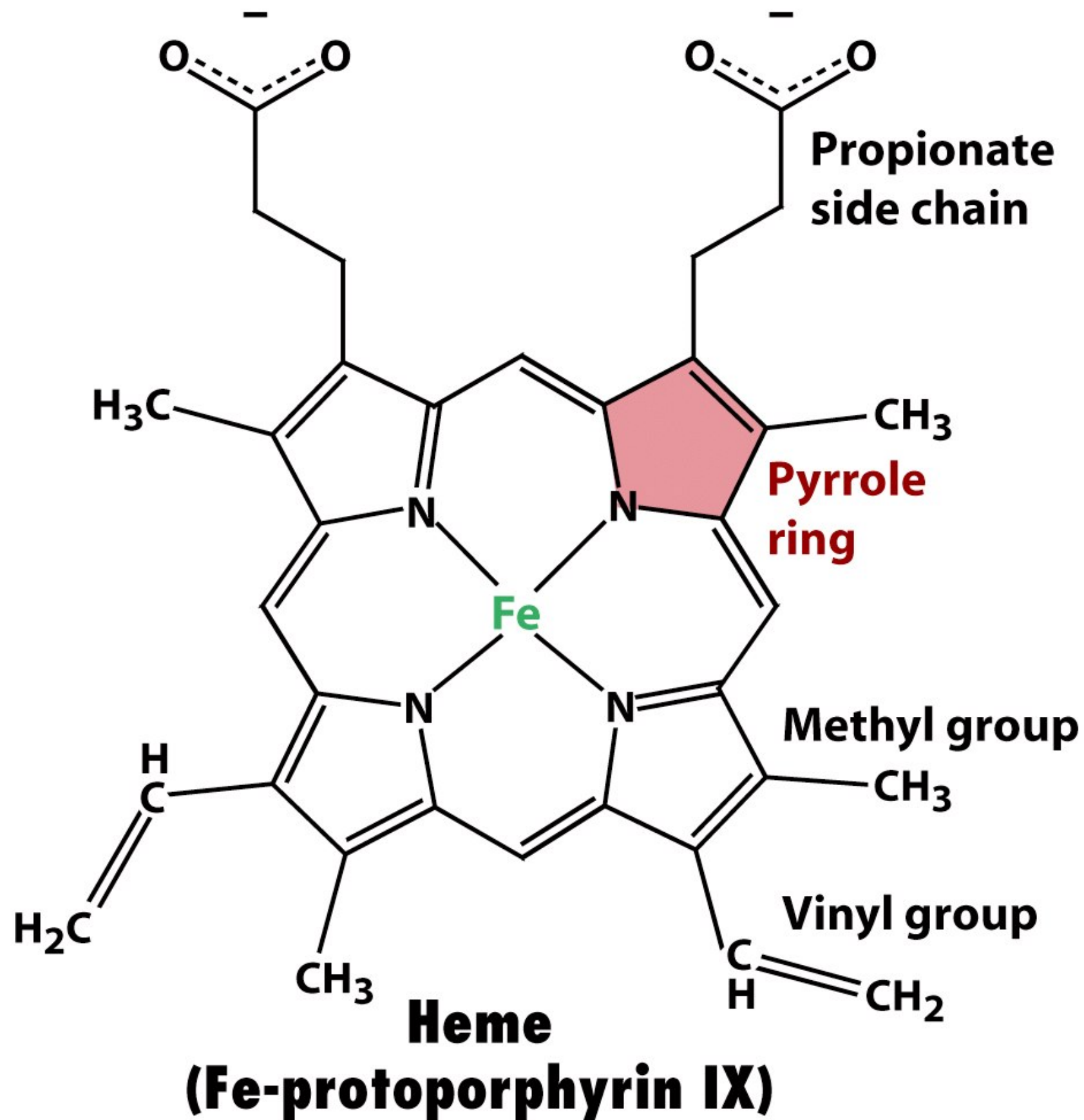


Figure 8-64
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Myoglobin

Figure 7-1
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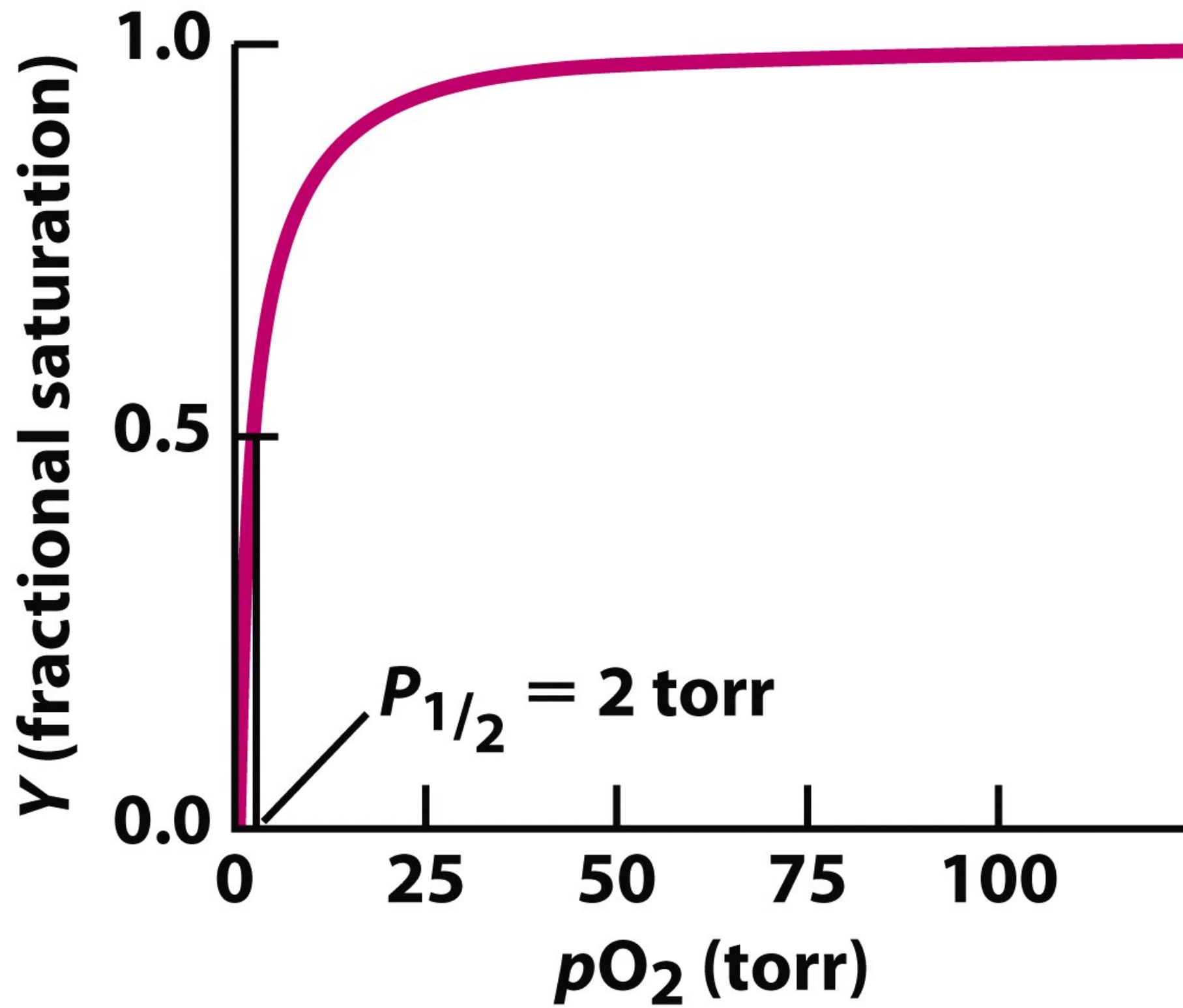


Figure 7-6
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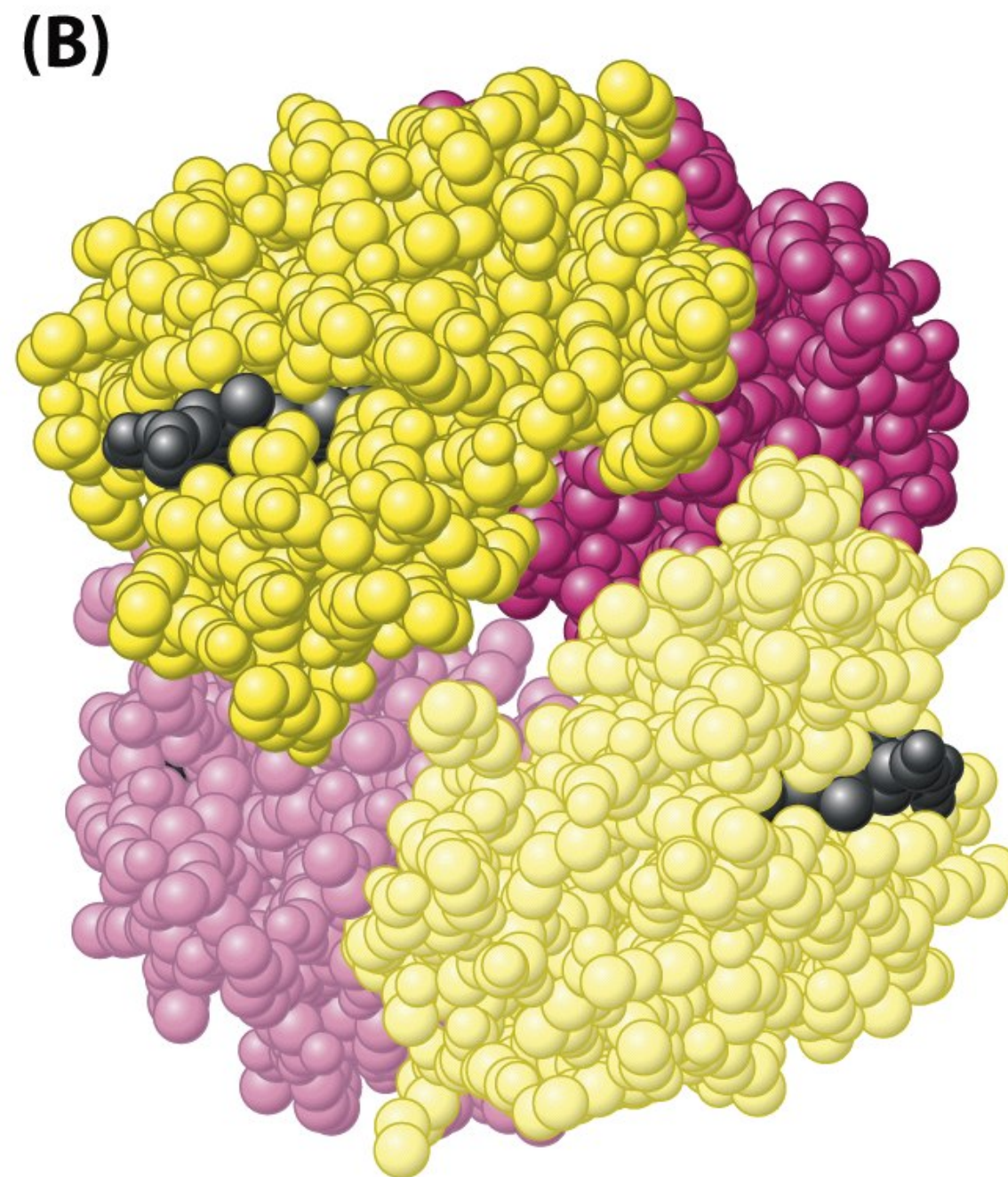
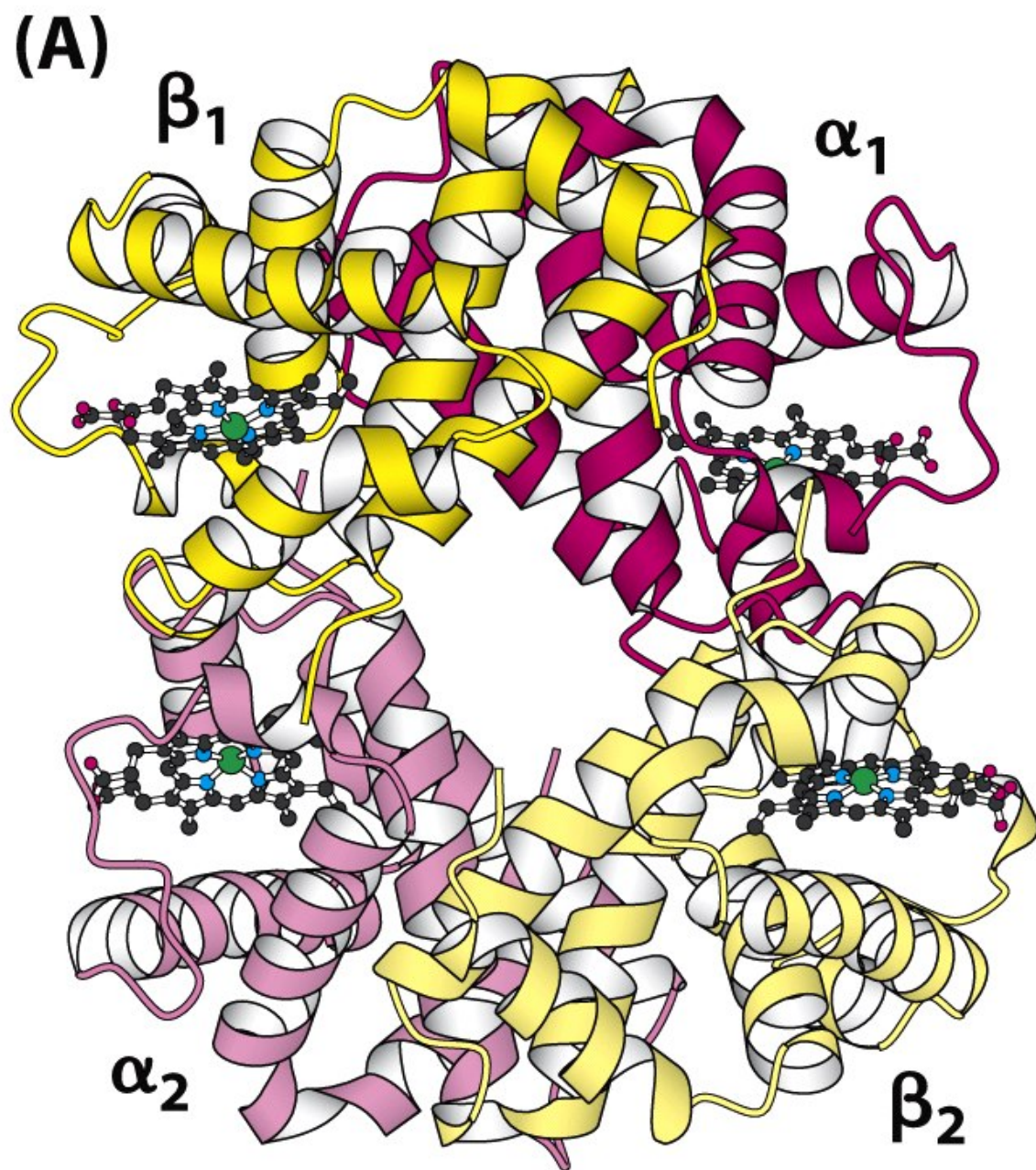


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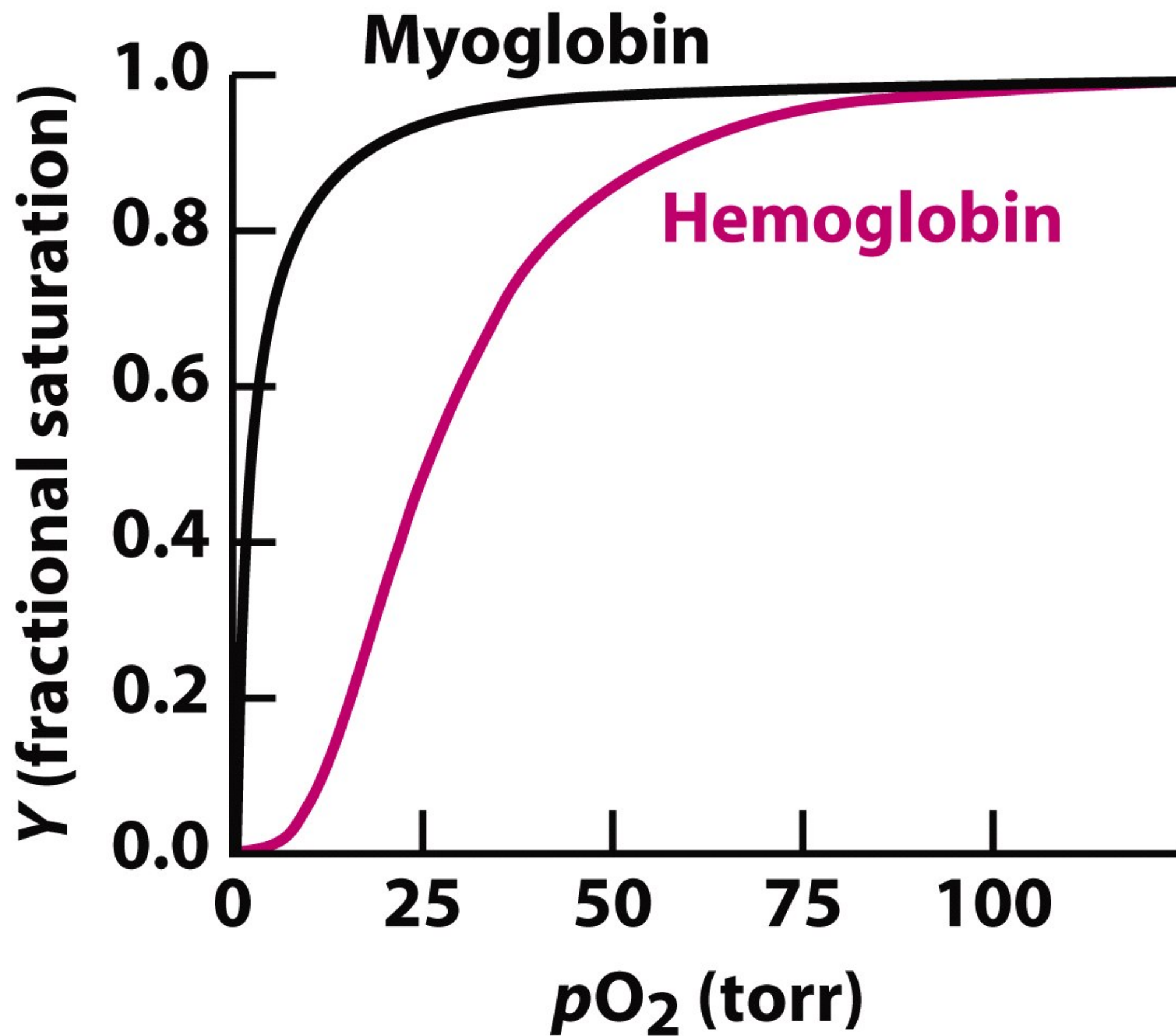


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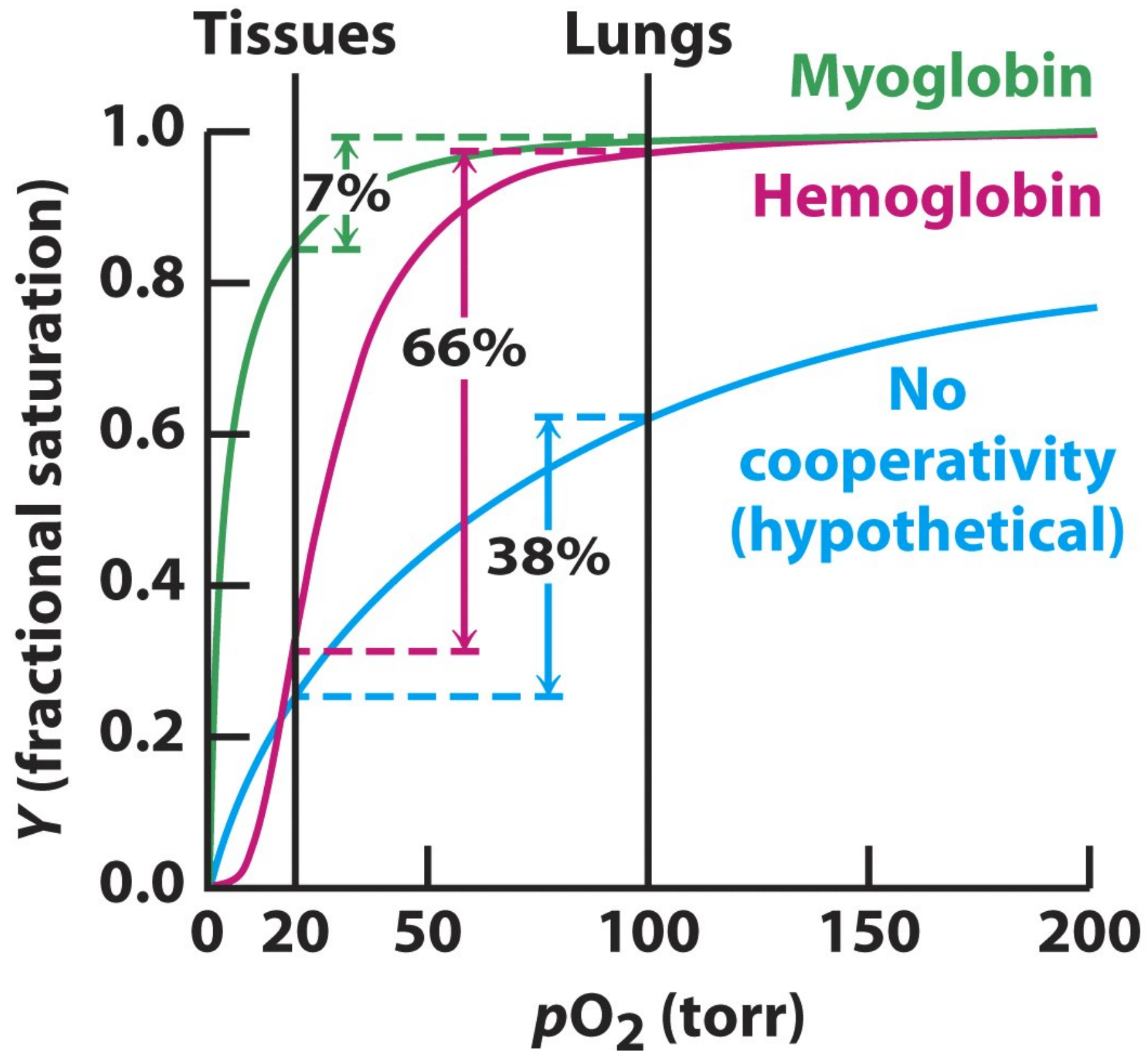


Figure 7-8
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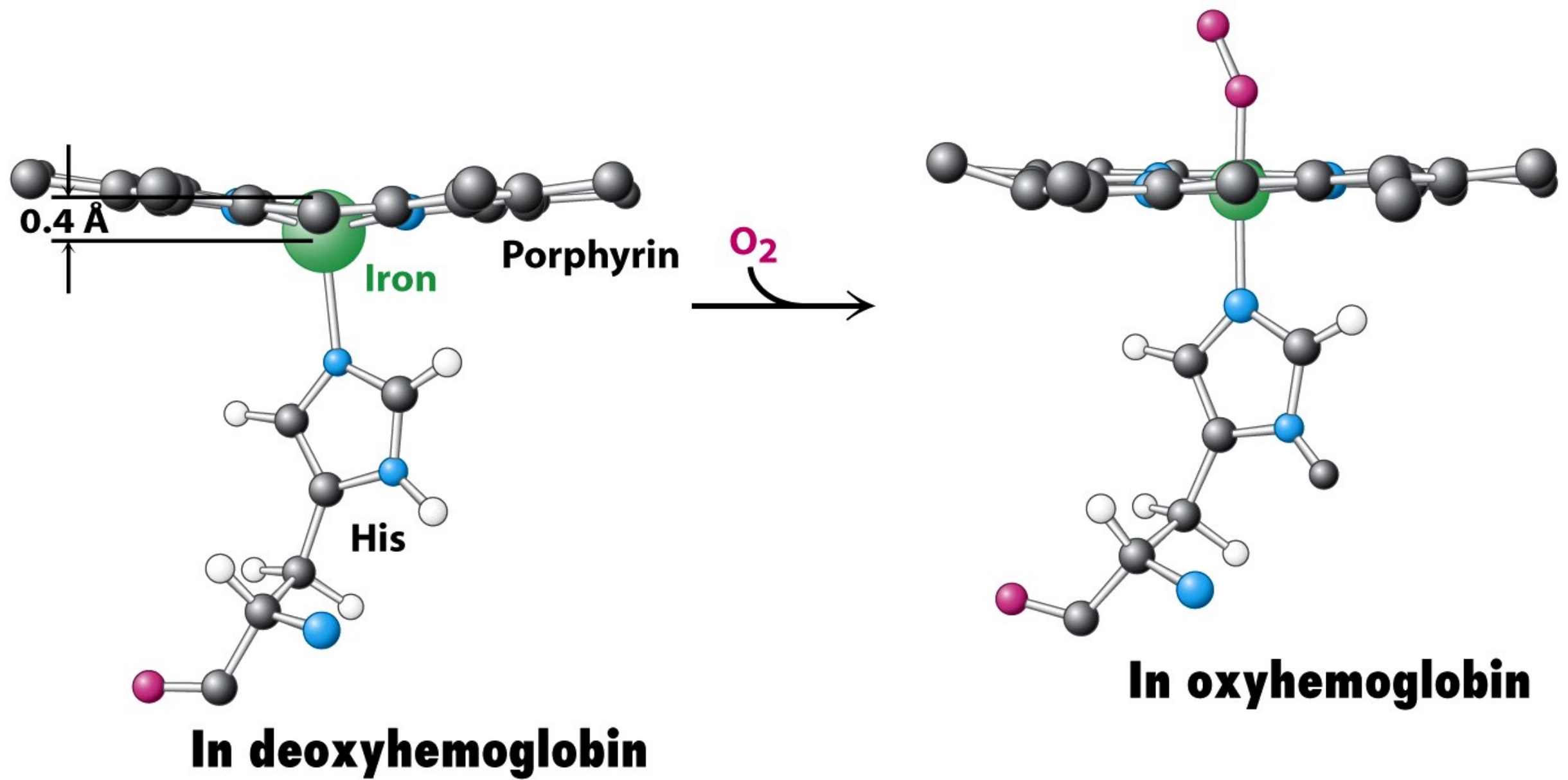
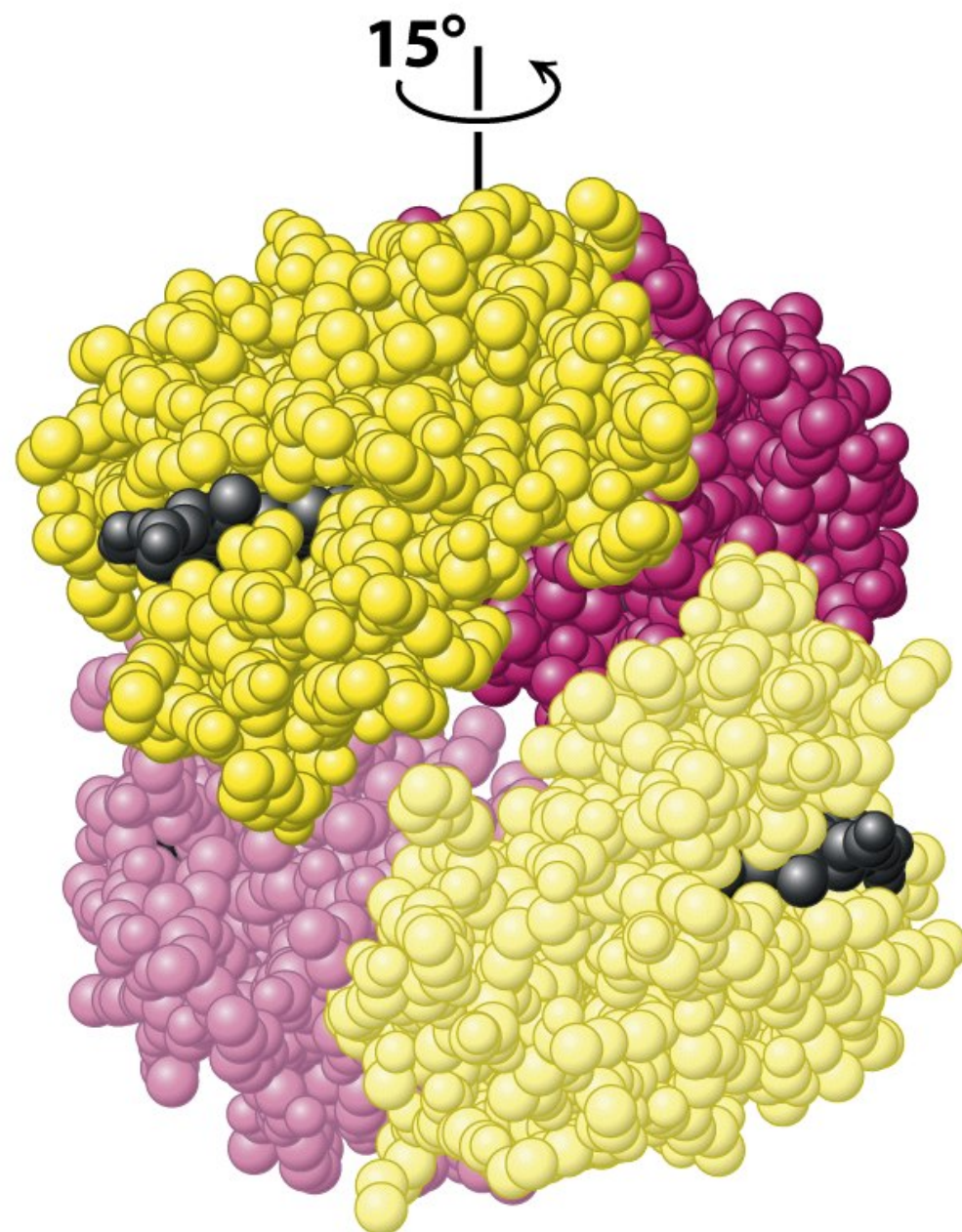
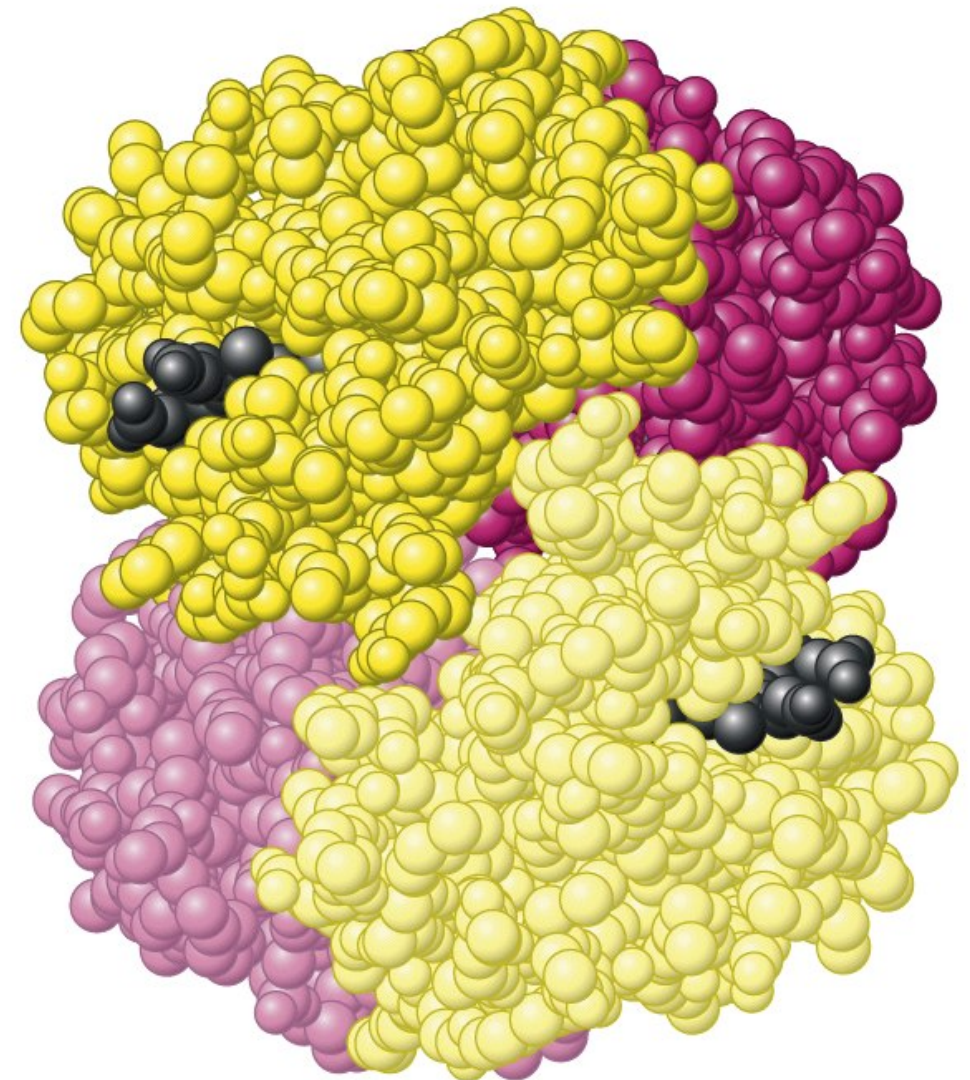


Figure 7-2
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Deoxyhemoglobin



Oxyhemoglobin

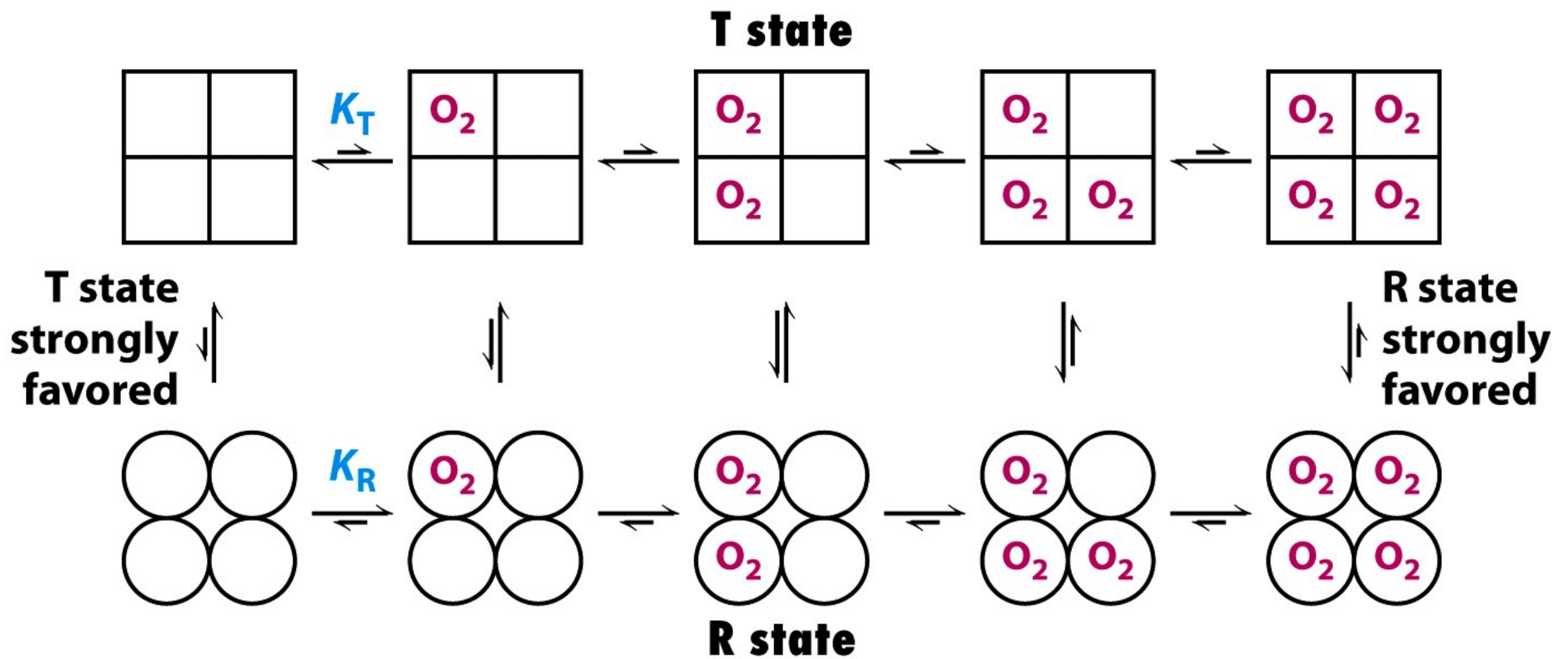


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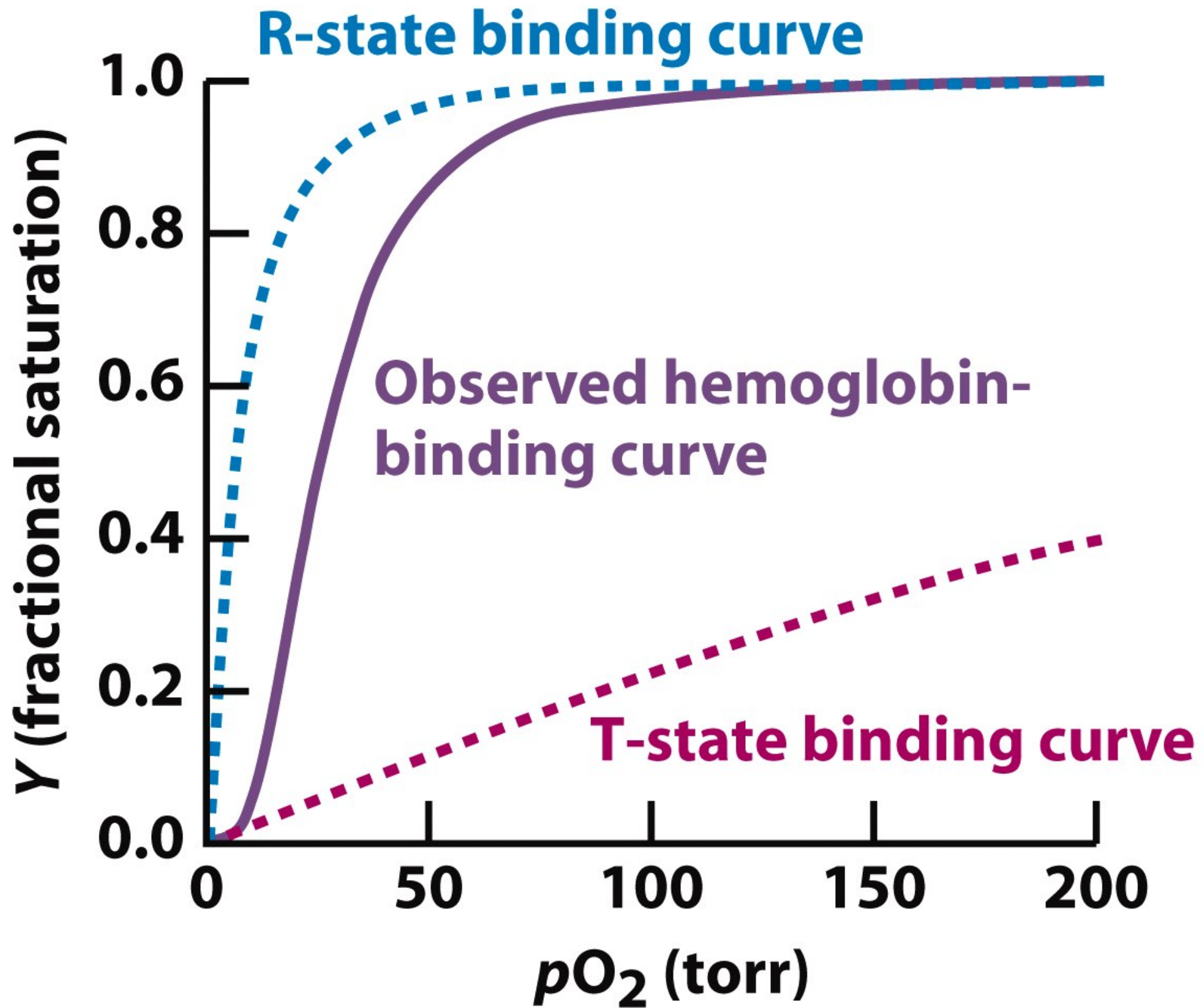
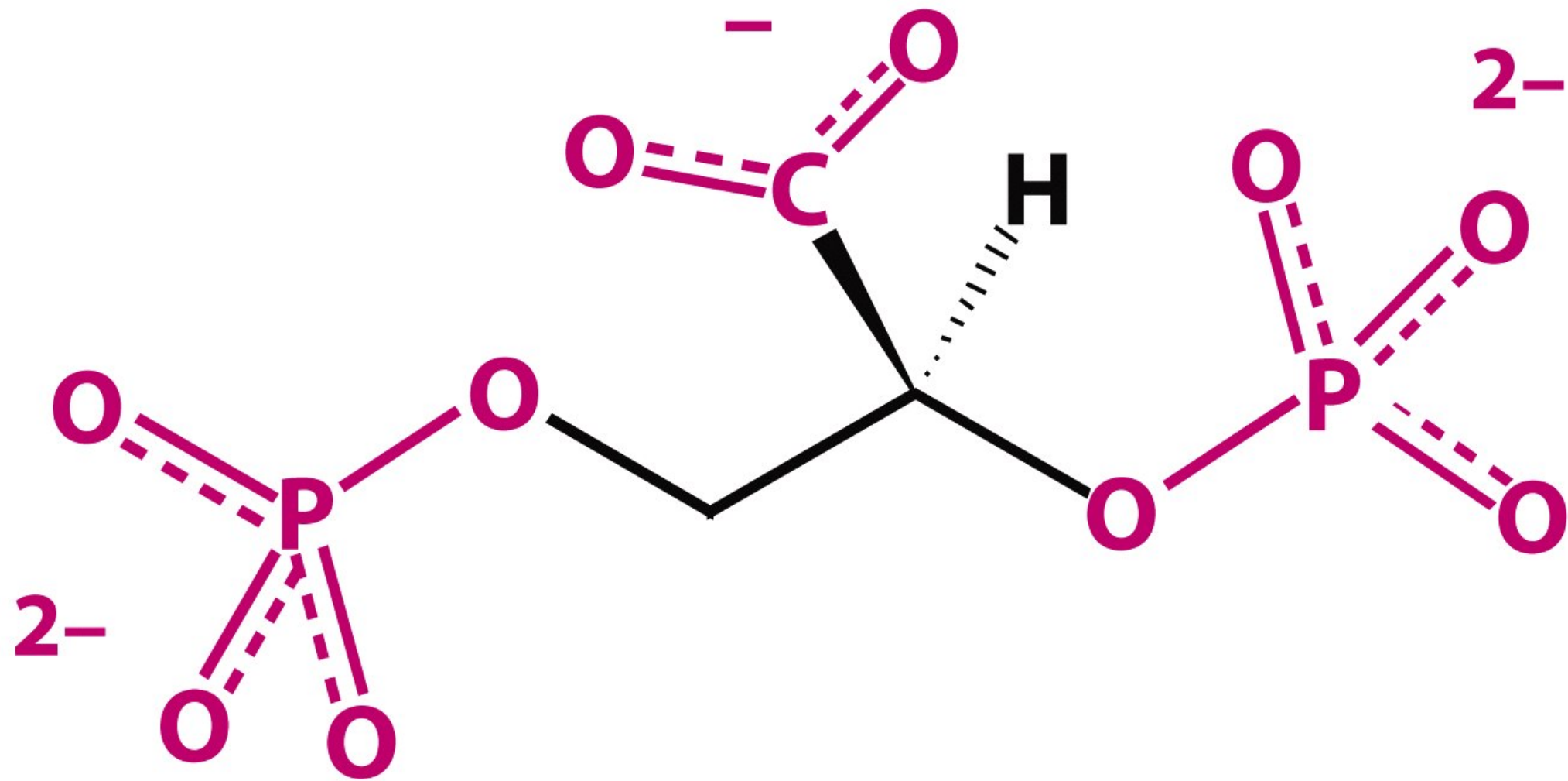


Figure 7-12
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2,3-Bisphosphoglycerate (2,3-BPG)

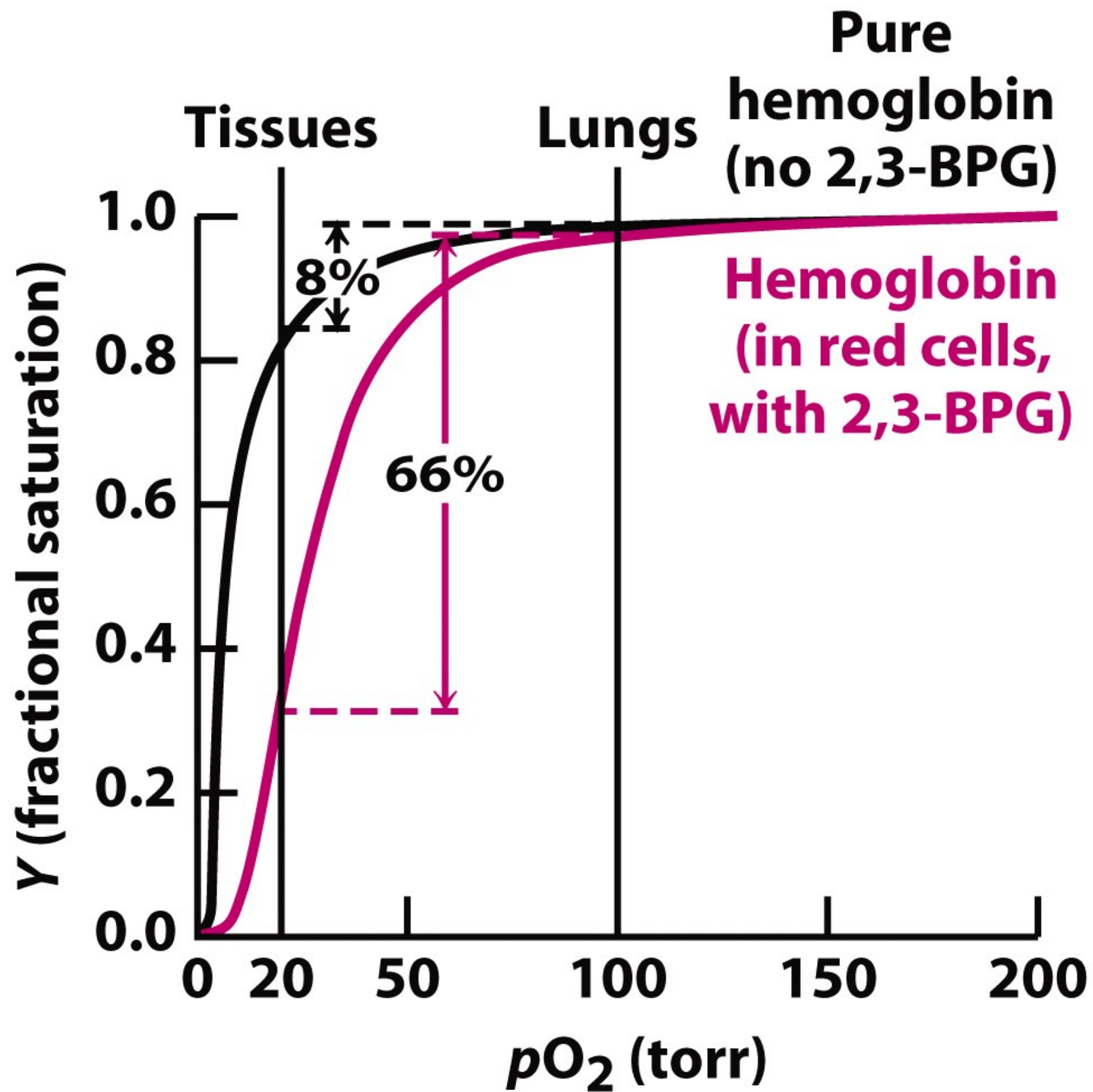


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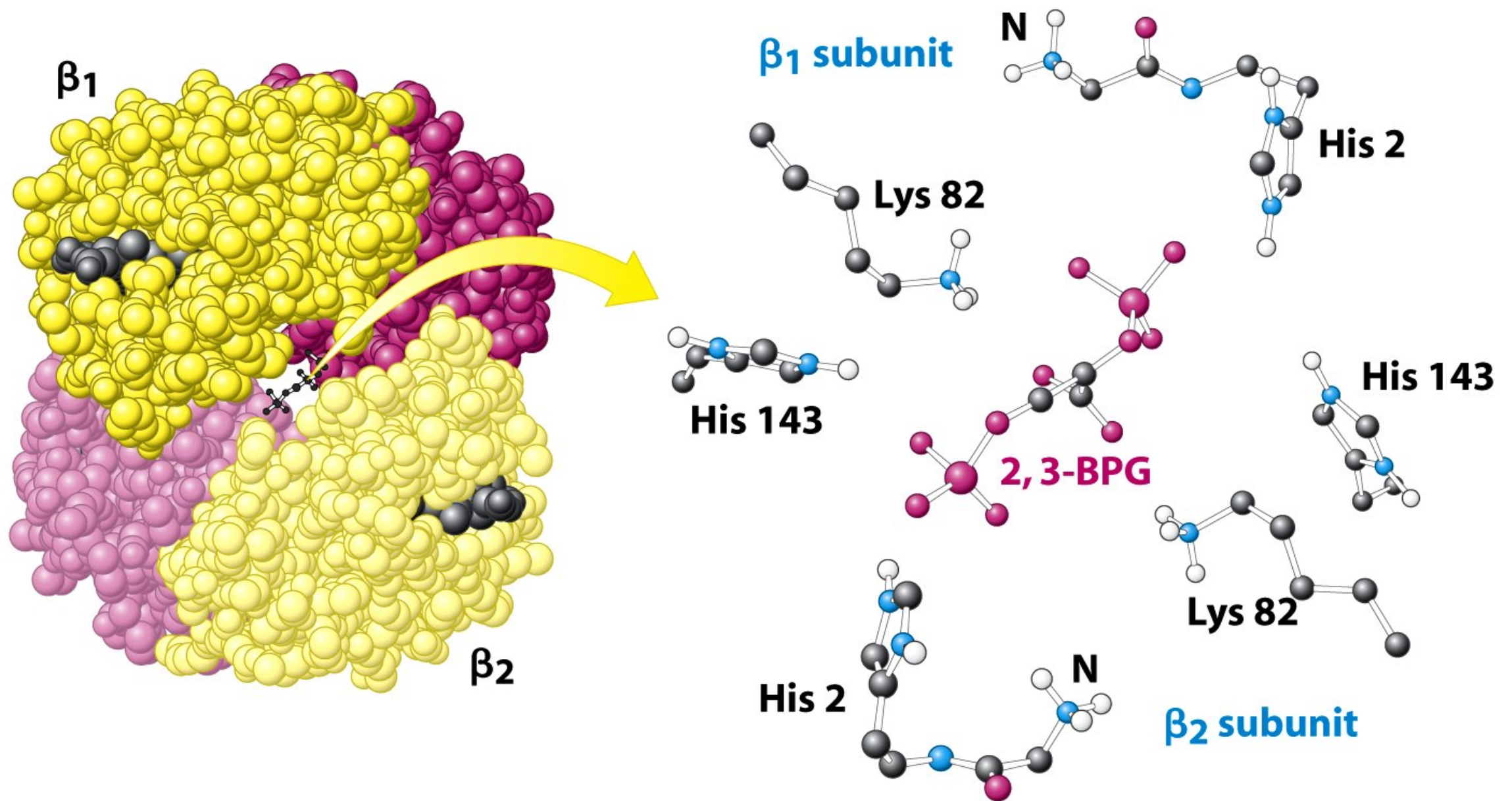


Figure 7-16
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