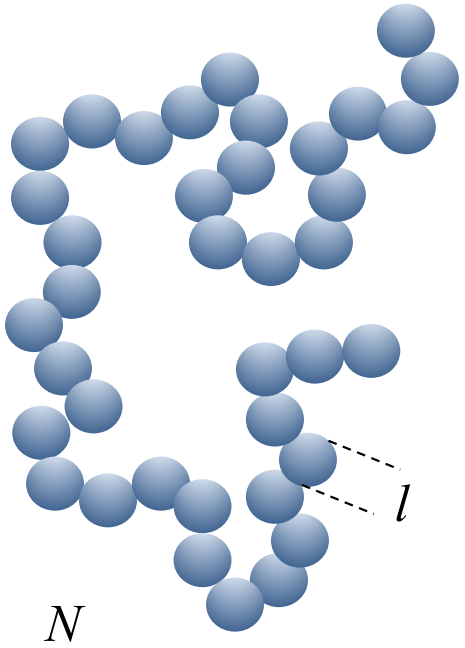
Conformations of macromolecules: Goal

polymer model



To understand **protein folding**, we require information about the **unfolded state** (that has an astronomical number of conformations)

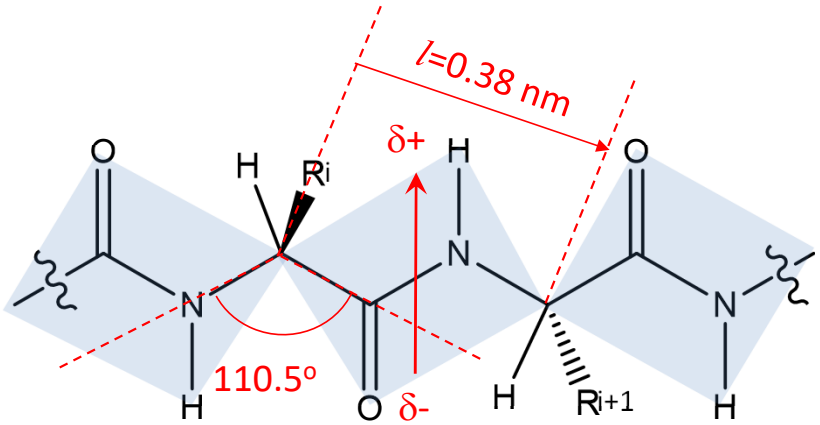
What can we know about such unstructured states? This includes **proteins** and other polymers such as **DNA**.

→ **Statistics**

Ignoring molecular details

- macromolecule consisting of N units of length *l*
- what are the allowed conformations?
- can we extract average properties (e.g. size)

Molecular details: The peptide unit revisited



amino acid i i+1

Dipole moment of 3.5 Debeye

bond length and angles are described by **harmonic potentials**

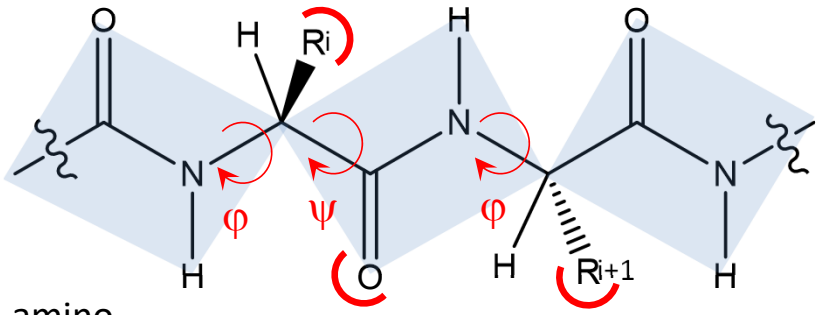
$$U(x) = \frac{1}{2}\phi\left(x - x_0\right)^2$$

force constant for bond flexing (C-C):
2761 kJ / Å^2 / mol

displacement of 0.05 Å more than kT → bond lengths are constant

For bond angles: 10x smaller

Molecular details: The peptide unit revisited



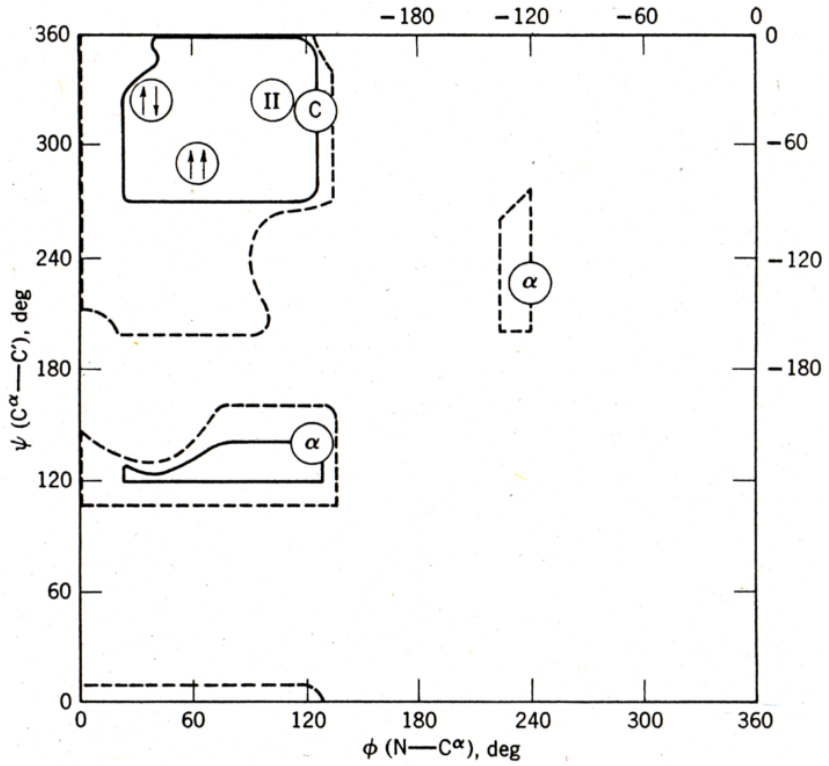
Torsion angles

Per amino acid, two rotatable bond in backbone

Complex potential

Rotation leads rapidly to steric interactions → restrictions in the allowed angles

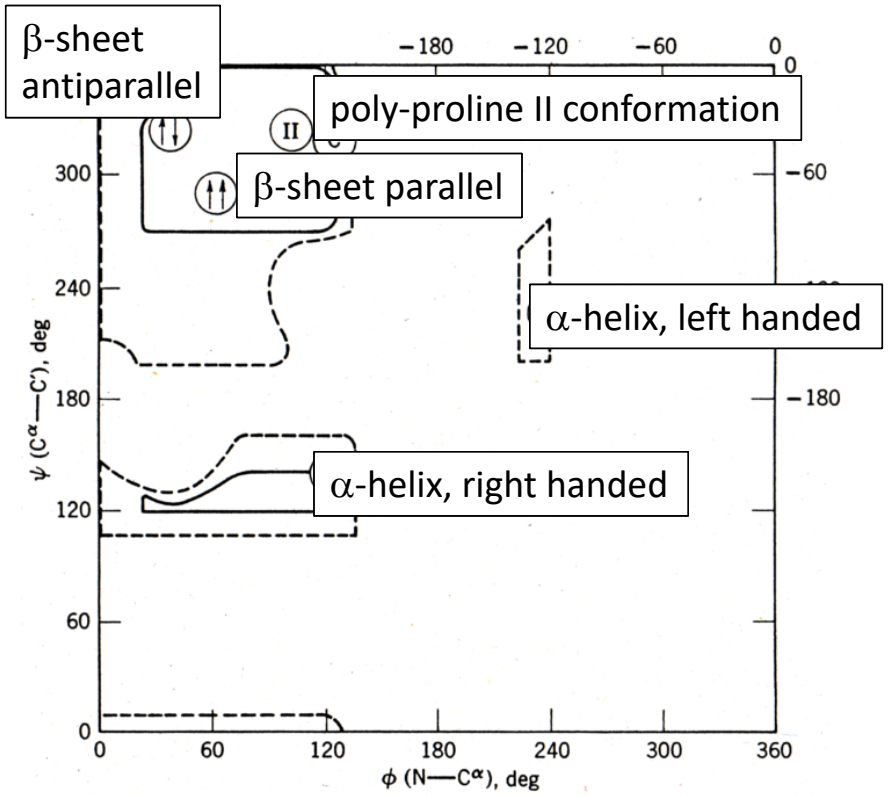
The Ramachandran steric map



G. N. Ramachandran
1922-2001

Mapped allowed angles based solely on **steric** grounds

The Ramachandran steric map



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Mapped allowed angles based solely on **steric** grounds

Conformational energy maps

What are the configurational distributions of **real peptide chains**?

Recalculation of the φ,ψ-maps using an energy function:

torsion angle potential

$$V(\varphi,\psi) = \frac{V_\varphi^0}{2}(1-\cos 3\varphi) + \frac{V_\psi^0}{2}(1-\cos 3\psi)$$

$$+ \sum_{k,l} E_{k,l}(\varphi,\psi) + E_C$$

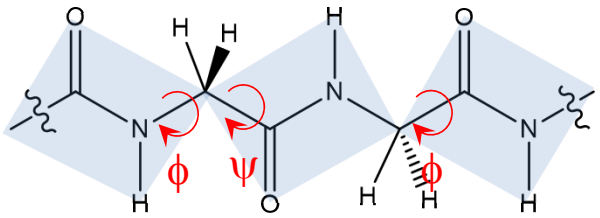
Coulomb interactions (charges and dipoles)

sterics and VdW interactions

$$E_{kl} = A_{kl} / r_{kl}^{12} - B_{kl} / r_{kl}^{6}$$

Paul John Flory
1910-1985
1974 Nobel Prize

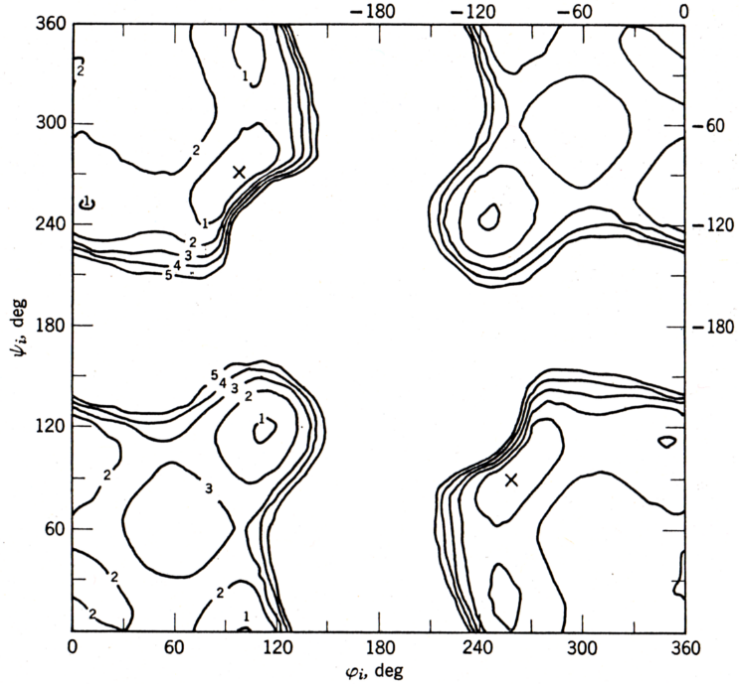
The glycine-glycine dipeptide



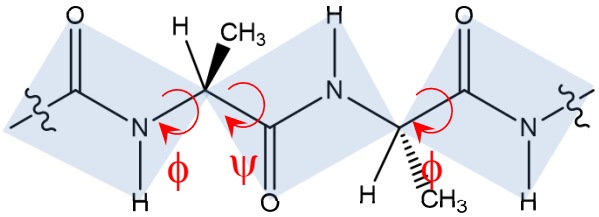
Glycine has **no sidechain**

large accessible conformational space, closest to ideal chain

high chain entropy



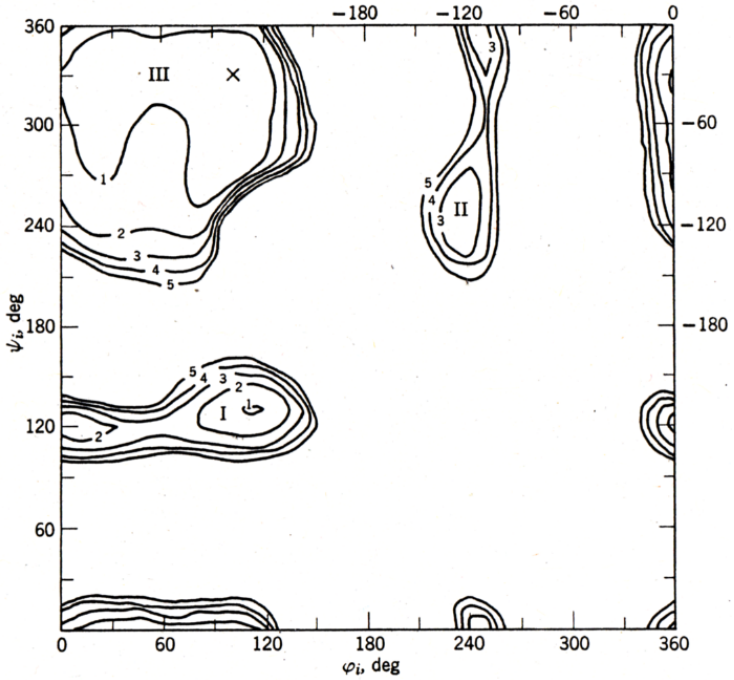
The alanine-alanine dipeptide



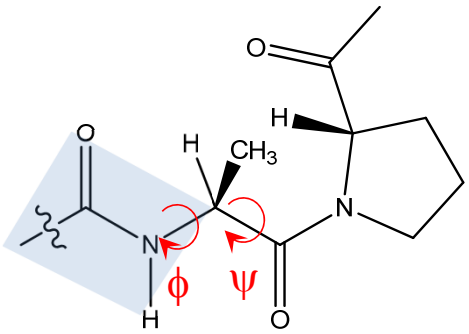
Alanine has a **small sidechain**

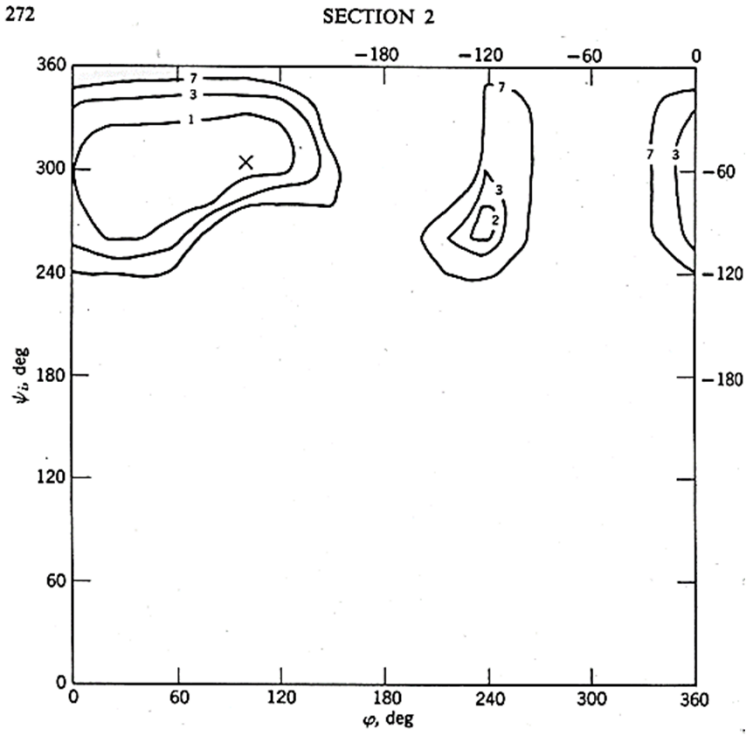
similar to Ramachandran map

β-branched amino acids are more restricted



The alanine-proline dipeptide





Proline has a **seriously restricted** conformational space

increases chain stiffness, but decreases chain entropy, as lower number of conformations are allowed

Chain stiffness & the characteristic ratio

To account for the **increased chain stiffness** due to torsion angle restriction

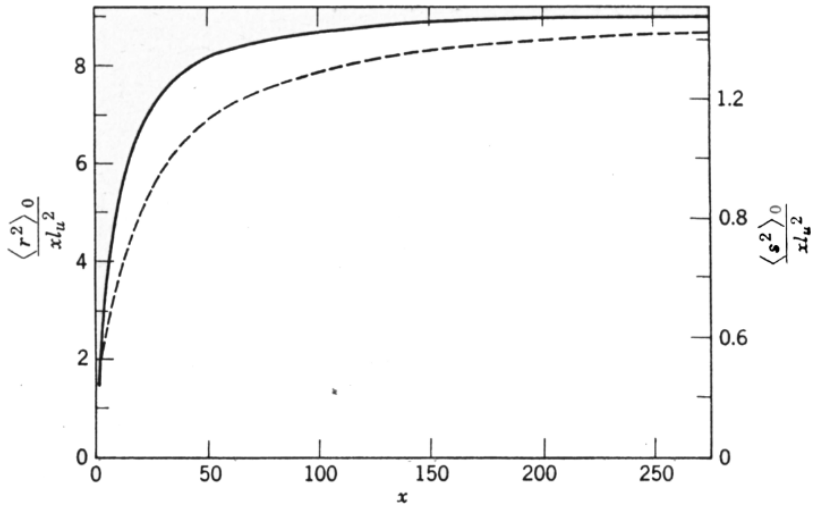
Flory introduced the **characteristic ratio**: $\left\langle R^2 \right\rangle = CNl^2$

$$C = \frac{\left\langle R^2 \right\rangle}{Nl^2}$$

C is dependent on the lenght of the polymer

for long polymers, C adopts a **limiting value**:

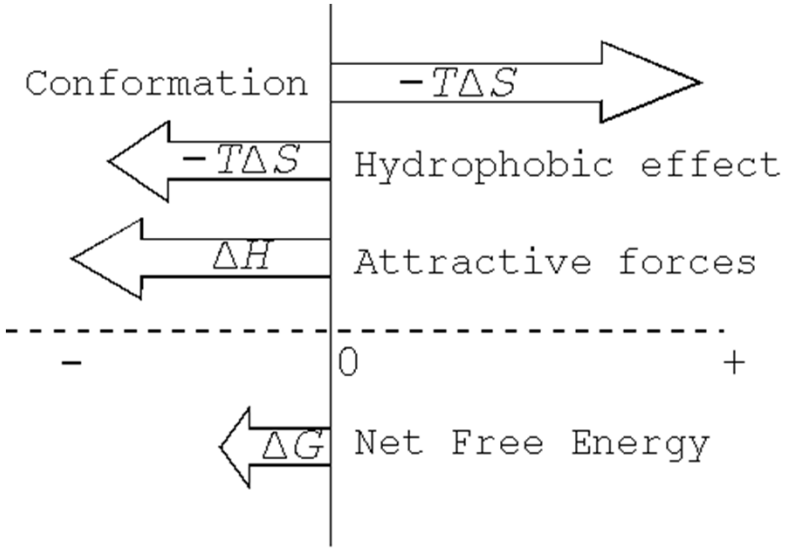
	C_∞
Gly	2.16
Ala	9.27
Pro	116



Summary - Energies

We have investigated all **energetic contributions to protein stability**

We have tried to characterize a ground state for protein folding – **the unfolded state**



What about protein structure?