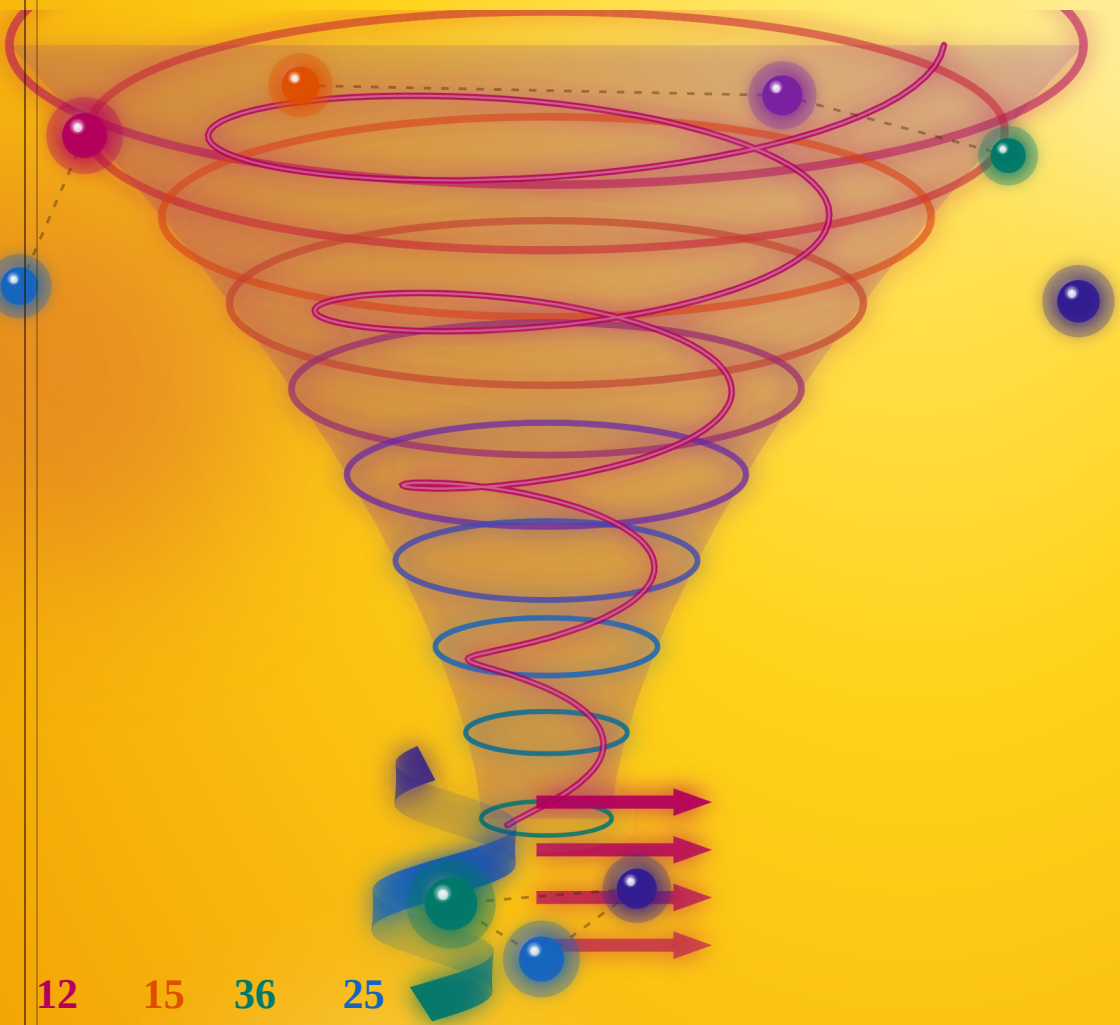
KECUDO

PREMIUM
II
CLASS TWO

PROTEIN

Forces, Folding and Architecture — *Class Two*

Why a Chain Becomes a Structure



12 CHAPTERS

15 FIGURES

36 EXERCISES

25 QUIZ QUESTIONS

The hydrophobic effect, the Ramachandran map, helices and sheets, the few folds that exist, and why the native state is stable by only the energy of a few hydrogen bonds.

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About this book

Forces, Folding and Architecture is the second of three classes in the Kecudo Protein Science series. Class 1 left a chain of known covalent structure and no shape. This book is about how that chain acquires one particular shape, why it holds it so loosely, and what structures are available to it.

It assumes Class 1 or an equivalent grounding in the chemistry of polypeptides. Where a quantity is stated it has been computed rather than quoted, and the method is given so that you can repeat it.

THERMODYNAMICS

Equilibrium constants and folded fractions were computed from $\Delta G = -RT \ln K$ with $R = 8.314$ J $K^{-1}mol^{-1}$ at 298.15 K, giving $RT = 2.479$ kJ/mol. Chemical denaturation uses the linear extrapolation model $\Delta G = \Delta G_{water} - m[D]$; the stability curve uses the Gibbs–Helmholtz form with a constant ΔC_p.

GEOMETRY

Helix and strand parameters — residues per turn, rise, pitch, rotation per residue and (φ,ψ) values — are standard crystallographic values. Distances derived from them (helix lengths, strand spans, fibril dimensions) were computed arithmetically from those parameters.

THE HYDROPHOBIC TERM

Taken as 0.105 kJ/mol per Å² of buried apolar surface, a widely used value from transfer experiments. Figures derived from it are estimates of magnitude, not precise measurements.

ILLUSTRATIVE DATA SETS

The contact-order and hydrogen-exchange figures use representative values chosen to show the relationship clearly; they are labelled as illustrative rather than as a published survey. Published contact-order correlations are strong but not as tight as the set shown.

EXERCISES

Each chapter ends with three exercises — thirty-six in all. Answers are revealed on click in the interactive edition and printed in full in the PDF.

SELF-ASSESSMENT

Twenty-five questions in five parts. Each answer locks once chosen and is explained immediately; your running score appears in the header. A printed copy includes the answer key.

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KECUDO · CLASS TWO

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ASSESSMENT

— Self-assessment: 25 questions 39
— Your rating 45

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Chapter One

The Forces That Fold a Protein

●○○ FOUNDATION

Class 1 ended with a chain of known covalent structure and no shape. This book is about how that chain finds one particular shape, and why it holds it so loosely.

Four interactions and one competitor

Nothing exotic is involved. The same interactions that hold any organic molecule together operate here, with one addition that changes everything: the chain is in water, and water competes for every polar contact.

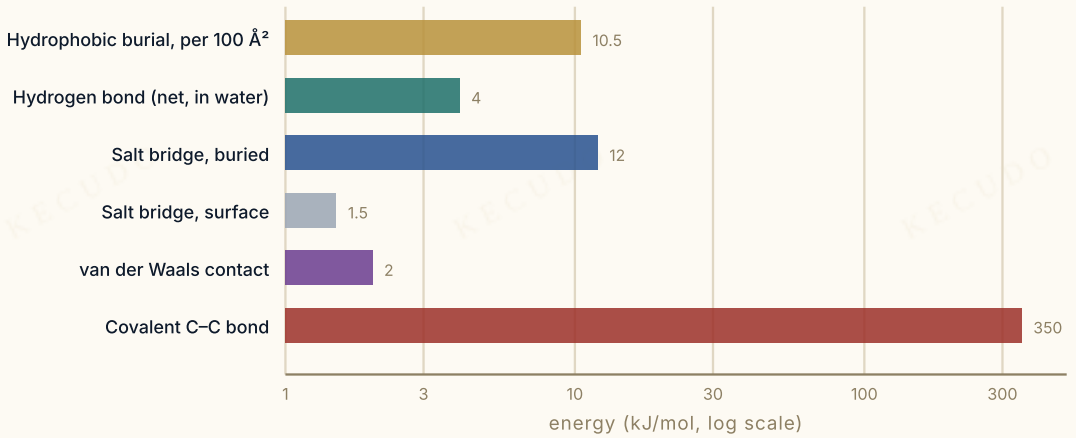


FIG 1.1 — Energy available from each interaction inside a folded protein, in water. The hydrophobic term is shown per 100 Å² of apolar surface buried, because it scales with area rather than with a discrete contact. Note how small everything is next to a covalent bond.

INTERACTION	NET VALUE IN WATER	ROLE IN FOLDING
Hydrophobic burial	~0.105 kJ/mol per Å²	The driving force
Hydrogen bond	2–6 kJ/mol net	Specifies geometry, not stability
Salt bridge, buried	4–20 kJ/mol	Local, context-dependent
van der Waals packing	0.4–4 kJ/mol each	Rewards exact shape fit
Covalent bond (for scale)	**150–450 kJ/mol**	**Not broken during folding**

> **The distinction to hold onto.** The hydrophobic effect provides the *energy* to fold; hydrogen bonds and packing provide the *specificity*. A chain driven only by burial would collapse into a greasy globule with no unique structure — the molten globule of Chapter 9.

The balance sheet of folding

Folding is a competition between a large favourable term and a large unfavourable one, and the difference between them is small. That single fact explains most of what follows.

TERM	TYPICAL MAGNITUDE, 100 RESIDUES	SIGN
Hydrophobic burial (~1 400 Å²)	~147 kJ/mol	Favourable
Hydrogen bonding and packing	~100–150 kJ/mol	Favourable
Conformational entropy of the chain	~280 kJ/mol	**Unfavourable**
Hydration of exposed polar groups	tens of kJ/mol	Mixed
Net ΔG of folding	**−20 to −60 kJ/mol**	Favourable, barely

Two terms of roughly 150 and 280 kJ/mol cancel to leave 40. A protein is stable by the energy of a handful of hydrogen bonds — the difference between two large numbers, each of which we can only estimate to within ten per cent.

> **Why marginal stability is not a design flaw.** A protein that was stable by 300 kJ/mol could not be unfolded for degradation, could not breathe to admit a ligand, and could not be regulated. Marginal stability buys dynamics, turnover and control — the subjects of Chapter 10 and Class 3.

EXERCISES

1. A protein buries 1 200 Å² of apolar surface on folding. What is the hydrophobic contribution at 0.105 kJ/mol per Å²?

   > 1 200 × 0.105 = **126 kJ/mol** favourable.

2. If that same protein has ΔG of unfolding of only 35 kJ/mol, where did the other ~91 kJ/mol go?

   > Overwhelmingly into the conformational entropy lost by the chain, plus the desolvation of polar groups. Folding is the small difference between large opposing terms.

3. Why would a protein stable by 300 kJ/mol be a problem for a cell?

   > It could not be unfolded for degradation or quality control, could not breathe to bind ligands, and could not be regulated by conformational change. Marginal stability is functional.

Chapter Two

The Hydrophobic Effect ●○○ FOUNDATION

The force that folds proteins is not an attraction between greasy groups. It is the behaviour of the water around them.

What actually happens

Place an apolar group in water and the surrounding molecules cannot hydrogen-bond through it. They reorganise into a more ordered arrangement around the solute, losing entropy. Bring two such groups together and some of that ordered water is released to the bulk — and *that* entropy gain drives association.

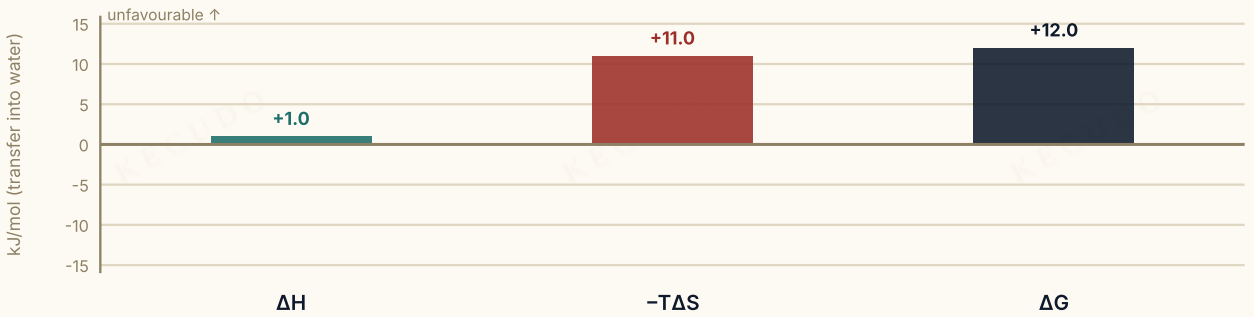


FIG 2.1 — Thermodynamics of transferring an apolar solute from a nonpolar solvent to water, at 25 °C. The process is close to enthalpically neutral and strongly entropically unfavourable — the signature of the hydrophobic effect. At higher temperature the entropic term weakens, which is why the effect is temperature-dependent.

PROPERTY	CLASSICAL HYDROPHOBIC EFFECT
ΔH of transfer to water	Near zero, sometimes slightly favourable
ΔS of transfer to water	Strongly negative
ΔG of transfer to water	Positive — apolar solutes avoid water
Heat capacity change ΔC_p	Large and positive on exposure
Scaling	**With buried *surface area*, ~0.105 kJ/mol per Å²**

The heat capacity signature. A large positive ΔC_p on unfolding is the experimental fingerprint of apolar burial, and it is the reason stability curves are parabolic rather than linear — and therefore why proteins can in principle denature at low temperature as well as high (Chapter 8).

PART A · BASICS

01 Which interaction supplies most of the *energy* for folding?

- **A** The hydrophobic effect
- **B** Backbone hydrogen bonds
- **C** Disulfide bonds
- **D** Salt bridges

02 How many residues per turn does an α helix contain, and which hydrogen bond defines it?

- **A** 3.0, i→i+3
- **B** 4.4, i→i+5
- **C** 2.0, i→i+2
- **D** 3.6, i→i+4

03 Approximately what fraction of the Ramachandran map is accessible to a general residue?

- **A** About 50 %
- **B** About 35 %
- **C** About 15 %
- **D** About 2 %

04 Why are parallel β sheets less common as isolated hairpins than antiparallel ones?

- **A** Their hydrogen bonds are weaker
- **B** They need a long crossover connection between adjacent strands
- **C** They cannot twist
- **D** Their φ,ψ values are forbidden

05 A β sheet in a globular protein is...

- **A** right-handed twisted
- **B** flat
- **C** left-handed twisted
- **D** helically coiled

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Thank you for learning with Kecudo.

NEXT IN THE SERIES

Class 3 · Proteins at Work. The folded, dynamic, marginally stable molecule of this book finally does something: recognises other molecules, catalyses reactions at rates no chemist can match, sits in membranes, works in a crowded cell, and is eventually taken apart.

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