CH 8613 Journal Club:

"Hydrophobicity of Amino Acid Residues in Globular Proteins"

Rose, *et al.* (1985) *Science.* ***229:*** 834-838.

Nicholas Fitzkee
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Key Questions

- Do proteins have a hydrophobic core or not? Is it this simple, or more complex?
- How much does hydrophobicity contribute to protein stability?
- Can buried surface be quantitatively related to hydrophobicity scales?

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Context: Transfer Free Energies

TABLE IX

Hydrophobicity scale: Δf_t for transfer of amino acid side chain from 100% organic solvent to water at 25°

Amino acid side chain[a]	Δf_t
	cal/mole
Tryptophan	3400[b]
Norleucine	2600[c]
Phenylalanine	2500[b]
Tyrosine	2300[b]
Dihydroxyphenylalanine	1800[d]
Leucine	1800[b]
Valine	1500[d]
Methionine	1300[d]
Histidine	500[b]
Alanine	500[d]
Threonine	400[d]
Serine	−300[d]

[a] No figure is given for proline. The rather large value given earlier is subject to greater uncertainty than any of the figures listed here.

[b] Average of values for ethanol and dioxane. For leucine and histidine the values for ethanol have been given double weight because of greater accuracy of extrapolation.

[c] Average of values for ethanol, butanol, and acetone.

[d] Values for ethanol only.

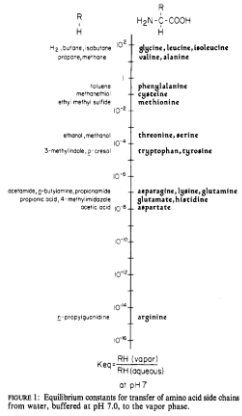

FIGURE 1: Equilibrium constants for transfer of amino acid side chains from water, buffered at pH 7.0, to the vapor phase.

- **Contributing factors:**
  - Side chain vs. entire backbone
  - Natural, charged amino acids vs. chemically modified uncharged amino acids
  - Type of solvent (ethanol, octanol, etc.)

Nozaki and Tanford. (1971) *J. Biol. Chem.* **246:** 2211. Wolfenden *et al.* (1981) *Biochemistry.* **20:** 849. 3

The Key Problem

- Classify side chains qualitatively: “Mostly buried” or “Mostly accessible”
  - Plenty of hydrophobic side chains are on the surface
- Residue surface area does correlate with hydrophobicity
  - But not so well with burial upon folding
- Is there a way to resolve this?

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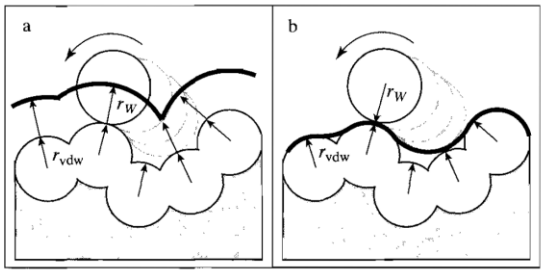
Tool: Accessible Surface Area

Figure 3.25 The solvent-accessible surface (solid line) of a molecule is calculated by rolling a ball of radius r_W over the molecular surface. The solvent-accessible surface is defined (a) by the path traveled by the center of the ball, or (b) by the contacts made between the ball and the van der Waals surface.



- Water is modeled as a sphere (typical radius is 1.4 Å)
- Panel a (solvent accessible surface area, or ASA) is more frequently used than b (vdW surface area)
- **Programs:** Naccess (J. Thornton) or Molecular Surface Package (M. Connolly)
- Also implemented in-house in the Fitzkee lab

Van Holde, page 156.

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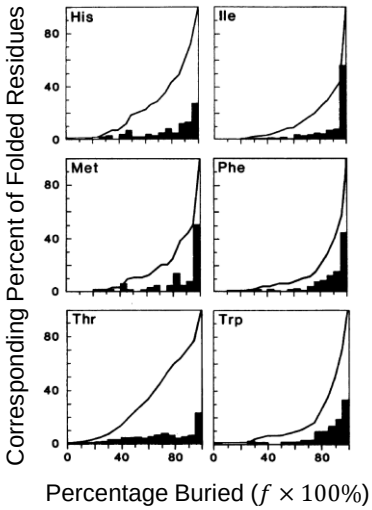
Key Insight: Fractional Burial

- Reference state is Gly-X-Gly tripeptide (A_0)
- Look at database of folded residues and calculate fractional burial:

$$f = \frac{A_0 - \langle A \rangle}{A_0}$$

- No longer qualitative, and normalized by residue size



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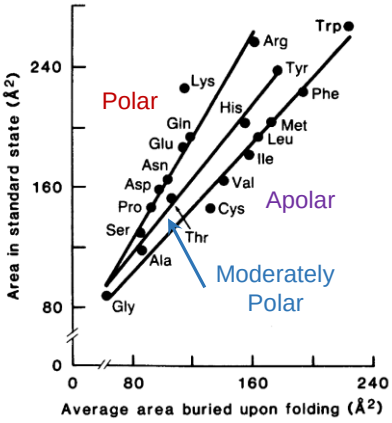
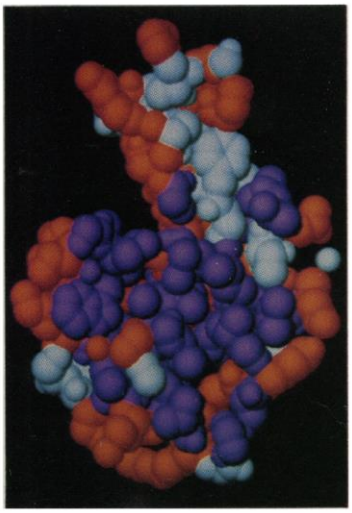
Three Classes of Residues





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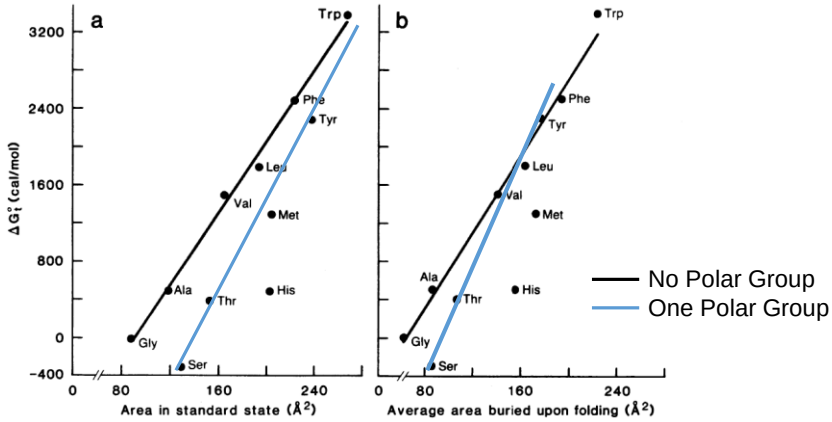
Hydrophobicity and Surface Area



- Very good agreement for hydrophobic residues

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Implications

- Once normalized to residue size, hydrophobicity does indeed correlate with residue burial
- Residue type also influences correlation
  - Later, an appreciation for “hydrophobic” vs “hydrophilic” ASA would be recognized
- The selection of hydrophobicity scale is important (dilute vapor vs. water, etc.)
- Hydrophobic contribution to folding can be estimated by looking at surface area burial

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Meta-Notes: Journal Club

- Be willing to go outside of the paper for clarity and context
  - Supporting Information
  - Important papers referenced
  - Your textbook or good web pages
- Not all figures and equations were included: Show what’s really important
- Don’t be afraid to digress to discuss a point your audience may not understand (e.g. rolling sphere ASA)
- Avoid PowerPoint slide themes; stick with simple and clean
- Practice, and *think* while you practice

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