
Water: What might CG models aims for?

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Water revisited – read Stillingner's paper

25 July 1980, Volume 209, Number 4455

SCIENCE

Water Revisited

Frank H. Stillingner

A comprehensive molecular theory for water is needed for two reasons. First, this substance is a major chemical constituent of our planet's surface and as such it may have been indispensable for the genesis of life. Second, it exhibits a fascinating array of unusual properties both in pure form and as a solvent. Physical scientists have attempted to respond

high dielectric constant; (vi) anomalously high melting, boiling, and critical temperatures for a low-molecular-weight substance that is neither ionic nor metallic; (vii) increasing liquid fluidity with increasing pressure; and (viii) high-mobility transport for H^+ and OH^- ions.

Some of these attributes are shared with other substances; perhaps we will

Hydrogen Bonding

The key to understanding liquid water and its solutions lies in the concept of the "hydrogen bond," which was first systematically studied by Latimer and Rodebush over half a century ago (3). In general terms it is found that specific attractions exist between electronegative atoms (such as nitrogen, oxygen, fluorine, and chlorine) and hydrogen (or deuterium) atoms, particularly when the latter are themselves chemically bonded directly to electronegative atoms (4). Hydrogen bonds are strongly directional; the chemical bond containing the hydrogen atom that is donated to the hydrogen bond tends to point directly at the nucleus of the hydrogen-accepting electronegative atom. The strengths of hydrogen bonds (≈ 5 kilocalories per mole) are normally intermediate between those of weak van der Waals interactions (≈ 0.3

Water revisited, Stillinger, Science, 1980

Summary. Liquid water consists of a macroscopically connected, random network of hydrogen bonds, with frequent strained and broken bonds, that is continually undergoing topological reformation. Anomalous properties of water arise from the competition between relatively bulky ways of connecting molecules into local patterns characterized by strong bonds and nearly tetrahedral angles and more compact arrangements characterized by more strain and bond breakage. However, these alternatives constitute virtually a continuum of architectural possibilities rather than a discrete pair of options. The singular behavior of supercooled water near -45°C and the “hydrophobic” attraction between nonpolar entities are due to the same underlying phenomenon, namely, the clumping tendency of relatively strain-free convex cages or polyhedra.

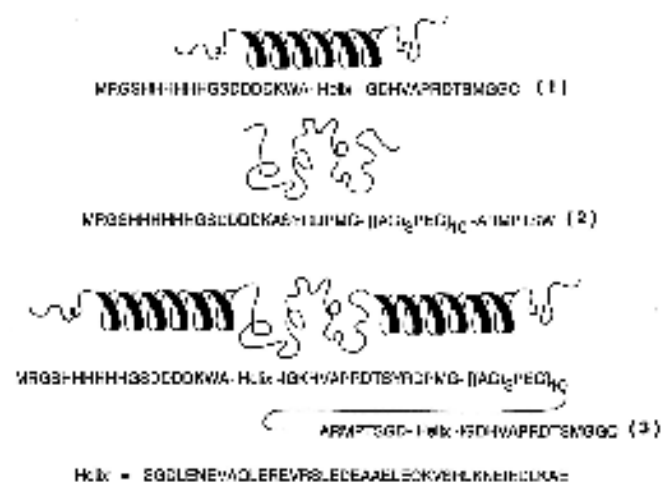
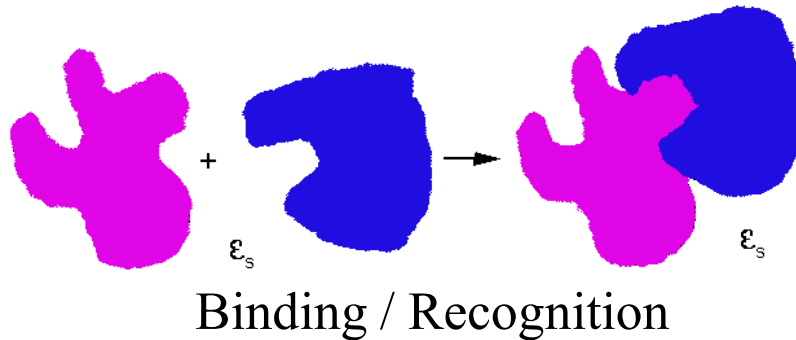
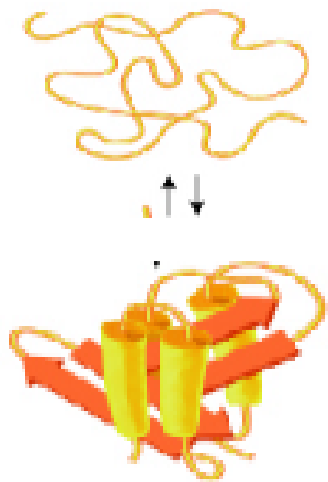
Coarse-graining of water?

- Please see a very interesting paper on this topic is by M. E. Johnson, T. Head-Gordon, and Ard A. Louis, J. Chem. Phys., 126, 144509, 2007.
- Teresa Head-Gordon will present this work in detail in one of her lectures. In my presentation yesterday, we have done preliminaries. If you read that paper, you will get a lot out her presentation.

Examples of self-assembly processes

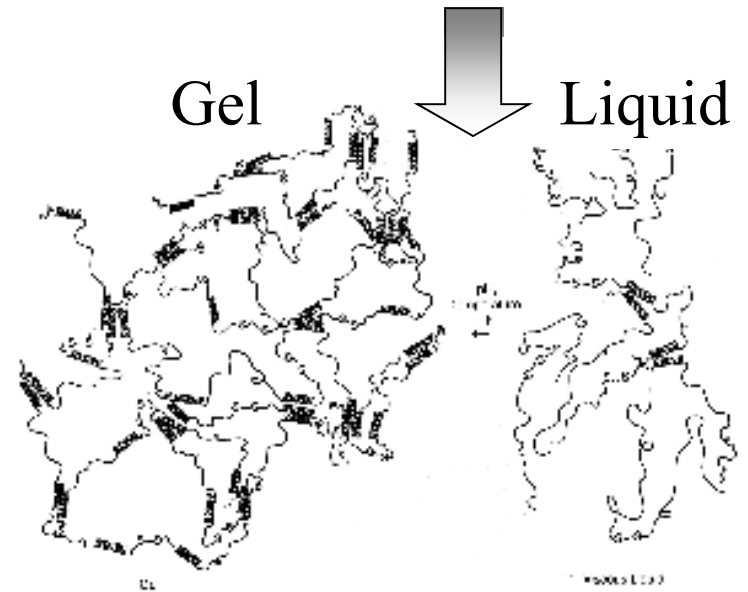
Biologically inspired self-assembly of synthetic molecules

Protein folding



Why is biomolecular self-assembly interesting?

Leads to 3-dimensional structures that can perform an exciting array of functions.



Petka et al., Science, 1998.

What aspects of water would I want the CG model to reproduce wrt self-assembly?

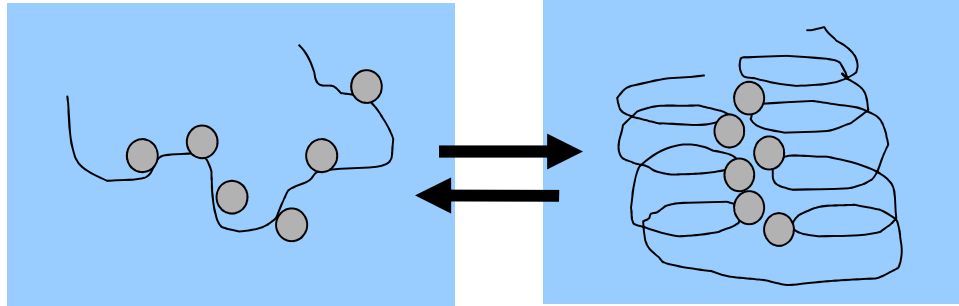
- “Reproducing anomalous properties/behavior is probably less important.” (S. Sastry).
- More important is to reproduce hydration phenomena and properties of water-mediated interactions between:

Hydrophobic solutes

Ionic solutes

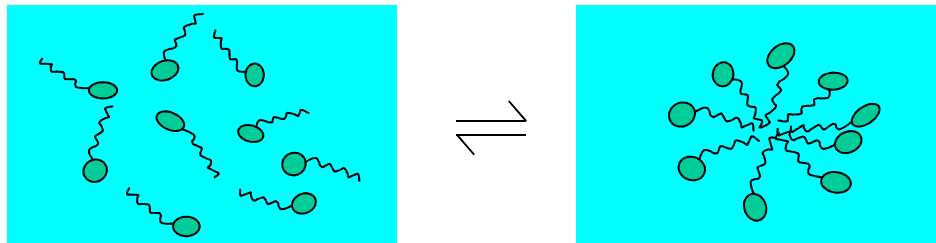
Common features of self-assembly processes...

Protein
Folding



● Hydrophobic
residue

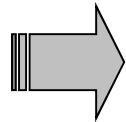
Micelle
formation



Similar physico-chemical interactions drive
these self-assembly processes

Water provides a driving force for self-assembly processes in solution

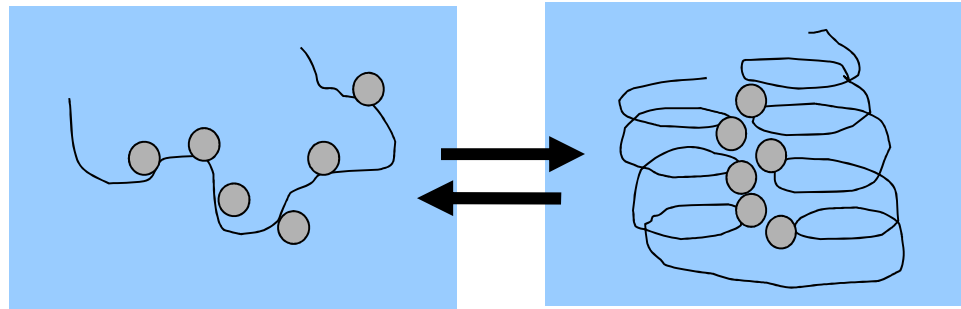
water
mediated
interactions



- * Non-covalent in nature
- * Result from specific solute-water interactions
- * Strong function of water structure

What is a good way to begin?

**Protein
Structure/
Stability**



● Hydrophobic
residue

What is the effect of T, P, salts etc. on protein stability?

Large-scale molecular dynamics simulations:

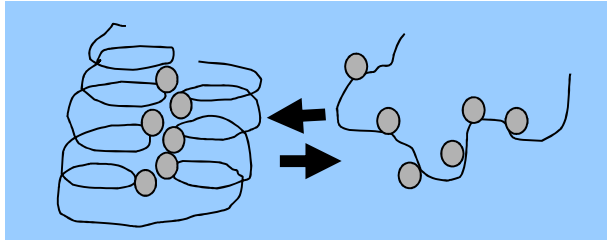
(problems? computationally intensive → only short time-scales can be probed)

Identify key stabilizing interactions and study those in detail → infer effect on proteins (qualitative)

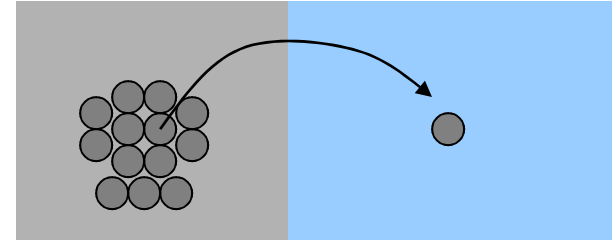
Focus on hydration and interactions of small solutes first!

Hydration of small solutes (as models for complex processes)

Actual process



Hydrophobic transfer model



Thermodynamics:

$$\Delta G > 0$$

$$\Delta C_p > 0$$

$$\Delta G > 0$$

$$\Delta C_p > 0$$

$$\Delta S \ll 0$$

← Water structure

Effect of salts/additives:

Kosmotropes

Chaotropes

on folding

stabilizing

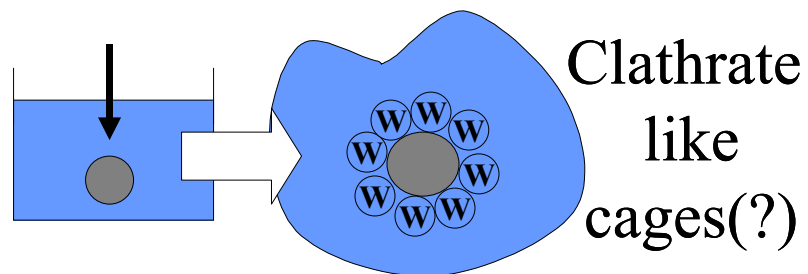
destabilizing

on hydrophobic solutes

Salt-out

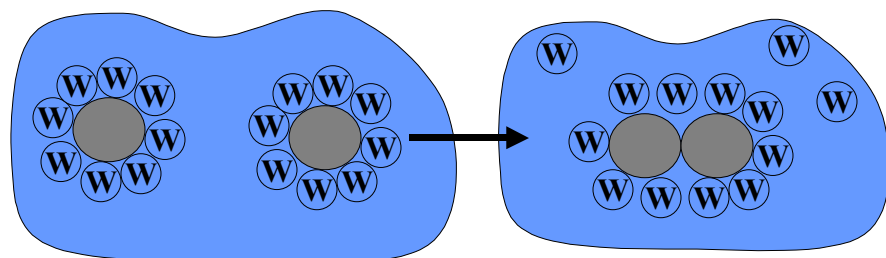
Salt-in

Hydrophobic hydration & interactions



$$\Delta S < 0$$
$$\Delta C_p > 0$$
$$\Delta G > 0$$

Hydrophobic hydration
is thermodynamically
unfavorable.



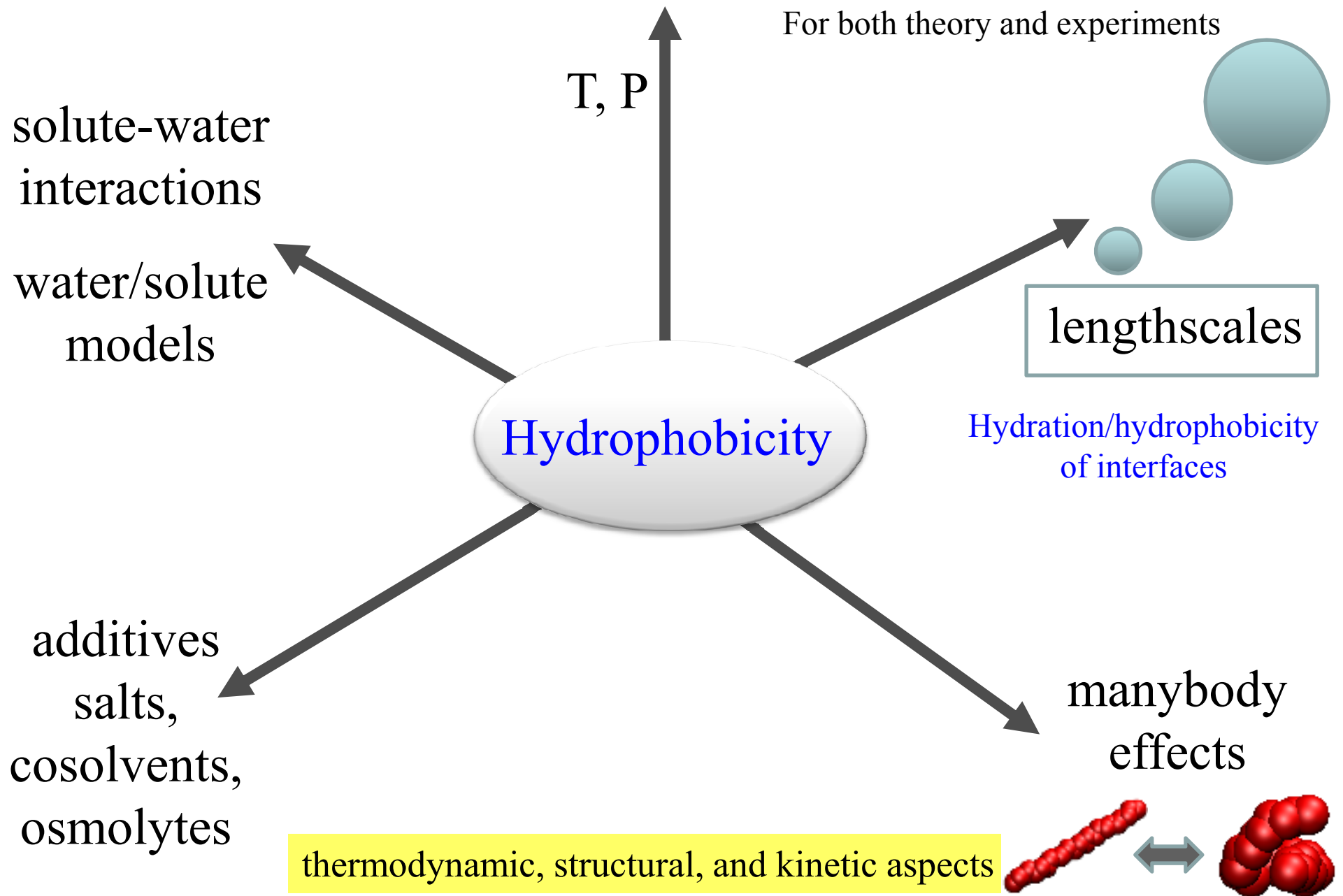
$$\Delta S > 0$$
$$\Delta G < 0$$

Hydrophobic association
is favored by increase in
water entropy (!)

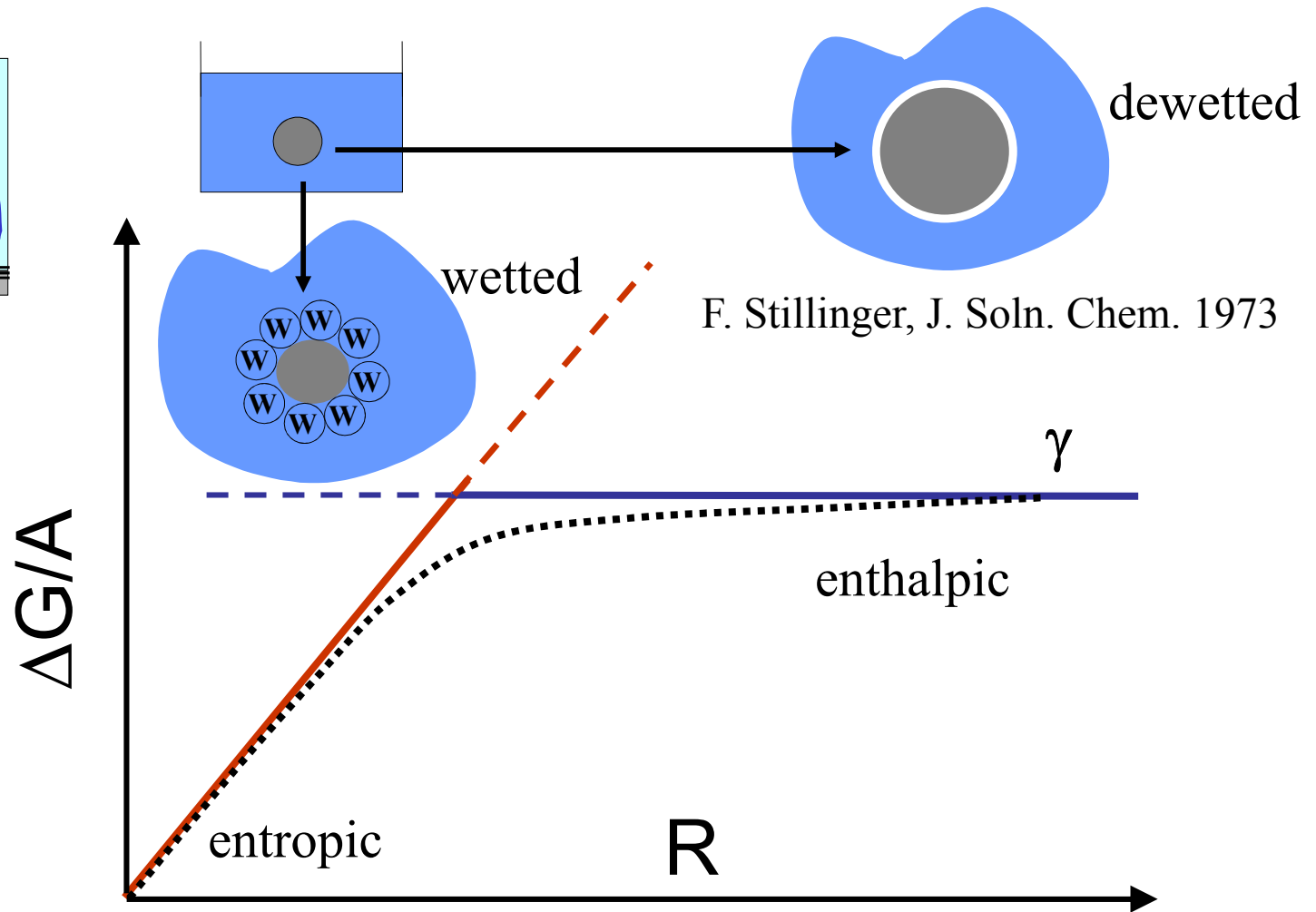
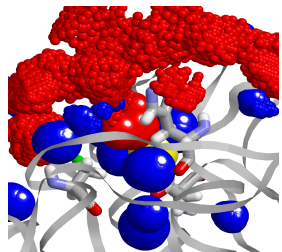
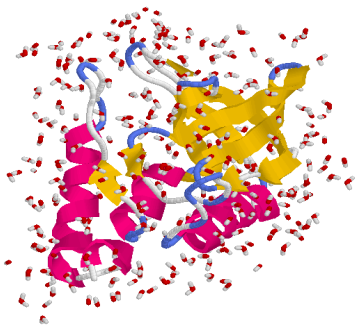
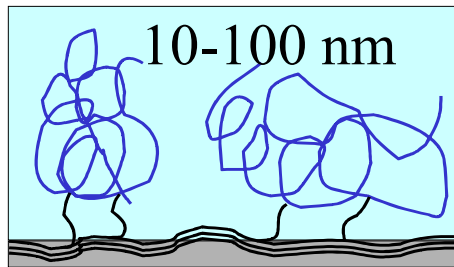
Water structure  Water-mediated interactions

This is typically characterized by the Me-Me PMF in water.

Hydrophobicity: a multidimensional challenge



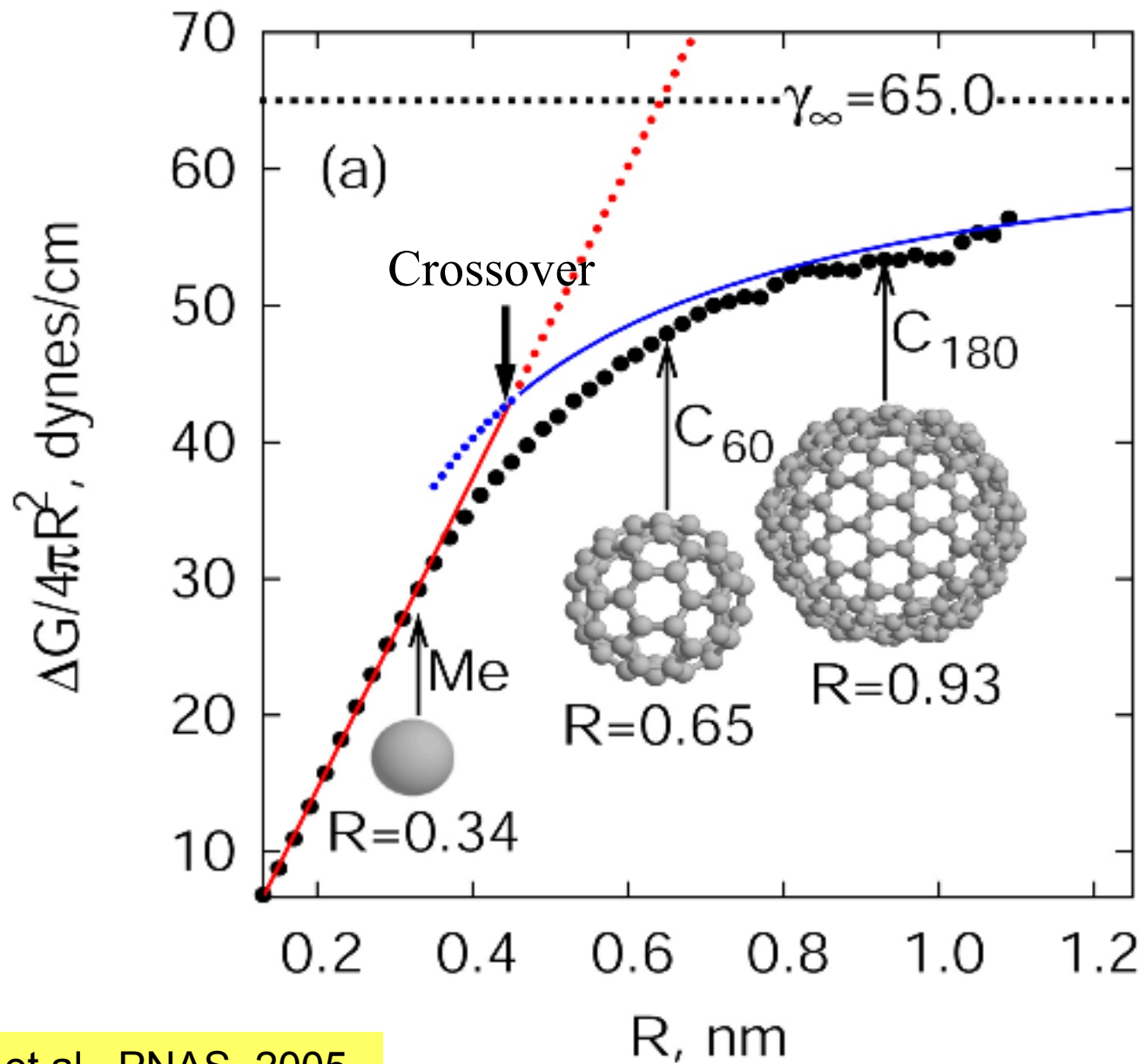
Lengthscale-dependent hydrophobic hydration



- Structural transition \rightarrow wetted to dewetted
- Thermodynamic transition \rightarrow entropy to enthalpy dominated

Lum, Chandler, Weeks, JPCB, **103**, 4570 (1999), Chandler, Nature, 2005.

Lengthscale-dependent hydrophobic hydration



Crossover lengthscale \sim Egelstaff-Widom lengthscale!

TABLE II. Values of $\chi\sigma$ for liquids at or near their triple points.

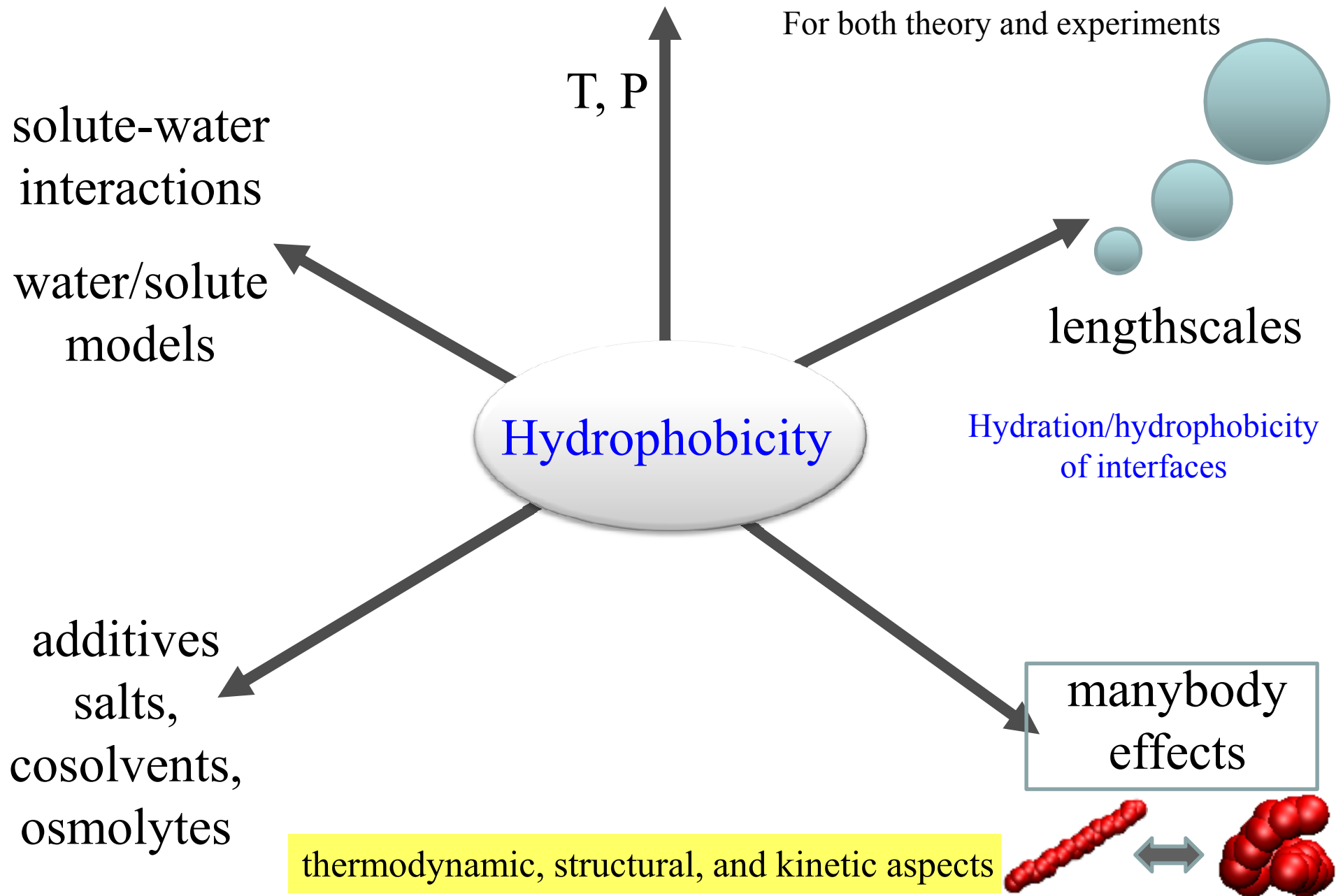
	σ (dyn/cm)	χ (cm ² /dyn $\times 10^{12}$)	$\chi\sigma$ (Å)
Other metals			
Iron	1790 ^e	1.43 ^d	0.25
Copper	1280 ^c	1.45 ^d	0.19
Silver	940 ^e	1.86 ^d	0.18
Zinc	785 ^e	2.4 ^b	0.19
Cadmium	666 ^e	3.2 ^b	0.21
Lead	470 ^e	3.5 ^b	0.17
Bismuth	395 ^f	4.3 ^b	0.17
Molten salts^g			
Sodium chloride	116	29	0.34
Potassium chloride	97	38	0.37
Sodium bromide	99	34	0.34
Potassium bromide	90	44	0.39
Sodium iodide	88	40	0.35
Potassium iodide	78	50	0.39
Water ^h	76	50	0.38

$$R_c \approx 6\chi\gamma$$

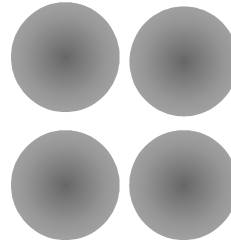
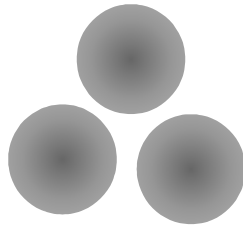
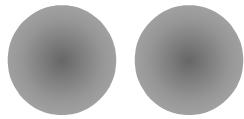
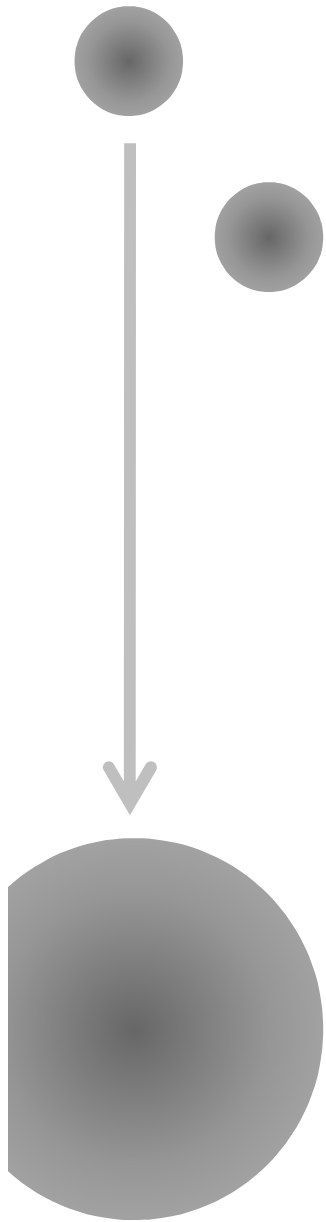
“Although, surface tension and compressibility of liquids vary by a factor of 150, it is shown that their product varies only by a factor of 3 and is equal always to a few tenths of an angstrom.”

Egelstaff and Widom, JCP, 1972

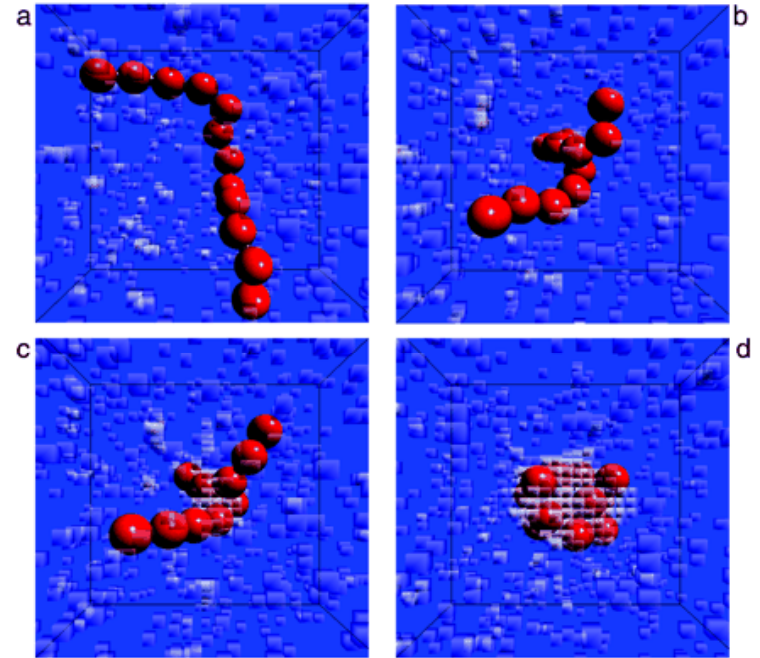
Hydrophobicity: a multidimensional challenge



Manybody hydrophobic effects



Shimizu and Chan, JCP.
Scheraga et. al.
Rank and Baker, Prot. Sci.
Ghosh and Garde, JPCB.



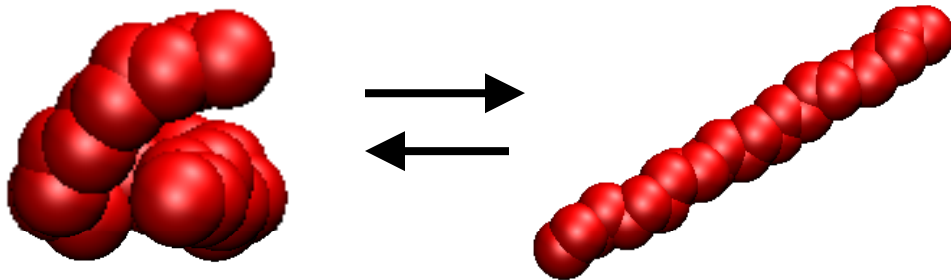
Drying induced collapse of a hydrophobic polymer

ten Wolde and Chandler, PNAS, 2002

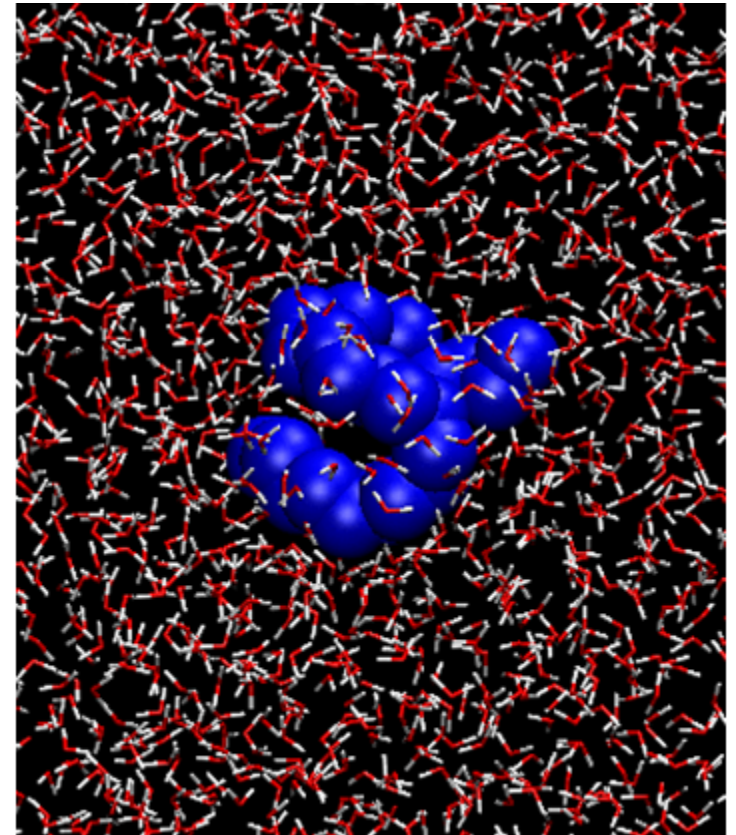
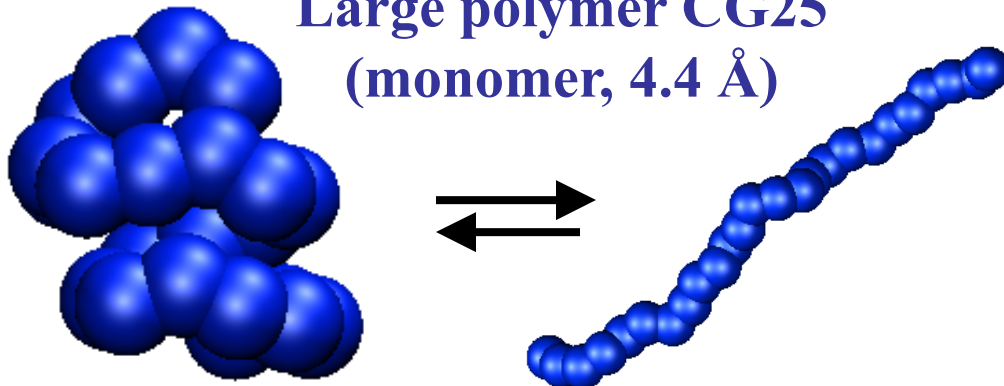
Hydrophobic collapse in water

We studied folding/unfolding of hydrophobic polymers in water using all atom MD simulations to probe structure, thermodynamics, and mechanism

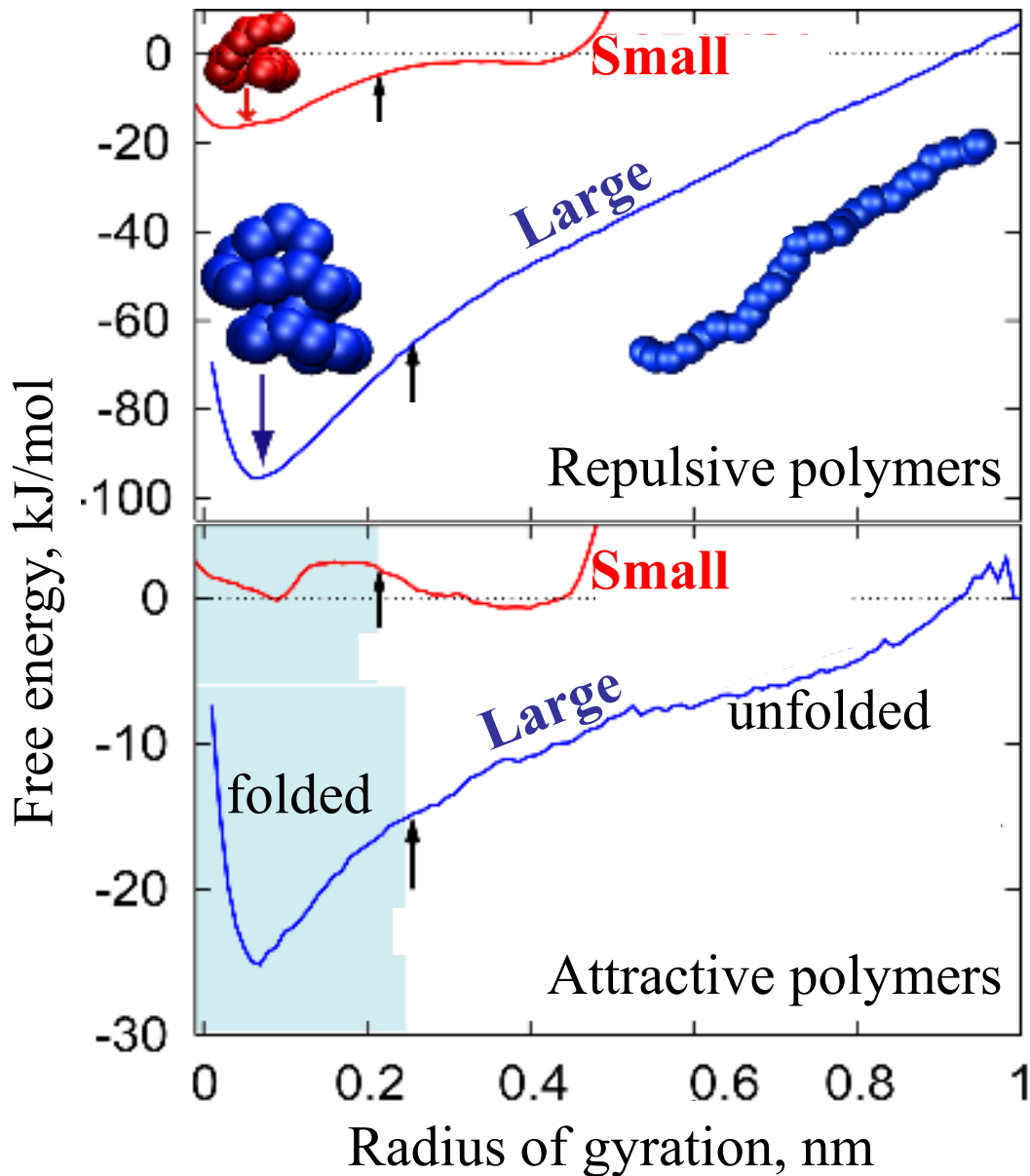
Small polymer C25
(monomer, 3.73 Å)



Large polymer CG25
(monomer, 4.4 Å)



Hydrophobic collapse of polymers



- Repulsive polymers show strong stabilization of compact folded states

- Larger the lengthscale → stronger the driving force for folding.

- Higher the attractions → lesser is the driving force for folding

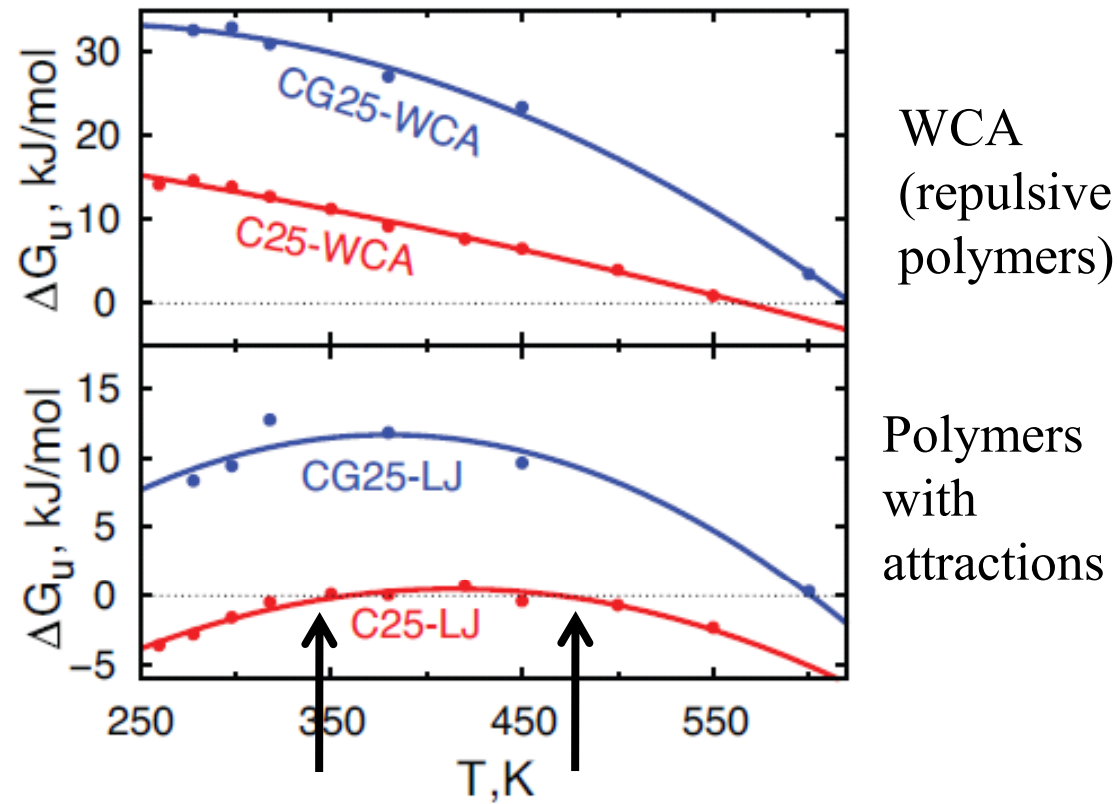


Fig. 3. Free energy of polymer unfolding. The free energy ΔG_U obtained by integrating $W(R_g)$ curve as $\exp(-\Delta G_U/k_B T) = \int_{R_g^{\text{cut}}}^{R_g^{\text{max}}} \exp(-W(R_g)/k_B T) dR_g / \int_{R_g^{\text{min}}}^{R_g^{\text{cut}}} \exp(-W(R_g)/k_B T) dR_g$ is shown by circles. The curves are obtained by fitting the data to form $\Delta G_U(T) = \Delta H_U(T_{\text{ref}}) - T\Delta S_U(T_{\text{ref}}) + \Delta C_{p-u}[(T - T_{\text{ref}}) - T \ln(T/T_{\text{ref}})]$ shown by solid lines, where $T_{\text{ref}} = 298$ K was used.

Osmolyte Trimethylamine-*N*-Oxide Does Not Affect the Strength of Hydrophobic Interactions: Origin of Osmolyte Compatibility

Manoj V. Athawale, Jonathan S. Dordick, and Shekhar Garde

The Howard P. Isermann Department of Chemical & Biological Engineering, and Center for Biotechnology & Interdisciplinary Studies, Rensselaer Polytechnic Institute, Troy, New York 12180

Guanidinium induced unfolding of hydrophobic polymers by direct interactions

Rahul Godawat, Sumanth N. Jamadagni, and Shekhar Garde *

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and Center for Biotechnology and Interdisciplinary Studies,
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(Dated: April 15, 2009)

Accepted,
JPCB

642

J. Phys. Chem. B **2005**, *109*, 642–651

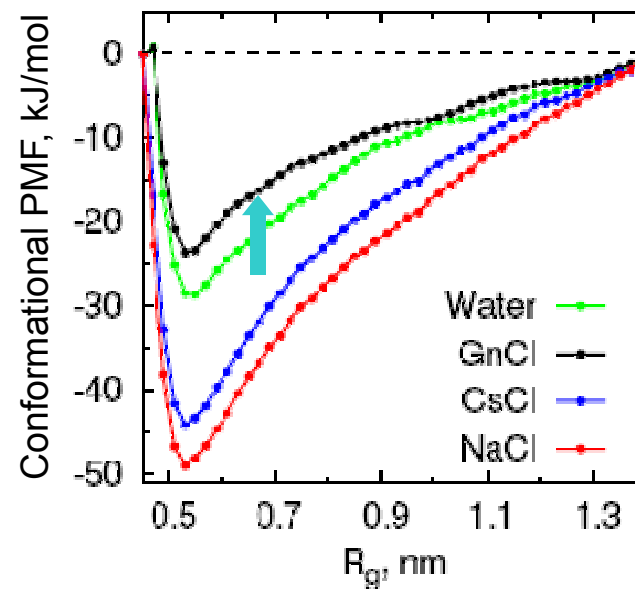
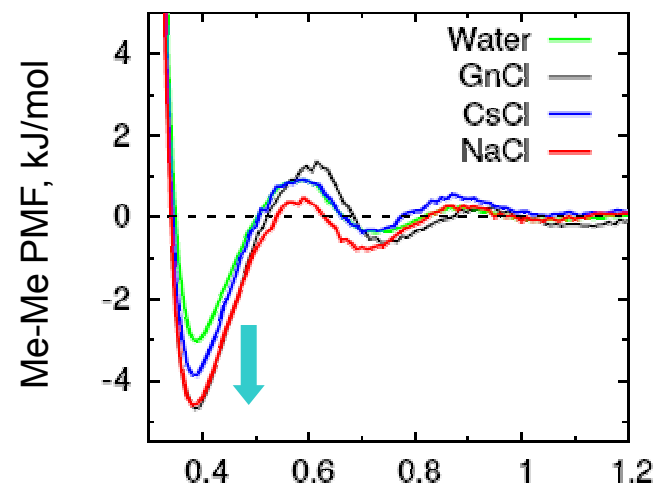
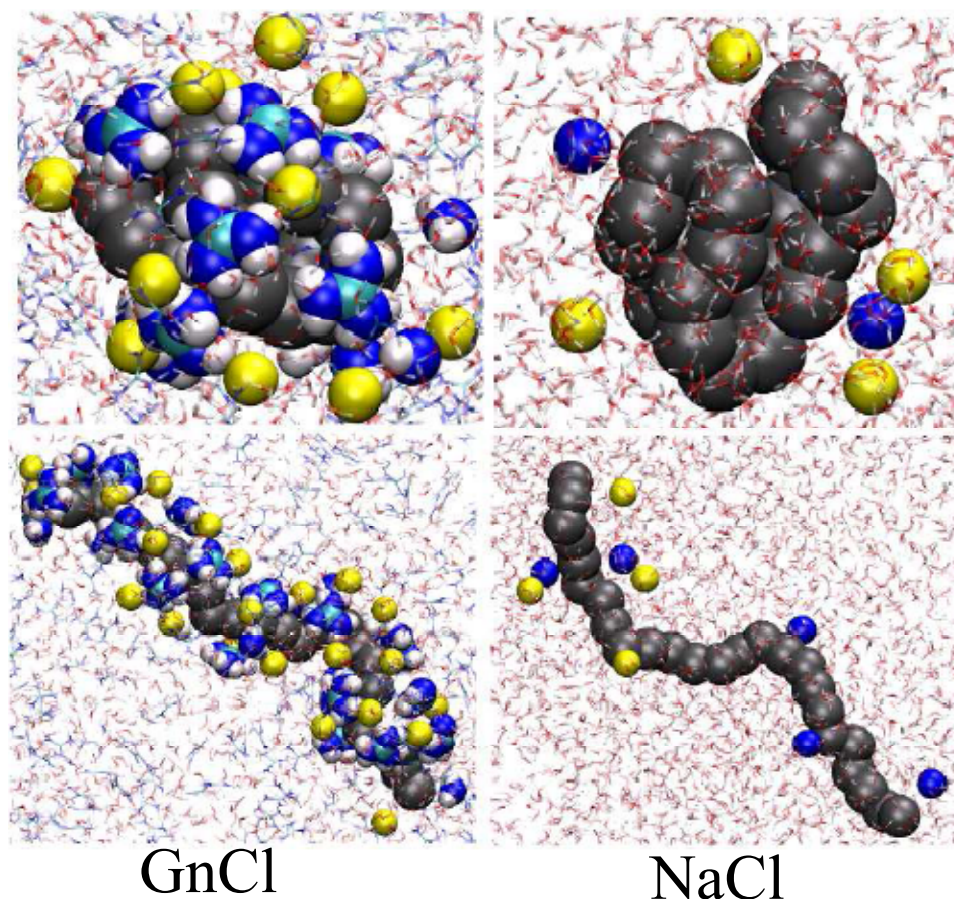
On the Salt-Induced Stabilization of Pair and Many-body Hydrophobic Interactions

Tuhin Ghosh, Amrit Kalra,[†] and Shekhar Garde*

*The Howard P. Isermann Department of Chemical & Biological Engineering, Rensselaer Polytechnic Institute,
Troy, New York 12180*

Received: June 6, 2004; In Final Form: October 5, 2004

How guanidinium chloride unfolds a hydrophobic polymer?



Hydrophobic polymer unfolds in GnCl solutions due to direct van der Waals interactions between polymer and GnCl.

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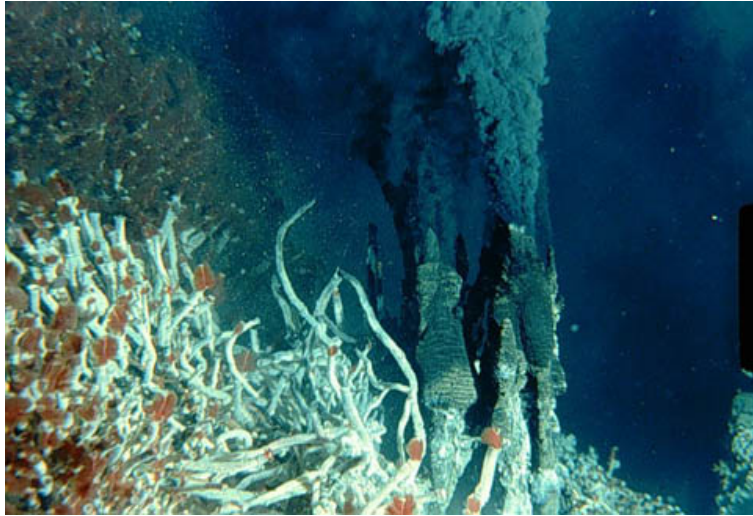
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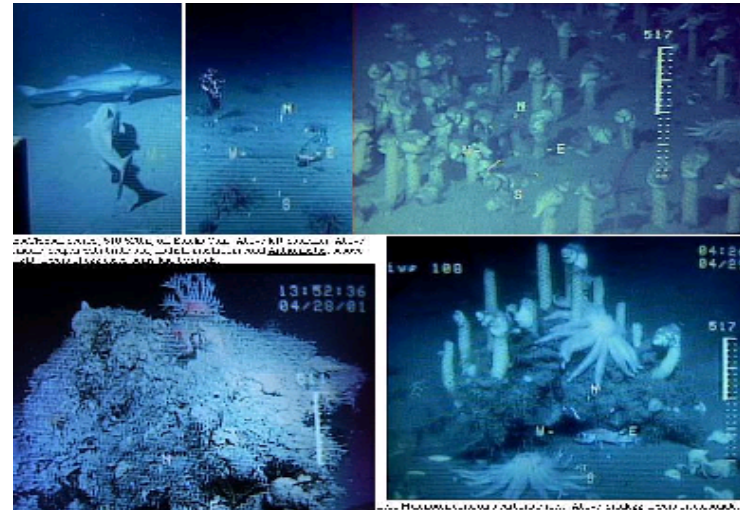
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Biologically stressed environments



Hydrothermal vents:
temperature stress



Ocean depths : Pressure stress

Problem → stress causes
perturbation of protein structure
and function within the cells.



Saturated brine: osmotic stress

How do organisms survive under stressful conditions?

Adaptation: a key to survival

Evolution of amino acid sequence:

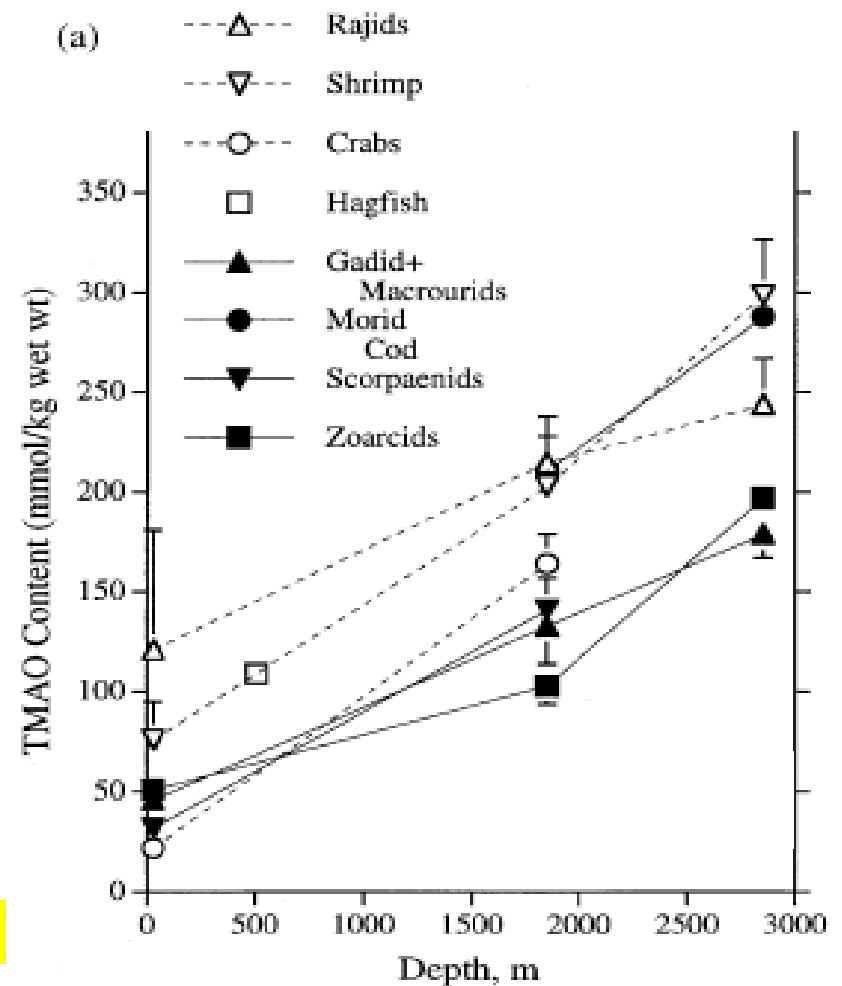
MKKYVCTVCG YEYDPAEGDP DNGVKPGTSF DDLPADWVCP VCGAPKSEFE AA----
--AKWVCKICG YIYDEDAAGDP DNGISPGTKF EELPDDWVCP ICGAPKSEFE KLED

Accumulation of osmolytes

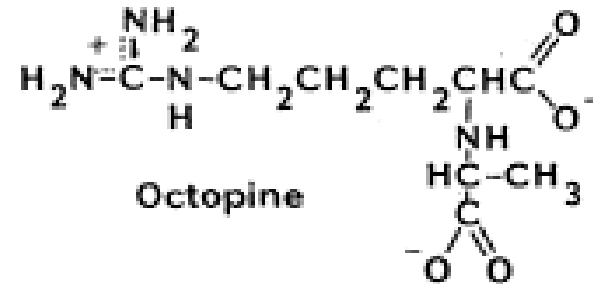
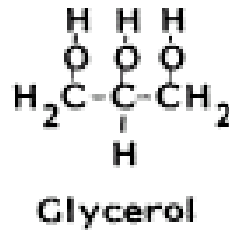
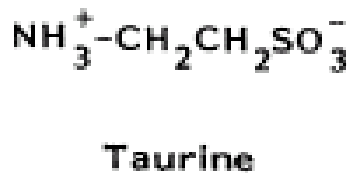
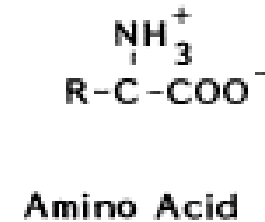
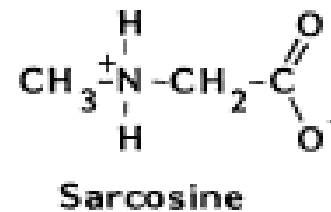
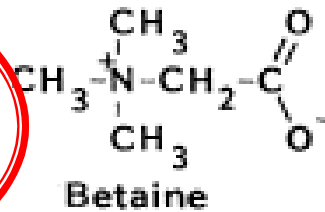
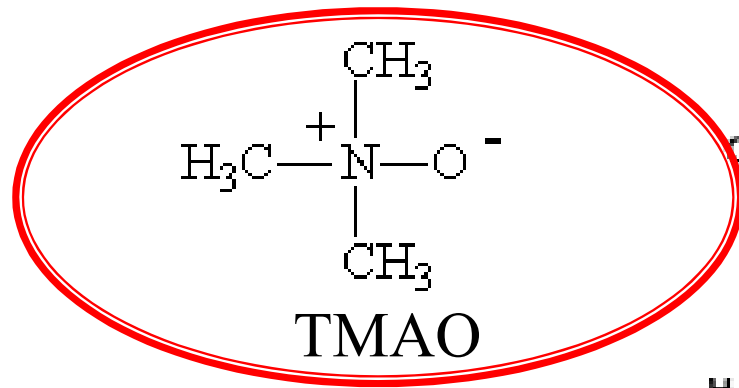
(polyols, sugars, amino acids and derivatives, methylamines)

osmolyte content increases linearly with increasing depth of the ocean in some groups of animals – a high pressure adaptation

Yancey et. al. 2002. *Comp. Biochem. Physiol.* 133:667-676

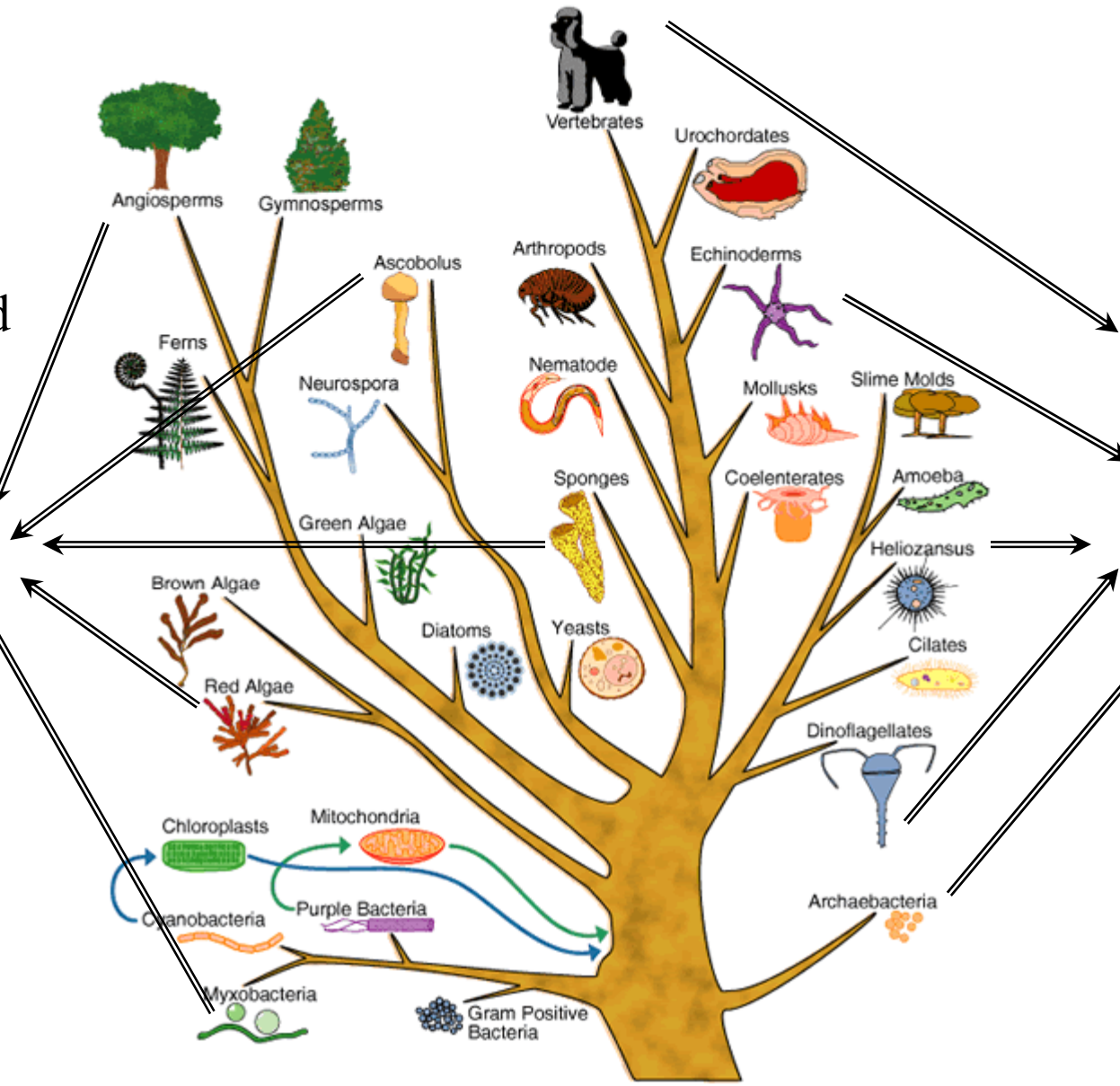


Adaptation: a key to survival



- Accumulated in very high (molar) concentrations.
- Compatible solutes \Rightarrow stabilize proteins without perturbing structure/function within the cell
- Unity in diversity

TMAO and a few common osmolytes are the solution despite the diversity



TMAO and a few common osmolytes are the solution despite the diversity

Nature has converged on a few selected osmolytes

Fundamental interest in osmolytes

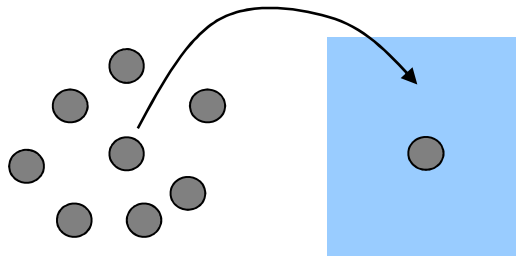
- How do osmolytes stabilize proteins ?

- **Stability**

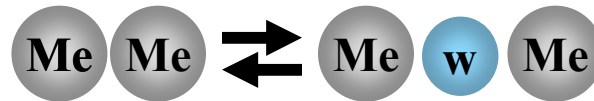
- How do cells tolerate high (molar) concentrations of these solutes? Can we explain the compatibility?

- **Compatibility**

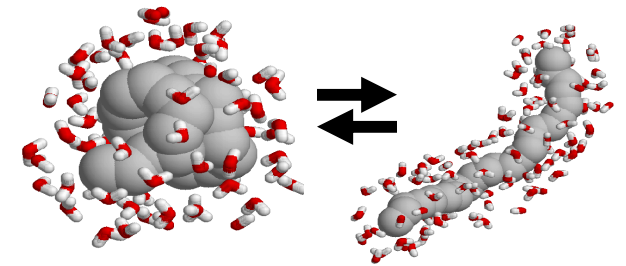
TMAO appears to have little effect on hydrophobic interactions \rightarrow biocompatibility?



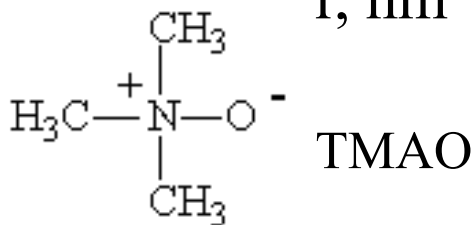
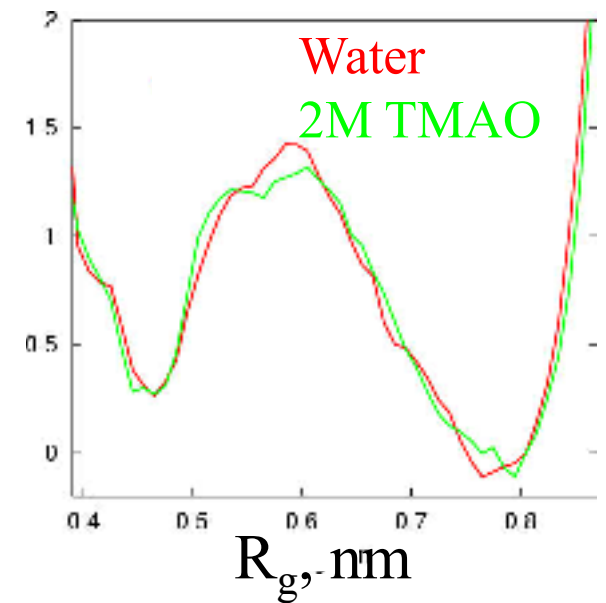
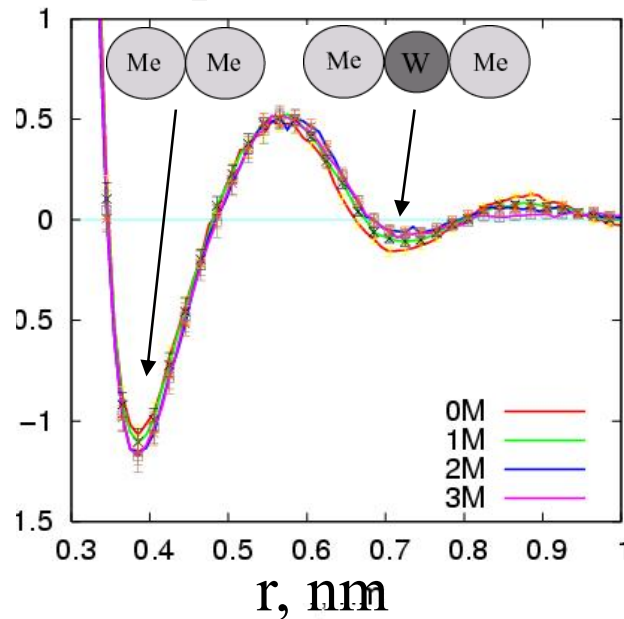
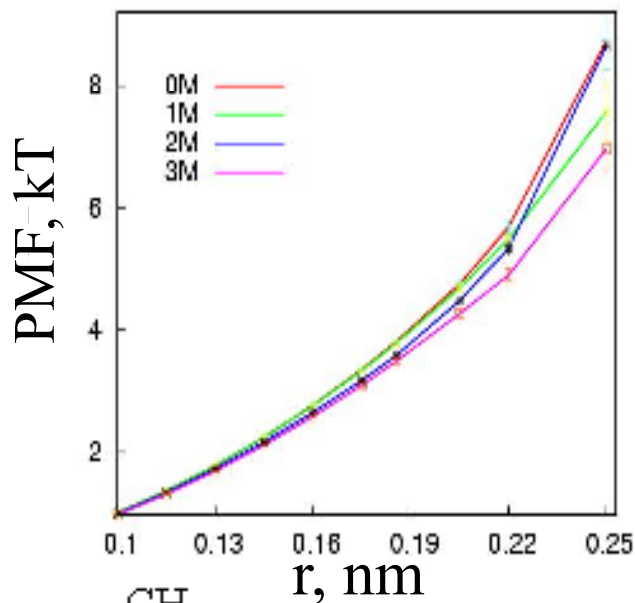
hydrophobic transfer



pair PMFs



manybody effects



Fundamental interest in osmolytes

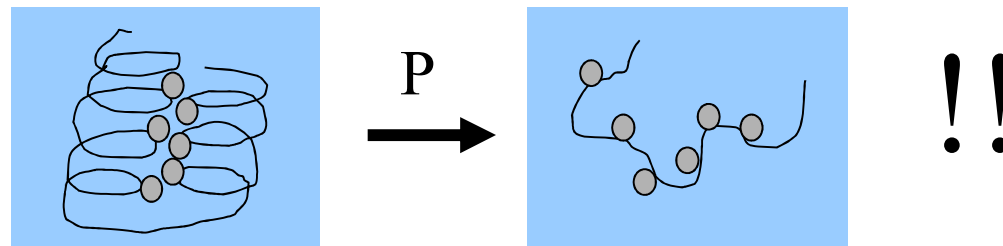
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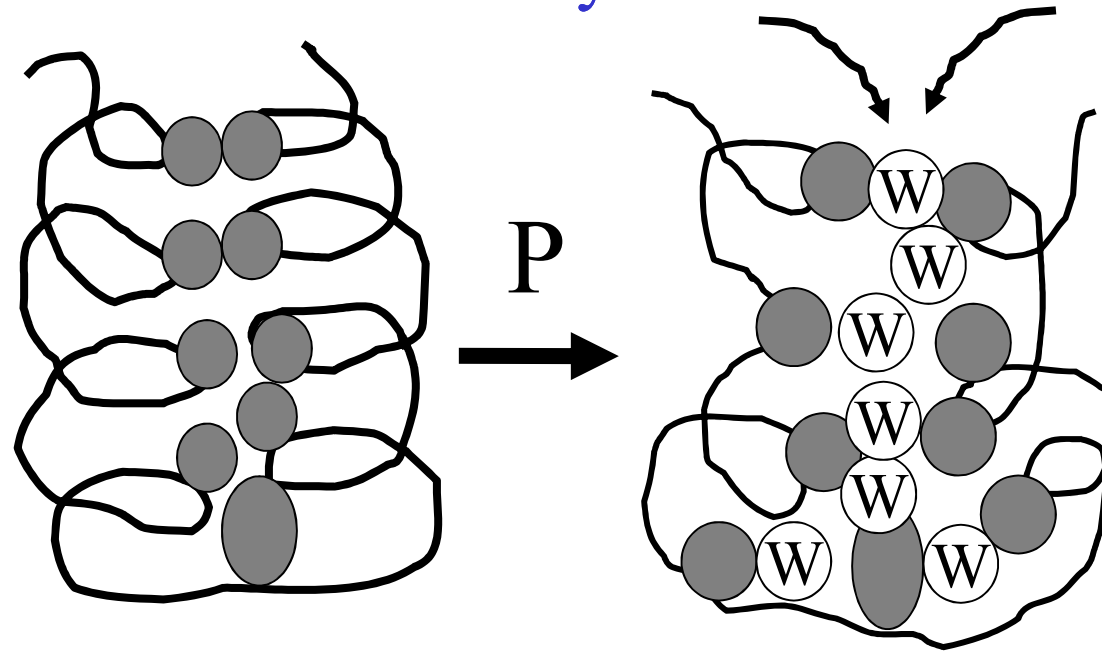
Proteins unfold upon application of hydrostatic pressure of the order of ~ 2000 atm.



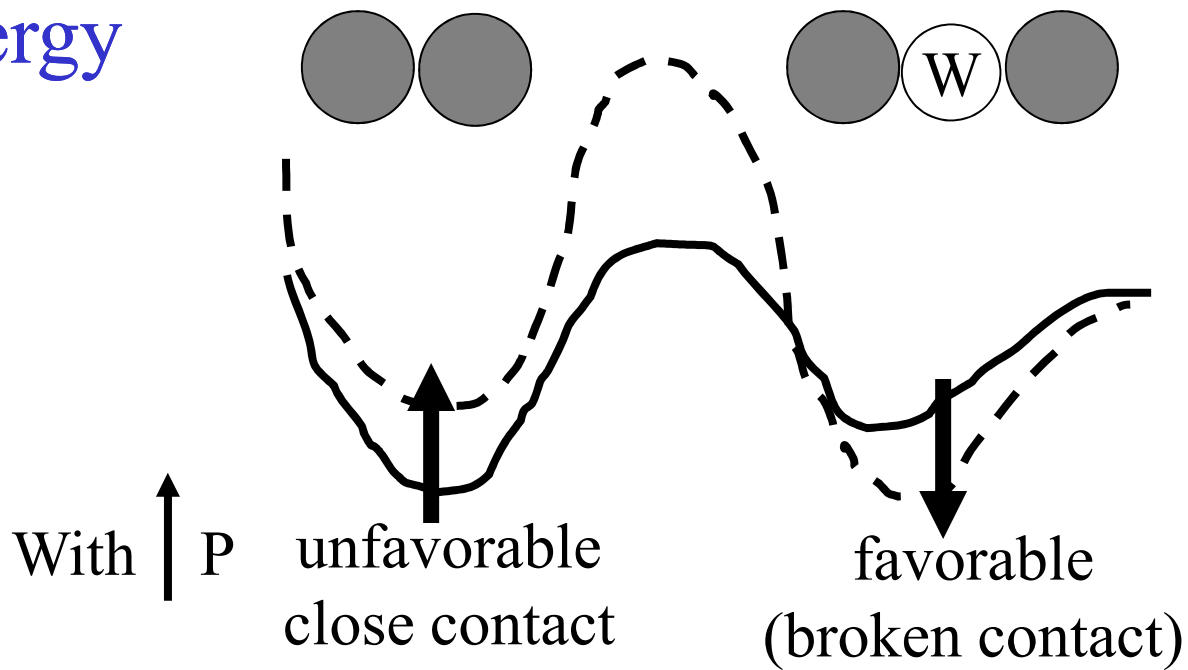
Bridgman, JBC, 1914; Kauzmann, and others.

Hypothesis: P-denaturation by water insertion and swelling

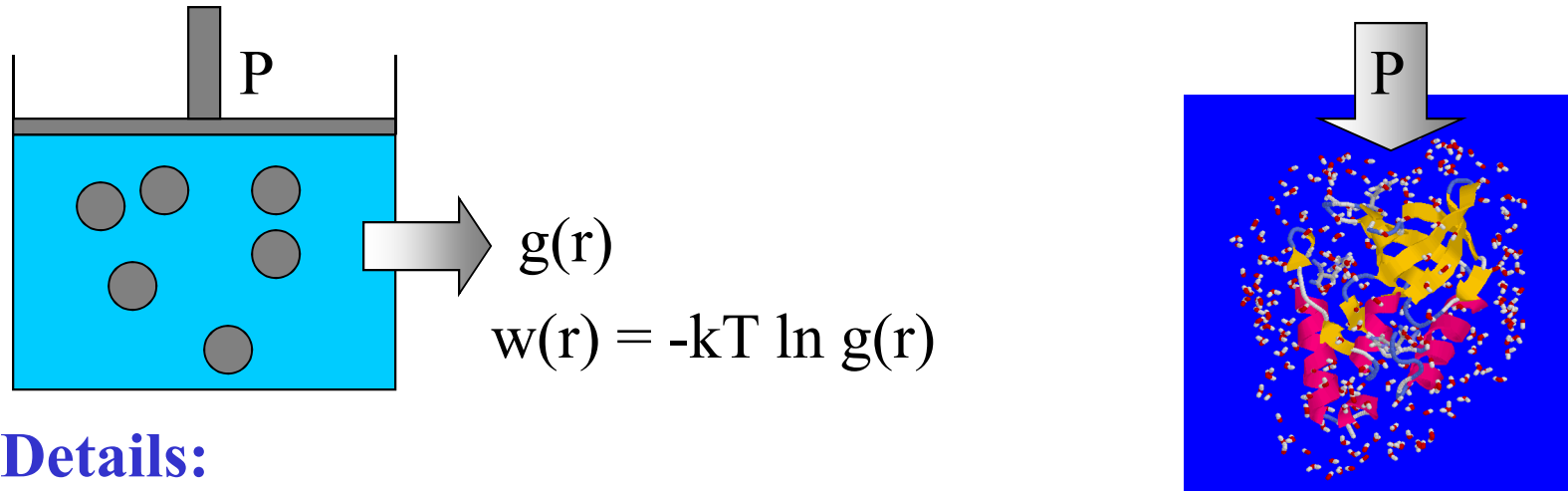
PNAS, 1998.



Free energy



Calculation of free energy of hydrophobic interactions by MD simulations



Details:

(i) Small solute system (**methanes in water**)

10 united atom methanes ($\sigma = 3.7 \text{ \AA}$, $\varepsilon = 0.295 \text{ kcal/mol}$) + 508 TIP3P water molecules

NPT simulations using Molecular Dynamics + Berendsen's barostat and thermostat

equilibration runs: 0.5 ns

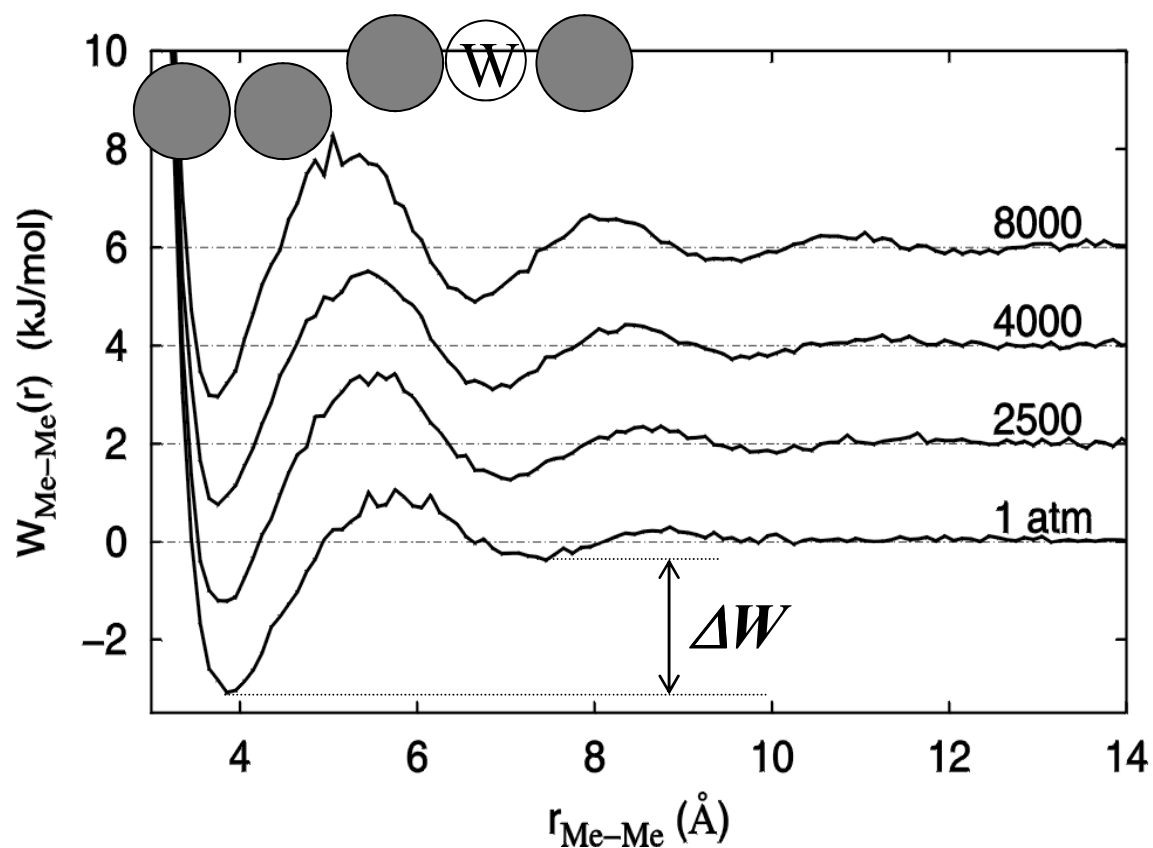
production runs: 6.0 ns

(ii) Macromolecular system (**protein in water**)

Preliminary simulations of native and pressure denatured states of Staphylococcal Nuclease (a relatively P-unstable well-studied protein).

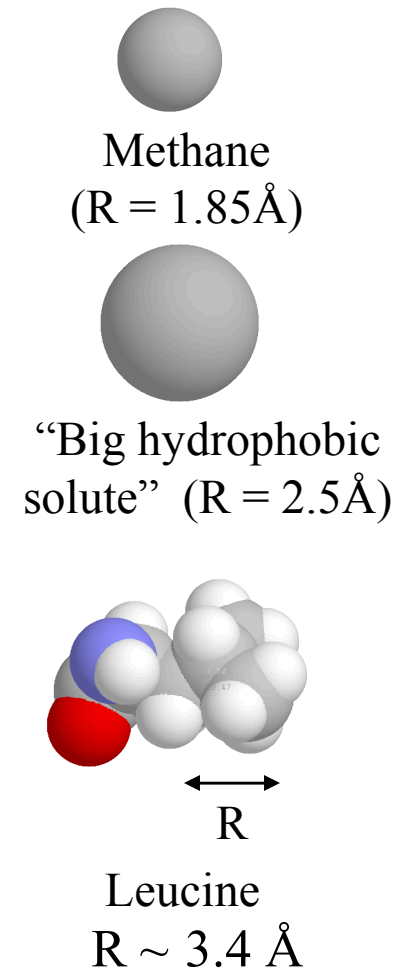
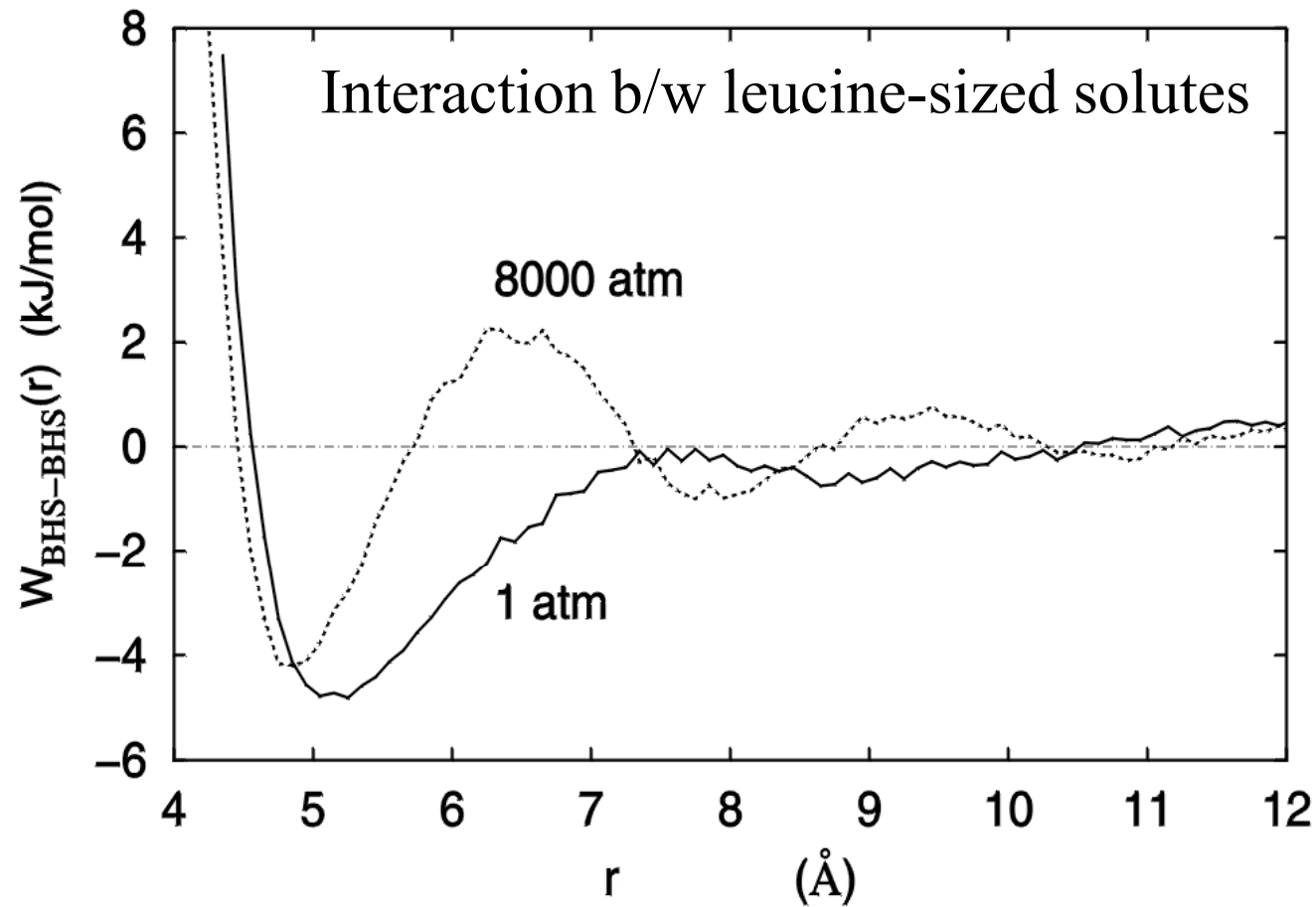
Pressure Effects on Hydrophobic Interactions.

Ghosh et al., JACS, 2001.



- Destabilization of hydrophobic contacts w.r.t solvent-separated configurations
- water swollen structures for P-denatured proteins
- Increase in barrier heights \Rightarrow slower kinetics

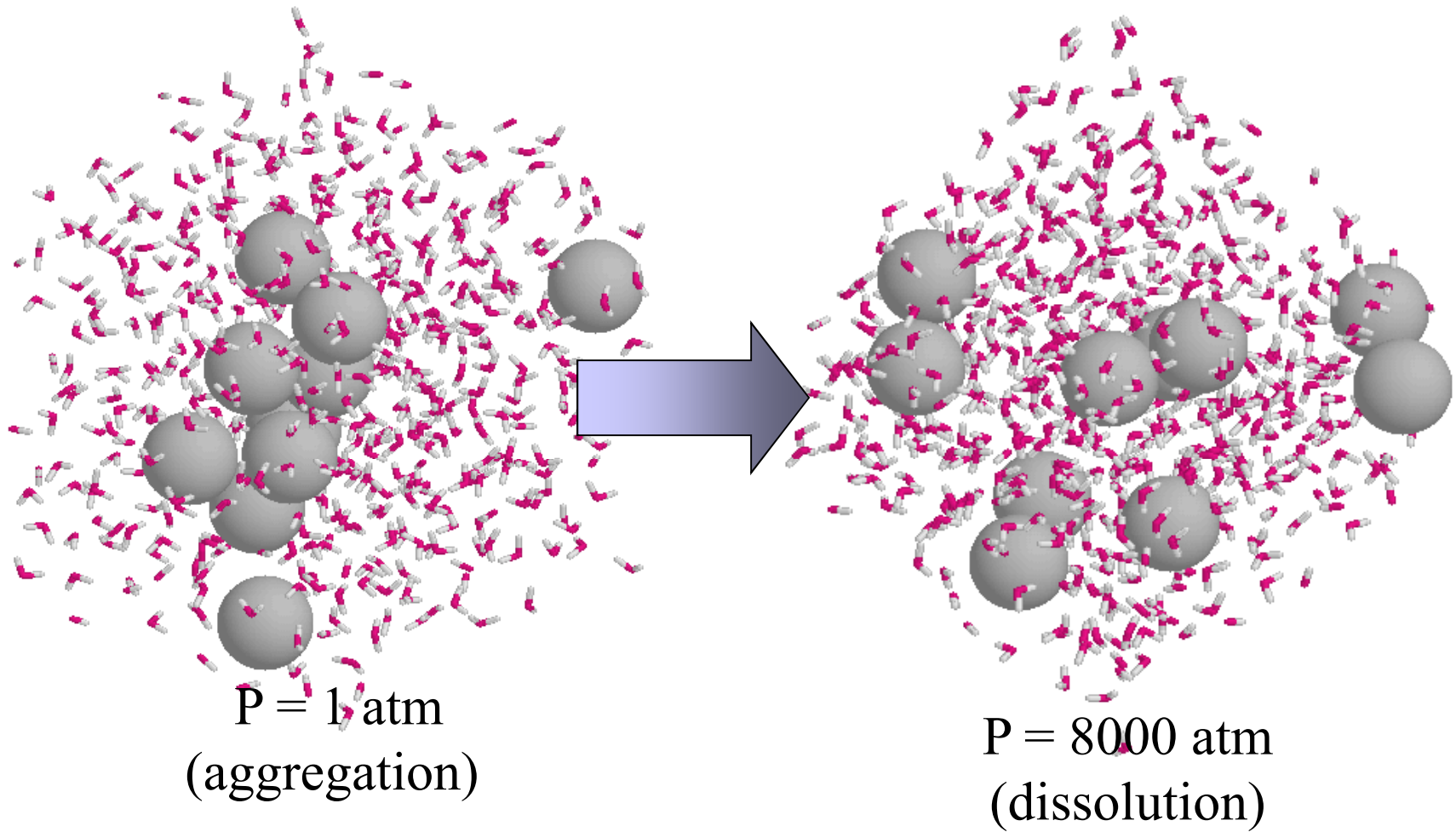
Solute Size Effects on P-dependence of Hydrophobic Interactions



Low pressure \Rightarrow “aggregation”

High pressure \Rightarrow dissolution of “aggregates”

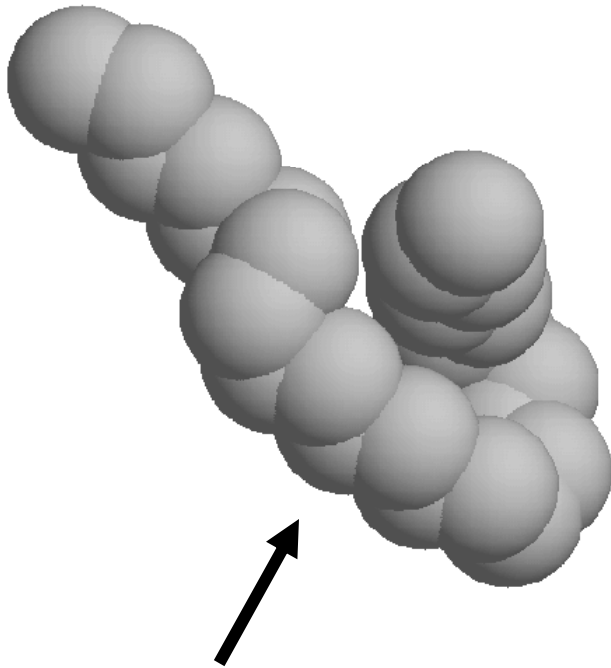
Destabilization of Hydrophobic Aggregates at High Pressures



How do we capture many-body effects?

Can we come up with a model hydrophobic polymer that shows hydrophobic collapse?

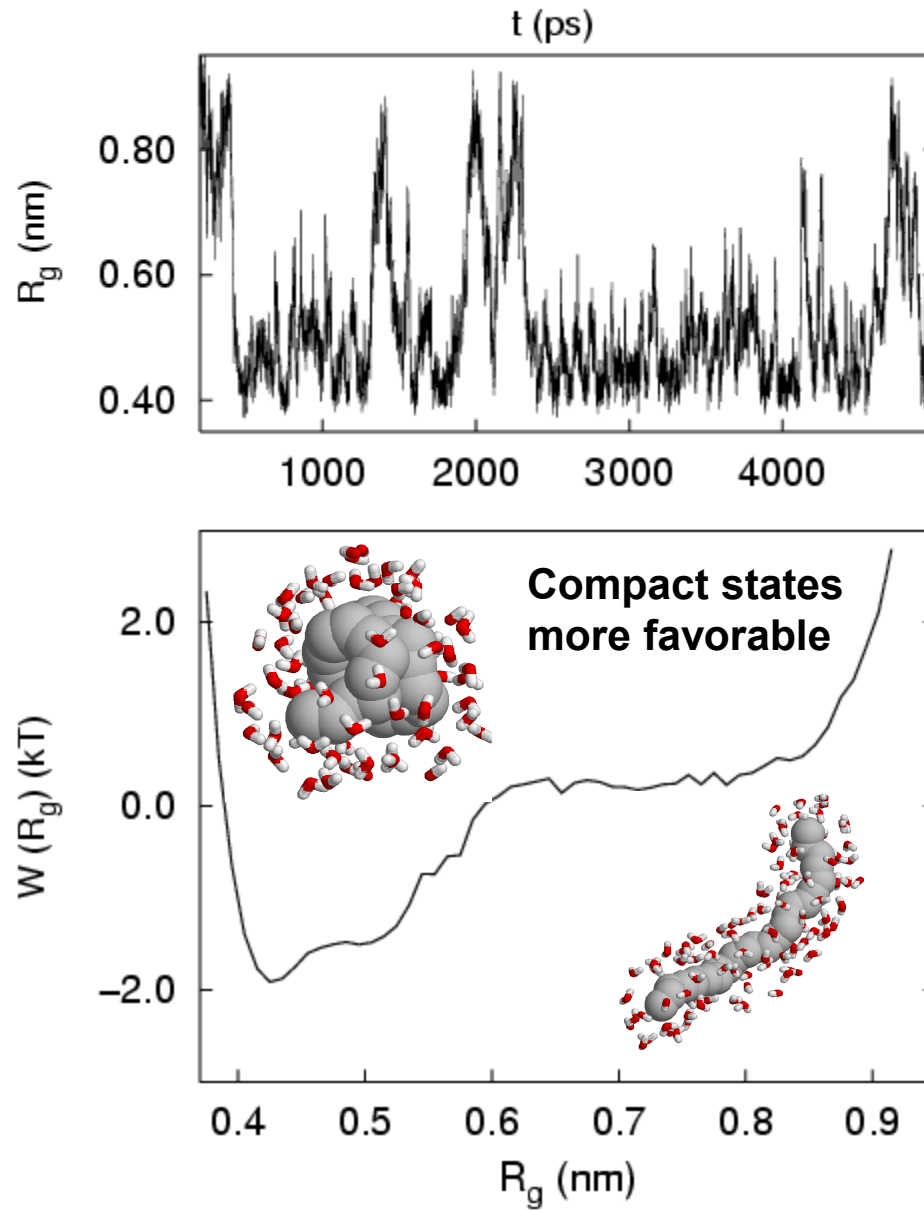
(2-state behavior? amenable to detailed simulations?)



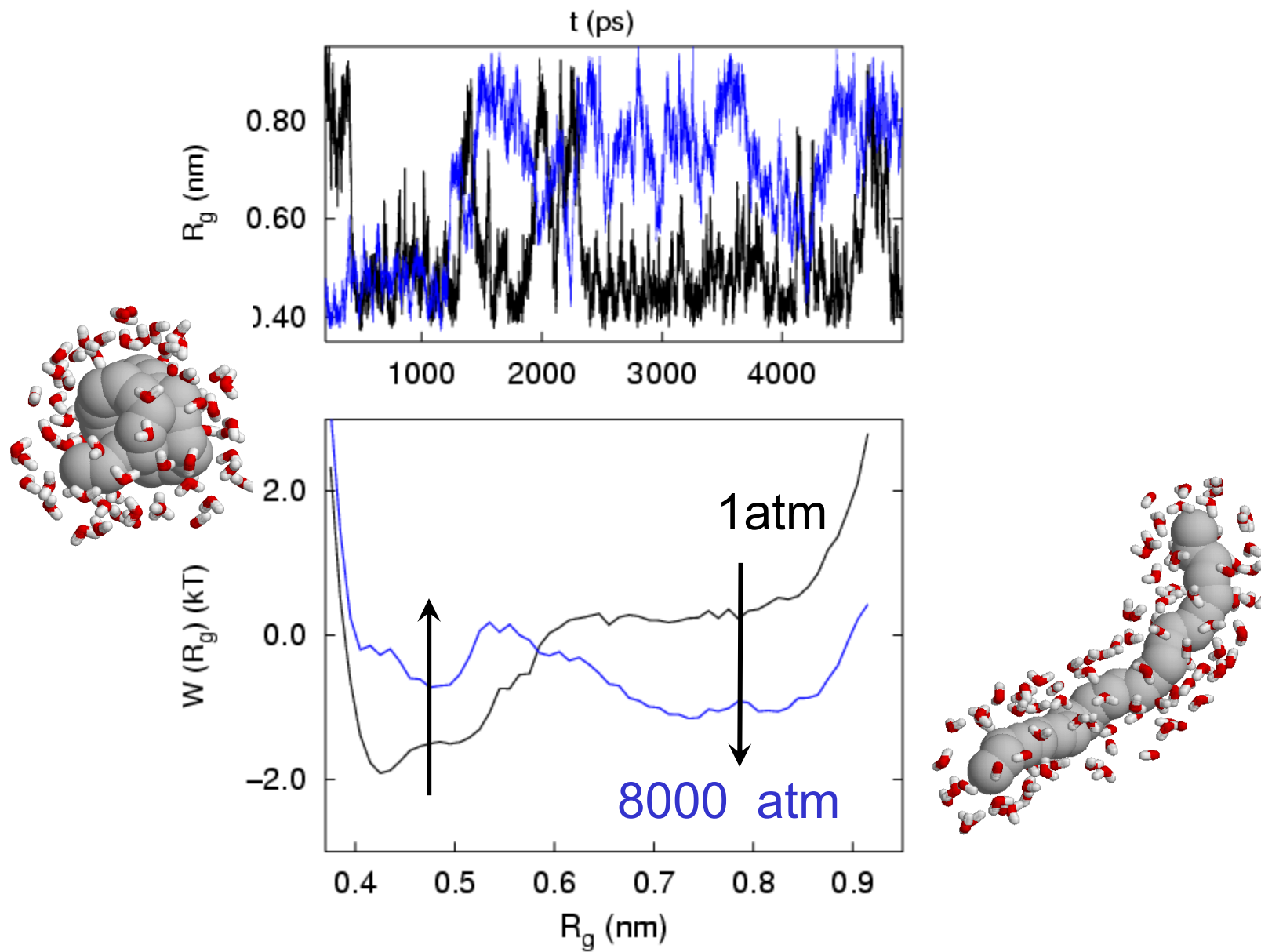
Large enough oligomer to bury substantial hydrophobic surface area.

A C-25 oligomer without angle or torsion potentials

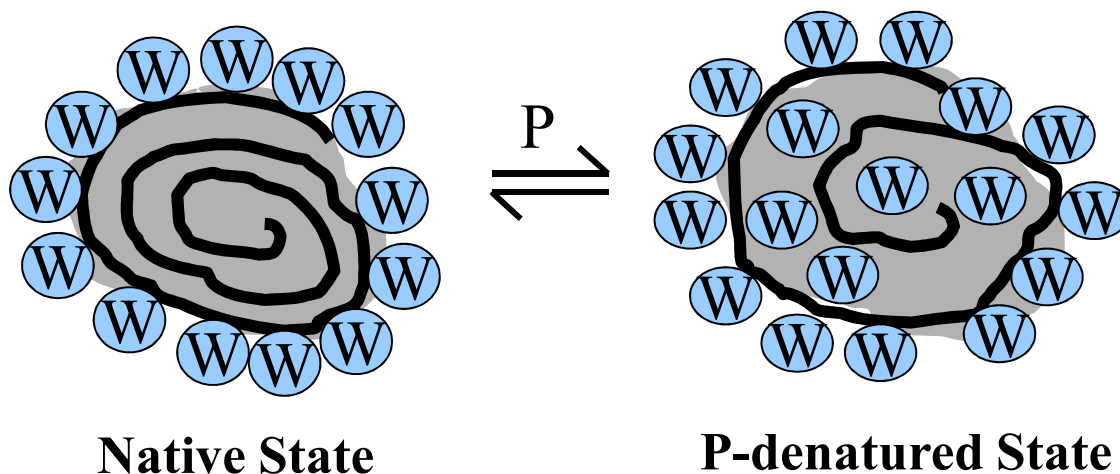
Characterizing folding of the oligomer



Pressure-induced “denaturation” of the folded oligomer



Can we unfold a protein in MD simulations?

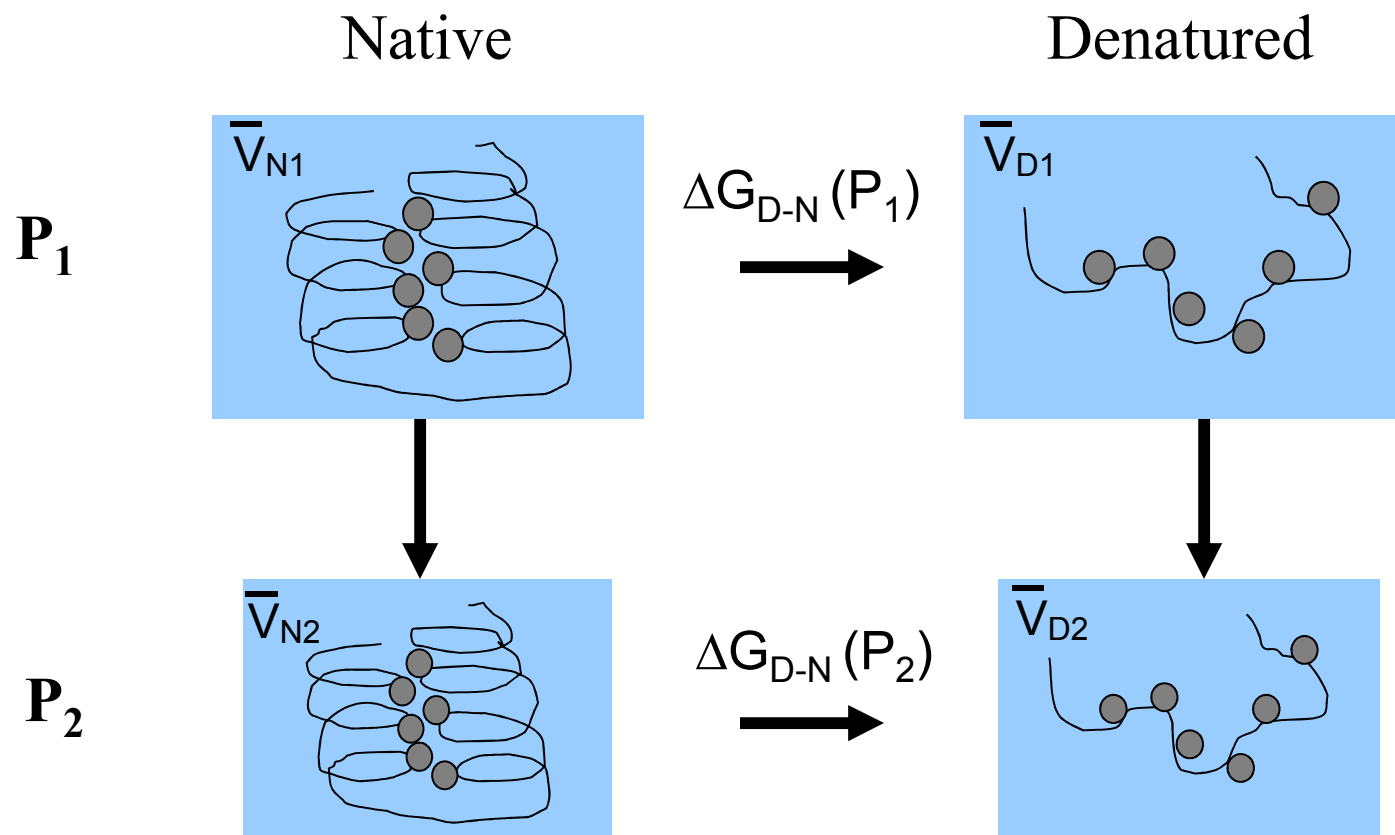


Complexities for brute force simulations:

- **Protein interior is tightly packed** => spontaneous formation of open transition state structures followed by swelling is highly unlikely
- **Relaxation times** at higher pressures are **extremely long** (~several hrs for Staph Nuclease)
- **Large system size requirement**
(2231 protein atoms + 10240 water molecules)

Brute force MD infeasible.
Novel strategy required !

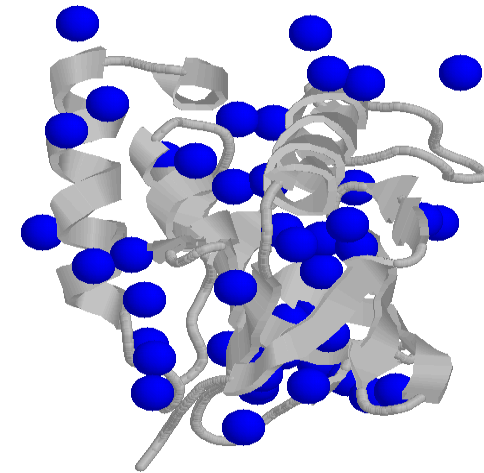
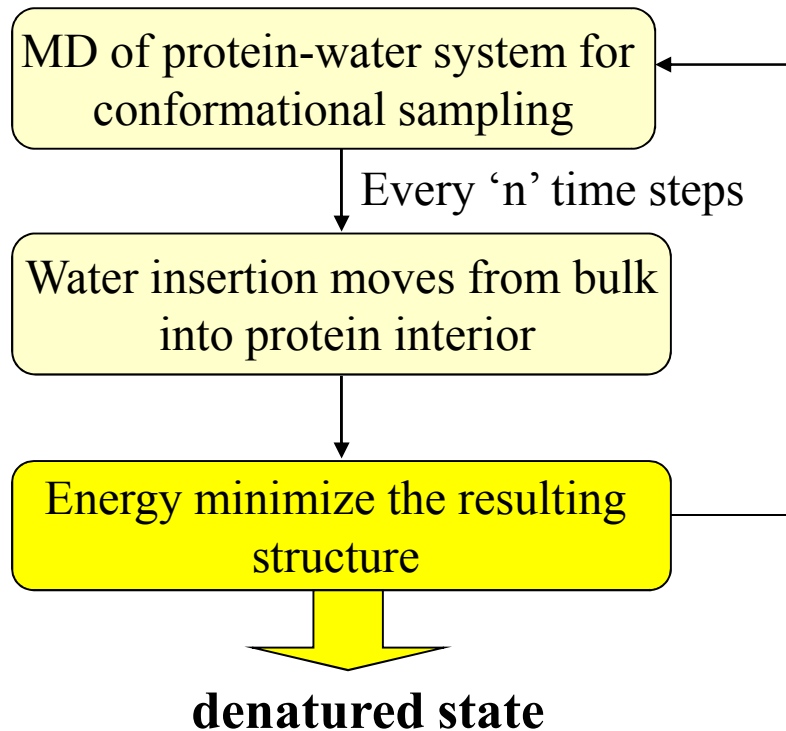
A Thermodynamic Cycle for P-Effects on Proteins



$$\Delta G_{D-N}(P_2) = \Delta G_{D-N}(P_1) + \int_{P_1}^{P_2} (\bar{V}_D - \bar{V}_N) dP$$

Generating conformations of denatured states...

Algorithm to force pressure unfolding:

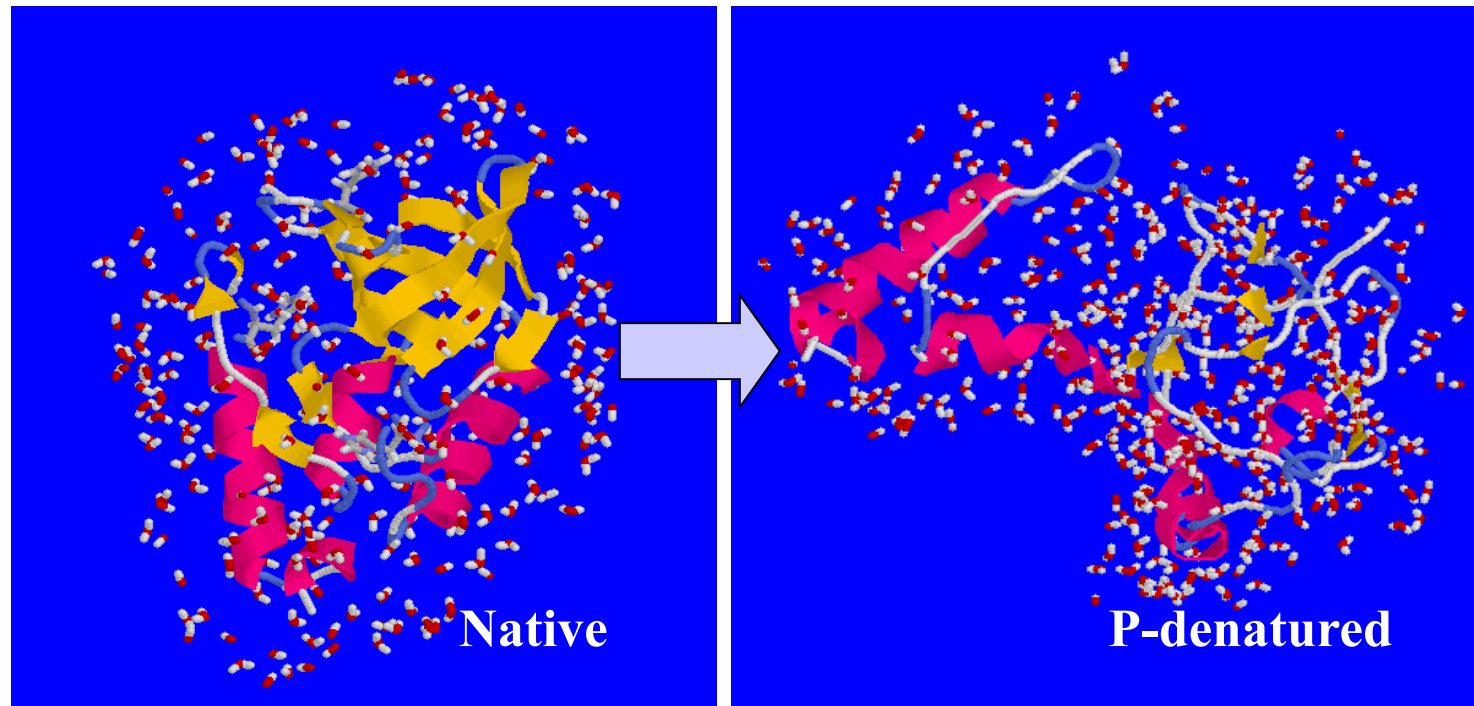


**Partially denatured Staph.
Nuclease**

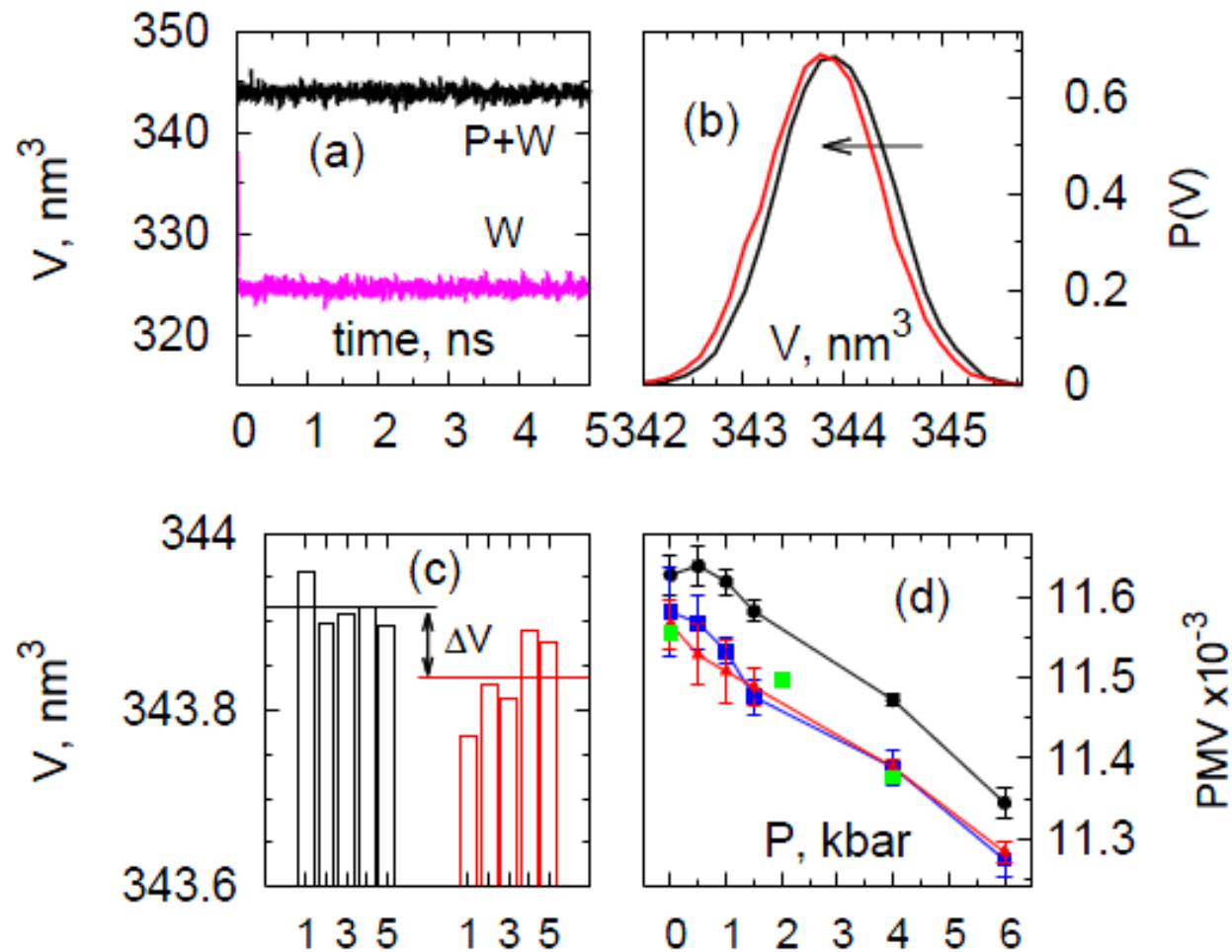
Perform simulations of native & denatured states at several pressures.

System: 2231 protein atoms + 10240 water molecules (~33000 atoms)

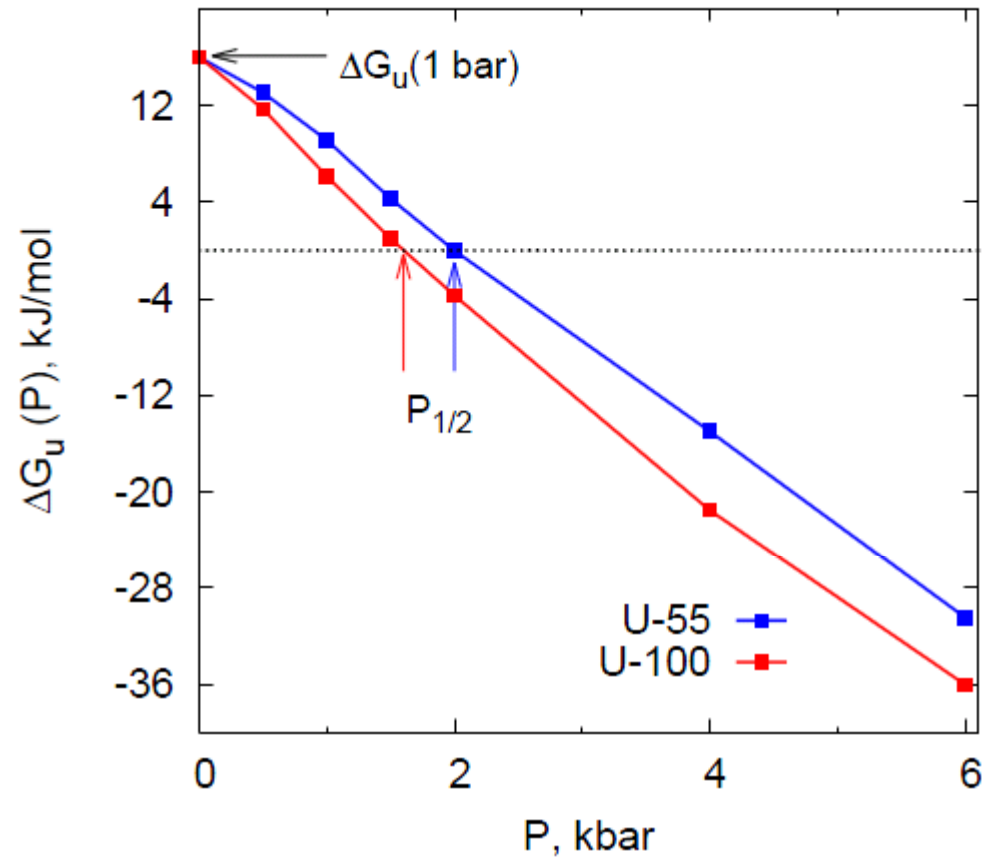
Pressure Denatured State of Staph. Nuclease



Volume of unfolding is indeed negative!



Predicting the Pressure-stability of Staph. nuclease



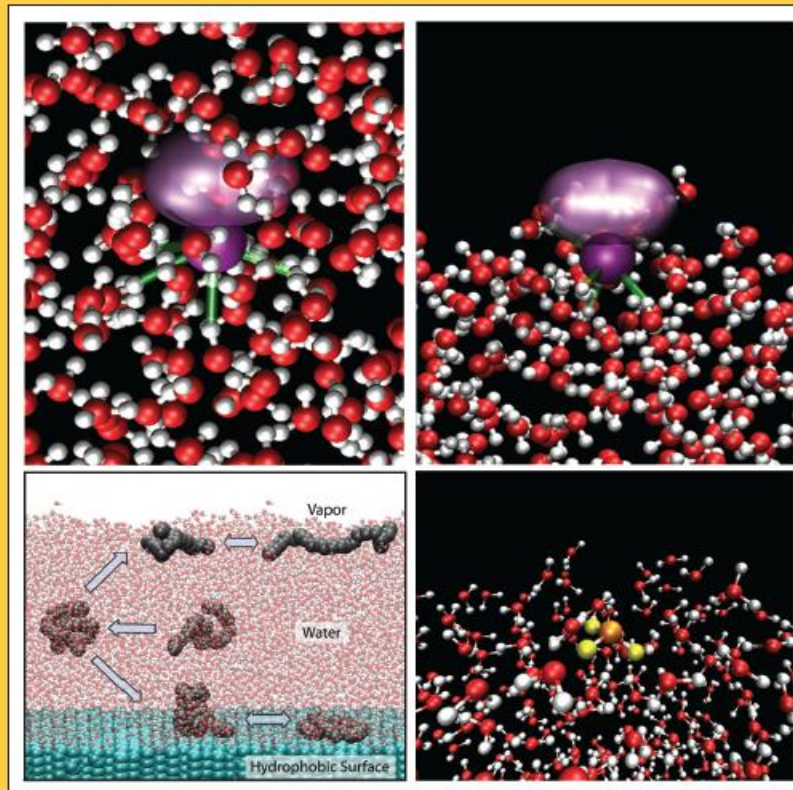
$$\Delta G_{D-N}(P_2) = \Delta G_{D-N}(P_1) + \int_{P_1}^{P_2} (\overline{V}_D - \overline{V}_N) dP$$

Conformational preferences of biomolecules at interfaces

APRIL 2, 2009
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THE JOURNAL OF PHYSICAL CHEMISTRY

B



Molecular
Description of
Simple Anions,
Hydronium, and
Hydrophobic
Polymers at Vapor/
Aqueous Interfaces
(see page XXXX)

SOFT CONDENSED MATTER AND BIOPHYSICAL CHEMISTRY

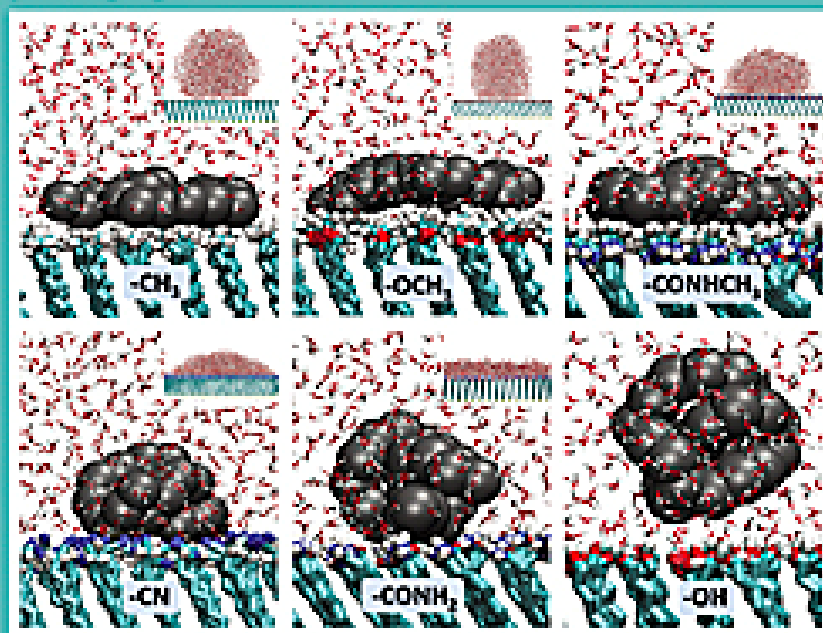
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NOVEMBER 17, 2009
VOLUME 25, NUMBER 22
pubs.acs.org/Langmuir



25th
ANNIVERSARY

Effect of Surface Wettability
on Hydrophobically Driven
Folding at Interfaces

(see p. 84)

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What aspects of water would I want the CG model to reproduce wrt self-assembly?

- “Reproducing anomalous properties/behavior is probably less important.” (S. Sastry).
- More important is to reproduce hydration phenomena and properties of water-mediated interactions between:

Hydrophobic solutes

Ionic solutes

Ion hydration: preliminaries

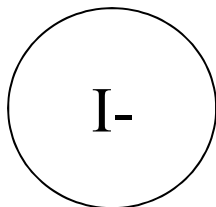
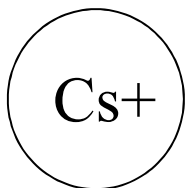
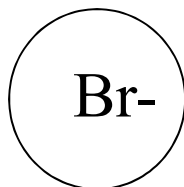
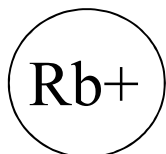
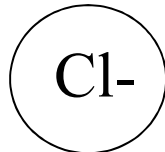
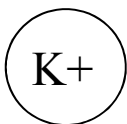
Continuum (Born model):

$$\Delta\mu^{\text{ex}} = -\frac{q^2}{2R} \left(1 - \frac{1}{\epsilon} \right)$$

- Free energy is **quadratic** in charge (& inversely proportional to the ion size).
- For the same size and charge the free energy of charging is identical. *i.e.*, hydration is **symmetric** about zero charge.

How consistent are these ideas with “microscopic reality?”

Kosmotropes



Chaotropes

Charge Density-Dependent Strength of Hydration and Biological Structure,
Kim D. Collins
Biophysical Journal, 72, 65-76, 1997.

- Smaller ions (higher charge density) are more favorably hydrated
- For a given size, negative ions are more favorably hydrated than positive ions

$$\Delta\mu^{\text{ex}} = -\frac{q^2}{2R} \left(1 - \frac{1}{\epsilon} \right)$$

Can we perform molecular simulations and pursue this question?

- Model: ions, water
- Calculation of long range interactions
- System size corrections
- Calculation of free energy differences?

$$\Delta\mu^{ex} = -k_B T \ln \left\langle \exp \left\{ -\beta [u(\lambda_1) - u(\lambda_2)] \right\} \right\rangle_{\lambda_0}$$

$$-\beta\Delta\mu^{ex} = -\beta u_s(1) \left[\Delta\lambda^2 + 2\lambda\Delta\lambda \right] + \sum_{n=1}^{\infty} \frac{(-\beta\Delta\lambda)^n}{n!} C_{n,\lambda}$$

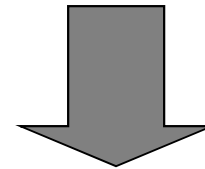
Basic idea behind calculating free energy changes from simulations

$$dG/dq \sim \langle \phi \rangle$$

$$d^2G/dq^2 \sim \langle \phi^2 \rangle - \langle \phi \rangle^2$$



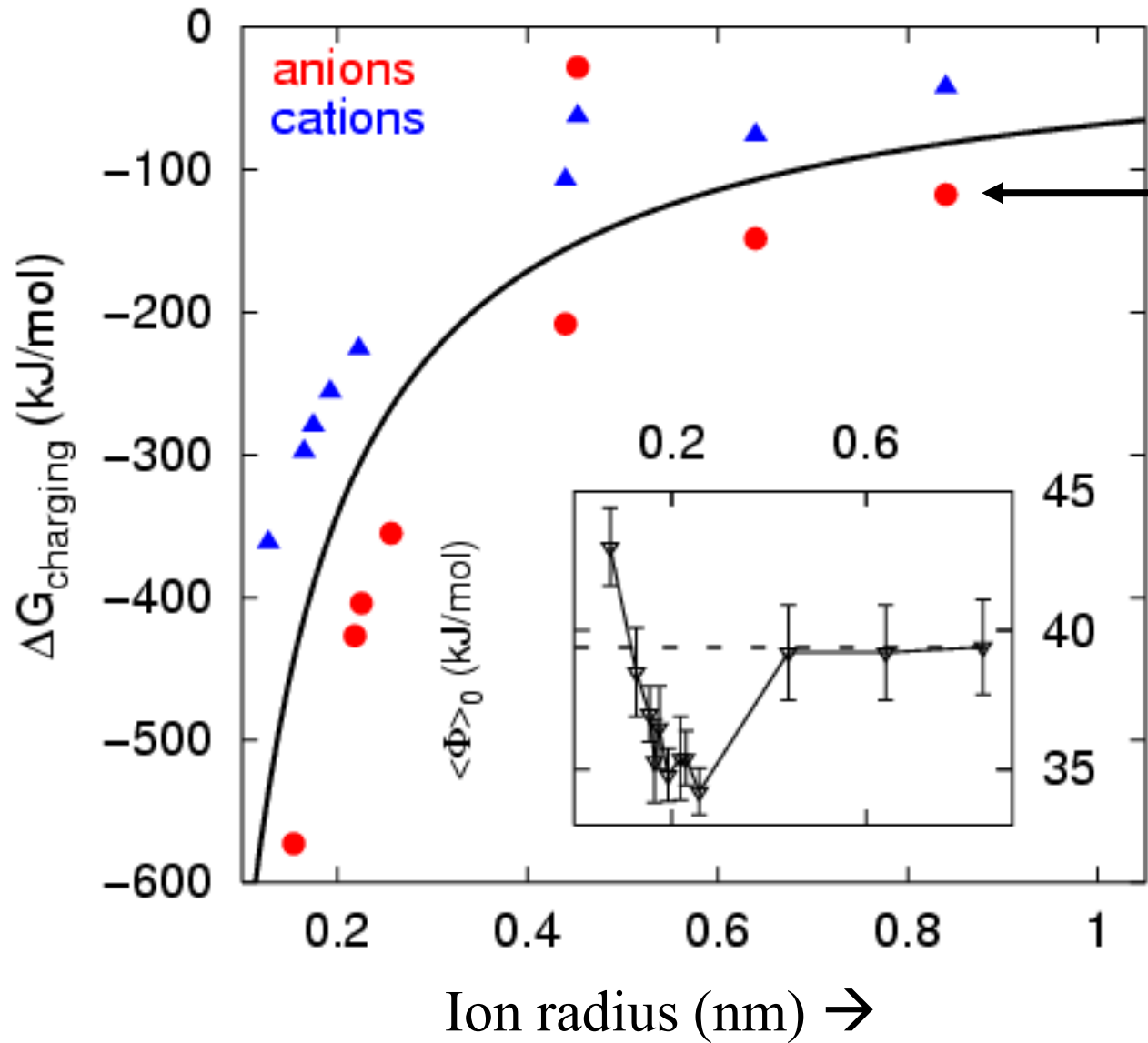
Calculate derivatives of free energy wrt charge at zero & fully charged states.



Use these derivatives in a 4th order FEPT expression to calculate free energy of charging

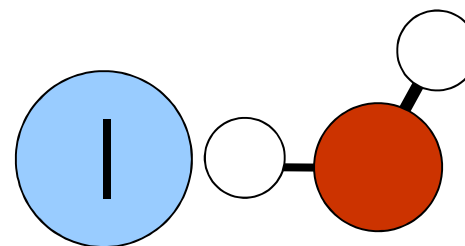
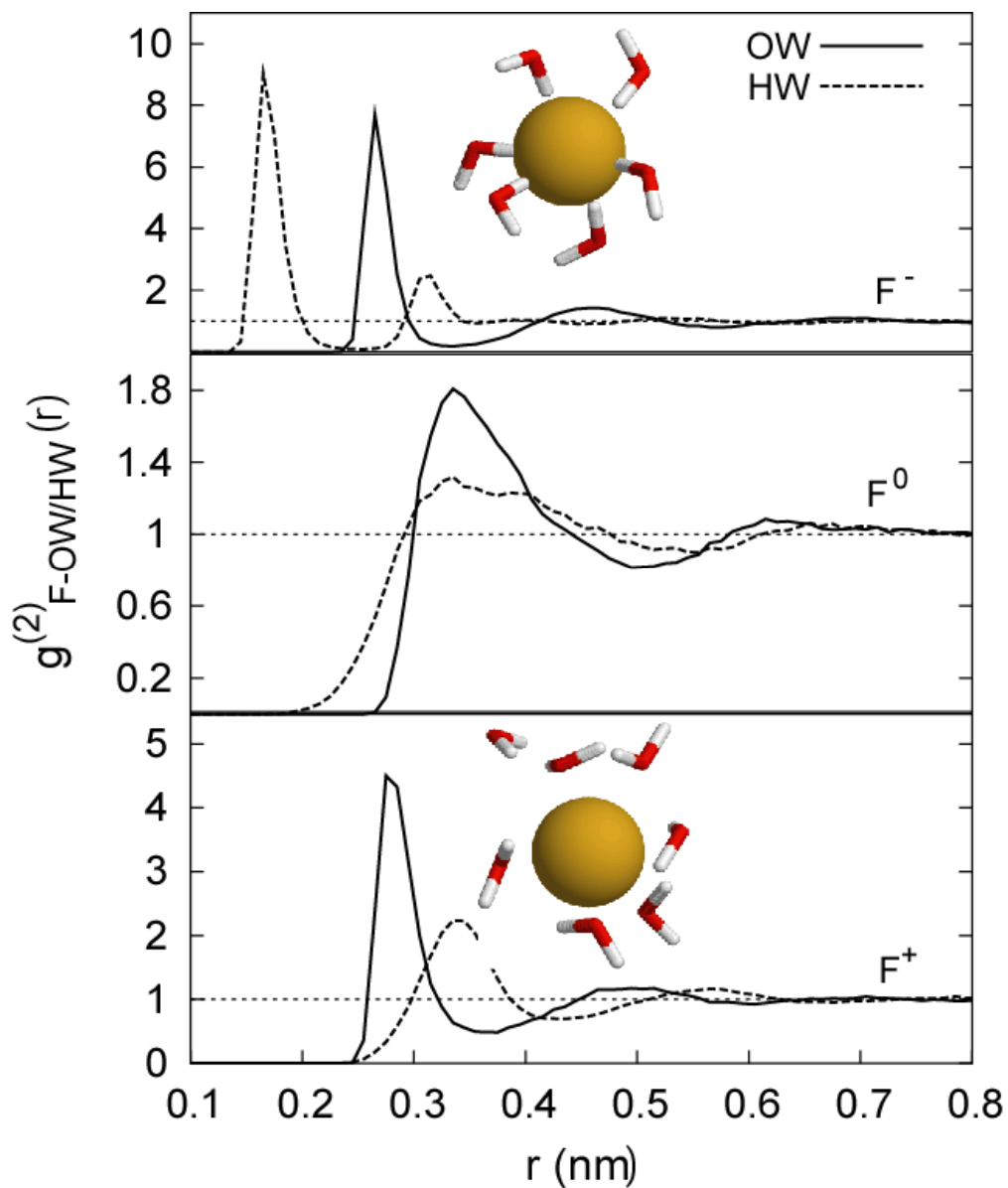
See Hummer's papers; esp. Hummer and Szabo, J. Chem. Phys.

Free energy of ion hydration

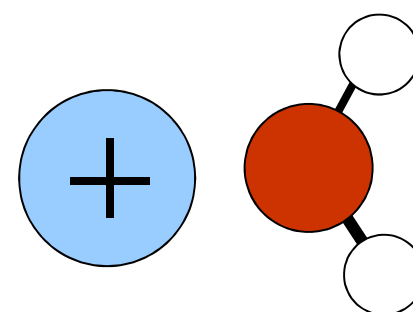


Negative ions are more favorably hydrated!

Understanding the asymmetry of ion hydration



Water structure biases charging in the negative direction!!



Peculiar structure of water near solutes leads to

- Characteristic features of the solute hydration thermodynamics
- Water-mediated interactions

CG models of model might aspire to get these phenomena right.

Summary

- Water is a remarkable solvent.
- Understanding and quantifying solvation phenomena in atomically detailed models of water is an exciting challenge.
- Developing CG models of water that reproduce key features of such solvation phenomena will be necessary if we are to model self-assembly in a computationally efficient manner.

Questions?