Protein-Ligand Interactions* and Energy Evaluation Methods

*with a revealing look at roles of water

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Where Do We Start?

Thermodynamics:
\( \Delta H, \Delta S, \Delta G \) are the language of energy and interactions, and it seems simple, but parsing atomic-scale observations into these terms is not often easy.

Chemistry (and Physics):
Everything that happens at the atomic scale is chemistry and/or physics; we must interpret interactions from this perspective before attempting energetic evaluations.
Interactions

Physics:

**Coulombic (electrostatic)**

\[
E_{\text{Coulombic}} = C \sum_{i=1}^{\infty} \sum_{j>1}^{\infty} \frac{Q_i Q_j}{\varepsilon_{ij} r_{ij}}
\]

All nonbonded Q_i and Q_j are *partial* atomic charges, e.g., from electronegativity differences between atoms i and j.

**van der Waals (London forces)**

\[
E_{\text{vdW}} = \sum_{i=1}^{\infty} \sum_{j>1}^{\infty} \phi_{ij} \left[ \frac{1.0}{r_{ij}^{12}} - \frac{2.0}{r_{ij}^{6}} \right]
\]
Interactions

Chemistry:

Hydrophobic
While pairwise van der Waals supports the hydrophobic effect, pairwise Coulombic forces contraindicate attraction between hydrophobic groups or atoms. The hydrophobic effect must be considered an emergent property of the entire system.
Interactions

Chemistry:

Desolvation of Ligand
Interactions

Chemistry:

Site-Ligand Complex
Thermodynamics

Enthalpy (ΔH):

- ΔH during a chemical reaction is the heat absorbed or released in the breaking or formation of bonds.
- This applies to ligand binding as well, even if no covalent bonds are changed:
  - van der Waals interactions
  - hydrogen bonding
  - charge (Coulombic) interactions
Thermodynamics

Entropy (ΔS):

• ΔS measures order (disorder) in the system. For a reaction to be spontaneous, the entropy of the universe, $\Delta S_{\text{total}}$, must increase.
• In ligand binding, this manifests as:
  • changes in solvent or counterion arrangement
  • rotational and translational changes
  • reflecting the degrees of freedom
Thermodynamics

Gibb’s Free Energy ($\Delta G$):

\[
\Delta S_{\text{total}} = \Delta S_{\text{system}} + \Delta S_{\text{surroundings}}
\]

\[
\Delta S_{\text{surroundings}} = -\Delta H_{\text{system}} / T
\]

\[
\Delta S_{\text{total}} = \Delta S_{\text{system}} - \Delta H_{\text{system}} / T
\]

\[
-T \Delta S_{\text{total}} = \Delta H_{\text{system}} - T \Delta S_{\text{system}}
\]

\[
\Delta G = \Delta H_{\text{system}} - T \Delta S_{\text{system}}
\]

Also, since for spontaneous reactions,

\[
\Delta S_{\text{system}} > \Delta H_{\text{system}} / T,
\]

then:

\[
\Delta G = \Delta H_{\text{system}} - T \Delta S_{\text{system}} < 0;
\]

i.e., the Gibbs free energy must be negative.
Thermodynamics

Enthalpy/Entropy Compensation (H/SC):

\[ \Delta H \sim \Delta S \]

\[ \Delta \Delta G \approx 0 \]
The Hydrophobic Effect:

- **Enthalpic or Entropic?**
  - It *seems* to be a lot like a van der Waals interaction, which is most certainly enthalpic.
  - But, things are not always what they seem!
  - Recall that the **origin** of the hydrophobic effect is related to water rearrangements (and possibly motion), i.e., as the water seeks to form better hydrogen bonds with other water molecules and polar species.
  - **The hydrophobic effect is thus entropic!**
Thermodynamics

Displacing Water I:

- **Enthalpic or Entropic?**

  - If the water is "isolated" in a hydrophobic pocket, it will make few interactions.
  - (This is potentially a highly entropic situation.)
  - Such a water will be easily displaced to "bulk".
  - New interactions with other waters in bulk are enthalpically favorable, but creates a loss of entropy!

  - However, if water is part of a cluster with inter-water interactions:
    - (More enthalpically favored, but less disorder/entropy.)
    - The enthalpic gain from displacement will be lessened, as will the gain in entropy.
Thermodynamics

Displacing Water II:

- **Enthalpic or Entropic?**
  - If the water is tightly bound in a polar pocket, it will be difficult to displace.
  - (This water is enthalpically favored where it is.)
  - Such a water may only be displaced if a large entropic gain can be found.
  - New interactions with waters in bulk may be less enthalpically favorable, but gain of entropy is possible.
  - However, a water less "locked" in place in a polar site has a much more complicated energetic profile:
  - Both enthalpy and entropy could be affected either favorably or unfavorably by its displacement!
Energy Evaluation Methods

Free Energy:

- It should be obvious that to get the complete picture of an interaction, both its enthalpic and entropic contributions must be considered.
- Estimating/calculating the hydrophobic effect is problematical – at best!
  - Few, if any, full-scale simulations have demonstrated this emergent property of the protein/ligand/solvent system.
  - Thus, “phenomenological” observations are usually used to estimate the hydrophobic contribution to an interaction
- But, the schizophrenic roles that water can play in mediating interactions are very difficult to predict.
  - Each case may be special. Only by supplementing models with complete experimental structural and thermodynamic data can the case-specific contributions of water be understood.
Energy Evaluation Methods

Free Energy:

- **Empirical and Knowledge-based Methods**
  - Structural and other experimentally measured data form the basis of several types of energy evaluation methods.
  - Knowledge-based methods presume that there is nothing new: just identify a similar collection of atoms and the results can be extrapolated.
  - Empirical methods (HINT) use relevant data from other phenomena (like logP) to evaluate interactions.

- Some programs:
  - HINT
  - PyWATER
  - WaterDock
  - PMF / wPMF
Energy Evaluation Methods

Free Energy:

- **Static Molecular Mechanics Methods**
  - Use forcefields to determine likely loci of water or other functional groups in a protein matrix.
  - Most docking algorithms apply molecular mechanics forcefields to energy-evaluate poses.
  - No real scope to simulate entropic terms.
- Some programs:
  - GRID
  - MCSS
  - FLAP/WaterFLAP
  - AutoDock
  - WaterMap
Energy Evaluation Methods

Free Energy:

- **Statistical Mechanics Methods**
  - Based on well-validated theories of fluid motion/mechanics and density functional theory.
  - Entropy is implicit in the models.
  - Some programs:
    - 3D-RISM
    - SPAM
**Energy Evaluation Methods**

**Free Energy:**

- **Molecular Dynamics / Monte Carlo Methods**
  - Attempt to “model” entropy with temperature- and/or time-dependent simulations.
  - Free Energy Perturbation methods have been widely and effectively used.
  - Explicit water simulations have often revealed roles and energetics of water in protein-ligand systems.
- **Some programs:**
  - BiKi Hydra
  - JAWS
  - RETI
  - STOW
  - WaterMap
Energy Evaluation Methods

Free Energy:

- **Continuum Solvent Model Methods**
  - Two key models: Poisson-Boltzmann (PB) and Generalized Born (GB). PB has better physics.
  - These are *implicit* solvation models, i.e., most (or all) of the effects of solvent molecules are treated as fields.
  - Best results obtained when hybridized with other methods.
  - Some programs:
    - DelPhi
    - Zap
    - SZMAP
Further Reading


Acknowledgments

VCU Colleagues:
Prof. Donald J. Abraham
Prof. J. Neel Scarsdale
Dr. Philip D. Mosier

University of Parma:
Prof. Andrea Mozzarelli
Prof. Pietro Cozzini
Dr. Francesca Spyrakis
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Mr. Ahmad Obaidullah
Mr. Claudio Catalano