Lecture of November 14: Chapter 7, Ligand Binding in the Gibb's Ensemble; MWC Model; Dimoglobin Model

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Section 6.2.2: Solute Chemical Potential

Gibbs Free Energy of Solute (S) in Water (H_2O)

$$G_{\text{tot}}(T, p, N_{H_2O}, N_s) = N_{H_2O}\mu^0_{H_2O}(T, p) + N_s\varepsilon_s(T, p) + k_B T\left(N_s \ln \frac{N_s}{N_{H_2O}} - N_s\right). \quad (6.85)$$

Chemical Potential of Solute (S)

$$\mu_s = \partial G/\partial N_s, \qquad \mu_s = \varepsilon_s + k_B T \ln \frac{c}{c_0}. \quad (6.86)$$

Below is the expression of a **general chemical potential** of i^{th} solute, μ_i with reference (0) chemical potential, μ_{i0}, and solute concentration, c, and reference concentration c_0.

$$\mu_i = \mu_{i0} + k_B T \ln \frac{c_i}{c_{i0}},$$

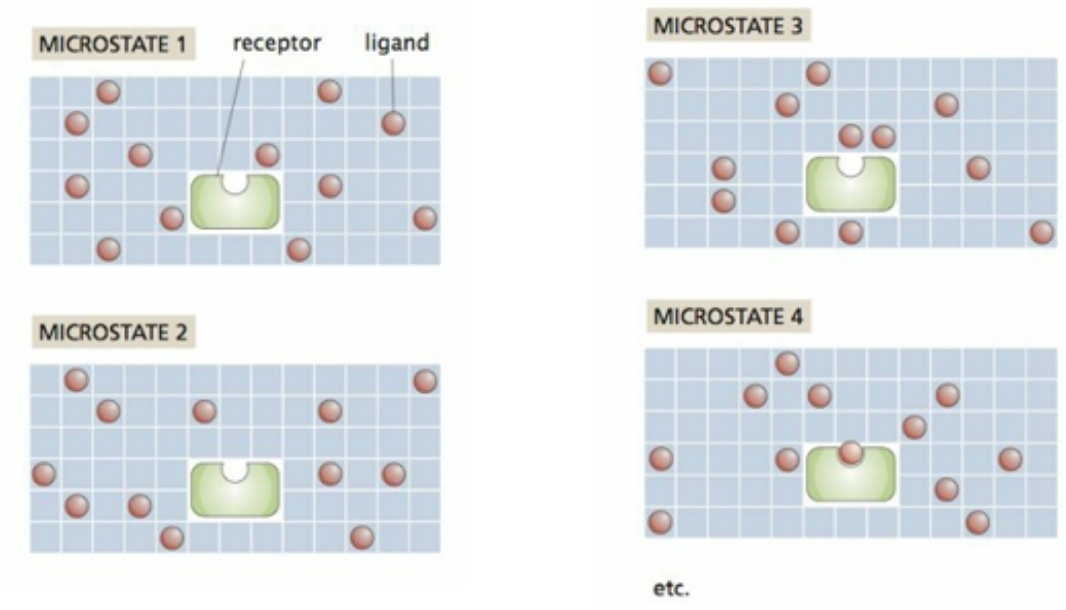
The Gibbs Distribution

$$p(E_s^{(i)}, N_s^{(i)}) = \frac{e^{-\beta(E_s^{(i)} - \mu N_s^{(i)})}}{\mathcal{Z}}, \tag{7.15}$$

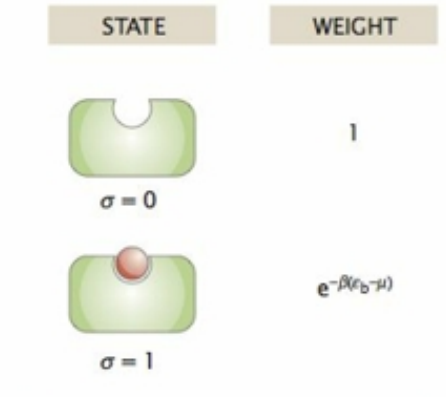
$$\mathcal{Z} = \sum_i e^{-\beta(E_s^{(i)} - N_s^{(i)}\mu)}. \tag{7.16}$$

$$\langle N \rangle = \frac{1}{\mathcal{Z}} \sum_i N_i e^{-\beta(E_i - N_i\mu)}, \tag{7.18}$$

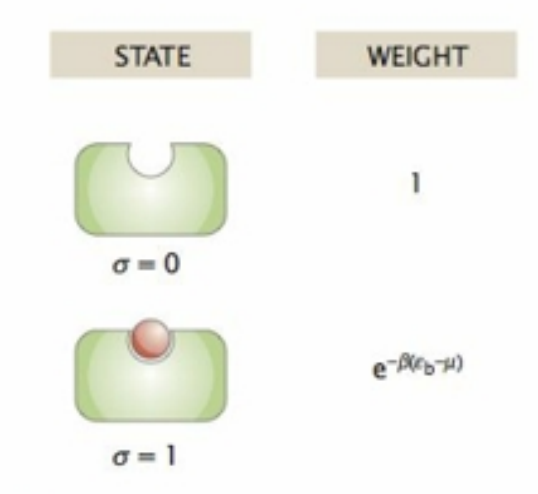
Ligand-Receptor Model in the Gibb's Ensemble



- Ligand binding to receptor is considered to be a chemical process that alter the Gibbs Free Energy by the chemical potential μ.
- The State and weight change to Figure 7.10 on the **right**



Ligand-Receptor Model in the Gibb's Ensemble



$$\mathcal{Z} = \sum_{\text{states}} e^{-\beta(E_{\text{state}} - N_{\text{state}}\mu)},$$

$$\mathcal{Z} = \sum_{\sigma=0}^{1} e^{-\beta(\varepsilon_b \sigma - \mu\sigma)}.$$

$$\mathcal{Z} = 1 + e^{-\beta(\varepsilon_b - \mu)}.$$

Normalized Average Number of Bound Ligand: $\langle N \rangle = \dfrac{e^{-\beta(\varepsilon_b - \mu)}}{1 + e^{-\beta(\varepsilon_b - \mu)}}.$

$$0 < \langle N \rangle < 1$$

$$\mu = \mu_0 + k_B T \ln(c/c_0)$$

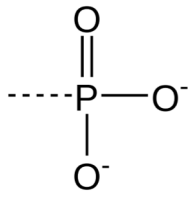
$$\langle N \rangle = \frac{(c/c_0)e^{-\beta\Delta\varepsilon}}{1 + (c/c_0)e^{-\beta\Delta\varepsilon}},$$

See Class Note for Detail that you are expected to know for the final exam

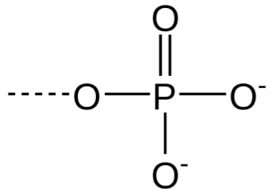
Phosphorylation of Proteins

- Phosphorylation of a molecule is an attachment of phosphoryl group ($P^{+}O_3^{2-}$).
- Phosphorylation activates a protein, while dephosphorylation inactivate a protein.
- Phosphorylation can turn a hydrophobic portion of a protein to hydrophilic, which can induce a conformation structural change via long-range **allostery**.
- Students must read section 7.2.3 on Phosphorylation, including **phosphorylation** in **signal transduction**.

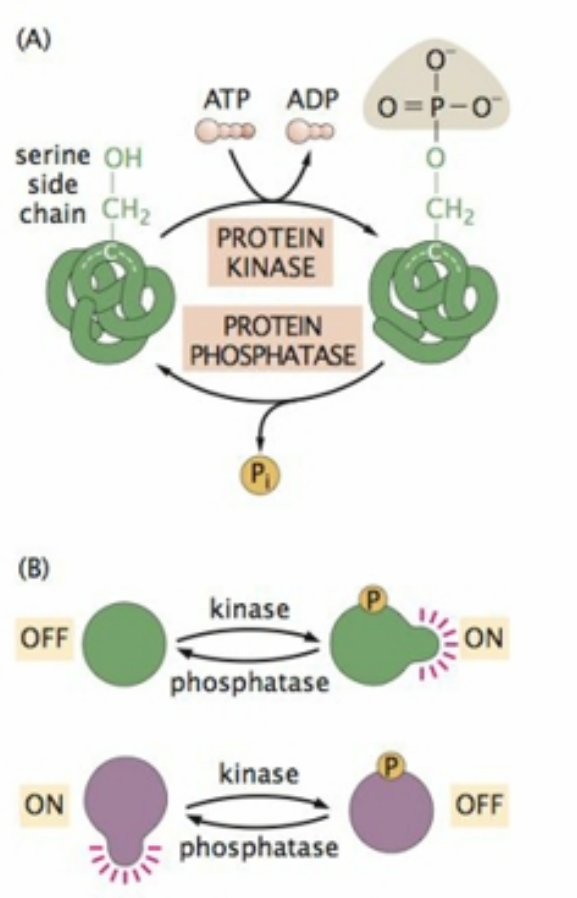
Phosphorylation of Proteins

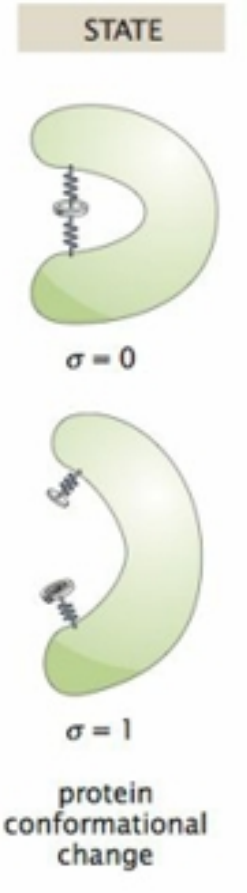


phosphoryl group



phosphate group





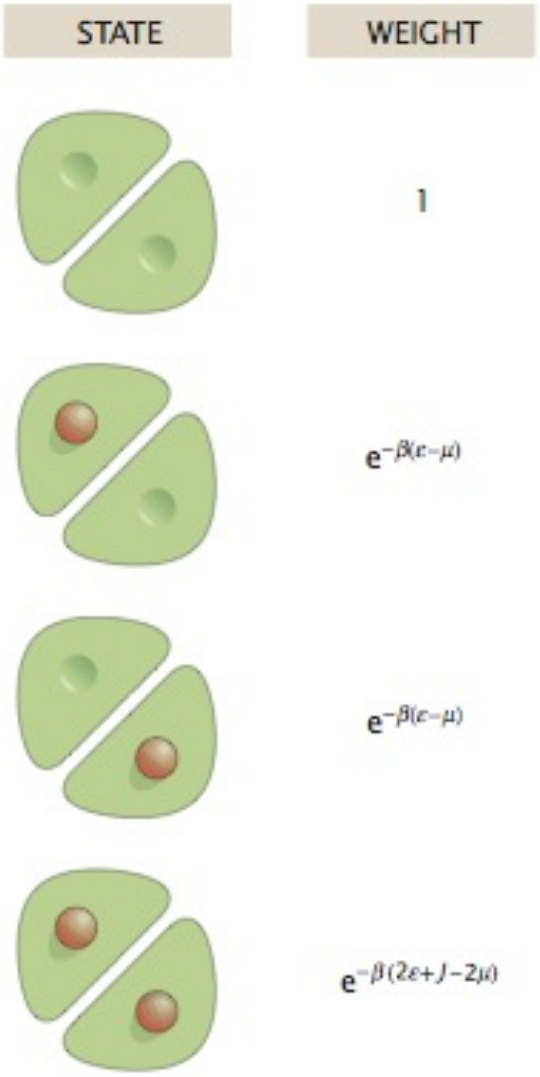
Cooperative Binding of O_2 to hemoglobin

- Earlier we discussed how **hemoglobin** (a protein in red blood cell, RBC) that has **4 sites** for **binding 4 O_2**. They can also bind 4 CO_2.
- The **binding** is **cooperative**, in that binding of **oxygen** increases the **affinity** of **hemoglobin** for more **oxygen**.
- Experiments (read section 4.2, Fig 4.4 and 4.5) found that hemoglobin either bind **no oxygen** of **4 oxygen**. The binding is cooperative, or two state, in that it **all** or **nothing**.
- The **molecular-level** explanation is that the binding of an O_2 causes a conformational change in the hemoglobin protein.

Dimeric Hemoglobin (Dimoglobin) Model for Cooperative binding of O_2

- First Model of Cooperative binding considered a fictitious protein that can bind 2 oxygens.
- The model must have a **Hamiltonian** or **Energy** that make it more favorable for an oxgen to bind if there's already one oxygen bound to it.
- The model discussed in section 7.4.2 is based on the **Ising Model** used to study **ferromagnetic materials**.

Dimeric Hemoglobin (Dimoglobin) Model for Cooperative binding of O_2



Each binding site is labeled by an index i = 1 or 2, i.e site 1 and site 2, with values:

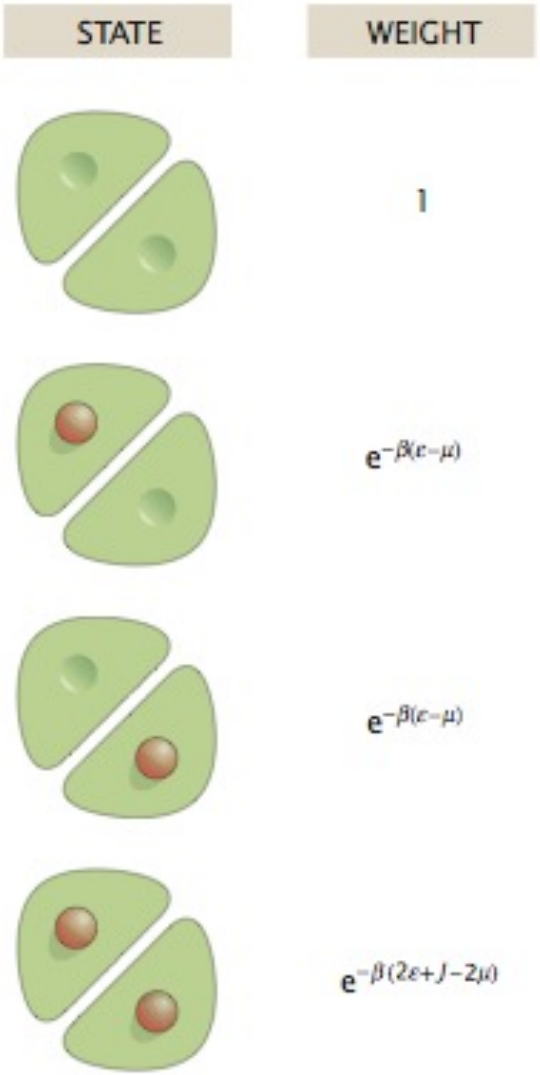
$$\sigma_i = \begin{matrix} 0 & no\ binding \\ 1 & one\ O_2\ binding \end{matrix}$$

Energy (i.e. Hamiltonian) is:

$$E = \varepsilon(\sigma_1 + \sigma_2) + J\sigma_1\sigma_2$$

- The term $J\sigma_1\sigma_2$ will favor cooperative binding if the **parameter** $j < 0$, which makes the **interacting energy** $J\sigma_1\sigma_2 < 0$ if both sites are bounded by oxygen, $\sigma_1 = 1$ and $\sigma_2 > 0$.
- Students of physics will know that this is nothing but the Ising Model.

Dimeric Hemoglobin (Dimoglobin) Model for Cooperative binding of O_2



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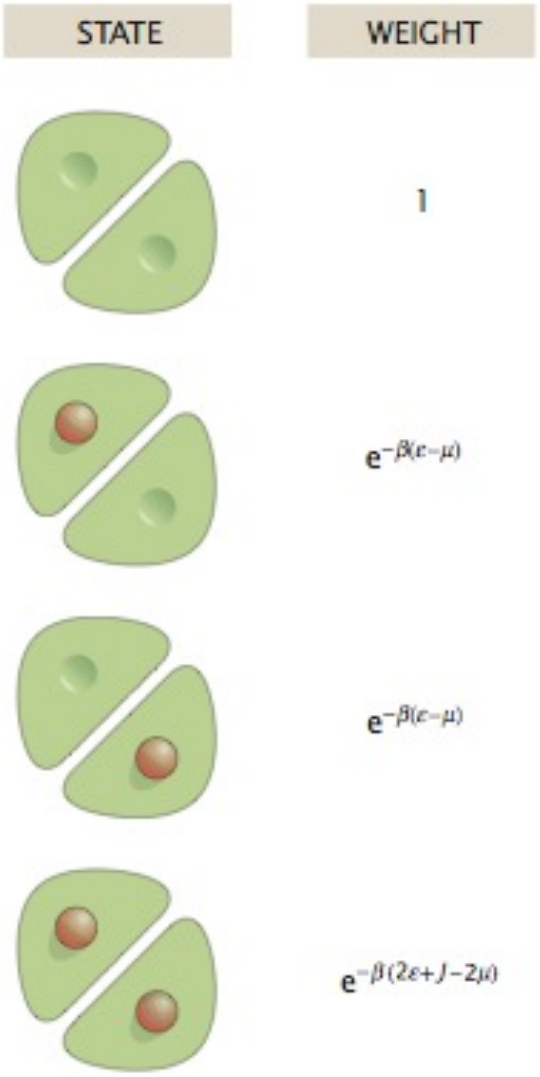


Energy (i.e. Hamiltonian) is:

$$E(\sigma_1, \sigma_2) = \varepsilon(\sigma_1 + \sigma_2) + J\sigma_1\sigma_2$$

Now we calculate the partition Function

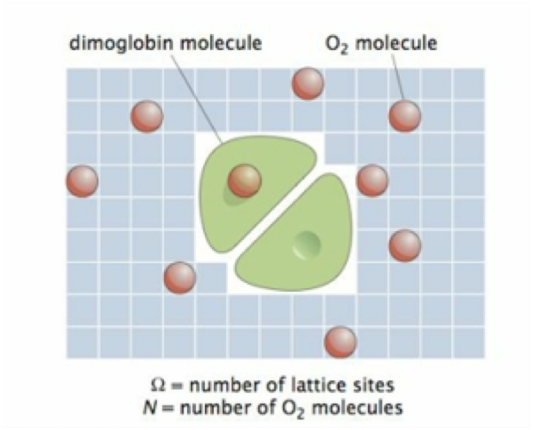
- $Z = \sum_{\sigma_1,\sigma_2=0,1} exp - \beta(E(\sigma_1, \sigma_2) - N_s\mu)$, where $N_s = \sigma_1 + \sigma_2$ is the number of **bound oxygen**.

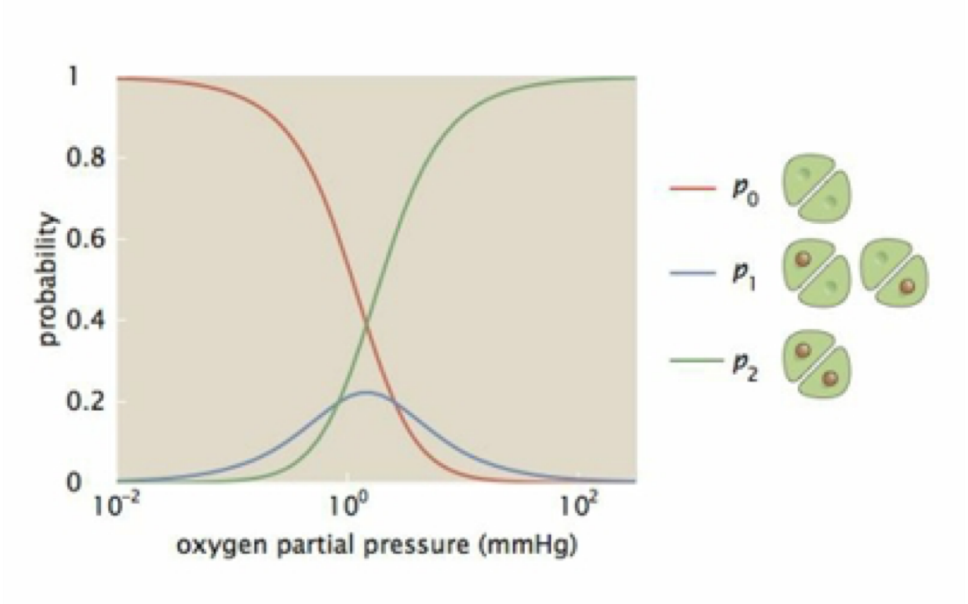
$$\mathcal{Z} = \underbrace{1}_{\text{unoccupied}} + \underbrace{e^{-\beta(\varepsilon-\mu)} + e^{-\beta(\varepsilon-\mu)}}_{\text{single occupancy}} + \underbrace{e^{-\beta(2\varepsilon+J-2\mu)}}_{\text{both sites occupied}}.$$

$$\langle N \rangle = \frac{2e^{-\beta(\varepsilon-\mu)} + 2e^{-\beta(2\varepsilon+J-2\mu)}}{1 + e^{-\beta(\varepsilon-\mu)} + e^{-\beta(\varepsilon-\mu)} + e^{-\beta(2\varepsilon+J-2\mu)}}.$$

Dimeric Hemoglobin (Dimoglobin) Model for Cooperative binding of O_2

Assignment 7, problem 7.3





The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding

- Section 7.2.4 MWC considers a Dimoglobin that can bind **2 oxygens**.
- The dimoglobin (a protein) can be in two states: **tense** (T) and **relaxed** (R).
- In the absence of ligands the T state has lower energy than R, and T is favored.
- Variable $\sigma_m = 0,1$ for T and R, respectively

The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding

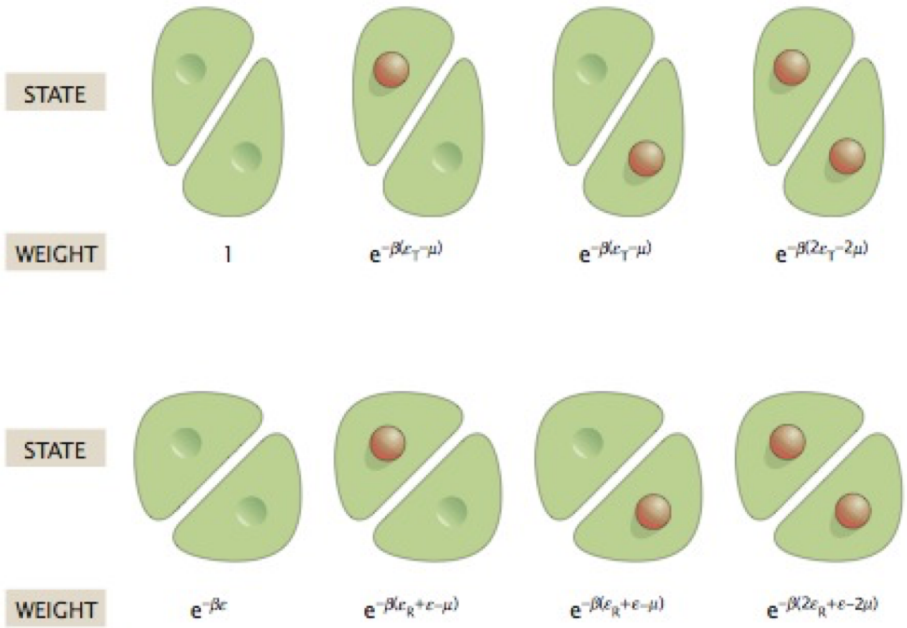
- As before $\sigma_1, \sigma_2 = 0,1$ quantifies whether a site has a bound oxygen
- Energy or Hamiltonian

$$E(\sigma_m, \sigma_i) = (1 - \sigma_m)\varepsilon_T \sum_{i=1}^{2} \sigma_i + \sigma_m \left(\varepsilon + \varepsilon_R \sum_{i=1}^{2} \sigma_i \right)$$

- Partition Function

$$Z = \sum_{\sigma_m = 0.1;, \sigma_i = 0,1} exp - \beta(E(\sigma_m, \sigma_i) - N_s \mu)$$

The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding



$$\mathcal{Z} = \underbrace{1 + 2e^{-\beta(\varepsilon_T-\mu)} + e^{-\beta(2\varepsilon_T-2\mu)}}_{\text{T terms}} + \underbrace{e^{-\beta\varepsilon}(1 + 2e^{-\beta(\varepsilon_R-\mu)} + e^{-\beta(2\varepsilon_R-2\mu)})}_{\text{R terms}}. \qquad (7.35)$$

The Monod-Wyman-Changeux (MWC) Model of Cooperative Binding

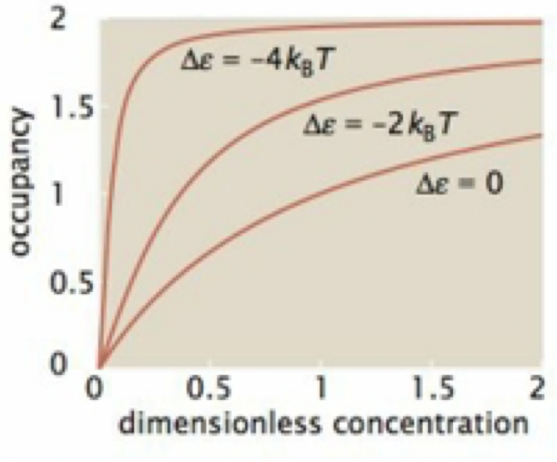
$$\mathcal{Z} = \underbrace{1 + 2e^{-\beta(\varepsilon_T - \mu)} + e^{-\beta(2\varepsilon_T - 2\mu)}}_{\text{T terms}} + \underbrace{e^{-\beta\varepsilon}(1 + 2e^{-\beta(\varepsilon_R - \mu)} + e^{-\beta(2\varepsilon_R - 2\mu)})}_{\text{R terms}}. \quad (7.35)$$

$$\langle N \rangle = \frac{2}{\mathcal{Z}}[x + x^2 + e^{-\beta\varepsilon}(y + y^2)],$$

$$x = exp\left(-\beta(\varepsilon_T - \mu)\right)$$

$$y = exp\left(-\beta(\varepsilon_R - \mu)\right)$$

$$\Delta\varepsilon = \varepsilon_R - \varepsilon_L < 0$$



Conclusion:

- Without O_2 T state is at a higher energy of ε than the R state
- Bound Ligands make T state energetically favorable