Week 3 problem solving
+ equations, + applications
S and G
Entropy and Gibbs Free Energy
Classical definition of $\Delta S = q/T$

- **Problem**: A calorimeter measured heat of 120J absorbed by a drug specimen while $T$ increased from 300K to 304K. What is the approximate entropy change during that process?
  - 8 kcal/K
  - 36 kJ K
  - 0.4 J/K
  - 2.5 SI units of entropy

- **Solution 1**: $\Delta S = q/T = 120J/300K = 0.4$ J/K
- **Or**: $\Delta S = C_p \ln(T_2/T_1)=C_p \ln(1+\Delta T/T) \approx C_p(\Delta T/T)=(q/\Delta T) (\Delta T/T)=q/T$
- **Answer**: 0.4 J/K
Micro-definition of $S_m = k \ln (N) = R \ln (n)$

**Problem:** One mole of molecules can exist in $10^{N_A}$ distinct equiprobable states under the given temperature and pressure conditions (here $N_A$ is the Avogadro number, $6 \times 10^{23}$). Estimate the entropy of the system.

- 19 kJ/K
- 183 J/K
- -5 J/(K mol)
- 85 kJ/K
- -2 J/K

**Solution:**
- Boltzmann definition: molar entropy equals $S = k \ln N = R \ln n$, where $n$ is the number of states of a single molecule
- $10^{N_A}$ states for a mole $\Rightarrow$ 10 states for a single molecule
- $S = 8.314 \times \ln 10 = 19$ J/K

**Hint:** $\ln 10 \sim 2.3$
Kirchhoff’s Law: entropy vs T

**Problem:** The standard entropy of formation of a compound at 0°C equals 150 J/(mol·K), and at 100°C 200 J/(mol·K). Which expression best approximates the molar heat capacity of this compound in the 0-100°C temperature range, in J/(mol·K) (assume \( C_p \) is constant)?

- \( C_p = \frac{50}{100} \)
- \( C_p = 50 \times 100 \)
- \( C_p = \frac{50}{\ln 1.37} \)
- \( C_p = 50 \times \ln 1.37 \)
- \( C_p = \frac{50}{\ln 100} \)
- \( C_p = 50 \times \ln 100 \)

**Solution:**

- Using Kirchhoff's Law, \( \Delta S = C_p \ln \left( \frac{T_2}{T_1} \right) \)
- \( C_p = \frac{(200-150) \text{(mol K)}}{\ln(373/273)} = \frac{50}{\ln 1.37} \text{ [J/(mol K)]} \)
Entropy upon protein-ligand binding depends on ligand movement and water shell changes

- Binding of anti-HIV drugs (HIV protease inhibitors) to their target (entropy contribution to $\Delta G$ is $-T\Delta S$, $\Delta S$ is entropy change upon binding):

<table>
<thead>
<tr>
<th>Generic name</th>
<th>$\Delta H$ (kcal/mol)</th>
<th>$-T\Delta S$ (kcal/mol)</th>
<th>$\Delta S$ (cal/mol·K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelfinavir</td>
<td>3.1</td>
<td>-15.9</td>
<td>53.0</td>
</tr>
<tr>
<td>Indinavir</td>
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<td>-14.2</td>
<td>47.3</td>
</tr>
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<td>Saquinavir</td>
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<td>-14.2</td>
<td>47.3</td>
</tr>
<tr>
<td>Tipranavir</td>
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<td>-13.9</td>
<td>46.3</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>-3.8</td>
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<td>Atazanavir</td>
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<td>-10.1</td>
<td>33.7</td>
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<tr>
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<td>31.3</td>
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<tr>
<td>Amprenavir</td>
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</tr>
<tr>
<td>Darunavir</td>
<td>-12.7</td>
<td>-2.3</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Why $\Delta S$ of Nelfinavir/Viracept increases so much upon binding? This drug is relatively rigid and very hydrophobic, logP = 6!
### Sign of Entropy and $G$ Changes

<table>
<thead>
<tr>
<th>$\Delta G = -T\Delta S$</th>
<th>![Graph]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta S &gt; 0$</td>
<td>More states $\uparrow$</td>
</tr>
<tr>
<td></td>
<td>• Melting</td>
</tr>
<tr>
<td></td>
<td>• Vaporization</td>
</tr>
<tr>
<td></td>
<td>• Heating</td>
</tr>
<tr>
<td></td>
<td>• Gas expansion</td>
</tr>
<tr>
<td></td>
<td>• Dissociation (= increase in the number of “particles”)</td>
</tr>
<tr>
<td></td>
<td>• Ideal mixing</td>
</tr>
<tr>
<td></td>
<td>• Dissolution (typically)</td>
</tr>
</tbody>
</table>

| $\Delta S < 0$           | Fewer states $\downarrow$ |
|                          | • Freezing  |
|                          | • Condensation  |
|                          | • Cooling  |
|                          | • Association (= decrease in the number of “particles”)  |
|                          | • Crystallization (typically)  |
Gibbs Free energy, $\Delta G$, has enthalpic and entropic components

- $\Delta G = \Delta H - T\Delta S$
- $\Delta H \equiv$ heat of reaction
  - $\Delta H = H(\text{products}) - H(\text{reactants})$
  - $\Delta H < 0$ means “$\Rightarrow$” is *exothermic* (produces heat)
  - $\Delta H > 0$ means “$\Rightarrow$” is *endothermic* (absorbs heat)
- $\Delta S \equiv$ reaction entropy
  - $\Delta S = S(\text{products}) - S(\text{reactants})$
  - $\Delta S > 0$ means “$\Rightarrow$” increases disorder (lower $\Delta G$)
  - $\Delta S < 0$ means “$\Rightarrow$” increases order (higher $\Delta G$)
Spontaneity: $\Delta G < 0$ (not $\Delta H$ or $\Delta S$)

- **Problem:** The standard *entropy* of dissolution of sodium naproxen in water at 293 K equals 240 J/(mol·K). Will the drug spontaneously precipitate from a saturated solution at this temperature?

  - the result is unknown because entropy alone does not determine the direction of processes
  - the drug will precipitate because the crystallization enthalpy is negative
  - the drug will not precipitate because the dissolution entropy is positive
  - the drug will not precipitate because the system is at equilibrium

- **Answer:** Entropy, $\Delta S$, alone does not determine the direction of processes, need to know $\Delta G = \Delta H - T\Delta S$
Gibbs free energy and spontaneity

**Problem:** An ice cube is taken from the freezer (-4°C) and placed in a cup with room temperature water (20°C), which initiates active melting. Which statement about molar Gibbs free energy, $G_m$, of the two phases is correct?

- $G_m$ of water is equal to $T \times G_m$ of ice and entropy gain compensates the enthalpy loss
- $G_m$ of water is equal to $G_m$ of ice
- $G_m$ of water is lower than $G_m$ of ice
- $G_m$ of water is higher than $G_m$ of ice

**Answer:** Active spontaneous melting indicates negative $\Delta G$, hence $G_m$ of water is lower than $G_m$ of ice
- Liquid is indeed the most stable phase of $\text{H}_2\text{O}$ at 20°C and P=1atm
Binding of drugs to targets: spontaneous with negative $\Delta G$

- Signs of molar $\Delta H_{bind}$ and $\Delta S_{bind}$ may vary
- $\Delta G_{bind} = \Delta H_{bind} - T\Delta S_{bind}$ is always negative
  - Otherwise they would not be drugs
  - Typically -12 to -15 kcal/mol

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Using equation $\Delta G = \Delta H - T\Delta S$

**Problem:** Lopinavir binding to HIV protease at 25°C is characterized by 1:1 stoichiometry, molar $\Delta G$ of -15.1 kcal/mol and molar $\Delta H$ of -3.8 kcal/mol. How does molar entropy change in the binding process?

- Decreases by 37.9 cal/(K mol)
- Increases by 37.9 cal/(K mol)
- Decreases by 11.3 cal/(K mol)
- Increases by 11.3 cal/(K mol)
- Remains unchanged
- Impossible to tell

**Solution:**

- $-T\Delta S = \Delta G - \Delta H = -11.3$ kcal/mol (entropy in favor of binding)
- $T\Delta S = 11.3$ kcal/mol > 0 $\Rightarrow \Delta S > 0$
- $\Delta S = 11.3$ kcal/mol / 298 K = 37.9 cal/(K mol)
Phase transitions: pure substances

\[ \Delta G_{trs} = 0 \]
\[ \Delta H_{trs} = T_{trs} \Delta S_{trs} \]

- **Triple point** – 3 equally stable phases
- Normal \( T_{boiling} \) and \( T_{freezing} \) are where \( P = 1 \text{ atm} \) intersects the s/l and l/g boundaries
Equilibrium phase transition

- **Problem:** ... The melting temperature of 1:3 mixture of Estradiol-Norethindrone is 25°C, and the crystallization enthalpy at this temperature is -8 kJ/mol. Which number is closer to the crystallization entropy at 25°C?
  
  - 25 kcal/mol K
  - 2.3 cal/mol K
  - 0.1 cal/K
  - -27 J/(mol K)
  - -90 J/K

- **Answer:** Phase transition at equilibrium:
  
  - $\Delta G_{trs} = 0$, so $T\Delta S_{trs} = \Delta H_{trs}$
  - $\Delta S_{trs} = \Delta H_{trs}/T \approx -8 \text{ kJ/mol} / 298 \text{K} \approx -27 \text{ J/(mol K)}$
  - Crystallization entropy is negative, disorder ↓