

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:** $\Delta S = q/T = 120\text{J}/302\text{K} = 0.4 \text{ J/K}$
- **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, 6×10^{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
 - $S = 8.314 \times \ln 10 = 19 \text{ J/K}$
- **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)?

- $C_p = 50 / 100$
- $C_p = 50 \times 100$
- $C_p = 50 / \ln 1.37$
- $C_p = 50 \times \ln 1.37$
- $C_p = 50 / \ln 100$
- $C_p = 50 \times \ln 100$

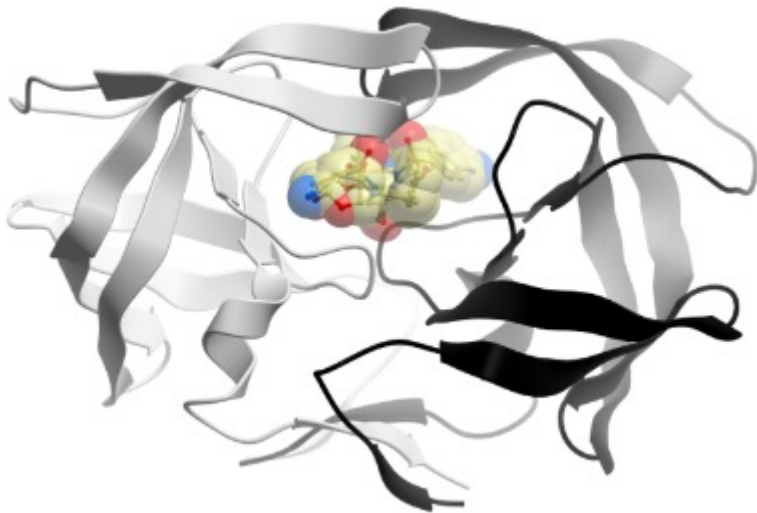
$$H(T_2) \approx H(T_1) + C_P(T_2 - T_1)$$
$$S(T_2) \approx S(T_1) + C_P \ln\left(\frac{T_2}{T_1}\right)$$

- **Solution:**

- Using Kirchhoff's Law, $\Delta S = C_p \ln(T_2/T_1)$
- $C_p = (200 - 150) \text{ (mol K)} / \ln(373/273) = 50 / \ln 1.37 \text{ [J/(mol K)]}$

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 ΔG is $-T\Delta S$, ΔS is entropy change upon binding):





Generic name	ΔH (kcal/mol)	$-T\Delta S$ (kcal/mol)	ΔS (cal/mol·K)
Nelfinavir	3.1	-15.9	53.0
Indinavir	1.8	-14.2	47.3
Saquinavir	1.2	-14.2	47.3
Tipranavir	-0.7	-13.9	46.3
Lopinavir	-3.8	-11.3	37.7
Atazanavir	-4.2	-10.1	33.7
Ritonavir	-4.3	-9.4	31.3
Amprenavir	-6.9	-6.3	21.0
Darunavir	-12.7	-2.3	7.7

Why ΔS of Nelfinavir/Viracept increases so much *upon binding*?

This drug is relatively rigid and very hydrophobic, $\log P = 6$!

Sign of entropy and G changes

$\Delta G = -T\Delta S$	
<p style="text-align: center;">—</p> <p style="text-align: center;">$\Delta S > 0$</p> <p style="text-align: center;">More states \uparrow</p>	<div style="text-align: center;"></div> <ul style="list-style-type: none">•Melting•Vaporization•Heating•Gas expansion•Dissociation (= increase in the number of “particles”)•Ideal mixing•Dissolution (typically)
<p style="text-align: center;">+</p> <p style="text-align: center;">$\Delta S < 0$</p> <p style="text-align: center;">Fewer states \downarrow</p>	<div style="text-align: center;"></div> <ul style="list-style-type: none">•Freezing•Condensation•Cooling•Association (= decrease in the number of “particles”)•Crystallization (typically)

The Gibbs Free energy, ΔG , 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 ΔG)
 - $\Delta S < 0$ means " \Rightarrow " increases order (higher ΔG)

Transition direction is defined by the sign of ΔG

G wants to be lower, which

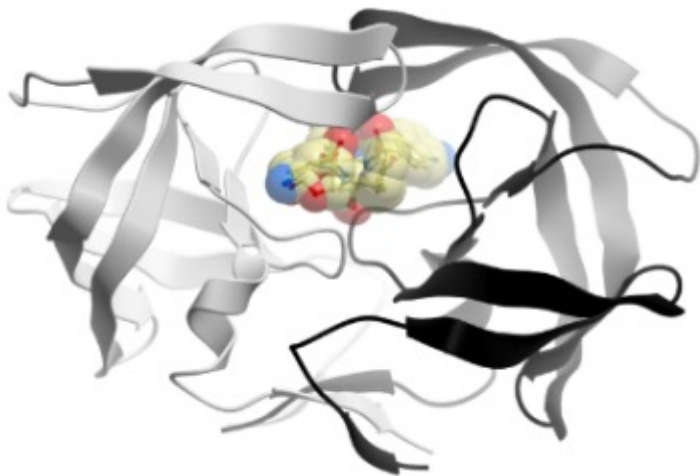
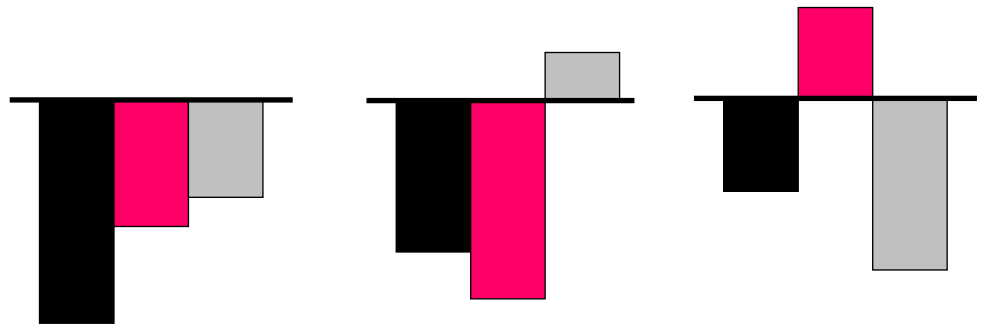
- **Problem:** The standard *entropy* of dissolution of sodium naproxen in water at 293 K equals +240 J/(mol·K). Will the drug spontaneously precipitate from a saturated solution at this temperature?
 - the result is unknown because entropy alone does not determine the direction of processes
 - the drug 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, ΔS , alone does not determine the direction of processes, one needs to know how $\Delta G = \Delta H - T\Delta S$ changes

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 while the cube is still melting and before the equilibrium is reached?
 - 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 ΔG , hence G_m of water is lower than G_m of ice
 - Liquid is indeed the most stable phase of H_2O at 20°C and $P=1\text{atm}$

Binding of drugs to targets: spontaneous with negative ΔG

- Signs of molar ΔH_{bind} and ΔS_{bind} may vary
- $\Delta G_{bind} = \Delta H_{bind} - T\Delta S_{bind}$ is always negative
 - **Otherwise, they would not be able to bind**
 - Typically, -11 to -15 kcal/mol



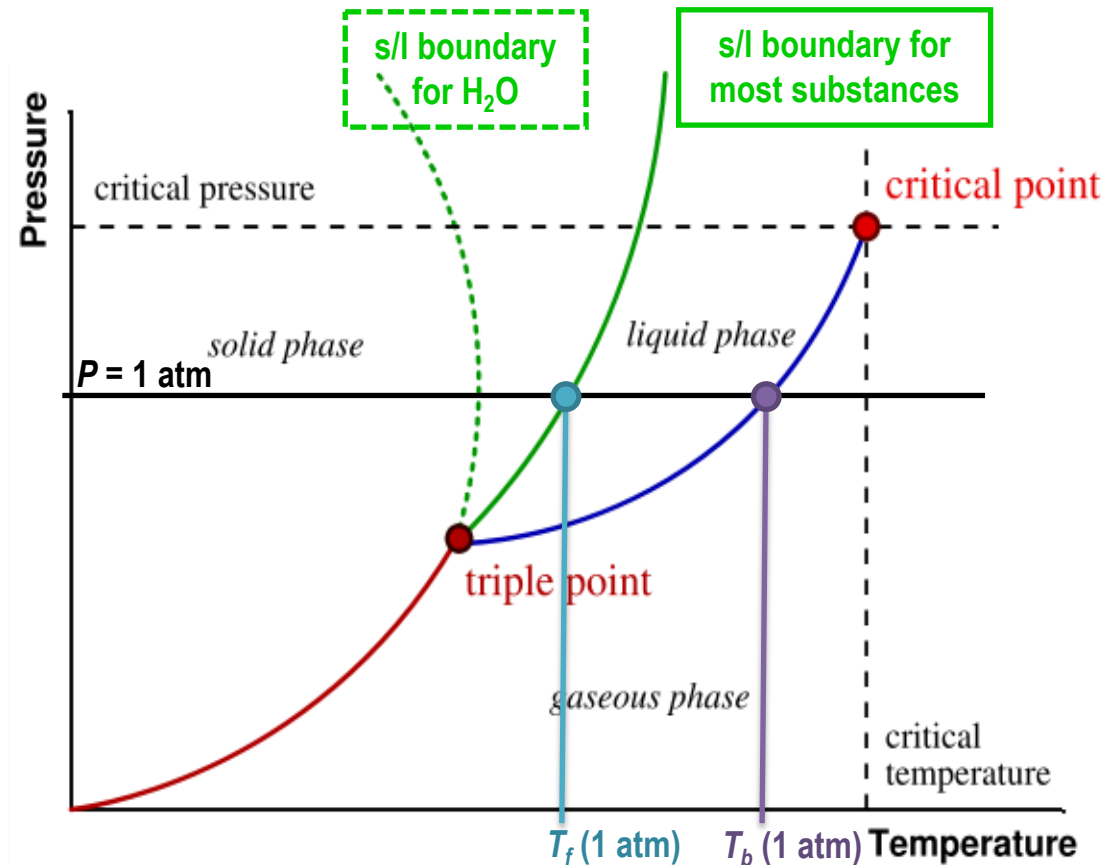
Generic name	ΔG (kcal/mol)	ΔH (kcal/mol)	$-T\Delta S$ (kcal/mol)
Nelfinavir	-12.8	3.1	-15.9
Indinavir	-12.4	1.8	-14.2
Saquinavir	-13	1.2	-14.2
Tipranavir	-14.6	-0.7	-13.9
Lopinavir	-15.1	-3.8	-11.3
Atazanavir	-14.3	-4.2	-10.1
Ritonavir	-13.7	-4.3	-9.4
Amprenavir	-13.2	-6.9	-6.3
Darunavir	-15	-12.7	-2.3

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 ΔG of -15.1 kcal/mol and molar ΔH 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 $T\Delta S_{trs} = \Delta H_{trs}$
 - $\Delta S_{trs} = \Delta H_{trs}/T \sim -8 \text{ kJ/mol} / 298\text{K} \sim -27 \text{ J/(mol K)}$
 - Crystallization entropy is negative, number of states goes down ↓