Chemical Physics
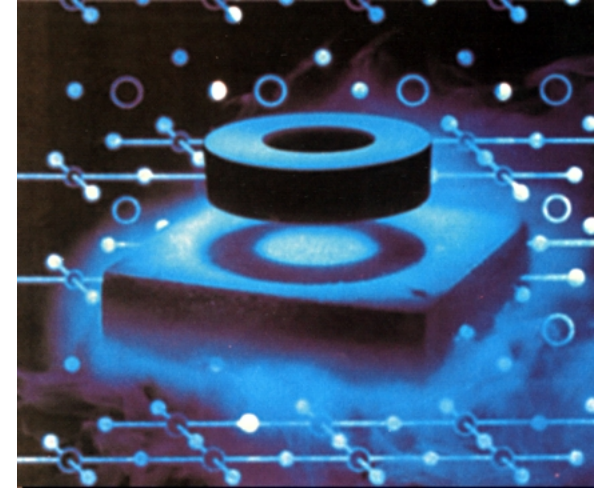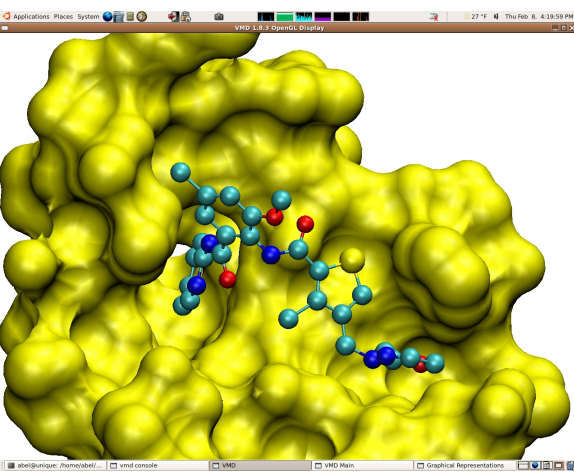
Themodynamics

Chemical Equilibria

Ideal Gas

Van der Waals Gas

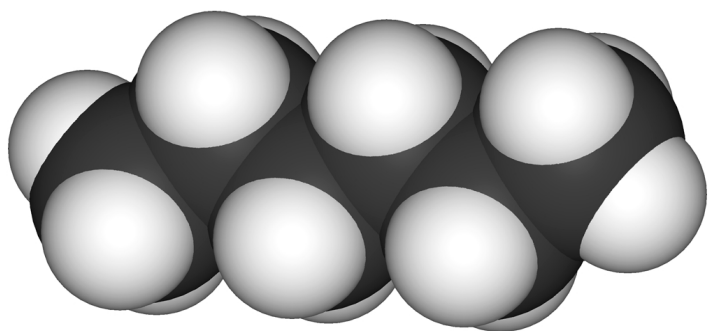Phase Changes

Ising Models

Statistical Mechanics

etc...

Today's Theme
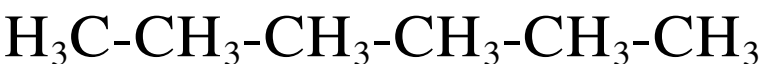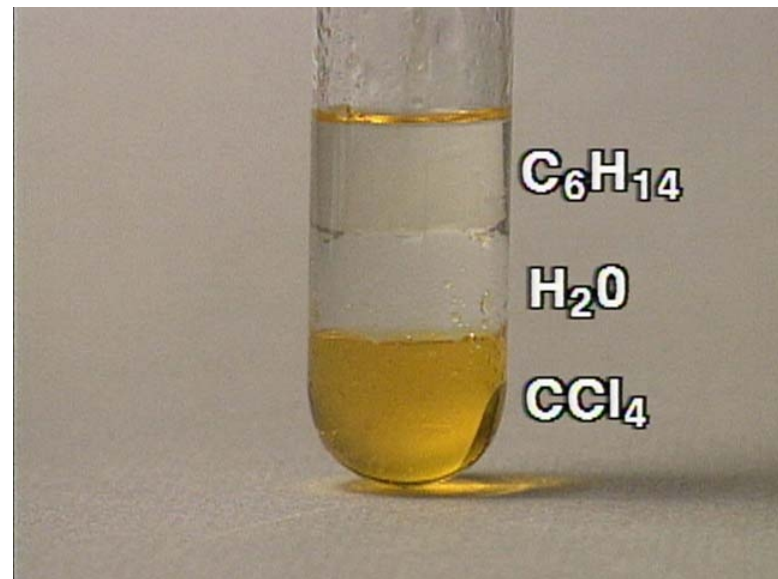
How can we understand the bulk properties of a substance from the properties of individual molecules

H_3C-CH_3-CH_3-CH_3-CH_3-CH_3

Density=0.6548 g/ml
Boiling point=69 °C
Melting point=−95°C
etc.

?

C_6H_{14}

H_2O

CCl_4

Not just an academic problem

- Biology
  - Design small molecules with drug-like properties
  - Determine the chemical reactivity and kinetics of enzymes from their atomic structure

- Chemistry
  - Design chemical systems with desired properties, such as heat resistance and longevity for batteries or house paints
  - Design catalysts

- Material Science
  - Develop high temperature superconductive materials
  - Develop lighter and more durable materials

The Game Plan

- Review of thermodynamics

  - The drugs you doctor prescribes work because of thermodynamics (We'll explore how)

  - introduction to a computational model for building a drug

- Intro to a "simple" example of statistical thermodynamics

  - Model of a simple 2 state system

  - relevant to why New York banned trans-fats

- Kinetic theories --> Ideal gas --> VdW gas

  - Where do the gas laws come from

  - How can we understand phase changes from them

  - Computational models of phase changes

Thermodynamics

Physics is the science that attempts to describe all aspects of all phenomena pertaining to the perceivable universe. It can be viewed as a large tree with many branches, such as mechanics, electromagnetism, gravitation, and chemistry, each specializing in the description of a particular class of phenomena. Thermodynamics is not a branch. It pervades the entire tree.

-Elias Gyftopoulos and Gian Beretta

Practical Thermodynamics Review

- What is an equilibrium constant

- What is the free energy

- What is entropy (this one is tricky, so we'll only use examples to qualitatively describe it)

- What is enthalpy

Medical Doctor's Thermo.

- Proteins regulate and perform nearly all chemistry occurring in your body

- Medicines most often work by inhibiting or stimulating the proteins that control these processes

  - Morphine binds to and activates the μ-opioid receptors in the central nervous system

  - Ibuprofin binds to cyclooxygenase, which prevents prostaglandin synthesis

  - Norfloxacin binds to bacterial DNA Gyrase, which is needed for DNA replication

- Thermodynamics is needed to explain how these small molecules (drugs) affect the bulk system (you)
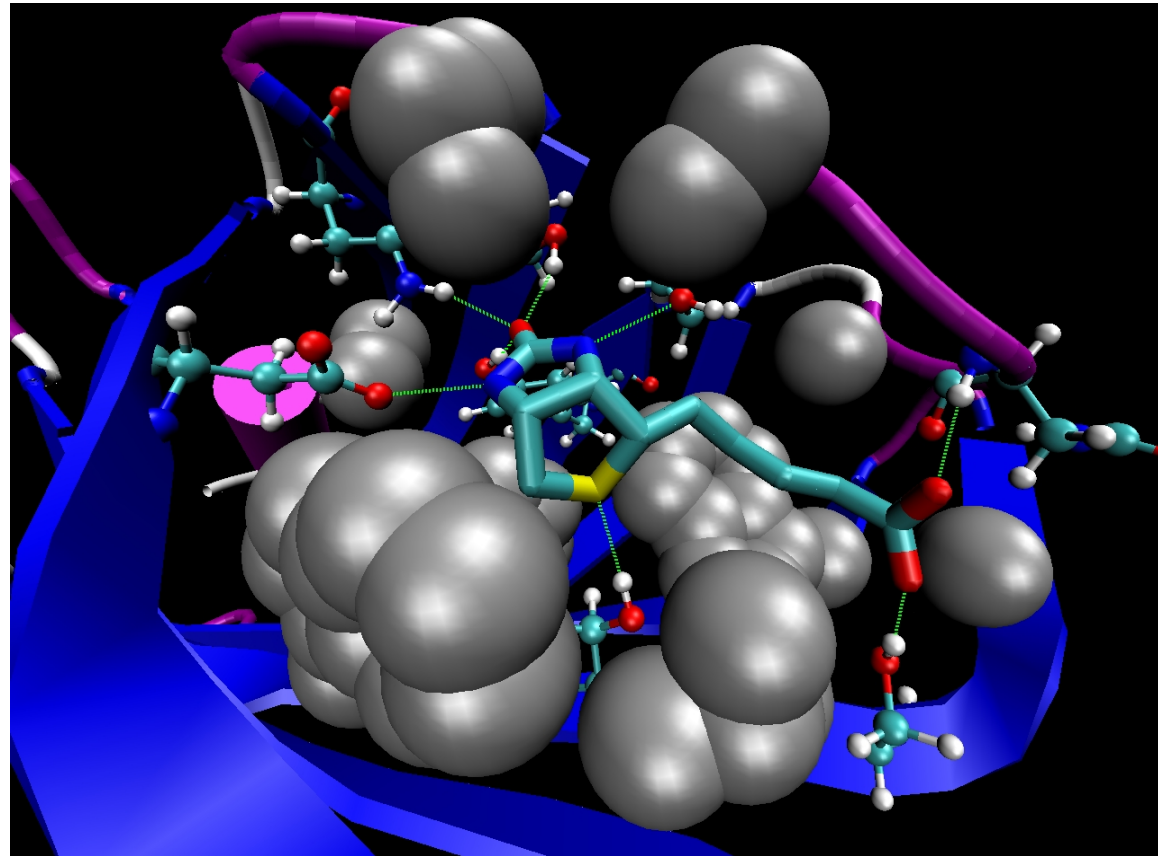
Medical Doctor's Thermo.

Given the rxn,

$$P + L \Leftrightarrow PL$$

we can define,

$$Q = \frac{[PL]}{[P][L]}$$

$$K = \frac{[PL]}{[P][L]} = \frac{k_{fwd}}{k_{rev}}$$

Medical Doctor's Thermo.

Given,

$$P \; + \; L \; \Leftrightarrow \; PL$$
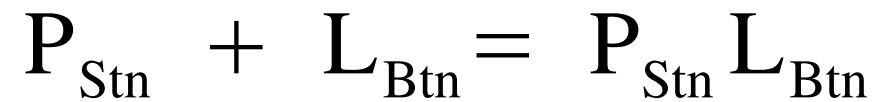
$$Q = \frac{[PL]}{[P][L]} \qquad K = \frac{[PL]}{[P][L]} = \frac{k_{fwd}}{k_{rev}}$$

we can define,

$$\Delta G = RT \ln \frac{Q}{K} \quad \text{and} \quad \Delta G^{o} = -RT \ln K$$

Medical Doctor's Thermo.

- So for the example of the small molecule biotin binding to the protein streptavidin

$$P_{Stn} + L_{Btn} = P_{Stn} L_{Btn}$$
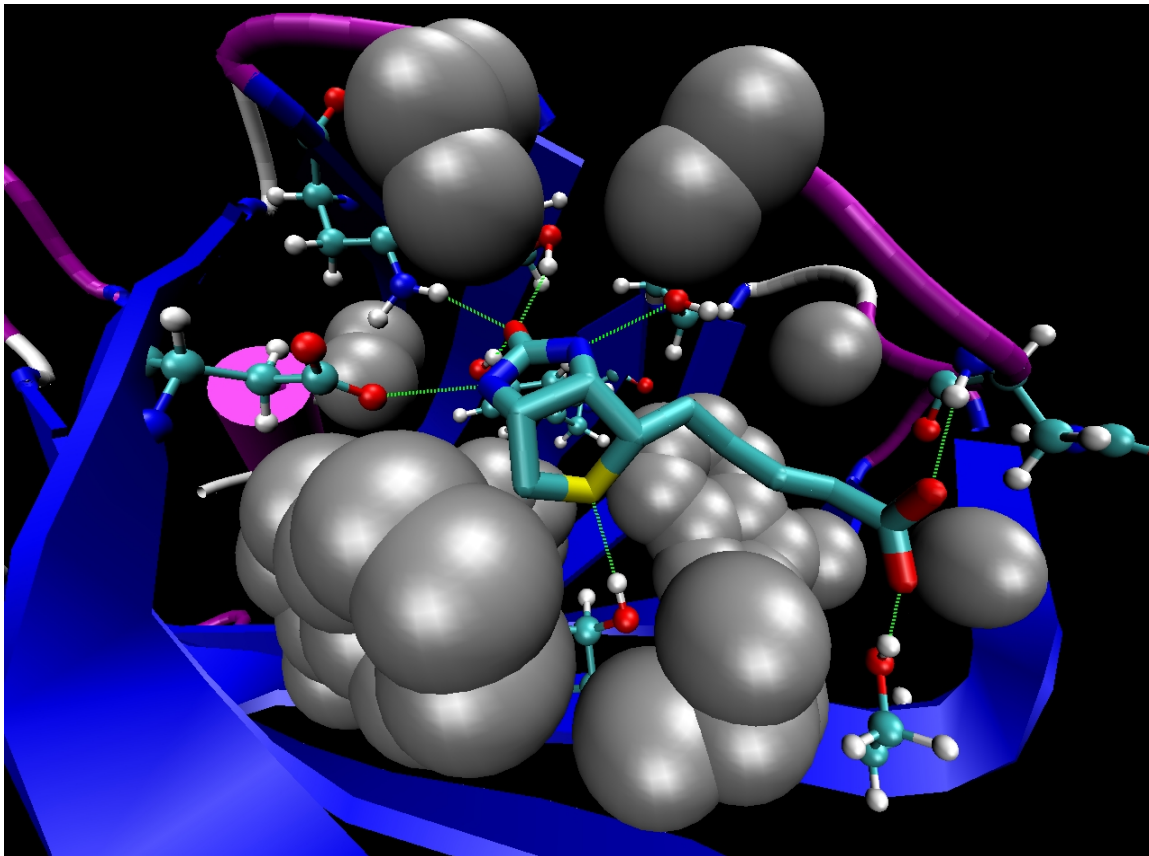
$$K = 10^{14}$$

$$\Delta G_o = -RT \ln(10^{14})$$
$$\Delta G_o \approx -19 \, kcal/mol$$

Medical Doctor's Thermo.

- Medicinal chemist tend not to use equilibrium constants or binding free energies

- Instead they report binding affinities:

$$\text{Set}, \quad [\text{PL}] \equiv [\text{P}]$$

$$\text{then}, \quad K = \frac{[\text{PL}]}{[\text{P}][\text{L}]} = \frac{1}{[\text{L}]_{1/2}}$$

- For the Biotin-Streptavidin complex [L]=10^-14 mol/L

Medical Doctor's Thermo.

- But have we learned anything molecular?

- We would like to be able to predict what small molecules will make good drugs

  - we need to build a bridge from bulk solution chemistry to small molecule interactions

  - this will let us make computer models to build new drugs

- This is a very important challenge

  - There are ~40 functional groups used to build organic compounds

  - About ~5-10 functional groups per small drug-like molecule

  - Then the "drug-search-space" is ~40^{10}=~10^{16} ie 10,500 trillion small molecules to test (this is gross underestimate)

Medical Doctor's Thermo.

More thermo to the rescue:

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

$$\Delta H = \Delta E + P \Delta V, \quad but \quad P \Delta V \approx 0 \quad for\ bio.$$
$$\Rightarrow \quad \Delta H \approx \Delta E$$

$$\Delta S = R \ln(V_2/V_1) \quad ideal\ gas\ approx.$$

$$\Rightarrow \Delta G_{PL} \approx \Delta E_{PL} - RT \ln(V_{bound}/V_{free})$$

Medical Doctor's Thermo.

For realistic protein ligand binding problems:

$$\Delta G_{PL} \approx \Delta E_{PL} - RT \ln \left(V_{bound} / V_{free} \right) \quad \text{where}$$

$$V_{free} = \left(1 \text{mol}/L \right)^{-1} = 1660 \, \mathring{A}^3 / \text{molecule}$$

$$V_{bound} \approx 1 \, \mathring{A}^3 / \text{molecule}$$

$$\Rightarrow \Delta G_{PL} \approx \Delta E_{PL} + 4.5 \text{kcal}/\text{mol}$$

For streptavidin ΔE_{PL} is measured to be $-26 \text{kcal}/\text{mol}$

Medical Doctor's Thermo.

- This is how the first computational models of protein ligand binding were developed

  – Estimate ΔS from the loss of translational, rotational, and conformational freedom once it binds

  – Estimate ΔE from the number of "good" hydrogen bonds, salt bridges, and hydrophobic contacts the ligand makes with the protein

 – Predict affinity with $\Delta G = \Delta E - T\Delta S$
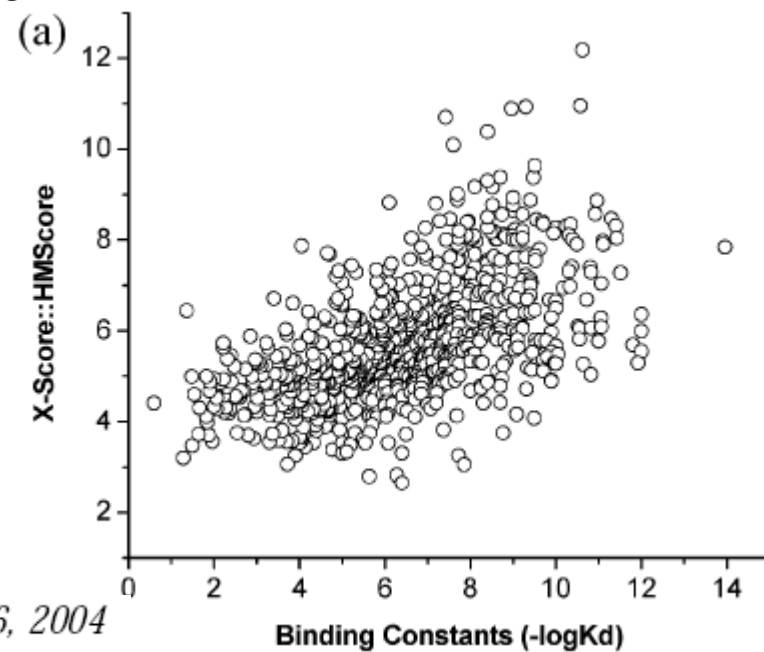
Statistical Thermodynamics

- In our previous example the 6.022E23 biotin molecules were assumed to interact with the 6.022E23 streptavidin molecules in exactly the same way

- Does this make sense?

- Consider a drop liquid water

  - would you expect every single water molecule to have the exact same number of hydrogen bonds?

  - how are those molecules at the surface different from thos inside the drop

  - what we have is an **ensemble** of water molecules

Butene Gas

- Some of the molecules of the gas will be in the cis conformation, others will be in the trans conformation:

cis- Same side of the double bond

trans- Opposite sides of the double bond
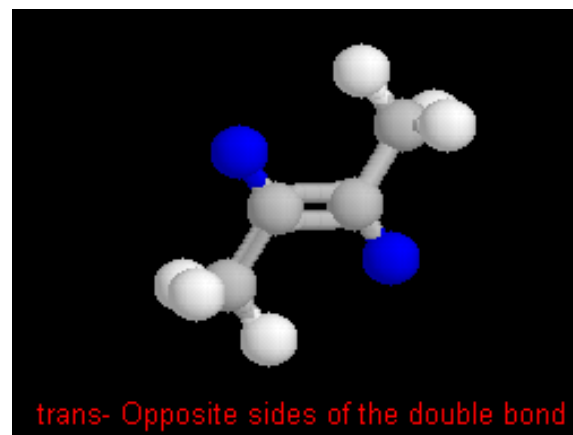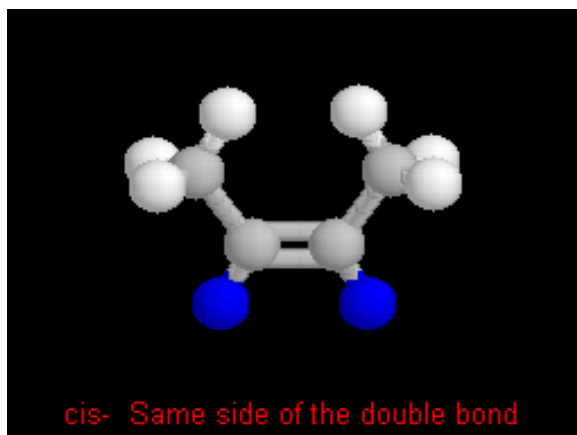
- What would we expect to be true about the **ratio** of cis butene molecules to trans butene molecules

Butene Gas

- This is a "real world" problem

    – Fats and cooking oils can either be cis fats or trans fats

    – In NY state "Restaurants will be barred from using most frying oils containing artificial trans fats by July and will have to eliminate the artificial trans fats from all of their foods by July 2008."   -MSNBC News Services 12/5/06

    – Trans fats are not needed by the human body and increase the risk of heart disease

Oleic acid
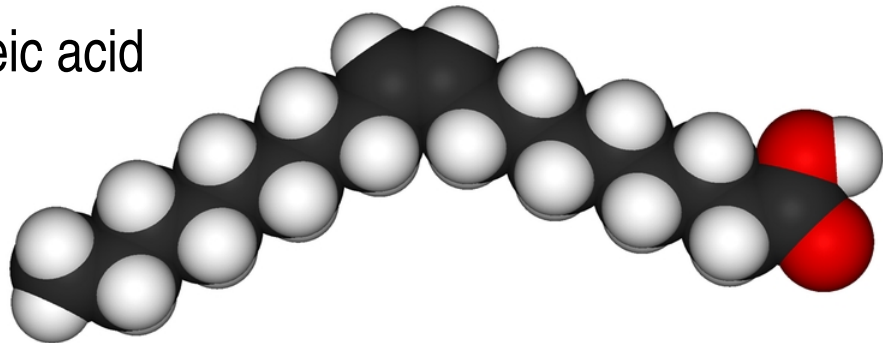
Elaidic acid
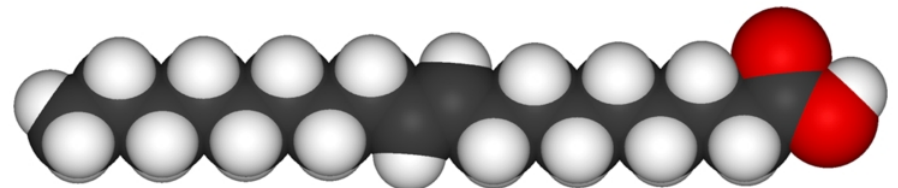
Butene Gas

- Lets solve the problem conceptually before we solve it mathematically

16kcal/mol $E_{act(forward)}$

$E_{act(reverse)}$ 19kcal/mol

ΔH 3kcal/mol

*NB: Spartan can compute these

*How do you expect the ratio of cis/trans isomers to behave?
*Consider both the high T and low T limits.
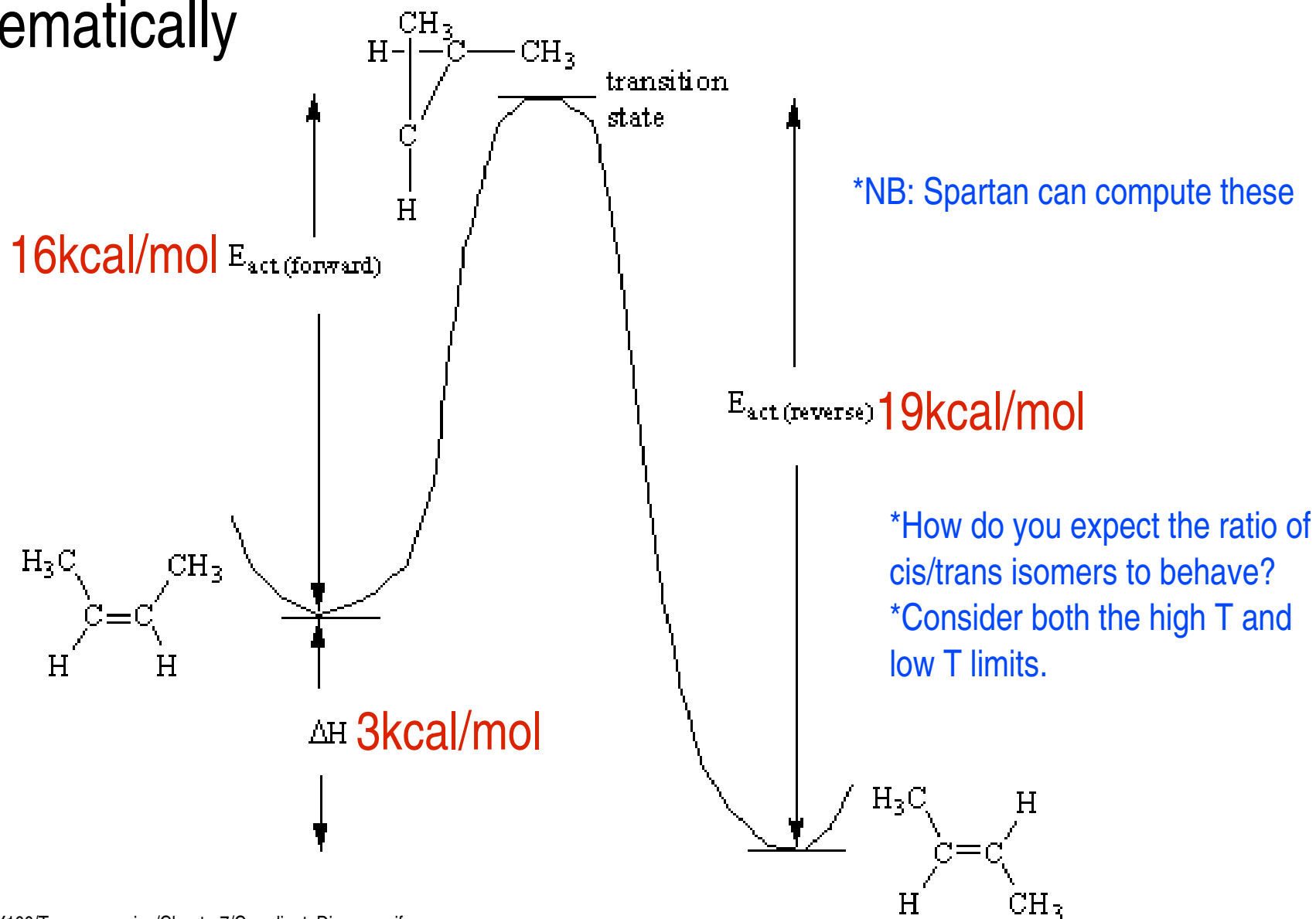
Butene Gas

- Now for some math,

  - If I flip a coin twice, what are the odds it will land heads up twice?

  - Two ways to solve,

    - counting: HH, HT, TH, TT --> P(HH)=1/4=.25

    - multiplying independent events: P(H)=.5 --> P(H)xP(H)=.5*.5=.25

  - Note: this may seem easy, but can get quite complicated

    - what do you think the probability is of flipping 10 quarters and exactly 5 of them flip heads up?

    - Would you bet on your result?

Butene Gas

- We can view the probability 1 molecule of butene is cis or trans as completely independent of whether any other butane molecule is cis or trans

- This probability should depend on
  - the energy difference between the cis and trans isomers
  - the temperature of the system

- The probability of two molecules being cis should equal to the square of the probability a single molecule being cis
  - this just means independent events should multiply

Butene Gas

So the cis/tran probability funcion should have the properties

$$P = P(T, E_t, E_c)$$

$$P(c) \cdot P(c) \cdot P(t) \cdot P(c)... = P(cctc...)$$

One function that satisfies this requirement is

$$P(i) = e^{\frac{-E_i}{RT}} \quad \text{where} \quad e^{\frac{-E_t}{RT}} \cdot e^{\frac{-E_c}{RT}} = e^{\frac{-(E_t + E_c)}{RT}}$$

for any exponential function

Butene Gas

This solution, athough formally correct, is inelegant.

We need

$$P(c) + P(t) = 1$$

$$P(T, E_c, E_t) = P(T, E_c - E_t) = P(T, \Delta E_{ct})$$

$$\Rightarrow P(\text{trans}) = \frac{1}{1 + e^{\frac{-\Delta E_{ct}}{RT}}} \quad \text{and} \quad P(\text{cis}) = \frac{e^{\frac{-\Delta E_{ct}}{RT}}}{1 + e^{\frac{-\Delta E_{ct}}{RT}}}$$
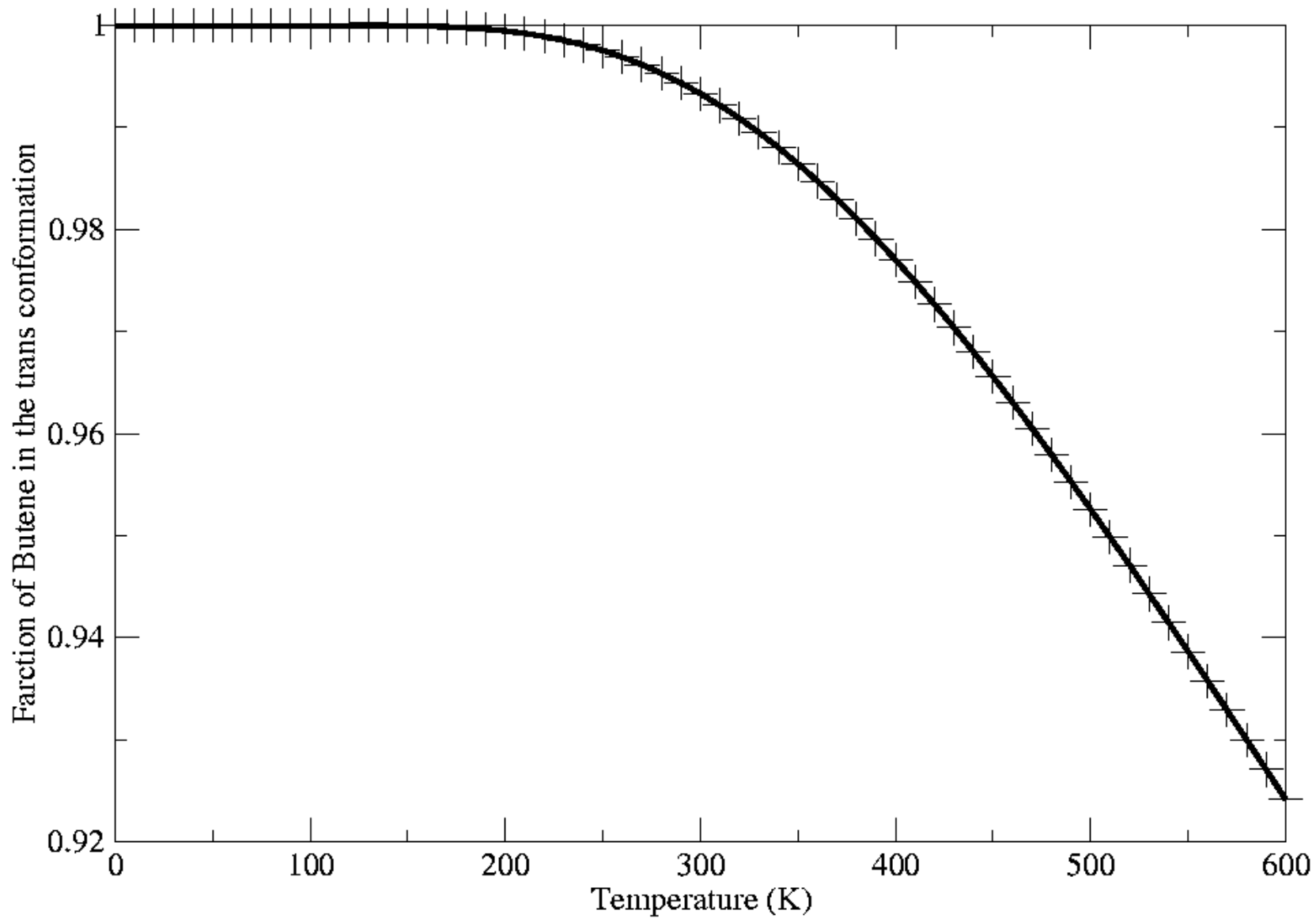
Butene Gas

- And finally we note that since all the molecules behave independently

$$P(\text{trans}) = \frac{1}{1 + e^{\frac{-\Delta E_{ct}}{RT}}} = \frac{1}{1 + e^{\frac{-3.0\text{kcal}/\text{mol}}{(.002\,\text{kcal}/\text{mol}\cdot K)T}}} = \chi(\text{trans})$$

$$\Rightarrow N_{\text{trans}} = P(\text{trans}) \cdot N = \frac{N}{1 + e^{\frac{-\Delta E_{ct}}{RT}}}$$

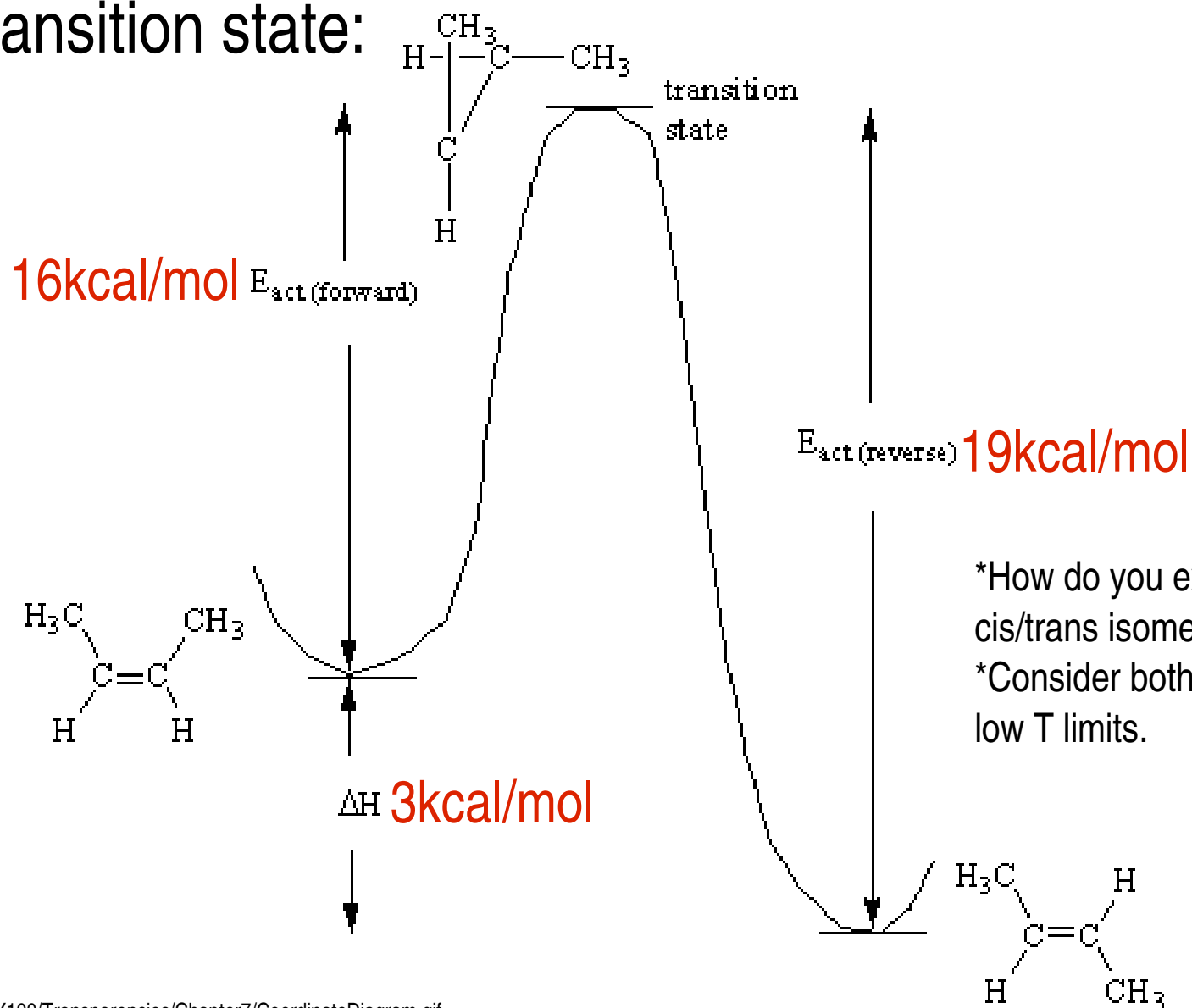# Butene Gas

Fraction of trans-butene versus temperature

Butene Gas

- So at low temperatures all of our butene is trans

- At very high temperatures the ratio approaches 50:50

- Since the ΔE for cis and trans fats is similar to that of butene, then

    – we expect to have all trans fats in cold food and mostly trans fats in our warm food

    – we will all get heart attacks and NY is wasting its time

    – but, clearly the NY legislature would never waste its time so something in our understanding must be wrong!

Butene Gas Kinetics

- To get from cis to trans, the molecule has to get through the transition state:

16kcal/mol $E_{act(forward)}$

$E_{act(reverse)}$ 19kcal/mol

ΔH 3kcal/mol

*How do you expect the ratio of cis/trans isomers to behave?
*Consider both the high T and low T limits.

Butene Gas Kinetics

- We can estimate the rate at which the a jug of butene will isomerize to trans butene by finding what fraction of the molecules at a given time are at the transition state

  - this is the same calculation we just did, but now $\Delta E = 16 \text{kcal/mol}$ instead of 3kcal/mol

$$k_{cis \to trans} \propto P(tst) s^{-1} = \frac{e^{\frac{-\Delta E_{c\,tst}}{RT}}}{1 + e^{\frac{-\Delta E_{c\,tst}}{RT}}} s^{-1} = \frac{e^{\frac{-\Delta E_{c\,tst}}{RT}}}{1 + e^{\frac{-16\text{kcal/mol}}{(.002\,\text{kcal/mol}\cdot K)T}}} s^{-1}$$

$$\Rightarrow k_{cis \to trans} \propto 10^{-12}/s \quad ie \quad 30000\text{yr halflife}$$

Butane Gas Kinetics

- This system is **inergodic**, ie will not explore its full potential energy surface within a "reasonable" amount of time

    – We will come back to this topic later because it is a major source of error for computational chemical models

- In the presence of a catalyst, the potential energy surface will completely change

    – A good catalyst, such as a strong acid for this reaction will make the the cis to trans energy barrier nearly vanish so interconversion will take place at room temperature

    – This is one of many reasons you should not add HCl to your deep fryer

Conclusions

- To make computer models of chemistry, we need to be able to determine the behavior of the bulk system from our computational simulation of at most ~100,000 atoms

- To do this we need to understand probability, statistics, thermodynamics, and energy models

- Next week we will cover a molecular description of the ideal gas, VdW gas, and phase changes