

Week 9

Reaction Energetics

9.1 Equilibria

- 10/29:
- Lecture 14 continued: Examples of hydrogen bonds.
 - Alex reviews strong, moderate, and weak hydrogen bonds (see Figure 8.14 and discussion).
 - Canonical hydrogen bonds.
 - Those in the bifluoride anion (HF_2^-).
 - Held together by such a strong hydrogen bond that it is stable and isolable.
 - Energy on the order of 39 kcal/mol.
 - Those between H_2O and H_3O^+ .
 - Relatively strong, persistent in solution, etc.
 - Energy on the order of 33 kcal/mol.
 - Those between H_2O and H_2O .
 - The loss of the charge leads to a significant decrease in strength.
 - > Charge-assisted hydrogen bonds are typically stronger!
 - Energy on the order of 5 kcal/mol.
 - Fluoroform (CHF_3) in water.
 - Energy on the order of 3 kcal/mol.
 - Geometric parameters relevant to hydrogen bonding (find these in crystallographic/biological databases).
 - Donor-acceptor bond length, and donor-acceptor bond angle.
 - The prevalence of different kinds of hydrogen bonds vs. the bond angle.

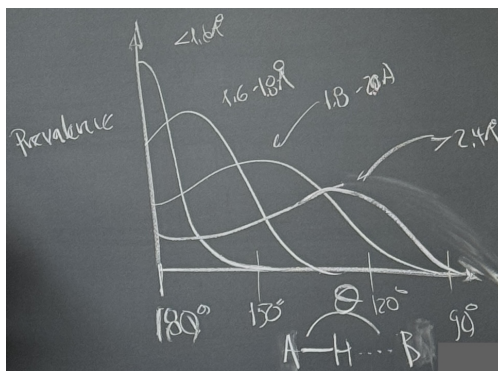


Figure 9.1: Stronger hydrogen bonds are more linear.

- We can think of this plot like a histogram.
- Takeaway: Stronger bonds are more linear, and weaker bonds are more bent.
- As the bond gets weaker, the molecules begin to explore a larger cone of orientations.
- Example: H-bonding in carbonyl species.

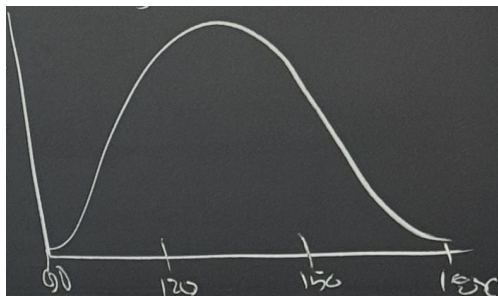


Figure 9.2: Carbonyl hydrogen bonds reflect $O(sp^2)$ hybridization.

- We're looking at the carbonyl $C=O^+-H$ bond angle.
- These bonds cluster around an area consistent with protonation of one of the lone pairs.
- This indicates that protons' mobile electron density is held to static carbonyl electron density.
- What about thiocarbonyls? What if we replace oxygen with its heavier sulfur analog? This may be on PSet 3!!
- Aside: Anslyn and Dougherty (2006) replaced a much older, worse book.
 - An ambitious book due to its breadth, but may alight or mangle details for a given topic.
 - Suffice to say, it's the best book we've got.
- **Hydrophobic effect:** It is energetically costly to solvate nonpolar molecules in H_2O .
 - Dennis Dougherty's opinion: The hydrophobic effect is the most powerful force in biological chemistry.
- Illustrating the hydrophobic effect.

Solute	ΔG_{tr}° (kcal/mol)	ΔH	$-T\Delta S$
PhH	4.62	0.50	4.12
PhMe	5.47	0.41	5.06
<i>n</i> -hexane	7.78	0.00	7.78

Table 9.1: Hydrophobic effect examples.

- Defined by the energy penalty ΔG_{tr}° to put a given solute in water.
- To put *n*-hexane into water, it costs about $\Delta G_{tr}^\circ = 7.78$ kcal/mol.
 - We can actually parse this in terms of its specific enthalpy and entropy.
 - $\Delta H = 0.00$. It's a wash in terms of dipole effects and energy interactions and everything.
 - $-T\Delta S = 7.78$. It's all in the entropy.
- It's every so slightly more favorable to put benzene or toluene in water thermodynamically.
- Chemists are pretty good at estimating enthalpy, but pretty bad with entropy.
 - Alex's goal for this class: We should all leave with a better understanding of entropy.

- Conclusion: The energetic penalty is mostly entropic.
 - If we put a hydrophobic link in the water, it disrupts the water's ability to randomly hydrogen bond with itself.
 - Less ability to H-bond means less dynamic and more ordered water, driving the hydrophobic effect. This is the best hypothesis we have so far; it's still hard for Alex to wrap his head around.
 - There's many chemists who study water, still!
- References.
 - Southall et al. (2002).
 - Grunwald and Steel (1995).
- We've indicated a couple of instances here where knowing a molecule's structure is not enough to predict it's reactivity!
 - *n*-hexane reacts differently as its own system vs. in H₂O.
 - We need to appreciate with greater clarity how thermodynamics operate in chemical systems.
- We now begin Lecture 15.
- Today: Reaction energetics.
 - Goal for the next two lectures: Understand how differences in free energy impact...
 - 1) Equilibria (today);
 - 2) Kinetic rates (next time).
- Overview concepts.
 - Consider a reaction

$$A \rightleftharpoons B$$
 - How do we understand such a reaction on a systems level, rather than on a molecular basis?
 - A good place to start is with a reaction coordinate diagram.
 - What we put on the *y*-axis will matter quite a bit.
 - We'll stick with ΔE (generic energy change) for now, and then get to ΔG .
 - The *x*-axis is the reaction coordinate along an arbitrarily defined interval 0-1.
 - The minima relative heights of the energy minima for A and B give us information about the position ΔG_{rxn} of the equilibrium.
 - This same formalism (with ΔG^\ddagger) allows us to learn about the rate as well.
- Recall gas phase dissociation.

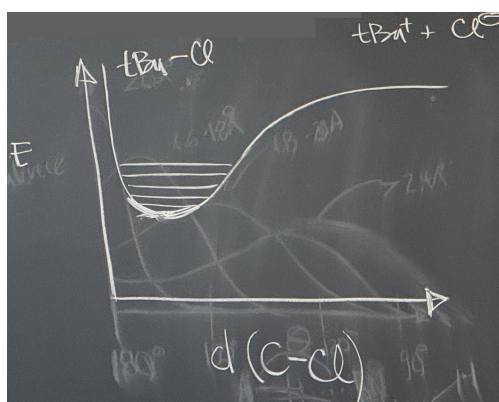


Figure 9.3: Energy diagram for the gas-phase dissociation of *t*-butyl chloride.

- Consider $t\text{Bu}-\text{Cl}$.
- The energy diagram is just Lennard-Jones, again.
- The vibrations of the $\text{C}-\text{Cl}$ bond along this potential surface are quantized. If you add enough energy, the ions can ping apart into $t\text{Bu}^+$ and Cl^- .
- Most reactions do not occur in the gas phase, though; they occur in condensed media.
- In the condensed phase, dissociation looks a bit different.

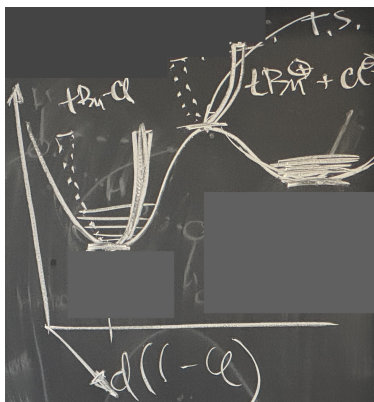


Figure 9.4: Energy diagram for the condensed-phase dissociation of *t*-butyl chloride.

- Bonds are still stable, but the ions will now be stabilized by the condensed media.
- There is a transition state along the potential energy surface.
 - This corresponds to some bond length where the atoms are separating but not yet solvated.
- Degrees of freedom of a molecule: $3N - 6$ or $3N - 5$ degrees of vibrational freedom.
 - Bear in mind that any potential energy surface that we draw is just a cut of the real surface.
 - These graphs help by zooming in on a given reaction coordinate. We get to define this though; there's nothing intrinsic about one reaction coordinate over any other.
 - Additional degrees of freedom may be represented as orthogonal paraboloids.
- The total derivative of the multidimensional potential energy surface $dE/dr = 0$ at local minima.
- Let r be the variable corresponding to our choice of reaction coordinate.
 - $\partial^2 E / \partial r^2 > 0$ at stable structures along the reaction coordinate.
 - $\partial^2 E / \partial r^2 < 0$ at the TS along the reaction coordinate.
- TS's have to be **first-order saddle points**.
- **First-order saddle point:** A point on a multidimensional surface that is a minimum along all the orthogonal vectors except one, on which it is maximized.
 - In our case, the one vector along which the saddle point is maximized is the reaction coordinate.
- Sergei: Why does the energy keep going up as the ions get farther apart? Shouldn't it just stop?
 - The other well *will* be anharmonically a well due to electrostatic interactions.
 - It might keep going up very shallowly, but it will still keep going up.
 - You can think of this as a residual effect of the solvated ions tugging on each other; even when solvated, opposite charges attract per the laws of physics, and it's more stable for them to be a meter apart than 2 meters apart.

- We now look at two-state systems.
 - This is a system in which two states A and B are in equilibrium via $A \xrightleftharpoons{K} B$.
 - K is defined by $K = [B]/[A]$.
 - Energetically, $\Delta G = -RT \ln K_{\text{eq}}$ and hence $K_{\text{eq}} = e^{-\Delta G/RT}$.
- Example: The two chair conformations of methylcyclohexane.
 - At 300 K, $K_{\text{eq}} = 19/1$ in favor of the equatorial position.
 - Here, $\Delta G = 1.74 \text{ kcal/mol}$ (this is the A-value for a Me group!).
- We can generalize this to useful energies.

Species		ΔG_{rxn} (kcal/mol)		
[A]	[B]	$-78^\circ\text{C} = 195 \text{ K}$	rt = 300 K	$100^\circ\text{C} = 373 \text{ K}$
1	1	0	0	0
1	2	0.27	0.41	0.51
1	10	0.89	1.37	1.71
1	100	1.78	2.74	3.41

Table 9.2: Free energy differences required for a given product distribution at different temperatures.

- Different ratios of products have different ΔG_{rxn} .
- The ΔG_{rxn} values are also different at different temperatures.
- Takeaways.
 - The position of an equilibrium is temperature dependent.
 - The energy differences needed to drive reactions significantly to completion are very small.
- Bond enthalpies are huge; the chemistry that we do in the condensed phase is *so* subtle.
 - Designing new reactions requires mastering subtle energies.
- The partition of species is given by Boltzmann distributions at different temperatures; this explains the table.
 - Essentially, per the Maxwell-Boltzmann distribution, higher temperatures lead to increasing thermal populations of excited states, so it takes a bigger energy difference to maintain selectivity.
- A quantitative analysis of equilibria (ΔG°) is constituent of both. . .
 - An enthalpy component (ΔH°);
 - Units: kcal/mol.
 - Coming from bond strengths and NCIs.
 - $\Delta H > 0$ is endothermic; distinct from endergonic ($\Delta G > 0$).
 - $\Delta H < 0$ is exothermic; distinct from exergonic ($\Delta G < 0$).
 - An entropy component (ΔS°).
 - Units: e.u. = cal/(mol K).
 - Entropy units are a measure of disorder.
 - This is a reflection of Boltzmann's law on microstates, $S = R \ln \Omega$, where Ω is the number of microstates available.

- Experimental determination of ΔH° and ΔS° : A **van't Hoff analysis**.

- Theoretically, begin finding a linear equation of the form $y = mx + b$ where m and b correspond to ΔH° and ΔS° , and y and x correspond to observables. In particular, we find

$$\begin{aligned} -RT \ln K_{\text{eq}} &= \Delta H^\circ - T\Delta S^\circ \\ R \ln K_{\text{eq}} &= -\Delta H^\circ \left(\frac{1}{T} \right) + \Delta S^\circ \end{aligned}$$

- Note that the first equality comes from the fact that the quantities on both sides of the equation equal ΔG° .
- So we experimentally measure K_{eq} at a range of temperatures and then use linearization to determine ΔH° and ΔS° .
- These are super fun and satisfying to do because when it works, you can just read out the chemical potential directly from an observable.
- Massive caveat: There are a limited range of temperatures under which an equilibrium can be established.
 - So we're only assaying an extremely small temperature range.
 - Thus, small systematic errors can lead to wide variation in the extrapolated values. So we need to treat these analyses with care.
- Moving on, consider a bimolecular reaction.
 - For example, consider oxidative addition of an aryl chloride to a palladium catalyst.
 - Two things become one in this step.
 - The reaction enthalpy will obviously depend on the bonds broken and formed, but what will be the qualitative sense of entropy?
- Qualitative prediction of equilibria.
 - How do we estimate the position?
 - Proton-transfer values can be helpful.
 - $\text{AH} + \text{B} \longrightarrow \text{A}^- + \text{HB}^+$.
 - Proton affinity and acidity report indirectly on the stability of the conjugate bases.
 - $\text{p}K_{\text{a}} = -\log K_{\text{a}}$, so $\Delta G = -1.4\text{p}K_{\text{a}}$. “A log unit gives 1.4 kcal/mol.” Therefore, we can know something about the energetics by looking at this reactive intermediate!
 - We can also follow H-atom transfers.
 - Look at alkane transfers; $\Delta\text{BDE} = \Delta H$.
 - Hydride ion affinity can also help us; these values are tabulated with respect to cation stability.
 - How do we estimate the entropy?
 - A fragmentation releases about 30 e.u., and a joining of a catalyst to a molecule costs about 30 e.u.. 30 e.u. times 300 K gives you about 9 kcal/mol! So the new bonds formed must exceed 9 kcal/mol.
 - You can't just do bonds formed and broken; “nah, man; you need 9 kcal/mol; that's real energy!”

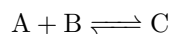
9.2 Transition State Theory

10/31:

- Lecture 15 continued.
- Consider a simple equilibria of the following form.

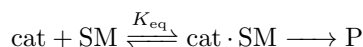


- We can characterize it by $\Delta G = -RT \ln K_{\text{eq}}$.
- We can parse ΔG in terms of ΔH and ΔS using the van't Hoff analysis.
- We now show that $\ln K_{\text{eq}}$ (and hence K_{eq}) is unitless for this equilibrium.
 - Units of ΔG : kcal/mol.
 - Units of T : Temperature.
 - Units of R : kcal/(mol K).
 - Therefore, $\ln K_{\text{eq}}$ is unitless since all units cancel in the equivalent fraction $\Delta G/RT$.
 - It follows that K_{eq} is unitless.
 - We can also see this from the fact that the two molarity units cancel.
- We can also characterize the equilibrium constant as $K_{\text{eq}} = [B]/[A]$.
- We can have much more complex equilibria, too, such as multicomponent equilibria.
- Consider the following associative equilibrium.



- Here,

$$K_{\text{eq}} = \frac{[C]}{[A][B]}$$
- Hence, K_{eq} has units of M^{-1} .
- This implies that ΔG is concentration dependent!
 - This is a profound statement.
- Consequence: A catalyst operating on a starting material.



- Example: TM catalyst on organic substrate, enzyme on a biological substrate.
- Assume: $K_{\text{eq}} = 100$ and 1 mol% catalyst.
- Let's think about this reaction sequence.
 - Consider the percent of catalyst bound by the starting material, i.e.,

$$\frac{[\text{cat} \cdot \text{SM}]}{[\text{cat}]_{\text{T}}}$$

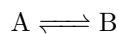
where $[\text{cat}]_{\text{T}}$ is the total amount of catalyst, bound and unbound.

- During the course of the reaction, the position of the equilibrium will decay. At some point, there will be more catalyst than SM!
- Case A (near 1 M SM): On a potential energy surface, $\text{cat} \cdot \text{SM}$ (the catalyst resting state) is lower in energy than the complex.
- Case B (low SM concentration): Less $\text{cat} \cdot \text{SM}$ at equilibrium. So potential energy surfaces are *not* static; they can depend on concentrations.
- It's not K_{eq} changing, but that Q is concentration dependent?? But Q can change ΔG , sure.

- So how do we standardize conditions to standard states?

– Use ΔG° , ΔH° , and ΔS° !

- Defining a standard state.



– Consider a simple two-state equilibrium to start, like the above.

– Define the equilibrium constant K_{eq} as before.

$$K_{\text{eq}} = \frac{[B]_{\text{eq}}}{[A]_{\text{eq}}}$$

– We now define another ratio at some arbitrary time t with some non-equilibrium concentrations.

$$Q = \frac{[B]_t}{[A]_t}$$

– Then we can define the free energy ΔG of a system at any time point with respect to the equilibrium!

$$\Delta G = -RT \ln \left(\frac{K_{\text{eq}}}{Q} \right) = \Delta G^\circ + RT \ln Q$$

- This value tells us the tendency of the reaction to proceed to equilibrium under *any* conditions.
- You can also think of this as the driving force at a given time point.
- This *rigorously* tells us that $\Delta G = 0$ at equilibrium.
- We can also define the standard state

$$\Delta G^\circ = -RT \ln K_{\text{eq}}$$

in which $Q = 1$.

- This value tells us about the tendency of the reaction to proceed to equilibrium under *standard* conditions.

- Example: Assume $K_{\text{eq}} = 3$ in a simple equilibrium $A \rightleftharpoons B$.

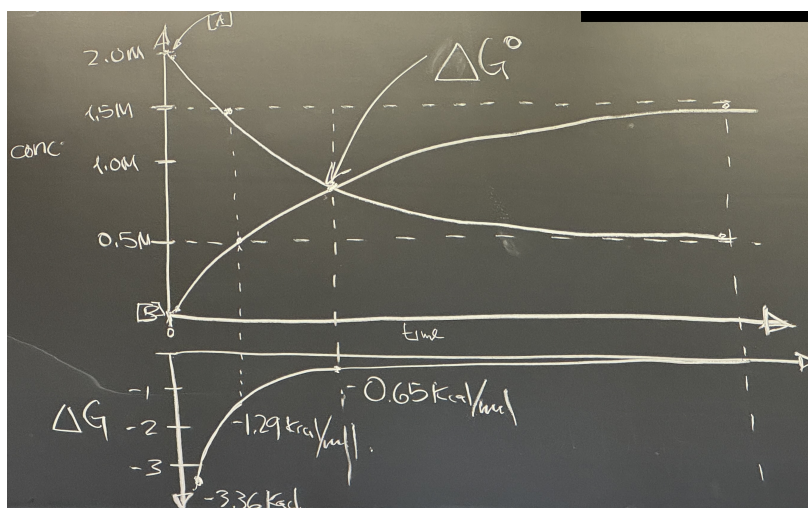


Figure 9.5: A time course vs. free energy.

- Let $[A]_0 = 2 \text{ M}$ and $[B]_0 = 0 \text{ M}$.
- Then in the end, $[A]_{\text{eq}} = 0.5 \text{ M}$ and $[B]_{\text{eq}} = 1.5 \text{ M}$.
- Consider a time course, i.e., how the concentrations change in time.
- After mixing the compounds, as quickly as we can get to the NMR, we take a time point.
 - So $[A]_1 < 2 \text{ M}$ and $[B]_1 > 0 \text{ M}$ slightly.
 - Suppose that specifically, $[A]_1 = 1.98 \text{ M}$ and $[B]_1 = 0.02 \text{ M}$.
 - Then $Q_1 = 0.01$, so $\Delta G_1 = -3.36 \text{ kcal/mol}$.
- Now underneath, we plot the free energy vs. time.
- $[A]$ decreases to equilibrium and $[B]$ increases to equilibrium over time.
- Second time point.
 - Suppose that specifically, $[A]_2 = 1.5 \text{ M}$ and $[B]_2 = 0.5 \text{ M}$.
 - Then $Q_2 = 0.33$, so $\Delta G_2 = -1.29 \text{ kcal/mol}$.
- Third time point.
 - Suppose that specifically, $[A]_3 = 1 \text{ M}$ and $[B]_3 = 1 \text{ M}$.
 - Then $Q_3 = 1$, so $\Delta G_3 = -0.65 \text{ kcal/mol}$.
- Fourth time point.
 - Suppose that specifically, $[A]_{\infty} = 0.5 \text{ M}$ and $[B]_{\infty} = 1.5 \text{ M}$.
 - Then $Q_{\infty} = 3$, so $\Delta G_{\infty} = 0 \text{ kcal/mol}$.
- The third time point is ΔG° since $Q = 1$!
 - So standard conditions start to tell us a bit about how the reaction goes.
- This concludes Lecture 15.
- Today: Transition state theory.
- Empirical observation: The rate of the reaction is proportional to the following.

$$\text{rate} = Ae^{-E_a/RT}$$

- This is the **Arrhenius law**.
- Even before we knew what atoms were, we could track the process of a reaction.
- What unified and predicted the Arrhenius law was a theoretical development from the 1930s called Transition State Theory.
- Two key assumptions.
 1. A so-called “activated complex” may be viewed as being in quasi-equilibrium with the starting material.
 - Essentially, reformulate $A \longrightarrow B$ as



- This allows us to bring to bear our mathematical treatment of equilibria on a kinetic argument.
- Call the quasi-equilibrium constant K^{\ddagger} , where

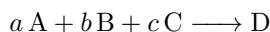
$$K^{\ddagger} = \frac{[\text{TS}]}{[A]}$$

2. Any molecule that makes its way to the transition state will then proceed onto the product barrierlessly.

- Thus, we can say that the rate of reaction is given by the following.

$$\text{rate} = \frac{d[B]}{dt} = k^\ddagger[\text{TS}] = K^\ddagger k^\ddagger[A]$$

- This winds up being useful for a variety of reasons.
- In particular, we can extrapolate this simple analysis to other processes with higher molecularity.
- Example: We can learn the stoichiometry of the rate law just by analysis of the reaction equation. Consider



- Then

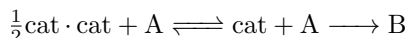
$$K^\ddagger = \frac{[\text{TS}]}{[A]^a[B]^b[C]^c}$$

$$[\text{TS}] = K^\ddagger[A]^a[B]^b[C]^c$$

- This means that

$$\text{rate} = K^\ddagger k^\ddagger[A]^a[B]^b[C]^c$$

- So we can learn about the components of the transition structure just by inspecting the rate law.
- Example: Multistep sequences.



- Imagine if the catalyst can either bind to A or off-cycle by dimerizing.
- This tells us something about the potential energy surface.
 - The overall rate-determining energy span covers not just the forward direction, but the off-cycling!
- This means that the catalyst has fractional order in the rate law.

$$\text{rate} = k[A][\text{cat}]^{1/2}$$

- Note that $k = K^\ddagger k^\ddagger$.
 - This tells us something about the transition state structure relative to the ground state, so knowing what the ground state is is essential.
- If we have a minor equilibrium on the other hand, then

$$\text{rate} = k[A][\text{cat}]$$

- Note that the transition state structure has a lifetime on the order of bond vibrations.
- Sergei: All the k's?

- K : Equilibrium constant.
- K^\ddagger : Equilibrium constant to the transition structure.
- k : Experimental or apparent rate constant.
- k^\ddagger : Kinetic efficiency of the transition structure proceeding to product.
- κ : We'll get there.
- k_B : The Boltzmann constant.

- Recall $t\text{BuCl} \longrightarrow t\text{Bu}^+ + \text{Cl}^-$.

- The rate for the formation of the product is given as

$$\text{rate} = \frac{d[\text{B}]}{dt} = K^\ddagger k^\ddagger [\text{A}]$$

- The facility with which the reaction proceeds is mostly C–Cl bond cleavage, so k^\ddagger must largely be proportional to a fudge factor κ (the transmission coefficient) times ν (the frequency associated with the relevant bond).

$$k^\ddagger = \kappa \nu$$

- In reality, this frequency will be the “imaginary frequency” at the transition state, not any real-numbered frequency.

- The point: There is a derivation in statistical mechanics through which we can more formally think about this.

- We get

$$K^\ddagger = \left(\frac{k_{\text{B}}T}{h\nu} \right) e^{-\Delta G^\ddagger/RT}$$

- h is Planck’s constant.

- Then we bring this together with the above to get

$$\text{rate} = \frac{d[\text{B}]}{dt} = \left[\kappa \left(\frac{k_{\text{B}}T}{h} \right) e^{-\Delta G^\ddagger/RT} \right] [\text{A}]$$

- From here, we can get the **Eyring equation**.^[1]

$$k = \kappa \left(\frac{k_{\text{B}}T}{h} \right) e^{-\Delta G^\ddagger/RT}$$

- David: Does the Eyring equation condense into the Arrhenius equation?
 - Short answer: No, but they’re close.
 - Devil’s in the details: It depends on what exactly is meant by “activation energy.” Additionally, in real life, the activated complex *can* rebound back into the starting material.
- The Eyring analysis allows us to predict a rate constant from an energy barrier, and vice versa.
- A few useful points.

ΔG^\ddagger (kcal/mol)	k (s ⁻¹)	$\tau_{1/2}$ (s)
3	3.8×10^{10}	1.8×10^{-11}
10	2.7×10^5	2.5×10^{-6}
15	5.9×10^1	1.2×10^{-2}
20	1.3×10^{-2}	55
25	2.7×10^{-6}	70 h
30	5.8×10^{-10}	38 y

Table 9.3: Relating the energy barrier to the rate.

- Let’s define ΔG^\ddagger (in kcal/mol at 298 K), the rate constant k (in s⁻¹), and the half-life $\tau_{1/2}$ (in s).
 - Example of a 3 kcal/mol process: Ethane bond rotation.
- Begin to internalize common kcal values!!
 - Print out a list and put it next to tooth-brushing mirror.

¹See CHEM26300Notes for the derivation.