

## 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 ( $\text{HF}_2^-$ ).
      - Held together by such a strong hydrogen bond that it is stable and isolable.
      - Energy on the order of 39 kcal/mol.
    - Those between  $\text{H}_2\text{O}$  and  $\text{H}_3\text{O}^+$ .
      - Relatively strong, persistent in solution, etc.
      - Energy on the order of 33 kcal/mol.
    - Those between  $\text{H}_2\text{O}$  and  $\text{H}_2\text{O}$ .
      - 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 ( $\text{CHF}_3$ ) 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.

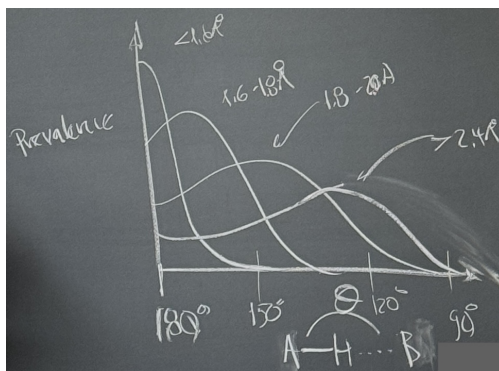


Figure 9.1: Stronger hydrogen bonds are more linear.

- 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.

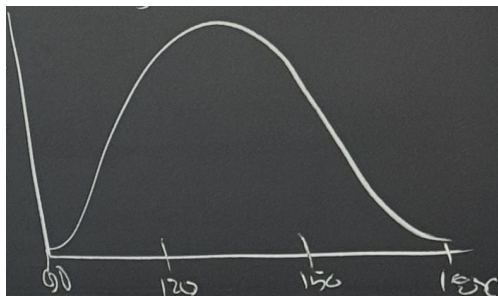


Figure 9.2: Carbonyl hydrogen bonds reflect  $O(sp^2)$  hybridization.

- 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	$\Delta G_{tr}^\circ$ (kcal/mol)	$\Delta H$	$-T\Delta S$
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  $\Delta G_{tr}^\circ$  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 H<sub>2</sub>O.
  - 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  $\Delta E$  (generic energy change) for now, and then get to  $\Delta G$ .
    - 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  $\Delta G_{\text{rxn}}$  of the equilibrium.
    - This same formalism (with  $\Delta G^\ddagger$ ) allows us to learn about the rate as well.
- Recall gas phase dissociation.

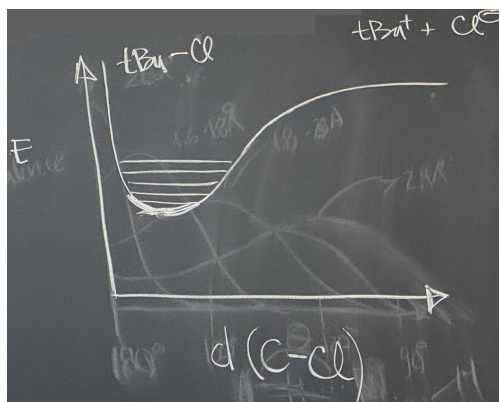


Figure 9.3: Energy diagram for the gas-phase dissociation of *t*-butyl chloride.

- 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  $\text{Cl}^-$ .
- Most reactions do not occur in the gas phase, though; they occur in condensed media.
- In the condensed phase, dissociation looks a bit different.

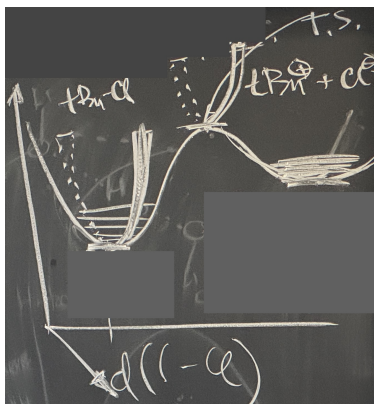


Figure 9.4: Energy diagram for the condensed-phase dissociation of *t*-butyl chloride.

- 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		$\Delta G_{\text{rxn}}$ (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  $\Delta G_{\text{rxn}}$ .
- The  $\Delta G_{\text{rxn}}$  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 ( $\Delta G^\circ$ ) is constituent of both. . .
  - An enthalpy component ( $\Delta H^\circ$ );
    - 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 ( $\Delta S^\circ$ ).
    - 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  $\Omega$  is the number of microstates available.

- Experimental determination of  $\Delta H^\circ$  and  $\Delta S^\circ$ : A **van't Hoff analysis**.

- Theoretically, begin finding a linear equation of the form  $y = mx + b$  where  $m$  and  $b$  correspond to  $\Delta H^\circ$  and  $\Delta S^\circ$ , 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  $\Delta G^\circ$ .
- So we experimentally measure  $K_{\text{eq}}$  at a range of temperatures and then use linearization to determine  $\Delta H^\circ$  and  $\Delta S^\circ$ .
- 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!”