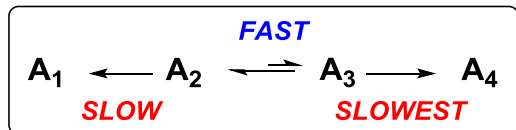
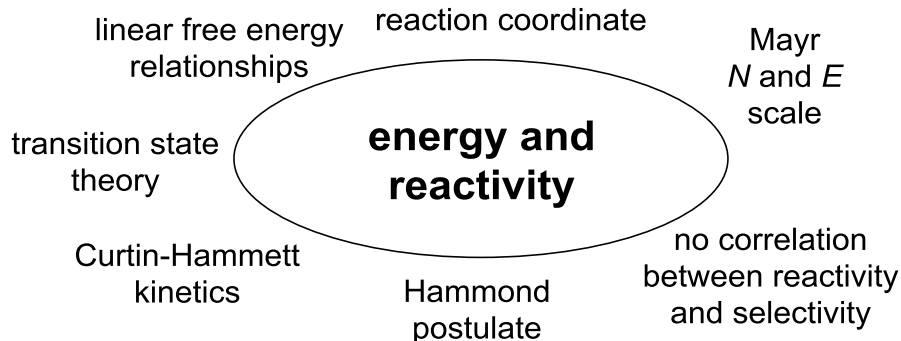


Energy and Reactivity

Eugene E. Kwan



Scope of Lecture

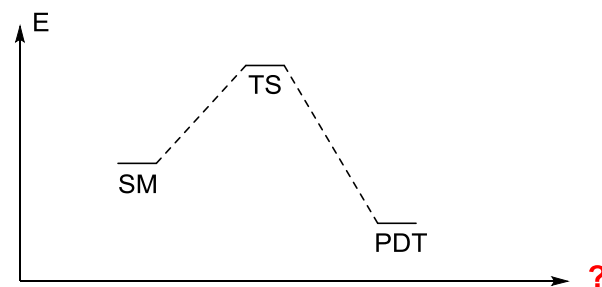


Helpful References

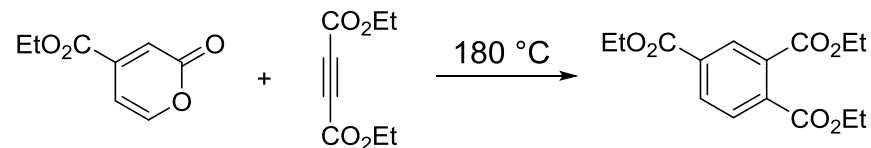
- "Rates and Equilibria of Organic Reactions" Leffler, J. E.; Grunwald, E. Wiley, **1963**. (Chapters 2, 4, 7).
- Mayr, H.; Ofial, A.R. *Acc. Chem. Res.* **2006**, *45*, 1844-1854. (RSP)
- Buncel, E.; Wilson, H. *J. Chem. Ed.* **1987**, *64*, 475-480. (RSP)
- Mayr, H.; Ofial, A.R. *J. Phys. Org. Chem.* **2008**, *21*, 584-595 (N and E)
- "Entropic Contributions to Rate Acceleration..." Page, M.I.; Jencks, W.P. *PNAS* **1971**, *68*, 1678-1683.

Key Questions:

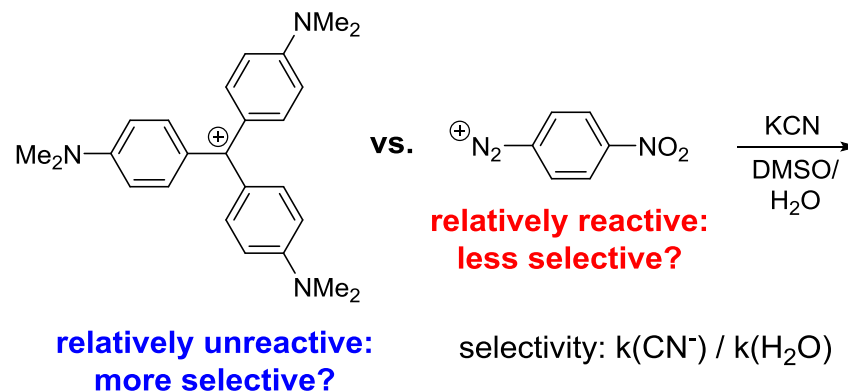
What is the reaction coordinate?



Why is this reaction thermodynamically favorable?

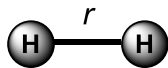


Are less reactive reagents always more selective?



The Potential Energy Surface (PES)

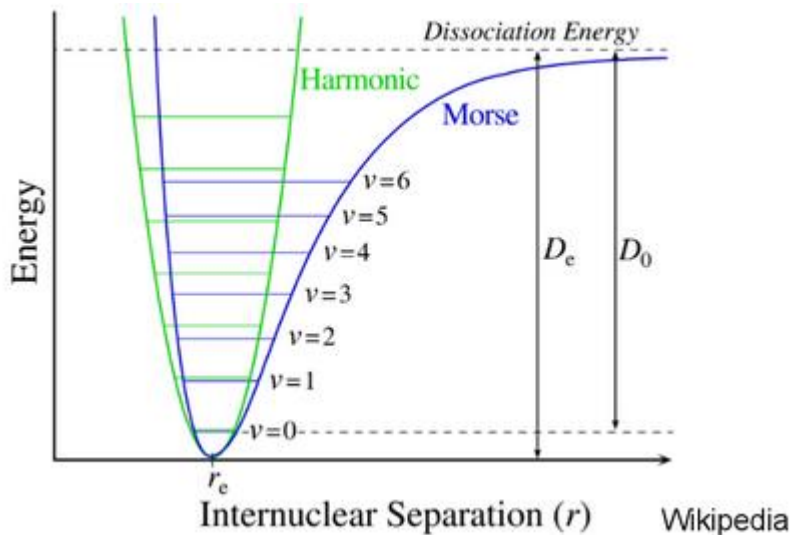
Consider dihydrogen:



How many variables do I need to describe the geometry of dihydrogen? Six. In Cartesian coordinates, I could say that the energy is a function of all the nuclear coordinates:

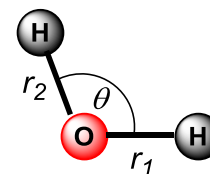
$$E(q) = E(x_1, y_1, z_1, x_2, y_2, z_2)$$

Now, if you're sharp, you can point out that we don't really care where the center of mass is, but what we really care about in terms of chemistry, is simply the bond length r . So in some sense, the PES is single-dimensional. The typical appearance of such potentials for bonds is something like:



Note that at the bottom of the well, the PES is described well by a **harmonic oscillator**--a quadratic function. This is an important approximation that is made in many calculations.

Now, a more complicated molecule will necessarily require more coordinates. For example, you can think of water as needing two O-H bond lengths and the H-O-H angle:



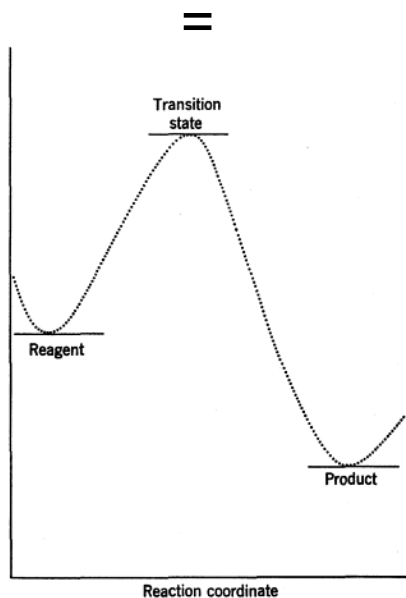
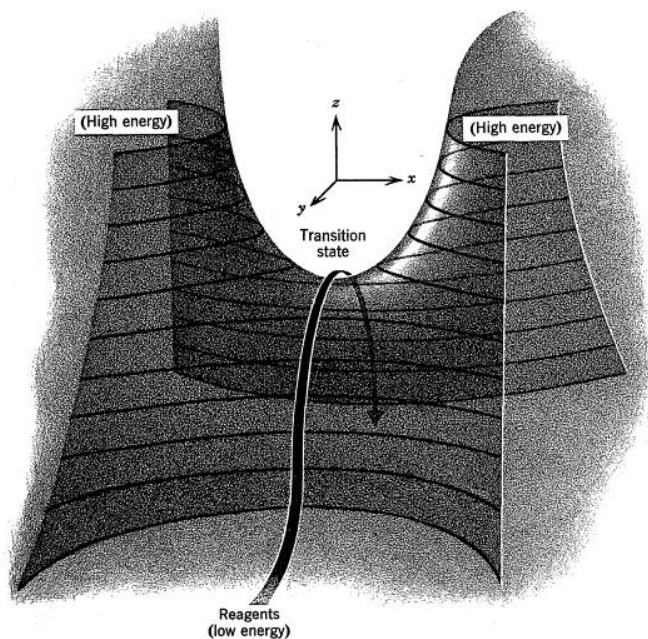
With a typical organic molecule, we will easily need tens of coordinates. As we begin to look at multi-molecule reactions, the dimensionality of the PES will quickly grow too large to be visualized easily. Fortunately, we rarely need to characterize the entire surface.

In fact, let's consider a simple chemical reaction. Convince yourself that this involves traveling from one local minimum to another on the PES.

To simplify the problem, we can imagine reducing the entire surface to two dimensions. To do this, we define a *reaction coordinate* by parametrizing a path satisfying the following conditions:

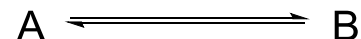
- 1) The path begins at the local minimum representing starting materials, and ends at the local minimum representing products.
- 2) At each point on the path, the system is at an energetic local minimum in all directions **orthogonal to the path**.

Along such a path, we can cross intermediate local minima, aptly termed *intermediates*, or saddle points, termed *transition states*. An illustration is provided on the next page.



Figures 4-2 and 4-3 from Grunwald

Let's consider a simple reaction with no intermediates:



After a long time, the movement of atoms on the potential energy surface will reach *equilibrium*. At this point, things are still moving back and forth, but the absolute populations of the two species are constant. Will there be more A or more B?

According to a famous result of statistical mechanics, at constant pressure, the equilibrium population of any species is proportional to:

$$[A] \propto \exp(-G_A/RT)$$

Here, G_a is the Gibbs free energy of species A. This is accurate up to a degeneracy factor which is almost always negligible in chemistry.

Taking a ratio of two populations, we arrive at an important relation:

$$\Delta G = -RT \ln ([B]/[A])$$

By slightly more rigorous mathematics, it is simple to show that this relation holds for reactions involving more than two species as well. As intuition would tell you, there is more of the energetically lower species. As temperature increases, we get closer and closer to a 1:1 mixture.

It would be nice to be able to talk about the energetics of reactions without needing to worry about concentrations and relative stoichiometries. The way to do this is by *setting a standard state*.

The usual standard state is 1 M (1 bar for gases) of all reactants and products, 298 K. We can define:

$$\Delta G^0 = -RT \ln K^0 \quad \text{at standard conditions}$$

which we call the standard Gibbs free energy change. We'll use standard thermodynamic quantities to talk about reactions from now on.

To apply this to general reactions, simply add a small correction.

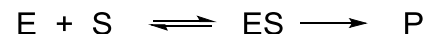
$$\Delta G = \Delta G^0 + RT \ln Q \quad \text{under any conditions of constant T, P}$$

Where Q is the familiar *reaction quotient*. At equilibrium, we have $\Delta G = 0$ and define $Q = K$, where K is the *equilibrium constant*.

Enzyme-Substrate Binding

While standard states are convenient, we must remember that the $RT \ln Q$ term is not negligible!

Consider an enzymatic reaction:



Here, enzyme (E) binds to substrate (S) to form a complex (ES), which then reacts to give product (P).

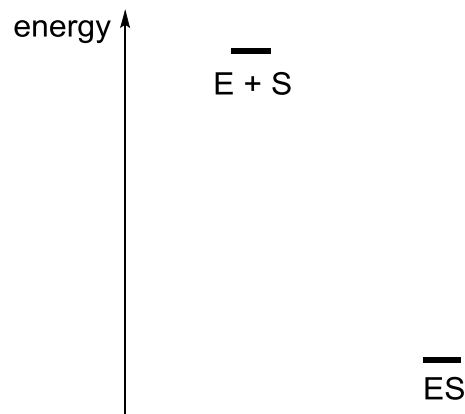
Q: What does the energy diagram look like for this reaction?

A: The appearance of the diagram *depends on the concentrations!*

Consider only the binding event. One can imagine two scenarios:

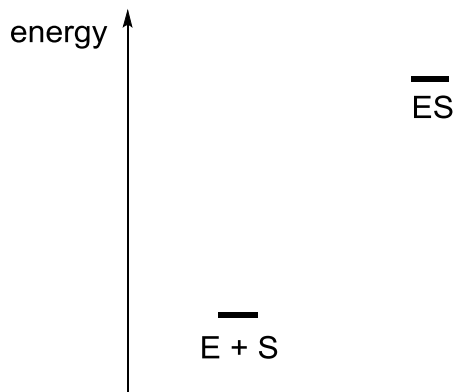
(1) very concentrated enzyme, very concentrated substrate

In this case, we expect to see a lot of complex. You might even expect *more* complex than enzyme and substrate:

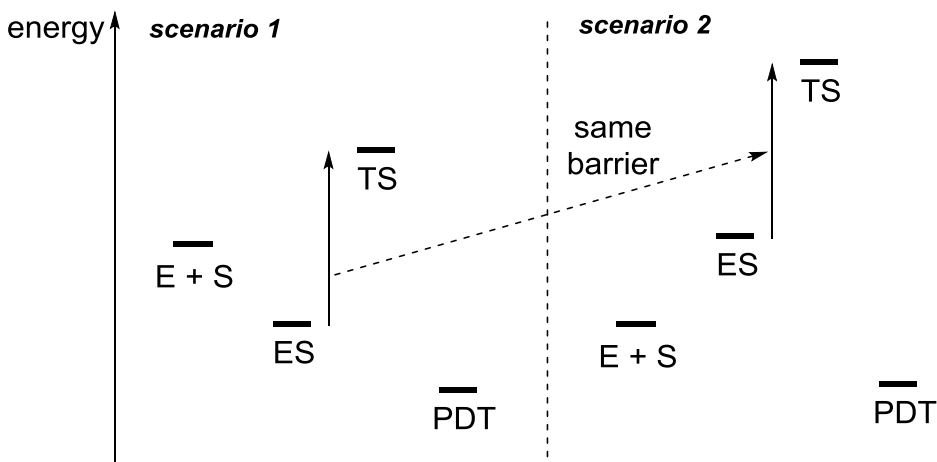


(2) very dilute enzyme, very dilute substrate

Now, imagine diluting this a lot. The ES complex now falls apart:



What about the product formation step? The barrier to reaction is relative to the enzyme-substrate complex, regardless of concentration:



As expected, if everything is bound as ES, the reaction has a lower barrier. We will explore rates more quantitatively later in this lecture.

Enthalpy and Entropy

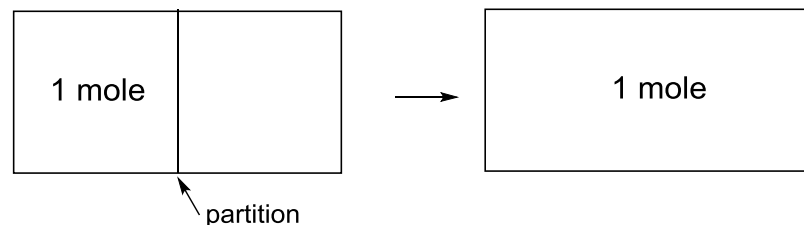
As just mentioned, a spontaneous reaction has:

$$\Delta G = \Delta H - T\Delta S < 0$$

Most organic chemists have a feel for enthalpy, and can speak of "tighter binding" and so forth. But what determines the size of the entropy term?

Entropy of Mixing

Imagine one mole of ideal gas in a box:

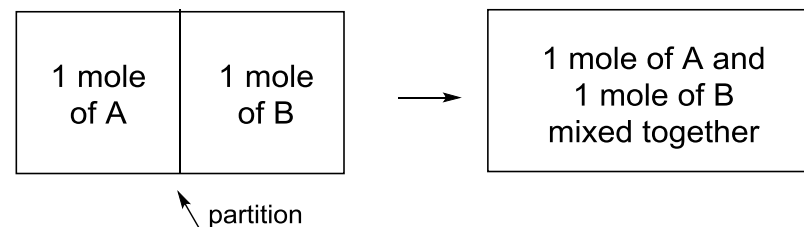


The box, which is at standard conditions, has a partition in it, which I take away. Because there are many more ways to arrange the gas particles in twice the volume, the gas spontaneously fills the box. There is no enthalpy change here, since it's an ideal gas.

initial conditions: gas on one side of the box

equilibrium conditions: gas on both sides of the box

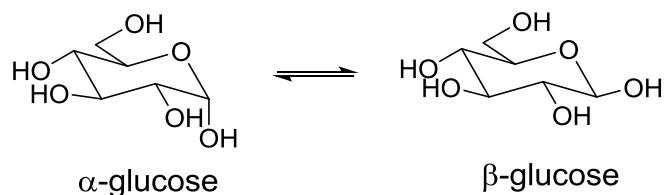
In a more complex scenario, there are two gases:



$$\Delta S_{\text{mix}} = -nR (x_1 \ln x_1 + x_2 \ln x_2)$$

The entropy change results from diluting both gases into each other: *entropy of mixing* (ΔS_{mix}). (x = mole fraction, n = number of moles)

Now imagine I start with a sample of pure α -glucose. At room temperature, the equilibrium α/β ratio is 36/64. What are the forces that drive the system towards equilibrium? (see Gary *J Chem Ed* **2004** 81 1599):



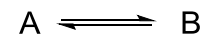
(1) Enthalpy

- exothermic: favors forward reaction

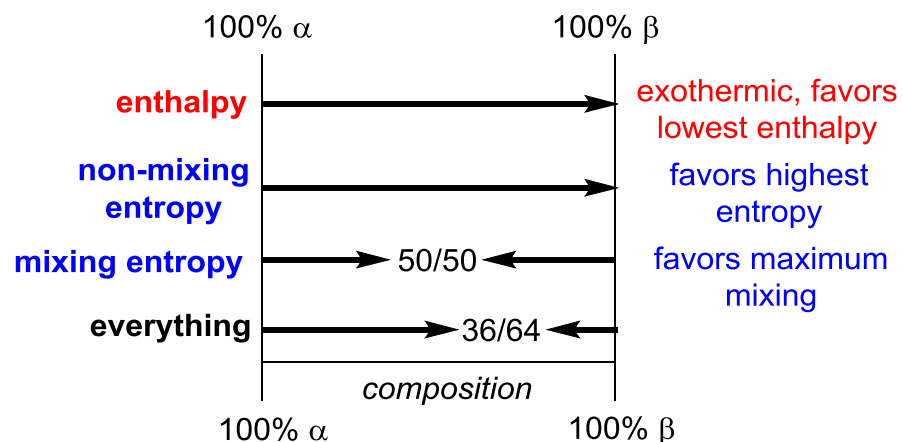
(2) Non-Mixing Entropy

- product: different vib., rot. energy levels
- effectively, a different set of microstates
- having an isolated molecule β -glucose instead of α -glucose seems to be slightly entropically favored
- thus, non-mixing entropy favors the forward reaction here

(3) Mixing Entropy

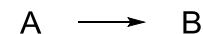


- the entropy of mixing favors a 50/50 ratio of A:B
- this is because $x_a x_b$ is maximized for $x_a = (0.5)(0.5)$



Configurational Entropy

The "non-mixing entropy" can be thought of as the "intrinsic" entropy change in turning just one molecule of A into a molecule of B:



Q: What determines the magnitude of ΔS ?

(This discussion is partly borrowed from Watson and Eisenstein *J Chem Ed* **2002** 79 1269.)

- (1) Entropy is related to the ways of distribution energy amongst the microstates of a system ($S = k_B \ln \Omega$)

(2) One way to distribute the energy is among the many **vibrational and rotational** levels. Since B has different levels than A, there is an entropy change.

(3) Another way to distribute energy between **electronic** levels. Because electronic energy levels are farther apart than vibrational and rotational levels, most organic molecules live in the ground state, so this contribution is negligible.

(4) What if B is a monatomic ideal gas? Then it has no rotational or vibrational levels. However, all molecules have **translational** entropy.

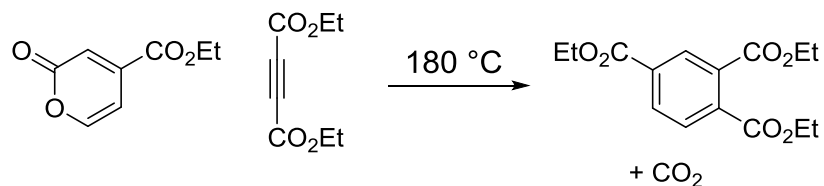
Translational Entropy

Translational momentum states are essentially continuous, so changes in translational entropy usually dominate the entropy term.

This is one reason that intramolecular reactions happen so much faster than intermolecular reactions. Consider two molecules becoming one. Can half the molecule be flying to the left and the other half flying to the right? Obviously not.

This entropic cost is absent in intramolecular reactions because the atoms were forced to translate together as a single molecule to begin with.

Now consider the following reaction, where two molecules become two different molecules:



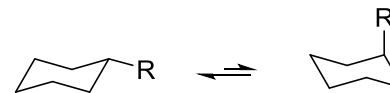
Even though it requires elevated temperatures, this tandem cycloaddition-cycloreversion process is still impressive! (Alder *Chem Ber* **1937** 70 1354)

Why does this reaction work? Certainly, the enthalpic stability of an aromatic ring and forming CO_2 is part of it. But another reason is that we are releasing a gas. Gas molecules move much more freely than those in solution, and reactions producing gases are often driven forward by entropy.

For reactions which release hydrogen, the expected entropy increase at 298 K is 8 kcal/mol. Larger extruded molecules, which are heavier and have more degrees of freedom, will be even more favored.

Steric Effects: Enthalpic or Entropic?

Please explain the following trend in *A* values:



R=Me 1.74
R=Et 1.79
R=*i*-Pr 2.21

Is it just because *i*-Pr is "bigger" than Me?

Steric Effects: Enthalpic or Entropic?

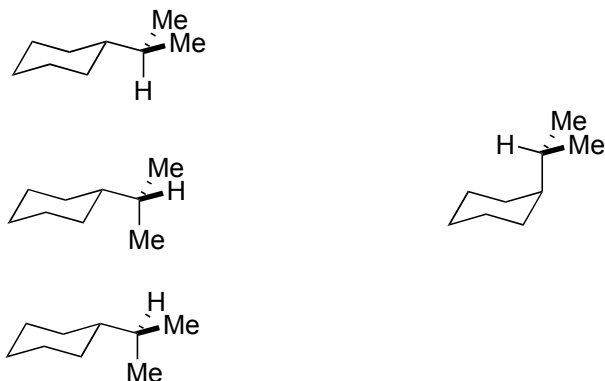
No! In fact, the *enthalpic* contribution is steady in this series, but the *entropic* contribution is not (Basic Organic Stereochem. Eliel, **2001**, standard edition, pg 447):

	$-\Delta H^0$	$-\Delta S^0$
R=Me	1.75	-0.03
R=Et	1.60	0.64
R=<i>i</i>-Pr	1.50	2.31

Incredibly, this shows that *i*-Pr is actually *smaller* than Me if one just considers enthalpy. Instead, it is the entropic term that accounts for the difference in free energies.

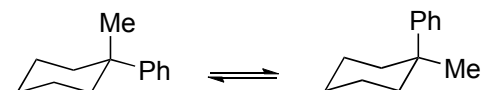
Interpretation: enthalpy restricts the number of viable conformations; this reduces the number of microstates; entropy goes down.

There are many more viable microstates when the *i*-Pr group is equatorial than when it's axial:



Wiberg *JOC* **1999** 64 2085

The case of 1-methyl-1-phenylcyclohexane is a classic case where *A* values are not additive because of substituent interactions:

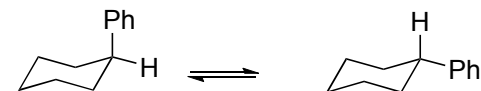


expected ΔG^0 : 2.9 - 1.8 = +1.1 kcal/mol

found ΔG : = -0.3 kcal/mol

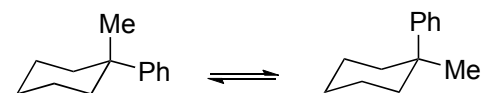
Thus, the conformation which places the phenyl *axially* is more stable! (NMR measurements at -100 °C)

Interestingly, calculations predict that for both phenylcyclohexane and 1-methyl-1-phenylcyclohexane, entropy favors placing the phenyl group equatorial. At -100 °C:



ΔS : = -1.3 eu (favors Ph ax by 0.2 kcal/mol)

ΔH : = -3.2 kcal/mol (favors Ph eq)



ΔS : = +1.4 eu (favors Ph ax by 0.2 kcal/mol)

ΔH : = +1.3 kcal/mol (favors Ph ax)

Thus, this equilibrium appears to be *enthalpy* driven. (Calculations were at quite a high level: QCISD/6-311+g(2df,p).)

Wiberg *JOC* **2000** 65 1181

How Fast do Reactions Go?

Thermodynamics gives a good description of equilibrium populations, but we would like to be able to model non-equilibrium situations as well. After all, a chemical reaction is essentially controlled **approach to equilibrium**. And while we can easily predict whether a reaction is thermodynamically favorable, it is much harder to predict at what rate it proceeds.

Empirically, most reaction rates k obey the **Arrhenius Equation**:

$$k = A \exp(-E_a / RT)$$

Unsurprisingly, this means reactions get faster as the temperature goes up.

Hard Sphere Collisions

There are two classical theories for predicting reaction rates. One assumes molecules are hard spheres:



Assumptions:

- (1) the molecules don't interact until they collide
- (2) the molecules don't deform in any way during collisions
- (3) the molecules only interact if they have enough kinetic energy along their line of centers (the barrier)

Although this is quite unrealistic, one still finds:

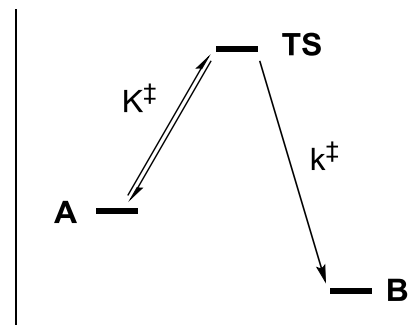
$$k \propto \exp(-E_0 / RT)$$

So even with a simple model, the exponential dependence comes out. (Various terms omitted; note that E_0 is not necessarily the same as E_a .)

More information: [Reaction Kinetics](#) Pilling, M.J.; Seakins, P.W.

Transition State Theory

This theory is more relevant to organic chemistry. One considers a unimolecular reaction:



One makes the *quasi-equilibrium assumption* that **A** and **TS** are in equilibrium, even if **A** isn't in equilibrium with **B**. The equilibrium constant for this is (uppercase) K^\ddagger . The rate constant of product formation from the TS is (lowercase) k^\ddagger . One finds that (**the Eyring Equation**):

$$k = k^\ddagger K^\ddagger = \kappa \frac{k_B T}{h} \exp\left(\frac{-\Delta G^\ddagger}{RT}\right)$$

where κ is the "transmission coefficient" which accounts for the fact that not every vibration leads to product, k_B is Boltzmann's constant, T is temperature, h is Planck's constant, ΔG^\ddagger is the free energy of activation. Once again, ΔG^\ddagger is not the same as E_a .

Some Numerical Examples

Example 1

What is the energy barrier for a unimolecular reaction that goes to completion in 24 hours at room temperature? (Assume this means five half lives and $\kappa=1$.)

The relevant equations:

$$k = k^\ddagger K^\ddagger = \kappa \frac{k_B T}{h} \exp\left(\frac{-\Delta G^\ddagger}{RT}\right)$$

$$t_{1/2} = \ln 2 / k \quad (\text{for first-order reactions})$$

24 hours is $24(60)(60)=86\,400$ s. Thus, one half life is 17280 s. Therefore,

$$4.01 \times 10^{-5} \text{ s}^{-1} = \frac{(3.30 \times 10^{-24} \text{ cal} \cdot \text{K}^{-1})(298 \text{ K})}{1.58 \times 10^{-34} \text{ cal} \cdot \text{s}} \exp\left(\frac{-\Delta G^\ddagger \text{ cal} \cdot \text{mol}^{-1}}{(1.99 \text{ cal} \cdot \text{K}^{-1} \cdot \text{mol}^{-1})(298 \text{ K})}\right)$$

This works out to a barrier of **23.5 kcal/mol**.

Here are some more rate constants for reactions that finish within:

1 second: 3.5 s^{-1}

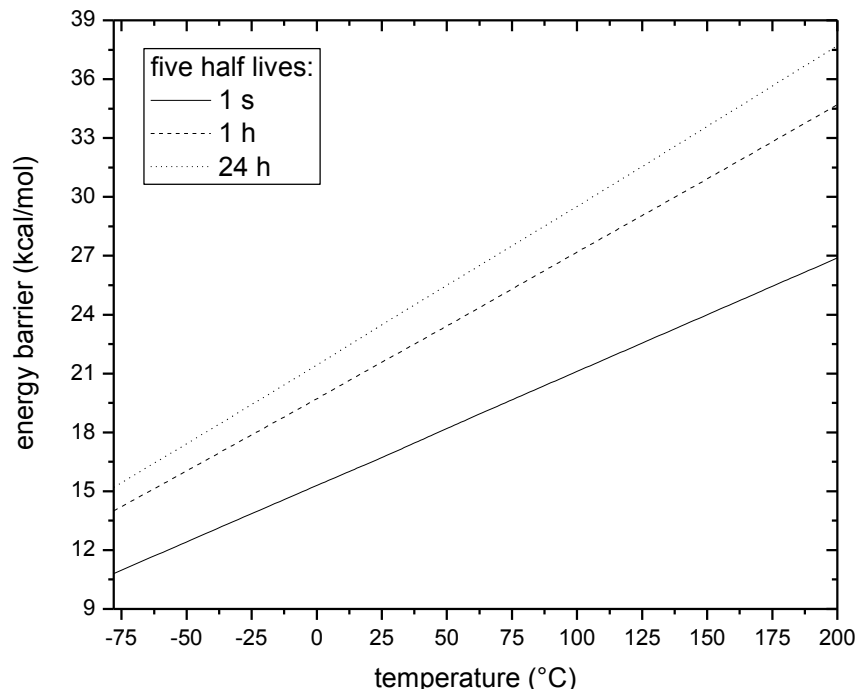
1 minute: 0.058 s^{-1}

1 hour: $9.6 \times 10^{-4} \text{ s}^{-1}$

6 hours: $1.6 \times 10^{-4} \text{ s}^{-1}$

12 hours: $8.0 \times 10^{-5} \text{ s}^{-1}$

The natural follow-up question is, what barriers are accessible at different temperatures and reaction times?



At room temperature:

- (1) **"The NMR timescale" - seconds: 15 kcal/mol**
(There is no single NMR timescale, though.)
- (2) **Fast Reactions - an hour: 21 kcal/mol**
- (3) **Slow Reactions - a day: 23 kcal/mol**

Example 2

Suppose a unimolecular reaction goes to completion within six hours at 298 K. If the temperature is raised to 50 °C, how long will the reaction take?

By an analogous calculation to that in example 1, this corresponds to a barrier of **22.6 kcal/mol**. The equation to be solved is:

$$\frac{5 \ln 2}{x \text{ s}} = \frac{(3.30 \times 10^{-24} \text{ cal} \cdot \text{K}^{-1})(323 \text{ K})}{1.58 \times 10^{-34} \text{ cal} \cdot \text{s}}$$

$$\exp\left(\frac{-2260 \text{ cal} \cdot \text{mol}^{-1}}{(1.99 \text{ cal} \cdot \text{K}^{-1} \cdot \text{mol}^{-1})(323 \text{ K})}\right)$$

One finds that the reaction will now take 17 minutes.

Example 3

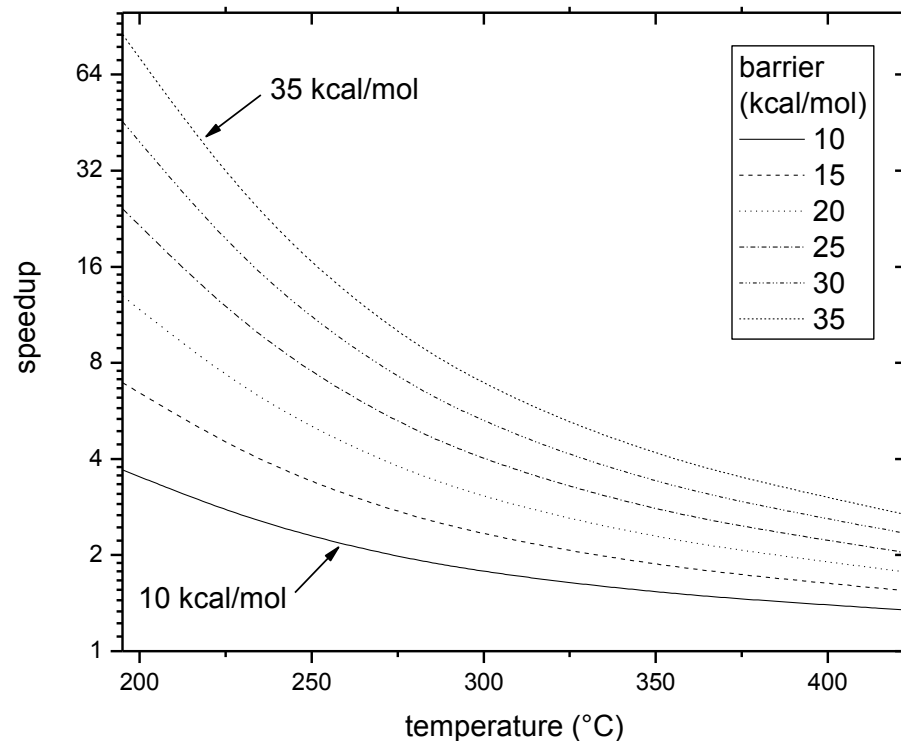
If the temperature of a reaction is increased by 10 °C, how much faster will it go?

The "textbook" rule of thumb says it's twice as fast. Let's see if this is true.

The expression for rate is:

$$k = k^\ddagger K^\ddagger = \kappa \frac{k_B T}{h} \exp\left(\frac{-\Delta G^\ddagger}{RT}\right)$$

Plotted here is speedup in rate k_2/k_1 , where k_2 is the rate at the higher temperature and k_1 is the rate at the lower temperature.



What conclusions can we draw?

- (1) Reactions with small barriers are fast already, and don't get sped up much by increasing temperature (and vice versa).
- (2) Incrementing low temperatures has a bigger effect than incrementing high ones.
- (3) Increasing the temperature by 10 °C at room temperature gives a speed of 2-5x.

Example 4

What free energy difference corresponds to a 1:10 ratio of A:B at 298 K?



This is easy:

$$\Delta G^0 = -RT \ln K = -1.99(298) \ln(10) = -1.4 \text{ kcal} \cdot \text{mol}^{-1}$$

This is good to remember: every pK_a unit difference means an energy difference of 1.4 kcal/mol.

Example 5

What ratio of A:B will an energy difference of 1.4 kcal/mol correspond to at 195 K (-78 °C)?

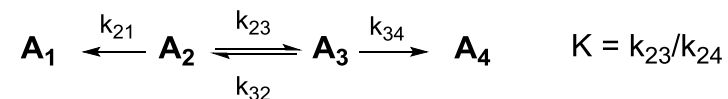
At standard concentrations,

$$-1400 = -1.99(195) \ln(x)$$

(Units omitted.) This works out to $x=37$. Thus, the 10:1 ratio is amplified to 37:1 in a dry ice-acetone bath.

Competing Pathways

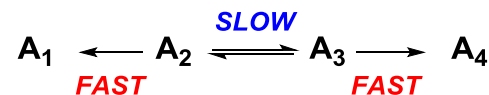
Sometimes, a reaction can give two products. Here is a prototypical scheme:



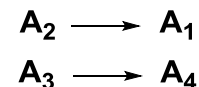
We would like to know what the product distribution of A_1 and A_4 are, given various rate constants.

Scenario 1: Kinetic Quench

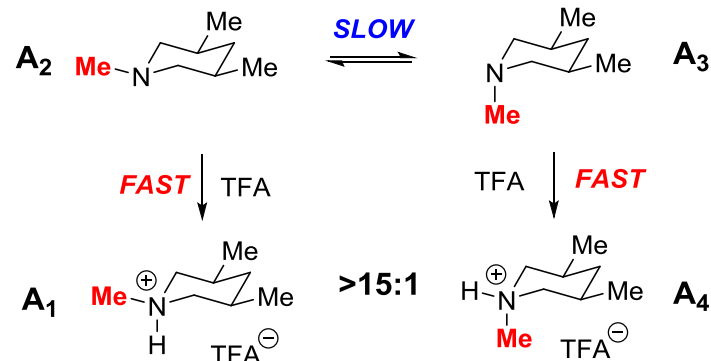
Mathematically, this is: $k_{21}, k_{34} \gg k_{23}, k_{32}$. What does this mean?



One perspective is that if the A_2/A_3 interconversion is infinitely slow, then there are effectively two isolated systems:

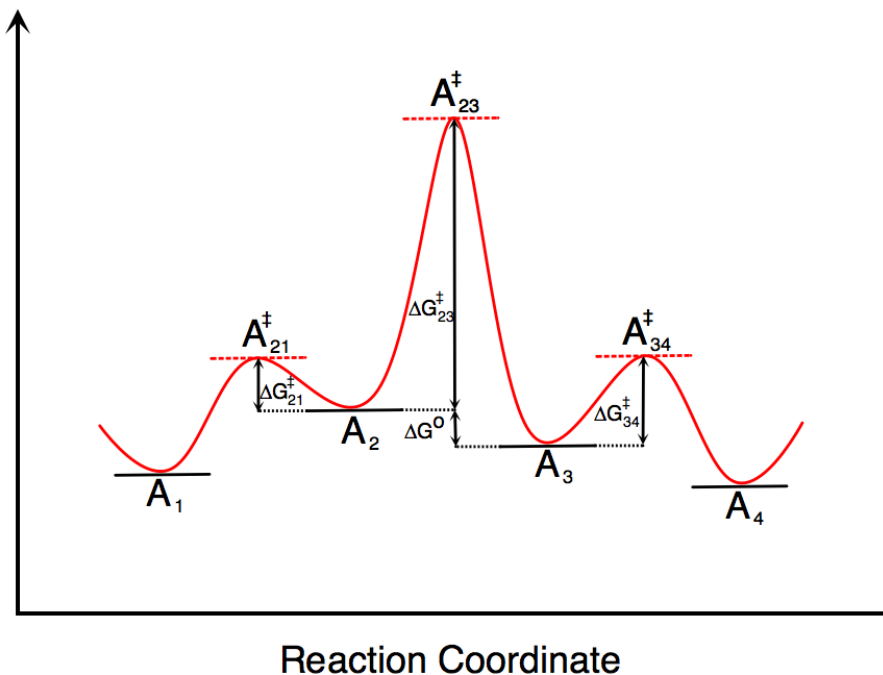


Thus, the product distribution simply reflects the starting material distribution.



So protonation is much faster than inversion at nitrogen, and the 15:1 ratio of the products simply reflects the starting material distribution, even though protonation of an axial lone pair might be faster.

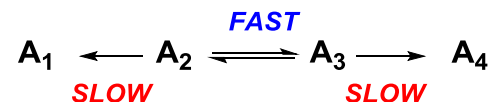
The same ideas can be expressed on an energy diagram. Slow rates mean high barriers:



For example, A_{21}^\ddagger represents the transition state on going from 2 to 1. Here, A_{21}^\ddagger and A_{34}^\ddagger are drawn at the same level, meaning there is no "intrinsic selectivity" in the reaction. One can imagine a scenario in which A_{21}^\ddagger is above A_{34}^\ddagger , but still far beneath A_{23}^\ddagger . The reaction is intrinsically selective for A_4 , but you can't tell, because there's no way to convert A_2 to A_3 .

Scenario 2: Curtin-Hammett Conditions

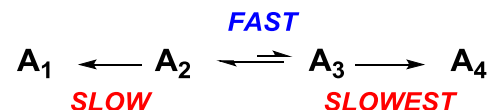
The opposite scenario is where A_2 and A_3 interconvert quickly, and it is the product formation steps which are slow:



Mathematically, this is: $k_{21}, k_{34} \ll k_{23}, k_{32}$. Most commonly, A_2 and A_3 represent rapidly interconverting conformers. Now, the product distribution will depend on both the amount of each conformers, and how fast each conformer reacts.

Now, we need to distinguish between two limiting cases.

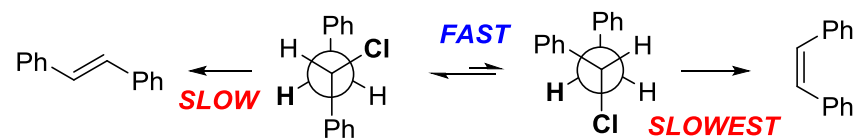
Case 2.1: The more stable conformer reacts fastest.



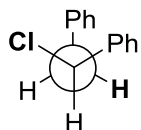
As the reaction proceeds, a fast A_2/A_3 equilibrium maintains $[A_2]/[A_3]$ at some constant ratio. But A_2 reacts to form A_1 faster than A_3 reacts to form A_4 . The overall selectivity is essentially a cooperation between the selectivity for A_2 in the ground state and selectivity for A_1 in the transition state.

Ideally speaking, this means that $[A_4]/[A_1] = K k_{34}/k_{21}$.

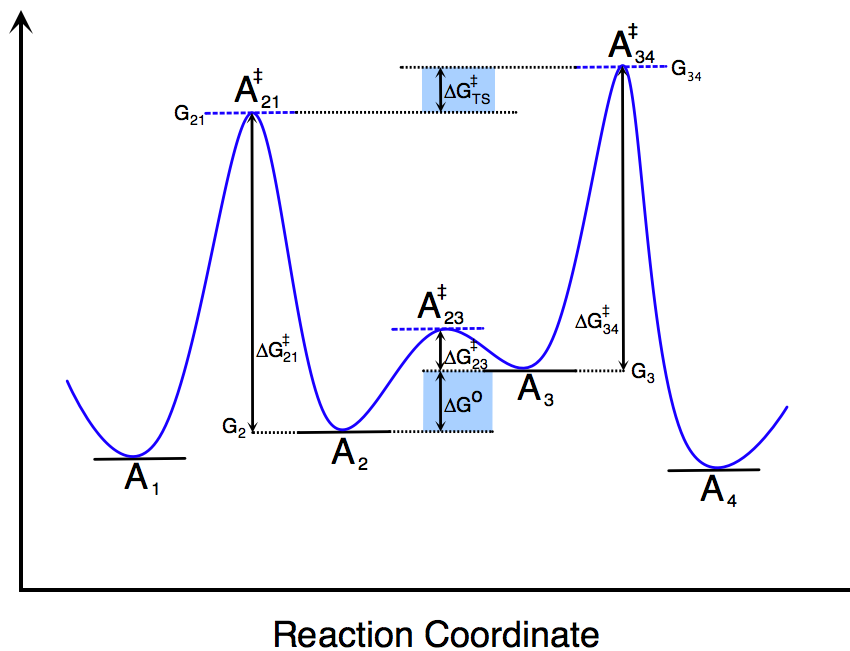
For example, consider this elimination:



- (1) Having the phenyl groups anti to each other is favored in the ground state.
- (2) The favored conformer has a hydrogen anti to the chlorine, whereas the disfavored conformer does not. Therefore, the more stable conformer also reacts faster. (This conformer would presumably also be fast, but is high in energy:

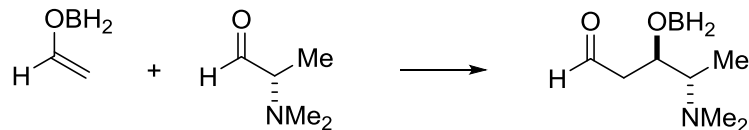


- (3) Thus, *trans*-stillbene is formed. Here is an energy diagram:

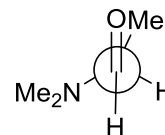


Whether ΔG_{21}^{\ddagger} is smaller or larger than ΔG_{34}^{\ddagger} is irrelevant; what matters is that A_{21}^{\ddagger} is below A_{34}^{\ddagger} . It is the absolute height of the barrier that determines rate, not the path the system took to get there.

One important case where ground state energy differences are the primary determinant of transition state energy differences is the 1,2-addition of nucleophiles to aldehydes:

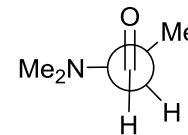


lowest energy conformation:



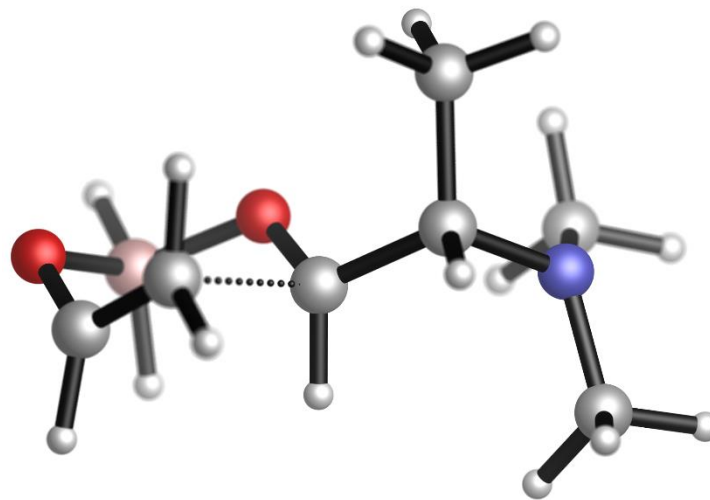
O=C-C-Me dihedral angle: 3°

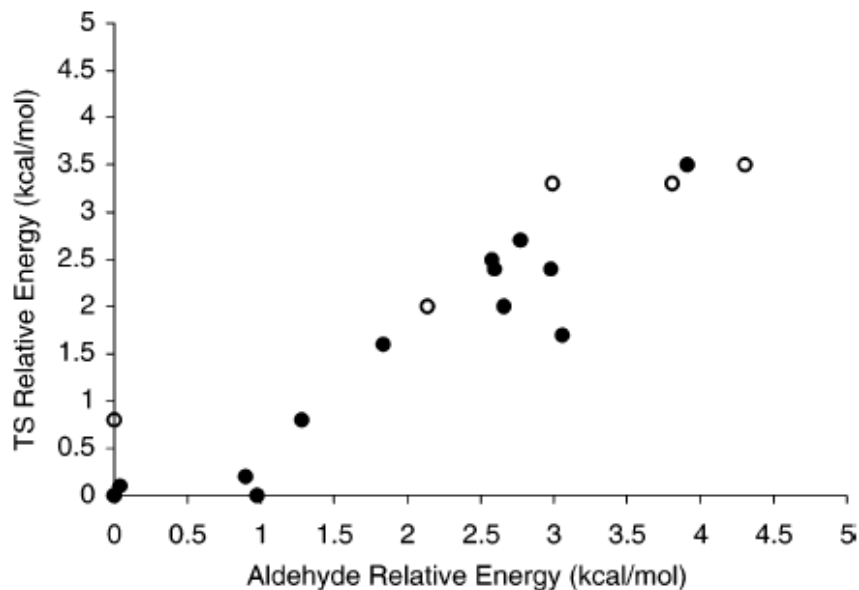
reactive conformation:



O=C-C-Me dihedral angle: 38°

The right hand structure is a fragment taken from the transition state. If the aldehyde alone is constrained to that dihedral angle, it gets raised in energy by about 0.4 kcal/mol.

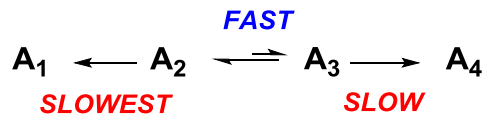




This shows the relative energy of the aldehyde is largely reflected in the relative energy of the transition state in 1,2-additions of enolboranes to aldehydes. These kinds of ground and transition state correlations are common and the basis for the simplifying assumptions in many reactivity models.

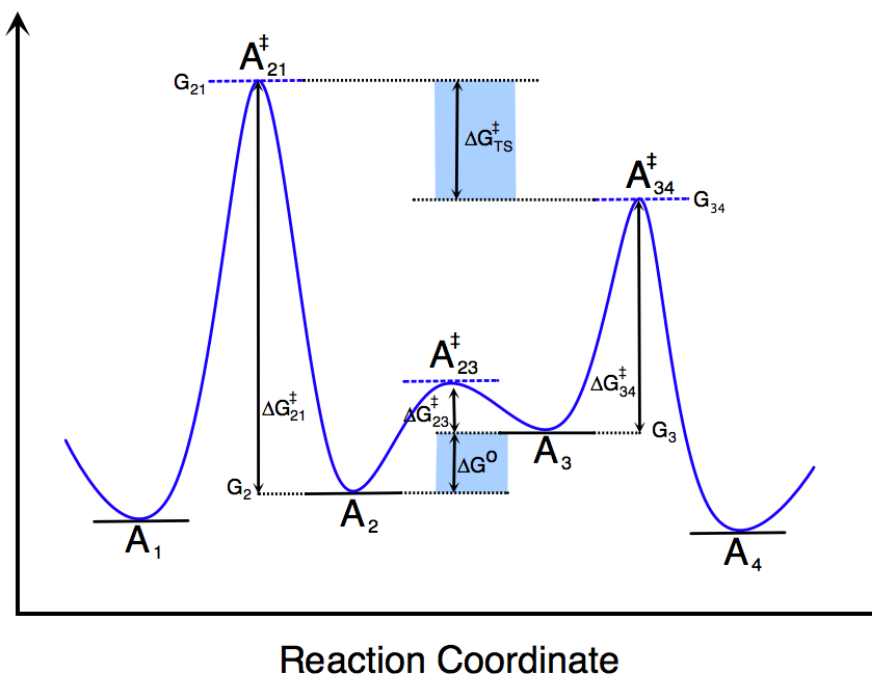
Evans, Cramer (JACS 2006 128 2920)

Case 2.2: The less stable conformer reacts faster.

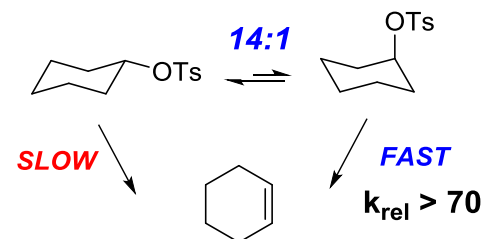


In this case, the ground-state preferences and the transition state preferences are opposed. The selectivity is still $[A_4]/[A_1] = K k_{34}/k_{21}$, but K is less than 1 and k_{34}/k_{21} is greater than 1 or vice versa. This presents an odd case where it is possible that the major product of the reaction actually derives from a conformer that is not visible in the ground state!

Here is the generic energy diagram:

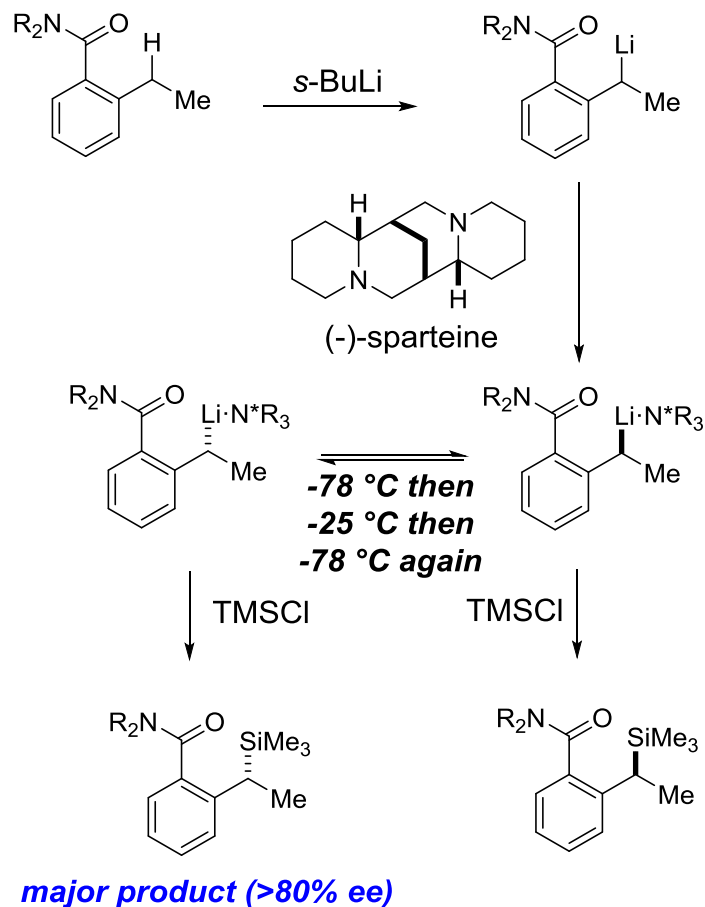


A classic example is the elimination of cyclohexyl tosylates:



Of course, both pathways lead to the same product; rates were extrapolated from conformationally locked systems.

Curtin-Hammett kinetics can be exploited in dynamic kinetic resolutions:



So is this Case 2.1 or Case 2.2? The fact that this required a warm-cool cycle for high ee suggests that equilibration is slow at low temperatures and fast at high temperatures. Thus, this is really neither; this is a kinetic quench with an intervening equilibration.

Linear Free Energy Relationships

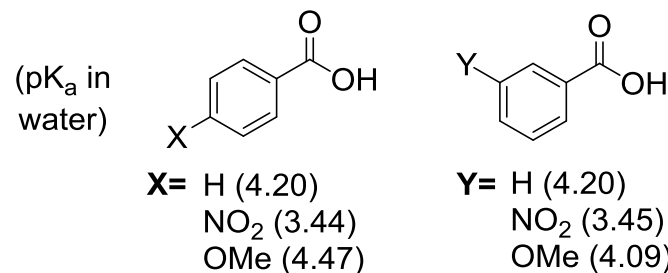
Using transition state theory, we were able to connect kinetics with thermodynamics. Even though the transition state is not a local minimum in the potential energy surface, we made the assumption that starting materials and transition state were in equilibrium. Doing so allowed us to make meaningful, quantitative predictions about rate.

Motivated by the connection between thermodynamics and kinetics, chemists in the mid-20th century sought to investigate relationships between easily measurable equilibria (ground state properties) and reaction rates (determined by transition state properties). One of the most famous of these *free energy relationships* was discovered by Louis P. Hammett.

$$\log \frac{k_{R=X}}{k_{R=H}} = \sigma \rho$$

"Hammett Substituent Constants and Resonance and Field Parameters." Hansch, C.; Leo, A.; Taft, R.W. *Chem Rev.* **1991**, *91*, 165-195. (comprehensive list of σ values)

Before explaining what these symbols mean, it is useful to consider the acidity of substituted benzoic acids in water:



Since benzoic acid dissociates to an anion, electron-withdrawing groups increase acidity with varying contributions from induction and resonance. **The dissociation of benzoic acids in water is defined to correspond to $\rho = 1$.**

In this case, $\log(k_{R=X}/k_H)$ corresponds to the ratio of the equilibrium constant for a substituted benzoic acid to that for benzoic acid itself. Thus, σ is a "substituent parameter" that corresponds to the difference in pK_a that adding the substituent causes. **Positive σ values mean electron withdrawing.**

This gives a basis for judging how sensitive an arbitrary reaction is to electronics. One can plot the ratio of rates for a range of substrates with different substituents against σ to find some slope ρ . As it turns out, such plots are often linear, or at least linear over various regions.

Here are some of the most important σ values:

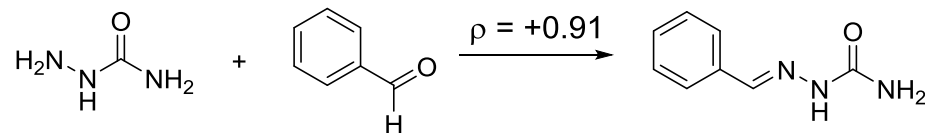
p-NH ₂ (-0.66)	p-CH ₃ (-0.17)	H (0)	p-Cl (0.23)	p-CN (0.66)	p-NO ₂ (0.78)
electron donating				electron withdrawing	

Q: Why are these numbers so small compared to pK_a values?

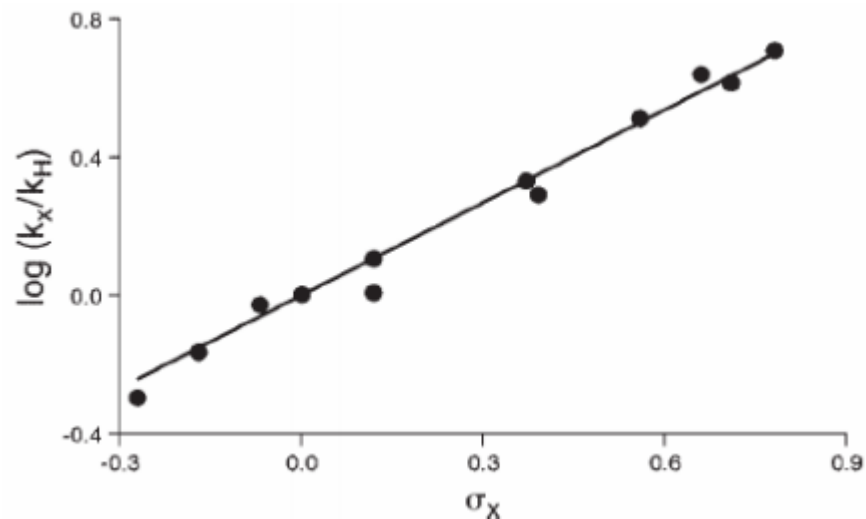
A: These represent *differences* between the pK_a of the substituted benzoic acid and benzoic acid itself, rather than absolute pK_a 's.

Interestingly, solvent has little effect on σ values, even though it has a huge impact on absolute acidities.

What do ρ values mean?



In semicarbazone formation (Jencks *JACS* **1960** 82 1773), $\rho = +0.91$, which means that the reaction is sped up by electron withdrawing groups (ρ is positive) but is a little less sensitive to electronic effects than benzoic acid dissociations is (the magnitude of ρ is less than 1).



The rate of reaction is increased for more electron poor aromatic rings. In energetic terms, a more electron poor aromatic ring destabilizes the partial positive charge at the benzylic carbon. Rate acceleration occurs because the transition state has less partial positive charge here than in the ground state.

Mayr Nucleophilicity/Electrophilicity Scale

Before the widespread availability of computational methods, finding free energy parameters to estimate rates was extremely popular. We will discuss more sophisticated examples and their applications to mechanistic chemistry in later lectures.

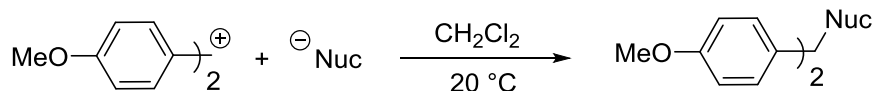
For now, let's suppose we only care about calculating rate. Mayr has developed a widely applicable set of empirical parameters to predict the rate of reaction between a nucleophile and an electrophile. An online database of these parameters is updated at regular intervals:

<http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html>

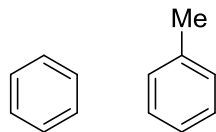
Mayr *ACIE* **1994** 33 938; *J Phys Org Chem* **2008** 21 584
ACIE **2006** 45 3869; *Acc Chem Res* **2003** 36 66

Development of the Scale

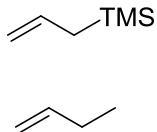
Nucleophiles and electrophiles have a very wide range of reactivities. For example, imagine that a set of "standard conditions" selected. Mayr and coworkers chose:



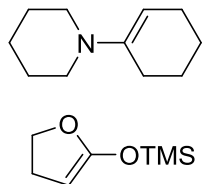
completely unreactive



variable rates



diffusion controlled



If alkenes or allylsilanes are used as nucleophiles, the reaction rate varies enough that it is possible to say whether one reagent is more nucleophilic than another. However, unactivated arenes don't react at all, while enamines react very quickly (diffusion-control)!

Still, modern methods allow rate constants to be measured from 10^{-5} s^{-1} to 10^9 s^{-1} ! To characterize a wider range of nucleophiles, more reference electrophiles are required.

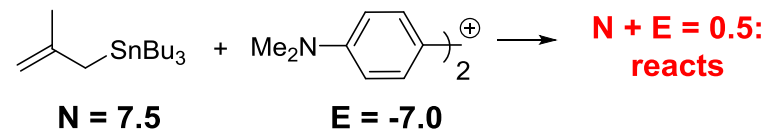
Mayr's key finding is that many reactions obey this equation:

$$\log k_{20^\circ\text{C}} = s(N + E)$$

Every electrophile is characterized by a single electrophilicity parameter, E, and every nucleophile is characterized by a single parameter N. (Bigger numbers mean more electro- or nucleophilic.) s is a "slope parameter" which depends on the nucleophile, and its origin is not understood. This method applies to a wide range of reactions (but not everything).

For $0.7 < s < 1.2$, more than 50% conversion will be reached within three hours when $N + E > -5.7$ to -3.3 . The simplified rule of thumb is:

reactions occur when $N + E > -5$.



N = 7.5

E = -7.0

**N + E = 0.5:
reacts**

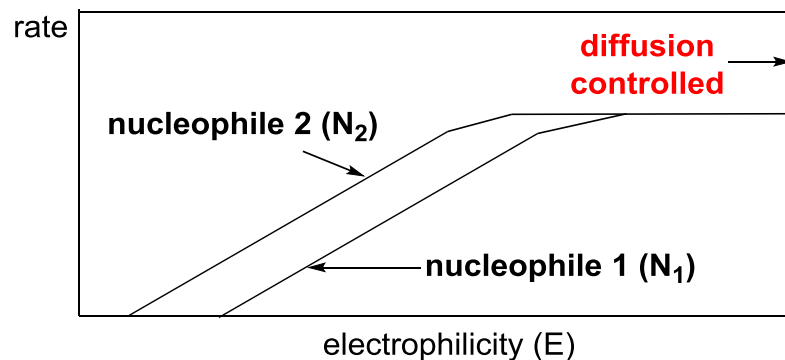
N = -2.4

E = -7.0

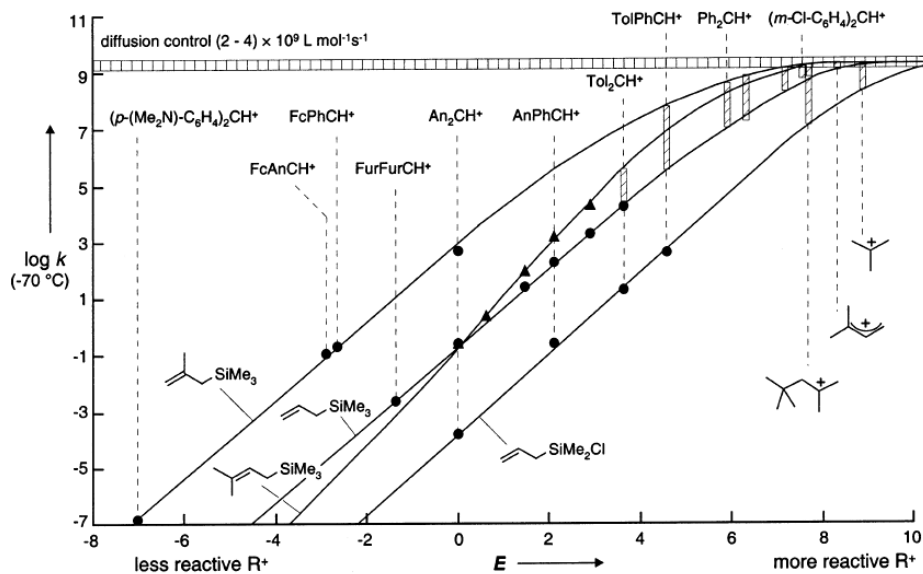
**N + E = -9.4:
no reaction**

Diffusion Control Leveling

Eventually, if an electrophile is reactive enough, its reactions will become diffusion controlled and the Mayr relationship will no longer hold:

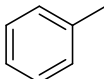
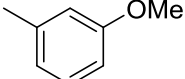

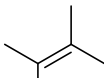



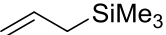
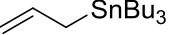
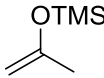
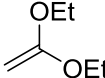
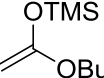
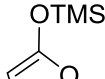

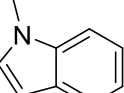
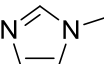

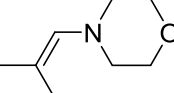
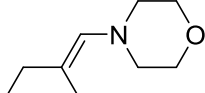
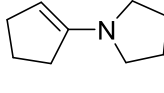
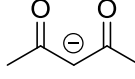
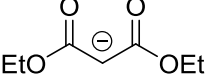



Each curve represents a different nucleophile. Here is an example:



Summary: Nucleophilicity

unreactive \longrightarrow reactive

aromatics	 -4.47	 0.13		
unactivated olefins	 -2.41	 -1.00	 0.65	 1.11
activated olefins	 0.78	 1.79	 5.46	
enol ethers	 5.41	 9.81	 10.21	 12.56
heterocycles	 3.61	 5.75	 9.91	 12.90
enamines	 10.04	 11.40	 15.91	
anions	 17.64	 20.22	 20.50	

reactive

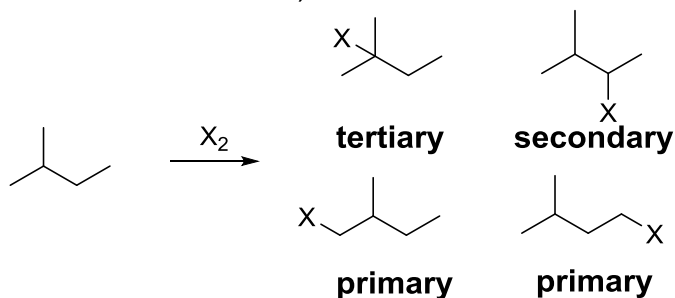
The Reactivity Selectivity Principle

Since the Mayr relationship allows us to predict the rate constant for the reaction between A and B (many parameters are available), it stands to reason we can also predict the selectivity of A for B vs. C.

It is commonly held that if A is less reactive, then it will give a higher selectivity. That is, if k_{ref} is the rate of reaction between A and some reference reactant, then it is proposed that $k_{\text{AB}}/k_{\text{AC}}$ will approach 1 as k_{ref} increases.

A Classic Example: Radical Halogenation of Alkanes

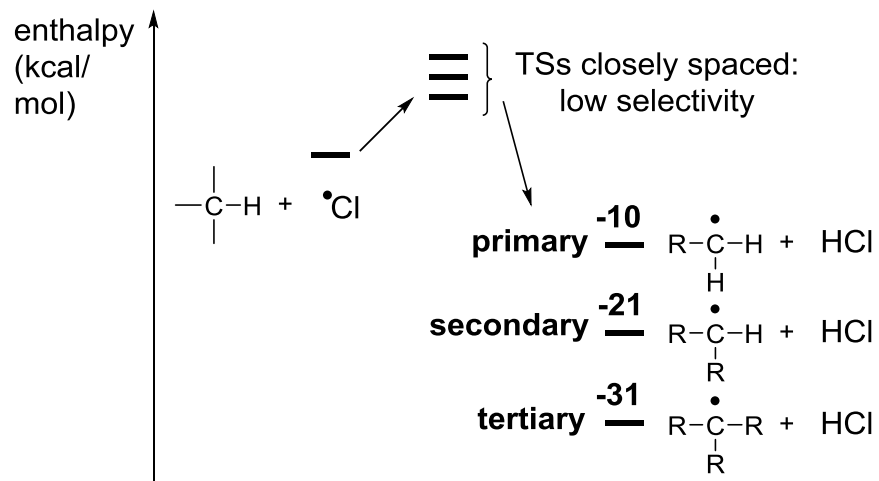
This is a classic example (discussed at length here: Mayr *ACIE* **2006** 45 1844-1854):



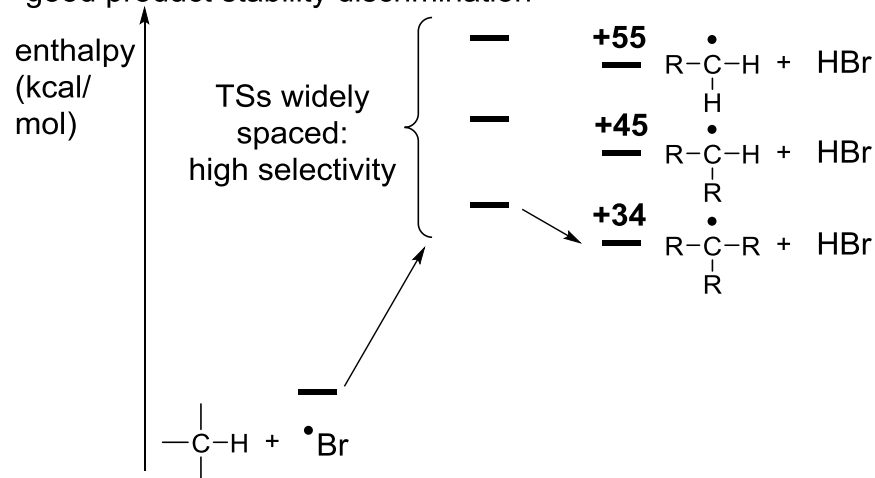
Product Distribution:
X = Cl (28 / 35 / 24 / 12)
X = Br (90 / 9 / <1 / <1)

The less reactive bromine reagent is apparently more selective. In a Hammond sense, this can be explained as follows.

- (1) Alkane is hard. Chlorine is harder than bromine. Chlorine-alkane will be more exothermic.
- (2) Chlorination: exothermic, transition states are starting material-like, little product stability discrimination



- (3) Bromination: endothermic, transition states are product-like, good product stability discrimination

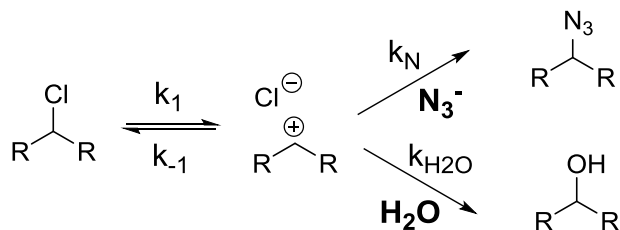


"Less reactive reagents are always more selective."

There is a vast amount of experimental evidence that **this statement is false**. It is thought that it is violated when the transition state cannot be thought of as a simple combination of reactant and product orbitals. Here, I will only address the contrary evidence, and leave the analysis to the experts.

The Ritchie Cases: Solvolysis of Alkyl Chlorides

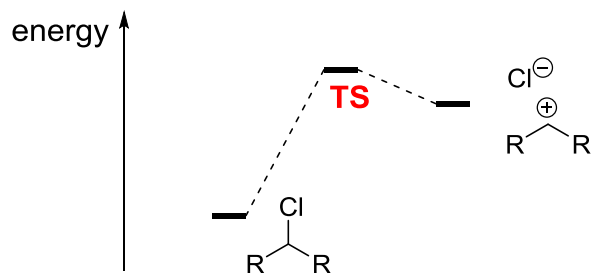
Consider a competition experiment in which an alkyl chloride and sodium azide are allowed to react in an aqueous medium:



Selectivity: k_N/k_{H_2O}

Reactivity: k_{solv} , rate of solvolysis without azide present

Note that the rate-determining step is ionization (k_1). Because carbocation formation is endothermic, the TS is late, and carbocation-like:

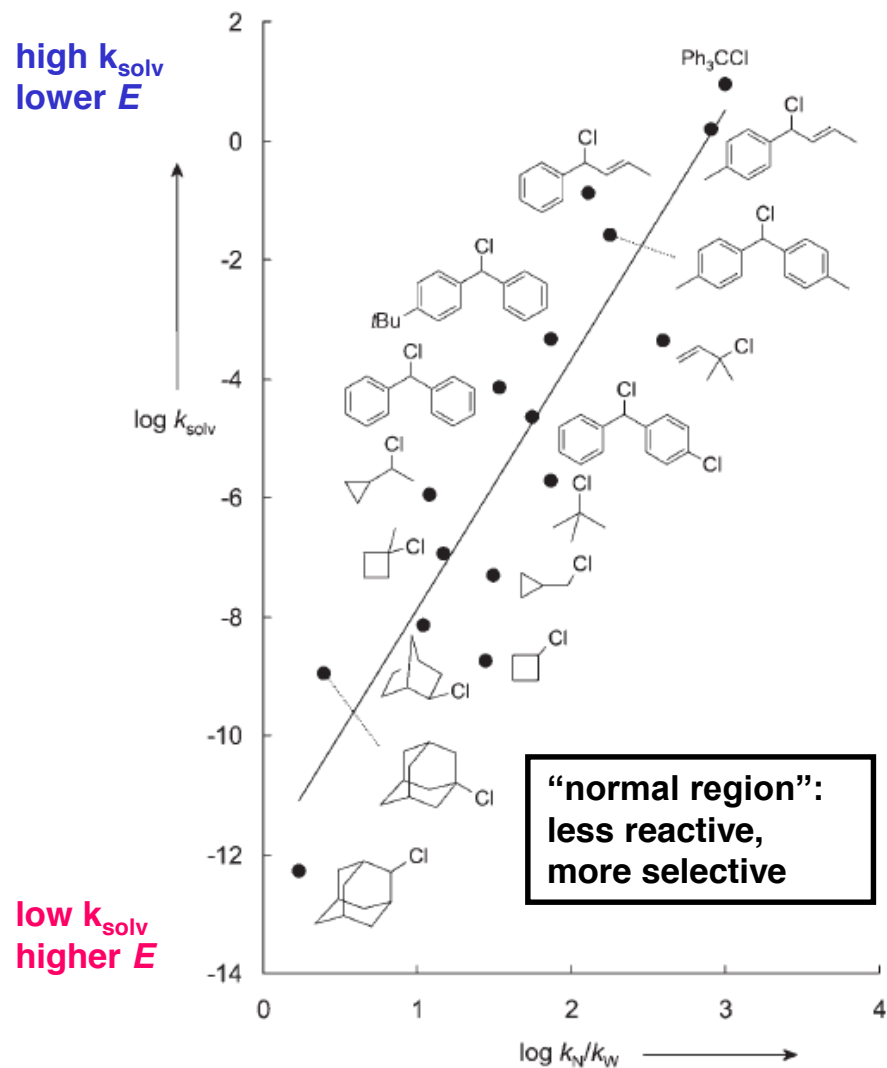


Thus, more stable carbocations will be formed faster. However, more stable cations will also mean slower reactions with nucleophiles (ground state stabilization means slower reactions).

One can view k_{solv} as a proxy for the Mayr electrophilicity parameter E : faster k_{solv} means lower E . (Note the **inverse** relationship here!)

Initially, it appeared that the "reactivity-selectivity principle" (less reactive, more selective) held:

figure below: Mayr *ACIE* **2006** 45 1844-1854



However, more detailed investigations also revealed a **constant-selectivity region** and an **inverted region**!

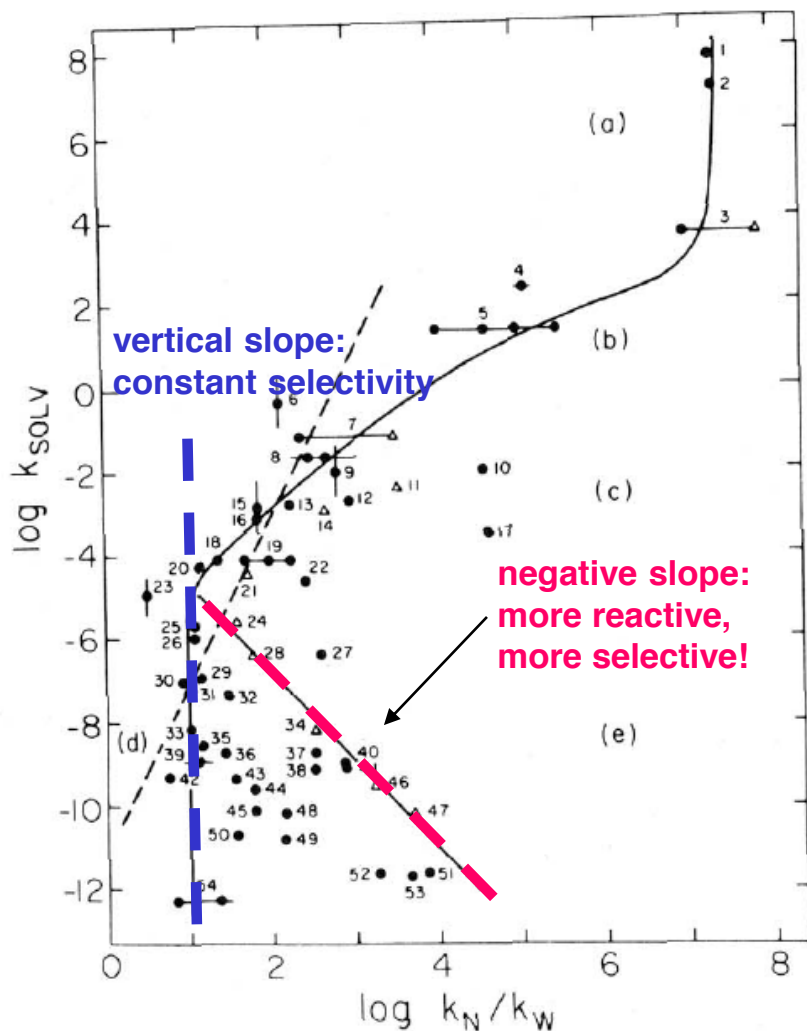


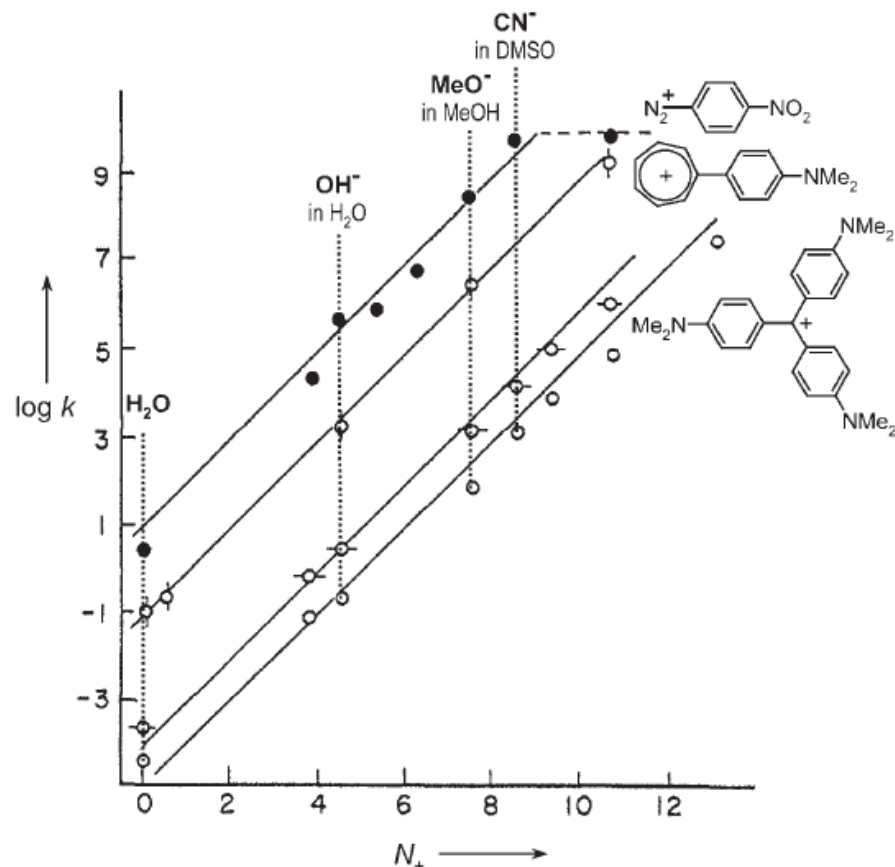
figure: Buncl *JCE* **1987** 64 475

(Do not worry about the details of this graph; the point is just to show that reactivity-selectivity principle is not obeyed, since the slope changes dramatically from region to region.)

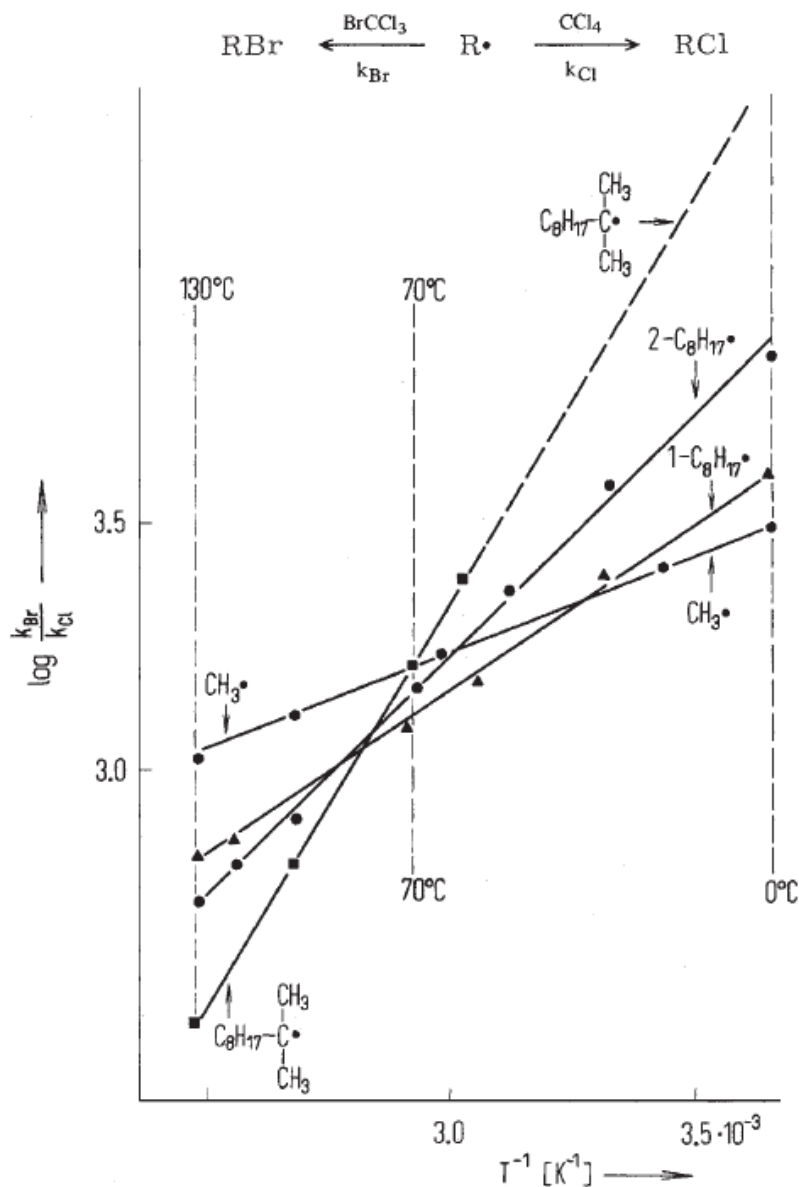
Apparently, the "normal region" of increasing selectivity with decreasing reactivity is simply one linear part of a much larger, non-linear graph!

Although this anomalous behavior was explained as the preferential solvation of the more reactive electrophiles, further studies indicated that it was not a fluke:

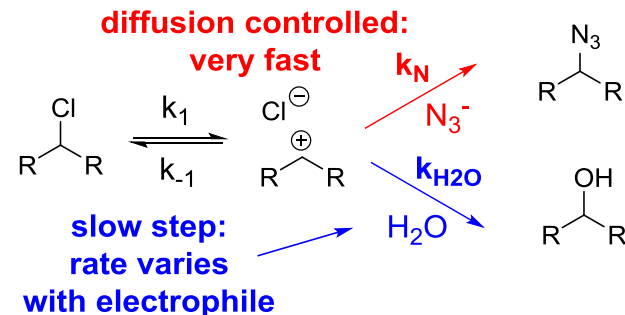
- (1) Constant reactivity-selectivity is observed in a variety of solvents (Ritchie *Acc Chem Res* **1972** 5 348)



- (2) Inversions in reactivity-selectivity can be observed with temperature: Giese *ACIE* **1977** 16 125



- (3) The selectivities measured in these experiments are competition-based. They only produce relative rates of reaction. If one measures the *absolute* rates with flash photolysis, one finds that the rate of reaction with azide, regardless of electrophile, is always very fast and diffusion-controlled:



This means that as the electrophile varies, k_{N} is fixed at a high number, while $k_{\text{H}_2\text{O}}$ varies. In fact, $k_{\text{H}_2\text{O}}$ increases as E increases, as anyone would guess. Therefore, $k_{\text{N}}/k_{\text{H}_2\text{O}}$ decreases asymptotically to ~ 1 as E increases. (At some point, reaction with water will also be diffusion-controlled, after which increasing E won't have any effect on $k_{\text{N}}/k_{\text{H}_2\text{O}}$.)

For competition experiments in which one nucleophile reacts at the diffusion limit, normal reactivity-selectivity must be expected. So the finding of normal reactivity-selectivity here was basically meaningless! In general, it is found that one can have normal, constant, or inverted selectivity. There's just no rule for predicting which.

Rappoport *JACS* **1983** 105 6082
McClelland *JACS* **1991** 113 1009