

1. Introduction

The determination of the empirical rate law for a reaction gives us some information concerning the existence of intermediates and the identities of elementary steps in an overall reaction. The next phase in our investigation of the mechanism of a reaction is usually an attempt to understand why the elementary steps proceed at whatever rates are observed, and how to control the rates and/or directions of the reactions.

Consider the fact that not all elementary steps of even related reactions proceed at the same rate. Based on this observation, we will start this phase of investigation by trying to understand exactly how an elementary step occurs. Clearly, the reactant species must come together in some way that somehow transforms them into products. As they come together, they must form an encounter complex (if only transiently). We would like to understand the nature of this "encounter complex", how it is formed, and how it is transformed into products. Before beginning, let's review some basic thermodynamics.

2. Review of Some Thermodynamic Quantities

The standard free energies, enthalpies, and entropies in which we are interested are actually the partial molar quantities. Let's begin with the partial molar free energy, which is often called the **chemical potential**.

2.1. The Gibbs Free Energy

The partial molar free energy of a molecular species i is given by:

$$\mu_i \equiv G_i \equiv \left(\frac{\partial G}{\partial \alpha_i} \right)_{T,P,m_j} \quad (1)$$

where G is the Gibbs free energy of the total system, and α_i is the activity of the species i . The subscripts on the partial derivative emphasize that temperature, pressure, and concentrations of all species except i are held constant. We usually choose some value of all these parameters (e.g., 298.15 °K, 1 atm, and one molar infinite dilution) to define the **standard state**. Thus, we can write the **standard chemical potential** of species i :

$$\begin{aligned} \mu_i^\circ &= \mu_i - RT \ln \alpha_i \\ &= \mu_i - RT \ln c_i - RT \ln \gamma_i \\ &= \mu_i - RT \ln c_i \end{aligned} \quad (2)$$

where $\alpha = c\gamma$, and c is the molar concentration and γ is the activity coefficient. Because the standard state involves "infinite dilution", $\gamma = 1$.

The criterion for thermodynamic equilibrium in any system is that the free energy of the system be at a minimum with respect to changes in the concentrations. For a chemical reaction



this criterion requires that

$$\begin{aligned} \frac{dG}{d\zeta} = 0 &= \sum_{i=1}^4 \frac{\partial G}{\partial c_i} \frac{dc_i}{d\zeta} \\ &= \sum_{i=1}^4 \mu_i \frac{dc_i}{d\zeta} \end{aligned} \quad (4)$$

and, therefore

$$\begin{aligned} 0 &= y\mu_C + z\mu_D - w\mu_A - x\mu_B \\ &= y\mu_C^\circ + z\mu_D^\circ - w\mu_A^\circ - x\mu_B^\circ + \\ &\quad + yRT \ln c_C + zRT \ln c_D - wRT \ln c_A - xRT \ln c_B \\ &= \Delta\mu^\circ + RT \ln \left(\frac{c_C^y c_D^z}{c_A^w c_B^x} \right) \end{aligned} \quad (5)$$

Because $\Delta\mu^\circ$ is a constant for a particular reaction, we can define a new constant, K , such that

$$\begin{aligned} \Delta\mu^\circ &= -RT \ln \left(\frac{c_C^y c_D^z}{c_A^w c_B^x} \right) \\ &= -RT \ln K \end{aligned} \quad (6)$$

An alternative expression, based on the equality $\Delta\mu^\circ \equiv \Delta G^\circ$, is the familiar

$$\Delta G^\circ = -RT \ln K \quad (7)$$

The take-home lesson from Eq (7) is that we can express the thermodynamic equilibrium constant for any reaction as a simple function of the standard Gibbs free energy change for the reaction:

$$K = e^{-\Delta G^\circ / RT} \quad (8)$$

At 298.15 °K (standard temperature), the product $RT = 0.593 \text{ kcal}\cdot\text{mol}^{-1}$ ($R = 1.99 \text{ cal}\cdot\text{mol}^{-1}\cdot\text{K}$), and we can estimate ΔG° from K and vice versa:

ΔG° (kcal·mol ⁻¹)	K
0	1
-1.0	5.4
-1.4	10
-2.0	29
-2.8	100
-3.0	157
-4.0	847
-4.2	1000
-5.0	4570

Note that for each factor of 10 increase in K , ΔG° decreases by 1.4 kcal·mol⁻¹. This is a useful rule of thumb for estimating orders of magnitude changes in equilibrium constants...

2.3. Comparing Two Reactions

Often, we'll be interested in comparing two reactions, or comparing the same chemical reaction occurring under different conditions. In such cases, we will be measuring differences in free energy changes. That is, for two reactions a and b , we can define:

$$\Delta\Delta G^\circ = \Delta G_b^\circ - \Delta G_a^\circ \quad (9)$$

and using Eq (7)

$$\Delta\Delta G^\circ = -RT \ln K_b + RT \ln K_a = -RT \ln(K_b / K_a) \quad (10)$$

After noticing the similarity between Eq (10) and Eq (7), we can discern a pattern in the relationship of $\Delta\Delta G^\circ$ with the ratio K_b / K_a :

$\Delta\Delta G^\circ$ (kcal·mol ⁻¹)	K_b / K_a
0	1
-1.0	5.4
-1.4	10
-2.0	29
-2.8	100
-3.0	157
-4.0	847
-4.2	1000
-5.0	4570

Note that for each factor of 10 increase in K_b / K_a , $\Delta\Delta G^\circ$ decreases by 1.4 kcal·mol⁻¹.

2.2. Enthalpy and Entropy Changes

We think of ΔG° as a measure of the spontaneity of a reaction. In turn, this thermodynamic parameter measures a combination of changes in heat, work, and entropy that occur during a reaction. We define the Gibbs function in terms of more fundamental thermodynamic quantities:

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (11)$$

where the sign is a result of the requirement that enthalpy (ΔH) must decrease but entropy (ΔS) must increase to create a driving force for a reaction.

Changes in enthalpy measure heat that is added to (or removed from) a sample and work done on the system. Thus, at constant pressure,

$$dH = dU + p \cdot dV \quad (12)$$

where U is the total energy content of the system, p is the pressure, and V is the volume. Remember that H is **extensive** (it depends on the amount of a substance considered) and is a **state function** (its value doesn't depend on the path taken between states). Also recall that there is no absolute zero for enthalpy, so we use the convention of setting $H = 0$ for the normal states of the elements at 25 °C. Hence, changes in enthalpy are important.

Entropy is a measure of randomness or states available to a system. Because thermal energy is the originator of motion in the kinetic theory, the thermodynamic definition of entropy expresses the change in randomness with heat exchange:

$$dS = dq/T \quad (13)$$

One more quantity we'll consider is the heat capacity of the system, which is defined as the amount of heat necessary to raise a unit mass of the sample by one unit of temperature. The heat capacity at constant pressure is defined by:

$$C_p = \left(\frac{\partial H}{\partial T} \right)_p \quad (14)$$

Hence, we can measure the enthalpy change for a reaction directly by measuring the change in heat capacity of a system between two temperatures (Eq (14)):

$$\Delta H = \int_{T_1}^{T_2} C_p dT \quad (15)$$

Similarly, the entropy change can be measured by integrating under the curve of C_p/T by substituting the relationship $dH = C_p dT$ from Eq (12) into Eq (11):

$$\Delta S = \int_{T_1}^{T_2} \frac{C_p}{T} dT \quad (16)$$

2.3. The Influence of Temperature on Equilibria

By rearranging Eq (7) and using the relationship in Eq (11), we can write

$$\ln K = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} \quad (17)$$

Thus, if we measure K as a function of temperature, a plot of $\ln K$ versus $1/T$ should yield a straight line with a slope of $-\Delta H/R$ and an intercept of $\Delta S/R$. This relationship can be expressed as a simple differential equation:

$$\frac{d(\ln K)}{d(1/T)} = -T^2 \frac{d(\ln K)}{dT} = -\frac{\Delta H}{R} \quad (18)$$

Eq (18) is known as the van't Hoff equation, and by performing a van't Hoff analysis, we can extract enthalpy and entropy changes for a reaction.

3. Relationship between Kinetics and Thermodynamics

Since the earliest rates studies, analogies have been drawn between rates and equilibria. In fact, we have seen that kinetics and stoichiometry are directly related for elementary steps. This suggests that there is a sort of analogy between the amount of product formed at equilibrium and the rate of formation of products. It is crucial to keep in mind, however, that some features of even elementary reactions are completely different for rates and equilibria. For example, it is not unusual to find that the less stable of two isomers is formed at a greater rate.

3.1. The Arrhenius Equation

The effect of temperature on rates of reactions was found empirically to produce a linear relationship between $\log(k_{\text{obs}})$ and $1/T$. In fact, the relationship is of the same form as that seen in van't Hoff analyses of equilibrium constants. This similarity suggested writing

$$\frac{\partial \ln(k_{\text{obs}})}{\partial (1/T)} = -E_a/R \quad (19)$$

where E_a is an empirical calorimetric parameter called the **activation energy**, k_{obs} is the observed rate of reaction, and T is the temperature in degrees Kelvin. More specifically, Arrhenius postulated that the equation could be written in integrated form:

$$k_{\text{obs}} = A \cdot \exp(-E_a / RT) \quad (20)$$

where A is a preexponential term with the same units as k_{obs} , R is the universal gas constant (1.99 cal/mol·K), T is the temperature in Kelvin. An assumption inherent in most applications of the Arrhenius Equation to kinetic analysis is that this energetic term has some inherent meaning, and correlates with the enthalpic activation barrier for the process being studied (see "The Reaction Coordinate" below). It turns out this is a pretty good assumption, at least for reactions that are characterized by large (> 10 kcal/mol) E_a 's. Similarly, the preexponential factor, A , is often qualitatively correlated with the entropic component of the activation barrier. The limits of these qualitative correlations will become clear in the discussion of the Eyring Equation below.

Note the similarity in the form of the Arrhenius Equation and the equation relating an equilibrium constant to the energetic difference between the equilibrating species:

$$k_{\text{obs}} = A \cdot \exp(-E_a / RT) \quad (20)$$

$$K = \exp(-\Delta G / RT) \quad (8)$$

As a practical matter, values of A and E_a are obtained from the following manipulations of the Arrhenius equation:

$$\ln(k_{\text{obs}}) = \ln[A \cdot \exp(-E_a / RT)] \quad (21)$$

$$= -E_a / RT + \ln(A)$$

Thus, a plot of $\ln(k_{\text{obs}})$ vs. $(1/T)$ will provide a line with a slope of $-E_a / R$ and an intercept of $\ln(A)$. (It is clearly necessary to extrapolate the rate data to $1/T = 0$ to obtain the latter parameter.)

3.2. The Eyring Equation

Unlike the Arrhenius Equation, the Eyring Equation is a theoretical rather than empirical construct. However, it is important to bear in mind that the Eyring equation also presumes the validity of mapping a reaction onto a Reaction Coordinate (again, see same). The most common form of the Eyring Equation is:

$$k_{\text{obs}} = (\kappa T/h) \cdot \exp(-\Delta G^\ddagger / RT) \quad (22)$$

where κ is the Boltzmann constant, h is Planck's constant, T is the temperature in Kelvin, R is the universal gas constant, and ΔG^\ddagger is the free energy of activation. (And, yes, we play a little fast and loose with the units when we apply this to bimolecular reactions.)

Setting aside the derivation of the Eyring Equation for a moment, and assuming its validity, it is instructive to compare the Arrhenius and Eyring Equations:

$$k_{\text{obs}} = A \cdot \exp(-E_a / RT)$$

$$k_{\text{obs}} = (\kappa T/h) \cdot \exp(-\Delta G^\ddagger / RT)$$

Applying these equations to the same k_{obs} , recalling that $\Delta G = \Delta H - \Delta S$, and indulging in a bit of algebraic manipulation, we arrive at:

$$A = (\kappa T/h) \cdot \exp(\Delta S^\ddagger / R) \quad (23)$$

$$E_a = \Delta H^\ddagger + RT \quad (24)$$

Expressing the "real" meaning of A and E_a in this form makes it clear why the Arrhenius Equation holds up best for reactions with large activation barriers (since $RT = 0.59$ kcal/mol at 298 K), and why A qualitatively correlates with the entropic barrier to reaction. It also illustrates one of the many reasons to *avoid* using the Arrhenius Equation: it is deceptively easy to conceptualize E_a as the activation barrier to the reaction (that is, the free energy of reaction) when in fact is only a reflection of the enthalpic component. In other words:

$$E_a \neq \Delta G^\ddagger \quad (25)$$

3.2.1. Derivation of the Eyring Equation.

The derivation of the Eyring Equation begins with the consideration of the unimolecular equilibrium:

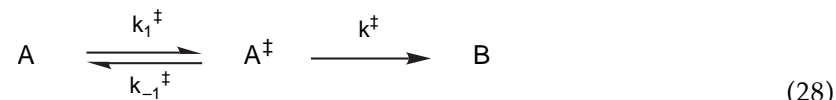


To simply matters further, focus only on one of the reactions, the conversion of A to B, assuming that the Principle of Microscopic Reversibility will allow us to apply anything we learn to the reverse reaction. Thus, we are dealing only with:



At any given time, only a subset of the molecules of A have sufficient energy, etc., to undergo conversion to B. If we assume that these reactive molecules (which we treat as populating the transition state) are in equilibrium with

the unreactive molecules, we can relate the relative populations by an equilibrium constant K^\ddagger :



$$[A^\ddagger] = (k_1^\ddagger / k_{-1}^\ddagger) \cdot [A] = K^\ddagger \cdot [A] \quad (29)$$

Further, since we have assumed that only the reactive molecules, A^\ddagger , undergo transformation to B, we can equate the bulk and microscopic rates:

$$k_1[A] = k^\ddagger \cdot [A^\ddagger] \quad (30)$$

and can therefore represent the bulk rate constant as:

$$k_1 = k^\ddagger [A^\ddagger] / [A] = k^\ddagger \cdot K^\ddagger \quad (31)$$

Now, after having survived Statistical Mechanics in P-Chem, it is intuitively obvious to even the most casual of observers (*not*) that we can express this as

$$k_1 = (\kappa T/h) \cdot K^\ddagger \quad (32)$$

(Seriously, though, there is a comprehensible and rigorous treatment of the derivation using statistical mechanics in Chapter 2, Appendix 1, of the Third Edition of the Lowry & Richardson textbook.) Now, relying on our old friends,

$$\Delta G^\ddagger = -RT \cdot \ln K^\ddagger$$

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

we arrive at the Eyring Equation:

$$\begin{aligned} k_1 &= (\kappa T/h) \cdot \exp(-\Delta G^\ddagger / RT) \\ &= (\kappa T/h) \cdot \exp(-\Delta H^\ddagger / RT) \cdot \exp(\Delta S^\ddagger / R) \end{aligned} \quad (33)$$

An extra preexponential term called the partition coefficient is sometimes included to correct for molecules that reach the transition state by revert to starting material rather than proceed on to product. For most systems, this partition coefficient is close to 1, so we've just ignored it here.

3.2.2. Application of the Eyring Equation

After transforming the latter expression of the Eyring Equation (eq 33),

$$k_1/T = (\kappa/h) \cdot \exp(-\Delta H^\ddagger/RT) \cdot \exp(\Delta S^\ddagger/R) \quad (34)$$

$$\ln\left(\frac{k_{\text{obs}}}{T}\right) = -\frac{\Delta H}{R} \cdot \frac{1}{T} + \frac{\Delta S}{R} + \ln\left(\frac{\kappa}{h}\right) \quad (35)$$

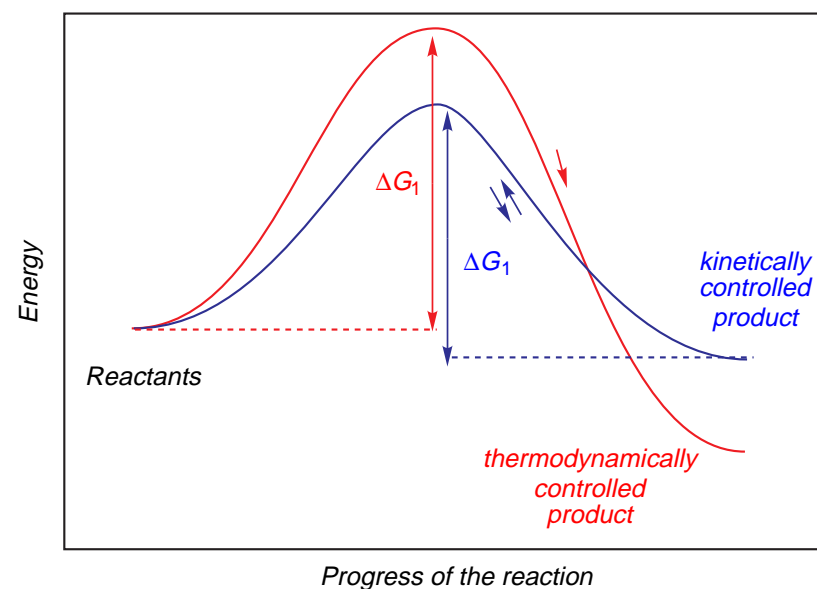
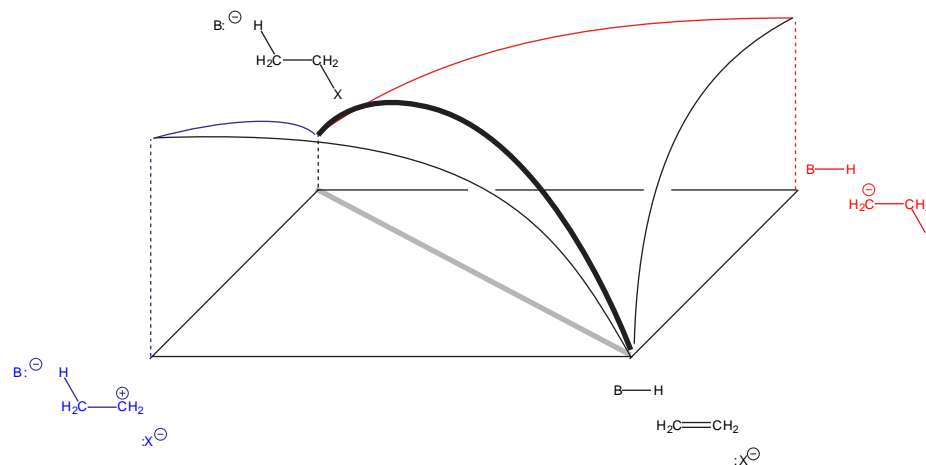
we can extract the values for ΔH^\ddagger and ΔS^\ddagger from kinetic data by plotting $\ln(k_{\text{obs}}/T)$ vs. $(1/T)$. Such a plot should provide a straight line of slope $-\Delta H^\ddagger/R$ and y-intercept $\Delta S^\ddagger/R + \ln(\kappa/h)$. (Again, it is necessary to extrapolate the data to $1/T = 0$ to obtain the latter value.)

A Cautionary Note:

The Eyring Equation is based on Transition State Theory, and is thus only as correct or truthful as TS theory itself. (See the section on TS theory for a discussion of its limitations.)

3.3. What the Hell is a Reaction Coordinate?

At this point, you are likely already familiar with reaction coordinates – we use them all the time, and one of the beauties of this way of representing the energetic continuum of a reaction is that it is both simple and fairly intuitive. In essence, the Reaction Coordinate is the lowest energy continuous path connecting the starting material and product on the potential energy surface of the reaction; the highest energy point along this path is the Transition State. (See the illustrations pirated from Isaacs, below.)



3.3.1. *Okay, It's Cute, But Whence Does It Come?*

Ultimately, the Reaction Coordinate is tied to Transition State Theory. One of the biggest assumptions involved is that the lowest energy reaction path can be regarded as a single fundamental vibration of a polyatomic system. That is, that the reaction path corresponds to some fundamental harmonic vibrational frequency of the system, in analogy to the vibration of the string of a musical instrument. Further, it is assumed that these correlated molecular motions can be regarded as completely orthogonal to (that is, independent of) all other motions in the system.

For the following reaction



we would say that the rate of the reaction depends on the frequency of the pseudo vibration associated with the transition state (ν^\ddagger):



Bearing in mind that a frequency, with units of s^{-1} , is also a rate, the qualitative connection between the pseudo-vibration and the rate of an elementary reaction can now be seen. (This is covered in somewhat more detail in the Derivation of the Eyring Equation.)

3.3.2. *Limitations of Transition State Theory*

Like any theory, TS Theory is now without its limitations. Chief among these are:

- Setting the motion of all reactants equal to a normal vibrational mode of the system is not necessarily a valid manipulation. While it works well, qualitatively, for a number of organic reactions (read: we can generate internally consistent analyses of kinetic data), it is not quantitatively correct for even simple systems such as $\text{H}\cdot + \text{H}_2 \rightarrow \text{H}_2 + \text{H}\cdot$. Another way of looking at this is that it may not be valid to try to separate motion along the reaction coordinate from other molecular motions in the reacting system.
- Similar to the last point, transition state theory does not appear to be well suited for the study of reactions that involve significant motion in more than one dimension. That is, it's probably okay for, say, $\text{S}_\text{N}2$ displacements,

but less likely to work for systems that involve (for instance) intermediates that can fragment by two pathways, one of which involves motions more similar to the transition state to the first intermediate and one of which involves motions that are less similar. (And, yes, this objection is a little contrived.)

- It is not quantum-mechanically correct. The phenomenon known as tunneling can (at least in principle) allow reactants with energies significantly lower than the transition state energy to react. This effect is most pronounced for light atoms (such as H), and is probably not a serious limitation for systems that do not involve hydride or hydrogen atom transfer.

4. Relative Rates of Reactions

At 298.15 °K (standard temperature), the product $kT/h = 6.21 \times 10^{12} \text{ s}^{-1}$ and the product $RT = 0.593 \text{ kcal}\cdot\text{mol}^{-1}$ ($R = 1.99 \text{ cal}\cdot\text{mol}^{-1}\cdot\text{K}$), and we can estimate ΔG^\ddagger from k_{obs} and vice versa using the Eyring Equation:

$$k_{\text{obs}} = (\kappa T/h) \cdot \exp(-\Delta G^\ddagger/RT) \quad (38)$$

For a simple, unimolecular process:

ΔG^\ddagger (kcal·mol ⁻¹)	k_{obs} (s ⁻¹)
0.1	5.2×10^{12}
1.0	1.2×10^{12}
1.5	4.9×10^{11}
2.0	2.1×10^{11}
3.0	3.9×10^{10}
4.0	1.4×10^9
5.0	2.3×10^7
10	2.9×10^5
15	6.4×10^1
20	1.4×10^{-2}
25	3.0×10^{-6}
30	6.6×10^{-10}

Note that for each 1.0 kcal·mol⁻¹ increase in ΔG^\ddagger , k_{obs} decreases by a factor of ≥ 5 , and that for each 5.0 kcal·mol⁻¹ increase in ΔG^\ddagger , k_{obs} decreases by a factor of 4600. This is a useful rule of thumb for estimating orders of magnitude changes in rate constants...

4.1. Comparing Two Reactions

Often, we'll be interested in comparing two reactions, or comparing the same chemical reaction occurring under different conditions. In such cases, we will be measuring differences in free energy changes. That is, for two reactions *a* and *b*, we can define:

$$\Delta\Delta G^\ddagger = \Delta G_b^\ddagger - \Delta G_a^\ddagger \quad (39)$$

and using Eq (7)

$$\Delta\Delta G^\circ = -RT\ln(k_b h/kT) + RT\ln(k_a h/kT) = -RT\ln(k_b/k_a) \quad (40)$$

After noticing the similarity between Eq (10) and Eq (7), we can discern a pattern in the relationship of $\Delta\Delta G^\circ$ with the ratio k_b/k_a :

$\Delta\Delta G^\ddagger$ (kcal·mol ⁻¹)	k_b/k_a
0	1
-1.0	5.4
-1.4	10
-2.0	29
-2.8	100
-3.0	157
-4.0	847
-4.2	1000
-5.0	4600

Note that for each factor of 10 increase in k_b/k_a , $\Delta\Delta G^\circ$ decreases by 1.4 kcal·mol⁻¹ for a reaction.

5. So, How Fast Do Things Really Happen?

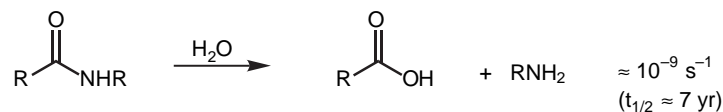
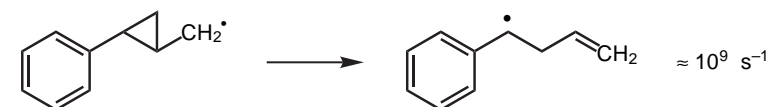
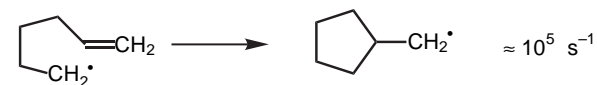
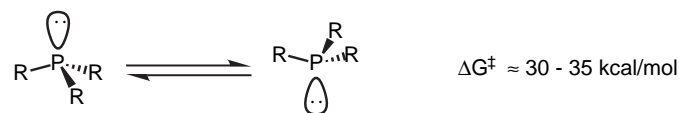
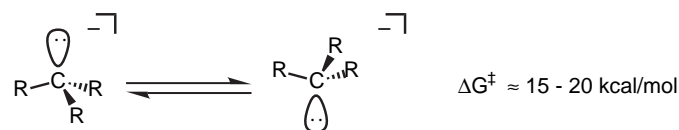
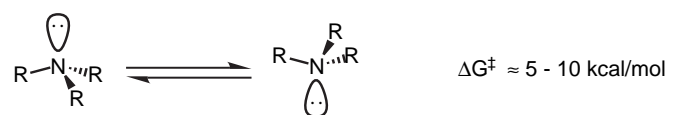
For simple unimolecular processes at RT, the following hold:

ΔG^\ddagger (kcal/mol)	k_{obs} (s^{-1})	$t_{1/2}$ ($= \ln 2 / k_{\text{obs}}$)
0.1	5.2×10^{12}	0.1 ps
1	1.1×10^{12}	0.6 ps
5	2.3×10^7	30 ns
10	2.7×10^5	2.6 μs
15	56	12 ms
20	1.2×10^{-2}	57 s
25	2.5×10^{-6}	3.2 days
30	5.4×10^{-10}	41 years

For perspective:

ΔG^\ddagger (kcal/mol)	k_{obs} (s^{-1})	relevant timescale
0.1	5.2×10^{12}	can be monitored by IR
1	1.1×10^{12}	
5	2.3×10^7	
10	2.7×10^5	can be monitored by microwave
15	56	
20	1.2×10^{-2}	can be monitored by NMR
25	2.5×10^{-6}	
30	5.4×10^{-10}	

Some rates and activation barriers worth knowing...



Diffusion Controlled Rate Limit: $\approx 10^9 - 10^{10} \text{ s}^{-1}$

Rate of C-C bond rotation in ethane $\approx 10^{12} \text{ s}^{-1}$

Rate of DNA hydrolysis (@pH 7) $\approx 10^{-13} \text{ s}^{-1}$
($t_{1/2} \approx 130,000 \text{ yr}$)

Rate of RNA hydrolysis (@pH 7) $\approx 10^{-11} \text{ s}^{-1}$
($t_{1/2} \approx 70,000 \text{ yr}$)