

Science of Temperature Dependence

SCIENCE OF TEMPERATURE IMPACT ON DEGRADATION RATES

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SUMMARY: This first white paper in a series of technical presentations discusses the nature of the temperature dependence on reaction rates, including the reactions that typically limit the shelf-life of such products as drugs. The Arrhenius equation is presented with special attention paid to the two key terms: the activation energy E_a , and collision frequency A . While the latter term is usually considered to be temperature-independent, we examine this assumption in more detail for gas, liquid and solid states. In liquids, the collision frequency is dependent on temperature linearly resulting in an apparent additional activation energy of 0.6 kcal/mol. In the solid state, the Arrhenius equation activation energy is proposed to be composed of two terms: one related to the barrier for the reaction and another related to the barrier for breaking intermolecular bonding to enable collisions. It is suggested here that observed higher activation energies associated with chemical reactions in the solid state compared to the same reactions in the solution state may be a result of this higher added activation process for movement in solids.

Activation Energy

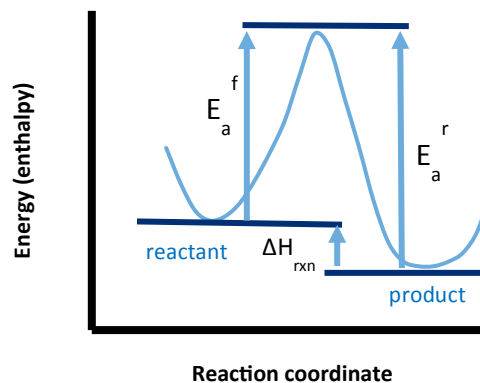
A reactant (e.g., active pharmaceutical ingredient, API) going to a degradation product has a driving force for the reaction to occur based on the difference in free energy (ΔG) between the starting materials and products. All reactions can be considered reversible, though the equilibrium constant (K) can be so lopsided as to make back reaction essentially non-existent. The equilibrium constant can be related to the difference in free energies, which in turn is related to the differences in enthalpy (ΔH) and entropy (ΔS) in the following relationship:

$$-RT \ln K = \Delta G = \Delta H - T\Delta S \quad (1)$$

Reactions with ΔG less than zero are considered spontaneous in the forward direction. As shown in Eq. 1, reactions with positive entropy differences (i.e., where there is more disorder in the products than in the reactants) will become increasingly favorable as the temperature increases.

The classic Arrhenius equation, which describes the temperature impact for a wide range of observed rate behaviors, can be derived based on the postulate that only molecules (or other species) with sufficient energy can go over an energy barrier and thereby undergo a chemical reaction (or other transformation) as shown in Figure 1. The y-axis in this graph is shown as energy (ΔH).

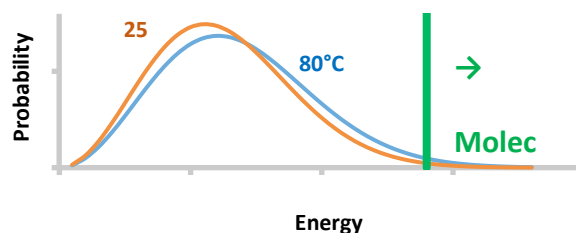
Figure 1 A barrier has to be overcome to go from reactant to product (E_a^f for the forward and E_a^r for the reverse reactions). The higher the barrier, the fewer molecules will have adequate energy to go over it, and the corresponding rate will be slower. The difference in energy between the reactant and product states (ΔH_{rxn}) combines with the entropy difference (ΔS) to determine the equilibrium constant (K). Catalysts lower the barrier height, but do not impact (ΔH_{rxn}).



At any given temperature, there will only be a certain percentage of molecules that have adequate energy to go over the barrier. The percentage with adequate energy (in a given time interval) can be determined based on the Maxwell-Boltzmann distribution for the energy of the individual molecules. This distribution shifts and broadens with increased temperature such that a greater proportion of molecules will have enough energy to go over the barrier as shown in Figure 2.

As temperature increases, more molecules have energy to go over the barrier. The rate of a reaction will depend on the probability of a molecule having sufficient energy to react, as shown in Figure 2.

Figure 2 The distribution of molecular energies shifts to greater energy as the temperature increases.



This change in rate with temperature is described by the Arrhenius equation, which can be shown in its exponential (Eq. 1) or logarithmic (Eq. 2) forms:

$$\frac{\text{Moles with energy for reaction}}{\text{time}} = k = Ae^{-\frac{E_a}{RT}} \quad (1)$$

$$\ln k = \ln A - \frac{E_a}{RT} \quad (2)$$

where E_a is the activation energy (barrier height, in energy units per mole), k is the rate constant, $\ln A$ is the "collision frequency," R is the gas constant (in energy units per Kelvin per mole), and T is the temperature in Kelvin. In general, the barrier height E_a is assumed to be independent of temperature; i.e., a plot of $\ln k$ vs. $1/T$ gives a straight line (with a slope of $-E_a/R$). The higher the

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activation energy, the greater the temperature dependence of a reaction.

As the temperature increases, every molecule will eventually have sufficient energy to react. Even so, reaction rates do not go to infinity. The rate of reaction at infinite temperature is limited by the collision frequency ($\ln A$). This collision frequency will be discussed in the following sections.

The Arrhenius equation is widely applicable; however, there are several circumstances where it will fail. The most common failures occur when another thermally induced process is coupled with the chemical changes being fitted. An example of this is when a material melts. A phase transition can cause the active to dramatically alter kinetics in a discontinuous fashion not modeled by the Arrhenius equation. Another example is when there are two steps in a chemical reaction with each having a different activation energy. As temperature changes, the rate-limiting step can change. This leads to non-linear Arrhenius behavior. A further case occurs when looking at multiple degradation products in the aggregate either by loss of potency (loss of active) or formation of total degradants. In this case, each degradation process itself may obey the Arrhenius equation; however, the sum can appear non-Arrhenius if the component degradation processes are sufficiently differentiated. For example, the dominant degradation at low temperature could be a process with a low activation energy, while at high temperature, a higher activation energy process might prevail. The result would be curvature in the overall Arrhenius behavior (and a difference in the product distribution as a function of temperature).

The Arrhenius equation, as described in Equations 1 and 2, assumes a rate constant. In practice, there are many cases where complex systems are difficult to describe with a single rate constant. This can be due to the following: multiple step processes, heterogeneous systems, autocatalysis, and inhibitory behavior. Deconvoluting the component rate constants is often impractical. The result is apparent curvature in the Arrhenius equation. A practical solution to this issue, used in the Accelerated Stability Assessment Program (ASAP) and the software *ASAPprime*[®], is the isoconversion principle. With isoconversion, one determines the effective rate constants based on a single level of product formed. Instead of a rate constant for a process, we replace this with a rate to a specified level of a given degradation product. In most cases, this level is the failure point for the parameter (i.e., the specification limit). The edge of failure is determined at a range of temperatures. Importantly, the isoconversion times at each temperature are more likely to show Arrhenius dependence than methods that do not explicitly determine component rate constants.¹

In spite of exceptions, the Arrhenius equation is widely applicable to a large range of reactions, especially with isoconversion and when phase transitions are avoided. Moreover, in most cases, observed linearity of the Arrhenius plots themselves supports the applicability of the Arrhenius equation.

Collision Frequency: General

The Arrhenius equation (Eq. 2) provides an intercept ($1/T = 0$) of $\ln A$ corresponding to the reaction rate when all molecules have sufficient energy to go over the barrier. Describing $\ln A$ as a "collision frequency" is somewhat misleading since it really involves not only how often a collision occurs (most critical for bimolecular reactions), but also what percentage of orientations (and collisions) are suitable for the reaction to occur. In other words, in addition to how hard it is for things to move, there is an entropic term related to how organized the molecule (or

molecules) needs to be for reaction to proceed; i.e., the importance of the orientation of the respective colliding molecules.

While the Arrhenius equation suggests that the collision frequency will be temperature-independent, in fact the intercept will be different depending on the temperature range used to fit the equation. In other words, there will be non-linearity in the Arrhenius equation as one looks at a wide enough range of temperatures. This temperature dependence of the collision frequency can mostly be accounted for by examining the temperature dependence of diffusion in the medium. Typically, as temperature increases, the diffusion rate also increases which results in increased reaction rates; i.e., the collision frequency will be higher using a higher temperature range for extrapolation than using a lower range. This can also be true in cases where internal reorganizations (e.g., intramolecular reactions) involve diffusional motion, typically in condensed phases.

Gas Phase

In the gas phase, the mean kinetic energy of molecules will increase proportionally to the square root of absolute temperature. Since even intramolecular reactions can involve collisions or internal motions to achieve specific orientations, the temperature dependence of the molecular motion predicts a change in the collision frequency that will also be proportional to $T^{1/2}$. However, the density of a gas will also decrease inversely proportionately to the absolute temperature (at a constant pressure), though this factor may only affect intermolecular collisions. In other words, the specific volume of the gas will increase as temperature increases making it less likely that two molecules will find each other. The overall result is that the collision frequency for reactions will theoretically vary with temperature according to Eq. 3 (assuming an ideal gas).

$$A \propto \left(\frac{n}{V}\right)(T^{1/2}) = \left(\frac{P}{RT}\right)(T^{1/2}) \quad \left(\frac{\partial A}{\partial T}\right)_P = T^{-1/2} \quad (3)$$

Here, A is collision frequency, n is the number of moles of gas, V is the volume, T is the absolute temperature, and P is the pressure. For diffusion-controlled reactions (i.e., where $E_a = 0$), the rate constant would then be proportional to the square root of absolute temperature (versus having no temperature dependence). This means that going from 25 to 75°C (298 to 348K) would give only a difference in diffusion-controlled rates of 8% with the overall rate slower at the higher temperature. To put this in perspective, if one had assumed that there was no temperature dependence for the collision frequency in this example, one would have measured an apparent negative activation energy of 0.3 kcal/mol. With common reactions, the activation energy would presumably make this variation difficult to observe. For the gas phase, we can therefore assume that the collision frequency ($\ln A$ term) is essentially temperature-independent in the temperature range we mostly care about.

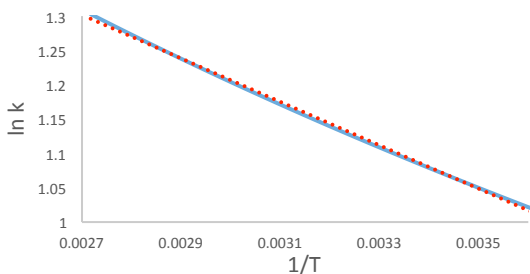
Liquid Phase

While liquid densities do not change as significantly as gas densities as a function of temperature, bimolecular collisions in the liquid state theoretically are more likely to show temperature dependence due to more significant changes in diffusion rates. In the liquid state, the diffusion coefficients of dissolved species vary directly proportionately to absolute temperature according to the Stokes-Einstein equation.² The impact of this deviation from Arrhenius linearity can be seen in Figure 3 looking at the temperature range available in water (assuming zero activation energy). As can be seen, the behavior actually appears to be approximately Arrhenius with a slope corresponding to 0.6

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kcal/mol. In other words, in the liquid state, an apparent Arrhenius linear behavior (i.e., $\ln k$ versus $1/T$) actually has two activation energies: one for the reaction barrier and a small apparent one for diffusion. This also means that the fitted Arrhenius parameters used to estimate ambient behavior from higher temperatures will have only a negligible error from the temperature impact on the collision frequency since the fitted activation energy incorporates most of this temperature dependence.

Figure 3 Arrhenius graph for a theoretical reaction having no activation energy in solution with the curve based only on the change in the collision frequency (A-factor) proportional to the absolute temperature, as expected from the diffusion coefficient temperature dependence (blue line). As shown, this temperature dependence of diffusion provides an approximately linear $\ln k$ versus $1/T$ behavior (dotted red line) with a slope corresponding to 0.6 kcal/mol.



Solid State

While in a gas and liquid, we make the assumption that the interactions between molecules are minimal such that diffusion is largely controlled by the average velocity of the diffusing species, in solids, the interactions between molecules are significantly higher. These interactions are especially high in the center of crystal lattices. Even when only due to van der Waals or hydrogen bond interactions, solids intrinsically involve greater resistance to movement than liquids or gases. In order for a molecule to move through a solid and enable collisions, these bonding interactions must first be broken. Since the bond energies represent another activation process, in a solid, diffusion itself obeys the Arrhenius equation. Solid-state diffusion involves an activation barrier even when a chemical reaction itself has no barrier (as with some oxidations). An example of this Arrhenius dependence for diffusion is seen with the change in moisture and oxygen permeability through polymers (moisture vapor transmission rate) as a function of temperature. While in the gas and solution phases, molecular motions contribute to the A-factor in a relatively temperature-independent way (dependence proportional to $T^{1/2}$ or T), in the solid-state, this dependence is exponential with an effective second activation energy, which is higher than the apparent activation energy seen in solution. We can therefore propose that overall, the combination of the activation energies from the two sources (chemical reaction barrier and barrier to motion in the solid-state) will appear additive as follows:

$$\ln k = \ln A - \frac{(E_{a1} + E_{a2})}{RT} \quad (4)$$

where E_{a1} is the activation energy for motion in the matrix and E_{a2} is the activation energy for the chemical reaction. A plot of $\ln k$ vs. $1/T$ will give a straight line with little deviation expected from linearity assuming there are no form changes. In this case, however, the slope includes both the activation energy for the decomposition and that for the diffusional process, which is related to the van der Waals, hydrogen and crystal bonding. The collision frequency term ($\ln A$) will still be the intercept (infinite

temperature) in an Arrhenius plot, but now, this term does not correspond to the value determined from solution experiments since the temperature-dependent diffusional component is not present (or less significant) in solution. The solid-state collision frequency can be viewed, therefore, as comprising a temperature-dependent diffusional term (incorporated into a new effective activation energy), a temperature independent term related to motion (reorganization, translation, rotation, etc.), and another temperature-independent term related to the entropy of activation (the degree of organization needed for a configuration or collision to lead to reaction).

The energy needed to move a molecule in a crystal is determined by the energy well each molecule is in. This barrier can be very significant for molecular collisions or even less dramatic intramolecular reorganizations. For diffusion in molecular crystals (basically migration of crystal holes), activation energies were found to range from 12 to 48 kcal/mol.³ Since this barrier is additive with the chemical activation energy for the degradation, it becomes clear why crystalline materials are generally quite stable.

In such complex solid systems as tableted drug products, crystalline actives can react at much faster rates than observed with the pure crystalline active. This supports the idea that the active is partially in a non-crystalline state such as a solid solution with the inactive components. In such non-crystalline states, the dominant activation for movement will be breaking of van der Waals, ionic and hydrogen bonding. Activation energies for breaking these bonds have, in each case, are approximately 1, 5 and 5 kcal/mol, respectively.⁴

The average activation energy for degradation found for 166 drug-like molecules in solution is 23.6 kcal/mol.⁵ The average activation energy found for degradation of 70 drug products (not the same drugs) in the solid state was 27.1 kcal/mol.⁶ While not proof, we suggest that the 3.5 kcal/mol higher average activation energy in the solid state could correspond to the additional activation energy for breaking the weak intermolecular bonds typically present in solids, consistent with the order-of-magnitude for these bonds discussed above. It should be noted that this 3.5 kcal/mol greater activation energy for the solid state compared to solution by itself corresponds to a 370-fold decrease in a degradation rate at 25°C in the solid versus solution state (assuming the same non-temperature dependent A factor, with the only difference assumed to be the temperature dependence on the collision frequency in the solid state), as shown below:

$$\frac{k_2}{k_1} = \exp \frac{\Delta E_a}{RT} = \exp \frac{3500 \text{ cal/mol}}{1.986 \text{ cal/(mol K)} 298 \text{ K}} = 370 \quad (5)$$

With an activation energy of 27 kcal/mol in the solid state, the average drug degradation will be about four times faster at 40°C compared to 30°C (rather than doubling the rate for every 10°C, a common rule of thumb that people often use as an assumption), as shown below:

$$\frac{k_2}{k_1} = \exp \left[\frac{E_a}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right) \right] = \exp \left[\frac{27000 \frac{\text{cal}}{\text{mol}}}{1.986 \frac{\text{cal}}{\text{mol K}}} \left(\frac{1}{303 \text{ K}} - \frac{1}{313 \text{ K}} \right) \right] = 4.2 \quad (6)$$

CONCLUSIONS

Increased rates of chemical reactions as temperatures increase are generally well-described by the Arrhenius equation. There are slightly different influences of temperature on the collision frequency term depending on the physical state of the medium. In the gas phase, a decrease in gas density as temperature increases (at a constant pressure) leads to a lower collision

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frequency. This is somewhat balanced out by an increase in the molecular velocity (mean kinetic energy) as temperatures increase, making the overall behavior only slightly non-linear in Arrhenius graphs ($\ln k$ versus $1/T$). In the liquid phase and solid phase, the temperature impact on density is comparatively low; however, the impact on diffusion rates are greater. In liquids, diffusional rates increase linearly with absolute temperature which makes the collision frequency have a slight temperature dependence. This deviation can be viewed as a slight addition of an activation energy (i.e., the linear temperature dependence can be approximated as exponential) leading to an approximately linear Arrhenius plot with an activation energy of about 0.6 kcal/mol, even with reactions having no activation barriers to the reactions themselves. In the solid-state, the diffusion itself is an activated process, which suggests that the collision frequency's temperature dependence should be able to be incorporated into an effective activation energy consisting of the barriers for the chemical transformation and for movement. This results in a linear Arrhenius plot with an observed activation energy higher than that for the chemical reaction itself and higher than that for reactions in solution.

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