

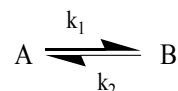
Determining the Energy of Activation Parameters from Dynamic NMR Experiments:

-Dr. Rich Shoemaker (Source: *Dynamic NMR Spectroscopy* by J. Sandstöm, and me)

- The results contained in this document have been published:
 - Zimmer, Shoemaker, & Ruminski, *Inorganica Chimica Acta*, **359**(2006) 1478-1484

The most common (and oft inaccurate) method of determining activation energy parameters is through the determination (often estimation) of temperature at which the NMR resonances of 2 exchanging species coalesce. The coalescence temperature (T_c) is then used in conjunction with the maximum peak separation in the low-temperature (i.e. slow-exchange) limit ($\Delta\nu$ in Hz). The biggest source of error using the method of coalescence is (1) accurately determining T_c and (2) accurately determining $\Delta\nu$. Often, the isotropic chemical shifts of the exchanging species are temperature dependent, so $\Delta\nu$ changes with temperature. If this happens, then the error in estimation of the activation energy barrier (ΔG^\ddagger) can be very large.

The rate constant (k_r) in these calculations, for nearly all NMR exchange situations, is actually k_1+k_2 in a system for A exchanging with B, where:



The equation to estimate ΔG^\ddagger using the coalescence temperature is:

$$\Delta G^\ddagger = aT \left[9.972 + \log \left(\frac{T_c}{\Delta\nu} \right) \right] \text{ where } a = 4.575 \times 10^{-3} \text{ for units of kcal/mol}$$

$$a = 1.914 \times 10^{-2} \text{ for units of kJ/mol}$$

Note: at the coalescence temperature, $k_c = \pi\Delta\nu/\sqrt{2}$

A second common method of determining the energy of activation (E_a) is by performing an *Arrhenius Plot*. If one knows the exchange rate constant (k_r) at several temperatures (always in Kelvin), one can plot $\ln(k)$ vs. $1/T$. The slope = $-E_a/R$ and the Y-intercept is = $\ln(A)$, where A is the Arrhenius frequency factor (described below).

Obtaining k_r at several temperatures can be accomplished by using transient exchange experiments (i.e. 2D-EXCHSY or 1D-EXCHSY (aka GOESY)) using several mixing times, and measuring the buildup rate of the exchange cross-peak vs. mixing time at several temperatures.

Alternatively, the more common method is to measure the 1D NMR at many temperatures (between the slow-exchange limit and fast-exchange limit), and then the exchanging resonances can be simulated using programs like DNMR or MEXICO. We have these simulation routines available in the lab within the SpinWorks software, written by Kirk Marat at the University of Manitoba. Good simulation requires time, patience, and practice.

The Arrhenius equation is: $k_r = A \cdot e^{-E_a/RT}$. Bear in mind that $E_a \neq \Delta G^\ddagger$, but E_a is related to ΔG^\ddagger in that $E_a = \Delta H^\ddagger + RT$ (of course $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ and at this point we don't have ΔS^\ddagger). At a given temperature, you can get ΔH^\ddagger from E_a because $\Delta H^\ddagger = E_a - RT$. (Remember that if you use 1.98717 for R, then RT is in units of calories, not kilocalories.)

Complete analysis of the activation energy parameters requires the use of the Eyring equation.

Eyring Equation:

$$k_r = \kappa \frac{k_b T}{h} e^{-\frac{\Delta G^\ddagger}{RT}}$$

Assuming a transmission coefficient (κ) = 1, you can calculate ΔG^\ddagger if you know k_r at any single temperature. A good estimate of ΔG^\ddagger can often be obtained if one has k_r at several temperatures, and you can use the equation below to calculate ΔG^\ddagger at each temperature.

$$\Delta G^\ddagger = RT \left[\ln \left(\frac{k_b T}{h} \right) - \ln(k_{rate}) \right]$$

or

$$\Delta G^\ddagger = RT \left[23.760 + \ln \left(\frac{T}{k_{rate}} \right) \right] \quad \text{use} \quad R = 1.9872 \text{ for calories/mol}$$

$$R = 8.3144 \text{ for Joules/mol}$$

In Sandstöm's book (page 96) this has been converted to a different form using base-10 logarithms:

$$\Delta G^\ddagger = aT \left[10.319 + \log \left(\frac{T}{k_{rate}} \right) \right]$$

where $a = 4.575 \times 10^{-3}$ for units of kcal/mol

$a = 1.914 \times 10^{-2}$ for units of kJ/mol

Knowing ΔG^\ddagger using this equation, and knowing E_a from an Arrhenius plot, one can get a good estimate of ΔS^\ddagger without doing an Eyring plot (described below).

$$\Delta S^\ddagger = \frac{[(E_a - RT) - \Delta G^\ddagger]}{T}$$

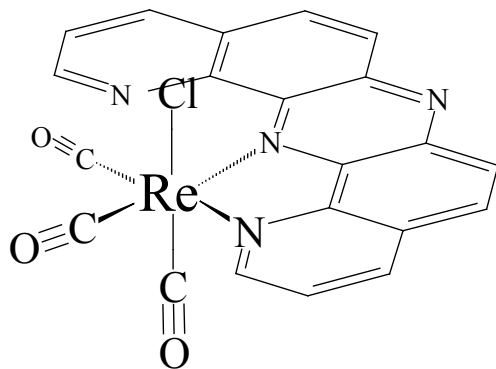
Eyring Plot: Plot $\ln(k_r/T)$ vs. $1/T$. Slope is $-\Delta H^\ddagger/R$; Intercept is $\Delta S^\ddagger/R + 23.7600$

{Note 23.7600 is $\ln(k_b/h)$ } The drawback of the Eyring Plot is that the Y-intercept (used to determine ΔS^\ddagger) is normally a large extrapolation from the experimental data. Therefore, if the linear fit of $\ln(k_r/T)$ vs. $1/T$ is not extremely good, the error in ΔS^\ddagger can be quite large.

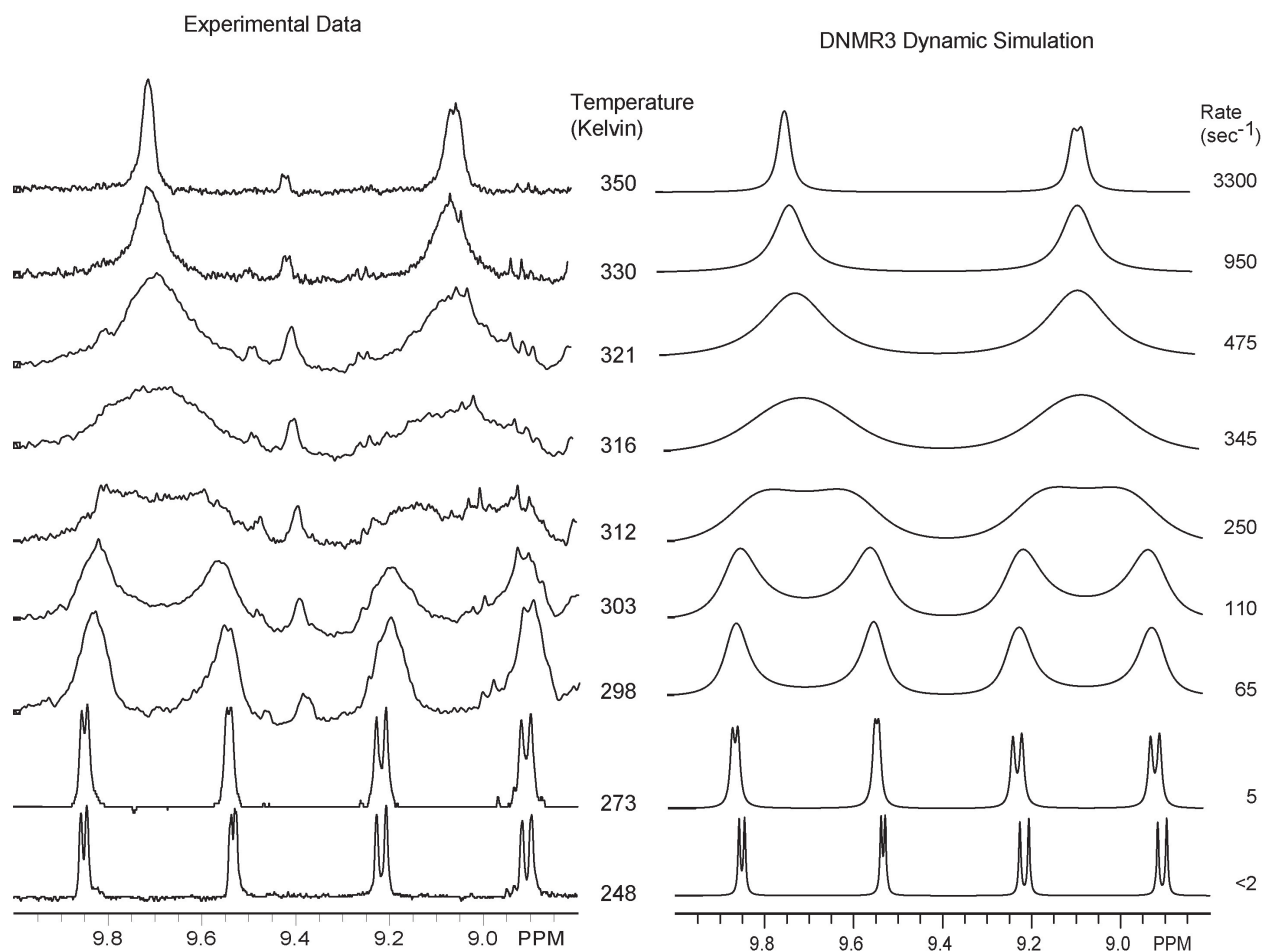
$$\ln \left(\frac{k_r}{T} \right) = -\frac{\Delta H^\ddagger}{RT} + \frac{\Delta S^\ddagger}{R} + \ln \left(\frac{k_b}{h} \right) \quad \{\text{remember: } \ln(k_b/h) = 23.7600\}$$

An example of these methods for a real dynamic system is presented on the following page:

Example of using variable-temperature NMR to evaluate the thermodynamic parameters governing chemical exchange: *Re*- *dpop'* (dipyrido(2,3-*a*:3',2'-*j*)phenazine). On this molecule, the coordinating nitrogens on the *dpop'* exchange between bound and unbound to the Re. This molecule was synthesized in the laboratory of Dr. Ron Ruminski, University of Colorado at Colorado Springs (*Inorganica Chimica Acta*, **359**(2006) 1478-1484).



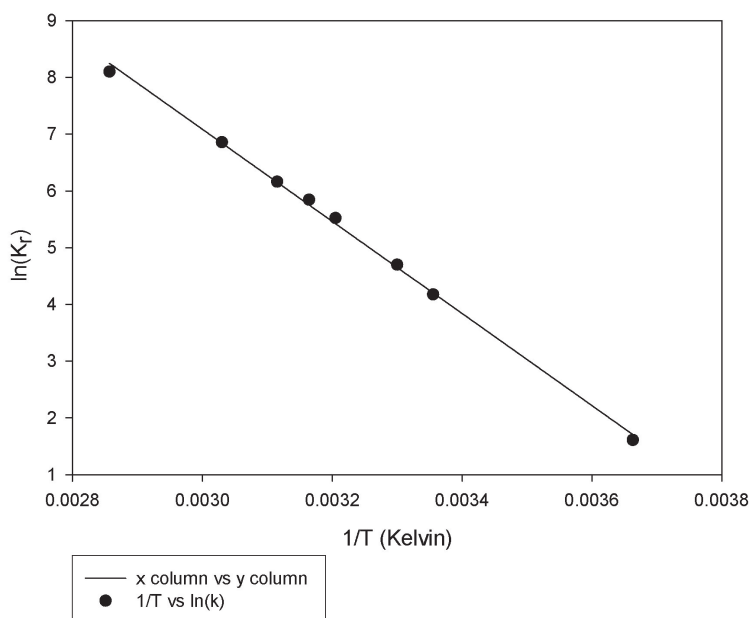
This low temperature ^1H NMR shows distinct NMR resonances for the protons on the aromatic rings on opposite ends of the *dpop'* ligand. The variable temperature NMR spectra, and the dynamic-NMR simulations (DNMR3 utility in the SpinWorks 2.4 software) are shown below, including the temperatures and the rates extracted from the simulations.



Using the best estimate of coalescence temperature (T_c) = 314 Kelvin, and $\Delta\nu=52.5$ Hz (at 248 Kelvin), $\Delta G^\ddagger = aT \left[9.972 \bullet \log \left(\frac{T_c}{\Delta\nu} \right) \right] = 15.3$ kcal/mol. This is our initial estimate of ΔG^\ddagger .

An Arrhenius plot of $\ln(k_r)$ vs. $1/T$ gives a very linear fit, with $r^2=0.998$.

Re-DPOP, Arrhenius Plot
 $\ln(K)$ vs. $1/T$ (Slope = $-E_a/R$)
 Slope = -8117.0; $E_a = 16.1$ Kcal/Mol



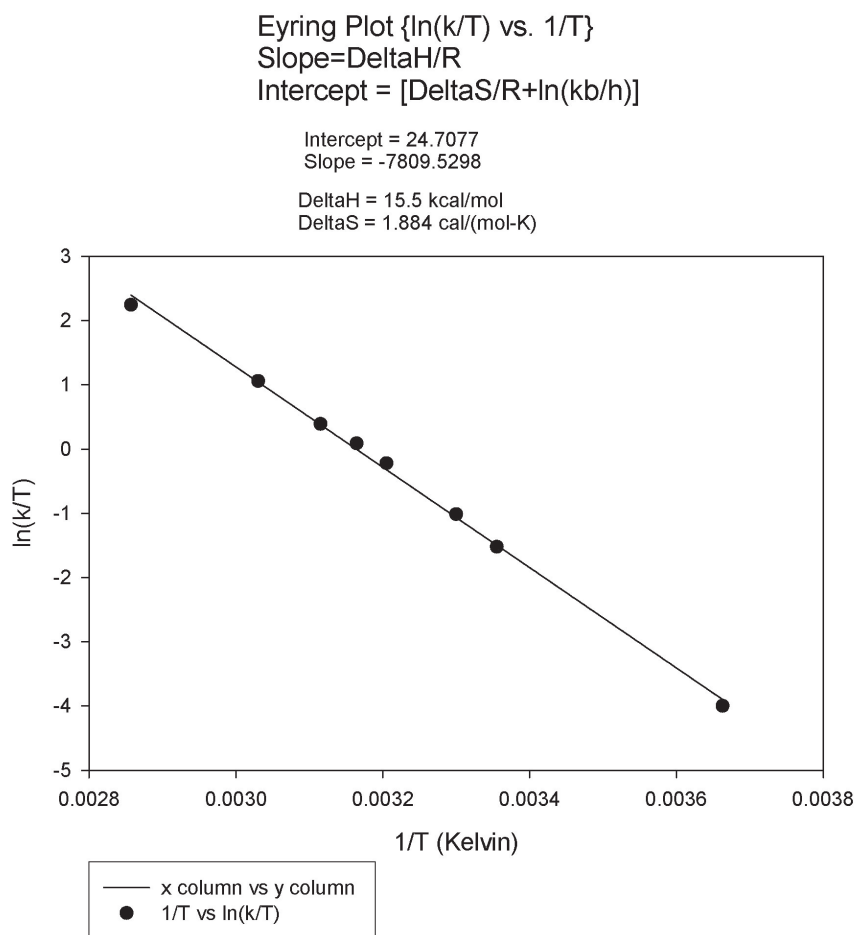
Using the Eyring Equation, ΔG^\ddagger can be calculated for every rate at every temperature (Note that ΔS^\ddagger is usually $\ll \Delta H^\ddagger$ so the temperature dependence of ΔG^\ddagger is usually undetectable within error)

Temp	Rate	ΔG^\ddagger kcal/mol
273	5	15.06
298	65	14.97
303	110	14.92
312	250	14.87
316	345	14.86
321	475	14.90
330	950	14.89
350	3300	14.96
Average		14.93
Std.Dev.		0.065

From the Arrhenius plot, $E_a = 16.1$ kcal/mol, so $\Delta H^\ddagger = E_a - RT = \underline{15.5 \text{ kcal/mol}}$ (using $T=314$ Kelvin, which is the best estimate of the coalescence temperature, and mid-range in the experiments).

Using $\Delta G^\ddagger=14.9$ kcal/mol, and $\Delta S^\ddagger = \frac{[(E_a - RT) - \Delta G^\ddagger]}{T}$, $\Delta S^\ddagger = 1.8$ cal/(mol-Kelvin).

A semi-independent method of obtaining ΔH^\ddagger and ΔS^\ddagger can be obtained by performing the Eyring Plot discussed earlier. This is *semi-independent* because the Eyring Equation was used to perform the ΔG^\ddagger calculation above. The results of the Eyring Plot of the data obtained from the variable-temperature NMR is shown below.



The slope yields a $\Delta H^\ddagger = 15.5$ kcal/mol, and $\Delta S^\ddagger = 1.88$ cal/(mol-Kelvin). Clearly, these numbers agree very well with the values calculated previously.

This document is a compilation of information that is readily available in the literature, and in various textbooks and resources; however, many find it difficult to pull out the *useful* information out of all of the mathematics. Hopefully, this document will be useful in clarifying how these methods can be applied to real-world research problems.