INTRODUCTION TO CHEMICAL EXCHANGE
WITH THE *MEXICO* PROGRAM

May, 2001

THE PHENOMENON

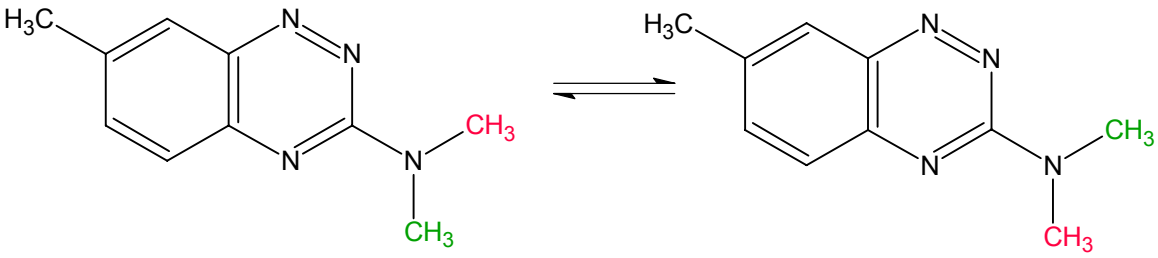


Figure 1

Consider the molecule in figure 1: 3-dimethylamino-7-methyl-1,2,4-benzotriazine. As it is drawn, the two methyl groups on the nitrogen are different (as shown by the colours), and should have distinct NMR signals. The bottom spectrum in figure 2, taken at relatively low temperature, shows this. However, the two methyl groups can exchange by rotation about the bond from the nitrogen to the ring. As the temperature of the sample is raised, the methyl signals broaden, move together, coalesce, and will eventually join to make a single sharp line (figure 2).

This is an example of the famous "NMR timescale". The resonant frequency of a nucleus is given by its specific magnetic environment. If nuclei change magnetic environments quickly (on this timescale), we see only an averaged spectrum. If nuclei move slowly (or not at all), we see individual environments. Between these extremes, we see the rich variety of chemical exchange lineshapes. The classic example is an *N,N*-dimethylamino group attached to a molecule with π bonding, such as in amides, or

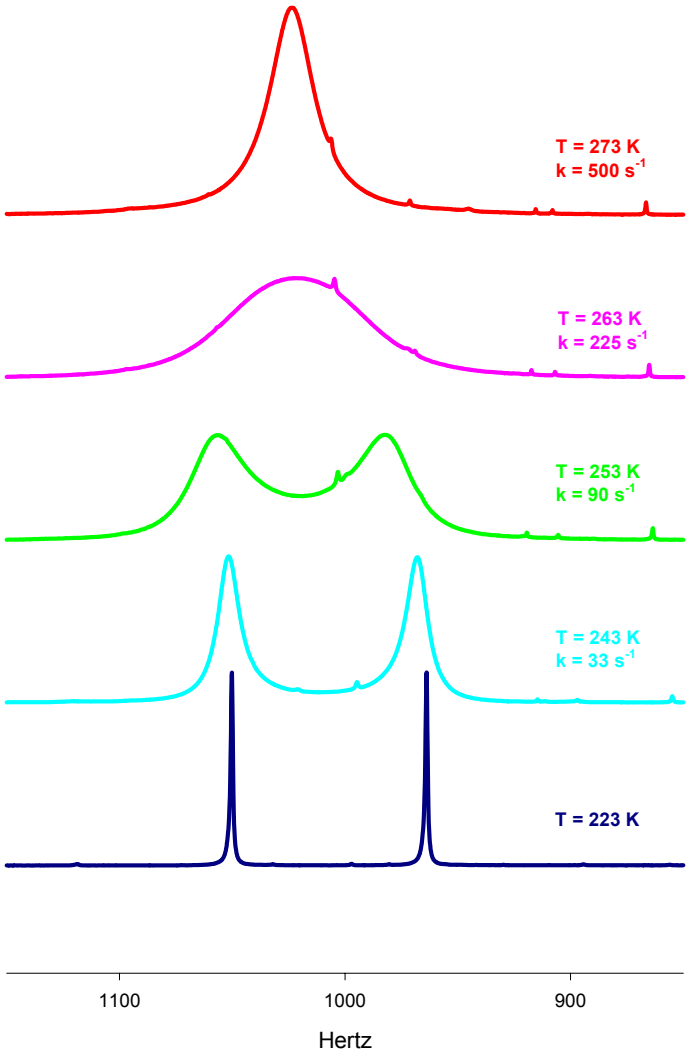

T = 273 K
k = 500 s-1
T = 263 K
k = 225 s-1
T = 253 K
k = 90 s-1
T = 243 K
k = 33 s-1
T = 223 K
1100
1000
900
Hertz

Figure 2

aromatic systems (figure 1). The lone pair of the nitrogen conjugates with the π system to create a partial double bond, resulting in a significant barrier to rotation of the dimethylamino group. The barrier height is comparable to thermal energies at accessible temperatures, so these effects are often seen in NMR spectra, as in figure 2. At low temperatures, two separate methyl signals are seen, but as the temperature is raised, the rate of rotation about the bond increases. The lines broaden and then coalesce.

The explanation of this lineshape is well-established, and the spectra can be readily simulated, given the correct rates and NMR parameters. The reverse of this question is now the important one – can we extract rates from experimental data? If we can, then the transition state in the reaction can be probed. This is what controls the chemistry.

TYPES OF CHEMICAL EXCHANGE

Chemical exchange means that a nucleus moves from one environment to another. It is a form of chemical kinetics, governed by forward and reverse rate constants, and the associated equilibrium constant. However, since we observe the spins only, the system is in macroscopic equilibrium. The sample remains the same, and we perturb the nuclei. Often, the reaction is a unimolecular re-arrangement of the molecule, but intermolecular exchange is also widely seen. Unimolecular reactions obey first-order kinetics, and the intermolecular reactions (as far as the NMR spectrum is concerned) are pseudo-first order. Even though the macroscopic reaction may be of higher order, all the effects on the spectrum are effectively first-order. This makes the kinetic treatment quite straightforward.

The simplest form of chemical exchange involves signals without scalar couplings, *e.g.* methyl singlets in a proton spectrum, or lines in a proton-decoupled ^{13}C spectra. In this case, when the nucleus exchanges, the NMR signal jumps to its new frequency. This situation can be easily described by a set of coupled Bloch equations. However, if scalar coupling is present, the situation can be much more complex. The one-to-one relationship between nuclei and lines in a spectrum no longer exists. The resonance of a single nucleus is split by the coupling. In a strongly coupled spectrum, a single spectral line may involve multiple nuclei. When the magnetic environment changes, a single line in one of the subspectra may map onto parts of several different lines in the other subspectrum. In order to treat this properly, a density matrix calculation is required. This may seem intimidating, but the theory section below shows that it is no more so than a static spectrum.

Mutual exchange is also a useful concept. If, when a nucleus jumps from site 1 to site 2, it is replaced by a nucleus jumping from site 2 to site 1, the molecule remains the same. For instance, figure 1 shows a mutual exchange. All that has happened is that the nuclei have been permuted. In this chemical exchange, the equilibrium constant is exactly 1, and the NMR parameters before and after the exchange are identical. This simplifies setting up the kinetic matrix, and makes the numerical calculation more efficient. Figures 3 and 4 show an example of coupled mutual exchange. The molecule is dissolved in CD_2Cl_2 and the spectra were run at 300 MHz. See figure 8 for the numbering and the parameters.

N,N-dimethyl-4-nitrosoaniline

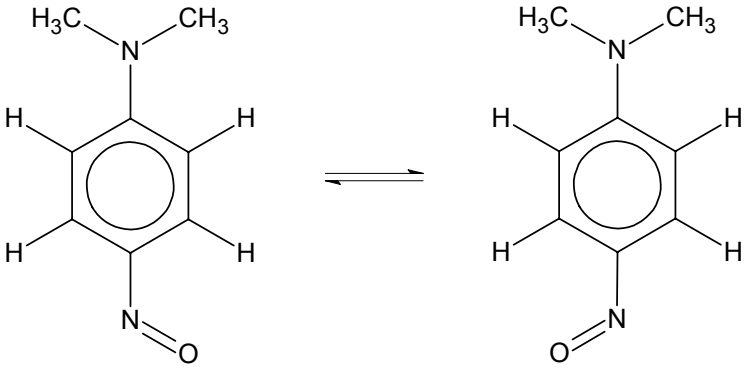


Figure 3

Variable temperature spectra of the aromatic protons of
N,N-dimethyl-4-nitrosoaniline

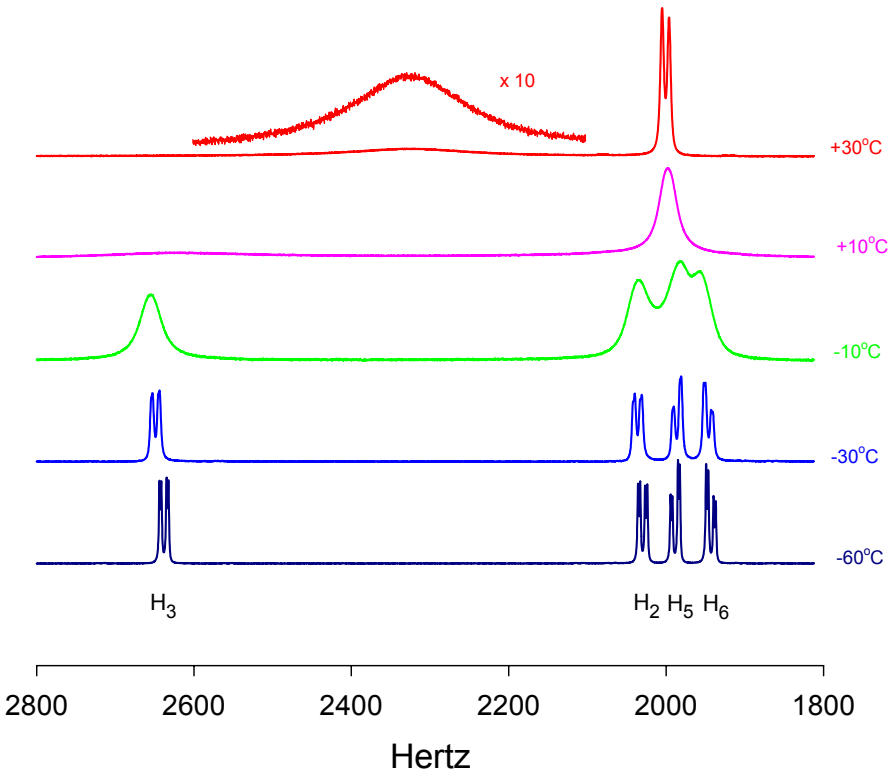


Figure 4

The equilibrium constant for mutual exchange must be 1, but this is not true for non-mutual exchange. The two forms are different, and will have different energies and Boltzmann populations. A classic example is furfural, in which the aldehyde group has two unequally-populated conformations which can be observed at ambient temperatures (figure 5). Of course, all molecules have conformations other than the ground state, but usually the other conformations have negligible populations. However, in some circumstances, we can see both conformations, and observe the effects of exchange between them. There is a forward and a reverse reaction rate, which are different and whose ratio is given by the equilibrium constant. The choice of which is the forward reaction is arbitrary, but the rate of the minor-to-major process must be the larger of the two rates, by the principle of detailed balance.

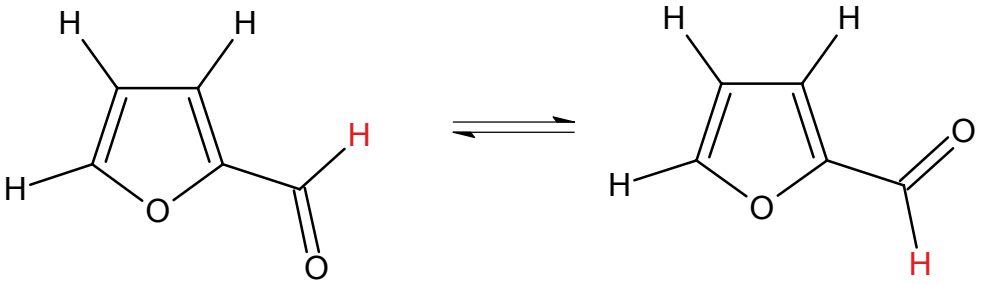


Figure 5

Therefore, a chemical exchange process needs to be classified: coupled or uncoupled, mutual or non-mutual, equally- or unequally-populated. All are approached the same way, but it is useful to take advantage of any simplifications.

THEORY

The original theory of the exchange lineshape was derived by coupling the Bloch equations corresponding to the two sites. This gave an equation for the strength of the

signal as a function of frequency, so the lineshape could be traced out. This is reminiscent of a continuous-wave NMR instrument – the pen traces the spectrum as the frequency is swept. Later, it was shown that this overall lineshape for two sites could be decomposed into two out-of-phase Lorentzian lines (figure 6). Further developments showed that this is always true – the lineshape is always a sum of transitions. This is a more appropriate picture for the Fourier transform generation. The transitions may be distorted in phase, amplitude, frequency and linewidth, but transitions they remain. In standard quantum mechanics, a transition has a position (frequency) and an intensity (transition probability).

The same is true for a dynamic system, except that now the frequency and transition probability are complex numbers, with real an imaginary parts. The imaginary and real part of a frequency give the position and width of the line, and the imaginary and real part of the transition probability give the phase and intensity of the line. The frequencies and transition probabilities are calculated from the eigenvalues and eigenvectors of the Liouvillian matrix, but the details need not concern us here.

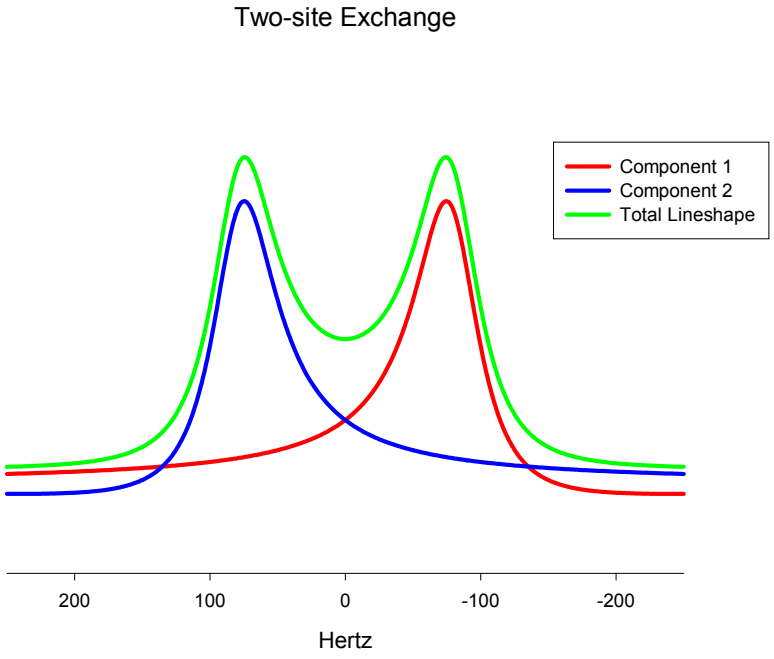

Two-site Exchange
Component 1
Component 2
Total Lineshape
200
100
0
-100
-200
Hertz

Figure 6

PREPARING FOR A SIMULATION

The NMR lineshape is determined by the parameters of each site, and the exchange rates. If the populations of the sites are not equal, then they will be temperature dependent, due to the Boltzmann distribution. Each site has chemical shifts, couplings, and linewidths determined by relaxation times. Combined with the natural linewidth is some overall linewidth due to magnetic field inhomogeneity. These parameters will depend on temperature, in general, and may be interdependent. The exchange, the natural linewidth and the shimming all contribute to line broadening, and it is usually not possible to separate their effects precisely. Before simulating chemical exchange lineshapes, some careful planning is useful.

Spectra well below the coalescence are useful, if they are accessible. The temperature dependence of chemical shifts may be obvious, as in figure 2, where the centre of the spectrum shifts to high frequency. The actual numbers can be judged from a set of spectra taken at temperatures below which the exchange effects are negligible. Trends can be seen (figure 7, for *N,N*-dimethyl-4-nitrosoaniline, as in figure 4), which can be extrapolated to higher temperatures. In slow exchange, we can separately determine chemical shifts and rates, whereas after coalescence, we can only determine their ratio. To extract a rate after coalescence, some independent estimate of the shifts is needed. For unequally-populated systems, these slow-exchange spectra will also define the temperature dependence of the equilibrium constant. In the regime past coalescence, these parameters are not very accessible, and extrapolations must be used.

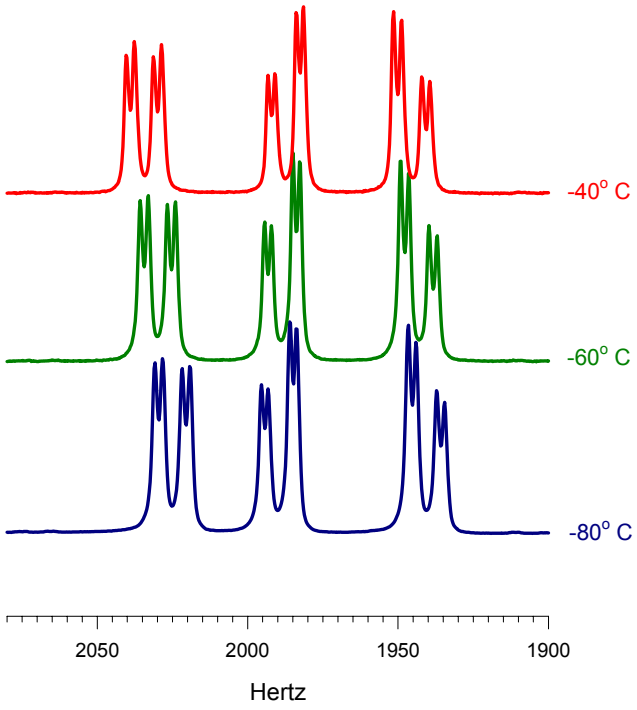


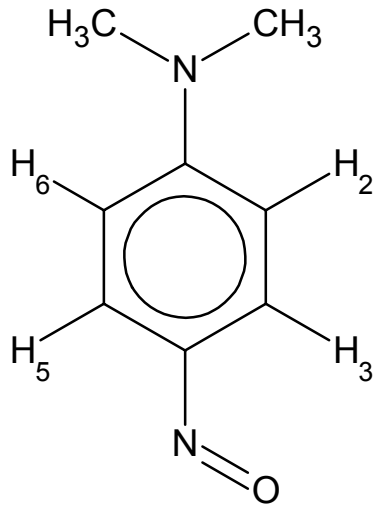
Figure 7

Natural linewidths are a constant problem. The shimming can be judged from some sharp signal (*e.g.* TMS, or a solvent peak), but care must be taken. For instance, the methyl peak in the spectrum of *N,N*-dimethyl-4-nitrosoaniline is itself temperature dependent, since it is in the fast exchange regime of its own chemical exchange process. Linewidths due to relaxation, particularly in coupled systems, are quite complex functions of T_1 and T_2. The safest approach is to stay in the range of rates where errors in the natural linewidths do not affect the lineshape significantly – *i.e.* where the rate dominates. For slow exchange, selective inversion experiments, or EXSY, give more reliable data.

Once the parameters for each site are defined, it is then a matter of guessing at a rate, and simulating the spectrum. This calculated spectrum can then be compared to the real spectrum, and adjustments made to the parameters to improve the fit. At the start, this adjustment is best made manually, but once a decent fit is achieved, a computer program can take over. It is useful to iterate on several parameters to achieve a "best" fit. In favorable cases (figures 8, 9) excellent fits should be possible. Once the rate has been determined, the process can be repeated for spectra taken at different temperatures.

The rate, as a function of temperature gives us the activation parameters for the reaction. An Eyring plot of log(rate/temperature) *vs* 1/temperature should give a straight line. The slope gives the enthalpy of activation, and the intercept at 1/temperature = 0 (a considerable extrapolation) gives the entropy. Figure 10 shows the results of the *N,N*-dimethyl-4-nitrosoaniline measurements.

N,N-dimethyl-4-nitrosoaniline



Chemical Shifts (ppm)

H_2 = 6.76

H_3 = 8.79

H_5 = 6.63

H_6 = 6.47

Couplings (Hz.)

$J_{2,3}$ = 9.1

$J_{2,6}$ = 2.5

$J_{5,6}$ = 9.5

$J_{3,5}$ = 2.1

Figure 8

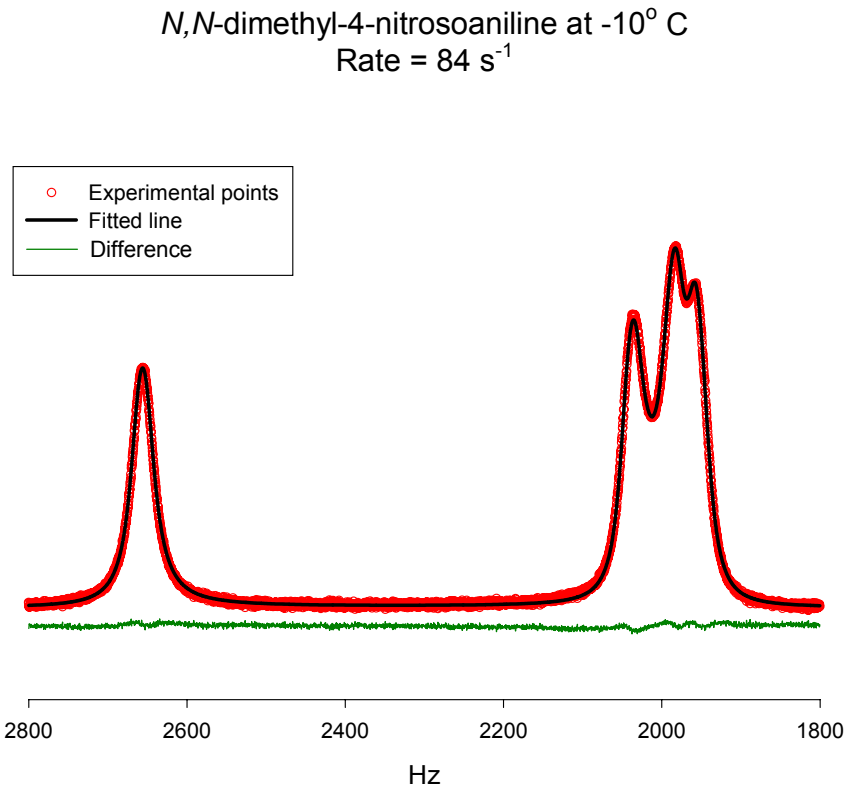

N,N-dimethyl-4-nitrosoaniline at -10° C
Rate = 84 s-1
Experimental points
Fitted line
Difference
2800
2600
2400
2200
2000
1800
Hz

Figure 9

Results of this quality are easily accessible for well-behaved systems. The limit for rate measurements is now the quality of the spectra themselves. The following table summarizes the data for this molecule, and figure 10 is the Eyring plot.

Temperature (K)	Rate (s^{-1})
243	6.4
248	12.9
253	24.5
258	47
263	84
268	155
273	258
278	430
283	716
303	4000

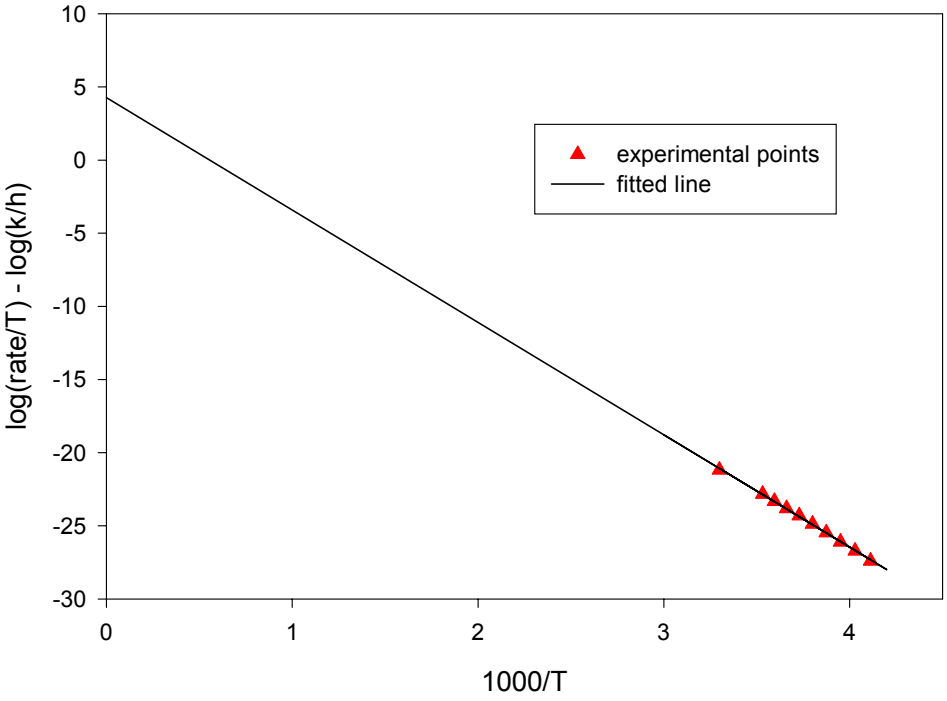


Figure 10

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