4.1: Kinetics and Mechanisms-

One of the most powerful sources of evidence for how a particular reaction proceeds comes from the study of reaction rates or reaction kinetics. In such studies, how the rate of a reaction changes[1] is measured as a function of the concentration of each reactant. One of the most common ways of measuring this change is by using a spectroscopic technique. For example, if the compound absorbs in the UV-VIS region of the spectrum, the absorbance is proportional to the concentration. Therefore, if the concentration of the substance changes, it can be measured by changes in the absorbance. The reaction is carried out several times with all but one of the reactants set as constant; then a different concentration of the remaining reactant is added and the rate of the reaction measured. This is repeated for each reactant over several concentrations. The end result of such a study is to produce what is known as the rate equation; for a generic reaction $A + B \rightarrow C + D$ the rate equation takes the form:

$$\text{Rate } = k[\text{A}]^x[\text{B}]^y \tag{4.1.1}$$

In this equation, k is the rate constant, and the exponents x and y tell us about how the concentration of each reactant influences the rate. The sum of the exponents (that is, $x + y + \dots$) is the order of the reaction. For example, if $x = 1$, then the rate is directly related to the concentration of A. If both x and $y = 1$, then the rate is directly proportional to both $[\text{A}]$ and $[\text{B}]$, and the overall reaction order is = 2. If an exponent = 0 then the rate is not dependent on that reactant concentration, and that reactant can be removed from the rate law equation (since $[n]^0 = 1$ no matter what the value of concentration of n is).

The most important idea to remember is that the rate equation **only contains the reactants that are involved in the rate-determining step** (that is, the slowest step) of the reaction. If the reaction proceeds by a number of steps, then the step with the highest activation energy will be rate-determining, and only those reactants that participate in this step will be present in the rate law.[2] Since the rate law is determined empirically, the rate law provides us with evidence about the mechanism of the reaction.

Evidence for the $\text{S}_\text{N}2$ Mechanism:

The reaction we discussed earlier in the course is known as an $\text{S}_\text{N}2$ reaction that is shorthand for *Substitution, Nucleophilic, Second order*. We proposed a mechanism for this reaction without providing any empirical evidence, but now let us use some of what you have learned to consider more carefully the evidence for this mechanism.
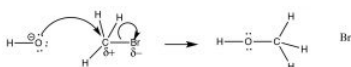

The reaction is second order:
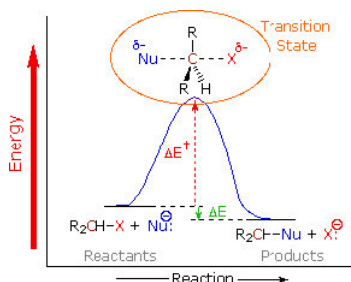
the first piece of evidence comes from the kinetic rate law. The rate of reaction depends on both the concentration of the substrate and the nucleophile: $\text{rate } = k[\text{RX}][\text{Nu}]$. This means that both must be present in the rate-determining step. The simplest explanation that is consistent with this finding is the one we have already proposed: the nucleophile attacks the electrophilic carbon *at the same time* as the leaving group leaves. That is, the reaction takes place in one continuous step. A reaction energy diagram in which we plot Energy v reaction progress looks like this ($\rightarrow$). In this reaction, there is only one energy barrier, only one maximum in the reaction pathway. The energy of this barrier is known as the activation energy ΔE_+^+. Looking at the reaction diagram, we also note that the reaction is exothermic (or exergonic if we plot Gibbs energy), since the ΔE of the overall reaction is negative). The species at the peak of the activation energy barrier is known as the *transition state*, and its structure and associated energy determines the rate of the reaction.

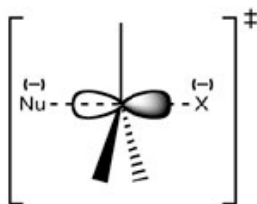### The structure of the substrate affects the rate:

Perhaps you have noticed in our earlier discussions of nucleophilic substitution that the organic substrate was always either a methyl or primary carbon attached to a good leaving group. The reason was that in the reactions we have considered, both the rate

and mechanism of reaction is highly dependent on the structure of the substrate. As the number of methyl groups attached to the primary carbon increases (from 0 for a methyl group itself to three [tertiary]) the reaction rate slows, as shown. The rate of an S_N2 reaction for a tertiary substrate is negligible.
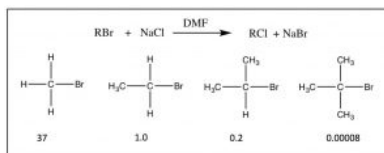
So two questions arise: first, why are these reaction rates different? and second, why is this change in reaction rates evidence for the S_N2 mechanism? Both can be answered by taking a closer look at the reaction from a molecular perspective. Remember, all of the reactants are dissolved in a solvent; thermal motion leads to their colliding with one another and with solvent molecules. For the nucleophile and the substrate to react with each other, they first have to *collide* with one another. For a reaction to occur, that collision has to transfer *enough energy* so that the complex (substrate + nucleophile) can form the transition state—moreover to form the transition-state molecule, the molecules must collide with one another in the *correct orientation*. Once formed, the transition state can decay to form the products of the reaction.
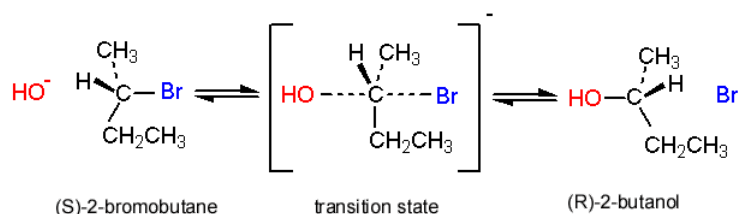
Recall that our proposed structure for the transition state for this reaction has the central carbon connected to five groups: the incoming nucleophile, the leaving group, and the three other substituents that do not change during the reaction (they are not part of the reaction). As the bond forms between the nucleophile and the substrate carbon, and the bond breaks between the carbon and leaving group, the carbon changes its hybridization state. What does that mean? In the substrate molecule, the reacting carbon is attached to surrounding groups ($H-$ or CH_3-)) with bonds formed from sp^3 orbitals. In the transition state, this carbon is still attached to those groups that will remain in the product molecule, but now with bonds formed from sp^2 orbitals. Additionally, it is still attached to both the leaving group and the incoming nucleophile using a p orbital to form these partial bonds. You can think of this process as electron density being funneled from the nucleophile through the carbon and out the other side to the leaving group. However, for this to occur the nucleophile can only begin to bond when it approaches from the back of the bond to the leaving group →.

At this point, you might well find yourself asking: what does all this have to do with the structure of the substrate? For a reaction to occur, the only productive collisions are those where the nucleophile begins to form a bond with the back part of the sp^3 hybrid orbital; but the structure of the substrate influences the probability of such an event. In the tertiary substrates (for example $(CH_3)_3CBr$) the approach to the substrate is hindered by the bulky alkyl groups such that the probability of the nucleophile interacting with the reactive center is low. This phenomenon is called *steric hindrance* and provides an explanation for the order of reaction of S_N2 reactions.

Accessibility of electrophilic carbon atom to nucleophilic attack

Reaction rate in S$_N$2 reactions
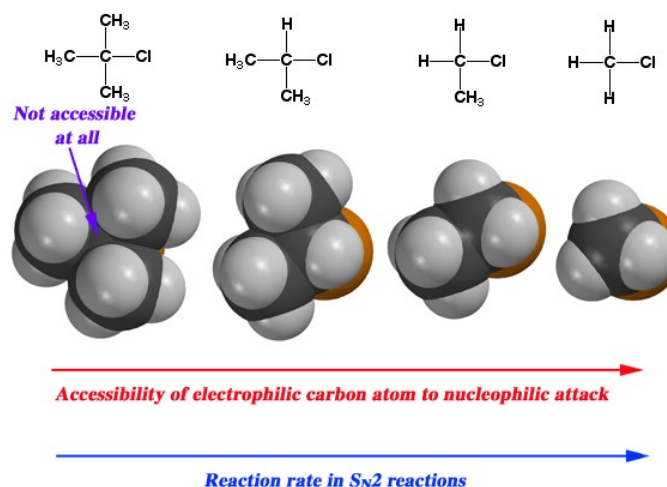
S$_N$2 reactions at a chiral center:

(S)-2-bromobutane   transition state   (R)-2-butanol

Another piece of evidence for the S$_N$2 mechanism is what happens when an S$_N$2 reaction takes place at a chiral center (within a molecule). It turns out that the configuration at that center is changed; the carbon inverts (like an umbrella blowing inside out in the wind) so that an S enantiomer is converted to an R enantiomer. In fact, it is possible to follow the progress of an S$_N$2 reaction involving a chiral center using a polarimeter (the instrument used to measure optical activity); as the reaction proceeds to completion, the optical rotation of the solution changes over time. For each particular substrate, the direction and magnitude of the rotation for the product will be different. This phenomenon is called the *Walden inversion* and provides another piece of evidence to support the proposed reaction mechanism.

The role of solvent in an S$_N$2 reaction:

Acetone   DMF   DMSO
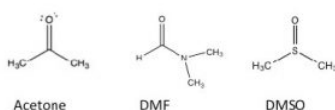
S$_N$2 reactions are generally carried out in a solvent (why is that?). Empirical studies reveal that such reactions proceed more rapidly when carried out in what is known as a polar aprotic solvent. So what is a polar aprotic solvent? The term means that the solvent is polar but without acidic protons. Examples of polar aprotic solvents are acetone, dimethyl formamide (DMF), and dimethylsulfoxide (DMSO): each is polar, but lacks a potentially acidic proton such as the H that is bonded to the O in ethanol CH_3CH_2OH or in water $H-O-H$. Water (and methanol and ethanol) is a polar protic solvent. In a polar aprotic solvent, the negative end of the $C=O$ or $S=O$ dipole is localized to the O, while the positive end is diffuse and delocalized. For example, in acetone, the oxygen has a $\delta-$ charge on the oxygen while the positive charge of the dipole is delocalized over both the C and the methyl groups as shown in the electrostatic potential map ($\rightarrow$). In practice, polar aprotic solvents can solvate cations well through interactions with the localized negative end of the dipole, but they cannot solvate anions very well.
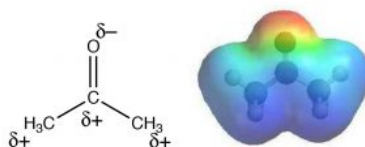
Recall that solvation is an interaction that lowers the energy of the system, making it more stable (less reactive). Therefore, a solvent that leaves the nucleophile (the anion) unsolvated will make it more reactive. In contrast, a polar protic solvent (such as water or ethanol) can solvate the nucleophile, through interactions with the positive end of a dipole that is localized on an acidic H, stabilizing the nucleophile and making it less reactive. In summary, S_N2 reactions occur in one step with inversion at a chiral center. Such reactions are generally faster for unhindered substrates and are accelerated when carried out in polar aprotic solvents.