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Three Dimensional Reaction Coordinates of Nucleophilic Substitution Reactions

Nucleophilic substitution reactions typically occur between an alkyl halide, RX , and a nucleophile, $Nu^{[1]}$. There are three possible reaction pathways for the reaction to occur. An alkyl halide can react with a nucleophile through an S_N1 , S_N2 , or addition-elimination mechanism^[2]. However, the S_N1 and S_N2 nucleophilic substitution reactions are far more common than the addition-elimination mechanism for nucleophilic substitution reactions. The reaction pathway through which a nucleophilic substitution occurs is dependent on the solvent in which the reaction takes place, the nucleophile, the class of the alkyl halide, and the stability of the possible intermediates and/or transition states.^[1,3] This discussion will focus on how the stability of intermediates and transition states can be used to predict the mechanism through which a nucleophilic substitution reaction will proceed.

The term " S_N2 " is an abbreviation for "substitution, nucleophilic, bimolecular." In this case, "bimolecular" means that the rate of the reaction is dependent on the concentration of two species. Since the rate of reaction depends on both the concentration of alkyl halide and nucleophile, S_N2 reactions experience second-order kinetics. The defining characteristic of a pure S_N2 reaction is that the reaction occurs in one step. The $R-X$ bond breaks at exactly the same time that the $R-Nu$ bond forms^[1].

The point during the reaction at which R is bonded to Nu and X in the $X-R-Nu$ complex is known as the transition state. Note that the transition state is not considered an intermediate^[1]. The transition state of a given reaction has a lifetime that is less than a molecular vibration, which is on the order of 10^{-13} seconds^[4]. The ability of the carbon atom in an alkyl halide to be bonded to X and Nu simultaneously depends on the degree of the carbon atom. S_N2 reactions are slow with secondary alkyl halides, and even slower with tertiary alkyl halides. The addition of an

extra R group in a tertiary alkyl halide creates steric hinderance in the molecule. This steric hinderance blocks the nucleophile from being able to attack the molecule from behind, which is essential in S_N2 reactions^[1].

Similar to the S_N2 reaction, “ S_N1 ” is an abbreviation for “substitution, nucleophilic, unimolecular.” When discussing rates of reactions, unimolecular refers to a reaction in which the rate of reaction depends only the concentration of one reactant. In S_N1 reactions, the rate of reaction is only dependent on the concentration of alkyl halide. Thus, S_N1 reactions follow first order kinetics^[1].

The defining characteristic of an S_N1 reaction is the fact that the reaction occurs in two steps. The first step of an S_N1 reaction is the formation of the carbocation intermediate, which is generated when the R-X bond dissociates into R^+ and X^- . Note that R-X must be a secondary or tertiary alkyl halide. The dissociation of R-X to R^+ and X^- is also the rate determining step. The second step of an S_N1 reaction is the addition of Nu to R^+ to give R-Nu. Since Nu can added to either side of the carbocation intermediate, a racemic mixture of products is produced when chiral tertiary alkyl halides are used^[1].

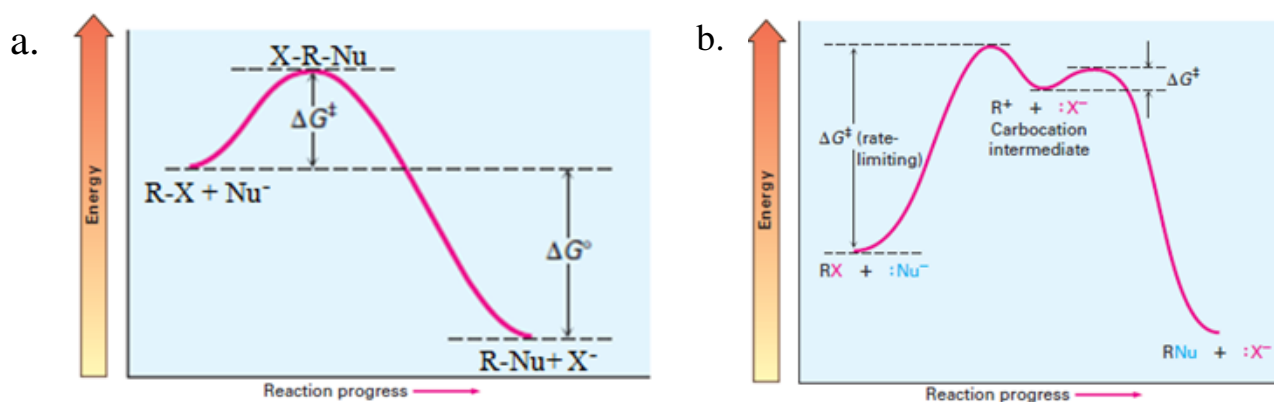


Figure 1. (a) Two dimensional energy diagram of an S_N2 reaction where the maximum energy point is the transition state. (b) Two dimensional energy diagram of an S_N1 reaction where the valley between the two energy maxima represents the carbocation intermediate. Both (a) and (b) have the reactants on the left side and the products on the right side^[1].

The third possible reaction pathway for nucleophilic substitution is the addition-elimination mechanism. This reaction takes place in two steps. The first step is the addition of Nu to R-X in order to give the carbanion intermediate X-R⁻-Nu. Then, the leaving group, X⁻, is eliminated^[2]. Note that the carbanion intermediate X-R⁻-Nu is different from the X-R-Nu transition state in an S_N2 reaction because it lasts longer than a molecular vibration. The addition-elimination mechanism is not seen very often, if ever, because the carbanion intermediate is highly unstable. However, this mechanism is a useful tool in predicting the character of the transition state of an S_N2 reaction and will be presented later in this discussion^[2].

As mentioned previously, the solvent and nucleophile can play a role in determining the mechanism of a nucleophilic substitution reaction or if a nucleophilic substitution will even occur. The best solvent for an S_N2 reaction is a polar aprotic solvent. Polar aprotic solvents decrease ΔG^\ddagger in Figure 1. (a) by raising the ground-state energy of the nucleophile. The best solvent for an S_N1 reaction is a polar protic solvent. Polar protic solvents can help stabilize the carbocation intermediate in Figure 1. (b). The best nucleophiles for the S_N2 reaction are both basic and negatively charged (OH⁻). However, the best nucleophiles for the S_N1 reaction are weakly basic (H₂O). If the nucleophile is relatively basic when reacting with a tertiary alkyl halide, it is likely that an elimination reaction will occur^[1].

The solvent, nucleophile, and degree of the carbon atom in RX can be used to give a rough prediction of the mechanism through which a nucleophilic substitution reaction proceeds. However, these variables cannot always accurately predict the mechanism through which a nucleophilic substitution reaction proceeds. There is another method that can be used to predict the mechanism for a nucleophilic substitution reaction more quantitatively. This method plots the potential energies at each possible “stage” during a nucleophilic substitution on the z-axis versus

R-Nu bond forming on the x-axis and R-X bond cleavage on the y-axis^[5]. The resulting plot is known as a “Three Dimensional Reaction Coordinate.” These plots are often depicted in two dimensional plots referred to as a “More O’Ferrall diagrams^[2,5,6]” or “More O’Ferrall-Jencks plots.^[7,8]” after the scientists who developed the concept. Examples of a three dimensional reaction coordinate diagram and a More O’Ferrall-Jencks plot are shown below in Figure 2.

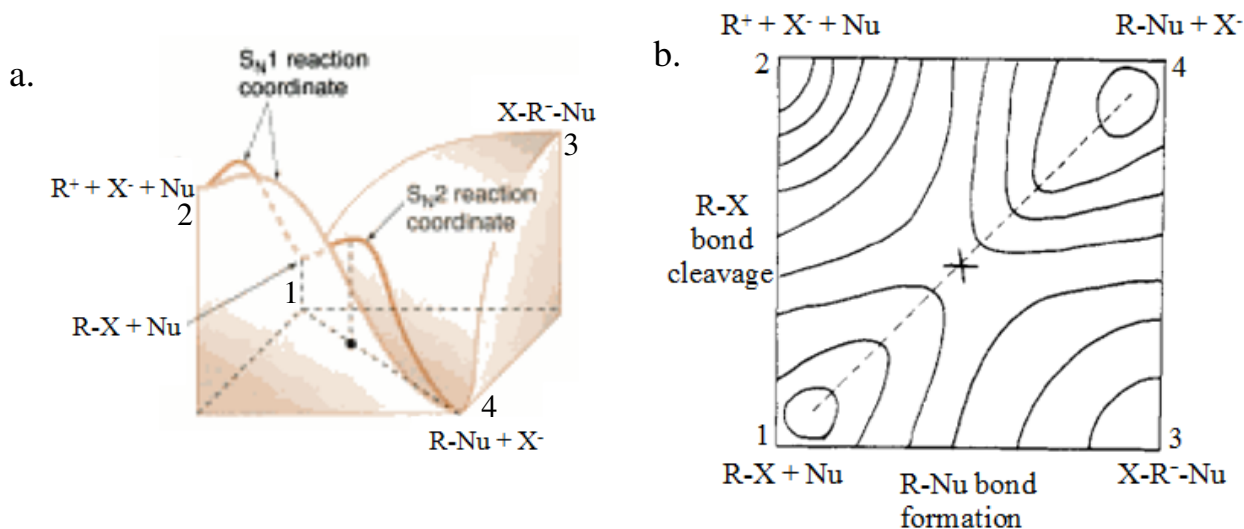


Figure 2. (a) General three dimensional reaction coordinate diagram where R= methyl and with S_N2 and S_N1 reaction pathways outlined^[8]. (b) Generic More O’Ferrall-Jencks plot of a nucleophilic substitution reaction with contour lines^[5].

In both Figure 2 (a) and Figure 2 (b), the reactants (R-X and Nu) are at point 1 and the products (R-Nu and X⁻) are at point 4. The x-axis is R-Nu bond formation and the y-axis is R-X bond cleavage^[5]. The z-axis is potential energy^[6] or free energy^[8]. Notice that point 1 is in the top left corner in Figure 2 (a) and in the bottom left corner in Figure 2 (b). The placement of point 1 is ambiguous as long as the adjacent points are 2 and 3, and the point diagonal to point 1 is point 4.

The potential energy surfaces of three dimensional reaction coordinates and More O'Ferrall-Jencks plots can be approximated using the quadratic equation: $G_{\text{surface}} = ax^2 + by^2 + cxy + dx + ey + f$. The terms "a" and "b" dictate the curvature of the saddle point that is parallel to the x and y axes in Figure 2 (a). "C" is known as the curvature parameter. The terms "d" and "e" represent energies at points 2, 3, and 4 in Figure 2 (a). The term "f" in the equation is a constant. The terms "a, b, and c" are directly related to Hammond and Cordes-Thorton coefficients^[7]. These coefficients will not be discussed further because the understanding of the mathematics of three dimensional reaction coordinates is not terribly important when applying the concept to nucleophilic substitution reactions.

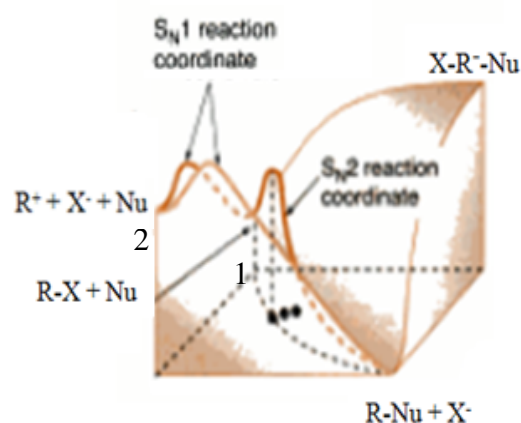
As suggested by Figure 2 (a), the reaction pathway 1→2→4 follows an S_N1 nucleophilic substitution mechanism. In the step 1→2, the R-X bond is cleaved and the carbocation, R⁺, is generated^[8]. The free energy at point 2 is a local minimum. This local minimum is referred to as a potential energy well^[4]. In the step 2→4, the nucleophile, Nu, is added to the carbocation, R⁺, and the final product R-Nu is formed^[8].

Another possible reaction pathway that could occur is the 1→3→4 reaction pathway. This reaction pathway follows the nucleophilic substitution addition-elimination mechanism. In the step 1→3, Nu is added to R-X and the carbanion X-R⁻-Nu is formed. This point is most likely has the highest potential energy because this carbanion is very unstable. In the following step, 3→4, the leaving group X⁻ is eliminated, leaving the final product, R-Nu, at point 4^[2].

The third possible reaction pathway which the reaction could proceed is through the 1→4 reaction pathway. The 1→4 reaction pathway follows the pure S_N2 substitution mechanism. The maximum energy point along the S_N2 reaction pathway represents the transition state, X-R-Nu.

Since $1 \rightarrow 4$ is a pure S_N2 mechanism, Nu adds to R-X at the exact same time as X leaves R-X. The resulting product is Nu-R^[8].

Figures 2 (a) and (b) propose the three possible reaction pathways that a nucleophilic substitution reaction could undergo. These reaction pathways are all considered to be competing mechanisms. Since the energy needed to undergo an S_N1 or addition-elimination mechanism is much greater than the S_N2 , the reaction would proceed through an S_N2 mechanism. The reaction will follow the lowest energy mechanism. However, it is possible for two reaction pathways to have similar potential energy maxima. Figure 3 shows the competing nucleophilic substitution reaction pathways for a secondary alkyl halide. The transition state of the S_N2 reaction pathway and the carbocation intermediate of the S_N1 reaction pathway are close in energy. Thus, it is possible that the reaction could undergo an S_N1 or S_N2 mechanism^[8].



Although the pure S_N2 mechanism is commonly taught in organic chemistry textbooks^[1], it is not uncommon for the transition state of an S_N2 reaction to have either some carbocation or carbanion character^[2,4,6-8]. The character of the transition state can be modified by changing X, R, or Nu^[2]. For example, increasing the size or bulkiness of R will cause the transition state to become more like the carbocation at point 2 in Figures 2 and 3. Also, it can be seen in Figure 3 that the S_N2 reaction coordinate is shifted towards carbocation intermediate^[8].

The transition state character can also be affected by the addition of substituent groups throughout the molecule. Figure 4. shown below represents a methyl benzyl derivative where X is a halide and Z is a substituent group. This molecule can undergo an S_N2 reaction with Nu. Assume that if Z=H, this molecule will undergo a pure S_N2 reaction and has a transition state that lies directly on the diagonal from 1→4 in Figure 2 (b). However, if Z is an electron donating group such as $-OCH_3$, the transition state will be shifted off the diagonal towards the carbocation intermediate at point 2 in Figure 5. This occurs because electron donating groups stabilize the possible carbocation intermediate if the reaction were to proceed through an S_N1 mechanism and destabilize the possible carbanion intermediate if the reaction were to proceed through an addition-elimination mechanism. Similarly, if Z is an electron withdrawing group such as $-NO_2$, the transition state will be shifted off the diagonal towards the carbanion intermediate at point 3 in Figure 5. This occurs because electron withdrawing groups stabilize the possible carbanion intermediate if the reaction were to proceed through an addition-elimination mechanism and destabilize the possible carbocation intermediate if the reaction were to proceed through an S_N1 mechanism^[2].

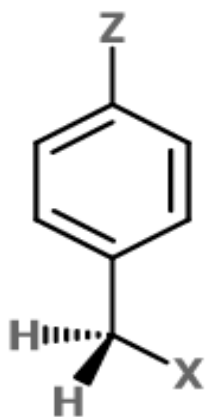


Figure 4. Methyl benzyl derivative

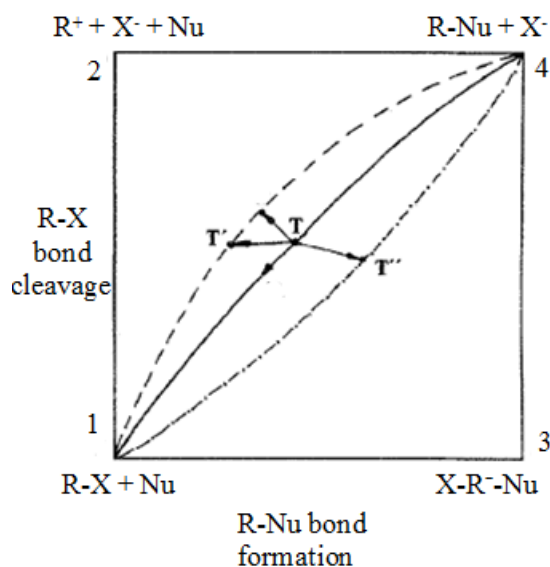


Figure 5. More O'Ferrall-Jencks plot of without contour lines that shows varying S_N2 transition state character. T' has more carbocation character and T'' has more carbanion character^[2].

This discussion presented two diagrams that can be used to help predict the mechanism through which a nucleophilic substitution reaction will proceed. Both diagrams plot the R-X bond cleavage on the y-axis and R-Nu bond formation on the x-axis. The z-axis of the three dimensional reaction coordinate diagrams plots the free energy or potential energy. This energy is represented in More O'Ferrall-Jencks plots using contour lines. Both diagrams compare the stability of the transition state and intermediates in order to predict the mechanism through which a nucleophilic substitution will proceed. They can also be used to predict how the addition of various substituents throughout the molecule will change the transition state character in the S_N2 reaction pathway. In conclusion, three dimensional reaction coordinate diagrams and More O'Ferrall-Jencks plots are useful tools in predicting which possible mechanism a nucleophilic substitution reaction will proceed.

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