

Bent Transition States

Effects of Angular Deformation on the Energetics of the S_N2 ReactionVincent de Paul N. Nziko^[a] and Steve Scheiner^{*[a]}

Abstract: Quantum calculations are applied to a number of model S_N2 reactions. The halides F^- , Cl^- , and Br^- were allowed to attack the central C atom of a set of CH_2RI molecules, with $R = H, CH_3, CH=CH_2, C\equiv CH$, and $C\equiv N$. For each system the $X\cdots C\cdots I$ angle was distorted in set increments from the optimized value and the activation energy computed for each an-

gle. The energy of the transition state rose in conjunction with this deformation. However, the distortion energy of the initial $X^-\cdots CH_2RI$ reaction complex was similar in magnitude. As a result, the activation energy of the reaction was quite insensitive to angular deformation.

Introduction

The bimolecular nucleophilic substitution reaction (S_N2) is one of the most useful and fundamental reactions in organic synthesis.^[1–7] The Williamson ether synthesis in which an alkoxide reacts with an alkyl halide is a typical S_N2 reaction. This reaction also plays a key role in biochemical reactions like methyl group transfer in which *S*-adenosylmethionine (SAM) serves as co-substrate.^[8–11]

Due to the versatility of this reaction, it has been intensively scrutinized in a number of experimental and theoretical studies over the years. It has been shown that S_N2 reactions can result either in inversion and/or retention of configuration at the central atom.^[12] The former proceeds through a backside attack and the latter through the front side attack on the central atom. Generally, the backside mechanism proceeds through a lower transition state energy and it is therefore kinetically dominant and more efficient. Efforts have been made to understand the factors that affect this reaction,^[13–17] including solvent effects and nucleophile and leaving group electronegativity.^[18–22] For example, Bento and Bickelhaupt^[23,24] used relativistic density functional theory to ascertain that backside S_N2 barriers increase as the halide nucleophile becomes less electronegative ($F^- < Cl^- < Br^- < I^-$) and obeys the opposite trend for the leaving group ($CH_3F > CH_3Cl > CH_3Br > CH_3I$).

With respect to the common backside mechanism, it is believed that the system strives toward linearity at the transition state, where the central C atom CA lies along the axis between the leaving group (LG) and the incoming nucleophile (Nu), viz.

$\theta(Nu^-\cdots CA\cdots LG)$ tends toward 180° . Unlike the situation where this reaction takes place between initially separate reactants in solution, when the various species are free to adopt their most stable orientations relative to one another, there are certain restrictions associated with a biological setting. In the context of an enzyme, the overall three-dimensional structure of the protein is the result of a host of interactions between various parts of the molecule. For example, H-bonds, which prefer a linear geometry, are seldom free to adopt this arrangement within a protein, but instead must make compromises and adjust their structure accordingly. The same sorts of restrictions would be expected between the nucleophile and substrate with respect to S_N2 reactions, which would prevent the linear approach that is intrinsically preferred. The methyl transfer reaction that takes place in glycine *N*-methyltransferase serves as one example. Soriano et al. showed, using QM/MM calculations, that the transition state angle for the transfer of the methyl group from SAM to glycine in both neutral and basic solutions are 172.4° and 170.9° , which deviate from linearity by about 10° .^[25] In this particular example, there would appear to be an H-bond between Arg175 and Gly137, which keeps the nucleophile from its preferred trajectory in attacking SAM at 180° , but other systems might certainly have other factors that cause angular deformations.

It is thus important to understand how angular distortions from linearity might affect the energetics and thus the rates of the S_N2 reaction. How, and by how much, is the activation energy of this reaction affected by angular deformation? How is the sensitivity of the energy barrier to deformation in turn affected by the nature of the attacking nucleophile, or by the groups attached to the central C atom? This work attempts to provide answers to these questions through a set of carefully designed quantum calculations. A range of nucleophiles are considered, in conjunction with a variety of different chemical groups attached to the central C. The range of properties con-

[a] Department of Chemistry and Biochemistry, Utah State University
Logan, UT 84322-0300, USA
E-mail: steve.scheiner@usu.edu
<https://chem.usu.edu/htm/steve-scheiner/>

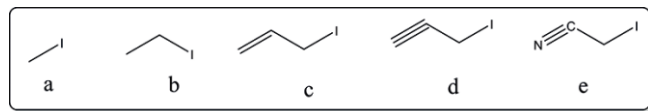
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sidered in the set of systems examined is chosen so as to be broad enough to cover a wide swath of chemistry and biochemistry.

Theoretical Methods

Calculations made use of the Gaussian 09 package of codes.^[26] Geometries were optimized at the ab initio MP2 level using the aug-cc-pVDZ basis set, which have together been shown to be of high accuracy when applied to molecular systems of this sort.^[27–29] Each system was composed of a tetravalent carbon (CA), bound to a leaving group (LG). A nucleophile (Nu) was allowed to approach CA from its backside relative to LG. An S_N2 reaction profile was traced out by reducing $R(\text{Nu}\cdots\text{CA})$ in small decrements. For each such fixed distance, the geometry of the entire system was fully optimized. The peak of this profile was deemed to be the transition state. Angular distortions were introduced by imposing a fixed angle $\theta(\text{Nu}\cdots\text{CA}\cdots\text{LG})$ upon the system. The reaction profile was traced out as before, with the addition of the restriction to this particular angle θ . Its peak was deemed to be the transition state for this angle θ .

Systems chosen for study are presented in Scheme 1. The leaving group (LG) was chosen to be I. The central C (CA) is bound to two H atoms, plus one additional group. This group varies from H, to methyl, vinyl, ethynyl, and cyano. In other words, the pendant group may contain single, double, or triple bonds, as well as a heteroatom. The approaching nucleophile took the form of one of the halides: F^- , Cl^- or Br^- .



Scheme 1. Molecules considered for the S_N2 reaction involving the replacement of I by a nucleophile.

Results

The transition states obtained for the case where F^- serves as the attacking nucleophile are exhibited in Figure 1 for each of the various substituents. The fluoride locates itself nearly opposite the I leaving group. The $\theta(\text{F}\cdots\text{C}\cdots\text{I})$ angle is 180° for the H substituent but deviates from linearity by as much as 14° in the case of the methyl group. For each system, it is this optimized angle, which is taken as the undistorted geometry. The structures for the other systems examined with Cl^- and Br^- nucleophiles were quite similar. The undistorted angles are displayed in Table 1 for all systems. Their deviation from 180° tends to grow along with the size of the approaching halide nucleophile.

In order to measure the sensitivity of the reaction to angular distortion, each complex was distorted from its fully optimized geometry in 2° increments. As indicated above, the reaction profile was mapped out by holding fixed the angle θ and optimizing the geometry of each structure for each $R(\text{X}\cdots\text{CA})$. The salient energetic quantities in each reaction profile are indicated in Scheme 2. Beginning with the fully separated nucleophile

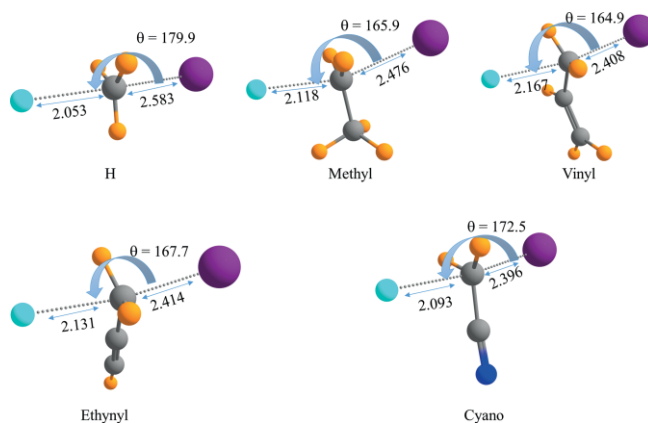
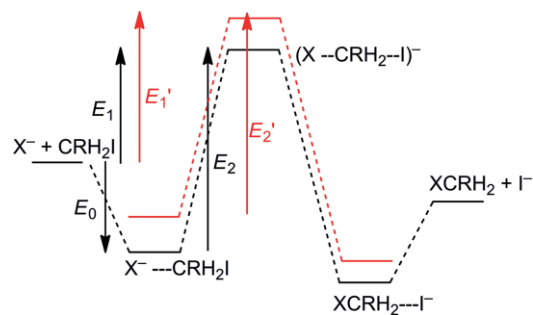


Figure 1. Transition state geometries of the S_N2 reactions with F^- as nucleophile. Interatomic distances in Å.

Table 1. $\theta(\text{F}\cdots\text{C}\cdots\text{I})$ angle in the transition state for $(\text{X}\cdots\text{CH}_2\text{R}\cdots\text{I})^-$.

R	F^-	Cl^-	Br^-
H	179.9	180.0	180.0
CH_3	165.9	163.6	163.1
$\text{CH}=\text{CH}_2$	169.4	166.5	166.0
$\text{C}\equiv\text{CH}$	167.7	166.2	165.7
$\text{C}\equiv\text{N}$	172.5	169.5	168.9

and the CRH_2I molecule, these two species first come together to form a reaction complex $\text{X}^-\cdots\text{CRH}_2\text{I}$, with a binding energy of E_0 . From that point, the system requires an energy E_2 to attain the transition state $(\text{X}\cdots\text{CRH}_2\cdots\text{I})^-$. E_1 refers to the energy of the transition state relative to the separated reactants.



Scheme 2. Energy profile of the S_N2 reaction. Red energies, and primed E quantities refer to angular distortions.

The red energy levels in Scheme 2 refer to the same structures, but with a deformation imposed upon their angular preference. As such, these red levels are placed higher in energy than are the undistorted black energy levels. Like their unprimed counterparts, E_2' and E_1' again correspond to the energy of the (distorted) transition state, relative to the reaction complex, and unassociated reactants, respectively.

The calculated quantities for the activation barriers are reported in Table 2, where $\Delta\theta$ refers in each case to the distortion of this angle from linearity. Focusing first on the values of E_1 , there is a fairly sharp rise in this barrier, relative to the separated

reactants, as angular distortions are imposed upon each system. The dependence of E_1 upon angular distortion is displayed in Figure 2 where the curves resemble parabolas.

Table 2. Calculated energy barriers to the S_N2 reaction [kcal/mol].

R	$\Delta\theta$	F ⁻		Cl ⁻		Br ⁻	
		E_1	E_2	E_1	E_2	E_1	E_2
H	0	0.10	16.17	6.64	10.87	6.79	9.86
	10	0.63	15.71	7.56	10.66	7.71	9.70
	20	2.73	15.55	9.79	10.41	9.90	9.40
	30	5.93	16.16	12.32	10.22	12.57	9.18
CH ₃	0	5.23	18.85	11.83	11.65	12.76	10.36
	10	3.22	18.84	10.27	12.42	11.12	11.37
	20	3.58	18.58	10.16	12.43	11.28	11.20
	30	5.38	18.44	11.46	12.21	12.55	10.96
CH=CH ₂	0	4.97	21.65	8.94	12.95	9.03	11.46
	10	5.21	21.30	8.40	13.86	8.21	12.23
	20	5.63	21.14	9.44	14.03	9.18	12.6
	30	7.53	21.12	12.24	13.76	10.62	12.34
C≡CH	0	0.99	17.24	4.63	9.43	6.78	8.39
	10	0.33	17.57	3.75	10.69	6.41	9.61
	20	1.04	17.55	4.25	11.35	7.51	10.24
	30	2.72	17.63	5.82	11.66	9.31	10.44
C≡N	0	0.81	26.34	5.02	16.21	6.03	14.58
	10	0.21	25.85	4.47	17.05	5.95	15.40
	20	1.25	25.31	5.44	17.4	7.41	15.76
	30	3.37	25.24	7.73	17.56	9.57	15.91

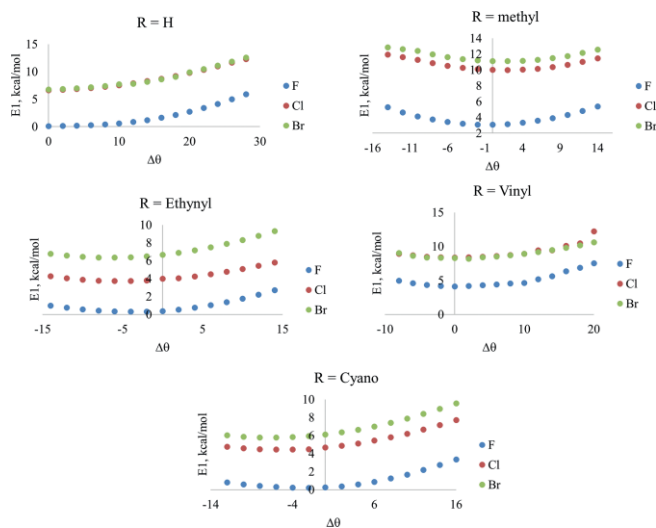


Figure 2. Dependence of activation energy E_1 to angular distortion. $\Delta\theta$ refers to distortion from the optimized angle, see Table 1.

And indeed, these data may be fit well by a quadratic function of the form in Equation (1):

$$E_1 = \frac{1}{2}k(\Delta\theta)^2 \quad (1)$$

The values of the distortion constant k are reported in Table 3, along with the correlation coefficient for its fitting. In terms of scale, a value of $k = 8 \text{ cal mol}^{-1}\text{deg}^{-2}$ in Table 3, a typical value, would correspond to a rise in E_1 by 3.6 kcal/mol

caused by a distortion $\Delta\theta$ of 30°. Inspection of the $R = \text{H}$ curves in Figure 2 indicates that the bromide and chloride curves are less steep than that of the fluoride. This trend is confirmed by the larger values of k for F⁻ than those for the other two halides in Table 3. With regard to R, the methyl group exhibits the highest sensitivity to angular distortion, followed by vinyl and then H. The triple-bonded species are least sensitive, with the exception of when they are coupled with bromide.

Table 3. Distortion constant k [$\text{cal mol}^{-1}\text{deg}^{-2}$] fit to Equation (1).

R	F ⁻		Cl ⁻		Br ⁻	
	k	R^2 [a]	k	R^2	k	R^2
H	9.2	1.0	7.4	1.0	6.1	1.0
CH ₃	11.5	1.0	8.8	0.99	8.3	0.97
CH=CH ₂	9.8	0.99	9.3	0.94	6.5	0.99
C≡CH	7.4	1.0	5.7	1.0	6.9	1.0
C≡N	8.7	1.0	7.0	1.0	7.4	1.0

[a] Correlation coefficient.

An alternative, and more common, means of assessing the barrier for a reaction such as this begins not with the separated reactants, but rather with the reaction complex. This barrier corresponds to the E_2 quantity in Scheme 2. Inspection of Table 2 suggests that this barrier is rather insensitive to angular distortions, typically remaining constant to within less than 1 kcal/mol, even after the introduction of as much as a 30° deformation. Taking the reaction of Cl⁻ with CH₃I as an example, E_2 diminishes from 10.87 kcal/mol in its undistorted geometry to 10.22 when the Cl...C...I angle is 30° removed from linearity.

It is perhaps puzzling at first sight to note such discrepant behavior between the two measures of activation energy. This difference can be explained by a glance at Scheme 2, wherein the black energies refer to an undistorted geometry, while distortions are indicated by the red levels and the primed quantities. Considering first the X...CRH₂ reaction complex, it of course becomes less stable upon introducing an angular distortion. But the same is true of the (X...CRH₂...I)⁻ transition state. If the distortion energies of the two geometries are similar, then only small changes can be anticipated in their energy difference E_2 . E_1 , on the other hand, takes as its starting point the fully separated reactants, with no possibility of distortion energy. The destabilization of the transition state thus cannot be compensated by any such rise in energy of the reactants, so the deformation will universally raise E_1 .

Summary and Discussion

The calculations have indicated that a distortion of the preferred angle of attack of the nucleophile toward the central C atom in an S_N2 reaction induces a strain energy into the system. Angular deformations raise the transition state energy, proportional to $(\Delta\theta)^2$. Depending upon the particular system, a 30° distortion increments this energy by between 2.5 and 5.2 kcal/mol. With respect to the variations on the theme of halide attacking the CH₂RI molecule, the sensitivity to angular deformation appears to be a function of both the nature of the halide

and the R group. For example, the methyl group is most sensitive to the angle for F^- and Br^- nucleophiles, but the vinyl group takes this distinction for Cl^- . There is a general trend of $F^- > Cl^- > Br^-$ but $Br^- > Cl^-$ for both the triple bonded $C\equiv CH$ and $C\equiv N$ groups. This rise in energy of the transition state increases the barrier of the reaction when the fully separated reactants are taken as the initial point of the reaction.

On the other hand, the idea of taking the infinitely separated reactants as a starting point for the reaction is not relevant to a situation as might occur within an enzyme. In such a case, the nucleophile is already engaged with the central C atom to a certain extent even before the reaction begins. It therefore is more sensible to begin the process with the nucleophile already in striking distance of the central C atom, with the leaving group still covalently bonded to it. And indeed, this sort of structure serves as the traditional starting point for a host of studies of the S_N2 reaction,^[30–35] even in the gas phase. In this context, the imposition of an angular deformation has a minor, perhaps even negligible, effect on the activation energy. The reason for this lack of sensitivity to angular strain arises from the fact that the initial structure for the reaction, analogous to a reaction complex, suffers from strain energy, just as does the transition state. And perhaps more importantly, this strain energy is roughly equal in the two geometries. As a result of both the starting point and transition state rising in energy by similar amounts, the activation energy is barely affected by the angular deformation.

The effects of angular distortion have been extensively studied for another reaction, that involving the transfer of a proton along a pre-existing H-bond.^[36–41] For this reaction, bends of the H-bond typically lead to increases in the transfer barrier, and quite sizable ones at that. These barrier increments were observed not only in E_1 , but also in E_2 , with reference to Scheme 2. That is, the barrier to proton transfer rises as a result of an angular deformation, whether one considers the barrier with reference to the separated reactants or to the pre-formed H-bonded reaction complex. In other words, the angular deformation yields a much more substantial destabilization of the transition state than of the reaction complex. This result is different from the S_N2 reaction examined here, where the reaction barrier E_2 is barely affected by angular distortion.

On a final note concerning the level of theory, a very recent set of calculations^[42] observed that MP2 energy barriers for the S_N2 reaction of the attack of F^- on the CH_3I molecule were quite similar to those computed using the much more accurate CCSD(T). This result adds to our confidence in the calculations described above.

Conclusions

The calculations present evidence that the energy barrier for S_N2 substitution is barely affected by angular distortions that might be imposed by external constraints. While the transition state suffers a destabilization from this distortion, a similar rise in energy occurs within the context of the reaction complex. The net effect is only a small change in the reaction barrier.

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