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# Origin of the Reactivity of Allyl Chloride and $\alpha$-Chloroacetaldehyde in $S_N2$ Nucleophilic Substitution Reactions: A Theoretical Comparison

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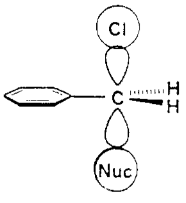
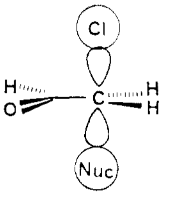
A comparison of the molecular orbitals of the transition state for the $S_N2$ nucleophilic substitution of chloride ion on allyl chloride and $\alpha$-chloroacetaldehyde was made by employing ab initio calculations. These data suggest that the enhanced rate of nucleophilic substitution for both reactions is the result of a low lying "allylic" bonding interaction present in the transition state. The origin of this relatively low lying molecular orbital is traced back to a three molecular orbital four-electron interaction between the nucelophile and the $\sigma$–$\pi$ conjugated bonding and antibonding molecular orbitals comprising the $\sigma_{CCl}$ and $\sigma^*_{CCl}$ bonds of the substrate.

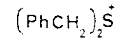
The relationship between structure and reactivity has intrigued organic chemists for many years. One of the earliest examples is the enhanced rate of bimolecular nucleophilic substitution at a saturated carbon adjacent to a multiple bond.[2] This reactivity has been ascribed to the ability of the multiple bond to delocalize the developing negative charge at the reaction site.[3] More recently, Dewar[4] has indicated that in benzylic substrates a $\pi$-bond overlap stabilizes the transition state (**1a**) resulting in the increased rate of nucleophilic substitution. The importance of this stabilization was pointed out by King[5] in model studies where $S_N2$ attack at the benzylic carbon occurred 8000 times faster in **2a** than in the cyclic analogue **2b**. In the latter case, the C–S $\sigma$-bond undergoing displacement is constrained to lie in the plane of the aromatic ring and cannot engage in $\sigma$–$\pi$ conjugation as depicted in transition state **1a**. This atypical "benzylic reactivity" is also observed in $\alpha$-halo nitriles and amides and is further enhanced in $\alpha$-carbonyl substrates.[6] On the basis of theoretical studies on $\alpha$-chloro carbonyls, it has been suggested[7a] that the enhanced rate was the result of an "allylic" interaction of the periplanar Cl---C---Nuc moiety with the polarizable carbonyl functionality as in **1b**. Despite the similarity of the $S_N2$ reactions involving allylic (benzylic)[7b] and $\alpha$-halo carbonyl substrates[4], no ab initio mechanistic study has been reported that demonstrates that there is a relationship between these reactions. This is partially the result of complicating features inherent in the $\alpha$-carbonyl reaction, such as the uncertainty as to the site of attack[8] and the dependence on the nucelophile.[9] As we have noted earlier,[7a] there was no bonding of the nucleophile to the carbonyl carbon, an observation also reported by Dewar.[4] We now provide a direct comparison of the molecular orbitals of the transition state for both reactions that clearly shows that the origin of the "electrophilicity" of both classes of compounds are quite similar in nature. The increased rate of nucleophilic attack may be ascribed to a relatively low lying conjugated "allylic" orbital that stabilizes the transition state.



1a

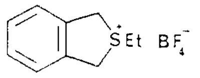


1b



$(PhCH_2)_2\overset{+}{S}Et\ BF_4^-$

2a



2b

**Table I. Total Energies (au) for the Optimized Structures (4-31G) for the Ground-State and Transition-State Species for the Addition of Cl⁻ to Conjugated (5) and Nonconjugated (3) $\alpha$-Chloroacetaldehyde**

| structure | $E_{TOT}$ |
|---|---|
| $Cl^-$ | −459.026 405 |
| $ClCH_2CHO$ (**3**) (nonconjugated) | −611.083 917 |
| $ClCH_2CHO$ (**5**) (conjugated) | −611.084 463 |
| nonconjugated (**6**) transition state | −1070.123 897 |
| conjugated (**7**) transition state | −1070.141 133 |

## Results and Discussion

The rate acceleration for $\alpha$-halo carbonyls and allylic (benzylic) substrates is dependent upon the ground-state conformation where the $\sigma_{CCl}$ bond is parallel to the p orbitals of the adjacent $\pi$-bond. The effect of this $\sigma$–$\pi$ interaction on the energy of the LUMO orbital is demonstrated in Figure 1.[10] The inductive effect of a carbonyl group, in a conformation where the $\sigma_{CCl}$ bond and the $\pi_{C=O}$ orbitals are orthogonal (**3**), has little effect on the energy level of the $\sigma^*_{CCl}$ orbital relative to that in methyl chloride. However, a 90° C–C bond rotation affords a conformer (**5**) where the upper filled antibonding combination (HOMO $= \sigma_{CCl} - \pi_{C=O}$) is elevated in energy as a result of a four-electron interaction and the LUMO, a bonding combina-

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[1] Lubrizol Fellowship, 1984–85.

[2] (a) Conant, J. B.; Kirner, W. R. *J. Am. Chem. Soc.* **1924**, *46*, 232. (b) Conant, J. B.; Hussey, R. E. *J. Am. Chem. Soc.* **1925**, *47*, 476.

[3] (a) Dewar, M. J. S.; Dougherty, R. C. "The PMO Theory of Organic Chemistry"; Plenum Press: New York, 1975; p 256. (b) Streitwieser, A., Jr. "Solvolytic Displacement Reactions", McGraw-Hill: New York, 1962; p 11.

[4] Carrion, F.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 3531.

[5] (a) King, J. F.; Tsang, G. T. Y. *J. Chem. Soc., Chem. Commun.* **1979**, 1131. (b) King, J. F.; Tsang, G. T. Y.; Abdel-Malik, M. M.; Payne, N. C. *J. Am. Chem. Soc.* **1985**, *107*, 3224.

[6] Bartlett, P. D.; Trachtenberg, E. N. *J. Am. Chem. Soc.* **1958**, *80*, 5808.

[7] For a comparison between SCF-MO and a valence bond (VB) approach, see: (a) Pross, A.; Aviram, K.; Klix, R. C.; Kost, D.; Bach, R. D. *Nouv. J. Chim.* **1984**, *8*, 711. (b) Pross, A.; Shaik, S. S. *J. Am. Chem. Soc.* **1981**, *103*, 3702.

[8] (a) Thorpe, J. W.; Warkentin, J. *Can. J. Chem.* **1973**, *51*, 927. (b) Ross, S. D.; Finkelstein, M.; Petersen, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 6411.

[9] Halvorsen, A.; Songstad, J. *J. Chem. Soc., Chem. Commun.* **1978**, 327.

[10] All geometry optimations used ab initio gradient methods employing the GAUSSIAN 80 series of programs.[11] The chlorine atom in 3-chloropropene was held perpendicular to the plane of the ethylene moiety. Relaxation of this gemoetry constraint led to a dihedral angle Cl–C–C–Ha of 65.7° and a relative stabilization of only 0.67 kcal/mol (STO-3G). The gauche conformation of 3-chloropropene is the most stable in both the gas and liquid phases. Barnes, A. J.; Holroyd, S.; George, W. D.; Goodfield, J. E.; Maddams, W. F. *Spectrochim. Acta* **1982**, *38A*, 1245.

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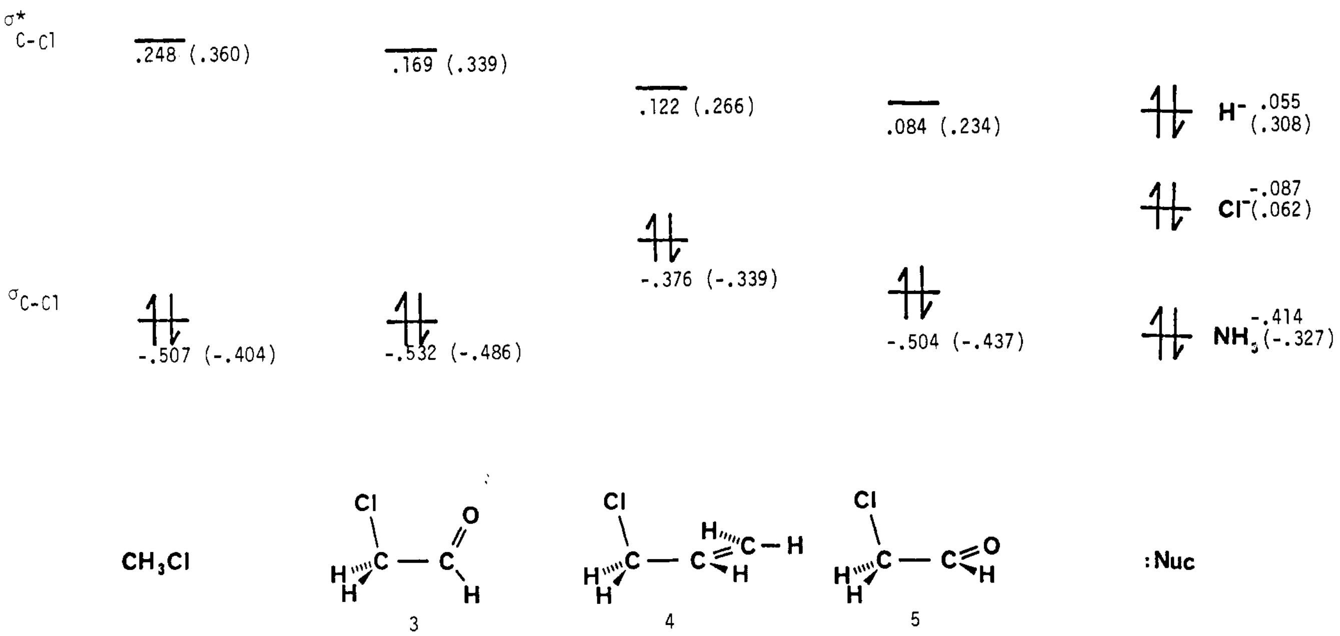

**Figure 1.** Calculated 4-31G (STO-3G) $\sigma_{CCl}$ and $\sigma^*_{CCl}$ energy levels (au) for molecules containing a carbon chloride bond and selected nucleophiles.

tion of $\sigma^*_{CCl}$ with $\pi^*_{C=O}$, is substantially lowered in energy by 0.105 au (66 kcal/mol).[12a] This significant electronic perturbation of the pertinent LUMO is accompanied by a marked increase in the rate of nucleophilic substitution. The corresponding energy level of the LUMO in allyl chloride is intermediate between methyl chloride and α-chloroacetaldehyde (Figure 1) in accord with their respective reactivities toward nucleophiles. The rate of nucleophilic substitution is, of course, affected by the interaction of the HOMO of the nucleophile with both the pertinent HOMO and LUMO energy levels of the substrate.[13]

A comparison of the frontier orbitals involved in $Cl^-$ displacement on the σ–π conjugated and nonconjugated conformers of α-chloroacetaldehyde will be instructive.[14] Since the effects of a σ-orbital in conjugation with a more polarizable carbonyl π-bond exceed those of a carbon–carbon double bond, the stereoelectronic effects are more evident. The charge transfer to the carbonyl group at the transition state is reminiscent of the stabilization of an enolate anion; an opposing flow of electron density occurs in the σ-framework.[7a] Thus, the rate enhancement due to the multiple bond is also a manifestation of the polarization of the π-system.

The five basic orbitals of the reactants that are involved in nucleophilic attack of $Cl^-$ on α-chloroacetaldehyde in the preferred conformation include a lone pair of electrons on the nucleophilic ($Cl^-$) and the σ and π bonding and antibonding orbitals of the active halide (Figure 2).[12a] The transition structure (4-31G) for the "degenerate" displacement by $Cl^-$ is 10.8 kcal/mol lower in energy[15] for the σ–π conjugated conformer **7** than for **6** (Table I). Upon examination of the resulting five molecular orbitals of the transition state (Figure 2), we note that the HOMO orbital has no contribution from the atomic p orbital of the "electrophilic" carbon atom. This is a consequence of the principle of atomic orbital coefficient cancellation.[13] In the next lowest pertinent MO ($\psi_{24}$), the partial C–Cl bonds are antibonding to the carbonyl π-bond. The only orbital with the proper symmetry to stabilize the transition state for nucleophilic substitution at the α-carbon in this conformation is $\psi_{22}$, *a molecular orbital far removed in energy from the HOMO orbital* ($\psi_{29}$). The resulting delocalized "enolate anion" interaction results in a lowering of the energy of this conjugated bonding MO (Figure 2) by 11.1 kcal/mol (4-31G) relative to the same molecular orbital in the unconjugated conformer in good accord with the EFMO analysis. We saw no significant σ-bridging of the incoming nucleophile with the "electrophilic" carbon and

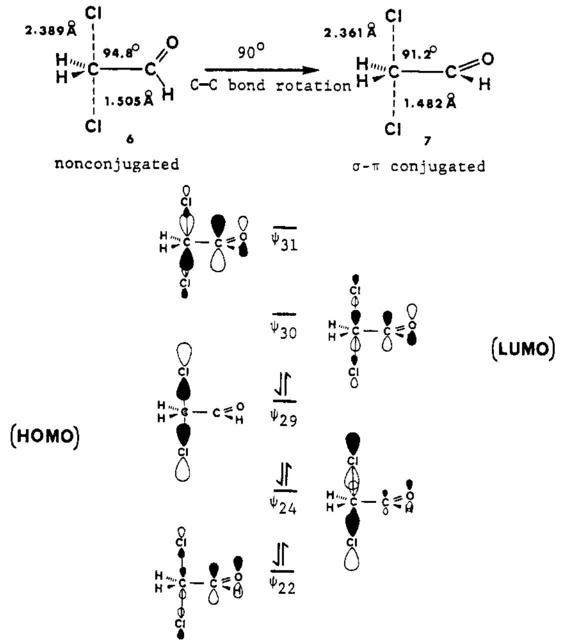

**Figure 2.** Frontier molecular orbitals on the principal axis of reaction for nucleophilic displacement by $Cl^-$ on α-Chloroacetaldehyde in the transition state.

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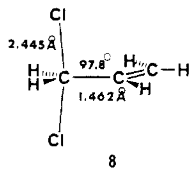
(12) (a) For the derivation of these molecular orbitals in allylic systems, see: Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1985**, *107*, 1352. (b) For a recent theoretical discussion on the accompanying $S_N2'$ reaction, see ref 12a.

(13) (a) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1401; (b) **1984**, *106*, 1410.

(14) For a recent theoretical discussion, see: Wolfe, S.; Mitchell, D. J.; Schlegel, H. B. *Can. J. Chem.* **1982**, *60*, 1291.

(15) The calculation (4-31G) energy differences between reactants and transition structures 7 and 6 are −18.99 and −8.49 kcal/mol, respectively. The ground-state energy of 5 is 0.3 kcal/mol lower in energy that 3 (Table I). No attempt was made to identify a gas-phase cluster for this reaction since we had restricted the approach of the chloride ion in both cases.



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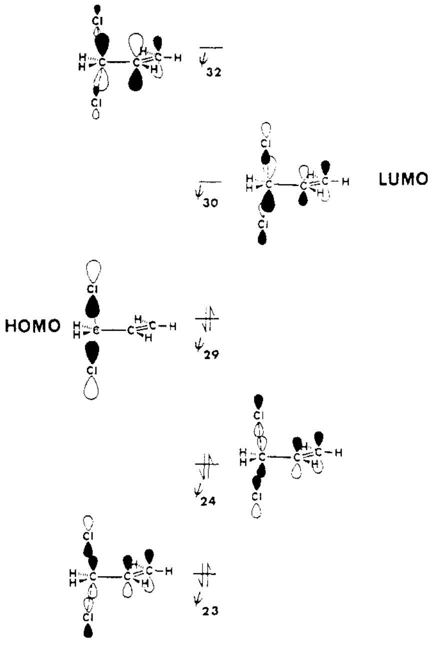

**Figure 3.** Frontier Molecular Orbitals (4-31G) for displacement by $Cl^-$ on 3-chloropropene in symmetrical transition state **8**.

the carbonyl carbon as initially advocated by Winstein.[16] Examination of the bonding interactions in the FMOs (Figure 2) also excludes partial bonding between the chloride ion and the carbonyl carbon as the basis for enhanced reactivity.[16b] The interactions of an incoming nucleophile with the bonding ($\psi_{22}$) and antibonding ($\psi_{24}$) "allylic" molecular orbitals in **5** would essentially cancel one another. We, therefore, attribute the enhanced reactivity of $\alpha$-substituted carbonyl compounds and by analogy allyl (benzyl)[7b] substrates to the *stabilization of the lower lying bonding combination* ($\psi_{22}$) consisting of the $\pi$-bond interacting with the principal axis of the reaction constituting the X--C--NUC $\sigma$-bond. Although it may be fortuitous, this delocalization energy (11.1 kcal/mol) accounts for the difference in energy (10.8 kcal/mol) between the nonconjugated (**6**) and $\sigma$–$\pi$ conjugated (**7**) transition structures (4-31G). By employing similar arguments this exercise may be extended to include the enhanced susceptibility of allylic substrates to direct $S_N2$ displacement.

The pertinent molecular orbitals of the symmetrical $S_N2$ transition state of $Cl^-$ and 3-chloropropene are shown in Figure 3.[12a] These orbitals are the result of the two- and four-electron interactions of the HOMO of the nucleophile with the four allylic molecular orbitals of the allyl system. Early along the reaction coordinate the effective HOMO will be the antibonding combination of the lone pair on the nucleophile with the carbon chlorine $\sigma$ bond ($n_{Cl}$–$\sigma_{CCl}$). Proceeding along the reaction coordinate, this developing MO increases in energy from the initial four-electron interaction to a point where the accompanying interaction with the LUMO ($\sigma^*_{CCl}$) becomes significant. This attendant stabilizing two-electron interaction serves to mediate the repulsive component of the reaction by lowering the energy of the "effective" HOMO. At the transition state (**8**) the two chlorines are identical by symmetry. As a direct result of the two opposing interactions, there is a cancellation of the p orbital at the central carbon in HOMO ($\psi_{29}$). Carrying this analysis further to NHOMO ($\psi_{24}$), symmetry considerations preclude the involvement of the carbon 2s atomic orbital in this molecular orbital. Evidence for the "allylic" stabilization present in this transition structure is seen in the lower lying bonding ($\sigma + \pi$) combination comprising molecular orbital $\psi_{23}$. *Considering the principal axis of the displacement reaction, $\psi_{23}$ is the only orbital that can result in the lowering of the energy of activation on an allylic substrate.*[12b]

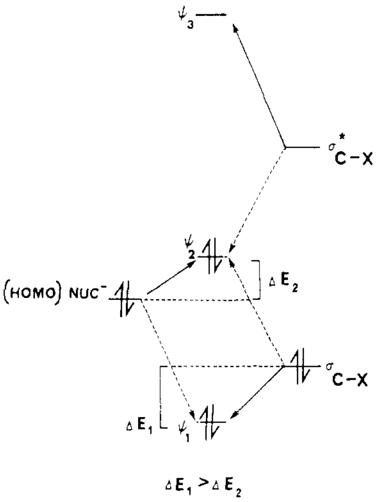

**Figure 4.** Three molecular orbital four-electron interaction diagram between a C–X $\sigma$ and $\sigma^*$ and an incoming nucleophile.

In both types of reactions the incoming nucleophile is net antibonding to the "electrophilic carbon" until that "null point" is reached where the phase of both the incoming nucelophile and that of the leaving group, with respect to the reaction site, must be the same. We have become accustomed to thinking about partial bonding of the attacking nucelophile to the "electrophilic carbon" along the reaction coordinate. Although this is true in the lower lying molecular orbitals, the net overlap of the nucelophile to carbon in HOMO, resulting in a symmetrical transition state, must by symmetry be antibonding until a point at or near the transition structure is achieved. A corrolary to this statement is that the leaving group should be net bonding when the overlap population is summed over all occupied MOs. The resultant symmetry about the "electrophilic carbon" is a consequence of destructive interference, i.e., $\sigma_{CCl}$ and $\sigma^*_{CCl}$ orbital cancellation.[13]

There remains the point that the rate enhancement is not nearly as pronounced for neutral nucleophiles (i.e., amines) as for ionic or charged nucleophiles. In some instances methyl iodide[9] or benzyl bromide[8b] can exhibit a higher reactivity than phenacyl bromide in the $S_N2$ reaction with amines. Considering Figure 1, it should be noted that the HOMO levels of the substrates ($\sigma_{CCl}$) are very close in energy to the HOMO of the amine nucleophile ($NH_3$). Thus, the initial electronic interaction between the two respective HOMOs results in a net destabilization as we have noted earlier.[13] In contrast, a HOMO–LUMO dominant interaction may occur between the higher lying charged nucleophile $H^-$ and the substrate LUMOs. In reactions with chloride ion where the HOMO energy level is intermediate between the filled and virtual orbital, the HOMO of the nucleophile will mix initially with both the

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(16) (a) Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700. (b) Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; Harper and Row: New York, 1981; p 347.

$\sigma_{CCl}$ and $\sigma^*_{CCl}$ in a three molecular orbital four-electron interaction (Figure 4).

As we have described elsewhere,[13a] interactions of this type can be net stabilizing. The initial four-electron interaction gives rise to a bonding combination, $\psi_1$, which is lowered in energy. The accompanying antibonding component is increased in energy to a point where it begins to mix into itself the higher lying virtual orbital ($\sigma^*_{CX}$) in a two-electron interaction. In most of the cases that we have examined thus far, the magnitude of this two-electron stabilization increases to a point where it equals or exceeds the intrinsic four-electron destabilization of this three MO four-electron interaction. Thus the HOMO orbital $\psi_2$ is stabilized at the expense of an empty orbital $\psi_3$ such that $\Delta E_1 > \Delta E_2$ (Figure 4). For both of these above cases when a charged nucleohile is involved, there is a significant stabilizing contribution to the overall energetics of the reaction early along the reaction coordinate. For a neutral nucleophile such as an amine, we would expect a greater influence of the four-electron interaction early along the reaction coordinate. Only after the level of the relatively low lying amine lone pair has been sufficiently raised in energy, as a result of its closed shell repulsion with the filled $\sigma_{CCl}$ orbital, should any significant two-electron stabilization resulting from the interation of the developing HOMO orbital with the $\sigma^*_{CCl}$ be realized. As pointed out elsewhere,[13] such reactions typically exhibit a barrier in the gas phase and involve a relatively late transition state. This is partially responsible for the smaller degree of rate enhancement observed with neutral nucleophiles. One must also take into consideration that charged nucleophiles are typically more highly solvated which also contributes to the activation barrier.

In our comparison of the $S_N2$ attack by $Cl^-$ at saturated carbon, we have concluded that the more polarizable carbonyl bond[7a] has a stronger activating influence than a carbon–carbon double bond. The difference in reaction rate is an obvious consequence of the ability of the carbonyl functionality to stablize a developing negative charge at the transition state. We propose a unifying mechanism where the increased rate of $S_N2$ displacement of allylic (benzylic) substrates relative to methyl chloride and especially *n*-propyl chloride[17] may also be attributed to the stabilizing influence of the delocalized allylic MO ($\psi_{23}$) in the transition state (Figure 3). Thus, no special explanation or multicenter bonding of the nucleophile to the electrophilic center and the adjacent carbonyl carbon need be involved in an explanation of the enhanced reactivity or "electrophilicity" of $\alpha$-halo carbonyls. Increased reactivity toward nucleophiles in the $S_N2$ reaction should be anticipated whenever the repulsive or four-electron component of the reaction can be decreased by electron delocalization via a conjugated molecular orbital ($\psi_{22}$) as depicted in Figure 2.[18]

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**Registry No.** Allyl chloride, 107-05-1; $\alpha$-chloroacetaldehyde, 107-20-0.

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(17) Streitwieser, A. "Solvolytic Displacement Reactions"; McGraw-Hill Book Company: New York, 1962; p 13.

(18) For a particularly clever theoretical experiment that demonstrates the importance of the four-electron interaction in $S_N2$ reactions, see: Kost, D.; Aviram, K. *Tetrahedron Lett.* **1982**, *23*, 4157.

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# Chemistry of Sulfenic Acids. 7.[1,2] Reason for the High Reactivity of Sulfenic Acids. Stabilization by Intramolecular Hydrogen Bonding and Electronegativity Effects

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It is proposed that the reason sulfenic acids (RSOH) are so reactive and usually not isolated or even detected is that they form thiosulfinates (RS(O)SR) so readily. This is a consequence of the sulfenic acid hydrogen-bonded dimer, 1, which lowers the energy of activation for thiosulfinate formation. The stability of the few sulfenic acids that have been isolated can be explained in terms of steric, electronic, and intramolecular hydrogen-bonding effects which prevent dimer formation. The importance of these effects on the stability of simple unstable sulfenic acids was demonstrated by flash vacuum pyrolysis (FVP) and the thiosulfinate/vinyl sulfoxide ratio. A novel, high yield, rearrangement of sulfenic acid **19f** to 1,3-benzothiazine **26** was observed.

Sulfenic acids (RSOH) have been of interest for more than three-quarters of a century. Their importance as transient intermediates in organic and bioorganic sulfur reactions is now well recognized.[3,4] The two most important reactions of a sulfhydryl group (RSH) in living systems, oxidation to higher sulfur oxides ($RSO_xH$) and to disulfides (RSSR), has recently been shown to involve sulfenic acid intermediates.[4a] Much of the chemistry of the penicillin sulfoxides is related to the relatively stable 2-oxazetidine-4-sulfenic acid.[5] Indeed, the spectrum of

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(1) Part 6: Davis, F. A.; Billmers, R. L. *J. Org. Chem.* **1985**, *50*, 2593.

(2) These results were taken in part from the Ph.D. Theses of R. L. Billmers, Drexel Univeristy, 1984, and L. A. Jenkins, Drexel University, 1985.

(3) For reviews on the chemistry of sulfenic acids see: Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 65; Hogg, D. R. *Compr. Org. Chem.* **1979**, *4*, 261.

(4) For leading references on the biological reactions of sulfenic acids see: (a) Davis, F. A.; Billmers, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 7016. (b) Allison, W. S. *Acc. Chem. Res.* **1976**, *9*, 293.

(5) Sammes, P. G. *Chem. Rev.* **1976**, *76*, 113; Stoodley, R. J. *Tetrahedron* **1975**, *31*, 2321.

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