

Solvation Effects on Alternative Nucleophilic Substitution Reaction Paths for Chloride/Allyl Chloride and γ -Methylated Congeners

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An adiabatic connection method, *mPW1PW91(0.581)/6-31G(d)*, was employed in conjunction with the continuum solvation model SM5.42 to study the effects of solvation on the S_N1 , S_N2 , and syn and anti S_N2' nucleophilic substitution reactions of chloride anion with allyl chloride and its γ -methylated analogues *Z*- and *E*-crotyl chloride and isoprenyl chloride. The impact of equilibrium solvation on the potential energy surfaces of these systems is large and leads to significant changes in both the geometries and the relative energetics of different reaction pathways for different species. The predicted effects of increased solvent dielectric constant are consistent with available experimental data and provide semiquantitative insights into the relative influence of different solvents on particular properties.

Introduction

Nucleophilic substitution reactions play a fundamental role in a variety of organic and biological mechanisms.¹ As a result, both unimolecular (S_N1) and bimolecular (S_N2) nucleophilic substitution reactions have been the focus of many experimental and theoretical studies in both solution and the gas phase.^{2–5} Not only have such studies been important in determining the mechanistic details of the reactions, including their activation energies, but they have also demonstrated the significant effects of solvation on these processes.^{6–10}

In an allylic system, both unimolecular and multiple bimolecular nucleophilic substitution reactions are possible (Figure 1). The S_N1 reaction involves rate-determining dissociation of the nucleofuge to form a carbocation intermediate that may subsequently be attacked by an incoming nucleophile. In the S_N2 reaction, the nucleophile attacks the α -carbon leading to concerted direct displacement

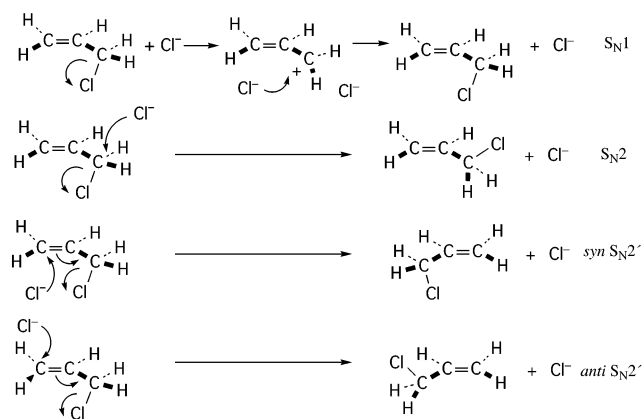


FIGURE 1. Nucleophilic substitution reactions of chloride anion with allyl chloride.

of the nucleofuge and inversion of stereochemistry (Walden inversion) at the halogenated center. An additional bimolecular nucleophilic substitution reaction available in allylic systems involves allylic rearrangement (S_N2'); in this reaction, the nucleophile attacks the γ -carbon either syn or anti to the nucleofuge with concerted allylic rearrangement and displacement of the nucleofuge.

An analogous and prototypical nucleophilic substitution reaction, namely the identity S_N2 reaction of chloride ion with methyl chloride, has seen particularly extensive study. Qualitatively, experimental^{11,12} and computational^{4,13–21} studies agree that this reaction is characterized in the gas phase by a double-well potential energy surface (PES) with reactants initially forming a stable ion–dipole complex of C_{3v} symmetry ($Cl^- \cdots CH_3Cl$), then proceeding through a D_{3h} transition state ($[Cl \cdots CH_3 \cdots Cl]^-$)

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to the complementary ion–dipole complex, and in the absence of stabilizing collisions, ultimately dissociating to narcissistic products. The fundamental feature of a double-well PES is generally accepted for all S_N2 reactions in the gas phase.

Most molecular modeling studies correctly predict a positive barrier for the gas-phase chloride ion with methyl chloride.^{13,15,16,19,21–25} The best ab initio molecular orbital (MO) theory studies have predicted a barrier height of 2–3 kcal mol⁻¹;^{19,21,24,25} accurate results have required extensive accounting for electron correlation and the use of a large basis set containing multiple diffuse and polarization functions.^{16,19,22,24,25} [We note that we use the term “barrier” to imply the potential energy difference between reactants and the transition state structure; we use the terms enthalpy or free energy of activation when zero-point vibrational energies and thermal contributions to these respective thermodynamic quantities are added to any computed potential energies. Comparisons to experimental quantities are always made on a consistent basis, i.e., barriers, enthalpies of activation, or free energies of activation.]

Density functional theory (DFT) in principle offers a less expensive alternative to ab initio calculations for determining barrier heights of nucleophilic substitution reactions. Several levels of DFT have been used to study the S_N2 chloride/methyl chloride barrier height. Deng et al.¹⁸ found that both the local density approximation (VWN)²⁶ and a gradient corrected functional (BP)^{27,28} yielded reasonable geometries but enormously underestimated the barrier heights. Since then, the observation has been made many times that modern “pure” DFT functionals are generally poor for predicting barrier heights for nucleophilic substitution reactions^{20,29,30} (as well as hydrogen-exchange reactions^{31–37}). Functionals

that incorporate some fraction of exact Hartree–Fock (HF) exchange in the DFT energy expression improve the situation somewhat. B3LYP^{38,39} (defined to incorporate 20% HF exchange) predicts an improved barrier (–1.3 kcal mol⁻¹),^{20,29} albeit one that is qualitatively incorrect insofar as the transition-state structure is predicted to be lower in energy than the asymptote corresponding to separated reactants. The *m*PW1PW91 functional (defined to incorporate 25% HF exchange) predicts a barrier of 1.7 kcal mol⁻¹,³⁰ and BH&HLYP⁴⁰ (defined to include 50% HF exchange) predicts an even better estimate of 2.6 kcal mol⁻¹,²⁰ although this level of theory has been found to be poor for the prediction of other properties.^{36,41–43} Pure HF theory significantly overestimates the reaction barrier, so good results from admixture of HF into DFT may to some extent derive from an arbitrary cancellation of competing errors; the evaluation of properties other than the energy (e.g., geometry) is critical to ensure that other errors are not introduced by this approach.

The gas-phase reaction of chloride with allyl chloride has also been studied computationally, although not to the same extent as its simpler methyl analogue. It has been shown that the S_N2 and S_N2' pathways have double-well PESs similar to that of chloride/methyl chloride,^{44–47} and that the S_N2 pathway has the lowest barrier in the gas phase, the syn S_N2' pathway the highest barrier, and the anti S_N2' pathway a barrier intermediate between these two.^{44,46,48,49} This trend is rationalized as follows: The S_N2 pathway is favored over the other two because the nucleophile directly attacks the most electrophilic carbon atom of the allyl fragment (the one substituted with a halogen) and because it avoids the energetic cost of rearranging the double bond. The anti S_N2' pathway is favored over the syn because of increased unfavorable Coulombic repulsions between the incoming and departing chloride anions in the latter transition-state structure. The highest level of theory employed to examine all three pathways for this system has been MP2/6-31++G(d,p), with which Lee et al.^{44,46} predicted the S_N2 , syn S_N2' , and anti S_N2' pathways to have barriers of 8.1, 20.5, and 11.5 kcal mol⁻¹, respectively.

Other considerations for nucleophilic substitution reactions in the gas phase include front-side nucleophilic substitution with retention of configuration and heterolytic dissociation corresponding to the S_N1 pathway. The propensity for occurrence of front-side attack in methyl systems has been studied by high-level ab initio molecular orbital calculations at the G2(+) level of theory by Glukhovtsev et al.⁵⁰ They determined that the barrier

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heights for $\text{CH}_3\text{X} + \text{X}^-$ ($\text{X} = \text{F}, \text{Cl}, \text{Br}, \text{I}$) front-side attack were vastly larger than those for backside attack, ranging from 57.4 kcal mol⁻¹ for $\text{X} = \text{F}$ to 49.4 kcal mol⁻¹ for $\text{X} = \text{I}$. There is no significant evidence for this pathway in solution in aliphatic or allylic systems, so it will not be further addressed here. The $\text{S}_{\text{N}}1$ pathway in the gas phase is highly improbable, because of the energetic cost associated with separating charges. However, the $\text{S}_{\text{N}}1$ pathway becomes more favorable when solvation is a factor.

Indeed, solvation has a significant effect on the energetics of *all* nucleophilic substitution pathways. For identity $\text{S}_{\text{N}}2$ reactions, solvent reaction rates are generally much slower than their corresponding gas-phase reaction rates.^{2,3,5,10,12,51,52} All stationary points on the PES are stabilized by solvation compared to the gas phase, but the isolated nucleophile, which has a very localized charge, is stabilized to a much greater extent than the transition state, which has a much more diffuse charge distribution. The large barrier in solution compared to the gas phase may thus be thought of as deriving mainly from desolvation of the nucleophile (both because of reduced interaction of coordinated solvent molecules with the more diffuse charge and because of steric shielding of one face of the nucleophile by the nucleofuge in the transition-state structure). Another characteristic of the solvated PES is the disappearance of stable ion-dipole complexes with increasing solvent dielectric due to a decreased attraction of the reactants.^{5,10,12,53} Several theoretical studies have focused on these solvation effects, particularly for the chloride/methyl chloride system.^{13,20,54-62} No prior computational studies have examined solvation effects on the reaction of chloride with allyl chloride.

While it is generally accepted that primary alkyl halides undergo nucleophilic substitution in solution via $\text{S}_{\text{N}}2$ pathways, substitution at more sterically encumbered sites is observed typically to follow instead an $\text{S}_{\text{N}}1$ pathway,^{5,9} the availability of which opens up in solution. The prototypical reaction for the $\text{S}_{\text{N}}1$ pathway is the heterolysis of *tert*-butyl chloride. The current view^{9,63} of the hydrolysis of *tert*-butyl chloride is that it follows the Winstein scheme⁶⁴ in which there is an initial separation of *tert*-butyl chloride to an intimate or contact ion pair ($t\text{-Bu}^+\text{Cl}^-$), followed by separation to a solvent-separated

ion pair ($t\text{-Bu}^+//\text{Cl}^-$), which is followed by dissociation to free ions ($t\text{-Bu}^+ + \text{Cl}^-$). Computational studies^{57,65-70} have found qualitative agreement with this reaction scheme, but are far from reaching a consensus about the energetics. According to these studies, there may or may not be a transition state associated with each step, and those that do agree on a similar PES vary greatly in their reports of the energies associated with the barriers as well as the C-Cl bond lengths at the stationary points. A key source of discrepancy is that nonequilibrium effects associated with the dynamic role of solvent fluctuations in the heterolysis process appear to be more important in determining the transition-state location and activation free energy of the $\text{S}_{\text{N}}1$ reaction than that of the $\text{S}_{\text{N}}2$ reaction.^{57,67-74}

Though there have been no prior computational studies on the effects of solvation on the preferred pathways for nucleophilic substitution of chloride/allyl chloride and its methylated congeners, there have been many experiments performed on these or analogous systems in a range of solvents to assess the mechanism(s) of reaction.^{2,75-94} The general consensus from the full scope of experiments is that allyl chloride reacts via $\text{S}_{\text{N}}2$ substitution,^{83,85,87,88} isoprenyl chloride reacts via $\text{S}_{\text{N}}1$ substitution,^{83-85,92} and crotyl chloride may react by both $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ pathways,^{75,76,78,82,83,85,87-89} although the $\text{S}_{\text{N}}2'$ pathway can be forced with appropriate steric bias.^{82,89,94} Sneen et al. proposed a particularly detailed ion-pair mechanism to rationalize the mixed $\text{S}_{\text{N}}1/\text{S}_{\text{N}}2$ results observed for the crotyl system.^{1,90-93}

The objective of the present study is to provide quantitative comparisons between different nucleophilic substitution pathways as a function of the allylic unit and the solvent. We apply a specific-reaction-parameter density functional method optimized especially for these reactions toward that end, and assess the effects of solvation using the SM5.42 continuum model. We find

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that for bimolecular nucleophilic substitution, the S_N2 pathway is in every case energetically preferred over the S_N2' pathways, although the difference can become small for more highly substituted systems in polar solvents. Polar solvents also enormously stabilize S_N1 ionization, however, so that this pathway is preferred in every case over bimolecular ones in water.

Computational Methods

Gas-phase molecular geometries for reactants and transition-state structures were optimized at several different levels of theory to enable direct comparison of structures and energies. The *ab initio* levels employed were restricted Hartree–Fock (RHF)^{95–97} and Møller–Plesset second-order perturbation theory (MP2).⁹⁸ Density functional levels of theory combined Becke exchange (B)²⁷ or Becke 3 hybrid exchange (B3)³⁹ with Lee, Yang, and Parr correlation³⁸ (BLYP and B3LYP, respectively) or combined the modified Perdew–Wang exchange functional (*mPW*)³⁰ or the one-parameter modified Perdew–Wang hybrid exchange functional (*mPW1*)³⁰ with Perdew–Wang correlation⁹⁹ (*mPWPW91* and *mPW1PW91*, respectively). All DFT structures were optimized with the 6-31G(d) basis set^{100,101} at each level of theory. To obtain more accurate energies,¹⁰² the calculations were then extended to optimizations at the level of multi-coefficient quadratic configuration interaction with single and double excitations (MC-QCISD),¹⁰³ followed by single-point energy calculations at the multi-coefficient Gaussian-3 (MCG3)^{104,105} level of theory. The MCG3/MC-QCISD level of theory has been shown to predict heats of formation to within a typical error of below 1 kcal mol⁻¹.

Consistent with the prior experience noted above, all of the DFT models significantly underestimated the barrier heights of the nucleophilic substitution reactions. However, given (i) the convenience of carrying out self-consistent reaction field (SCRF) calculations within a single-determinantal formalism directly incorporating electron correlation and (ii) our prior success in designing a specific-reaction parameter (SRP) DFT model for narcissistic halide/alkyl halide substitution reactions,¹⁰² we elected to examine the degree to which an SRP model might be particularly useful here. To that end, we optimized the fraction of exact exchange in *mPW1PW91*/6-31G(d) to best reproduce the four energy barriers calculated for chloride/allyl chloride at the MCG3/MC-QCISD level of theory. The optimal model was found to incorporate 58.1% HF exchange, *mPW1PW91*(0.581)/6-31G(d).

Solvation free energies for all gas-phase molecular geometries were calculated in carbon tetrachloride ($\epsilon = 2.2280$, 298 K) and water ($\epsilon = 78.3$, 298 K) with use of the SM5.42R solvation model;^{106–108} molecules were then reoptimized in

solution (indicated by the notation SM5.42 without the following “R”).¹⁰⁹ These continuum solvation models are based on SM5 empirical atomic surface tensions and self-consistent reaction field (SCRF) calculations with CM2 Class IV charges.¹¹⁰ The CM2 charges and SM5 atomic surface tension coefficients for *mPW1PW91*(0.581)/6-31G(d) were obtained by using the parameters optimized for HF/6-31G(d) based on good correspondence between the Löwdin charges (that are used as input in determining CM2 charges)¹¹⁰ computed by these two levels for equivalent geometries (RMS error of 0.025 charge units over all structures).

The nature of all stationary points was verified by computation of analytic vibrational frequencies. Thermal contributions to 298 K gas-phase free energies were computed from standard ideal-gas, rigid-rotator, harmonic-oscillator statistical mechanical protocols.⁹⁵ Free energies in solution were computed as the sum of 298 K gas-phase free energies and free energies of solvation.

All MO and DFT gas-phase calculations were performed with Gaussian98, revision A.9.¹¹¹ All solvation effects were incorporated by using the Minnesota-Gaussian Solvation Module, (MN-GSM, version 99.8).¹¹² Multicoefficient calculations employed the MULTILEVEL code.¹¹³

Results and Discussion

Gas Phase. The gas-phase energetics for the S_N1 , S_N2 , *syn* S_N2' , and *anti* S_N2' reactions of chloride/allyl chloride were calculated at a number of levels of theory to evaluate the best level at which to continue studies with the methylated analogues and to include the effects of solvation. The 6-31G(d) basis set was chosen for purposes of efficiency for use with all levels of theory other than the benchmark MCG3 level; we note, however, that the MCG3 and MC-QCISD levels of theory both employ basis sets of quality up to highly augmented and polarized valence triple- ζ . In other words, the benchmark numbers should be highly reliable in the “normal” fashion, especially for nucleophilic substitution,¹⁰² as they derive from attempting to converge electron-correlation and basis-set effects, while good performance of the other levels, if observed, will necessarily derive in part from a cancellation of errors associated with using the smaller 6-31G(d) basis set and taking less complete account of electron correlation. However, taking advantage of such cancel-

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TABLE 1. Computed Barrier Heights (kcal mol⁻¹) for Chloride/Allyl Chloride Nucleophilic Substitution Reactions and Errors for Model/6-31G(d) Calculations Compared to MCG3/MC-QCISD^a

| pathway and error analysis | level of theory | | | | | | | |
|----------------------------|-----------------|-------|-------|-------|-------|-----------------|------------------|-------------------------|
| | MCG3 | RHF | MP2 | BLYP | B3LYP | <i>m</i> PWPW91 | <i>m</i> PW1PW91 | <i>m</i> PW1PW91(0.581) |
| S _N 1 | 176.1 | 158.5 | 180.2 | 173.2 | 173.8 | 179.2 | 178.8 | 178.3 |
| S _N 2 | 2.6 | 5.9 | 5.9 | -10.6 | -5.2 | -8.7 | -2.4 | 3.6 |
| syn S _N 2' | 11.9 | 20.7 | 13.4 | -6.0 | 0.9 | -5.1 | 3.0 | 11.9 |
| anti S _N 2' | 9.4 | 13.2 | 10.4 | -10.2 | -3.4 | -8.9 | -0.9 | 7.7 |
| MSE | | -0.4 | 2.5 | -13.4 | -8.5 | -10.9 | -5.4 | 0.4 |
| MUE | | 8.4 | 2.5 | 13.4 | 8.5 | 12.4 | 6.7 | 1.2 |
| RMSE | | 10.2 | 2.8 | 14.9 | 9.4 | 13.8 | 7.4 | 1.5 |

^a Barrier heights for S_N1 refer to the electronic energies of infinitely separated allyl cation and chloride anion relative to allyl chloride and for the other reactions refer to the electronic energy of the relevant transition-state structure relative to infinitely separated allyl chloride and chloride ion, i.e., the minimum of energy is *not* taken to be the ion-dipole complex in any case.

lation of errors permits more facile study of substituted and solvated systems in a self-consistent way.

An error analysis of the other levels of theory compared to MCG3/MC-QCISD calculations is provided in Table 1. Consistent with the prior observations discussed above, all of the DFT methods severely underestimate the barrier heights for the bimolecular reactions, as indicated by their large negative mean signed errors (MSEs). The lowest error for a “standard” model is given by MP2, for which the MSE and mean unsigned error (MUE) are 2.5 kcal mol⁻¹ (i.e., the MP2 level overestimates every barrier height). However, modifying the fraction of Hartree-Fock (HF) exchange in *m*PW1PW91 to 58.1% provided much better agreement with the four MCG3/MC-QCISD barrier heights (note that for the S_N1 reaction, we loosely use the term “barrier height” to mean the energy difference between the neutral reactant and the infinitely separated product ions). The *m*PW1PW91(0.581) level exhibits MSE, MUE, and root-mean square error (RMSE) values of 0.4, 1.2, and 1.5 kcal mol⁻¹, respectively.

In the creation of an SRP model that successfully relies on cancellation of errors to predict molecular energetics, there is no guarantee that favorable cancellations will also hold for other molecular properties. For the purposes of the present study, we will be concerned with molecular geometries to a similar degree as with energetics. Table 2 compares key heavy atom bond lengths for allyl chloride and the three bimolecular TS structures at all of the levels of theory investigated here. Accounting for the effects of electron correlation at the MP2 or MC-QCISD levels significantly decreases C-Cl bond lengths compared to HF, particularly in the TS structures. Interestingly, however, in the DFT models it is inclusion of HF exchange that leads to C-Cl bond shortening and better agreement with the MC-QCISD benchmarks. Though all of the *m*PW1PW91(0.581) bonds except the S_N2 C-Cl bonds are slightly underestimated compared to MC-QCISD, this SRP model still boasts errors lower than those from any other DFT model, and is moreover competitive with the MP2 model in its relatively good agreement with MC-QCISD (we note that the particular error values are somewhat skewed by large numerical values for the Cl-Cl separation in the syn S_N2' TS structure, but assessment of the relative qualities of the models is insignificantly changed if this value is left out).

Having validated the performance of the *m*PW1PW91(0.581)/6-31G(d) level for chloride/allyl chloride, we next applied it to explore the energetics and structures of the

methylated systems, chloride/*Z*-crotyl chloride, chloride/*E*-crotyl chloride, and chloride/isoprenyl chloride. We expect the perturbing effect of methyl substituents to be sufficiently small, albeit in the range of chemical interest, that the SRP model optimized for the allyl parent system should be highly applicable. The free energies of activation for the various nucleophilic substitution reactions of these systems compared to the allyl case are provided in Table 3. The precipitous decrease in ΔG^\ddagger for the heterolytic S_N1 dissociation pathway tracks nicely the increased stability of the more highly substituted allyl cations; the most highly substituted system, isoprenyl, has a heterolysis free energy 24.2 kcal mol⁻¹ lower than that of the unsubstituted allyl system.

In the gas phase, the reaction mechanism having the lowest ΔG^\ddagger value is in every case the S_N2 pathway. While ΔG^\ddagger for this reaction coordinate is relatively insensitive to allylic substitution, the magnitude by which it is preferred over the two S_N2' pathways increases with increased allylic substitution. Such a trend is expected insofar as the S_N2 reaction does not move the position of the double bond, while the S_N2' reactions do, and in so doing generate a less substituted double bond. Less substituted double bonds are thermochemically less stable than more substituted cases, and this is reflected in the net reaction free energies for the S_N2' reactions of *Z*- and *E*-crotyl and isoprenyl chlorides, which are 1.1, 1.5, and 3.1 kcal mol⁻¹, respectively.

There is also a steady increase in preference for the anti S_N2' pathway over the syn case with increasing substitution at the γ carbon. Geometric analysis provides some insight into why this might be. Figures 2–5 provide ball-and-stick structures for all relevant stationary points for the various substrates, with key heavy-atom bond lengths and Löwdin partial atomic charges. With increased allylic substitution, the breaking and forming C-Cl bonds become longer in the TS structures, as would be expected based on the greater stability of the more highly substituted allylic cations. However, any such increased cationic charge on the allyl fragment must be balanced by increased negative charges on the chloride anions. In the anti S_N2' TS structure, the two chloride anions are sufficiently distant from one another that this is not particularly relevant, but in the syn TS structure they are separated by only about 4.5 Å. Unfavorable chloride-chloride interactions in the latter case thus mitigate overall geometric and charge relaxations, and indeed Figures 2 and 5 indicate that the net changes in

TABLE 2. Selected Heavy-Atom Bond Lengths (Å) in Allyl Chloride and Cl⁻/Allyl Chloride Nucleophilic Substitution TS Structures

| | level of theory | | | | | | | |
|-------------------------------------|-----------------|-------|-------|-------|-------|-----------------|------------------|-------------------------|
| | MC-QCISD | RHF | MP2 | BLYP | B3LYP | <i>m</i> PWPW91 | <i>m</i> PW1PW91 | <i>m</i> PW1PW91(0.581) |
| allyl chloride | | | | | | | | |
| C ¹ -Cl ⁴ | 1.799 | 1.804 | 1.798 | 1.867 | 1.835 | 1.837 | 1.809 | 1.781 |
| C ¹ -C ² | 1.491 | 1.495 | 1.491 | 1.498 | 1.492 | 1.493 | 1.488 | 1.481 |
| C ² -C ³ | 1.335 | 1.318 | 1.338 | 1.345 | 1.333 | 1.342 | 1.330 | 1.318 |
| S _N 2 | | | | | | | | |
| C ¹ -Cl ^{4/5} | 2.349 | 2.475 | 2.358 | 2.501 | 2.448 | 2.439 | 2.392 | 2.355 |
| C ¹ -C ² | 1.466 | 1.464 | 1.463 | 1.459 | 1.458 | 1.459 | 1.459 | 1.456 |
| C ² -C ³ | 1.337 | 1.319 | 1.342 | 1.352 | 1.339 | 1.348 | 1.335 | 1.319 |
| syn S _N 2' | | | | | | | | |
| C ^{1/3} -Cl ^{4/5} | 2.211 | 2.437 | 2.187 | 2.397 | 2.329 | 2.302 | 2.246 | 2.195 |
| C ¹ -C ² | 1.400 | 1.382 | 1.401 | 1.405 | 1.397 | 1.405 | 1.397 | 1.388 |
| C ² -C ³ | 1.400 | 1.382 | 1.401 | 1.405 | 1.397 | 1.405 | 1.397 | 1.388 |
| Cl ⁴ -Cl ⁵ | 4.440 | 5.143 | 4.576 | 5.092 | 4.925 | 4.913 | 4.764 | 4.619 |
| anti S _N 2' | | | | | | | | |
| C ^{1/3} -Cl ^{4/5} | 2.285 | 2.527 | 2.255 | 2.448 | 2.389 | 2.357 | 2.309 | 2.272 |
| C ¹ -C ² | 1.391 | 1.377 | 1.394 | 1.401 | 1.392 | 1.400 | 1.391 | 1.381 |
| C ² -C ³ | 1.391 | 1.377 | 1.394 | 1.401 | 1.392 | 1.400 | 1.391 | 1.381 |
| MSE | | 0.093 | 0.008 | 0.098 | 0.064 | 0.062 | 0.032 | 0.003 |
| MUE | | 0.108 | 0.017 | 0.099 | 0.066 | 0.063 | 0.035 | 0.025 |
| RMSE | | 0.219 | 0.039 | 0.199 | 0.144 | 0.138 | 0.091 | 0.051 |

TABLE 3. Computed 298 K Free Energies of Activation (ΔG^\ddagger , kcal mol⁻¹) for Gas-Phase Nucleophilic Substitution Reactions of Chloride/Allyl Chloride, Chloride/*Z*-Crotyl Chloride, Chloride/*E*-Crotyl Chloride, and Chloride/Isoprenyl Chloride^a

| pathway | allyl | <i>cis</i> -crotyl | <i>trans</i> -crotyl | isoprenyl |
|------------------------|-------|--------------------|----------------------|-----------|
| S _N 1 | 168.7 | 155.6 | 153.7 | 144.5 |
| S _N 2 | 9.8 | 8.8 | 10.0 | 8.8 |
| syn S _N 2' | 18.7 | 19.8 | 20.9 | 22.1 |
| anti S _N 2' | 14.4 | 14.5 | 15.4 | 15.7 |

^a At the *m*PW1PW91(0.581)/6-31G(d) level.

C-Cl bond lengths and chloride charges on going from the allyl to the isoprenyl system are only about half as large for the syn TS structures as for the anti ones.

SM5.42R Solvation: Energetics. The SM5.42R model is designed to compute solvation free energies for structures held rigid at their gas-phase geometries. Thus, it accounts for electronic relaxation, since it is a SCRf model, but not for geometrical relaxation. Solvated ΔG^\ddagger values computed at this level for the various nucleophilic substitution pathways discussed thus far are provided in Table 4 for carbon tetrachloride and water as solvents. Not present in the table, but worthy of comment, are data for the chloride/allyl chloride ion-dipole complex. In the gas phase, two ion-dipole complexes, one intervening along the S_N2 reaction coordinate and the other along the anti S_N2' coordinate, are computed to lie 7.7 and 7.1 kcal mol⁻¹, respectively, below separated reactants. In

CCl₄ these structures are computed respectively to be 2.2 and 2.5 kcal mol⁻¹ less stable than separated reactants, and in H₂O this difference increases to 6.0 and 5.9 kcal mol⁻¹, respectively. Insofar as the ion-dipole complexes do not appear to remain as minima on the solvated reaction coordinates, we take no further account of them in the following discussion.

In CCl₄, solvation of the separated ions *reduces* the S_N1 activation free energy by 75 to 80 kcal mol⁻¹ and *increases* the S_N2 and S_N2' activation free energies by 13 to 15 kcal mol⁻¹. Qualitatively, this is the behavior one expects based on better solvation of isolated, small, charged species compared to TS structures with more dispersed charge distributions. The quantitative magnitudes of the different solvation effects are insufficient, however, to overcome the gas-phase preference for the S_N2 pathway over the S_N1 alternative.

Although the net solvation free energies for the different S_N2 and S_N2' TS structures are all about the same, there is a small, consistently better solvation of the syn S_N2' TS structure compared to the anti one. The greater concentration of negative charge opposite a single face of the allyl fragment in the syn TS structure would be expected to lead to such differentiation. However, the magnitude of the difference is only 1 to 2 kcal mol⁻¹, which is not enough to overcome the gas-phase preference for the anti path over the syn one.

In H₂O, with its much larger dielectric constant, the

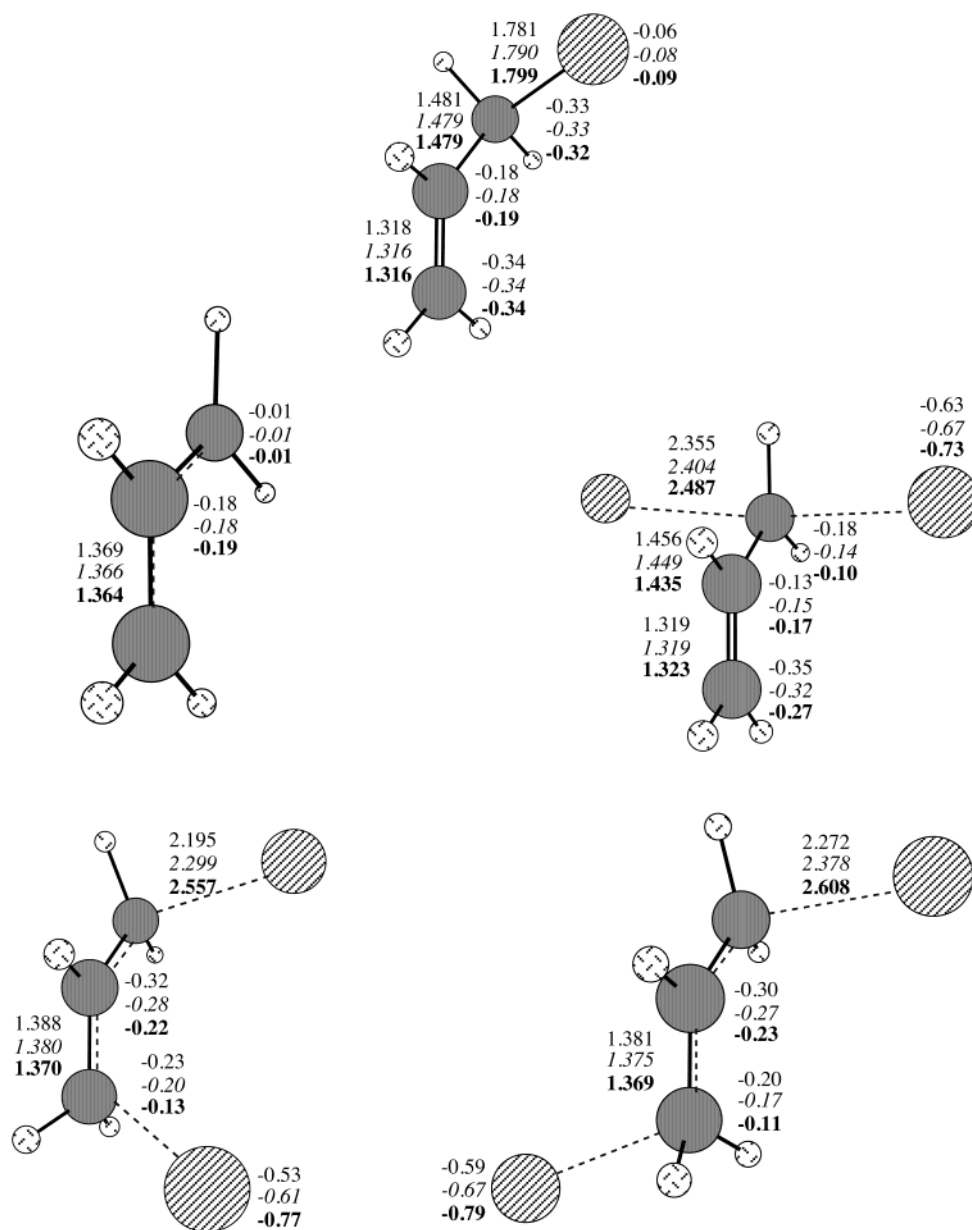


FIGURE 2. Unique heavy-atom bond lengths and Löwdin partial atomic charges for allyl chloride, allyl cation, and the three bimolecular nucleophilic substitution TS structures in the gas phase (roman), CCl_4 (italic), and H_2O (bold) at the $m\text{PW1PW91}(0.581)/6\text{-}31\text{G(d)}$ and $\text{SM5.42}/m\text{PW1PW91}(0.581)/6\text{-}31\text{G(d)}$ levels.

qualitative trends observed in CCl_4 are further amplified to the extent that the $\text{S}_{\text{N}}1$ activation free energy is predicted to be lower than the $\text{S}_{\text{N}}2$ one in every case. The preference ranges from 8 kcal mol⁻¹ in the allyl case to 19.4 kcal mol⁻¹ in the isoprenyl case. Within the bimolecular TS structures, the same trends found in CCl_4 persist in H_2O . The only noteworthy difference is that the preference for anti vs syn $\text{S}_{\text{N}}2'$ reaction is further reduced in water; in the allyl system the difference in ΔG^\ddagger values is only 0.9 kcal mol⁻¹.

As a technical point, the use of separated allyl and chloride ions to compute $\text{S}_{\text{N}}1$ ΔG^\ddagger values may not be an optimal best choice, since heterolysis in solution may actually involve multiple steps associated with (i) separation to a contact-ion pair, (ii) additional separation to a solvent-separated ion pair, and (iii) dissociation to free ions. However, such structures obviously do not exist as

stationary points in the gas phase, so they cannot be accounted for within the context of the frozen-geometry SM5.42R model. We now turn instead to the SM5.42 model to assess the importance of relaxed geometries and the general effect of solvation on the various reaction coordinates.

SM5.42 Solvation: Energetics and Structure. Free energies of activation computed after reoptimization of all structures in solution with the SM5.42 model are compiled in Table 5. Relaxed heavy-atom bond lengths and Löwdin partial atomic charges are listed in Figures 2–5, where they may be compared to gas-phase values. In general, geometric relaxation has negligible impact on ΔG^\ddagger for the $\text{S}_{\text{N}}1$ reaction, implying that the relaxation energies of the neutral reactants and cationic products are about equal in all cases (obviously the monatomic chloride anions cannot “relax” their structure). The TS

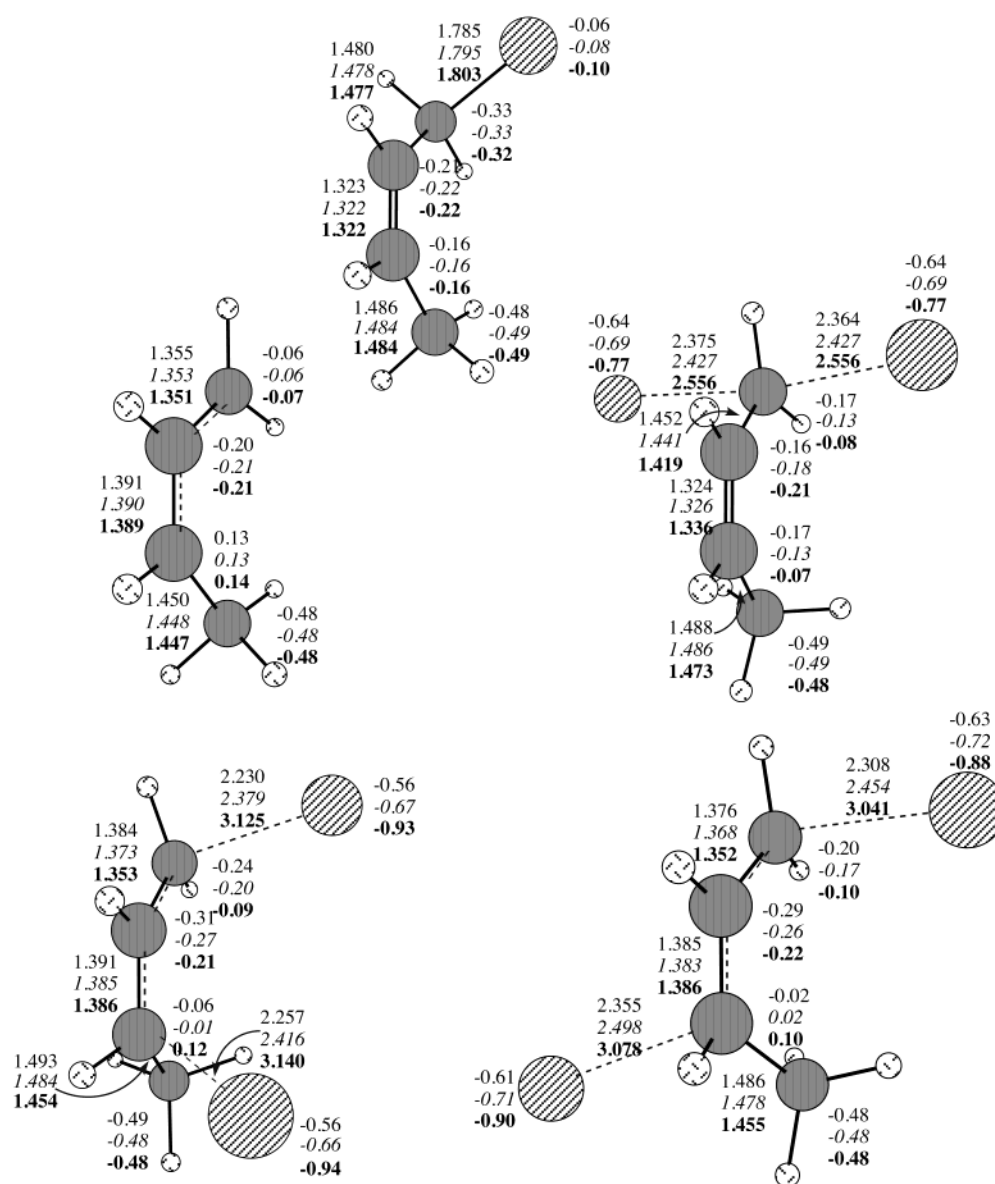


FIGURE 3. Heavy-atom bond lengths and Löwdin partial atomic charges for *Z*-crotyl chloride, *Z*-crotyl cation, and the three bimolecular nucleophilic substitution TS structures in the gas phase (roman), CCl_4 (italic), and H_2O (bold) at the $m\text{PW1PW91}(0.581)/6-31\text{G}(d)$ and $\text{SM5.42}/m\text{PW1PW91}(0.581)/6-31\text{G}(d)$ levels.

structures for the $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}2'$ reactions, on the other hand, with their partially formed/broken bonds, are much more prone to being influenced by solvation, and indeed the relaxed ΔG^\ddagger values for these reactions in CCl_4 are predicted to be up to 2 kcal mol⁻¹ smaller than when frozen geometries are used.

Examination of Figures 2–5 indicates that the primary effect of CCl_4 solvation on the bimolecular TS structures is to lengthen the C–Cl bonds and to slightly decrease the length of most C–C bonds. The trend is for solvation to amplify bond distance differences already present in the gas phase owing to different stabilities of the different allyl cations. Thus, in the unsubstituted allyl system, the C–Cl bonds lengthen by 0.049, 0.104, and 0.106 Å respectively in the $\text{S}_{\text{N}}2$, syn $\text{S}_{\text{N}}2'$, and anti $\text{S}_{\text{N}}2'$ TS structures. In the most heavily substituted isoprenyl system, by contrast, the changes (averaged over the two now nonsymmetrically related C–Cl bond lengths) are

0.077, 0.215, and 0.218 Å. With increasing “looseness” of the TS structure, there is also increased build-up of negative charge on the chlorine atoms. This geometric polarization effect is intimately coupled with the electronic polarization induced by the continuum solvent reaction field and leads to negative charge increases on chlorine of up to 0.15 atomic charge units in the various TS structures.

As expected, changing the solvent from CCl_4 to H_2O greatly amplifies most of the above-mentioned effects. In the most dramatic case, the TS structure for the syn $\text{S}_{\text{N}}2'$ reaction in *Z*-crotyl chloride, the two C–Cl bonds are each longer in water than in the gas phase by an average of 0.89 Å and the negative charge on the chlorine atoms increases by an average of 0.37 au. This very significant lengthening in a sense reaches an apparent limit in the *Z*-crotyl system, so that optimized TS structures for $\text{S}_{\text{N}}2'$ processes cannot be found in the *E*-crotyl and isoprenyl

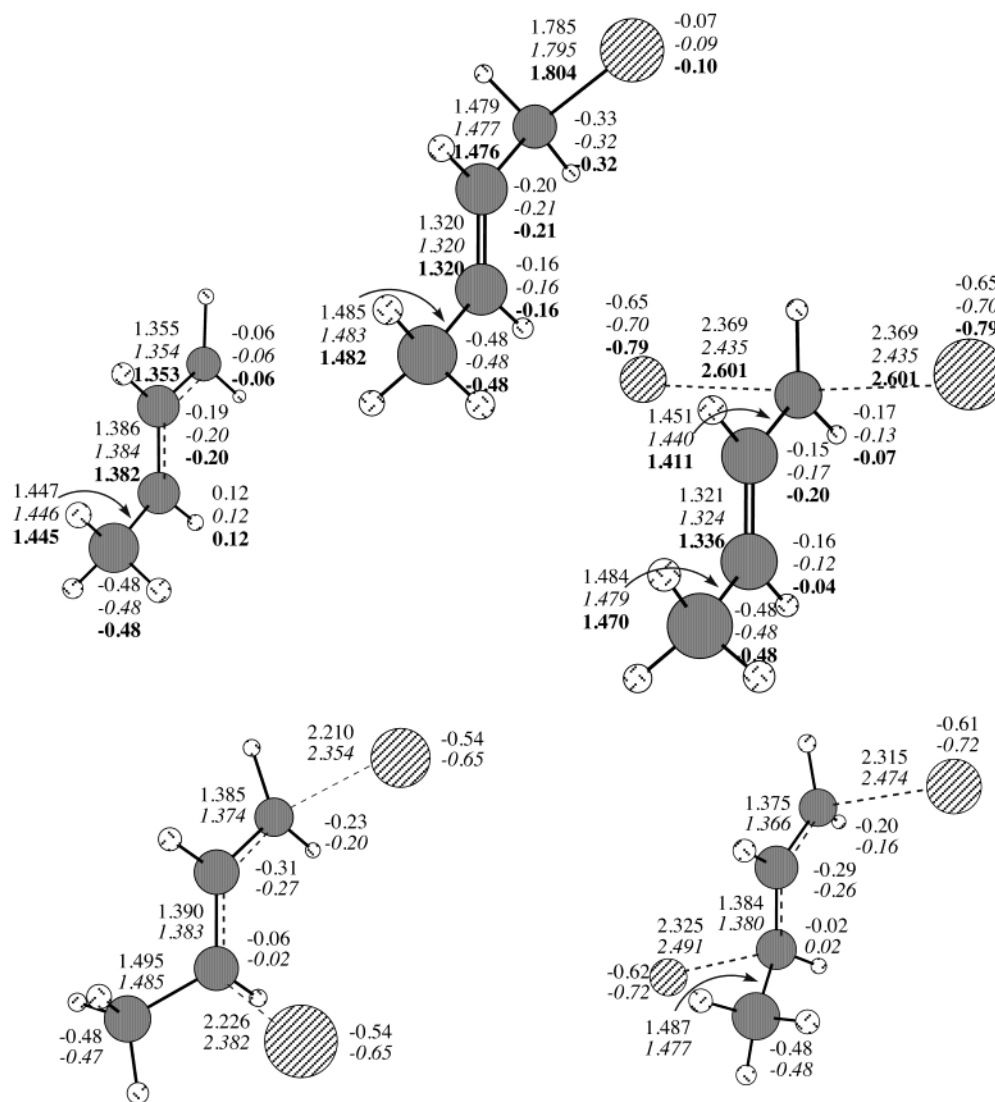


FIGURE 4. Heavy-atom bond lengths and Löwdin partial atomic charges for *E*-crotyl chloride, *E*-crotyl cation, and the three bimolecular nucleophilic substitution TS structures in the gas phase (roman), CCl_4 (italic), and H_2O (boldface) at the $m\text{PW1PW91}(0.581)/6\text{-}31\text{G(d)}$ and $\text{SM5.42}/m\text{PW1PW91}(0.581)/6\text{-}31\text{G(d)}$ levels. No $\text{S}_{\text{N}}2'$ TS structures are observed in water.

systems. That is to say, the desolvation penalty associated with bringing a chloride ion nucleophile up to the substituted allyl chloride electrophile is never sufficiently balanced by partial bonding interactions to generate a TS structure. It is instead more energetically favorable simply to heterolyze the allyl chloride and subsequently trap with another chloride. Figure 6 provides a graphical representation of the computed energies of activation associated with the $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2'$ processes (computed without gas-phase thermal contributions to free energy) as a function of dielectric constant in CCl_4 ($\epsilon = 2.2280$), *o*-xylene ($\epsilon = 2.5454$), diisopropyl ether ($\epsilon = 3.38$), propylamine ($\epsilon = 4.9912$), pentanal ($\epsilon = 10.00$), acetone ($\epsilon = 20.493$), ethanol ($\epsilon = 24.852$), methanol ($\epsilon = 32.613$), and water ($\epsilon = 78.3$). As $\text{S}_{\text{N}}1$ ionization becomes increasingly facile, the dielectric constant beyond which $\text{S}_{\text{N}}2'$ TS structures are impossible to locate becomes smaller. In the isoprenyl case, the relevant curves intersect at a dielectric constant of about 15, while for *E*-crotyl chloride, the intersection is found closer to $\epsilon = 40$.

Returning to the issue of the $\text{S}_{\text{N}}1$ “transition states”,

all efforts with SM5.42 to identify a point on the solvated heterolytic dissociation curve higher than the separated ionic products were unsuccessful. Physically, a continuum model is not the ideal choice to model an $\text{S}_{\text{N}}1$ reaction in solution, not only because failure to include explicit solvent molecules probably prohibits identification of solvent-separated ion pairs, but also because *nonequilibrium* solvation effects associated with the dynamic role of solvent fluctuations may play a significant role in generating a barrier to heterolysis in solution. When modeling the solvent based solely on its bulk dielectric constant, a continuum model is intrinsically limited to capturing bulk equilibrium solvation effects. These various points have been duly noted previously in the literature.^{57,67–74} However, to the extent that dynamical and nonequilibrium effects contribute to higher barriers for the $\text{S}_{\text{N}}1$ processes, the magnitude of these effects seems unlikely to be more than a few kilocalories per mole, which does not impact on the major qualitative difference seen for solvation as it affects the $\text{S}_{\text{N}}1$ vs the $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}2'$ pathways.

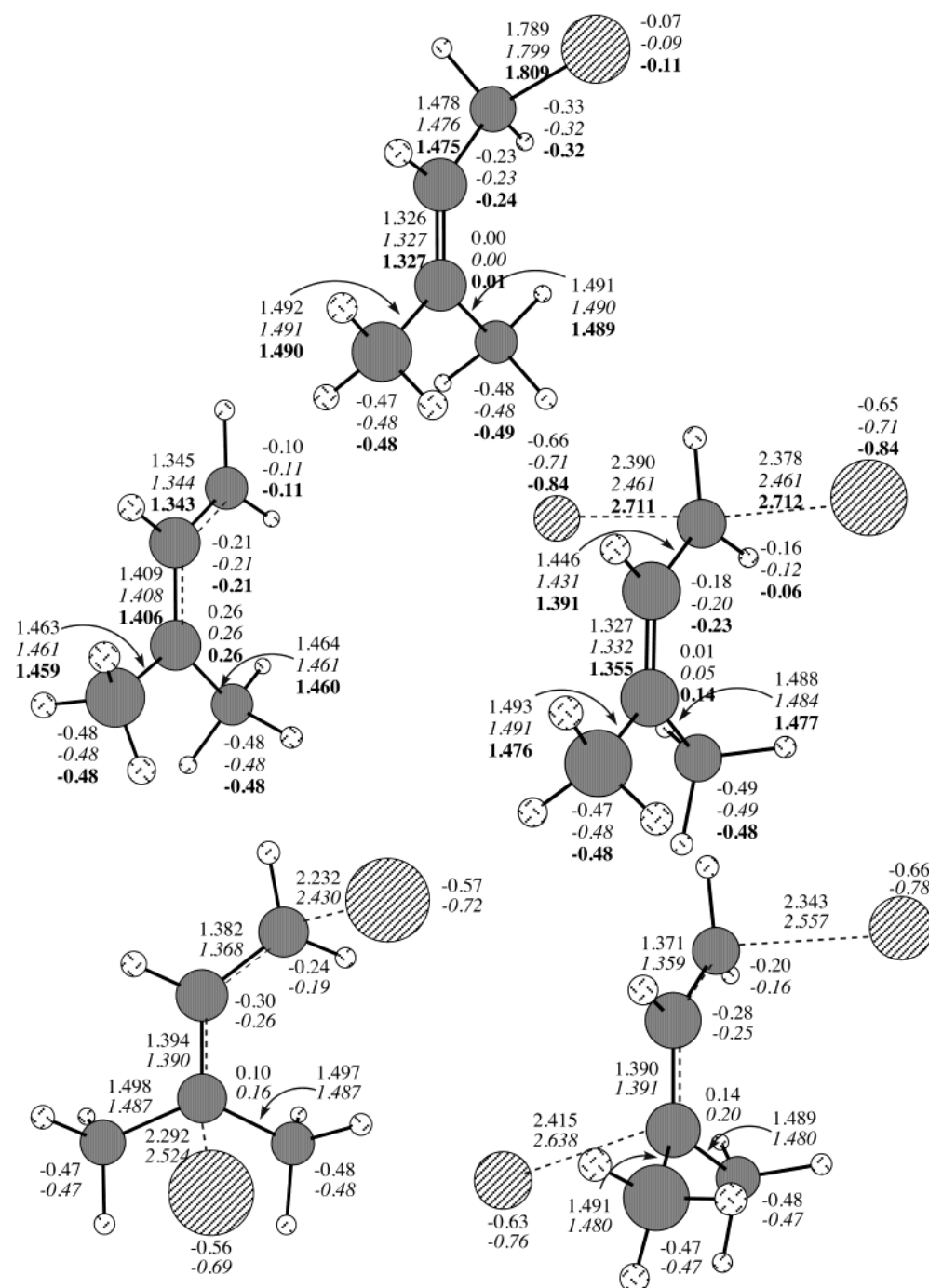


FIGURE 5. Heavy-atom bond lengths and Löwdin partial atomic charges for isoprenyl chloride, isoprenyl cation, and the three bimolecular nucleophilic substitution TS structures in the gas phase (roman), CCl_4 (italic), and H_2O (bold) at the $m\text{PW1PW91}(0.581)/6\text{-}31\text{G(d)}$ and $\text{SM5.42}/m\text{PW1PW91}(0.581)/6\text{-}31\text{G(d)}$ levels. No $\text{S}_{\text{N}}2'$ TS structures are found in water.

Implications and Comparisons to Experimental Observation. There are some limited experimental data with which to compare the present calculations. The bulk of the experimental data available for allyl chloride has been interpreted to suggest that it reacts primarily via the $\text{S}_{\text{N}}2$ mechanism in most organic solvents.^{83,85,87,88} This is consistent with our calculations; a very large dielectric constant, like that for water, is required to bring the free energy of activation for the $\text{S}_{\text{N}}1$ process below that for the $\text{S}_{\text{N}}2$. We note that Brubacher et al.⁸⁷ studied the hydrolysis of allyl chloride in water in 1968, and reported

a 298 K ΔG^\ddagger of $25.5 \pm 2 \text{ kcal mol}^{-1}$ for this process. This is in quantitative agreement with the corresponding value reported in Table 5 for allyl chloride ionization ($\text{S}_{\text{N}}1$) in water.

In the majority of nonaqueous solvents, experimental studies have been interpreted to indicate that crotyl chloride also seems to prefer the $\text{S}_{\text{N}}2$ pathway,^{78,85,89} consistent with the CCl_4 predictions in Table 5 (as an example of a nonpolar medium) and Figure 6. In aqueous solvents, however, it has been variously reported that crotyl chloride hydrolyses can be $\text{S}_{\text{N}}2$,^{76,78} $\text{S}_{\text{N}}1$,^{75,88} or a

TABLE 4. Computed 298 K Free Energies of Activation (ΔG^\ddagger , kcal mol⁻¹) for Frozen-Geometry Solvated Nucleophilic Substitution Reactions of Chloride/Allyl Chloride, Chloride/Z-Crotyl Chloride, Chloride/*E*-Crotyl Chloride, and Chloride/Isoprenyl Chloride^a

| pathway | allyl | Z-crotyl | <i>E</i> -crotyl | isoprenyl |
|------------------------|-------|----------|------------------|-----------|
| CCl ₄ | | | | |
| S _N 1 | 88.1 | 78.6 | 76.7 | 70.0 |
| S _N 2 | 23.4 | 22.6 | 23.1 | 22.0 |
| syn S _N 2' | 31.2 | 32.4 | 33.8 | 34.8 |
| anti S _N 2' | 28.6 | 28.9 | 29.6 | 29.8 |
| H ₂ O | | | | |
| S _N 1 | 25.2 | 18.5 | 16.5 | 12.0 |
| S _N 2 | 33.2 | 32.6 | 32.3 | 31.4 |
| syn S _N 2' | 40.4 | 41.2 | 42.5 | 43.1 |
| anti S _N 2' | 39.5 | 39.6 | 39.8 | 39.9 |

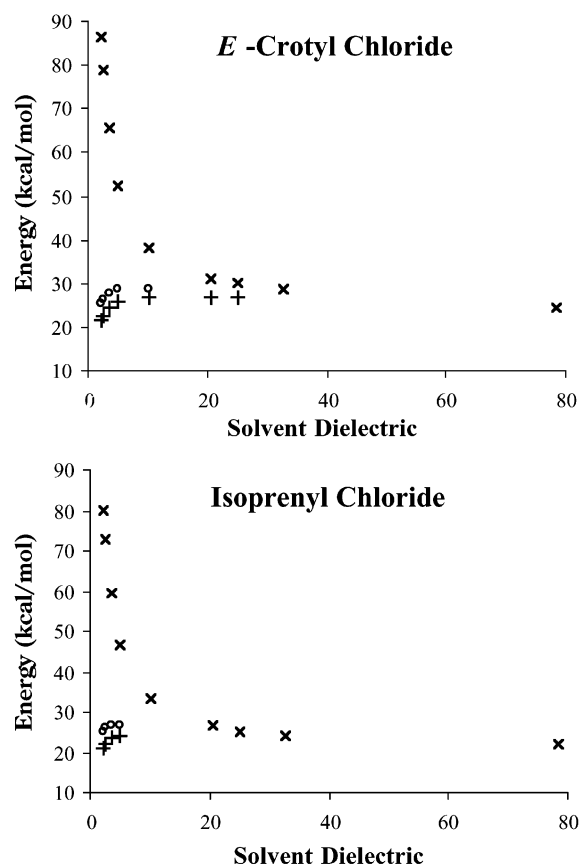
^a At the SM5.42R/*m*PW1PW91(0.581)/6-31G(d) level.**TABLE 5.** Computed 298 K Free Energies of Activation (ΔG^\ddagger , kcal mol⁻¹) for Relaxed Geometry Solvated Nucleophilic Substitution Reactions of Chloride/Allyl Chloride, Chloride/Z-Crotyl Chloride, Chloride/*E*-Crotyl Chloride, and Chloride/Isoprenyl Chloride^a

| pathway | allyl | Z-crotyl | <i>E</i> -crotyl | isoprenyl |
|------------------------|-------|----------|------------------|-----------|
| CCl ₄ | | | | |
| S _N 1 | 88.7 | 78.7 | 77.0 | 70.2 |
| S _N 2 | 23.0 | 21.5 | 22.6 | 21.0 |
| syn S _N 2' | 30.3 | 31.1 | 33.2 | 33.0 |
| anti S _N 2' | 28.3 | 27.5 | 28.1 | 27.8 |
| H ₂ O | | | | |
| S _N 1 | 25.8 | 18.7 | 16.7 | 12.2 |
| S _N 2 | 31.7 | 30.2 | 29.3 | 25.4 |
| syn S _N 2' | 37.0 | 32.5 | <i>b</i> | <i>b</i> |
| anti S _N 2' | 36.0 | 30.6 | <i>b</i> | <i>b</i> |

^a At the SM5.42/*m*PW1PW91(0.581)/6-31G(d) level. ^b No corresponding TS structures were found.

mixture of both.^{83,87} The predictions in Table 5 suggest, however, that the S_N1 pathway should strongly dominate over the S_N2 for crotyl chloride in water. Brubacher et al.⁸⁷ reported 298 K ΔG^\ddagger values of 22.5 ± 0.2 and 21.7 ± 0.4 kcal mol⁻¹ for hydrolysis of *Z*- and *E*-crotyl chloride, respectively. These values are 4 to 5 kcal mol⁻¹ higher than the predictions in Table 5, which may reflect the influence of nonequilibrium solvation effects on the reaction coordinate not accounted for by a continuum model (see above for discussion). However, they are also substantially below the predicted S_N2 free energies of activation, so that assignment of an S_N1 pathway in water seems secure (especially given the good agreement in the allyl case, where the preference of S_N1 over S_N2 should be *smaller* than in the crotyl system). In a separate interesting comparison, Hatch and Nesbitt⁸¹ reported in 1951 that *Z*-crotyl chloride reacted 5.3 times faster with sodium iodide in acetone at 293 K than did the *E* isomer. From transition-state theory, this would correspond to a difference in free energies of activation of about 1 kcal mol⁻¹. This value is in almost perfect agreement with the difference in S_N2 activation free energies predicted for the crotyl isomers reacting with chloride in CCl₄ (Table 5). While the processes are sufficiently different in nucleophile and solvent that quantitative comparison is not necessarily meaningful, the qualitative comparison is still of interest.

Nucleophilic substitution of isoprenyl chloride has also been reported to proceed via an S_N2 mechanism in nonaqueous solvents,^{84,85} consistent with data in Table

**FIGURE 6.** Energy barriers (as electronic energies plus free energies of solvation) for S_N1 (x) and S_N2' (O, syn; +, anti) pathways as a function of increasing solvent dielectric constant.

5 and Figure 6. As with the crotyl system, both S_N1^{83,84} and S_N2^{84,85} have been invoked in aqueous solution depending on reaction conditions, but our present results suggest that only the S_N1 pathway should be kinetically important.

Conclusions

The specific-reaction-parameter *m*PW1PW91(0.581)/6-31G(d) model permits electron-correlation and continuum solvation effects to be included simultaneously in electronic structure calculations that are computationally tractable for studying the narcissistic nucleophilic substitution reactions of chloride/allyl chloride and its γ -methylated analogues. In particular, this level of theory describes the energetics and geometries of these allylic systems very well in the gas phase when compared to very high-level molecular orbital calculations with the MCG3/MC-QCISD protocol, and provides qualitative and in some cases quantitative agreement with solution data. The model predicts S_N2 substitution pathways in all cases to be preferred over S_N2' alternatives, although that preference decreases somewhat with increasing solvent polarity. Of the two possible S_N2' pathways, the anti is always preferred over the syn, although again that preference decreases in solvents of increasing polarity. With respect to the S_N1 pathway (i.e., heterolysis of the allylic chloride), the intrinsic cost of separating unlike charges causes this pathway to be energetically unfavor-

able in the gas phase and in nonpolar media. However, solvation effects strongly stabilize the charge-separated products, so that in every case the S_N1 pathway is ultimately preferred over the S_N2 alternative with a sufficiently polar solvent. The point at which this occurs depends on the intrinsic stability of the allyl cation: earlier for isoprenyl than for crotyl, and the latter earlier than for allyl. Solvation effects are also predicted to strongly influence the geometries of the transition-state structures for bimolecular nucleophilic substitution, the most noteworthy effect being significant lengthening of

C–Cl bonds in solution compared to the gas phase (up to 0.9 Å for the most extreme case of the syn S_N2' reaction of *Z*-crotyl chloride in water).

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Supporting Information Available: Cartesian coordinates (Å) and energies (E_i) for all optimized structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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