less structure than in the bulk. These effects are essentially limited to the first solvation shell but increase in magnitude with the size of the hydrophobic solute. Loss of structure relative to bulk is also observed in the nonpolarizable water around the solute, but dependence on solute size is absent.

In accord with previous findings we see that the major influence on the nonpolar solute on the water phase is to slow down the motion of the waters surrounding it; the effect to which the important unfavorable entropic contributions to hydrophobic solvation have been attributed.[2]

Due to the weakened electrostatic interactions, polarizable water surrounding the solute, being able to reorient faster than nonpolarizable water, will have its motion less affected. It is suggested that here too the size and possibly shape of the nonpolar solute would influence the magnitude of the decrease for the polarizable water but not for the mean-field one.

In line with the results reported here on the subtle influence of electronic polarization on the structural properties of water surrounding a single methane, we find that molecular dynamics simulations with both water models yield very similar values for the methane hydration free energies, which are furthermore in good agreement with the experimental measures (results to be presented elsewhere).

The most remarkable outcome of this study concerns the striking influence of including electronic polarization effects for water on the computed methane–methane potential of mean force. The energy barrier to separate the two methanes is higher, while that for squeezing out the water from the solvent-separated configuration is lower, nearly abolishing the minimum corresponding to the solvent-separated configuration. The latter has been reproduced by a large number of previous studies, all using noninducible water models, but was regarded by many as counterintuitive. The present results and the recent findings that polarizable models also yield a more realistic representation of pure water diffusion properties[27,28] suggest that including electronic polarization in water simulations yields an improved physical description of the system, and should be instrumental in future studies of hydrophobic association in water.

Registry No. H_2O, 7732-18-5; CH_4, 74-82-8.

Theoretical Studies of Elimination Reactions. 3. Gas-Phase Reactions of F^- with $(CH_3)_2CHCl$ and $CH_3CH_2CH_2Cl$. The Effect of Methyl Substituents

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Abstract: The effect of methyl substitution on E2 and S_N2 mechanisms was evaluated by applying high-level ab initio calculations to the gas-phase reactions of F^- with $(CH_3)_2CHCl$ and $CH_3CH_2CH_2Cl$. E2 (anti and syn) as well as S_N2 pathways were investigated, and transition states were located at the 6-31+G* level. The nature of all stationary points was confirmed with analytical frequencies. Energy comparisons were made at the MP2/6-31+G**//HF/6-31+G* level, corrected for zero-point vibrations (scaled by 0.9). As expected, the addition of a methyl group at the α-carbon increases the S_N2 barrier (by 2.2 kcal/mol); however, in the proper conformation, a methyl group at the β-carbon reduces the barrier (by 1.7 kcal/mol). Methyl groups at either carbon stabilize the E2 transition states by about 2–3 kcal/mol. Both systems have a strong stereochemical preference ($\sim$13 kcal/mol) for anti rather than syn eliminations. The E2(anti) transition states are periplanar, and their geometries suggest a synchronous E2 elimination. The E2(syn) reactions are more E1cb-like and involve syn clinal rather than syn periplanar transition states. The FH_β–C_β–C_α–Cl dihedral is $\sim 35°$. In the syn transition states, the barrier to rotation around the C_α–C_β bond is small and the transition-state energy varies little for dihedral angles between 0 and 60° (1–3 kcal/mol). A review of past theoretical work indicates that syn clinal rather than syn periplanar conformations may be generally preferred for gas-phase syn eliminations. A comparison of the energetics of the S_N2 and E2 reactions predicts that elimination will dominate in the propyl systems.

Introduction

The S_N2 substitution and E2 elimination reactions have played fundamental roles in the development of modern physical organic chemistry.[1-4] During the past 50 years, there have been countless reports on the kinetics and selectivities of these reactions. On the basis of this work, detailed mechanisms have been formulated and generalizations have been developed concerning the effects of substituents. In fact, substituent effects have played a pivotal role in characterizing the mechanisms and transition states of S_N2 and E2 reactions. Although it is clear that the S_N2 reaction simply

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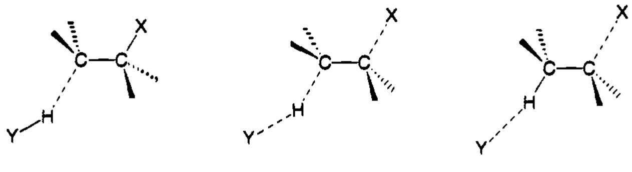
involves a concerted Walden inversion,[4] the nature of the E2 transition state is still under debate.[1-3] Because the E2 mechanism involves more bonding changes, it is inherently more complicated. From condensed-phase studies, it has been postulated that E2 reactions are concerted but not necessarily synchronous.



E1cb -Like E2 E1 - Like

As a result, a spectrum of transition states from E1cb-like to E1-like is possible;[2] however, many studies indicate that bimolecular eliminations usually are constrained to transition states in the E1cb-like to E2 limits of the spectrum.[1d] In addition, the conformation of the transition state must be considered. It has been generally accepted that the transition state prefers either a syn or an anti periplanar conformation.[13] Although the stereochemistry of most bimolecular eliminations is anti, there is ample evidence that syn eliminations can be favored under certain conditions.[1] The ratio of syn/anti elimination is often highly dependent on the solvent and base, so it is clear that solvation plays an important role in determining the stabilities of the transition states.[5]

Anti-Periplanar Syn-Periplanar

Although this body of work has given us a basic understanding of the S_N2 and E2 reactions, all condensed-phase studies suffer from a common dilemma: how can solvation and ion pairing effects be separated from factors inherent to the mechanism? In other words, does a substituent affect the electronic structure of the transition state, or does it simply perturb the solvation structure of the transition state? In general, it is difficult, if not impossible, to distinguish between these possibilities in condensed-phase work. Of course, these are important questions because substituent studies are often used to probe the electronic structures of transition states. In addition, because the S_N2 and E2 reactions involve charged species, solvation effects play a particularly important role.

More recently, S_N2 and E2 reactions have been studied in the gas phase using mass spectrometric techniques. Here the mechanisms can be investigated in the absence of solvation, and in the past decade several groups have reported accurate kinetics as well as isotope effects for the gas-phase reactions of nucleophiles with alkyl halides and related substrates.[6-15] One complication in mass spectrometric studies is that, in general, only the ionic products can be identified. Because both mechanisms lead to the same ionic products, it is often difficult to determine whether an S_N2 or E2 mechanism is active and only in a few instances has it been possible to cleanly distinguish between S_N2 and E2 pathways in gas-phase nucleophilic reactions.[7-9,15]

Theory provides an alternative method for studying the S_N2 and E2 mechanisms in the absence of solvation. An advantage of theory, particularly in regard to the E2 mechanism, is that the geometry of the transition-state structure is determined directly. Moreover, the energetics of each mechanism can be evaluated independently and compared to assess the competition between S_N2 and E2 paths. Over the past two decades the S_N2 reaction has been extensively studied with ab initio methods, and many high-level studies are available.[16-18] In contrast, relatively little work has been reported on the E2 reaction, and most ab initio studies have dealt with only simple substrates such as ethyl halides.[19-22] Using the AM1 method, Dewar and Yuan[23] have investigated a wide variety of E2 reactions, but the ability of the semiempirical method to characterize these complicated systems is uncertain. Recently, we have presented the first truly high-level ab initio studies of E2 eliminations. In one study, the gas-phase reactions of F^- with CH_3CH_2Cl were characterized at the MP4(SDQ)/6-31(+)G**//HF/6-31(+)G* level.[22] In this system, the S_N2 and E2 (syn and anti) mechanisms were investigated, and the transition-state energies indicate that the S_N2 and E2(anti) pathways are competitive. The E2(anti) reaction involves a prototypical E2 transition state in which proton transfer, double bond formation, and leaving group expulsion occur simultaneously. In contrast, the E2(syn) transition state has significant E1cb character and is much less stable. In a study of the E2 reaction of HO^- with $CH_3CH_2OCH_3$, we discovered that for E1cb-like reactions, it is possible for syn eliminations to adopt syn clinal rather than syn periplanar transition states.[24]

In the present study, we investigate the effects of substituents on the transition states of S_N2 and E2 reactions. Building on our earlier work with the $F^- + CH_3CH_2Cl$ system,[22] we consider the effects of methyl substitution at the α- and β-carbons of ethyl chloride ($F^- + (CH_3)_2CHCl$ and $F^- + CH_3CH_2CH_2Cl$, respec-

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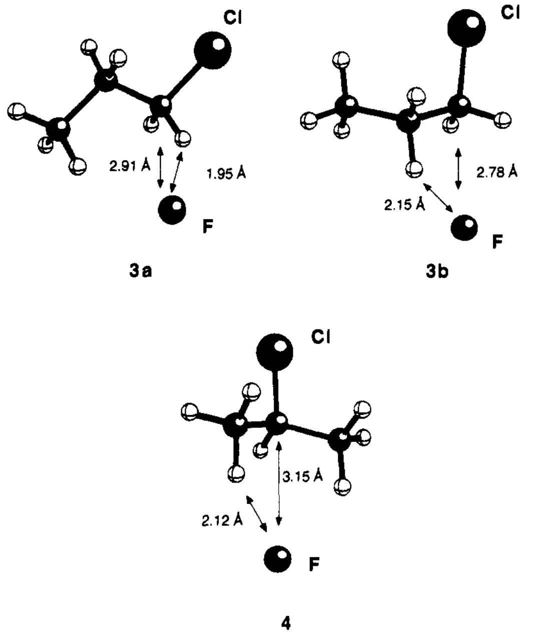

Figure 1. Optimized structures (6-31+G*) of ion–dipole complexes. Halides, dark shading; carbon, light shading; hydrogen, no shading.

tively). To thoroughly characterize these systems, S_N2 and E2 (anti and syn) pathways are evaluated and relevant ion–dipole complexes are located. These studies allow us to quantitatively predict the effects of alkyl substitution on the barriers to S_N2 and E2 reactions. In addition, the effect of methyl substituents on the nature and conformation of the E2 transition-state structure can be discerned. Throughout this work, comparisons will be made to the parent system $F^- + CH_3CH_2Cl$. Finally, the topological properties of the transition states are analyzed with Bader's PROAIM program.[22,25]

Methods

All calculations were carried out on a Multi-Flow Trace 14 or a Cray-YMP computer using the GAUSSIAN 90 quantum mechanical package developed by Pople and co-workers.[26] All structures were fully optimized using basis sets derived from the standard 6-31G* basis set.[27] When appropriate, the existence of multiple stable rotamers was investigated. For anionic systems, diffuse sp orbitals were added to all heavy centers (6-31+G*).[28] Neutral systems were optimized with the standard 6-31G* basis set. The curvature of the potential energy surface at all minima and transition states was confirmed with analytical second derivatives, and frequencies are reported in the supplementary material. For energy comparisons, single-point calculations were done on the optimized geometries using a basis set that included polarization (p) functions on the hydrogens (6-31+G**).[29] To correct for correlation effects, frozen-core Moeller-Plesset perturbation theory was applied up to the second level (MP2).[30] Earlier work suggests that this is an adequate level for S_N2 and E2 systems.[31] Energies also were corrected for zero-point energy differences (scaled by 0.9).[32]

Table I. Energies of Minima and Transition States[a]

structure	HF/ 6-31+G*	HF/ 6-31+G**	MP2/ 6-31+G**	ZPE[b]
1a	−676.585 836	−676.597 434	−677.375 980	57.7
1b	−676.586 194	−676.596 839	−677.375 779	57.7
2	−676.589 654	−676.600 380	−677.381 363	57.4
3a	−676.613 021	−676.624 521	−677.404 814	57.8
	(−17.0)	(−16.9)	(−18.0)	
3b	−676.611 901	−676.623 012	−677.402 066	57.7
	(−16.1)	(−16.4)	(−16.5)	
4	−676.617 466	−676.629 079	−677.411 087	57.5
	(−17.3)	(−17.9)	(−18.5)	
5a	−676.598 069	−676.609 166	−677.379 852	57.5
	(−7.9)	(−7.6)	(−2.6)	
5b	−676.603 822	−676.615 015	−677.385 611	57.4
	(−11.4)	(−11.7)	(−6.5)	
6	−676.605 652	−676.617 294	−677.385 378	56.8
	(−10.6)	(−11.2)	(−3.1)	
7	−676.587 358	−676.601 658	−677.385 304	53.6
	(−5.0)	(−6.7)	(−9.9)	
8	−676.592 418	−676.606 782	−677.385 759	53.6
	(−5.5)	(−7.8)	(−6.6)	
8[c] (MP2)		−676.604 947	−677.391 549	
		(−6.7)	(−10.2)	
9	−676.564 404	−676.580 599	−677.364 922	53.7
	(+9.4)	(+6.6)	(+2.9)	
10	−676.569 129	−676.585 350	−677.370 768	53.4
	(+8.9)	(+5.4)	(+2.6)	

[a] Absolute energies given in hartrees. Energies relative to separated reactants given in parentheses (kcal/mol). For the elimination reactions of *n*-propyl chloride, the anti conformation is used to calculate relative energies. Geometries from 6-31+G* or 6-31G* optimizations. [b] In kcal/mol, scaled by 0.9, see ref 31. For **8** (MP2), the zero-point energy from the Hartree–Fock geometry is used. [c] Geometry optimized at the MP2/6-31+G* level.

To analyze the topological properties of the transitions states, integrated electron populations and critical point densities were calculated using Bader's PROAIM package modified to run on a Sun 4/110 workstation. The details of these calculations have been described elsewhere.[22,25]

Results and Discussion

Ion–Dipole Complexes. In gas-phase ion–molecule reactions, the first minimum on a reaction coordinate is generally a loosely-bound ion–dipole complex. For systems as large as *n*-propyl chloride (**1a,b**, anti and gauche) and isopropyl chloride (**2**), there is the possibility of several energetically similar complexes. In the present study, only complexes in which the F^- interacts with the back side of the α-carbon were considered. The structures of the ion–dipole complexes of fluoride with *n*-propyl chloride (anti, **3a**, and gauche, **3b**, conformations) and isopropyl chloride (**4**) are shown in Figure 1. The $F–C_\alpha$ distance varies considerably in these complexes from a minimum of 2.78 Å in **3b** to a maximum of 3.15 Å in **4**. In **3b** and **4**, the fluoride has a short-range interaction with a hydrogen on the β-carbon (2.15 and 2.12 Å, respectively), whereas in **3a**, the fluoride instead interacts with a hydrogen on the α-carbon ($F–H_\alpha = 1.95$ Å). Nonetheless, at the MP2/6-31+G** level (Table I), the complexation energies of **3a**, **3b**, and **4** vary by only 2.0 kcal/mol. Consequently, in these systems the complexation energy is based more on the gross polarity and polarizability of the neutral rather than any specific short-range interactions. At the same level of theory, the complexation energy of $F^- + CH_3CH_2Cl$ is −14.9 kcal/mol;[22] therefore, the additional methyl group has a modest effect (~3 kcal/mol) on the complexation energy.

S_N2 Reactions. The transition states for the S_N2 reactions of F^- with *n*-propyl chloride (anti, **5a**, and gauche, **5b**, conformations)

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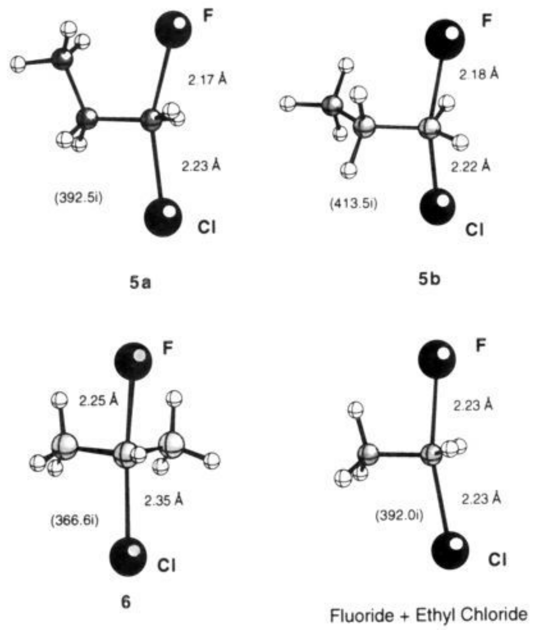

Figure 2. Optimized structures (6-31+G*) of S_N2 transition states. Halides, dark shading; carbon, light shading; hydrogen, no shading. Imaginary frequencies (cm^{-1}) given parenthetically.

were located at the 6-31+G* level, and the structures are shown in Figure 2. As expected for exothermic substitutions, both transition states occur early on the reaction coordinate.[33,34] The C–F distances are long (~2.18 Å), and the C–Cl bonds (~2.23 Å) are somewhat elongated. At the MP2/6-31+G* level, transition states **5a** and **5b** have energies of −2.6 and −6.5 kcal/mol with respect to the separated reactants. Negative activation barriers are well known for gas-phase ion–molecule reactions and do not imply that a collision-controlled rate will be observed.[35] Brauman has pointed out that entropic barriers must be considered and has predicted that activation energies as negative as −8 kcal/mol may reduce the rate below the collision-controlled limit.[12,36] The gauche conformation is preferred in the S_N2 reaction (**5b**) because it suffers from less steric crowding. In the anti conformation, the back side of the C–Cl bond is blocked by the β-methyl group, and as a result the S_N2 transition state (**5a**) is destabilized. Although the gauche conformation of *n*-propyl chloride is slightly less stable than the anti, the back side of the C–Cl bond is blocked by a hydrogen and the fluoride is less affected by crowding in the S_N2 transition state. It should be noted that structure **5a** has C_s symmetry and a single imaginary vibration, but rotation around the C_α–C_β bond involves a very low frequency (28 cm^{-1}).

The reaction of fluoride with ethyl chloride can be used to assess the effect of β-methyl substitution on the energy of the S_N2 transition state. At a similar level of theory, the barrier to the reaction of F^- with CH_3CH_2Cl is −4.8 kcal/mol; therefore, in a gauche conformation the β-methyl group lowers the S_N2 activation barrier by 1.7 kcal/mol. The stabilization of the transition state presumably results from the greater polarizability of the substrate. For comparison, Dewar and Yuan's AM1 study suggested S_N2 barriers of 0.9 and 0.7 kcal/mol for the reactions of CH_3O^- with ethyl chloride and *n*-propyl chloride.[23] Given that CH_3O^- is a stronger base (nucleophile)[37] than F^-, it appears that the AM1 method overestimates the S_N2 barrier and underestimates the substituent effects in this system. The ab initio results also indicate that steric crowding in the anti conformation of *n*-propyl chloride (**5a**) leads to an S_N2 barrier that is 2.2 kcal/mol greater than that of ethyl chloride. Although a full dynamics treatment would be required to quantify the effects,[38] these results suggest that the gas-phase S_N2 reaction of fluoride with *n*-propyl chloride should occur more readily than that with ethyl chloride. That is, a β-methyl group effectively reduces the S_N2 barrier. Although one transition state is disfavored (**5a**) in *n*-propyl chloride, the stabilizing effect of the β-methyl group in the gauche transition states (1.7 kcal/mol) is sufficient to overcome this disadvantage. Experimentally, Caldwell, Magnera, and Kebarle[14] have observed a similar effect for β-substituents. Using variable temperature studies, they deduced that the activation barrier for the gas-phase S_N2 reaction of Cl^- with *n*-butyl bromide was 1.3 kcal/mol lower than that with ethyl bromide.

Transition state **5a** gives insight into the anomalous gas-phase reaction of fluoride with neopentyl chloride. In condensed-phase S_N2 reactions, neopentyl halides are several orders of magnitude less reactive than methyl halides.[39] The rationalization is that the three methyl groups on the β-carbon effectively block the back side of the C–Cl bond and prevent S_N2 reactions. However, in the gas phase fluoride reacts at similar rates with neopentyl chloride and methyl chloride.[6] The steric crowding in **5a** is analogous to what is expected in the reaction of fluoride with neopentyl chloride—there is a β-methyl group that is anti to the C–Cl bond. The neopentyl group's two other methyls are gauche to the C–Cl bond and should have little adverse effect on the S_N2 reaction because the transition state occurs early on the reaction coordinate (little C–Cl cleavage). For example, in **5b** the presence of a β-methyl group gauche to the C–Cl bond slightly lowers the activation barrier. Therefore, it is reasonable to assume that the barrier to the S_N2 reaction of F^- with neopentyl chloride should not differ much from that of F^- with *n*-propyl chloride in its anti conformation (**5a**). An activation energy of approximately −2 kcal/mol is consistent with the efficient gas-phase reaction observed for F^- with neopentyl chloride. The bare, unsolvated fluoride anion is sufficiently small that methyl substitution at the β-carbon (anti to the Cl) only modestly destabilizes the transition state. Evidence that size plays a role in these substitutions is found in the gas-phase reaction of CH_3O^- with neopentyl chloride. Although CH_3O^- is more basic than F^- in the gas phase, its S_N2 reaction with neopentyl chloride is less efficient.[6] Given that gas-phase S_N2 rates generally correlate with basicities,[37] this result indicates that the S_N2 barrier in neopentyl chloride is very sensitive to the size of the incoming nucleophile. Solvation of the nucleophile greatly increases its effective size, and as a result the S_N2 reactions of neopentyl halides involve greater steric crowding and, consequently, substantially larger barriers in solution.

The effect of α-methyl substitution on the S_N2 reaction can be analyzed using the reaction of F^- with isopropyl chloride. The S_N2 transition state (**6**) has C_s symmetry and is shown in Figure 2. As with *n*-propyl chloride, an early transition state is observed;[40] however, both the C–F and C–C distances (2.25 and 2.35 Å, respectively) are approximately 0.1 Å longer in this transition state. At the MP2/6-31+G** level, the activation barrier for this S_N2 reaction is −3.1 kcal/mol, or 1.7 kcal/mol larger than that observed in the reaction of F^- with ethyl chloride. The lengthening of the C–F and C–Cl bonds as well as the larger barrier is consistent

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[33] Hammond. G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

[34] The gas-phase S_N2 reaction of F^- with *n*-propyl chloride has a $\Delta H°$ value of −31.2 kcal/mol. Data taken from: (a) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. No. 1. (b) Stull, D. R.; Westrun, E. F.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1969.

[35] (a) *Gas Phase Ion Chemistry*, Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. I. (b) Lim, K. F.; Brauman, J. I. *J. Chem. Phys.* **1991**, *94*, 7164.

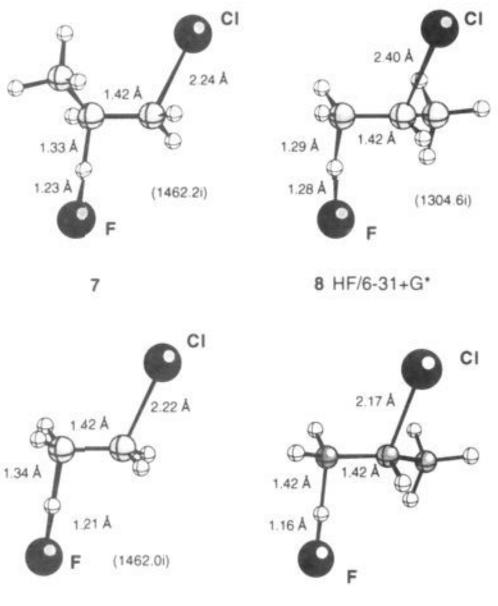
[36] Han, C.-C.; Brauman, J. I. *J. Am. Chem. Soc.* **1989**, *111*, 6491.

[37] A good correlation between base strength and S_N2 efficiencies has been observed in gas-phase substitutions, see ref 6 and Damrauer, R.; DePuy, C. H.; Bierbaum, V. M. *Organometallics* **1982**, *1*, 1553. With the exception of neopentyl chloride, methoxide and fluoride give similar efficiencies in reactions with alkyl chlorides, see ref 6.

[38] For sample dynamics studies of gas-phase ion–molecule reactions, see: (a) Tucker, S. C.; Truhlar, D. G. *J. Am. Chem. Soc.* **1990**, *112*, 3338. (b) Tucker, S. C.; Truhlar, D. G. *J. Phys. Chem.* **1989**, *93*, 8138. (c) Chesnavich, W. J.; Bass, L.; Su, T.; Bowers, M. T. *J. Chem. Phys.* **1981**, *74*, 2228.

[39] Streitwieser, A., Jr. *Solvolytic Diplacement Reactions*; McGraw-Hill: New York, 1962.

[40] The S_N2 reaction of F^- with isopropyl chloride has a $\Delta H°$ of −29.1 kcal/mol, see ref 34.



7

8 HF/6-31+G*

Fluoride + Ethyl Chloride

8 MP2/6-31+G*

Figure 3. Optimized structures (6-31+G*) of E2(anti) transition states. Halides, dark shading; carbon, light shading; hydrogen, no shading. Imaginary frequencies (cm^{-1}) given parenthetically.

Table II. Integrated Populations and ρ-Values[a]

structure		charge[b,c]	ρ[d](e/au^3)
1a	CH_3	+0.02 (−0.09)	
	$C_\beta H_2$	+0.10 (+0.20)	
	$C_\alpha H_2$	+0.22 (−0.06)	
	Cl	−0.34 (−0.06)	C–Cl, 0.179
	C_β	+0.26 (−0.09)	
1b	CH_3	+0.02 (−0.05)	
	$C_\beta H_2$	+0.09 (+0.10)	
	$C_\alpha H_2$	+0.22 (+0.07)	
	Cl	−0.35 (−0.13)	C–Cl, 0.177
	C_β	+0.26 (−0.17)	
2	CH_3	+0.10 (−0.13)	
	C_α	+0.22 (+0.07)	
	H_α	+0.02 (+0.17)	
	Cl	−0.36 (−0.18)	C–Cl, 0.173
	C_β	+0.25 (−0.46)	
5a	Cl	−0.72 (−0.61)	C–Cl, 0.061
	F	−0.93 (−0.85)	C–F, 0.037
	CH_3	+0.07 (−0.11)	
	$C_\beta H_2$	+0.12 (+0.17)	
5b	Cl	−0.72 (−0.65)	C–Cl 0.062
	F	−0.93 (−0.86)	C–F 0.036
	CH_3	−0.06 (−0.17)	
	$C_\beta H_2$	+0.12 (+0.22)	
6	Cl	−0.77 (−0.74)	C–Cl 0.047
	F	−0.97 (−0.87)	C–F 0.032
	CH_3	+0.13 (−0.03)	
7	Cl	−0.71 (−0.63)	C–Cl 0.061
	F	−0.88 (−0.74)	H_β–F 0.136
	H_β	+0.56 (+0.44)	H_β–C_β 0.158
	CH_3	−0.03 (−0.10)	
	C_β	−0.02 (−0.32)	C_α–C_β 0.304
8[e]	Cl	−0.69 (−0.61)	C–Cl 0.072
	F	−0.88 (−0.69)	H_β–F 0.124
	H_β	+0.59 (+0.44)	H_β–C_β 0.164
	CH_3	+0.09 (−0.02)	
	C_β	−0.03 (−0.69)	C_α–C_β 0.305
9	Cl	−0.58 (−0.43)	C–Cl 0.098
	F	−0.88 (−0.62)	H_β–F 0.232
	H_β	+0.71 (+0.51)	H_β–C_β 0.084
	CH_3	−0.14 (−0.21)	
	C_β	−0.05 (−0.45)	C_α–C_β 0.285
10	Cl	−0.58 (−0.44)	C–Cl 0.098
	F	−0.89 (−0.64)	H_β–F 0.216
	H_β	+0.70 (+0.52)	H_β–C_β 0.092
	CH_3	+0.05 (−0.13)	
	C_β	−0.06 (−0.81)	C_α–C_β 0.279
ethyl chloride + F^- (S_N2)	Cl	−0.72 (−0.65)	C–Cl 0.061
	F	−0.94 (−0.88)	C–F 0.037
ethyl chloride + F^- (E2(anti))	Cl	−0.71 (−0.63)	C–Cl 0.064
	F	−0.88 (−0.79)	H_β–F 0.143
	H_β	+0.58 (+0.46)	H_β–C_β 0.149
	C_β	+0.01 (−0.51)	C_β–C_α 0.301
ethyl chloride + F^- (E2(syn))	Cl	−0.58 (−0.46)	C–Cl 0.097
	F	−0.88 (−0.80)	H_β–F 0.195
	H_β	+0.67 (+0.63)	H_β–C_β 0.103
	C_β	−0.16 (−0.70)	C_β–C_α 0.281

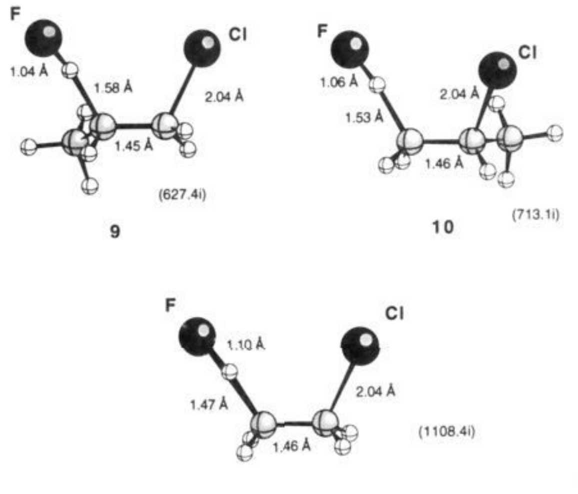
[a] Wave functions generated with 6-31G** or 6-31+G** basis sets. Values for ethyl chloride reactions from ref 22. [b] Integrated population from volumes defined with Bader procedure. For fragments, atom populations were summed. [c] Net charge from Bader calculation. Mulliken charges given parenthetically. [d] Critical point densities from Bader analysis. [e] Geometry from MP2/6-31+G* optimization.

with the α-methyl group crowding the pentacoordinate transition state. However, the effect on the activation barrier is relatively minor and is only apparent when correlation effects are considered. At the Hartree–Fock level, the reactions of F^- with ethyl chloride and isopropyl chloride have similar barriers (−10.8 and −11.2 kcal/mol, respectively). The need for correlation corrections in calculating S_N2 barriers is well known, but previous studies indicate that the MP2 level is adequate for characterizing most systems.[18] Experimentally, Kebarle et al.[14] found a larger effect in the reaction of Cl^- with isopropyl bromide. Here, the addition of an α-methyl group increases the barrier by 4.3 kcal/mol.

The effects of α- and β-methyl substitution on the S_N2 transition state can also be evaluated in terms of the electronic structure. Using Bader's PROAIM program,[25] integrated electron populations as well as critical point densities were computed (Table II). As anticipated from the geometries and energies, the electronic structures of **5a**, **5b**, and **6** are similar to that of the S_N2 transition state of $F^- + CH_3CH_2Cl$. As has been noted before for S_N2 transition states,[22] the nucleophile and leaving group have significant negative charges which are balanced by a large positive charge on the intervening carbon. For example, in **6**, the fluorine and chlorine have large negative charges (−0.97 and −0.77, respectively) and the isopropyl group has a net charge of +0.74.

E2(anti) Reactions. The structure of the E2(anti) transition state of F^- + *n*-propyl chloride(**7**) is given in Figure 3. The geometry is consistent with a synchronous E2 reaction in which proton transfer, π-bond formation, and leaving group expulsion have each progressed to approximately the same extent at the transition state. The C–H_β bond is long (1.33 Å), the C_α–C_β bond has contracted to 1.42 Å, and the C–Cl bond has stretched to 2.24 Å. The bond lengths are almost identical to those found in the E2(anti) elimination of $F^- + CH_3CH_2Cl$. At the MP2/6-31+G**//HF/6-31+G* level, the energy of transition state **7** is −9.9 kcal/mol with respect to the separated reactants. For comparison, the activation barrier for the E2(anti) reaction of $F^- + CH_3CH_2Cl$ is −7.1 kcal/mol at a similar level of theory.[22] Therefore, the addition of a β-methyl group lowers the E2(anti) barrier by almost 3 kcal/mol but has little effect on the geometry. Although the β-methyl group stabilizes the transition state by its polarizability, there is little evidence in the calculated charges and ρ-values (Table II). In going from the reactant (*n*-propyl chloride) to the transition state (**7**), the charge on the CH_3 group increases by 0.05 electron, indicating only a small polarization of the CH_3–C_β bond in response to the developing charge at C_β. The β-methyl group has virtually no effect on the charges and ρ-values associated with the atoms directly involved in the elimination (H_β, C_β, Cl, and F).

At the Hartree–Fock level, the transition state for the E2(anti) reaction of F^- with isopropyl chloride (**8**) has significant E1-like character. Specifically, the C–Cl distance is long (2.40 Å), indicating that leaving group expulsion has progressed to a greater extent, and the C–H_α distance is short (1.29 Å), indicating that proton transfer has progressed to a lesser extent. However, this geometry appears to be an artifact of the Hartree-Fock wave function. In contrast to all the E2 transition states we have previously studied, MP2 corrections reduce the relative stability



9

10

Fluoride + Ethyl Chloride

Figure 4. Optimized structures (6-31+G*) of E2(syn) transition states. Halides, dark shading; carbon, light shading; hydrogen, no shading. Imaginary frequencies (cm^{-1}) given parenthetically.

of this transition state. This result led us to reoptimize the transition state at the MP2/6-31+G* level. The reoptimization led to significant changes in the geometry. In particular, the transition state lost its E1-like character and adopted a structure similar to that of **7**. The C–H_α distance is 1.41 Å, and the C_α–Cl distance is 2.17 Å. Apparently, at the Hartree–Fock level the ability of the methyl group to stabilize positive charge at the α-carbon is overestimated, and E1-character results.[41] At the MP2/6-31+G**//MP2/6-31+G* level, the activation energy for the E2(anti) elimination reaction of F^- isopropyl chloride (−10.2 kcal/mol) is about the same as that calculated for F^- + *n*-propyl chloride (−9.9 kcal/mol). Therefore, addition of a methyl group at either the α or the β-carbon of ethyl chloride lowers the E2(anti) activation barrier by about 3 kcal/mol. In contrast, Dewar and Yuan's AM1 calculations[23] predict that an α-methyl group has little effect on the barrier, whereas a β-methyl group reduces the barrier by 1.5 kcal/mol. It should be noted that the E2 reaction of *n*-propyl chloride is more exothermic than the eliminations of either isopropyl chloride or ethyl chloride (by 3.9 and 3.2 kcal/mol, respectively); consequently, the effect of the methyl substituent on the transition-state energy is independent of its effect on the stability of the products or reactants.[34] The topological properties of transition state **8** are similar to those found for **7** and for the E2(anti) transition state of F^- + CH_3CH_2Cl (Table II).

E2(syn) Transition States. The E2(syn) transition state for the reaction of F^- with *n*-propyl chloride (**9**) is given in Figure 4. The transition state is not syn periplanar and has a Cl–C_α–C_β–H_β dihedral angle of 35°. Although the transition state is not completely staggered (dihedral = 60°), it is best described as syn clinal.[42] In contrast, the syn elimination of F^- + CH_3CH_2Cl is perfectly syn periplanar (C_s symmetric). A syn clinal E2 transition state was recently reported in the reaction of HO^- with $CH_3CH_2OCH_3$; however, that system is strongly biased toward an E1cb-like transition state.[24] In **9**, the steric demands of the β-methyl group are sufficient to force the transition state out of the eclipsed conformation required for a syn periplanar transition state. Because a syn clinal transition state limits the π-overlap between the α- and β-carbons, the double bond formation and leaving group expulsion steps are delayed, and as a result an E1cb-like transition state is observed. In **9**, the C_β–H_β distance is stretched to 1.58 Å and the F–H_β distance is reduced to only 1.04 Å. In contrast, the C–Cl bond is only slightly stretched (2.04 Å). Although the transition state is twisted, there is some π-bonding and the C_α–C_β distance has contracted to 1.45 Å. Previous theoretical work indicates that syn eliminations should have more E1cb-like character than anti eliminations;[19,20,22] however, the effect is surprisingly large in this system. For comparison, in the E2(syn) reaction of F^- with CH_3CH_2Cl, the C–H_β distance is 1.47 Å.[22] In fact, **9** has the longest C–H_β distance ever reported for an E2 reaction (ab initio). The high degree of E1cb character is consistent with the methyl group stabilizing the incipient carbanion at the β-carbon.

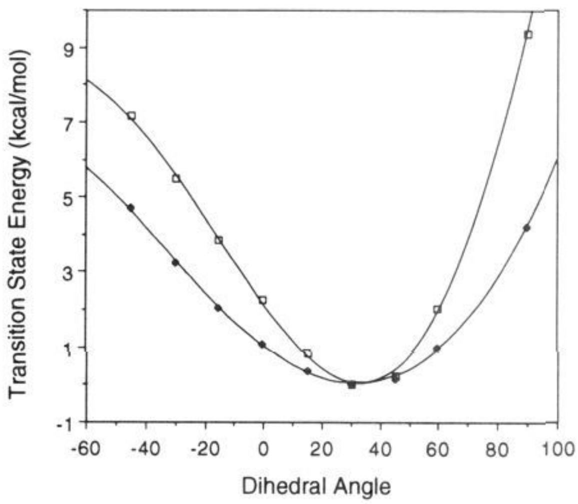
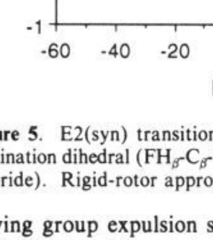
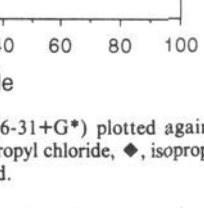


Figure 5. E2(syn) transition-state energy (6-31+G*) plotted against elimination dihedral (FH_β-C_β-C_α-Cl). (□, *n*-propyl chloride, ◆, isopropyl chloride). Rigid-rotor approximation is used.

There is the possibility of two distinct syn clinal transition states (the β-methyl can be either pseudo-anti or pseudo-gauche to the chloride); however, only **9** (pseudo-gauche methyl) is observed.



pseudo-gauche methyl



pseudo-anti methyl

To be certain that the syn clinal transition state is not an artifact of the Hartree–Fock wave function, **9** was reoptimized at the MP2/6-31+G* level. Correlation has only minor effects on the geometry of **9**, and an H_β–C_β–C_α–Cl dihedral of about 25° is observed. A survey of the potential energy surface indicates that the barrier to rotation around the C_α–C_β bond is very small. In Figure 5, a rigid rotor approximation is used to calculate the energy of the transition state at various dihedral angles (H_β–C_β–C_α–Cl). A single minimum appears, and for dihedral angles between 0 and 60°, the energy varies by less than 3 kcal/mol. The shallowness of the well indicates that subtle effects determine the preferred conformation. Moreover, the presence of a single minimum indicates that conformational preference is not based solely on relieving steric strain; otherwise, one would expect that rotation in either direction (positive or negative dihedral angle) would reduce the energy of the transition state. Apparently, the transition state prefers a slight overlap between the C_β–CH_3 and the C_α–Cl bonds.

As expected, the syn elimination has a larger activation barrier than the anti elimination. At the MP2/6-31+G**//HF/6-31+G*

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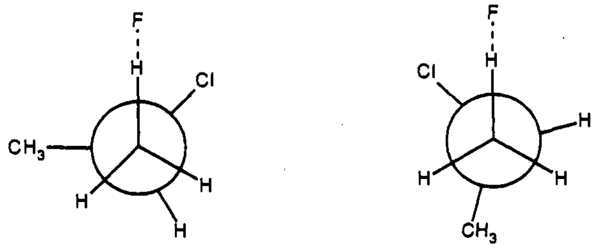
(41) To confirm that optimizations at the MP2 level were only necessary for **8**, transition state **7** was also reoptimized at the MP2 level. At the MP2/6-31+G* level, **7** adopts slightly more E1cb character (C–Cl = 2.12 Å, C_β–H_β = 1.40 Å); however, there is little effect on the energy (<1 kcal/mol).

(42) In our previous study of staggered syn eliminations (ref 24), the transition state was referred to as syn gauche; however, earlier work by Klyne and Prelog defined such a transition state as syn clinal. For consistency, we will adopt their nomenclature: Klyne, W.; Prelog, V. *Experentia* **1960**, *16*, 521.

level, the barrier for the E2(syn) reaction of F^- + *n*-propyl chloride is 2.9 kcal/mol, or 12.8 kcal/mol above the barrier of the E2(anti) reaction. For comparison, the reaction of F^- CH_3CH_2Cl has an E2(syn) barrier of 5.5 kcal/mol and an E2(syn) – E2(anti) difference of 12.6 kcal/mol.[22] Therefore, the addition of a β-methyl group lowers the E2(syn) barrier by 2.6 kcal/mol. The disadvantage of the syn clinal conformation (reduced π-overlap) is outweighed by the advantages of having a polarizable group at the β-carbon. The fact that the β-methyl group provides nearly the same stabilization in both the E2(anti) and E2(syn) transition states of *n*-propyl chloride is another indication that the twisting of the C_α–C_β bond in the syn conformation has little energetic consequence.

The E2(syn) transition state of F^- + isopropyl chloride (**10**) is given in Figure 4. The transition state is syn clinal and adopts a conformation similar to that of **9**. The H_β–C_β–C_α–Cl dihedral is 34°. Two syn clinal conformations are also possible in this system (the α-methyl can be either pseudo-anti or pseudo-gauche to the F–H_β group), but only one (**10**) is a true transition state (pseudo-gauche α-methyl). A plot of transition-state energy versus dihedral angle is given in Figure 5. Compared to **9**, the potential energy surface is less sensitive to the dihedral angle, and the transition-state energy varies by approximately 1 kcal/mol for dihedral angles between 0 and 60°. Given that the rigid rotor approach will overestimate the angular dependence, this result suggests that the potential energy surface is nearly flat in this region.[43] It is difficult to rationalize why one direction of rotation around the C_α–C_β bond (with respect to syn periplanar) is preferred over the other; however, in both the E2(syn) transition states (*n*-propyl chloride and isopropyl chloride), the preferred conformation places the more polarizable group closer (gauche) to the breaking bond. Transition state **10** has a high degree of E1cb character. The proton transfer is nearly complete (F–H_β = 1.06 Å, C_β–H_β = 1.53 Å), but C–Cl bond cleavage has just begun (C–Cl = 2.04 Å). The π-overlap in the transition state reduces the C_α–C_β bond length to 1.46 Å. The activation energy for the E2(syn) elimination of F^- + isopropyl chloride is 2.6 kcal/mol, or approximately 3 kcal/mol less than that for the syn elimination of F^- + ethyl chloride.[22] Once again, the addition of a methyl group leads to a twisted transition state but reduces the barrier to the E2(syn) elimination.



pseudo-gauche methyl pseudo-anti methyl

The E1cb-like nature of the syn clinal transition states can be analyzed in terms of the electron populations and ρ values of the systems.[44] Comparing the topological properties of the anti and syn eliminations of *n*-propyl chloride (**7** and **9**), it is obvious that proton transfer has progressed to a greater extent in **9**. Specifically, there is a larger positive charge on the transferring proton (+0.71), and the ρ-value for the F–H_β bond is much larger (0.232 compared to 0.136). In addition, the ρ-value for the C_β–H_β bond is smaller (0.084 compared to 0.158). Evidence of the polarizability of the β-methyl group can be seen in its integrated population. In **9**, the population on the β-methyl group increases to 9.14 electron, 0.16 greater than in *n*-propyl chloride. The polarization is localized in the C–H bonds of the β-methyl group, and each of the hydrogens carries a significant charge (−0.14 electron in **9** as compared to −0.07 electron in *n*-propyl chloride). Therefore, in response to the charge at the β-carbon, the CH_3 acts as an *electron-withdrawing group* and stabilizes the transition state. From gas-phase studies, there is ample evidence that alkyl groups can polarize their electron density in order to stabilize nearby anions.[45] A similar polarization is not observed in **7** because in the more prototypical E2 transition state there is less charge development at the β-carbon and, therefore, the polarization is less directed.

The E1cb character of transition state **10** is also obvious in the ρ-values and charges. As in **9**, a large ρ-value for the F–H_β bond (0.216) and a small one for the C_β–H_β bond (0.092) indicates that proton transfer is nearly complete. In addition, a small charge on the Cl (−0.58) relative to that in **8** (−0.69) indicates that leaving group expulsion is lagging. The polarization of the methyl group in **10** is less evident. At the α-carbon, the methyl group is isolated from the center of localized charge (β-carbon), and therefore its polarization is not as obvious.

Syn Periplanar Transition States. On the basis of orbital overlap arguments, it has been assumed that syn bimolecular eliminations should adopt periplanar conformations.[1] In this way, the transition state maximizes its π-overlap and is already in the proper orientation to smoothly form a planar alkene moiety. However, Bach[19] has pointed out that the π-interaction between the α- and β-carbons is limited in a syn conformation, and therefore anti periplanar transition states are preferred. Nonetheless, if orbital overlap dominates in determining the preferred conformation, then syn eliminations should involve periplanar geometries. The obvious disadvantage of a syn periplanar transition state is that it requires an eclipsed conformation along the C_α–C_β bond. Even in an unsubstituted system (CH_3CH_3), an eclipsed conformation causes about 3 kcal/mol of destabilization.[46] Therefore, eliminations must overcome a strong bias for a staggered conformation in order to adopt a syn periplanar transition state.

Although it has been widely accepted that syn eliminations adopt periplanar transition states, there is little evidence that this is the case. Because syn periplanar and syn clinal transition states give the same stereochemical results, experimental studies generally cannot distinguish between the two mechanisms. To date, high-level ab initio methods have been used to investigate the E2(syn) eliminations of only five substrates: CH_3CH_2F,[19,20] CH_3CH_2Cl,[20,22] $CH_3CH_2OCH_3$,[24] $CH_3CH_2CH_2Cl$, and $(CH_3)_2CHCl$. The last three of these systems give syn clinal transition states. The ether elimination may be discounted because it is biased toward an E1cb-like transition state—CH_3O^- is a poor leaving group. In fact, even the anti periplanar transition state is E1cb-like in the ether system. However, the fluoride-induced eliminations of *n*-propyl chloride and isopropyl chloride do not exhibit this bias. Their E2(anti) eliminations clearly involve prototypical E2 transition states (proton transfer, π-bond formation, and leaving group expulsion occur synchronously). In fact, they are very similar to the E2(anti) transition state observed in the reaction of CH_3CH_2Cl with F^-. Nonetheless, the E2(syn) reactions of *n*-propyl chloride and isopropyl chloride clearly prefer transition states with syn clinal conformations. The only theoretical evidence for syn periplanar E2 transition states comes from ab initio studies of the eliminations of ethyl halides.[19,20,22] However, the barrier to rotation around the C_α–C_β bond appears to be exceedingly small in these transition states. For example, in the E2(syn) reaction of F^- + CH_3CH_2Cl, the vibration associated with this motion has a frequency of only 33 cm^{-1}. If there is only a marginal preference for syn periplanar transition states in unsubstituted systems, then it is not surprising that steric (or electronic) effects in substituted systems force the transition state into a syn clinal conformation. *In general, syn clinal transition states*

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(43) Since only the minimum is fully optimized, the energies of the rotated stuctures are overestimated.

(44) The ρ-value is related to the strength of the covalent interaction and the length of the bond. For related analyses, see: (a) Bader, R. F. W.; Tang, T.-H.; Tal, Y.; Biegler-Konig, F. W. *J. Am. Chem. Soc.* **1982**, *104*, 946. (b) Knop, O.; Boyd, R. J.; Choi, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 7299. (c) Bader, R. F. W. *Atoms in Molecules*; Oxford University Press: Oxford, 1990.

(45) For example, see: (a) Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 5986. (b) DePuy, C. H.; Gronert, S.; Barlow, S. E.; Bierbaum, V. M.; Damrauer, R. *J. Am. Chem. Soc.* **1989**, *111*, 1968. (c) Reference 34a.

(46) Lowe, J. P. *Prog. Phys. Org. Chem.* **1968**, *6*, 1.

are preferred for exothermic syn eliminations and only unsubstituted or, possibly, E1-like systems are expected to adopt syn periplanar transition states. However, the E2(syn) transition-state energy is relatively insensitive to the dihedral angle (H_β–C_β–C_α–Cl), and therefore the reaction has exceptional conformational freedom. Important exceptions are systems in which the transition state occurs late on the reaction coordinate (endothermic or marginally exothermic eliminations). In these systems, there can be extensive π-bonding in the transition state, and therefore, syn periplanar transition states would be expected. E1-like systems have not been studied theoretically, and there is little information concerning the conformational preferences (syn periplanar or syn clinal) of their transition states.

The present results can be reconciled with DePuy's classic study of syn eliminations.[3] DePuy et al. found that in 2-arylcyclopentyl tosylates, syn elimination occurs nearly as readily as anti elimination ($k_{anti}/k_{syn} = 14$). In contrast, there is a large rate difference in the analogous 2-arylcyclohexyl tosylates ($k_{anti}/k_{syn} > 10^4$). The authors reasoned that it would be much easier for the cyclopentyl system to attain a syn periplanar transition state. On the basis of the present results, it may be argued that in the ground state the cyclopentyl system is in an acceptable conformation for a syn clinal elimination (dihedral angle ≈30°). In contrast, the dihedral angle in the cyclohexyl system is too large (~60°), so some ring deformation must occur, and as a result a larger barrier is encountered.[47]

E2 versus S_N2 in Alkyl Halides. The competition between E2 and S_N2 pathways has been the subject of many experimental studies. Unfortunately, relatively little is known about the competition in the gas phase because most of the experimental techniques are capable only of identifying ionic products (for alkyl halides, both mechanisms give the same ionic product). In an early study, Lieder and Brauman[9] identified ethyl fluoride as a product in the reaction of $F^- + CH_3CH_2Cl$; however, they were unable to determine whether the elimination product $CH_2{=\!=}CH_2$ was also present. Jones and Ellison[8] employed neutral trapping techniques to investigate the reaction of $CH_3O^- + CH_3CH_2CH_2Br$. The only observed neutral product was $CH_2{=\!=}CH{-\!-}CH_3$, the elimination product. Gronert, DePuy, and Bierbaum[7] have used primary deuterium isotope effects to distinguish between S_N2 and E2 processes with alkyl chlorides and bromides. They found that the reactions of $(CD_3)_2CHCl$ with weak oxygen bases such as $CF_3CF_2CH_2O^-$ exhibited large primary isotope effects ($k_H/k_D = 4.7$), indicating that E2 was most likely the dominant mechanism. The alkyl bromides exhibited smaller isotope effects, but a clear distinction could be made between ethyl bromide and isopropyl bromide. In the reaction of CD_3CD_2Br with $(CF_3)_2CHO^-$, only a modest isotope effect was observed ($k_H/k_D = 1.17$), but when $(CD_3)_2CHBr$ was the substrate, a significant primary isotope effect was seen ($k_H/k_D > 1.9$). This result is consistent with the E2 mechanism playing a larger role in the reaction of the isopropyl halide.

The present theoretical results are in accord with these experimental observations. For *n*-propyl chloride and isopropyl chloride, theory predicts that the E2(anti) pathway should have a lower activation barrier (by 3.4 and 7.1) kcal/mol, respectively) than the S_N2 pathway. In addition, Brauman[12] has pointed out that S_N2 transition states are highly ordered and, consequently, disfavored entropically. As a result, even if the enthalpic barriers of the S_N2 and E2 reactions were similar, the E2 path would be preferred on the basis of the entropic considerations. This can be tested using an RRKM approach and the calculated vibrational frequencies.[12] Assuming momentarily that the barriers to the S_N2 and E2 reactions of F^- with *n*-propyl chloride are the same, the RRKM calculation predicts that the E2 path would be favored by 2:1. Using the theoretical energy difference in the S_N2 and E2 barriers (3.6 kcal/mol), the RRKM calculation predicts that elimination will account for >99% of the products. In the reaction of F^- with isopropyl chloride, the RRKM calculation predicts that elimination will completely dominate. As expected, theory also suggests that substitution should be more competitive with ethyl halides. In the reaction of fluoride with ethyl chloride, the difference in activation barriers for the E2 and S_N2 reactions is calculated to be only 2.3 kcal/mol at a similar level of theory, and therefore substitution should play a more important role.[48]

Conclusion

Ab initio studies of the reactions of F^- with $(CH_3)_2CHCl$ and $CH_3CH_2CH_2Cl$ have led to new insights into the effects of substituents on the barriers and transition states of gas-phase S_N2 and E2 reactions.[49] For S_N2 reactions, alkyl substitution at the β-carbon reduces the barrier (by ~1.5 kcal/mol) if the substrate can adopt a conformation that places a hydrogen rather than an alkyl group anti to the C–Cl bond; otherwise, crowding increases the barrier (by ~2.2 kcal/mol). The addition of an α-methyl group crowds the S_N2 transition state and increases the barrier (by ~1.7 kcal/mol). In E2 reactions, methyl substitution at either carbon stabilizes the transition state and reduces the barrier by about 3 kcal/mol. It may be argued that in the eliminations the methyl substituent plays no specific role but acts simply as a polarizable group that allows for greater delocalization of the charge. This interpretation is strengthened by the fact that a methyl group provides a similar stabilization to the inital ion–dipole complexes (~3 kcal/mol). As has been noted elsewhere for E2 reactions, there is a strong preference for anti periplanar transition states. In the anti conformation, the transition state is consistent with a synchronous E2 mechanism. Surprisingly, the syn eliminations of these systems involve syn clinal rather than syn periplanar conformations. Although the E2 (syn) reaction of $F^- + CH_3CH_2Cl$ adopts a syn periplanar transition state, the methylated systems (*n*-propyl chloride and isopropyl chloride) prefer transition states with FH_β–C_β–C_α–Cl dihedral angles of ~35°; however, the potential energy surface is very shallow with respect to C_β–C_α rotation. As a result, E2(syn) reactions have exceptional conformational freedom with respect to the dihedral angle between the eliminating groups. The syn clinal conformation reduces steric crowding, but also reduces π-overlap. As expected, the syn clinal transition states have a high degree of E1cb character. Since syn periplanar transition states have been found for only the ethyl halides, it appears that gas-phase syn eliminations might generally adopt syn clinal transition states. Comparison of the energetics of the S_N2 and E2 processes suggests that elimination should dominate in the gas-phase reactions of the propyl chlorides.

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Supplementary Material Available: Tables of Z-matrix energies, geometries (bond distances and bond angles), and frequencies at specified optimization levels for **1a**, **1b**, **2**, **3a**, **3b**, **4**, **5a**, **5b**, **6**, **7**, **8**, **9**, and **10** (9 pages). Ordering information is given an any current masthead page.

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(47) Studies of E2 reactions in cyclopentyl and cyclohexyl systems are underway, and the results will be presented in subsequent publications.

(48) It should be noted that at higher levels of theory the S_N2–E2 transition-state energy difference is usually reduced; however, the magnitude of this effect should not affect the present qualitative analysis.

(49) Studies of other substituents have been completed and will be presented in subsequent publications.