Theoretical Studies of Eliminations. 6. The Regiochemistry and Stereochemistry of the Gas-Phase Reactions of 3-Halocyclohexenes with Fluoride. An *ab Initio* Study[†]

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The gas phase reactions of fluoride with 3-chlorocyclohexene and 3-fluorocyclohexene have been investigated with *ab initio* calculations up to the MP2/6-31+G** level. Transition states were located for 1,4-eliminations and 1,2-eliminations as well as S_N2 and S_N2' substitutions. For each reaction, a variety of stereochemical outcomes was explored. For both systems, the preferred pathway is an anti 1,4-elimination, but syn 1,4-eliminations and anti 1,2 eliminations have transition states that are nearly as stable. The two modes of substitution (S_N2 and S_N2') have similar barriers, but are much less favorable than elimination. The results are compared to recent experimental studies of related systems.

Introduction

Elimination reactions are fundamental, yet surprisingly complicated, processes in organic chemistry. Despite a tremendous amount of work in the condensed phase,[1−4] questions remain concerning the inherent regioselectivity and stereoselectivity of eliminations. Over the past 20 years, the development of gas phase techniques has allowed chemists to investigate the nature of eliminations without the confounding effects of solvation and ion-pairing.[5−13] This work has been supported by theoretical studies and has led to a clearer picture of the inherent stereoselectivities of base-induced 1,2-eliminations.[14−25] More recently, there has been interest in allylic systems because they are capable of not only 1,2-eliminations, but also 1,4-eliminations.[10−12,26] Compared to 1,2-eliminations, there has been relatively little theoretical work on 1,4-eliminations. In addition to a recent density functional theory (DFT) study by Nibbering, there are early, semiquantitative studies by Fukui,[27] Anh,[28] and Tee.[29] Numerous studies in solution indicate that 1,4-elimination usually dominates (although there are notable examples where 1,2-elimination is preferred)[30−33] and that, in contrast to 1,2-eliminations, a syn pathway is generally preferred.[34−37] The preference for syn elimination was also predicted in the early theoretical efforts. However, gas phase results present a slightly different pattern. Using a flowing-afterglow, Rabasco and Kass have shown that in cyclic allylic ether systems (*i.e.*, 3-methoxycyclohexenes), there is competition between 1,4-elimination and 1,2-elimination with the former dominating when strong bases are used and the latter when weaker bases are employed.[11,12] Contrary to this observation, Nibbering and co-workers have observed almost exclusive 1,4-elimination in the gas phase reactions of 2-butenyl ethyl ethers.[10] As for stereochemistry, Rabasco and Kass have used their cyclohexenyl systems to show that the selectivity for the 1,2 and 1,4 processes shifts from anti to syn as the strength of the base is reduced.[26] Taken together, these results suggest that there is a delicate balance in the gas phase between the possible pathways and that subtle differences in sub-

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[†] Dedicated to Professor Charles H. DePuy on the occasion of his 70th birthday.

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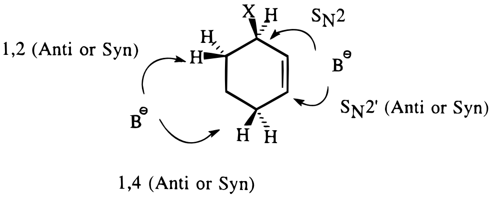
Scheme 1



strate structure as well as changes in base strength can alter the selectivity pattern.

To investigate the regioselectivity and stereoselectivity of the eliminations of allylic systems, we have chosen to study the reactions of fluoride with 3-chlorocyclohexene and 3-fluorocyclohexene. These systems model the reactions studied by Rabasco and Kass,[11−13,26] but are computationally more tractable because they involve fewer atoms, and the degrees of freedom in the leaving group and base are more limited. This is critical because the reaction coordinates of 1,4-eliminations involve complex atomic motions on a relatively shallow potential energy surface. As a result, transition state searches are demanding and are easily contaminated by low frequency modes (*e.g.*, rotation around an O−H bond with HO^- as the base). The chloro system offers a good leaving group, a moderate base, and a highly exothermic elimination[38−40]—a situation favoring a synchronous E2 pathway. In contrast, fluoride is a poor leaving group, and the elimination of 3-fluorocyclohexene is endothermic.[41] This will lead to a late transition state and should shift the mechanism toward a more E1cb-like path. In previous computational work by Nibbering and co-workers,[10] E1cb intermediates were identified in the reactions of hydroxide and fluoride with 2-butenyl methyl ether, and it was determined that these intermediates are formed *via* barrierless proton transfers. In addition, they found that the bare allylic anion (*i.e.*, $^-CH_2CH{=}CHCH_2OCH_3$) is stable with respect to loss of methoxide. As a result, they concluded that the 1,4-eliminations of 2-butenyl methyl ether are truly E1cb. In the present study, we will use the 3-fluorocyclohexene system to investigate whether E1cb mechanisms are general for 1,4-eliminations involving poor leaving groups.

Overall, the 3-halocyclohexene system offers a surprisingly wide range of reactivity because along with the eliminations, substitutions are also possible. Moreover, the eliminations as well as the S_N2' pathway offer the possibility of anti or syn stereochemistries. In Scheme 1, the various pathways are outlined. Taking all the regiochemistry and stereochemistry in to account, there are fundamentally seven different routes leading to two products, cyclohexadiene or a 3-substituted cyclohexene. In addition, some pathways have more than one conformation for the transition state because the halogen can be in either an axial or an equatorial orientation. As a result, these systems provide diverse reactivity and a good test of the ability of computational approaches to distinguish between competing reaction paths.

Methods

All calculations were carried out on HP-720, HP-735, or IBM 39H computers using the GAUSSIAN92[42] or GAUSSIAN94[43] quantum mechanical packages developed by Pople and co-workers. All structures were fully optimized using a 6-31+G* basis set.[44] The curvature of the potential energy surface at all minima and transition states was confirmed with analytical second-derivatives at the Hartree−Fock level. When appropriate, the possibility of multiple rotamers was investigated. To account for correlation effects, the geometries were reoptimized at the MP2/6-31+G* level, and final energies are reported at the MP2/6-31+G** level. Using the Hartree−Fock frequencies, corrections were made for zero-point energy (ZPE) differences (scaled by 0.9135).[45] All energies in the text are reported at 0 K and include ZPE corrections. Previous work indicates that this approach leads to energies that are in good accord with more demanding computational methods (*i.e.*, (G2+)).[18,25]

Results and Discussion

3-Chlorocyclohexene. Ion−Dipole Complex. For a substrate such as 3-chlorocyclohexene, there will be many, energetically similar ion−dipole complexes. For the sake of simplicity, only one was located in this study. In Figure 1, a complex is shown where the fluoride interacts with hydrogens (anti) at the β and δ carbons (**I**). Based on the $F\cdots H$ distances, it appears that the interactions are almost equally strong with only a slight preference for the β carbon. The complex is 17.9 kcal/mol more stable than the separated reactants.[46] The fluoride has only a modest effect on the C−H and C−Cl distances in **I**. For comparison, 3-chlorocyclohexene has C−H (carbons 4 and 6, axial) and C−Cl distances of $\sim$1.09 and 1.828 Å, respectively.

1,4-Eliminations. Within the pseudo-chair conformation of 3-chlorocyclohexene, the chlorine can adopt either an axial or equatorial position. This leads to two possible pathways for the anti and syn 1,4-eliminations. The structures of the transition states of the anti eliminations (axial, **II**, and equatorial, **III**) are shown in Figure 2, and the energies are listed in Table 1. Both of the anti transition states are more stable than the separated reactants, but there is a strong preference (7.2 kcal/mol) for **II** because it allows the departing proton and chloride to adopt axial positions. This maximizes the overlap with

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(38) Using data and estimates from references 39−40, a ΔH_{rxn} value of approximately −27 kcal/mol is calculated for the gas phase reaction.

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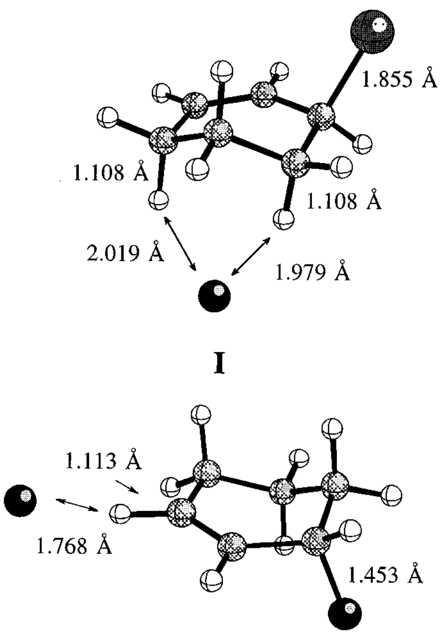

I

XII

Figure 1. Ion−dipole complexes at the MP2/6-31+G* level (carbon: lt gray; hydrogen: white; chlorine: dk gray; fluorine: black).

the intervening π-bond and stabilizes the transition state. The $H_\delta-C_\delta-C_\gamma-C_\beta$ and $Cl-C_\alpha-C_\beta-C_\gamma$ dihedral angles are 81.8° and 74.5° in **II** whereas the corresponding values in **III** are 107.4° and 121.1°, respectively.[47] Of course, dihedral angles of 90° would maximize the overlap. A manifestation of the enhanced π-overlap in **II** is an earlier transition state with a significantly shorter proton transfer distance ($C_\delta-H_\delta = 1.57$ Å vs 1.67 Å in **III**). Given the differences in energy, the anti 1,4-elimination should be dominated by **II**.

The syn 1,4-elimination transition states are also shown in Figure 2. In **IV**, the chlorine is axial, and in **V**, it is equatorial. Once again, there is a preference for losing the chloride from an axial position, but the difference is much smaller (3.4 kcal/mol). This is expected because in both of the syn 1,4-elimination transition states, one of the departing groups must be equatorial, and therefore neither can attain the preferred departure orientation (both departing groups axial). As a result, the π-overlap in the transition states is more limited than in the anti/axial example above. The $H_\delta-C_\delta-C_\gamma-C_\beta$ and $Cl-C_\alpha-C_\beta-C_\gamma$ dihedral angles in **IV** are 113.8° and 75.2°, whereas the corresponding values in **V** are 75.8° and 121.2°, respectively. The preference for **IV** suggests that it is more important to have the halide rather than the proton in an axial position. Although the preference is smaller than in the anti eliminations, the results indicate that syn 1,4-eliminations should proceed *via* **IV**.

All the 1,4-eliminations have relatively early transition states. This is best demonstrated by the lengths of the forming and breaking double bonds in the transition states. In each case, the forming double bonds (1.405−1.457 Å) are longer than the breaking double bond (1.386−1.398 Å). These bond lengths as well as the $H_\delta-C_\delta$ bond lengths indicate that for the loss of an equatorial chloride (**III** and **IV**), the transition states occur later on the reaction coordinate. This is consistent with the larger barriers for losing an equatorial chloride. It also should be noted that these eliminations are truly concerted. The intermediate required for an E1cb mechanism (3-chlorocyclohexene deprotonated at the 6 position) is not stable and expels chloride with no activation barrier.

For the 1,4-elimination, the most stable transition state (**II**) leads to anti stereochemistry; however, the most stable syn transition state (**IV**) is only 2.5 kcal/mol higher in energy. Consequently, the anti pathway should be favored, but some competition from a syn elimination is expected. This result is in accord with experimental observations for 1,4 eliminations, but is in sharp contrast to the 1,2-eliminations of simple alkyl chlorides. For example, in the E2 reaction of fluoride with chlorocyclohexane, anti elimination is preferred by 15.3 kcal/mol over syn![17] Clearly, the intervening π-bond mediates the anti/syn preference in these eliminations (see discussion below). The intervening π-bond also has a significant effect on the reaction barrier. In the E2 reaction of fluoride with chlorocyclohexane, the anti and syn barriers are −9.9 and 5.4 kcal/mol, respectively.[17] Therefore, the intervening π-bond in 3-chlorocyclohexene stabilizes the anti and syn transition states by 4.7 and 17.5 kcal/mol, respectively. This must be due in part to the increased acidity of the transferring proton. The preferential stabilization of the syn pathway is notable and can be explained in terms of orbital overlap. In early computational work, Bach[22] pointed out that syn 1,2-eliminations suffer from poor orbital overlap between the incipient lone pair at the β-carbon and the σ^* orbital of the C−X bond (Scheme 2). A key factor is that the departing proton localizes the incipient lone pair on the wrong side of the carbon for maximum overlap. The opposite is true for the anti orientation.

In the 1,4-elimination, the anti/syn stereochemistry determines the localization of the incipient lone pair on the δ-carbon. The interaction with the σ^* orbital of the C−X bond is mediated by conjugation through π-orbitals on the γ and β carbons. The departing proton causes little polarization in the π-orbital of the β carbon, and therefore its orientation (anti or syn) has relatively little effect on the overlap between the β carbon and the σ^* orbital (C−X bond) or the stability of the transition state. Consequently, anti and syn pathways should have similar barriers.

The small preference for an anti transition state is not consistent with the predictions of Fukui[27] and Anh.[28] Their semiquantitative MO theory approach suggested that syn elimination should be the dominant pathway. In the present case, the preference for the anti transition state (**III**) may be evidence of a subtle inherent preference for anti elimination or could be a consequence of the conformations of cyclohexenyl derivatives—**III** is the only transition state where both departing groups are axial. In any case, the computational results indicate that there is not a strong preference for anti or syn stereochemistry in 1,4-eliminations.

It is interesting to note that when the chloride is in an equatorial position, the barrier to syn elimination (−8.7 kcal/mol) is smaller than the barrier to anti elimination (−7.4 kcal/mol). Therefore, in substrates where the chloride is forced to be equatorial, syn elimination is expected. This can be explained by the fact that in the anti elimination (**III**), both the departing groups

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[47] Note that C_β is the olefinic carbon in 1,4-eliminations and the methylene carbon in 1,2-eliminations.

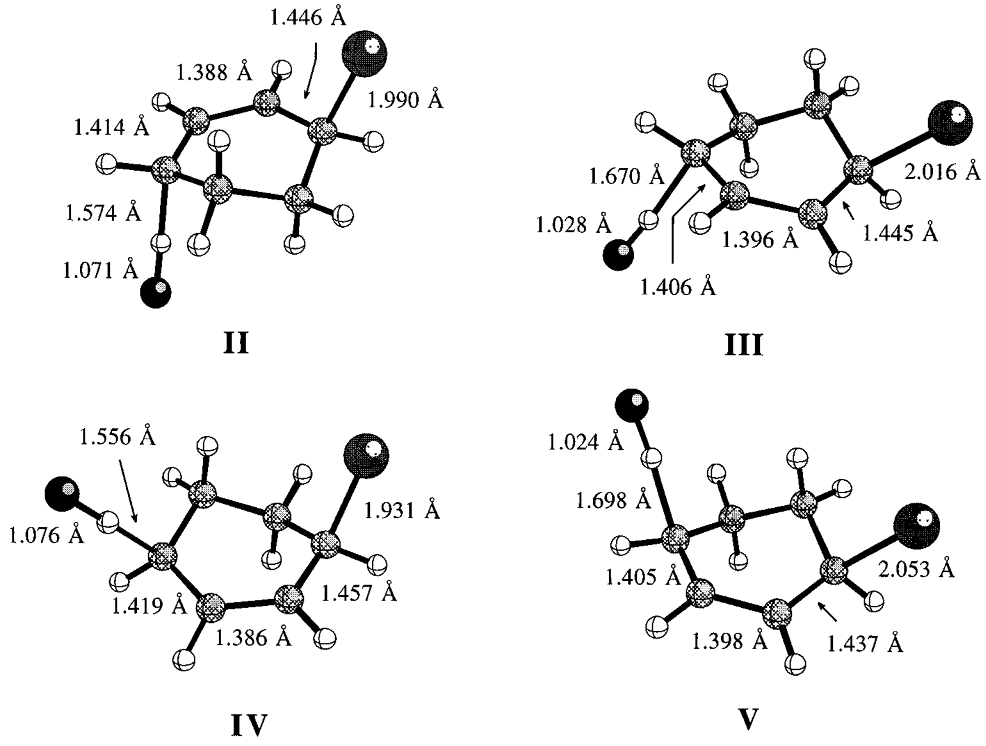


Figure 2. Transition states of the 1,4-eliminations of 3-chlorocyclohexene at the MP2/6-31+G* level (carbon: lt gray; hydrogen: white; chlorine: dk gray; fluorine: black).

Table 1. Energies for the Reactions of 3-Chlorocyclohexene and Related Substrates[a]

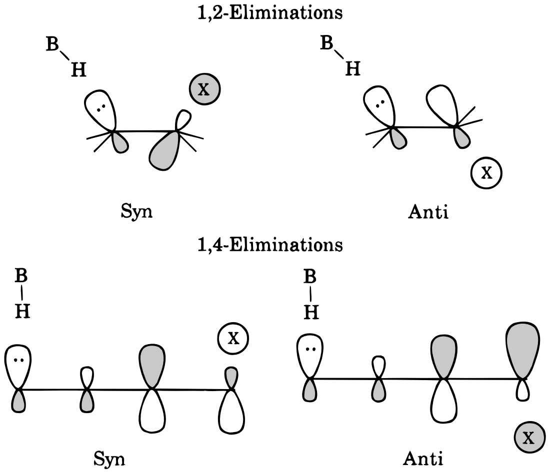
	structure	HF/6-31+G*	MP2/6-31+G**	ZPE	MP2 relative energies
			3-Chlorocyclohexene		
complex	**I**	−791.372159	−792.563420	92.70	−17.9
1,4-eliminations					
anti,axial	**II**	−791.346068	−792.551364	87.96	−14.6
anti,equatorial	**III**	−791.338672	−792.541657	89.24	−7.4
syn,axial	**IV**	−791.341048	−792.547323	87.96	−12.1
syn,equatorial	**V**	−791.341457	−792.544088	89.39	−8.7
1,2-eliminations					
anti,axial	**VI**	−791.353221	−792.550553	88.55	−13.6
syn,axial	**VII**	−791.328731	−792.531432	87.88	−2.2
syn,equatorial	**VIII**	−791.326385	−792.529538	88.02	−0.9
substitutions					
S_N2	**IX**	−791.361644	−792.544977	91.96	−7.0
S_N2',anti	**X**	−791.353346	−792.540850	91.67	−4.6
S_N2',syn	**XI**	−791.345059	−792.541945	91.99	−5.0
			Chlorocyclohexane[b]		
1,2-eliminations					
anti,axial					−9.9
syn,axial					5.4
syn,equatorial					8.1
substitution					
S_N2					−1.8

[a] Absolute energies in hartrees. Zero-point energies (ZPE) in kcal/mol. Relative energies (compared to separated reactants) contain ZPE corrections (scaled by 0.9135) and are in kcal/mol. MP2 energy for 3-chlorocyclohexene (equatorial) is −692.910931 hartree and its ZPE is 92.57 kcal/mol. MP2 energy for fluoride is −99.623847 hartree. Axial and equatorial refer to the halide position in the pseudo-chair conformation. [b] Data from reference 17.

(proton and chloride) are in equatorial positions and π-overlap is minimized.

1,2-Eliminations. The transition states for the 1,2-elimination reactions of fluoride with 3-chlorocyclohexene are shown in Figure 3 and the energies are listed in Table 1. In this case, syn elimination is possible with either an axial (**VII**) or equatorial chlorine (**VIII**), but anti elimination is limited to a conformation with an axial chlorine (**VI**)—anti elimination with an equatorial chlorine leads to the formation of a trans alkene. In the anti transition state (**VI**), the geometry is slightly distorted from periplanarity (F···H−C−C−Cl dihedral angle = 167°). The syn transition states are also distorted from periplanarity with **VII** experiencing a greater twist in the F···H−C−C−Cl dihedral angle than **VIII** (25° vs 11°). It is interesting to note that despite the greater twist angle in **VII**, it is about 1 kcal/mol more stable than **VIII**. This can be attributed to the advantage of having the leaving group in an axial position, but also is an indication that periplanarity has a very modest effect on the stability of syn transition states. We have noted this before in several E2 systems.[15−17] It appears as if **VII** has more E1cb-character than **VIII** (a longer C−H···F distance), but otherwise they are relatively similar in

Scheme 2



energy and structure. For the 1,2-elimination, there is a very strong preference for anti stereochemistry, and transition state **VI** is over 10 kcal/mol more stable than **VII** or **VIII**. The results also indicate that the presence of a vinyl substituent at the α-carbon significantly stabilizes the transition states of the 1,2-eliminations. In comparison to the 1,2-eliminations of 3-chlorocyclohexane,[17] transition states **VI**, **VII**, and **VIII** are stabilized by 3.7, 7.6, and 9.0 kcal/mol, respectively. Although the differences in the geometries are subtle, they indicate that the vinyl substituent enhances leaving group expulsion and reduces the E1cb-character of the transition states.

Substitutions. As noted in the introduction, the 3-chlorocyclohexene system allows for several substitution pathways including the typical S_N2 reaction and various S_N2' reactions. In the present study we have investigated three transition states: S_N2, S_N2'(anti), and S_N2'(syn). The transition states are shown in Figure 4, and the energies are given in Table 1. For the latter two reactions, we have only considered pathways with the departing chloride in an axial position because test calculations suggest that the loss of an equatorial chloride has a higher barrier and would not be competitive. The breaking and forming bond lengths in the S_N2 transition state (**IX**) are similar to those found in our previous study of the reaction of fluoride with 3-chlorocyclohexane; however, substitution in the allylic system (**IX**) has a smaller barrier (−7.0 vs −1.8 kcal/mol).[17] This is not surprising because it is well known that vinyl substituents accelerate S_N2 reactions.[48−51] It is tempting to explain the enhanced S_N2 reactivity on the basis of conjugation to the π-bond; however, this interaction is absent in the transition state of the S_N2 reaction of fluoride with allyl chloride—the π-orbitals are orthogonal to the $F-C_\alpha-Cl$ axis.[52] Moreover, Brauman has used the results of gas phase studies on benzyl halides to conclude that conjugation is of little importance.[53] In the present system, the vinyl substituent probably stabilizes the transition state by reducing some of the steric crowding and torsional strain characteristically found in the S_N2 reactions of cyclohexane derivatives.[54]

In allylic halides, the nucleophile can also attack at the double bond to give an S_N2' reaction.[51,55] The most favorable pathway is fluoride attack syn to the chlorine (**XI**) leading to the formation of 3-fluorocyclohexene with an axial fluorine. Anti substitution can proceed through transition state **X**, but involves a slightly higher barrier than **XI** (−4.6 vs −5.0 kcal/mol). As expected for an exothermic process, the transition state occurs early on the reaction coordinate. This is best demonstrated by the lengths of the forming and breaking double bonds (1.423 vs 1.387 Å in **X**). In comparison to **IX**, **X** and **XI** are tighter transition states with both the C−F and C−Cl bond lengths being shorter. Nonetheless, the barrier to the S_N2' pathway is about 2 kcal/mol larger than that of the simple S_N2 reaction. Given the small energy difference, it is difficult to determine the factors that lead to this preference, but **X** and **XI** are at a disadvantage because one of their carbons is forced to accept significant carbanion character. Similar results have been observed for the substitution reactions of $F^- +$ allyl chloride.[52]

3-Fluorocyclohexene. Ion−Dipole Complex. An ion−dipole complex between fluoride and 3-fluorocyclohexene (**XII**) is shown in Figure 1, and the energies are given in Table 2. The complex is characterized by an interaction between the fluoride and a vinylic hydrogen. It should be noted that the search for this complex began with an orientation analogous to **I**. The course of the optimization sequence suggests that the surface is relatively flat and that many orientations might give similar energies. The interaction with the vinylic hydrogen is significant and leads to an unusually long vinylic C−H distance (~1.11 Å). The complex is 15.4 kcal/mol more stable than the reactants.

1,4-Eliminations. The transition states of the 1,4-elimination reactions of fluoride with 3-fluorocyclohexene are shown in Figure 5, and the energies are given in Table 2. Again, the leaving group can be axial or equatorial, and the stereochemistry can be anti or syn. The reactions are endothermic,[41] and as a result, the transition states are much later on the reaction coordinates. In particular, the proton transfers are nearly complete ($H_\delta-C_\delta$ distances from 1.929 to 2.041 Å), and leaving group expulsion is highly advanced ($C_\alpha-F$ distances from 1.782 to 1.915 Å). In addition, the forming double bonds (1.372−1.404 Å) are shorter than the breaking double bonds (1.428−1.436 Å). Overall, it is clear that these transition states are close to the products and could almost be viewed as complexes of cyclohexadiene with HF and fluoride. It is interesting to note that there is a significant bend in the proton transfer linkage, and $F-H_\delta-C_\delta$ angles of about 160° are observed. Although it is not evident from the transition states, these reactions are far from synchronous in nature and have a high degree of E1cb-character. Analysis of the intrinsic reaction coordinates shows that proton transfer occurs first and then is followed by loss of fluoride. As an example, the potential energy surface for the anti/axial 1,4-elimination was generated at the HF/6-31+G* level using the intrinsic reaction coordinate option of GAUSS-

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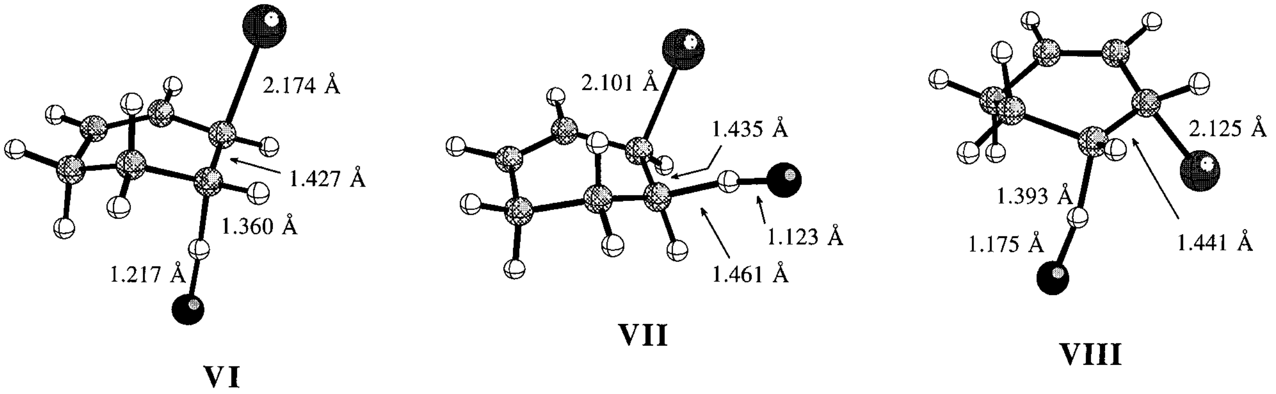

Figure 3. Transition states of the 1,2-eliminations of 3-chlorocyclohexene at the MP2/6-31+G* level (carbon: lt gray; hydrogen: white; chlorine: dk gray; fluorine: black).

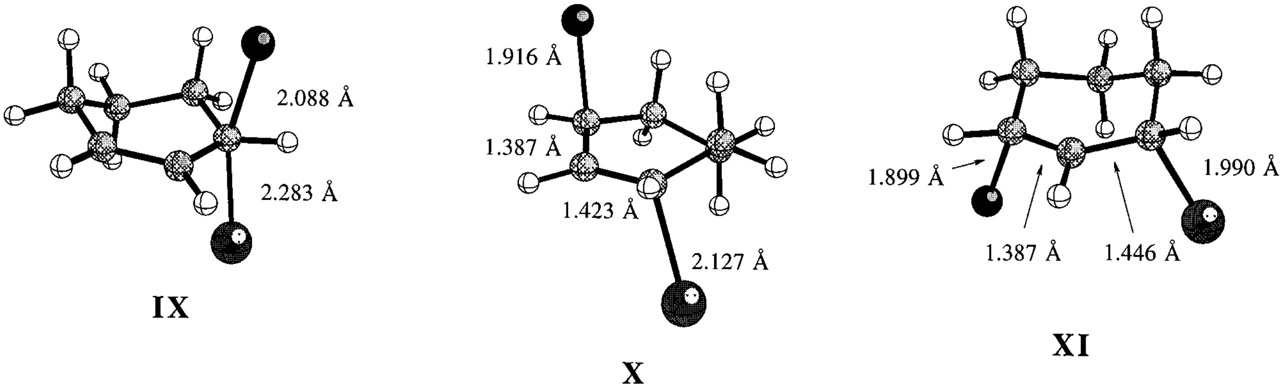

Figure 4. Transition states of the substitutions of 3-chlorocyclohexene at the MP2/6-31+G* level (carbon: lt gray; hydrogen: white; chlorine: dk gray; fluorine: black).

Table 2. Energies for the Reactions of 3-Fluorocyclohexene and Related Substrates[a]

	structure	HF/6-31+G*	MP2/6-31+G**	ZPE	MP2 relative energies
		3-Fluorocyclohexene			
complex	**XII**	−431.323860	−432.555731	93.58	−15.4
1,4-eliminations					
anti,axial	**XIII**	−431.280778	−432.536728	90.26	−6.5
anti,equatorial	**XIV**	−431.272940	−432.529270	90.05	−2.0
syn,axial	**XV**	−431.278950	−432.534742	90.22	−5.3
syn,equatorial	**XVI**	−431.272527	−432.528639	90.01	−1.6
1,2-eliminations					
anti,axial	**XVII**	−431.275822	−432.533081	90.21	−4.2
syn,axial	**XVIII**	−431.264283	−432.519369	90.05	4.2
syn,equatorial	**XIX**		−432.519126	90.00	4.3
substitutions					
S_N2	**XX**	−431.282608	−432.527606	92.72	1.5
S_N2',syn (int)	**XXI**	−431.291383	−432.533576	93.42	−1.6
S_N2',syn (ts)	**XXII**	−431.289696	−432.533136	93.05	−1.7
S_N2',anti	**XXIII**		−432.528568	93.00[c]	1.2
		Fluoroethane[b]			
1,2-eliminations					
anti					−2.4
syn					5.3
S_N2					4.4

[a] Absolute energies in hartrees. Zero-point energies (ZPE) in kcal/mol. Relative energies (compared to separated reactants) contain ZPE corrections (scaled by 0.9135) and are in kcal/mol. MP2 energy for 3-fluorocyclohexene (equatorial) is −332.907357 hartree and its ZPE is 93.50 kcal/mol. MP2 energy for fluoride is −99.623847 hartree. Axial and equatorial refer to the halide position in the pseudo-chair conformation. [b] Data from reference 18. [c] MP2 ZPE scaled by 0.9646.

IAN94 (Figure 6). Clearly the early part of the reaction coordinate is dominated by an extension of the C−H distance whereas the later part is mainly cleavage of the C−F bond. Across the reaction coordinate there is a steady rise in energy so it does not appear that there is an E1cb intermediate (complexed carbanion) in these systems; however, the potential energy surface is very flat in this region, and it is possible that an E1cb intermediate exists, but could not be detected in our surveys at the HF/6-31+G* level. It should be noted that the bare E1cb intermediate (3-fluorocyclohexene deprotonated at the 6 position) is not stable at the MP2 level and expels fluoride with no activation barrier. It is interesting to point out that in the reactions of fluoride with 3-fluorocyclohexene, the structure of the transition state does not effectively reveal the nature of the mech-

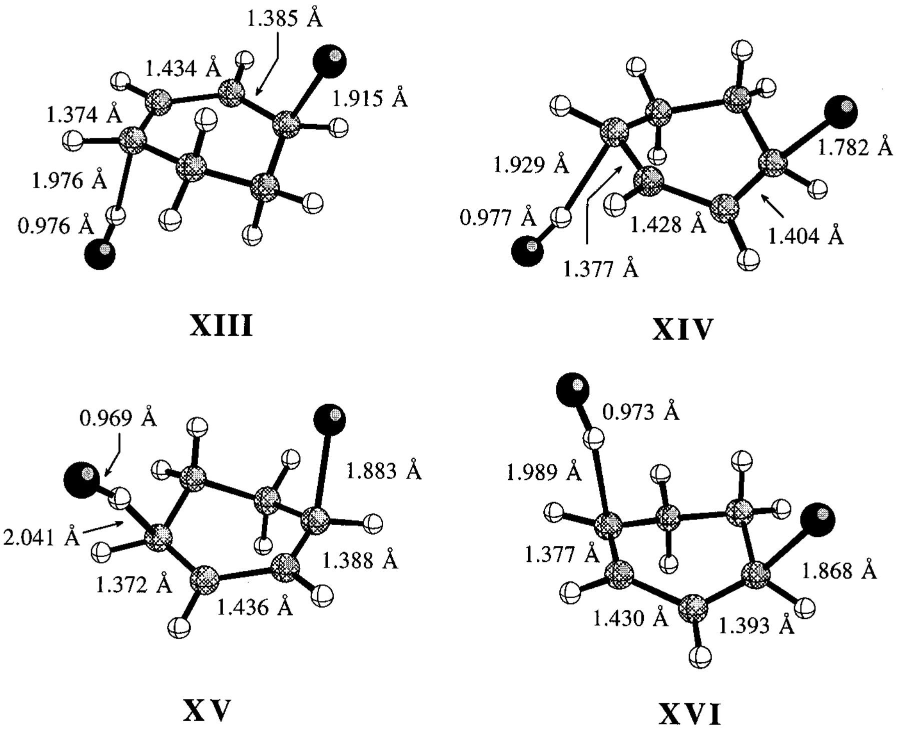

Figure 5. Transition states of the 1,4-eliminations of 3-fluorocyclohexene at the MP2/6-31+G* level (carbon: lt gray; hydrogen: white; chlorine: dk gray; fluorine: black).

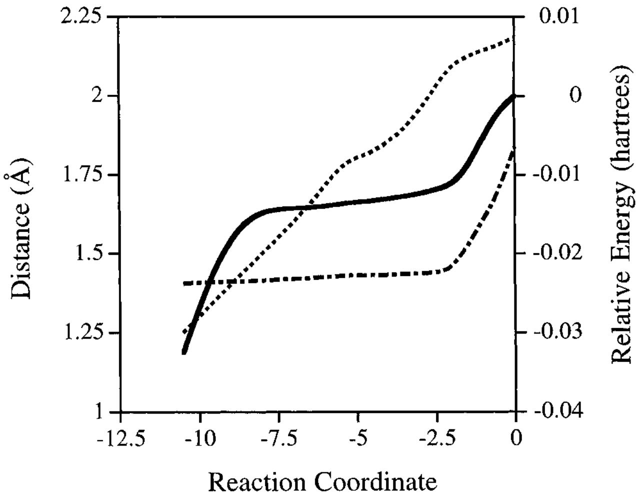

Figure 6. Intrinsic reaction coordinate plot (HF/6-31+G*) for the 1,4-elimination (anti,axial) of 3-fluorocyclohexene. The reaction proceeds from left to right with the transition state at zero. The solid line (—) represents energy, the dotted line (····) represents the C−H bond length, and the dot-dash line (·-·) represents the C−F bond length. Reaction coordinate units are bohr amu$^{1/2}$.

anism. With long C−H and C−F distances in transition states **XIII**−**XVI**, the eliminations could be synchronous E2 reactions, but simply late on the reaction coordinate. Only an analysis of the full reaction coordinate gives a clear picture of the mechanism (Figure 6).

The situation in Figure 6 is different from what Nibbering and co-workers[10] found in their DFT studies of butenyl methyl ether. They found a true intermediate (allylic anion complexed to the protonated base) in the reaction with fluoride. However, given the flat nature of the potential energy surface in these reactions and the moderate levels of theory employed by Nibbering and ourselves, it is not possible to definitively assign mechanisms. These 1,4-eliminations clearly have a high degree of E1cb character, but no firm conclusion about the existence of an allylic anion intermediate can be drawn from the available calculations. However, it should be noted that in Nibbering's gas-phase experiments, it was concluded that the putative E1cb intermediates (M − 1 anions of butenyl methyl ether) "consist of weakly bound C_4H_6 and RO^- fragments".[10] Of course this conclusion is consistent with either a concerted mechanism leading to an C_4H_6/RO^- ion−dipole complex or an E1cb mechanism leading to an allylic intermediate that is barely bound.

All of the 1,4 elimination transition states for the reaction of fluoride with 3-fluorocyclohexene are fairly close in energy with a span of less than 5 kcal/mol from best to worst. As with 3-chlorocyclohexene, the preferred path is anti elimination with an axial leaving group, and a barrier of −6.5 kcal/mol is seen. Syn elimination with an axial leaving group is only slightly less favorable and has a barrier of −5.3 kcal/mol. Loss of fluorine from an equatorial position leads to barriers of about −2 kcal/mol. These results suggest that there should be competition between syn and anti eliminations in this system. Moreover, a comparison to the results with 3-chlorocyclohexene indicates that as the reaction becomes less exothermic, the anti preference is diminished (from 2.5 to 1.2 kcal/mol for an axial leaving group). This is in accord with experiment (see below). Moreover, in systems where formation of a complexed product (*i.e.*, FHF^-) is the only exothermic channel, syn elimination has the advantage of having the protonated base in close proximity to the leaving group.

In our previous study of eliminations in cyclic systems, we did not consider fluoride as a leaving group; therefore, the effect of the intervening π-bond can only be assessed by comparison to the reaction of fluoride with ethyl fluoride. At the MP2 level, the barrier to the anti 1,2-elimination of fluoride + ethyl fluoride is −2.4 kcal/mol

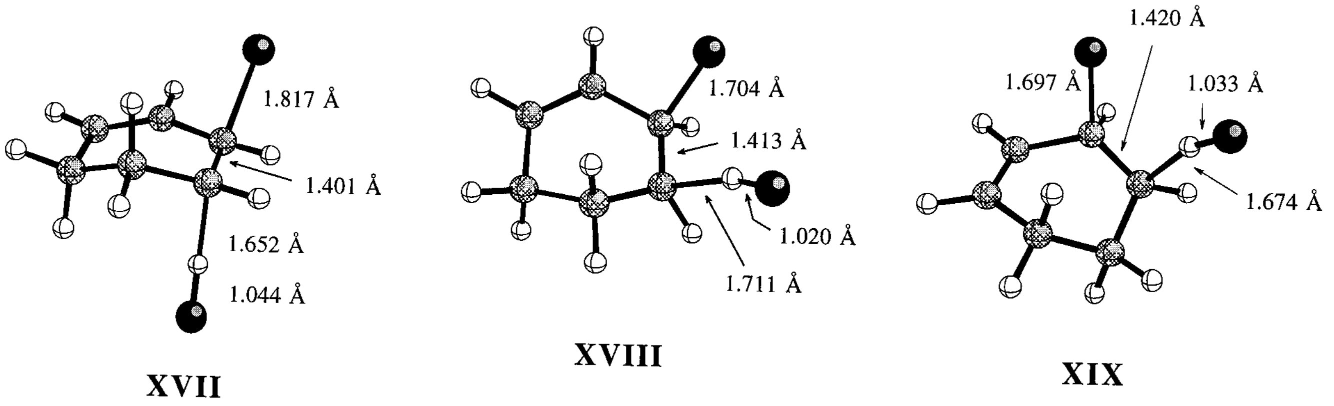

Figure 7. Transition states of the 1,2-eliminations of 3-fluorocyclohexene at the MP2/6-31+G* level (carbon: lt gray; hydrogen: white; chlorine: dk gray; fluorine: black).

or 4.1 kcal/mol larger than the barrier for the anti 1,4-elimination of 3-fluorocyclohexene. The stabilizing effect of the intervening π-bond is greater in the syn elimination (10.6 kcal/mol), and this leads to the small anti preference seen in this 1,4-elimination.

1,2-Eliminations. The transition states for the 1,2-eliminations of fluoride + 3-fluorocyclohexene are shown in Figure 7, and the energies are given in Table 2. As noted for the 1,4-eliminations, the transition states are late on the reaction coordinate, and proton transfer as well as leaving group expulsion are well advanced. The anti/axial transition state (**XVII**) is the most stable and is associated with a barrier of −4.2 kcal/mol to elimination. There is a strong preference for anti stereochemistry, and **XVII** is over 8 kcal/mol more stable than the syn transition states (**XVIII** or **XIX**). At the MP2 level, the barrier to the anti 1,2-elimination of 3-fluorocyclohexene is 1.8 kcal/mol smaller than the barrier to the 1,2-elimination of fluoride + ethyl fluoride. Once again, there is evidence that a vinyl substituent at an α-carbon stabilizes elimination transition states. In this case, the vinyl substituent preferentially stabilizes the anti transition state because geometric constraints in the syn transition states do not allow for good overlap between the π-system and the breaking C−F bond. As a result, the anti preference is enhanced in the 3-fluorocyclohexene system (8.4 vs 7.7 kcal/mol for ethyl fluoride).[18]

Along with lower barriers, the 1,2-eliminations of 3-fluorocyclohexene have earlier transition states than the reactions of ethyl fluoride. For example, the breaking C−H and C−F bonds are ~0.2 Å shorter in the 1,2-eliminations of 3-fluorocyclohexene. In comparison to the 1,4-eliminations of 3-fluorocyclohexene, there is less E1cb-character in the 1,2-eliminations because the proton is less acidic. This was also seen with 3-chlorocyclohexene, but is more pronounced in the fluorine system.

Substitutions. The transition states for the S_N2 and S_N2' reactions of fluoride + 3-fluorocyclohexene are shown in Figure 8 and energies are listed in Table 2. The S_N2 reaction (**XX**) has a barrier of 1.5 kcal/mol and therefore is 8 kcal/mol above the lowest energy elimination pathway. As noted earlier, a vinyl substituent stabilizes S_N2 transition states, and **XX** is ~3 kcal/mol more stable than the S_N2 transition state of F^- + ethyl fluoride. The S_N2' pathways present fairly complicated potential energy surfaces and offer the possibly of a stable carbanion intermediate. For syn addition of fluoride to the double bond, a stable, symmetric intermediate is formed (**XXI**). It is a cyclohexyl anion stabilized by two vicinal fluorines. This intermediate is 1.6 kcal/mol more stable than the reactants and is formed *via* transition state **XXII**.[56] At the MP2/6-31+G** level, this transition state has a higher electronic energy than **XXI**, but when ZPE corrections are included, the transition state appears to be slightly more stable than the intermediate. This situation implies that the reaction is effectively concerted, but will pass over an exceptionally flat plateau region near structures **XXI** and **XXII**. The anti S_N2' pathway appears to be concerted, and no intermediate carbanion could be located on the surface at the Hartree−Fock or MP2 level. The transition state (**XXIII**) is 1.2 kcal/mol less stable than the reactants. Similar results have been obtained at this level of theory for the S_N2' reaction of fluoride + allyl fluoride.[52] In an earlier MNDO study, Dewar[51] located stable intermediates for both the anti and syn S_N2' reactions of chloride with allyl chloride; however, this result must be viewed with caution because MNDO does not incorporate diffuse functions and therefore naturally disfavors small, localized anions (*i.e.*, Cl^-).

For 3-fluorocyclohexene, the substitution pathways have barriers that range from −1.6 to 1.5 kcal/mol. The best route appears to be the syn S_N2' pathway followed by the conventional S_N2. One explanation for the syn preference in the S_N2' pathway is that it allows both the leaving and adding groups to be pseudoaxial whereas one group must be pseudoequatorial in the anti pathway. It is also evident from the calculations that the potential energy surfaces for S_N2' reactions are very flat near the transition states.

1,2-Elimination vs 1,4 Elimination. For the reactions of fluoride with both 3-chlorocyclohexene and 3-fluorocyclohexene, the calculations indicate that 1,4-elimination should be favored; however, the preference is small. Using the most stable transition state in each case (axial/anti), the preference is 2.3 kcal/mol for the fluoro system and only 1 kcal/mol for the chloro system. Clearly, this leaves the opportunity for competition between the mechanisms and is in accord with the findings of Rabasco and Kass.[11,12] The present results do not explain why Nibbering saw so little 1,2-elimination in the reactions of 2-butenyl ethyl ether;[10] however, in that system, one is comparing the formation of a conjugated diene (1,4-elimination) with the formation of ethene (1,2-elimination). As the authors note, the greater exo-

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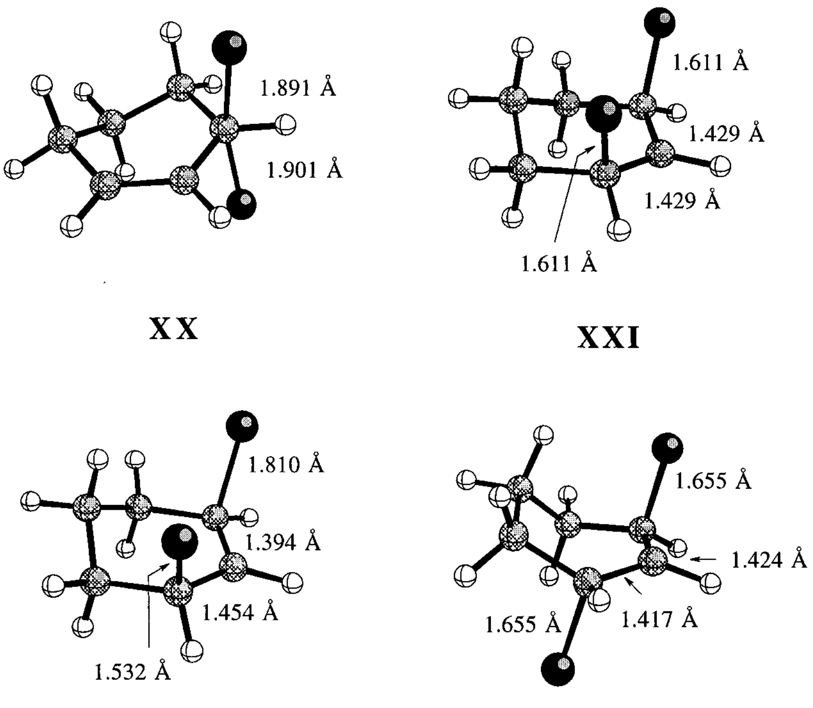
(56) At the MP2 level, this transition state could not be located in an automated transition state search. Instead, the transition state was located by manually varying the breaking C−F distance while optimizing all other geometric parameters.

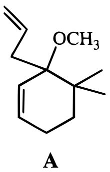


XX **XXI**

XXII **XXIII**

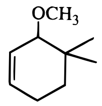
Figure 8. Transition states of the substitutions of 3-fluorocyclohexene at the MP2/6-31+G* level (carbon: lt gray; hydrogen: white; chlorine: dk gray; fluorine: black).

thermicity of the 1,4-elimination may tip the balance in this case. It should also be noted that although both the 1,2- and 1,4-eliminations of the 3-halocyclohexenes give the same product (cyclohexadiene), the 1,4-elimination has an advantage in that the departing proton is particularly acidic (allylic). In fact this is the most likely explanation for the 1,4 selectivity. A clear manifestation of this effect is the greater extent of proton transfer in the transition states of the 1,4-eliminations (particularly in the fluoro system). Rabasco and Kass[11,12] have illustrated the importance of acidity in determining the selectivity by preparing substrates (*e.g.*, **A**) where the protons involved in the 1,2- and 1,4-eliminations are both activated (allylic). This not only shifts the system toward 1,2-eliminations, it also reverses the trend with respect to base strength (stronger bases favor 1,2-eliminations). Therefore, the conclusions from the present study must be restricted to the competition between 1,4-eliminations and unactivated 1,2-eliminations.



A

Anti vs Syn in 1,4-Eliminations. For 1,4-eliminations, the calculations predict that the stereochemical preference for an anti orientation is fairly small. In the chloro system, it is 2.5 kcal/mol, and in the fluoro system, it is only 1.2 kcal/mol. Consequently, competition is likely and low selectivity is expected in reactions where the transition state occurs late on the reaction coordinate. This is in good accord with gas-phase studies of the 1,4-eliminations of isotopically-labeled 3-methoxycyclohexenes (*i.e.*, **B**). Rabasco and Kass[26] found that with strong bases the 1,4-elimination had little selectivity with a slight preference for anti stereochemistry.



B

With a weak base such as fluoride, elimination leads to the formation of a $[CH_3O{\cdots}HF]^-$ complex with high syn selectivity. This is consistent with a shift to a pathway where the protonated base complexes with the methoxy group and assists the leaving group expulsion phase of the elimination. Of course a syn orientation is favored in this case because the proton transfer occurs in close proximity to the leaving group. This type of pathway has been implicated by Nibbering[8,9] in elimination reactions that would be endothermic in the absence of leaving group complexation. In the elimination transition states located in this study for the reaction of fluoride with 3-fluorocyclcohexene, there is no interaction between the protonated base and the leaving group;[57] however, it is likely that complexation would occur later on the reaction coordinate because product separation is only exothermic if FHF^- is formed.[58] In the 3-chlorocyclohexene system, complexation is also possible, but direct

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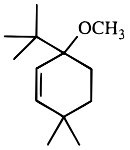
(57) This situation suggests that in reactions that require the formation of a product complex, the true dynamic bottleneck may occur after the calculated transition state and involve the complexation process to some extent. Therefore, an interaction between the leaving group and the protonated base is not required in the transition state (electronic potential energy surface). It should be noted that anti elimination can also lead to complexed products so complexation cannot be used to distinguish between anti and syn mechanisms.

(58) If complexation occurs, the elimination is exothermic by approximately 34 kcal/mol Wenthold, P. G.; Squires, R. R. *J. Phys. Chem.* **1995**, *99*, 2002.

product separation to give Cl^-, cyclohexadiene, and HF is exothermic.

It should be noted that in solution, syn stereochemistry generally dominates in 1,4-eliminations.[34−37] Given the above considerations, it seems likely that this is the result of an ion pairing effect rather than an inherent preference in the elimination process. In other words, the syn pathway is preferentially stabilized by an interaction between the base's counterion and the leaving group.

Anti vs Syn in 1,2-Eliminations. The calculations indicate a strong preference for anti stereochemistry in all of the 1,2-eliminations. This is consistent to some extent with the results of Rabasco and Kass on substrates such as **C**.[13]



C

Here, anti elimination is favored with all the bases they tested, but the selectivity is moderate with anti/syn ratios from 72/28 to 57/43. The small preference for anti is surprising given the large energetic advantage predicted in our calculations (8.4 to 11.4 kcal/mol). Previous calculations on the eliminations of aliphatic ethers also indicate a significant anti preference (4.4 kcal/mol).[15,59] These results suggest that a large energetic advantage in the transition state does not necessarily result in a strong anti preference in the observed products. This may be the result of a dynamical effect. For example, the site of attack (syn or anti) could be governed by the initial site of coordination during the formation of the ion−dipole complex (*i.e.*, once the base coordinates to one side of the ring, it is unlikely for it to shift to the other before the elimination takes place). This would diminish selectivity, and others have used a similar argument to explain low selectivity in proton transfers.[60] Alternatively, the large *tert*-butyl group in **C** may disfavor anti elimination. In any case, the calculations correctly predict that the 1,2-elimination should preferentially lead to anti products.

Substitution vs Elimination. In the reaction of fluoride with 3-chlorocyclohexene, both the S_N2 and E2 pathways are exothermic and have transition states that are more stable than the separated reactants. Consequently, both are viable and potentially observable. As Brauman and others[14,61,62] have noted, the S_N2 pathway is highly ordered and suffers an entropic disadvantage with respect to an E2 transition state. For example, the frequency calculations indicate that the eliminations are favored by 5 to 8 eu in these systems.[63,64] Given that the E2 transition states are enthalpically favored by about 7 kcal/mol in the 3-chlorocyclohexene system, elimination should dominate over substitution.

In the reactions with 3-fluorocyclohexene, the S_N2 process is thermoneutral and the E2 processes are endothermic unless a product complex (FHF^-) is formed. As in the chloro system, the elimination transition states are significantly more stable than the substitution transition states (by ∼5 kcal/mol). As a result, elimination is expected to dominate with the formation of complexed products (*e.g.*, FHF^-).

It should be noted that the cyclohexyl system is particularly poor for S_N2 reactions. For example, the barrier to the S_N2 reaction of 3-chlorocyclohexane is 2.5 kcal/mol higher than that of 2-chloropropane.[17] In contrast, a six-membered ring has little effect on the barriers of elimination reactions.[17] Therefore in acyclic systems, the bias against substitution will be reduced, but it is unlikely that this would be sufficient to shift the preference when a hard nucleophile such as fluoride is used. However, it is known that soft nucleophiles are inefficient for gas-phase eliminations and therefore could easily shift the 3-halocyclohexenes to a substitution pathway.[14]

Conclusions

In the gas phase reactions of fluoride with 3-chlorocyclohexene and 3-fluorocyclohexene there is competition between several elimination pathways leading to various regio- and stereochemical outcomes. For each substrate, the lowest barrier is for an anti 1,4-elimination, but the barriers to syn 1,4-elimination as well as anti 1,2-elimination are within 2.5 kcal/mol of the preferred path. This suggests that there is a delicate balance between these three pathways and that subtle factors could easily alter the relative energies and shift the dominant mechanism. This in accord with condensed phase studies that have shown that the competition between 1,4-elimination and 1,2-elimination (as well as the competition between syn and anti elimination) is very sensitive to the reaction conditions and the nature of the substrate. Although the substrates are somewhat different, the present results are generally in accord with recent gas phase studies by Rabasco and Kass.

Finally, the calculations indicate that there is a strong bias against substitution in these systems, but the S_N2 and S_N2' routes have fairly similar barriers. Therefore, by choosing a nucleophile that suppresses elimination (*i.e.* a soft nucleophile), these systems may provide a platform for investigating the competition between S_N2 and S_N2' pathways.

Acknowledgment. S.G. wishes to thank the NSF (CHE-9625708) for generous financial support.

Supporting Information Available: Tables of Cartesian coordinates for relevant species (9 pages). This material is available in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(63) Entropy estimates derived from G94 frequency calculations should be viewed with caution because they contain strong contributions from low frequency modes that are not well characterized by this approach.

(64) The entropy differences between the various elimination pathways are relatively small.