Theoretical Studies of Elimination Reactions. 4. Gas Phase Reactions of F^- with Cyclopentyl and Cyclohexyl Chloride. Stereochemical Preferences of E2 Eliminations

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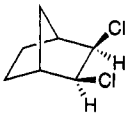
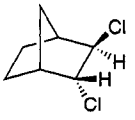
High-level ab initio calculations (MP2/6-31(+)G**//MP2/6-31+G*) were used to investigate the title reactions, and transition states were located for the E2(anti), E2(syn), and S_N2 pathways. In cyclopentyl chloride, the barrier to syn elimination (−0.9 kcal/mol) is only 9.3 kcal/mol larger than that of anti elimination (−10.2 kcal/mol). The 5-membered ring forces the syn elimination to be periplanar, and the enhanced π-overlap leads to a unusually stable syn transition state. In cyclohexyl chloride, the ring has little effect on the eliminations, and the barriers to syn (5.4 kcal/mol) and anti (−9.9 kcal/mol) elimination are similar to those found in acyclic analogs. The results are compared with DePuy's original experimental studies of syn eliminations (*J. Am. Chem. Soc.* **1962**, *84*, 1314). The calculations also predict that elimination will dominate over substitution in these systems.

Introduction

Over the past 30 years there has been intense interest in the stereochemistry of concerted (E2) eliminations.[1-4] From product studies, it is well established that both anti and syn pathways are available, but information about the conformational preferences of the transition states is much more limited. In early work, DePuy and coworkers compared the reactivity of cyclopentyl and cyclohexyl tosylates and discovered that syn elimination was much more competitive in the 5-membered ring system.[2] They suggested that the difference in reactivity was a result of the inability of the cyclohexyl system to adopt a syn-periplanar transition state. In a related study, Cristol and Hoegger[3a] found that syn elimination was faster than anti elimination in a dichloronorbornane system. Again, the difference in reactivity has been explained by the fact that only the syn elimination can adopt a periplanar transition state. These and other results have led to the general conclusion that periplanarity is required for an efficient elimination reaction.[1-3]



slow anti elimination



fast syn elimination

Recent theoretical investigations of eliminations have resulted in new insights into the conformational preferences of the transition states.[5-7] In anti eliminations, orbital overlap is maximized and torsional strain is minimized in a periplanar transition state. As a result, there is little question that anti eliminations have a strong preference for periplanarity. This conclusion is supported by all available theoretical studies.[5-10] In syn eliminations, a periplanar transition state is favored by orbital overlap considerations, but requires an eclipsed conformation. Work from our laboratory indicates that the competition between these factors leads to an exceptionally shallow potential energy surface with respect to the $H_\beta-C_\beta-C_\alpha-X$ dihedral angle. In the substituted systems[6,7] that we have studied, there is a slight preference for syn-clinal transition states with dihedral angles ranging from 20–60°. Syn-periplanar transition states have only been observed in unsubstituted systems[5,8,10] or in reactions that have late transition states.[11]

To further understand the results of DePuy's original experiments, we have completed a high-level, ab initio investigation of the stereochemistry of eliminations in cyclopentyl and cyclohexyl systems. Building on earlier work with ethyl[5] and propyl chlorides,[7] we have located the anti and syn E2 transition states of the reactions of F^- with cyclopentyl and cyclohexyl chloride. In the past, Dewar[9] has theoretically investigated eliminations in cyclic systems, but he employed exceptionally exothermic reactions and used a semiempirical approach. Both of these factors limit the utility of these earlier calculations.

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For example, our work with propyl halides suggests that correlated wave functions are necessary to properly describe the geometries of E2 transition states. In the present study, results up to the MP2/6-31(+)G**//MP2/6-31(+)G* level are reported. For completeness, the S_N2 reactions of F^- with cyclopentyl and cyclohexyl chloride are included.[12]

Methods

All calculations were carried out on a Multi-Flow/Trace14, Cray-YMP, or HP-735 computer using the GAUSSIAN90[13] or GAUSSIAN92[14] quantum mechanical packages developed by Pople and co-workers. All structures were fully optimized using basis sets derived from the standard 6-31G* basis.[15] For anionic systems, diffuse sp orbitals were added to all heavy centers expected to bear a negative charge (F, Cl, and a β-carbon).[16] This basis set will be referred to as 6-31(+)G*. 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. Earlier work has shown that the Hartree–Fock level overestimates the degree of E1 character in concerted eliminations;[7] consequently, geometries were reoptimized at the MP2/6-31G* or MP2/6-31(+)G* levels and final energy calculations were completed at the MP2/6-31(+)G** level.[17] Using the Hartree–Fock frequencies, corrections were made for zero-point energy differences (scaled by 0.9).[18] Past experience suggests that this approach is generally reliable to ±1 kcal/mol in relative energies.

Results and Discussion

Ion–Dipole Complexes. In systems of this size, there is the possibility of several, energetically similar ion–dipole complexes. For the purposes of this study, we have limited our search to complexes where the F^- interacts with the backside of the C–Cl bond and/or a hydrogen on the β-carbon. The complex of F^- with cyclopentyl chloride (**1**) is shown in Figure 1. As expected, there is a relatively long intermolecular separation and the strongest interaction is with a β-hydrogen. Complex **1** is 18.5 kcal/mol more stable than the reactants (Table 1). In cyclohexyl chloride, complexes were located for both conformations (axial (**2**) and equatorial (**3**) Cl). The complexation energy of the equatorial conformer (15.8 kcal/mol) is considerably smaller than that found for the axial conformer (18.3 kcal/mol). This can be attributed to two factors. First, in **3**, steric effects prevent the fluoride from positioning itself directly behind the C–Cl bond, the favored position based on dipole considerations. Second, in **2**, the anti-periplanar relationship of the β-hydrogens with respect to the chlorine allows for more effective hydrogen bonding with the fluoride. This leads to longer C_β–H_β bonds in **2** (the β C–H bonds are stretched by ~0.006 Å) and of course is related to the inherent preference for anti elimination. The similarity of the complexation energies found in **1** and **2** suggests that the difference in polarizability of cyclopentyl and cyclohexyl chloride has a negligible effect on the stability of the complexes.

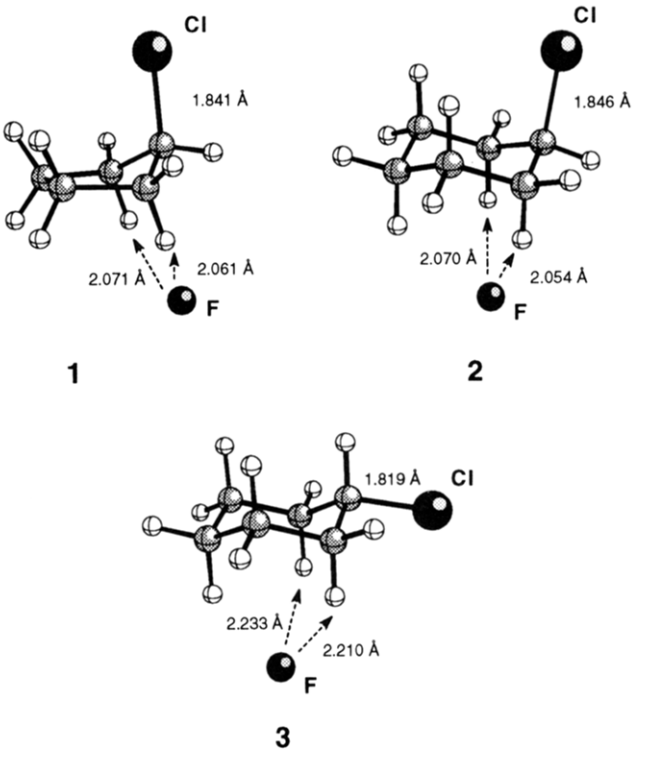

Figure 1. Structures of ion–dipole complexes **1**–**3** (MP2/6-31(+)G*).

E2(anti) Reactions. In the E2(anti) transition state of the reaction of F^- with cyclopentyl chloride (**4**), the cyclopentyl moiety maintains an envelope conformation and the departing groups are aligned in an almost perfectly periplanar arrangement (Figure 2). As in other fluoride/alkyl chloride eliminations,[5,7] proton transfer is somewhat advanced with respect to Cl^- expulsion, and therefore, the transition state has some E1cb character—the C_β–H_β bond is stretched by 27% whereas the C_α–Cl bond is only stretched 21%. The geometry of this transition state is very similar to those found for the analogous eliminations of *n*-propyl and isopropyl chlo-

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(17) For a full discussion of these basis sets, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986, and references therein.

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Table 1. Energies of Substrates and Transition States for the Reactions with Fluoride

structure[a]		HF/6-31(+)G*	MP2/6-31(+)G**	relative energies[c] ZPE[b]	HF	MP2
cyclopentyl chloride		−654.07085	−654.92821	80.0		
cyclopentene			−194.68499	70.9		−16.0[d]
cyclohexyl chloride (ax)		−693.11440	−694.12074	97.9	1.2[g]	1.0[g]
cyclohexyl chloride (eq)		−693.11622	−694.12216	97.8		
cyclohexene			−233.87648	88.7		−15.4[d]
cyclopentyl chloride complex	**1**	−753.51684	−754.58164	80.1	−17.1	−18.5
cyclohexyl chloride (ax) complex	**2**	−792.56093	−793.77545	98.0	−16.2	−18.3
cyclohexyl chloride (eq) complex	**3**	−792.55588	−793.77133	98.0	−13.0	−15.7
cyclopentyl chloride E2(anti)	**4**	−753.49308	−754.56232	76.3	−6.0	−10.2
cyclohexyl chloride E2(anti)	**5**	−792.53762	−793.75587	94.1	−5.5	−9.9
cyclopentyl chloride E2(syn)	**6**	−753.47111	−754.54689	75.8	7.3	−0.9
cyclohexyl chloride (ax) E2(syn)	**7**	−792.50785	−793.73106	93.8	13.0	5.4
cyclohexyl chloride (eq) E2(syn)	**8**	−792.50465	−793.72681	93.8	15.0	8.1
cyclopentyl chloride S_N2	**9**	−753.50598	−754.55985	79.7	−10.7	−5.2
cyclohexyl chloride S_N2	**10**	−792.54725	−793.74777	97.1	−8.5	−1.8
isopropyl chloride			−577.75774	57.4		
isopropyl chloride S_N2			−677.38755	56.8		−4.3
2-chlorobutane[e]			−616.93669	74.8		
2-chlorobutane E2(anti) → *cis*[f]		−715.62549	−716.56975	70.9		−9.5
2-chlorobutane E2(syn) → *cis*[f]		−715.59682	−716.54588	70.5		5.0
F^-		−99.41859	−99.62385	0.0		
HF			−100.21575	5.6		
Cl^-			−459.67115	0.0		

[a] Structures optimized at the MP2/6-31G* (neutrals) or MP2/6-31(+)G* (anions) levels. Energies are in hartrees. Energies at the HF/6-31(+)G* level involve Hartree−Fock optimized geometries (HF/6-31(+)G*). [b] Scaled by 0.9, see text. [c] Relative energies in kcal/mol. Referenced to substrate + F^-. For cyclohexyl chloride, substrate is taken as the equatorial conformer. [d] Energy of products (alkene + HF + Cl^-) − reactants (alkyl halide + F^-). [e] In a conformation analogous to those found in cycloalkyl halides. [f] The product is *cis*-2-butene. [g] Energy relative to equatorial conformer.

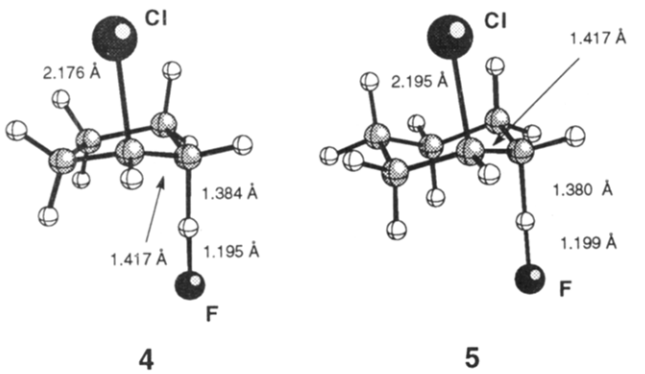


Figure 2. Structures of E2(anti) transition states **4** and **5** (MP2/6-31(+)G*).

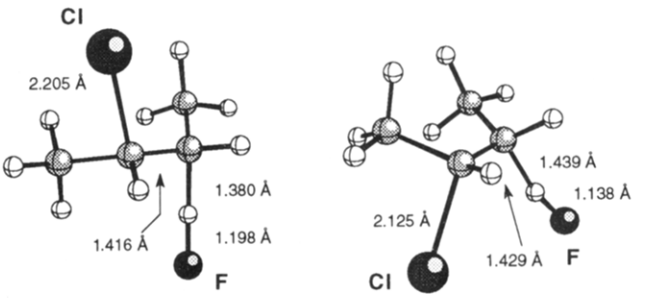


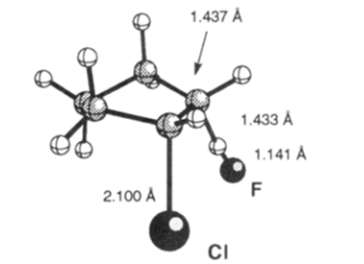
Figure 3. Structures of E2(anti) and E2(syn) transition states from the reaction of F^- + 2-chlorobutane (MP2/6-31(+)G*).

ride.[7] The transition state is 10.2 kcal/mol more stable than the separated reactants at the MP2/6-31(+)G**// MP2/6-31(+)G* level of theory. For comparison, the calculated activation energies for the fluoride-induced eliminations of ethyl, *n*-propyl, and isopropyl chloride are −7.1, −9.9, and −10.2 kcal/mol, respectively.[5,7] This suggests that the cyclopentyl ring imparts little or no strain on the transition state. In fact, the activation energy is very similar to that of a more analogous, acyclic system, F^- + 2-chlorobutane → *cis*-2-butene (E_{act} = −9.5 kcal/mol, Figure 3).[19]

To complete an anti elimination in cyclohexyl chloride, the chloride must adopt an axial position. The E2(anti) transition state of F^- + cyclohexyl chloride, (**5**) is very similar to the one observed in the cyclopentyl system. Again, an almost perfectly periplanar conformation is adopted and the transition state has E1cb character. Not surprisingly, the energetics of the two eliminations are similar. Using the equatorial Cl conformation of cyclohexyl chloride for calculating relative energies, transition state **5** is 9.9 kcal/mol more stable than the reactants. It should be noted that the calculations predict that the axial conformer of cyclohexyl chloride is 1 kcal/mol less stable than the equatorial conformer; therefore **5** is 10.9 kcal/mol more stable than its parent conformation. The small difference in E2(anti) activation energies between the cyclopentyl and cyclohexyl systems suggests that the rings add little strain to the transition states of these reactions. It should be noted that the elimination is slightly more exothermic in the cyclopentyl system.

E2(syn) Reactions. The transition state for the syn elimination of F^- with cyclopentyl chloride (**6**) is given in Figure 4. Although syn-clinal transition states are normally observed in fluoride/alkyl chloride eliminations,[7,19] transition state **6** is almost perfectly periplanar—a dihedral angle (H_β−C_β−C_α−Cl) of ~2° is observed. In other respects, the geometry is similar to those found in analogous, syn-clinal transition states (for example, see Figure 3). The activation energy for the syn elimination (−0.9 kcal/mol) is 9.3 kcal/mol greater than that of the anti elimination. This is the smallest anti/syn difference that we have observed in a fluoride/alkyl chloride E2 reaction. For comparison, anti/syn differences of ap-

(19) A thorough study of the 2-chlorobutane system has been completed, and the results will be presented in a subsequent publication.



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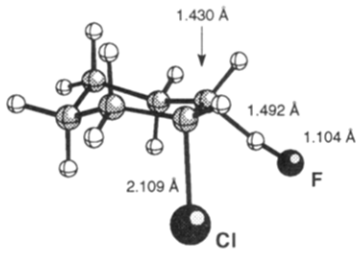

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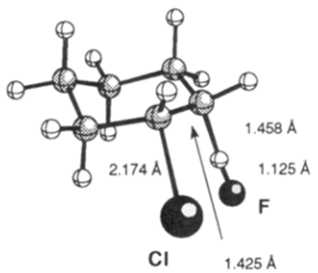

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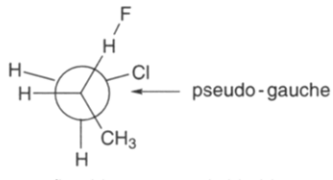
Figure 4. Structures of E2(syn) transition states **6**–**8** (MP2/6-31(+)G*).

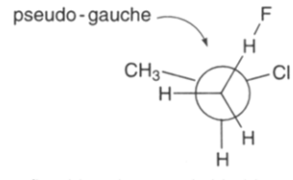
proximately 13 kcal/mol are found for the reactions of F^- with ethyl, *n*-propyl, isopropyl, and *sec*-butyl chloride.[5,7]

The relatively low activation barrier for syn elimination suggests that periplanarity provides significant stabilization to transition state **6**. At first glance, this result seems to question our assertion that syn-clinal transition states are generally preferred for syn eliminations; however, it is simply an artifact of the envelope conformation of the cyclopentyl ring. In this conformation, one of the C–C bonds must adopt a nearly eclipsed orientation. As a result, *the cyclopentyl system gains no additional torsional strain by adopting a syn-periplanar (eclipsed) transition state*. In contrast, acyclic systems have staggered conformations in their ground states and therefore must accept additional torsional strain if they adopt a syn-periplanar (eclipsed) conformation for the transition state. Earlier work indicates that in syn eliminations there is a delicate balance between the advantages of orbital overlap and the disadvantages of torsional strain. In ethyl chloride, the torsional strain is relatively minor, and as a result, a syn-periplanar (eclipsed) transition state is observed.[5] In substituted systems (*i.e.* propyl chlorides), the torsional strain is somewhat more severe and syn-clinal (staggered) transition states are observed.[7] In all cases, the potential energy surface for rotation about the C_α–C_β bond in the transition state is very flat, indicating that there is a nearly perfect balance between the two effects. Assuming that the strain energy of an eclipsed conformation is approximately 4–6 kcal/mol in these systems,[20] we can estimate that the enhanced π-overlap of a syn-periplanar transition state must result in roughly that amount of stabilization. In the syn elimination of cyclopentyl chloride, periplanarity is achieved without the cost of additional torsional strain; therefore, the activation energy should be about 4–6 kcal/mol smaller than those observed in acyclic analogs. In fact, the barrier to the syn elimination of cyclopentyl chloride is 5.9 kcal/mol smaller than that observed in the syn elimination of 2-chlorobutane to give *cis*-2-butene.

In the cyclohexyl system, there are two realistic syn elimination pathways depending on whether the chlorine is axial to equatorial. In transition state **7**, fluoride attack at an equatorial β-hydrogen leads to the loss of an axial chlorine. The transition state is clearly syn-clinal and a dihedral angle (H_β–C_β–C_α–Cl) of ~32° is observed. Other than the dihedral angle, the geometries of **6** and **7** are fairly similar. The major difference is that the C_β–H_β distance is 0.059 Å longer in **7** (more E1cb-like). The activation energy of this syn pathway (5.4 kcal/mol) is 15.3 kcal/mol above that of the anti elimination. If the chlorine is equatorial, F^- attack at an axial hydrogen leads to transition state **8**. As in **7**, the transition state is syn-clinal and a dihedral angle of ~36° is observed. The two syn transition states have similar bond distances, but **8** appears to be somewhat less E1cb-like. Energetically, transition state **8** is 2.7 kcal/mol less stable than **7** in spite of the fact that an equatorial chlorine is favored in ground-state cyclohexyl chloride. Experimentally, a similar effect has been observed. Jones *et al.* found that in the syn eliminations of a series of substituted cyclohexanes, there was a 4:1 preference for having the leaving group in the axial position.[4] Earlier work with the propyl chlorides suggests a rationalization for this selectivity.[7] In the syn-clinal transition states of the reactions of F^- with *n*-propyl and isopropyl chloride, there is a definite preference for placing the substituent (methyl) pseudo-gauche to the breaking bond (C_β–H_β or C_α–Cl). This interaction is



fluoride + *n*-propyl chloride



fluoride + isopropyl chloride

strongest with the C_α–Cl bond (*n*-propyl chloride) where a H_β–C_β–C_α–Cl dihedral angle of −35° is preferred by 6 kcal/mol over one of +35° (pseudo-anti). The corresponding preference in isopropyl chloride (pseudo-gauche to the C_β–H_β bond) is only ~4 kcal/mol.[21] In the cyclohexyl system, only one of the two alkyl substituents (CH_2 groups) attached to the eliminating bond can be pseudo-gauche. In **7**, the alkyl groups are pseudo-gauche to the C_α–Cl bond and pseudo-anti to the C_β–H_β bond.

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

(21) This effect is still being investigated. The pseudo-gauche arrangement places the polarizable alkyl group closer to the charged center (leaving group or base). Electron density analysis of acyclic analogs indicates that as the C_α–C_β bond is rotated from a pseudo-anti to pseudo-gauche arrangement, the polarization of the alkyl group increases. Full details of this analysis will appear in a subsequent publication.

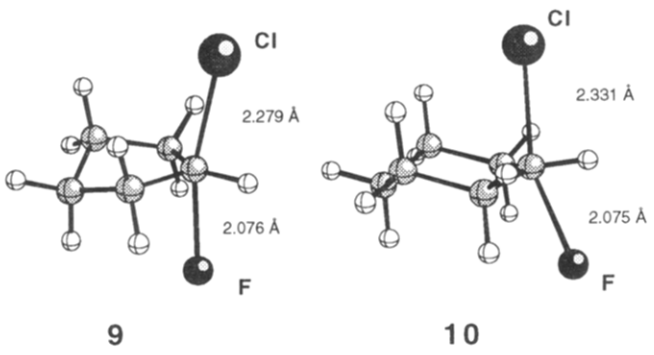


Figure 5. Structures of S_N2 transition states **9**−**10** (MP2/6-31(+)G*).

In **8**, the alkyl groups are pseudo-anti to the C_α−Cl bond and pseudo-gauche to the C_β−H_β bond. Based on these observations, it is not surprising that **7** is favored over **8** by about 2 kcal/mol. Moreover, in the syn elimination of F^- + 2-chlorobutane to give *cis*-2-butene, the transition state is syn-clinal (H_β−C_β−C_α−Cl = −21.6°) and the C_α−C_β bond is twisted in the same direction as in **7**—the pseudo-gauche interaction is with the C_α−Cl bond.

Using the lowest energy pathway for syn elimination (**7**), the anti preference in cyclohexyl chloride is over 15 kcal/mol. This is significantly larger than the preference found in cyclopentyl chloride (~9 kcal/mol) but only slightly larger than that found in the formation of *cis*-2-butene from F^- + 2-chlorobutane (14.5 kcal/mol). In other words, the cyclohexyl system has only a slight bias against syn elimination when compared to acyclic analogs, whereas the cyclopentyl system yields an unusually facile syn elimination. This interpretation is consistent with DePuy's original explanation.[2] However, our work suggests that torsional strain will generally force exothermic, syn eliminations to adopt syn-clinal transition states. The cyclopentyl system is an exception because the 5-membered ring allows for an essentially strain-free syn-periplanar conformation. Therefore, the difference in syn reactivity is best described as an activation of the cyclopentyl system as opposed to a deactivation of the cyclohexyl system.

S_N2 Reactions. The transition states of the S_N2 reactions of F^- with cyclopentyl and cyclohexyl chloride are shown in Figure 5. Both reactions have early transition states and overall, the geometries are relatively similar. In each system, the C−Cl bond lengths are stretched by only about 26%, but the C−F bond lengths are over 50% longer than normal. This is consistent with the Hammond postulate for exothermic reactions.[22] Comparing **9** and **10**, the barrier to substitution is smaller in the cyclopentyl system (−5.2 vs −1.8 kcal/mol). Again, the envelope conformation is favoring the reaction. During the inversion process in a 5-membered ring, the sp^2-like orientation of the α-carbon allows for a structure with no eclipsing interactions. In contrast, inversion of a 6-membered ring introduces two new eclipsing interactions. Therefore, substitution should be more facile in cyclopentyl chloride. This effect has been observed experimentally[23] and interpreted[24] in the past. In comparison to acyclic systems, the calculated S_N2 activation energy for cyclopentyl chloride is slightly smaller than that found for F^- + isopropyl chloride (−4.3 kcal/mol),[25] whereas the added torsional strain in the cyclohexyl system leads to a substantially larger barrier.

As noted for other alkyl chlorides, the reactions of cyclohexyl and cyclopentyl chloride with F^- should be dominated by elimination.[7] In the gas phase, these E2(anti) reactions are favored by ~5−8 kcal/mol over substitution and this bias should increase in solution because solvation of the nucleophile should destabilize the crowded S_N2 transition state.[26] The calculations also predict that anti elimination should dominate over syn elimination; however, this dominance is greatly reduced in the cyclopentyl system. The next question is how substituents might affect the stereochemical preferences. In earlier work,[7] we found that as the E1cb character of the transition state increased, the preference for anti elimination decreased. Therefore, substituents that stabilize charge at the β-carbon should reduce the preference for anti elimination. In DePuy's example,[2] the cyclopentyl tosylate contained a stabilizing group (aryl) at the β-carbon and consequently was perfectly designed for maximizing the relative rate of syn elimination.

Conclusion

High-level ab initio calculations confirm DePuy's assertion that the bias toward anti elimination is reduced in cyclopentyl systems because syn-periplanar transition states are possible. In the envelope conformation of a cyclopentane ring, one of the C−C bonds is already in an eclipsed conformation; therefore, the adoption of a syn-periplanar transition state enhances π-overlap but does not substantially increase the torsional strain of the system. As a result, the activation energy for the syn elimination of cyclopentyl chloride is about 5 kcal/mol smaller than that found in analogous acyclic systems. The ring has little effect on the anti elimination. In cyclohexyl chloride, the syn elimination avoids an eclipsed conformation by adopting a syn-clinal transition state. The 6-membered ring imparts relatively little strain on the syn or anti transition states, and the activation barriers are similar to those found in acyclic analogs. In both ring systems, elimination is favored over substitution, but the S_N2 barrier is smaller in the 5-membered ring.

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Supplementary Material Available: Tables of Cartesian coordinates for all species (8 pages). This material is contained 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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(25) This value differs from the one in ref 7 because the transition state has been reoptimized at the MP2/6-31(+)G* level.
(26) Direct analogies to solution are difficult because solvation decreases base strength and opens the possibility of unimolecular processes (S_N1 or E1). However, our calculations suggest that when strong bases are employed, elimination should be favored in solution.