

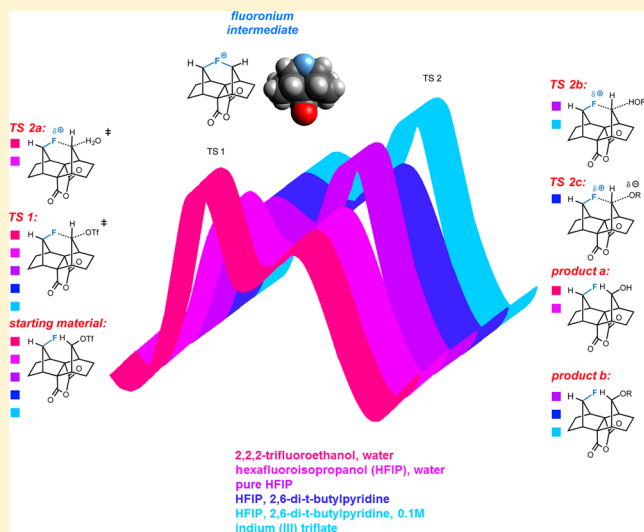
Search for a Symmetrical C–F–C Fluoronium Ion in Solution: Kinetic Isotope Effects, Synthetic Labeling, and Computational, Solvent, and Rate Studies

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S Supporting Information

ABSTRACT: Recently, we reported evidence for the generation of a symmetrical fluoronium ion (a $[C-F-C]^+$ interaction) in solution from a cage-like precursor, relying heavily on a single isotopic-labeling experiment. Paraphrasing the axiom that a strong claim must be met by as much evidence as possible, we seek to expand upon our initial findings with comprehensive labeling studies, rate measurements, kinetic isotope effect (KIE) experiments, synthetic studies, and computations. We also chronicle the development of the system, our thought process, and how it evolved from a tantalizing indication of fluoronium ion assistance in a dibromination reaction to the final, optimized system. Our experiments show secondary KIE experiments that are fully consistent with a transition state involving fluorine participation; this is also confirmed by a significant remote isotope effect. Paired with DFT calculations, the KIE experiments are indicative of the trapping of a symmetrical intermediate. Additionally, starting with an epimeric *in*-triflate precursor that hydrolyzes through a putative frontside S_Ni mechanism involving fluorine participation, KIE studies indicate that an identical intermediate is trapped (the fluoronium ion). Studies also show that the rate-determining step of the fluoronium forming S_N1 reaction can be changed on the basis of solvent and additives. We also report the synthesis of a nonfluorinated control substrate to measure a relative anchimeric role of the fluorine atom in hydrolysis versus μ -hydrido bridging. After extensive testing, we can make the remarkable conclusion that our system reacts solely through a “tunable” S_N1 mechanism involving a fluoronium ion intermediate. Alternative scenarios, such as S_N2 reactivity, do not occur even under forced conditions where they should be highly favored.



INTRODUCTION

To new students of organic chemistry, the story of the halonium ions is almost magical; these strange species seem to be counterintuitive to everything they had theretofore learned about bonding by such electronegative atoms. Perhaps the most familiar of the haloniums is the bromonium ion; in its formation, bromine, an electronegative atom that normally attaches itself to carbon through a single bond, becomes instead a formally positively charged member of a bromocyclopropane ring.¹ The first hint of its existence came through stereochemical studies, namely, the strong preference for *trans*-addition of dibromine to double bonds. Analogous behavior was documented in chlorination reactions as well.² In a short span of time, the viability of symmetrical chloronium, bromonium, and iodonium³ ions, whose stability increases in that order, became well established. However, a gap existed; namely, it was not clear that fluorine, the most electronegative atom by most measures, could form a fluoronium ion in which equal bonding exists between carbon atoms, i.e., $[C-F-C]^+$. Given the explosive growth in

the importance of fluorine to synthetic,⁴ pharmaceutical,⁵ and biochemistry⁶ of late, the problem is especially timely—that is, to what extent can divalent fluorine be compelled to withstand a formally positively charged environment in solution?

Assuming that the fluoronium would share similar properties with other halonium ions, it should be able to engage in analogous modes of bonding. For example, bromonium ions can form three-membered rings, they can be acyclic, or the bromine can be part of a larger ring. Thus, the fluorine atom also can be imagined as a part of a fluoracyclopropane, with similar bonding interactions (Figure 1). We also note that the system may not be symmetric (i.e., both C–F interactions equivalent) depending on the substituents; at some point, the asymmetrical fluoronium can devolve into an electrostatic interaction. Such a scenario can be anticipated when the C–F bond approaches its normal length.

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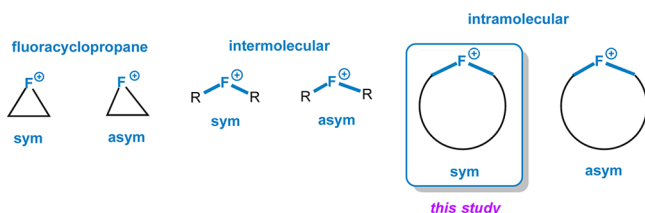


Figure 1. Fluoronium configurations.

Recently, we communicated evidence for the generation of a symmetrical fluoronium ion in solution, relying heavily on a key isotopic-labeling experiment.⁷ Herein, we confirm and extend our initial findings with comprehensive labeling studies, kinetic isotope effect (KIE) experiments, synthetic studies, solvent effects, and computations. We also detail the thought process behind the evolution of the chosen system from interesting but ambiguous clues. Overall, our guiding principle derives from the saying that a strong claim must be met by similar evidence—and as the ions we report herein are not directly observed, as much indirect evidence as possible should be amassed.

PRECEDENTS

A diverse and often ingenious set of precedents undergirds research on fluoronium ions. In the gas phase, Morton et al. have generated a cationic fluoracyclopropane whose existence was confirmed by a neutral product study (Figure 2).⁸ In more

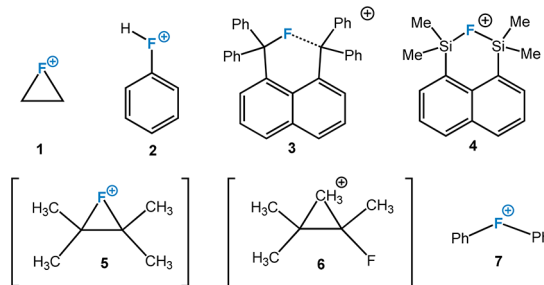


Figure 2. Antecedents.

recent work, Dopfer and Solca characterized F-protonated fluoro-benzene **2** by IR spectroscopy, also in a gas phase study.⁹ Moving to solution phase chemistry, Gabbai et al. have reported the synthesis of a carbocation engaging in an interaction with a neighboring C–F bond in the 1,8-disubstituted naphthalene system **3**.¹⁰ Although not a fluoronium per se, this remarkable species undergoes rapid fluoride shifts, as witnessed by NMR equilibration at elevated temperatures. The disilane analogue **4** reported by Müller et al., on the other hand, possesses equivalent distances between Si and F.¹¹ These works stand in contrast to a notable paper by Olah et al. in which the authors demonstrated that cation **6** isomerizes in solution strictly through methyl group shifts rather than the putative fluoronium shift depicted in **5**; this result suggests that achieving a reversible fluoride-shifting system in a small ring would be a challenge.¹² In loose regard to the intramolecular asymmetrical case (Figure 1), we reported a system that undergoes irreversible fluoride shifts that are initiated by aryl cations.¹³ More recently, Erdélyi et al. were able to observe a unique, asymmetric [N–F–N]⁺ interaction by trapping it as its bispyridine complex.¹⁴ Peterson et al.¹⁵ have observed a fluoride shift initiated by a vinylic cation; whether this shift occurred through asymmetric fluoronium transition states or intermediates is unclear.

There are also claims in the literature of putative symmetrical diarylfluoronium ions (**7**), although considerations of theory and stability would seem to rule both out.¹⁶

DESIGN OF SYSTEM

Whenever one has to design a new system, it pays to start simply. However, although the simplest system—[Me–F–Me]⁺—is a stable minimum computationally, the idea that it could exist in solution under any circumstances is far-fetched. In order to imagine a viable system that could at least be generated as a reactive intermediate, certain design precepts must be considered: (1) the fluoronium ion should form intramolecularly;¹⁷ (2) the fluorine atom should be positioned between secondary carbons (primary would render a system very unstable, whereas tertiary carbons are less likely to form a symmetrical fluoronium);¹⁸ (3) we posit that, if an ether linkage can fit comfortably between the two carbon atoms, the isoelectronic, formally positively charged fluorine should as well.

Bearing these conditions in mind, we determined that a cage hydrocarbon¹⁹ would be an ideal framework to anchor a fluoronium interaction. Initially, we screened commonly occurring cages that could be modified to become a fluoronium ion. Figure 3 shows the theoretical fluoronium molecules

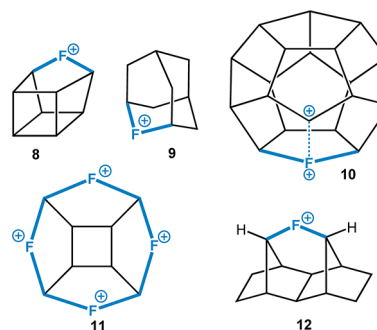


Figure 3. Possible fluoronium ion cages.

as energetic minima (vacuum at B3LYP/6-311++G** [abbrev. “B3”] or ω B97XD/6-311+G** [“B97”] levels). The structures had to match our original criteria, along with providing identical, elongated C–F bond lengths (over that of a typical C–F bond) at the energetic minima. Structure **8** is based on cubane,²⁰ **9** on adamantane,²¹ the more fanciful **10** is a distorted dodecahedrane dicationic cage, in which the fluorine engages in interactions with three carbon atoms,²² two equivalently and the third more distantly. The tetracation **11**, derived from a gaslamp-type skeleton, of course, would likely live only in imagination, confirming that theory can only guide us so far. On the other hand, the most synthetically reasonable in our eyes was the basic sesquinorbornane structure **12**, which we imagined (substituted with an anhydride) could be constructed through a series of diastereoselective Diels–Alder reactions (*vide infra*).

Why was our first choice to ensconce a fluoronium within a cage? Perhaps by releasing the restraints that the cage imposes, piece by piece, we can gain insight (Figure 4). For example, fluoronium **13** is stable relative to kinetically accessible isomers at all HF, MP2, and DFT based levels of theory that we investigated. Likewise, if we remove the anhydride group, the fluoronium interaction appears to be sustained. However, if we eliminate the ethano-bridges, thus removing strain from the

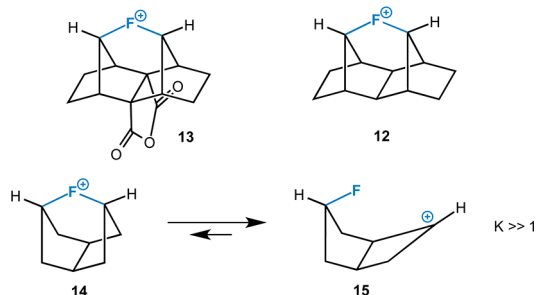
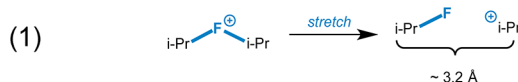


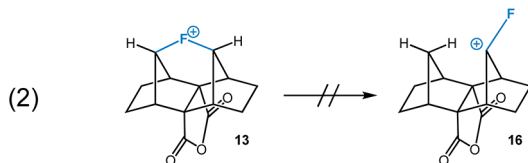
Figure 4. Loosening restraints in the fluoronium system.

system and increasing potential degrees of freedom, we see that classical isomer **15** becomes more stable relative to fluoronium **14**, which is still a defined intermediate and not a transition state (B97, H₂O solvent dielectric).

Another insight was provided by calculations on the intermolecular model, [i-Pr-F-i-Pr]⁺ (B97, vacuum). Fully optimized, the C-F-C angle is 125° and the C-F bond distances are equivalent (1.61 Å); the C-C distance is 2.86 Å. As this C-C distance is stretched, the symmetrical structure is retained until the C-C distance reaches ~3.2 Å. At 3.3 Å, a “classical,” equilibrating structure is predicted (eq 1).



Thus, there are limits to the size of C-C distances within a preferred cage, and the framework provided by **13** seems to be closer to optimal if not a bit tight (2.66 Å). Another virtue of this cage is that intramolecular hydride shifts of virtually any type are precluded. For example, a hydride shift could potentially lead to an α-fluorocarbenium ion, as seen in eq 2.²³



Not only is such a shift sterically impossible in our system, but the calculated energy of the α-fluoro cation is higher than the fluoronium at several DFT levels (e.g., B3, B97), in contrast to the expected trend.

■ THERMODYNAMIC STABILITY

The next logical step was to compare the calculated energy of the fluoronium ion to some well-known carbocations. We chose to employ isogyric²⁴ equations (B97) to estimate the stability of fluoronium **13** with respect to more common carbocations (Scheme 1). In an aqueous dielectric, cation **13** is less stable than t-butyl²⁵ and 2-norbornyl²⁶ but more stable than the isopropyl and 7-norbornyl.²⁷ Note that the isopropyl cation has a debatable independent existence in aqueous solution.²⁸ On the other hand, comparison with similarly strained cage systems may be more germane. Whereas theory predicts that the fluoronium is more stable than the μ-hydrido-bridged species **18** (*vide infra*), the chloronium, not surprisingly, is quite a bit more stabilized.

Various widely used levels of theory (DFT and MP2) are in basic agreement on cation **13**'s structure (Table 1). The C-F

Scheme 1. Isogyric Comparisons of Fluoronium 13 versus Common Cations (B97, Aqueous Dielectric)

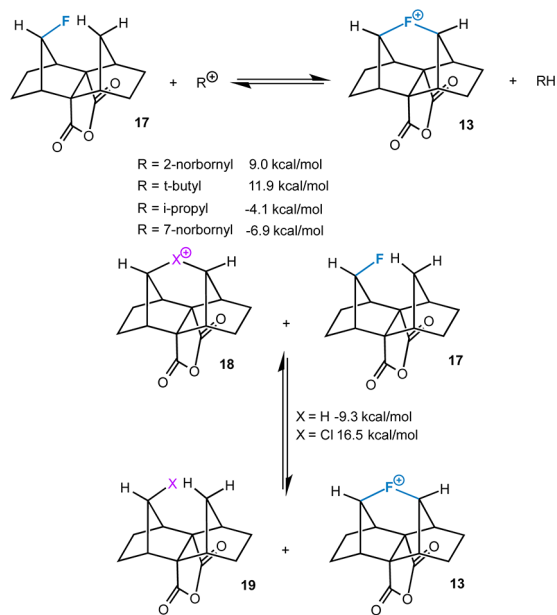


Table 1. Optimizations of Cation 13 at Various Levels of Theory

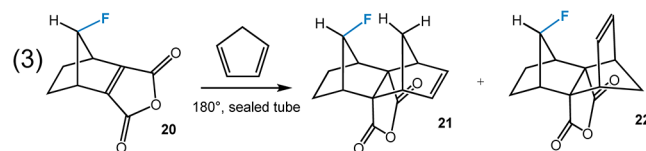
method/basis set	d (Å) C-F	C-F-C angle (deg)
B3LYP/6-311++G**	1.60	115
B3LYP/6-311++G**	1.58	116 ^a
B3LYP/cc-pVTZ	1.59	115
EDF2/6-311++G**	1.59	115
MP2/6-311++G**	1.57	115
PBEPBE/6-311++G**	1.61	114
mPW1PW91/cc-pVTZ	1.55	116 ^a
HCTH/cc-pVTZ	1.57	114 ^a
ωB97XD/cc-pVTZ	1.55	116 ^a
B3PW91/cc-pVTZ	1.57	115
ωB97XD/6-311+G**	1.56	116 ^a
BPV86/cc-pVTZ	1.59	114 ^a
M06/cc-pVTZ	1.56	116
TPSSTPSS/cc-pVTZ	1.60	114

^aCalculations were performed with the default Gaussian solvation model for water.

bond length average is 1.58 Å among the methods chosen in the table; the C-F-C bond angle averages about 115°. An atoms-in-molecules²⁹ analysis (B97) shows that each C-F interaction constitutes a little less than half of a normal C-F covalent bond (electron density at bond critical point $\rho = 0.14$), in the roughest sense.

■ SYNTHETIC APPROACHES

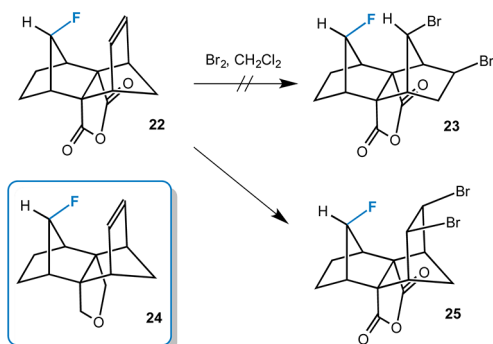
As a test, the first approach to the basic skeleton involved the thermal Diels-Alder reaction of fluorinated dienophile **20**³⁰ with 1,3-cyclopentadiene (eq 3). This reaction, conducted in



a sealed tube, produced two diastereomers in comparable amounts (**21**, 30%; **22**, 40%). Easy as the reaction proved to be, compound **21** turned out to be a dead end (other than the interesting through-space interaction between bridgehead H and F it displays).³¹ All attempts to functionalize **21** at the methano-bridge by oxidation invariably failed.

Next we turned our attention to alkene **22**, in which the fluorine interacts closely with the double bond on the opposing bridge. Following the well-established precedents of Paddon-Row et al.³² and Winstein et al.³³ on similarly configured carbon frameworks, we expected that bromination of **22** would result in rearrangement of the carbon skeleton to provide product **23** that could then be further elaborated. However, to our surprise, this did not occur (Scheme 2). Thinking that the

Scheme 2. Putative Rearrangement of **22** upon Bromination



poor migratory ability of the electron deficient carbon vicinal to the anhydride group was partly responsible, we employed a reduced version in the form of cyclic ether **24**, but this more propitious substrate also failed to rearrange upon bromination.

With this result in hand, we reasoned that addition of an electrophile to this unusual alkene **22** must involve anchimeric assistance from the lone pairs on the fluorine atom, which would thereby reduce the impetus for rearrangement. In fact, reaction of **22** with Br_2 affords the *cis*-dibrominated product **25** exclusively. The structure of **25**, determined from single-crystal X-ray diffraction, reveals some interesting features, including a close interaction of the *in*-F with two H atoms on the ethano-bridge (Figure 5). A through-space ^1H – ^{19}F coupling of 4.4 Hz

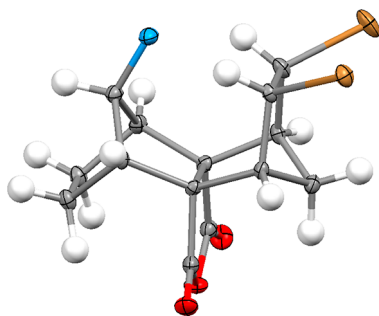
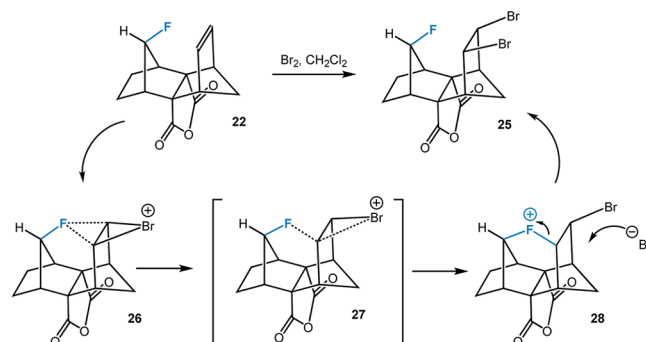


Figure 5. Displacement ellipsoid plot (50% probability level) of **25** at 110(2) K.

was detected, weaker than the interaction of the two methano-bridges but still notable. Although highly selective *cis*-dibrominations are rare (especially in simple, unsubstituted cycloalkenes), similar reactions are precedented.³⁴ *Cis*-products can be observed in cases where a bromonium isomerizes to a

carbocation that can undergo free rotation. In our case, this is not possible, but a “double inversion” involving assistance from the fluorine would also explain the *cis* stereochemistry, thereby implicating fluorine in an anchimeric role (Scheme 3).

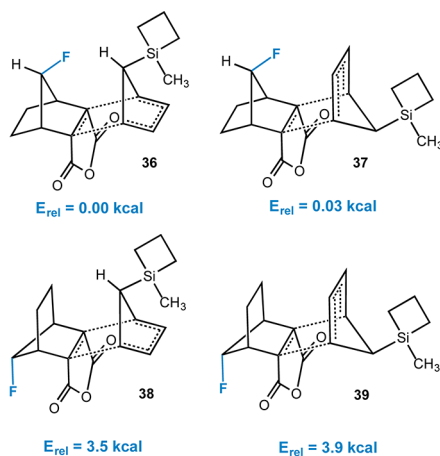
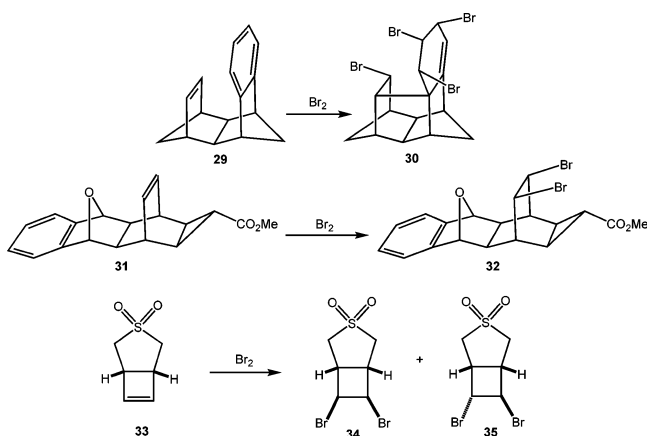
Scheme 3. Proposed *cis*-Dibromination Mechanism



One could argue that the fluorine is merely a steric impediment to the reaction of a *trans*-bromide ion, but we may well expect the aforementioned skeletal rearrangement to resolve this problem. We turned to computations to provide some guidance; calculation of bromonium ion **26** at (B97, CH_2Cl_2 dielectric) shows a significant interaction of both carbon atoms with fluorine through an AIM analysis (ρ at BCP = 0.020). However, lying slightly lower in energy (0.76 kcal) is the (not quite symmetrical) fluoronium ion **28**, which can then be trapped by bromide ion through an internal $\text{S}_{\text{N}}2$ reaction to provide the product. Something along these lines may indeed happen, as ion **26** should not normally engage in frontside trapping of bromide. Although the explanation is attractive, it does not provide solid proof. However, the fluorine should not be immediately dismissed as just a blocking group, as a number of examples show.

An especially beautiful parallel to the fluorine participation in system **25** can be seen in the work of Prinzbach et al.,³⁵ who treated olefin **29** with Br_2 and isolated tetrabromide **30**. The “backside” aromatic ring evidently participates in the bromination to form a σ -complex that is in turn trapped by bromide; further bromination then yields **30**. The newly formed C–C bond provides compelling evidence for anchimeric assistance, allowing the observer to conclude that the aromatic ring provides more than just steric hindrance. Another example³⁶ involves putative participation of an ether oxygen as an anchimeric assistor in an olefin whose two faces are sterically hindered. Last is a case³⁷ that involves postulated backside anchimeric assistance of a sulfone group to produce a 1:1 mixture of diastereomers in the bromination of **33** (Scheme 4).

Ironically, premature fluorine participation in these initial attempts may have thwarted the synthesis of **23**. Our next approach to system **13** instead involved the use of a 5-trialkylsilyl-substituted cyclopentadiene. Silane **40**³⁸ was chosen, as precedent existed that the silyl substituent would be amenable to the stereoselective Fleming–Tamao oxidation³⁹ in a subsequent step. We were optimistic about this approach thanks to several transition state calculations, whose relative energies we have found to be quite accurate for fairly nonpolar cycloaddition reactions.⁴⁰ At B97, the two most favorable diastereomeric transition states lie close together in energy (Figure 6). The desired isomer **36** is calculated to be lowest in energy, with **37** only 0.03 kcal higher in energy. The other two

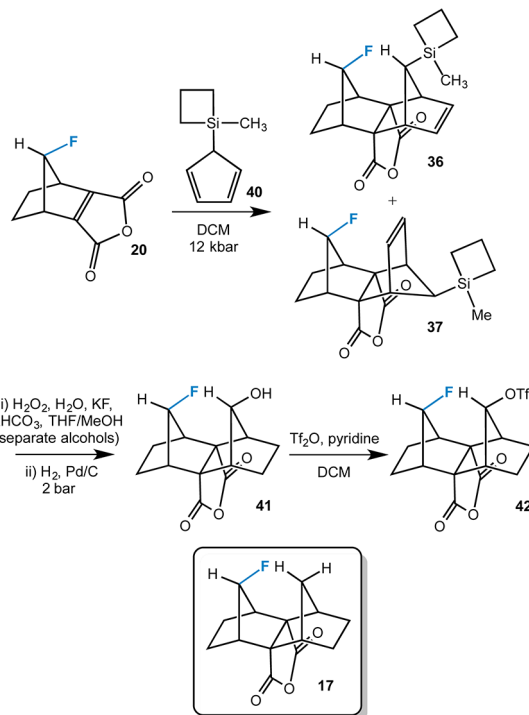
Scheme 4. Anchimeric Assistance in Bromination and Notable *cis*-Dibromination Reactions That May Utilize ItFigure 6. Transition state calculations for the Diels–Alder reaction of **20** and **40** (B97, vacuum).

possible isomers are unlikely to form, as the transition states are considerably higher in energy (3.5 and 3.9 kcal). At the very least, this calculation led us to believe that the Diels–Alder reaction would have an excellent chance of producing at least some of the desired diastereomer.

To begin the synthesis, cyclopentadiene **40** was made by the reaction of sodium cyclopentadiene with 1-chloro-1-methylsilacyclobutane.³⁸ Unfortunately, all attempts at a thermal or Lewis acid catalyzed Diels–Alder using diene **40** and dienophile **20** reaction utterly failed. The diene, it appeared, was very susceptible to rearrangement⁴¹ and decomposition—a finding not surprising in light of the migratory aptitude of electropositive silicon groups.

At this juncture, our approach to system **13** appeared to be in serious jeopardy. As a last resort, we tried a reaction under very high pressure; the literature is replete with examples of failed Diels–Alder reactions whose fortunes were transformed by a high-pressure apparatus.⁴² The reaction was conducted in a 10 mL syringe (1:3 mixture of **20**:**40**; 3 M in CH₂Cl₂) for 3 d at 12 kbar. The crude ¹⁹F NMR showed the presence of two major diastereomers whose structures we presumed to be those favored by calculation. On the basis of the prediction of ¹⁹F chemical shifts ($\delta = -0.914i + 142.63$; i = isotropic shielding at B3),⁴³ the desired diastereomer was produced in a slightly higher yield than **37**, as expected. The crude mixture was then subjected to Fleming–Tamao oxidation; separation

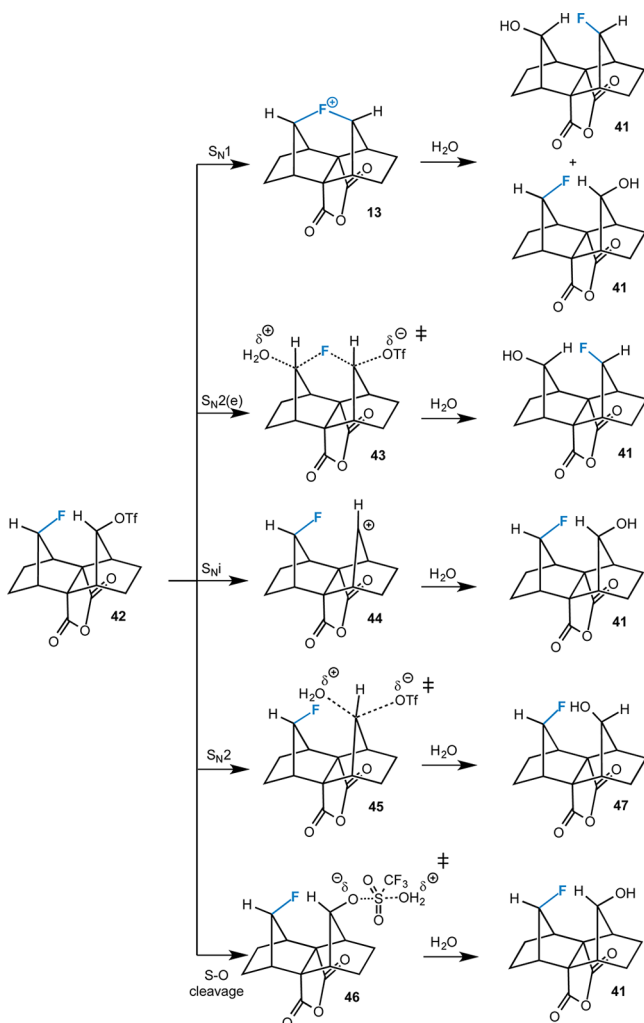
of the crude products by column chromatography on silica (yielding the desired alcohol in 36%) was followed by hydrogenation with palladium on carbon at 2 bar (99% yield) and triflation (97% yield). Our synthetic approach is detailed in Scheme 5.

Scheme 5. Synthetic Approach to **42**

We chose to use triflate as a leaving group, as it is a good candidate for the generation of very reactive cationic intermediates.⁴⁴ Triflate **42** is an interesting species in its own right; the fluorine atom and the *in*-H engage in what we've termed a "jousting" interaction⁴⁵ in which the effects of bond compression are modulated by hydrogen bonding. For example, the through-space ¹H–¹⁹F is 25 Hz, implying a large interaction. In addition, the characteristic *C-in*-H stretch is seen in the IR spectrum at 3147 cm⁻¹, blue-shifted from nonalcohol control **17** by 39 cm⁻¹. The percent *s*-character of the *C-in*-H bond is calculated to be a remarkable 29%.⁴⁶ We also obtained a crystal structure of triflate **42**, revealing the close interaction of F and the *in*-H (1.86 Å) at its estimated position.⁴⁷ With that in mind, we surmised that hydrolysis of **42** would release a fair amount of strain energy. This triflate proved to be the key molecule for our studies; however, due to the bottleneck created by the low throughput high pressure reaction and Fleming–Tamao oxidation, making it in large quantities proved impossible—thus, very judicious choices of its use were in order.

Initially, the hydrolysis of **42** was attempted in several different solvent systems (due to its low solubility in pure water). A particularly well-behaved example was a combination of the polar, ionizing 2,2,2-trifluoroethanol (TFE)⁴⁸ and water. In 70/30 v/v TFE/water, **42** smoothly hydrolyzed to afford **41** in almost quantitative yield (98%). This indicated to us that we had a remarkably stable system with no apparent propensity to rearrange; however, the identity of the product provided little useful information about the mechanism of the substitution reaction. Consider a number of mechanistic scenarios (Scheme 6), such as S_N1, an S_N2 reaction that is "extended" to involve

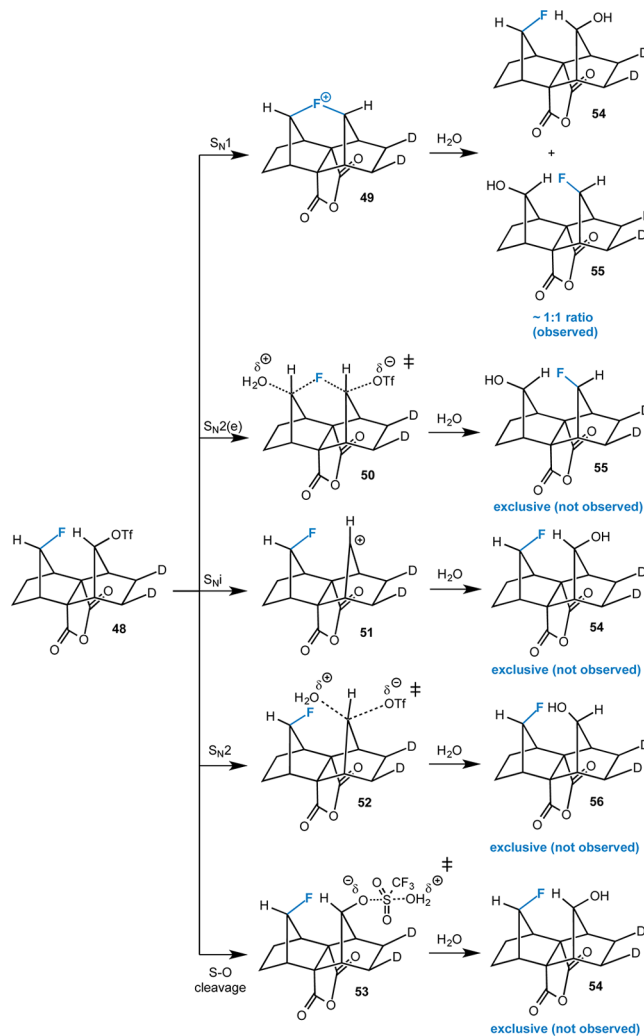
Scheme 6. Probable Mechanistic Pathways for the Hydrolysis of 42



fluorine [$S_N2(e)$], an S_N1 “frontside” reaction (S_{Ni}),⁴⁹ a garden-variety S_N2 , or cleavage of an S–O bond. The penultimate, somewhat less plausible S_N2 variant can immediately be ruled out, as we do not isolate this particular diastereomer, but the others cannot be distinguished on the basis of the product, which is the same in all of the cases.

We then turned to an isotopic labeling experiment, which allowed differentiation between various mechanistic alternatives; scrambling between positions is a classic indication of a cloaked symmetrization process. We went about labeling our compounds by replacing the hydrogenation step in Scheme 5 with a deuterated diimide reduction, which upon triflation affords d_2 -isotopomer 48. When this labeled substrate is subjected to hydrolysis in TFE/water 70/30 v/v, we obtain an approximate (1:1) mixture of isotopomeric products 54 and 55. The situation is now greatly clarified (Scheme 7). Were the reaction proceeding through an S_N2 or the S_{Ni} , a 1:1 ratio would not be expected. The 1:1 ratio is thus the likely result of equal trapping on both electrophilic sites of a symmetrical intermediate. Although highly suggestive, the case is obviously circumstantial. Circumstantial evidence is most compelling when it is overwhelming—thus, we sought to accumulate as much evidence for the nature of this symmetrical intermediate as we could. In particular, kinetic experiments, especially isotope effect studies, proved to aid us greatly.

Scheme 7. Mechanistic Outcomes for the Hydrolysis of 48



■ TRANSITION STATE CALCULATIONS

In order to predict kinetic isotope effects using DFT,⁵¹ we need information about the putative transition states. We performed calculations to find potential transition states for the ionization of triflate 42 and trapping of fluoronium 13 at several levels of theory. For example, a transition state for the ionization of triflate 42 (at B97, H₂O solvent model) was found to reveal some interesting features. The distance of the ionizing C–O bond is 2.37 Å; the structure also shows a forming C–F bond as well ($d = 2.20$ Å). Thus, the fluorine atom rapidly closes in on the carbon as the ionization proceeds.

Calculation of the transition states using other functionals (M06, PBEPBE) afforded comparable results in terms of geometry. The activation free energy for the process is calculated to be 26.5 kcal/mol at 55 °C (H₂O dielectric), with the cation resting in an energy well about 12.5 kcal below (Figure 8). The thermochemistry of such calculated reaction pathways should be approached with a high degree of caution,⁵² and mechanistic conclusions derived therefrom subject to experimental verification. A salient example of this danger is provided in the calculated (S_N1) mechanism of the reaction of water with triflate 42. The transition state for trapping of fluoronium 13 by water was also modeled; the distances of the forming/breaking bonds were similar if not identical to the ionization of triflate 42 (C–F = 2.23 Å; C–O = 2.34 Å; B97, H₂O solvent model).

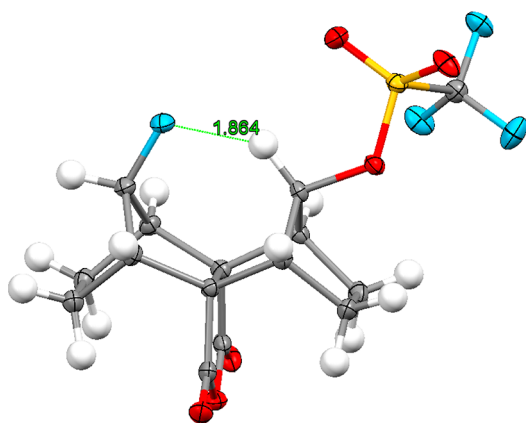


Figure 7. Displacement ellipsoid plot (50% probability level) of **42** at 110(2) K. The distance of the C–H bond opposite the fluorine was restrained to match the value calculated from the DFT equilibrium calculation (1.08 Å) using the DFIX instruction in SHELXL.⁵⁰

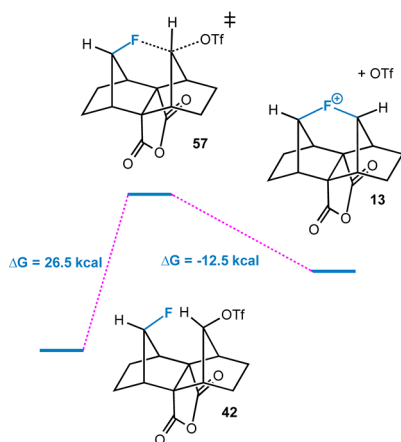


Figure 8. Calculated free energy of ionization for triflate **42** (B97, aqueous dielectric).

At B97 (H₂O dielectric), the second, water-trapping step is predicted to be rate-determining. It is obvious that the difference in the charged nature of the transition states and the role of specific solvation combined with the continuum solvent model give rise to an erroneous conclusion in terms of the energy.

As mentioned, we proposed an “extended S_N2” reaction as a viable mechanistic alternative, a possibility seemingly ruled out by the labeling study. In addition, neither the kinetics (*m* value > 1)⁵³ of the reaction nor the stereochemical outcomes are consistent with this exotic form of the S_N2. What is more, we were unsuccessful at locating transition states that would describe this process. In fact, there is a very strong tendency for nucleophiles/Lewis bases to interact with the methano-bridges of system **13** through hydrogen bonding instead of engaging in incipient nucleophilic attack. For example, the depicted structure of a dihydrated version of cation **59** (B3) reveals this tendency (Figure 9).

RATE STUDIES

We measured the activation free energy for the ionization of triflate **42** (70/30 v/v TFE/H₂O) in the temperature range 50–81°. An Eyring plot⁵⁴ (a plot of ln *k* vs 1/*T*) afforded a straight line whose slope corresponds to a Δ*H*_{act} value of 14 kcal/mol. In addition, Δ*S*_{act} is –21 cal/mol K and

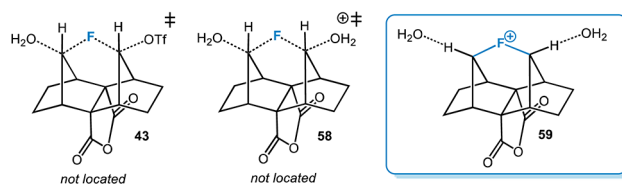


Figure 9. Hypothetical S_N2(e) transition states (not found) and a disolvated cation (minimum; found). Calculations at B3.

Δ*G*_{act} (55°) is 20.7 kcal/mol, which is less than that predicted by theory (26.5 kcal/mol); the enthalpy and entropy terms independently also differ substantially. The exceptionally negative entropy of activation deserves comment; although S_N1 reactions display negative values routinely,⁵⁵ this magnitude is unusually large. We attribute the large negative value to the ionizing role of the acidic fluorinated alcohol, which can effectively stabilize the developing negative charge on the departing triflate ion. This ionization ability has been shown by Berkessel et al. to propagate through a mutually reinforcing and ordered network of solvent molecules (e.g., **57**•solv, Figure 10).⁵⁶ This organized transition state assembly would be expected to reduce entropy.

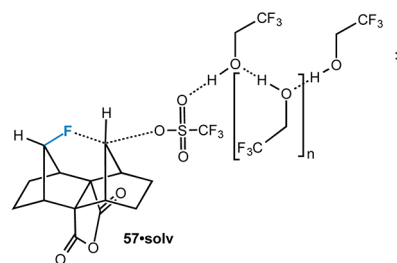
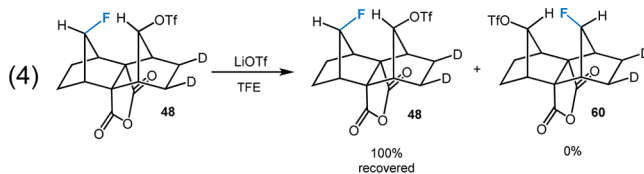


Figure 10. Solvation model of transition state **57**.

COMMON ION EFFECTS

Common ion studies are often used to shed light on the role that ion pairs play in solvolysis reactions.⁵⁷ We chose LiOTf as a point of comparison; in the presence of varying quantities of (0.01–0.1 M) LiOTf, the rate of reaction remains essentially the same within error. Consistent with this observation, recovered starting triflate **48** does not scramble its labels to any measurable extent; monitoring the solvolysis of triflate-*d*₂ **48**, we see no isomerization that would be indicative of external return. These results are not surprising—given the very low nucleophilicity of the triflate ion, it possesses little ability to compete with the water in the solution.

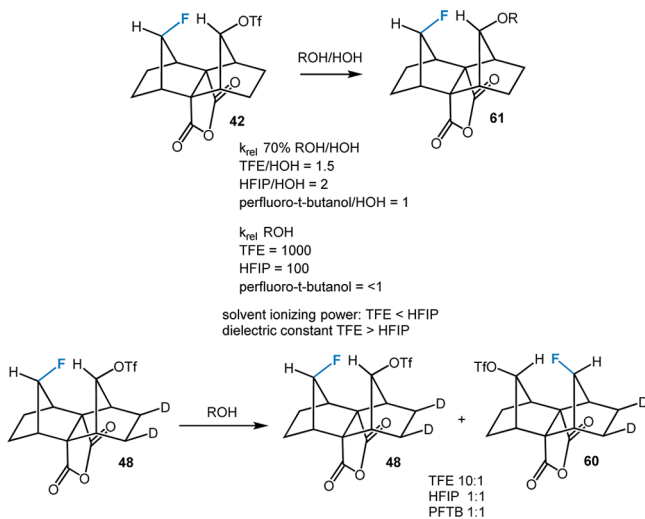


SOLVOLYTIC BEHAVIOR OF TRIFLATE 48 IN PURE POLYFLUORINATED ALCOHOLS

As shown, hydrolysis and alcoholysis experiments were generally performed in mixtures of water and polyfluorinated alcohols. We most commonly employed TFE; rate trends in mixtures of TFE and various proportions of water comport with those expected for S_N1 reactions. Rates in mixtures of

1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and water (70/30 v/v) are only slightly higher than those of analogous mixtures in TFE and perfluoro-*t*-butanol (PFTB) and significant conclusions are difficult to reach (Scheme 8). On the other hand, what about the

Scheme 8. Effects of Solvent on Solvolysis Rate



pure alcohols themselves as reaction media? Polyfluorinated alcohols such as TFE are unusual solvents in several ways; for example, whereas the ionizing power increases in the order $\text{TFE} < \text{HFIP}$,⁵⁸ the dielectric constant decreases as $\text{TFE} > \text{HFIP}$.⁵⁹ Thus, as their ability to ionize substrates increases, their corresponding ability to dissociate ion pairs decreases. The properties of the pure solvents give rise to an interesting observation; in pure TFE, the rate of alcoholysis of **42** is 10 times greater than that in HFIP,⁶⁰ and more than 1000 times greater than PFTB! This would suggest that the RDS of the triflate solvolysis has changed—instead of ionization, the RDS is now nucleophile trapping. Ingold et al.⁶¹ first documented this behavior in the context of triarylmethyl halide solvolyses, and a subsequent convention settled on the (somewhat misleading) name $\text{S}_{\text{N}}2\text{C}^+$ to specify this mechanistic variant.⁶² It is a less common phenomenon, and usually occurs in the context of highly stable and hindered carbocations. On the other hand, one can argue that hydrogen bonding of the acidic polyfluorinated alcohols to the anhydride group of triflate **42** could be responsible for inhibition of ionization. In light of Creary's results on the generation of α -keto carbocations from the respective triflates,⁶³ this seems much less likely but must be considered.

If we were seeing a change in the RDS, then a simple experiment would confirm the hypothesis. Under hydrolytic conditions (e.g., 70/30 v/v TFE/water), recovered quantities of labeled triflate **48** show no isotopic scrambling, consistent with the fast trapping of water by the cationic intermediate. However, when the reactions are conducted in pure TFE, evidence of a partial degree of scrambling is shown by NMR ($\sim 10\%$), in addition to formation of the ether product. When either HFIP or PFTB is employed, complete scrambling is observed in recovered triflate ($48:60 = 1:1$), confirming that the cation-forming transition state is surmounted but the RDS has changed so that alcohol trapping is now rate determining (Scheme 8). These results illustrate the difference between solvents that foster ionization and those that promote dissociation; whereas water promotes both, the polyfluorinated alcohols are ionizing but much less dissociating (smaller dielectric) than water.

Hence, “tight” ion pairs form in these media that can collapse back to the starting triflate. In aqueous media, however, dissociation is rapid and irreversible (i.e., lack of a common ion effect). Finally, the nucleophilicity of the pure alcohols is low, thereby increasing the barrier of the second step. In the case of PFTB, steric hindrance becomes a very large player as well.

■ SOLVOLYSIS IN THE PRESENCE OF A LEWIS ACID AND A HINDERED BASE

This solvent dependent mechanistic “switch” prompted us to investigate other methods by which the $\text{S}_{\text{N}}1$ reaction coordinate could be altered. Two experiments immediately come to mind. The first experiment would be the addition of an alcohol-tolerant Lewis acid such as $\text{In}(\text{OTf})_3$. In theory, the Lewis acid could coordinate to the triflate leaving group to aid in its removal, thus lowering the barrier of the first transition state. The other endeavors to answer the question of whether the addition of a base could lower the energy of the transition state of the second step ($\text{TS}2^\ddagger$) by improving the nucleophilicity of the solvent molecules, as well as scavenging any triflic acid formed in the reaction (additional base has virtually no effect on the rates of solvolysis in aqueous media). Thus, a Lewis acid in combination with a noncoordinating base could result in an even greater increase of the rate than with the base alone. For these experiments, we chose to use HFIP as solvent, $\text{In}(\text{OTf})_3$ as Lewis acid, and 2,6-di-*tert*-butylpyridine (DTBP) as the noncoordinating base. Initially, it looked as though our theory was correct. In a conventional solvolysis reaction with **42** and the Lewis acid (0.1 M $\text{In}(\text{OTf})_3$, 65 °C), we observed no discernible change in rate compared to pure HFIP, an expected result, as the second step is rate determining. However, when we attempted the same solvolysis reaction with base alone (1.5 equiv of DTBP, 65 °C), a large increase (34 times compared to pure HFIP) in rate was observed. When 0.002 M $\text{In}(\text{OTf})_3$ was added in addition to the base, the rate of reaction was found to decrease slightly (31 times faster than pure HFIP). At much higher concentrations of Lewis acid (0.1 M), the reaction rate decreased to 5 times that of pure HFIP. A possible explanation for this surprising result could be that deprotonated hexafluoroisopropoxide may be tied up through binding to $\text{In}(\text{III})$ (Scheme 9). This would counteract the effect of the base, and again make the nucleophile trapping step rate determining. Also, it is not out of the realm of possibility that liberated triflate ions from the Lewis acid may also play a role. These findings demonstrate that a change in rate-determining step in an $\text{S}_{\text{N}}1$ reaction can produce counterintuitive, if not peculiar, results (Figure 11).

These data can be summarized by comparison of qualitative reaction coordinate diagrams A–D (Figure 12); for simplicity's sake, ion pairs are neglected. In a lower nucleophilicity, higher ionizing medium (pure HFIP), the first step of the solvolysis reaction—loss of the triflate group ($\text{TS}1^\ddagger$)—decreases in energy, whereas the second step, nucleophilic attack by the solvent ($\text{TS}2^\ddagger$), increases (A \rightarrow B). When a hindered base is added (2,6-di-*tert*-butylpyridine), the energy barrier of the second step drops significantly, such that the rate is greater than in the mixture of HFIP and water by almost a factor of 2 (B \rightarrow C). When $\text{In}(\text{OTf})_3$ is added, quenching the alkoxide, the second step presumably increases in energy once again, and triflate is liberated. The fact that a large decrease in rate occurs in B \rightarrow C indicates that a common ion effect must be considered as well. This was shown to be unlikely as the addition of LiOTf (0.1 M) to a solvolysis reaction in pure HFIP has no meaningful effect on the rate. In addition, the previously discussed analogous

Scheme 9. Putative Mechanism for the Solvolysis of 42 in the Presence of DTBP and In(OTf)₃, Showing the Trapping of the Alkoxide

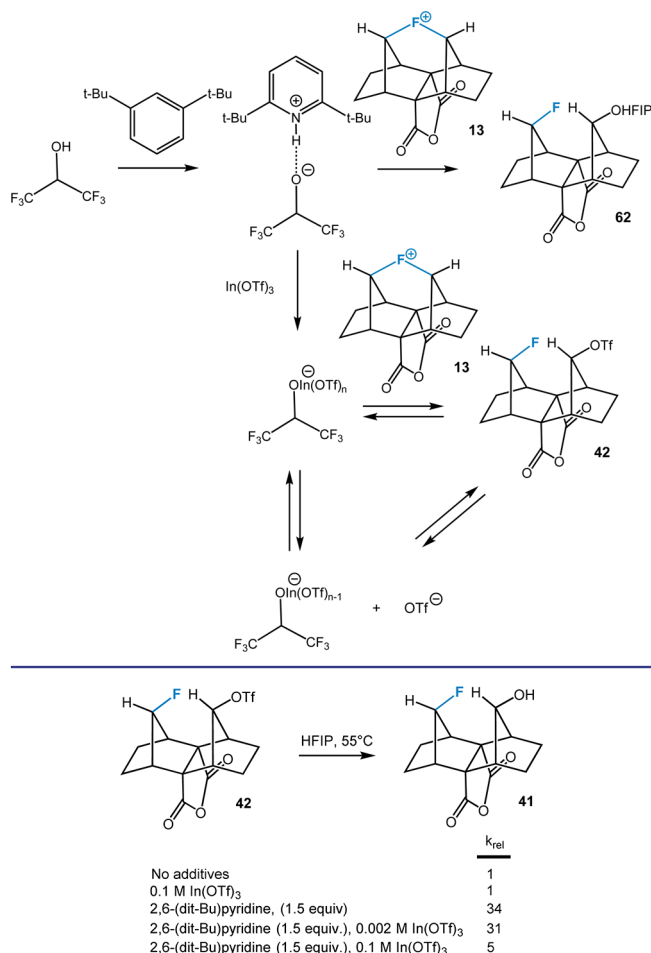


Figure 11. Effect of base and In(OTf)₃ on the rate of solvolysis of 42.

control reaction (0.1 M In(OTf)₃) in pure HFIP also showed no appreciable change in the rate.

KINETIC ISOTOPE EFFECTS

In our original report, we used deuterium atoms as labels to differentiate between the two alcohol or ether products of a putative fluoronium intermediate for purposes of integration. The deuterium atoms were positioned remotely to the [C–F–C]⁺ array; thus, integration resulted in a 1:1 ratio (within the error limits of our experiment at that time).

It occurred to us, however, that, even though the labels were remote, they may still exert a steric effect⁶⁴ in the transition state for both (S_N1) ionization of triflate 48 and the trapping of cation 49 by water. In fact, triflate-*d*₂ 48 ionizes 1.04 times faster than 42 ($k_H/k_D = 0.963 \pm 0.003$), as indicated by careful integration of product mixtures. This measurement is in rough concord with isotope effect calculations at B97 and B3, in which the free energies of labeled and unlabeled transition states for ionization of 42 and 48 were compared in a water dielectric ($k_H/k_D = 0.90$ and 0.95, respectively, at 328 K).

Due to deuterium atoms being effectively “smaller” than hydrogens, trapping of water proximally to the deuterium atoms should also be favored. Thus, the ratio of products 54:55 is measured at 0.93. The calculated isotope effect for trapping

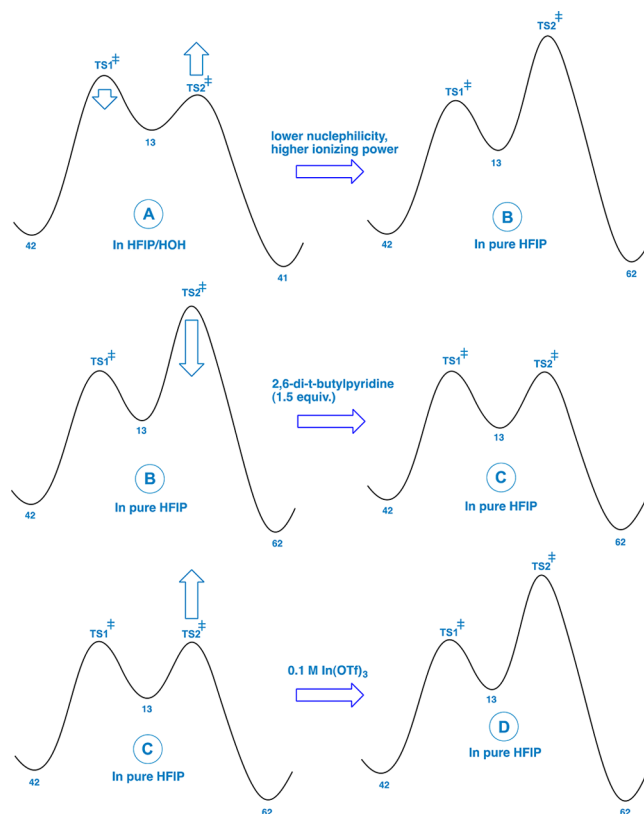
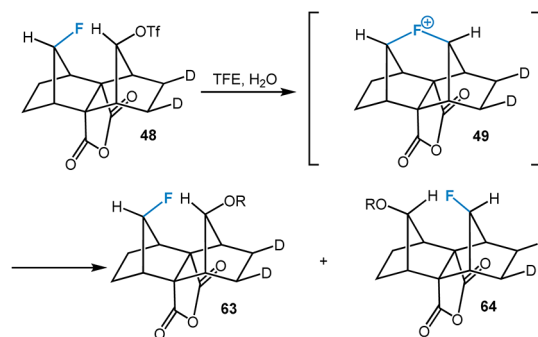


Figure 12. Alterations to the reaction energetics of the solvolysis reaction of 42 due to solvent effects and additives.

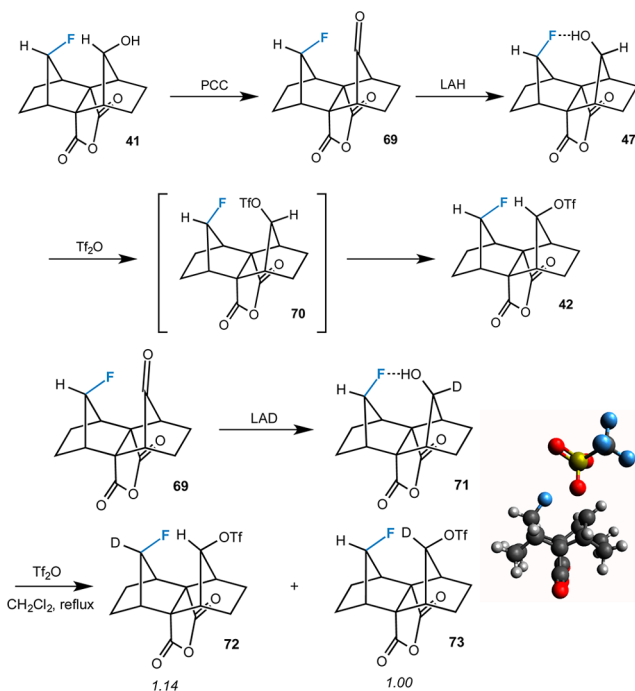
of water likewise predicts the same direction in close agreement with the experiment ($k_{distal}/k_{proximal} = 0.93$ and 0.94 at B97 and B3, respectively, at 328 K). Most importantly, these product ratios do not change with conversion, whereas the isotope effect for consumption of triflate 48 trends toward 1.00 at 100% conversion. In the case of water trapping, the isotope ratios are the same as measured at 10% conversion; this observation is in line with the trapping of a symmetrical intermediate.

More interesting and relevant would be the introduction of deuterium labels on the carbon atoms anchoring the [C–F–C]⁺ bond; this, however, represented a synthetic challenge. We know that *out*-alcohol 41 (Scheme 11) can be oxidized (PCC, CH₂Cl₂, 75% yield) to ketone 69, and reduced again with LAH to effect an epimerization to *in*-alcohol 47 (32% yield).⁶⁶ By using LiAlD₄ (LAD), a deuterium label can be introduced

Scheme 10. Basic Isotopic Labeling Study^a



^aProducts are either alcohols or ethers depending on the presence of water.

Scheme 11. In-to-Out Isomerization upon Attempted Triflation of Alcohol 71 and the Installation of Isotopic Labels in the C–F–C Array^a


^aPicture: calculated transition state for ionization of 70 showing front-side participation of fluorine.

α - to the OH group to form *in*-alcohol 71 (34% yield, >98% D incorporation). It should be noted that the anhydride of the caged system is virtually inert to hydrolysis or reducing agents;⁶⁵ the trajectory needed for nucleophilic attack is precluded by steric interference from C–H bonds residing on the ethano-bridges.

At this point, a fortuitous discovery was exploited; in an attempted triflation of *in*-alcohol 47,⁶⁶ we instead isolated *out*-triflate⁶⁷ 42 in high yield (94%). Apparently the *in*-triflate 70, being more strained (calculated activation free energy of ionization = 22.3 kcal/mol (B97, 40 °C, CH₂Cl₂ dielectric)), ionizes very rapidly, and retraps the triflate ion in the *out*-position. Thus, we can effectively use this *in situ* triflation to epimerize the *in*-labeled alcohol 71 back to the *out*-position. Note, however, that this triflation/rearrangement produces a mixture of label isomers 72 and 73 in the ratio of 1.14:1. If we can turn our attention back to the transition state 67 for trapping of triflate ion by the fluoronium, we can see why (Figure 13). The calculated isotope effect 1.07 (B97, 40 °C, CH₂Cl₂ dielectric) and more accurately at B3 ($k_{\text{dist}}/k_{\text{prox}} = 1.12$, 40 °C, CH₂Cl₂ dielectric) is congruent with what we observed, and represents a normal α -secondary deuterium isotope effect (Scheme 11). What is more, the predicted transition state (B97, CH₂Cl₂ dielectric) for ionization of the *in*-triflate 70 is a fascinating structure in its own right; it reveals a highly unusual S_Ni reaction with very evident frontside participation of fluorine (C–F distance = 2.71 Å, C–O distance = 2.20 Å). An atoms-in-molecules (AIM) analysis reveals a bond critical point (BCP) between F and C in the transition state, indicating some type of interaction. Interestingly enough, another BCP is predicted to exist between F and the triflate ether oxygen.

However, we must be careful in interpretation; if fluorine assists in the transition state, a *remote* isotope effect would be

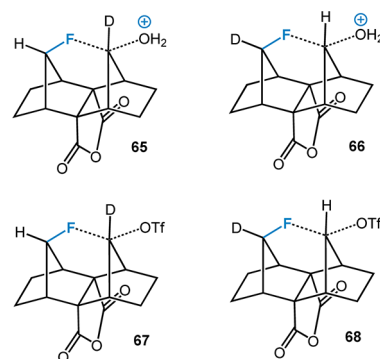
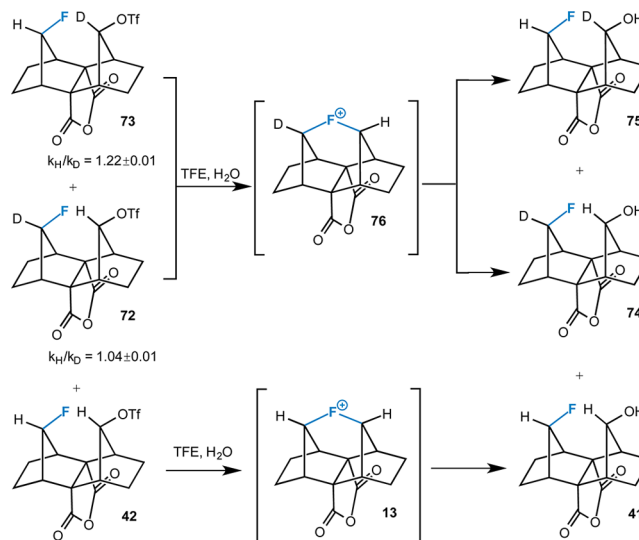


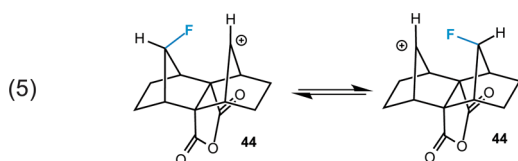
Figure 13. Isotomeric transition states for C–F–C labeled molecules.

expected to diminish the phenomenological effect from the otherwise “limiting” value (which can be as high as ~1.4⁶⁸ for pure S_N1 reactions in related systems). A remote isotope effect on trapping of water also means a remote effect on ionization. An additional experiment, starting with the labeled triflates 72 and 73, allows us to separate the remote KIE from the α -secondary KIE upon ionization. To start, triflation of a 1:1.14:1.5 mixture of α -labeled isomers 74 and 75 and protio-42 produces a perfectly corresponding ratio of labeled triflates that are then isolated. As we have established an S_N1 process and rate determining ionization, we can now take the liberty of measuring KIEs by internal competition. A competition was set up between isomer 72, isomer 73, and unlabeled isomer 42 in the said ratio (1:1.14:1.5) (Scheme 12). Two significant kinetic

Scheme 12. Kinetic Isotope Effects for the Hydrolysis Reaction as a Result of the Isotopic Labeling of the [C–F–C]⁺ Positions


isotope effects were measured; the first, representing the rate of consumption of labeled isomer 72 (geminal D) versus unlabeled triflate, was found to be $k_{\text{H}}/k_{\text{D}} = 1.22 \pm 0.01$, once again a significant α -secondary effect. For comparison, the α -secondary KIE for the solvolysis of 7-norbornyl triflate in TFE/H₂O is 1.13 at 65°. On the other hand, $k_{\text{H}}/k_{\text{D}} = 1.04 \pm 0.01$ for the position α - to the fluorine atom (removed through space from the position of the triflate group). The fact that a measurable *remote* KIE⁷⁰ exists is indicative of participation of the fluorine in

ionization, once again consistent with the model. *Ipso facto*, if fluorine is participating in ionization, it participates that much more heavily in the cationic species, thus disfavoring a rapidly equilibrating set of classical isomers (eq 5). On the other hand,

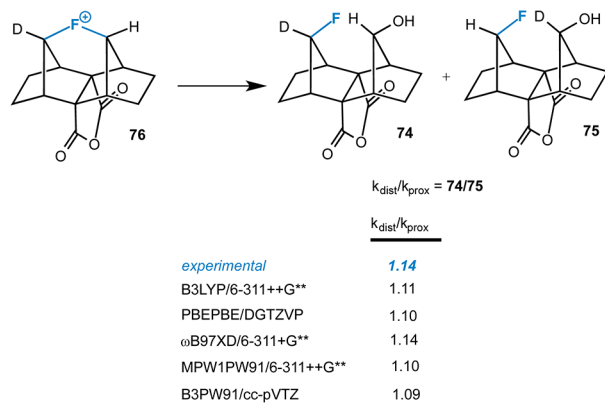


one can argue that a remote effect may be at least partly attributable to relief of steric strain upon ionization, although the computational model strongly favors direct participation of fluorine.

Predicted isotope effects were derived from analysis of the transition state of **76** (B97, 55 °C, water dielectric) and computed to be k_H/k_D (α position) = 1.27 and k_H/k_D (remote position) = 1.07, roughly in line with what we found. Finally, isotope effects for the trapping of water by substrates **74** and **75** were found once again to be 1.14. These results are very important from a confirmatory standpoint—given stereochemically unique substrates (both *out*- and *in*-triflate isomers), we observe the exact same outcome, thus implying the exact same intermediate. Regardless of the starting ratio, the presence of a fluoronium intermediate commands an identical ratio of label isomers, which is what we observe.

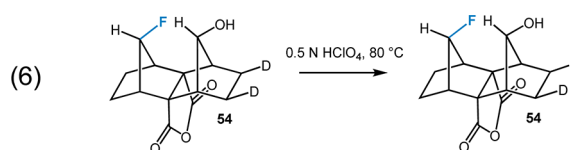
We thought at this point in time that it would be good to calibrate the method for kinetic isotope effect calculations by applying various levels of DFT-based theory to the water-trapping reaction (Scheme 13). In general, most seem to be in fairly good agreement, including B3 and B97 (the latter chosen for its ability to take good account of dispersion effects).⁷¹

Scheme 13. Comparison of Calculated Isotope Effects at Various Levels of Theory (Water Dielectric, 55 °C)



POTENTIAL ROLE OF EQUILIBRIUM ISOTOPE EFFECTS

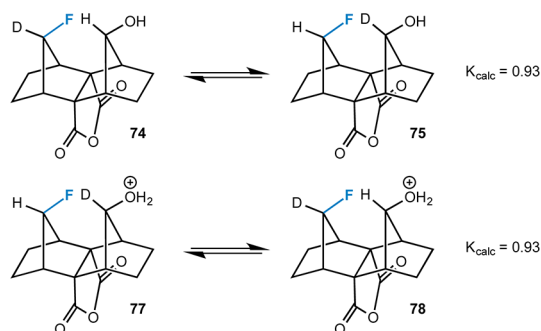
One potential criticism of the overall model is that *in situ* protonation of alcohol **75** followed by ionization can produce isotopic scrambling in the product. When we subjected isotopomers **74–75** and **77–78** to calculation, we predict an equilibrium isotope effect⁷² at B97 of 0.93, which is inverse to what is expected from a KIE. That, in addition to the lack of scrambling in alcohol **54** when treated with strong acid at high temperatures (eq 6), leads us to rule out equilibration as a source of isotope effects under all circumstances.



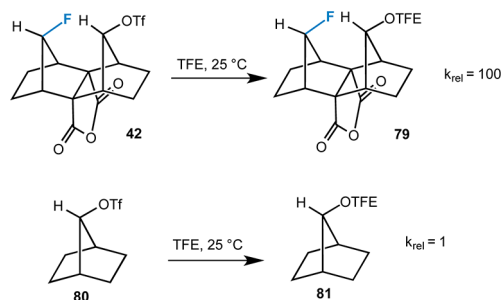
FLUORINE PARTICIPATION IN THE TRANSITION STATE

The transition state models for hydrolysis all predict substantial fluorine participation. Fluorine's role, borne of its propinquity, would appear to be both inherently stabilizing as well as space-filling. This begs the question, what would happen to the rate if fluorine were absent from the system? The obvious comparison, for which rate data exist, is the 7-norbornyl triflate system. At 65 °C, triflate **42** solvolyzes in anhydrous TFE almost 100 times faster than does 7-norbornyl triflate (Scheme 15).⁶⁹ Although

Scheme 14. Calculated Equilibrium Isotope Effects for Alcohols and Oxoniums



Scheme 15. Rate Comparison of Triflate **42 to 7-Norbornyl Triflate **80****



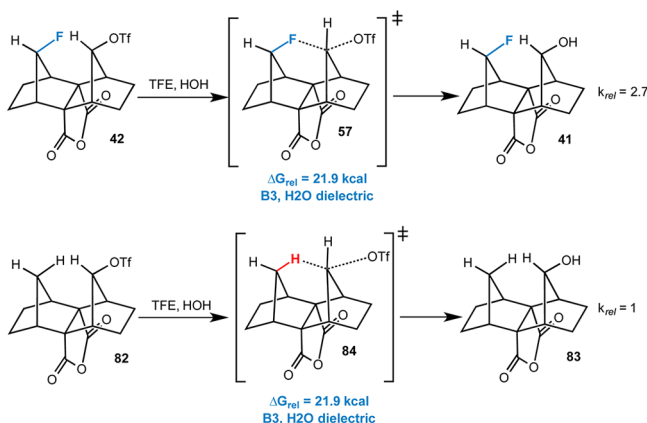
implying a stabilizing role for the fluorine, one should bear in mind that system **42** also relieves strain upon ionization. The presence of the electron-withdrawing anhydride group in **42** is expected to retard the rate of hydrolysis of **42** with respect to **80**, leading to an underestimation in the effect that the fluorine plays in hydrolysis. The issue here is that the simple 7-norbornyl framework is structurally removed from that of system **42**, and is perhaps not an ideal control.

COMPARISON TO μ -HYDRIDO BRIDGING

It is doubtful that an "ideal" control would exist for this system. Nevertheless, the most conservative control is one in which *only* the F atom is removed or replaced. A model system such as triflate **82** should provide an illuminating contrast. It is nearly identical to triflate **42**, shorn of fluorine's participation. Instead, a hydrogen atom replaces fluorine, but the anhydride group and the same general amount of strain remain. Of course, hydrogen

can provide stabilization to an S_N1 transition state through incipient μ -hydrido-bridging (and it is very likely that a cationic intermediate in the hydrolysis of **84** is μ -hydrido-bridged), as Sorensen et al.,⁷³ McMurry et al.,⁷⁴ and others have shown. μ -Hydrido-bridging is no longer a controversial topic and is known to provide an energetic benefit to numerous carbocationic systems; a comparative system would allow us to benchmark μ -hydrido-bridging versus fluoronium formation. In any case, the rate comparison of control **82** places a lower limit on what stabilization may be expected through fluorine participation. We found triflate **82** to be less reactive to hydrolysis than triflate **42** at 65 °C by a factor of 2.7, implying a modest stabilizing role for fluorine in the transition state for hydrolysis exceeding that for μ -hydrido bridging, as paralleled by our previous isogyric equations (Scheme 16).

Scheme 16. Rate Comparison of Fluoro- to a μ -Hydrido-Bridging Control



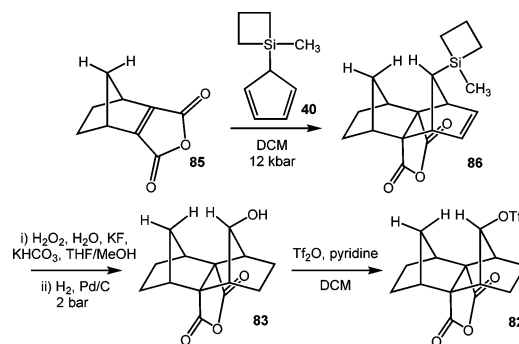
The activation free energy for S_N1 ionization of **57** is computed to be about the same as that of triflate **84** at B3 (H₂O dielectric, TS for ionization of **82** at B97 was not found). Although there is no calculated free energy gap between them, a comparison of the transition state geometries is more illustrative and tells a different story. In both cases, anchimeric participation plays an evident role in stabilizing the transition states (F and H). First, both the C–H and C–F bonds have lengthened a small amount in the transition states. However, in the case of **84**, the scission of the C–O bond has progressed much further (2.73 Å versus 2.37 Å for **57**). The X–H distance is lessened in **84** (X = H, 1.86 Å) vs **57** (X = F, 2.20 Å); in simple terms, the H moves much more than F in its transition state. The conclusion is that **84** represents a somewhat “later” transition state.⁷⁵ While H and F both participate (anchimerically assist), F is apparently more effective than H in this role.

The synthesis of control **82** parallels that of triflate **42** (Scheme 17). Known dienophile **85**⁷⁶ is treated with silane **40** under high pressure (12 kbar) for 72 h; the silane is immediately cloven by a Fleming–Tamao oxidation (15% yield). This is followed by hydrogenation with palladium on carbon (95% yield) and triflation (94% yield) to afford the product **82**, which can be purified by chromatography on silica. The synthetic method can be seen in Scheme 17.

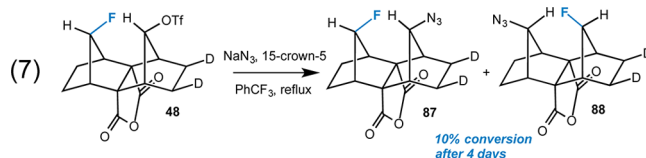
■ ATTEMPTING TO FORCE $S_N2(E)$ REACTIVITY

Thanks to our labeling studies, a role for the $S_N2(e)$ reaction has been ruled out in the hydrolytic reactivity of triflate **42**. However, what would happen if the reaction conditions

Scheme 17. Synthesis of μ -Hydrido Control **82**



strongly favored an $S_N2(e)$ mechanism and disfavored an S_N1 mechanism? Would that be enough to force the reaction to follow the $S_N2(e)$ pathway? The answer seems to be no—employing a reactive S_N2 nucleophile (NaN₃, 15-crown-5) in a fairly nonionizing solvent (benzotrifluoride) at 106 °C affords a reaction but only in low conversion (~10%) over extended periods of time (4 d). Use of labeled triflate **48** confirms that this reaction proceeds through an S_N1 mechanism (~1:1 ratio of isotomeric products (eq 7)). An examination of models

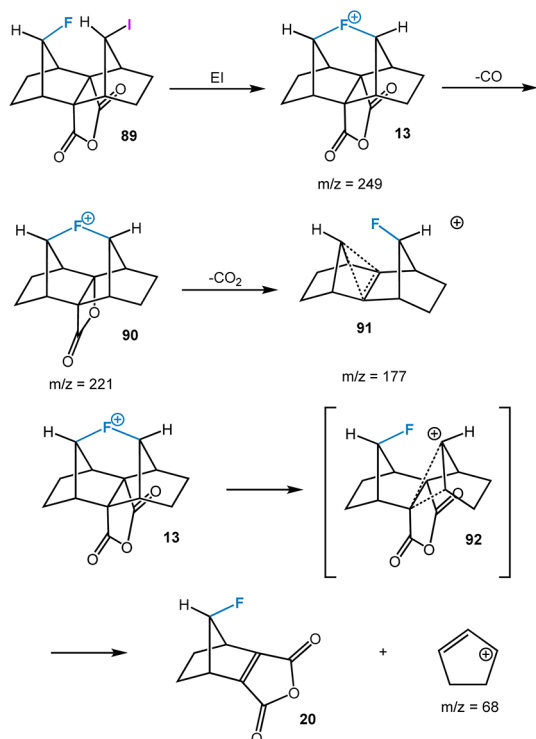


indicates that the triflate **48** simply presents a very poor possible attack trajectory for S_N2 reaction. This result is also consistent with what is seen in the well-studied 7-norbornyl system; S_N2 attack at the 7-position²⁷ is disfavored sterically, in contrast to conventional secondary systems. To summarize, we have found no conditions in which an $S_N2(e)$ is observed, even when highly favored.

■ MASS SPECTROMETRY

One of the notable features of the cage system is its resistance toward rearrangements. In some hydrolysis experiments of triflate **42**, the yields of alcohol **41** are close to quantitative. The analysis of the mass spectrometry of cation **13** can provide some fundamental information on the basic reactivity of the cage. Although not solution-phase experiments, they are illuminating nonetheless. For the fragmentation experiment, we first chose the previously synthesized iodide adduct **89** as a starting point. Electron impact ionization of **89** produces four major fragments in the mass spectrum (the parent ion is formed in trace amounts). A prominent mass corresponding to cation **13** is present; its identity can be confirmed by exact mass as well. The other two major fragments can be rationalized by sequential extrusion of CO ($m/z = 221$) and CO₂ ($m/z = 177$). Optimization of ion **90** (vacuum) (B3, B97) also reveals a symmetrical fluoronium structure (C_s symmetry). However, loss of CO₂ produces a putative bishomocyclopropenyl ion⁷⁷ in which the hypervalency of fluorine is disrupted. Finally, expulsion of 2-cyclopenten-1-yl cation ($m/z = 68$) through **92** represents the fourth fragment. Overall, the ionization pattern is generally clean and straightforward, confirming the potential energy surface for the formation and decomposition of **13** is fairly uncomplicated. What is most interesting is that each of the major three fragments indicates retention of the fluorine

Scheme 18. Fragmentation Pathway of 89 and 13



atom on a core ion or neutral species. ESI ionization of the triflate 42 produces a similar ionization pattern as iodide 89. Under these conditions, when the ion corresponding to fluoronium 13 is trapped and fragmented, only three fragments (the m/z 249, 221, and 177) are detected (the 2-cyclopenten-1-yl cation at $m/z = 68$ is missing). Once again, the fragmentation pattern is remarkably clean and straightforward.

■ THREE-CENTER BONDING IN A MODEL

Analysis of the C–F–C interaction in cation 13 is made somewhat difficult by the admixture of atomic orbitals (AOs) from the cage framework. If we remove the cage, we are left with the question of three-center bonding in the model system $[\text{Me}-\text{F}-\text{Me}]^+$ (imposed C_{2v} symmetry). Various levels of theory are in basic agreement on orbital topology and energy (Figure 14 depicts the four lowest lying molecular orbitals involve the three-center bonding of the C–F–C interaction). The lowest lying filled orbital A involves overlap of atomic s-orbitals. The next highest orbital B involves a p orbital on fluorine, the 2s orbitals on the carbons, and the 1s orbitals on the hydrogens, whereas the two higher energy orbitals C–D involve p-AO's on carbon and fluorine. The relative energies of the orbitals are carried over two DFT levels, one MP2 and one CCSD, providing us with a consistent picture.

Often in discussions of three-center bonding, the question arises as to the viability of the so-called “classical”, or two-center, alternative. In the case of the fluoronium system 13, a classical alternative is not a stable minimum on the calculated potential energy surface. In order to estimate the energy of a hypothetical classical structure, we employed the procedure of Schleyer et al.⁷⁸ Namely, the corresponding radical was optimized and then corrected by the computed vertical ionization energy. The resulting artificial cation was found to be 21 kcal (B3) and 22.6 kcal/mol (B97) higher in energy than fluoronium 13—no wonder it is not a minimum. It is a

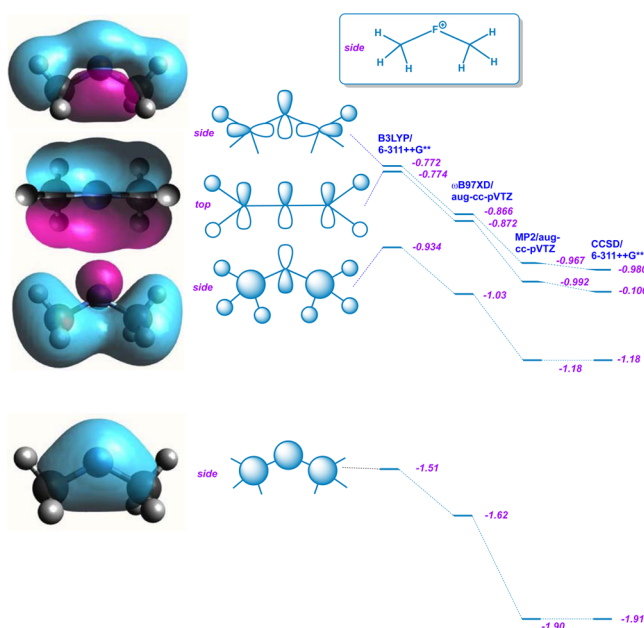


Figure 14. Calculated three-center bonding orbitals of dimethyl-fluoronium (C_{2v} symmetry) and their energy levels (eV) at several levels of theory (orbital C shown from top view, A, B, and D shown from side view).

Scheme 19. Schleyer Method for the Calculation of the “Classical” Carbocation

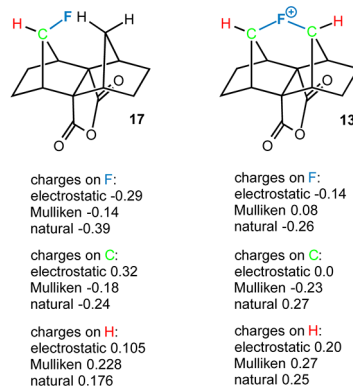
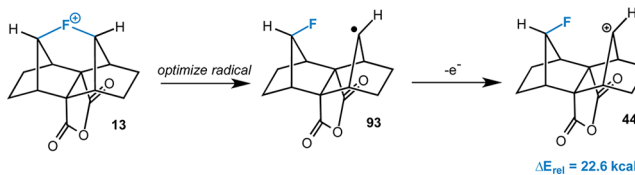


Figure 15. Comparison of charge disposition upon fluoronium formation (B97 vacuum; trend holds for other theoretical levels and with solvent models).

reasonable assumption that a carbocationic center will derive stabilization from any nearby lone pair of electrons (in this case from the fluorine atom).

Although electron-counting schemes are arbitrary and sometimes hazardous to interpret, a trend can be discerned upon formation of the fluoronium from a model precursor such as 17 through a hypothetical hydride transfer (B97, vacuum). The fluorine atom becomes more positively charged, as do the two hydrogens on the methano-bridges. This gives some credence

to the hydrogen bond, dihydrated cation **59**. On the other hand, the carbon atoms become more negatively charged, a pattern that may be ascribed to a natural consequence of three-center, four-electron bonding.

CONCLUSION

We have sought to expand upon our initial evidence with a comprehensive study involving several lines of experiment and argument to reach a more compelling conclusion about the generation of the putative symmetrical fluoronium ion **13** in solution. In turn: (1) Isotopic labeling studies show scrambling consistent with the trapping of a symmetrical intermediate. (2) Rate measurements reveal the operation of an S_N1 mechanism through which a fluoronium ion must be generated. (3) In pure polyfluorinated alcohols, the RDS of the reaction changes from ionization to nucleophile trapping on a presumably hindered carbocation. (4) Kinetic isotope effect (KIE) experiments are consistent with precedent and calculation in implicating participation by fluorine in the transition state for ionization of **42** (with unusual remote isotope effects reinforcing this conclusion), thus disfavoring the historically oft-postulated “rapidly equilibrating set of isomers” alternative. (5) Starting with an epimeric precursor that hydrolyzes through a putative frontside S_Ni mechanism involving fluorine participation, KIE studies indicate that the identical intermediate is trapped (the fluoronium ion). (6) Isotopic distributions in the trapping of putative ion **76** by water are invariant to concentration and conversion and are also consistent with a symmetrical intermediate. (7) Comparisons with control compounds reveal probable anchimeric assistance in the transition state for the hydrolysis of **42**; for example, one experiment demonstrated fluorine’s role from an energetic standpoint relative to commonly encountered μ -hydrido-bridged systems. (8) Computations at multiple levels of theory all agree fairly well on the structure of the fluoronium and the transition states leading thereto. Thus, we can reach the notable conclusion that system **42** reacts solely through an S_N1 mechanism via a symmetrical fluoronium ion.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07066.

General experimental procedures, kinetic data, spectral data, crystallographic information, and computational files. For crystallographic data, see also CCDC 11418292 and 1418293.

(PDF)

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Notes

The authors declare no competing financial interest.

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