1. Introduction

As the most electronegative element, fluorine usually gets its way with other atoms, much in the manner a wild cat gets his way with prey. Once part of a C–F bond, the fluorine atom is tamed and has a much-diminished desire to interact strongly with other species. What would it then take to get fluorine, as part of a C–F bond, to do the chemist’s bidding? One possibility is to capture it within a cage, or else to make it part of the structure of the cage itself. In fact, the cages of particular interest to us are not of the “encapsulating” form, in which the cage totally surrounds an entrapped entity. Instead, we have explored the “interacting” forms, in which the cages anchor substituents and set the stage for very close intramolecular contacts (both covalent and noncovalent), thus making fluorine in essence part of the cage’s structure. In the history of organic chemistry, this type of system has most notably permitted the characterization of some remarkably short nonbonded H···H and H···Ar interactions.[1]

Our particular stratagem is to place fluorine, as part of a C–F bond, within an “open door” cage precursor whereby it is pointed directly at, and could interact at close range with, a prominent organic functional group. The resulting interaction would thus effectively shut the “door” to the cage. Shown in Scheme 1 are several molecules, each representing a different molecular interaction between fluorine and a closely positioned functional group. The interactions, which are of various strengths, define the “tightness” of the cage.

Weak cages are exemplified by interactions of the C–F bond with C=C and C=O bonds, stronger cages are revealed by hydrogen bonding interactions (F···HO, F···HC); and a B···F interaction is only predicted to form a cage in its transition state. The strongest cage is represented by a symmetrical C-F-C fluoronium ion, in which the C-F-C interaction is highly covalent. A weak cage arises again in novel aromatic substitution chemistry in which F interacts with an aryl ring.

For a starting system, we turned for inspiration to the decahydro-1,4,5,8-dimethanonaphthalene skeleton, made in substituted form by Winstein and Svensson,[2] and later in unsubstituted form by Ermer.[3] Hydrogen bonding interactions of the one-carbon bridge substituents partly close the cage, whereas a fluoronium would fully close it (Scheme 2).
A couple of ingenious species are known for encapsulating fluoride, or a covalent $X-F$ linkage in a cage, as sometimes in olden days aforementioned wild cats were put in cages for good or ill. For instance, Bassindale and co-workers have synthesized an inclusion compound in which a lone fluoride ion resides in a siloxane cage (1, Figure 1). Additionally, Pascal and co-workers have ensconced a silyl fluoride linkage in a cage that forces it into close proximity with the $\pi$-system of an arene (2, Figure 1).

From a more general standpoint, cage molecules are venerable in the history of non-natural products chemistry, wherein they serve as architecturally intricate scaffolds for remarkable cations, radicals, and other reactive intermediates not easily accessible by other means. They can be small, like cubane [5], in which nothing can fit, or they can be large like the fullerenes [6] or the amazing supramolecular structures that abound in today’s literature and that can accommodate guests with ease. [7] From an aesthetic point of view, cage molecules are often architecturally elegant [8], and have engendered colorful trivial names in the chemical lexicon, as so eloquently recounted in Nickon’s and Silversmith’s “The Name Game.”

2. First Forays: Interaction of $C-F$ Bonds with $C-H$ and $C=C$ Bonds

The construction of cage molecules often utilizes the Diels–Alder reaction; thus we anticipated that a series of Diels–Alder reactions could lead to the basic open-cage framework. Our endeavor started with 5-fluoro-1,3-cyclopentadiene 3 generated in situ; this species can be trapped with dimethylacetylene dicarboxylate 4 [10]. Hydrogenation and anhydride formation result in the key dienophile 5 which plays a prominent role in much of the chemistry highlighted within this Minireview. The most notable feature of dienophile 5 is the highly fortuitous cis-disposition of the C–F bond and the unsaturated anhydride ring. The remarkable selectivity of this Diels–Alder reaction (only traces of the trans isomer are observed) has been ascribed to the controversial “Cieplak effect.” [11]

Reaction of 5 with 1,3-cyclopentadiene affords two diastereomers 6 and 7 in roughly equal quantities (Scheme 3). [12] Isomer 6 shows the F atom jammed against an H atom on the opposite bridge. The through-space coupling constant ($J_{HF} = 7.4$ Hz) is indicative of a fairly tight...
interaction between them. Likewise, isomer 7 shows a close interaction of the F atom, this time with the C=C bond constituting the opposing bridge. In both cases, a bond critical point (BCP), in atoms-in-molecules (AIM) parlance, exists between F and the opposing H atom or C=C bond. Especially in the latter case, it is debatable whether this interaction is strong enough to consider it as a formal cage (in fact it may be repulsive), nevertheless, spin–spin couplings between $^{19}$F, $^{13}$C, and the vinyl $^1$H atoms reveal significant perturbations. The radical cation of 7 ($^7^+$) presumably formed in the corresponding EI mass spectrum, reveals a much stronger interaction ($d$(C···F) = 2.40 Å at oB97xvd/6-311 + g**; same used for all calculations except 8-I) as opposed to 2.68 Å in 7, and a BCP higher in magnitude. In any event, these results serve as a warm-up for more interesting studies.

We then moved forward to synthesize a series of molecules in which very close C–F···H–C α-bond interactions (that we nicknamed “jousting”) can be enhanced through both red- and blue-shifted hydrogen bonding (Figure 2).[13] These interactions were induced by the placement of various functional groups geminal to the H–C bond, thereby probing the relationship between hydrogen bond strength and bond vibration frequencies. “Jousting” interactions appear to be an admixture of F···H hydrogen bonding and C–H bond compression. The associated electronic effects resulting from changes induced by the functional group at the X position on these systems are documented by IR, X-ray crystallography, $^1$H NMR, and $^{19}$F NMR spectroscopy.

The synthesis of the jousting molecules (Scheme 4) is more adventurous than the synthesis of the first probe molecules. In the present case, the crucial Diels–Alder reaction had to be performed under high pressure. Elaboration of diastereomer 10 through Fleming–Tamao oxidation, triflate formation, and functional group interconversion led to a series of products with different substituents geminal to the inward hydrogen.

Depending on the nature of the functional group, both red- and blue-shifted hydrogen bonding can be induced relative to the standard methylene group. For example, iodide 8-I produces a blue shift between F and H ($d = 1.85$ Å), whereas cyanide 8-CN produces a red shift and behaves more as a classical H-bond ($d$(F···H) = 1.83 Å); in both cases $J_{HF}$ is large (38 Hz for 8-I, 50 Hz for 8-CN). As we stated, “the direction of the IR shift of the X–H (in our case, C–H stretch) is often independent of the magnitude of the interaction. In our case, the size of the through-space H–F spin–spin couplings may be more indicative of the strength of the interactions” (Scheme 5).

3. A Symmetrical Fluoronium Ion in Solution: Shutting the Door on the Cage

The interactions highlighted in the previous examples are best described as noncovalent, which means that the “door” to the cage is partly open or else weak. One way to close it completely (to form a desadamantyl type structure with a predicted C–F distance of 1.58 Å) would be through the displacement of a good leaving group by a C–F bond at the opposing bridgehead (Scheme 6). It is no accident that a symmetrical C–F–C fluoronium ion in solution was not observed until recently—we are asking fluorine to assume a formal positive charge in valence bond terms, or to become

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Figure 2. A series of molecules with different groups geminal to the inward hydrogen used to probe “jousting” interactions.

Scheme 4. Synthesis of “jousting” probe compounds. DAST = (diethylamino)sulfur trifluoride, TF = trifluoromethanesulfonyl.

Figure 2.
much more positively charged (although still somewhat negative) in modern theoretical, electron-counting terms.

The first experiment that we performed was the hydrolysis of triflate $\text{11}$; this reaction was both surprisingly fast and clean (Scheme 7).\(^{[14]}\) It clued us in to the fact that something unusual was going on during the reaction, perhaps the formation of the fluoronium itself. Still, while this experiment provided promising evidence, it was far from definitive proof.

An isotopic labeling study served to clarify things. One issue with studying the unlabeled compound is that as the fluoronium intermediate is symmetrical, it is not possible to distinguish it from its alternatives. One would expect the same result from “simple” triflate hydrolysis or an extended $S_n2$ mechanism wherein water attacks from the back of the C/C$_0$F bond as fluorine displaces the triflate.

Deuterium-labeled isomer $\text{[D$_2$]-11}$ gave an almost equal proportion of labeled products upon hydrolysis, with an ever-so-slight preponderance of $\text{13a}$ that we attribute to a steric isotope effect (Scheme 8). This result was strongly suggestive of a symmetrical intermediate, but did not completely rule out the possibility of rapidly equilibrating classical secondary carbocations, with fluorine “jumping” from bridge to bridge.

To determine the nature of the intermediate, other isotope effects were measured, most importantly those involving labels proximate to the developing fluoronium bond ($\text{14}$ and $\text{15}$). Both phenomenological isotope effects for hydrolytic disappearance of the triflate, and the corresponding appearance of the trapped products (alcohols), comported well with theoretical calculations (Figure 3).\(^{[15]}\)

### 4. No Cage, Door Shuts, Door Cracks Open

We also documented a type of cage interaction in a C–F bond directed Diels–Alder reaction.\(^{[16]}\) The process is best illustrated by the competition experiment shown in Scheme 9, whereby dienophile $\text{5}$ outcompetes its epimer $\text{20}$ in a Diels–Alder reaction with borole $\text{19}$,\(^{[17]}\) presumably by stabilizing the transition state through a B···F Lewis acid/Lewis base reaction. Diels–Alder reactions of $\text{5}$ are usually more difficult to achieve than those of its sans-inward-fluorine siblings, requiring higher temperatures to proceed. Calculations indicated that the low energy transition state benefits from the B···F interaction (2.27 Å, Figure 4) which is significantly stronger in the transition state than in the product, where it is mitigated (now 2.60 Å) by the fully formed homoaromatic boracyclopentene interaction. Thus, in the starting materials there is no cage, in the transition state there is a cage albeit weakly locked, and in the product the cage’s door is cracked open! Another way to view the situation is in analogy to a yo-yo.

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*Scheme 5. Examples of blue-shifted and red-shifted F···H interactions.*

*Scheme 6. A C-F-C fluoronium ion and its precursor.*

*Scheme 7. Results of preliminary hydrolysis of triflate $\text{11}$. TFE = 2,2,2-trifluoroethanol.*

*Scheme 8. Results of the isotopic labeling study. Hydrolysis conducted with 20% H$_2$O in pure TFE at 60°C affords $\text{13a} + \text{13b}$ (96% R = H, remainder is TFE ethers).*

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a salient example is provided by alcohol 27, in which a strong hydrogen bond exists between F and the OH group \((d(F\cdots O) = 2.51 \text{ Å by crystallography})\).\(^{[18]}\) Alcohol 27 is made by the epimerization of out alcohol 8-\textbf{OH} through an oxidation/reduction sequence (Scheme 10).

The hydrogen bond in 27 is unusual in that the frequency of its \(\text{OH}\) stretch is not much different than that of its epimer, alcohol 8-\textbf{OH}, in a variety of solvents (Figure 5). This “no shift” bond appears deceivingly to be virtually absent by IR spectroscopy, but in fact NMR \(J_{HF}\) coupling constants (68 Hz) indicate a very strong interaction, which is typically not the case for \(C\cdots FC=O\) hydrogen bonds.\(^{[19]}\) This cage, closed by hydrogen bonding \((d(F\cdots HO) = 1.59 \text{ Å})\), is a case of an admixture of blue-shifting (bond compression) and red-shifting (traditional H-bonding) forces cancelling each other in the IR spectrum. This phenomenon seems to come uniquely from the interaction of fluorine and the hydroxyl group; as discussed previously, interactions with fluorine and \(C\cdots H\) bonds in 8 produced both blue and red shifts, and the interaction between a hydroxyl group and an alkene resulted in a strong red shift.\(^{[20]}\)
6. F···Ar and F···Carbonyl Interactions: Electron Density and Nuclear Shielding

After our early investigations of the F···alkene interaction, we decided to synthesize new compounds that would highlight different types of F···π interactions: an F···arene interaction\[21\] and an F···carbonyl interaction.\[22\] Ketone 26 proves to be an excellent model system to investigate the F···carbonyl interaction, which turns out to be surprisingly complex. We obtained crystallographically-derived static electron deformation density maps that are analyzed in the context of comparison molecules (see Figure 6). It is clear that there is some repulsion occurring between the oxygen and fluorine atoms, but it is not immediately obvious to what extent an attractive fluorine lone pair···C=O π* donation (\(d(F···C)=2.44\) Å by crystallography) plays a role. Compared to nonfluorinated control molecules, the C=O stretching frequency is blue-shifted by \(\approx 20\) cm\(^{-1}\).\[25\] which suggests that there is some steric compression between the ketone and fluorine, a fact corroborated by the relative deshielding of 26 compared to control 28 (Figure 6) by 6.73 ppm. This deshielding decreased (by 1 ppm) when the ketone was complexed with a bulky aluminum-based Lewis acid\[23\] (Scheme 11, left), showing that when an oxygen lone pair is tied up by aluminum, its ability to compress the C–F bond decreases. Attempts to form complexes with a less bulky aluminum compound resulted in binding to the anhydride carbonyls (Scheme 11, right). The said chemical shift difference is accompanied by a red-shifted carbonyl stretch (70 cm\(^{-1}\)) in the IR spectrum.

According to results of theoretical studies, the structure with an unconstrained F···C distance (compared to various fixed F···C distances) maximizes the blue-shift in the C=O stretch, and minimizes the C=O bond length. This led us to conclude that the interaction between the fluorine atom and the ketone compels the minimum energy structure to lie at the point of balance between competing oxygen–fluorine repulsion and incipient nucleophilic attack on the carbonyl carbon by the fluorine atom. The interaction consists of a combination of attractive and repulsive forces, reminiscent of the strange no-shift hydrogen bond in 27.

Turning to the F···arene interaction, we start once again with the keystone dienophile 5 (shown rotated 180° from its previous depictions for clarity in Scheme 12) to make probe molecule 29 through a Diels–Alder reaction with anthra-
In the resulting adduct, the fluorine atom is positioned over the π-cloud of an aromatic ring, close to the center ($d = 2.68\,\text{Å}$ by crystallography to the nearest aryl carbon atom). Though fluorine as part of a C–F bond is traditionally believed to not be very susceptible to anisotropic perturbations,[25] we thought that the proximate arene might have an interesting effect on the fluorine nucleus in the NMR spectrum.

Whereas ring current effects traditionally effect shielding normal to the plane of the aromatic ring, we found that the fluorine nucleus of 29 is deshielded relative to its out counterpart 33 by 15.8 ppm. The hypothesis that we devised to explain this result was that deshielding from orbital compression[26] may be outcompeting ring current shielding. As the electron cloud about the fluorine atom would be distorted anisotropically by electron repulsion from the arene π-cloud that is compressing the C–F bond, we expected to see the $^{19}$C–$^{19}$F coupling constant increase.[27] This is what we found: this geminal coupling constant is greater in 29 by 21 Hz (relative to that in 33).

We strove to observe directly the electronic environment created by the F···arene and F···ketone interactions, so we collected X-ray data at subatomic resolution and used multiple refinements to generate static electron deformation density maps for 26 and 29, with 28[21,28] as a control compound (Figure 6). Both 26 and 29 show distortions about the fluorine compared to control 28, but in the case of ketone 26, they are much more dramatic: the symmetrical toroidal region of electron density in 28 is significantly distorted in 26. In the case of 29, the distortion is lessened, but it is evident that a compressive effect is tilting the electronic structure away from the C > C–F line.

7. The F···Ar Interaction: Partly Closing the Cage to Promote Aromatic Substitution

The prior studies on symmetrical fluoronium ions prompted us to wonder whether we could use a “fluoronium-like” interaction to stabilize a transition state or reactive intermediate in aromatic substitution chemistry. In a way, it would be a different form of arene activation, with fluorine’s lone pair stabilizing positive charge on the aryl ring (Scheme 13). As predicted, nitration of 29 afforded exclusive substitution on the top ring (Scheme 13). Control experiments indicated strongly that the fluorine atom acts as a stabilizing force in the successful reaction chemistry.

Using valence bond arguments, the notable “fluoronium” resonance form shows how the cage is “closed” (albeit weakly) in the intermediate and transition state (Scheme 14). Although by no means a full-fledged fluoronium ion, the principle of σ-stabilization through fluorine’s lone pair stabilizing positive charge on the aryl ring (Scheme 13). As predicted, nitration of 29 afforded exclusive substitution on the top ring (Scheme 13). Control experiments indicated strongly that the fluorine atom acts as a stabilizing force in the successful reaction chemistry.

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8. Conclusion

The incorporation of fluorine into the body of a cage structure enabled us to probe novel noncovalent and covalent interactions of fluorine, learning about new ways in which its reactivity can be influenced by subtle forces. We also envisage some creative future directions for cage interactions. Building on the H-bonding principle, a charged bond of F to NH⁺ and OH⁺ can be imagined. A stronger interaction of B and F is possible by reduction of the homoaromatic double bond mentioned in Section 5; furthermore bridging N-F-C and C-F-Si species; finally incipient attack of F as a nucleophile at an oxenium carbon atom (Figure 7).

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Conflict of interest

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Fluorinated Cage Molecules

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Fluorine in a C–F Bond as the Key to Cage Formation

An open and shut case with fluorine: Rigid cage structures can be used to investigate the close noncovalent interactions of fluorine with other functional groups and to determine how mutual proximity affects both physical properties and reactivity. An unusual covalent interaction of fluorine leads to closure of the cage, resulting in the first solution-phase C-F-C fluoronium ion.