Elemental Fluorine as a "Legitimate" Reagent for Selective Fluorination of Organic Compounds†

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In a sense, elemental fluorine is one of the oldest potential reagents in chemistry. Its isolation more than a century ago resulted in the award of the Nobel Prize to the French chemist Moissan in 1906.[1] Moissan himself started experiments on organic substrates with fluorine as a reagent,[2] but the results were such that the next set of experiments was conducted only a generation later, this time with the important finding that diluting the fluorine with an inert gas and lowering the reaction temperature resulted in some interesting nonviolent reactions mainly of radical nature.[3] However, these results did not attract many followers, apparently because fluoro-organic chemistry was still in its infancy and because chemists were too well aware of the extreme reactivity of the first halogen.

The Second World War generated a very intense interest in fluorine chemistry, mainly associated with the Manhattan Project. This required chemicals with extreme properties such as uranium derivatives with high volatility and materials with high stability toward very corrosive conditions. The former requirement was satisfied by compounds such as UF_6, while the latter was found in fluorine-containing polymers.

Although interesting biological activity had already been discerned in certain fluoro-organic derivatives before the war, the boom in this area started mainly in the 1950s, along with an accelerated development of fluorinated solvents and polymers. Today many billions of dollars are associated with fluoro-organic chemistry, thousands of relevant publications appear every year, and many chemists devote their entire research to this field. It is therefore somewhat surprising to notice that until recently most if not all of this chemistry was based on nucleophilic reactions using various types of fluorides. A few reactions were also accomplished by various radical pathways, again using fluorine salts such as CoF_3 and HgF_2.

One notable exception was perchloryl fluoride ($FClO_3$), which tended to attack electron-rich sites associated with very activated double bonds.[4] Its common use, however, was relatively short, since a number of tragic explosions occurred whose origin was the frequently developed chlorate moiety.[5]

Professor Barton was the first to introduce the term electrophilic fluorination. He employed the known, but new to organic chemistry, CF_3OF.[6] Shortly afterward, we[7] and many others[8] started to work with this commercially available gas in which the oxygen-bound fluorine acts as an electrophile. Unfortunately, after a few years this new fluorinating agent ceased to be commercially available, and the number of the relevant publications dropped drastically. The O–F bond, however, greatly resembles the bond in the fluorine molecule (42 vs 39 kcal/mol), a fact that encouraged us to evaluate the potential of fluorine itself in preparative organic chemistry.

At the beginning of the 1970s one very important use of F_2 began to emerge. Lagow showed that when properly handled, fluorine could replace all the hydrogens in a given organic molecule by stepwise radical reactions, thus affording important perfluoro derivatives.[9] Our interest, though, was aimed mainly at selective monofluorination, since many compounds of this type have a pronounced biological activity. The main question was whether regio- or even stereoselective reactions could be achieved, since expecting selectivity from this most reactive of elements seemed at first to be almost a contradiction in terms.[10]

Direct Fluorination

A. Electrophilic Activation of C–H Bonds. Electrophilic reactions on saturated carbon–hydrogen bonds are known and comprehensively summarized in an excellent recently published book by Olah.[11] Still, the existing examples are very few in comparison with general nucleophilic reactions or electrophilic ones on

Professor Shlomo Rozen was born in 1942 in Bulgaria. He received his B.Sc., M.Sc., and Ph.D. at the Hebrew University in Jerusalem, where he worked with I. Shahak and the late Ernst D. Bergmann, the pioneer of fluorine chemistry in Israel. He then spent 3 years at the Research Institute for Chemistry and Medicine in Cambridge, MA, with D. H. R. Barton, R. H. Hesse, and M. M. Pechet, where he began his work with elemental fluorine. In 1976 he joined the School of Chemistry at Tel-Aviv University. Since then he has also spent nearly two years in the Central Research Department of E. I. du Pont de Nemours in Wilmington, DE.

† Dedicated to Professor D. H. R. Barton on the occasion of his 70th birthday.

(1) In 1986, during the events dedicated to the centenary of the discovery of fluorine, the French Post Office honored Moissan for his achievements by issuing a beautiful commemorative stamp. In this stamp, however, the obvious reaction of $F_2 + H_2 \rightarrow 2HF$ was presented instead of the one describing Moissan's main achievement: $2HF \rightarrow F_2 + H_2$.

(2) Moissan, H. *Ann. Chim. Phys.* **1891**, *19*, 272.

(3) Bockemuller, W. *Justus Liebigs Ann. Chem.* **1933**, *506*, 20. Miller, W. T.; Calfee, J. D.; Bigelow, L. A. *J. Am. Chem. Soc.* **1937**, *59*, 2072. Fukuhara, N.; Bigelow, L. A. *J. Am. Chem. Soc.* **1938**, *60*, 427.

(4) Djerassi, C.; Chamberline, J. W. *Steroid Reactions*; Holden Day: San Francisco, 1963; p 155.

(5) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 125.

(6) Barton, D. H. R.; Godhino, L. S.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* **1968**, 804. Barton, D. H. R.; Danks, L. J.; Ganguly, A. K.; Hesse, R. H.; Tarzia, G.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* **1969**, 227.

(7) Rozen, S.; Shahak, I.; Bergmann, E. D. *J. Org. Chem.* **1975**, *40*, 2966.

(8) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.

(9) Adcock, J. L.; Lagow, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 7588. Many useful variations to this method have been introduced since. See, for example: Lin, W. H.; Bailey, W. I., Jr.; Lagow, R. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1350. Persico, D. F.; Gerhardt, G. E.; Lagow, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1197. Adcock, J. L.; Cherry, M. L. *Ind. Eng. Chem. Res.* **1987**, *26*, 208. Adcock, J. L.; Robin, M. L. *J. Org. Chem.* **1984**, *49*, 1442 and references therein.

(10) Recently, the link between reactivity and selectivity has been reevaluated: Pross, A. *Isr. J. Chem.* **1985**, *26*, 390 and references therein.

(11) Olah, G. A.; Prakash, G. K. S.; Williams, R. E.; Field, L. D.; Wade, K. *Hypercarbon Chemistry*; Wiley: New York, 1987.

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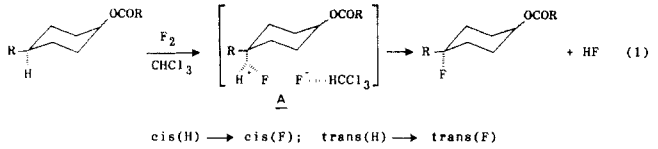
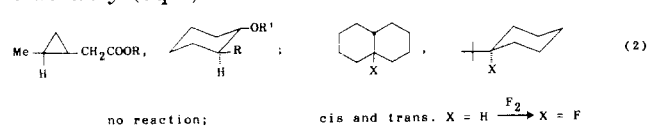
unsaturated centers. If fluorine were induced to react in an ionic mode, it would of course be a very strong electrophile and would have the advantage over others in its efficiency and in the ease of product identification. One factor that may suppress rival radical reactions is a low fluorine concentration. This, however, was not enough, since when fluorine, diluted by an inert gas, was passed through solutions, in a nonpolar solvent, of suitably protected 4-methylcyclohexanol, only fluorine-containing tars were produced. The reaction course was altered dramatically by a change in the solvent system. When the same reaction was repeated, this time in a 1:1 mixture of $CFCl_3$ and $CHCl_3$, substitution of the tertiary hydrogen at C-4 by fluorine occurred in 60% yield. This proceeded with full retention of configuration in both the cis and the trans series (eq 1).[12]



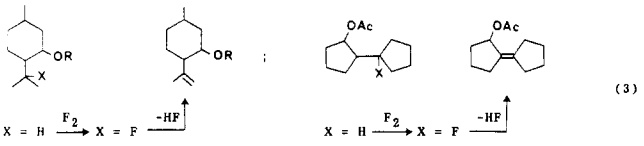
The addition of chloroform, or other polar solvent, such as AcOH or CH_3NO_2, serves several purposes: it is a good radical scavenger; it provides a polar medium, which is helpful whenever an ionic type reaction is to be encouraged; and not least, it acts as an acceptor for the developing F^- through hydrogen bonding. The substitution mechanism that accommodates all the observations is one involving the nonclassical carbocation A (eq 1) resulting from the attack of the positive pole of the fluorine molecule on the electrons of the tertiary C–H bond.[13] Such a mechanism, typical of electrophilic reactions,[11] should lead to a full retention of configuration, but this is the first time that such a retention has clearly been shown to exist in all the examples studied.

This type of electrophilic σ substitution bears some similarities to the more familiar process around regions rich in π electrons. It is thus not surprising that the reaction is largely governed by electronic factors and will target mainly on tertiary C–H bonds. Indeed, calculating the hybridization of all the hydrogens in many molecules revealed that the attack always took place on the C–H bond with the highest p-orbital contribution.[13] It is thus understandable that a substitution of a tertiary hydrogen with an exceptionally low hybridization, such as one on a cyclopropane ring or in a very close proximity to an electron-withdrawing group, could not take place, and the starting materials were recovered even after prolonged treatment with F_2. On the other hand, when the electron-withdrawing group is more distant from the tertiary center, or when none is present as in paraffins,[14] the yields increased considerably (eq 2).

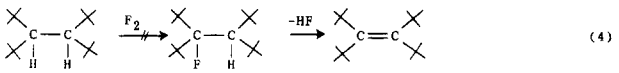


The same trend was found in both the aliphatic[15] and the bicyclic series.[16] Examples are presented by protected 2-methylbutanol and nopinone, where the degree of hybridization of the tertiary C–H bond is very low because of either the proximity of the oxygen or the involved strain. In neither case was any specific substitution observed, while with protected 6-methyl-2-heptanol or adamantane derivatives the yields of specifically fluorinated products were very good.

The uniqueness of this substitution reaction lies in the activation of sites that usually are extremely unreactive to other reagents. Such fluorination provides an excellent entry for further chemical transformations. This can be accomplished via dehydrofluorination, using BF_3, HF, NaOH, or MeMgX (eq 3).[13]

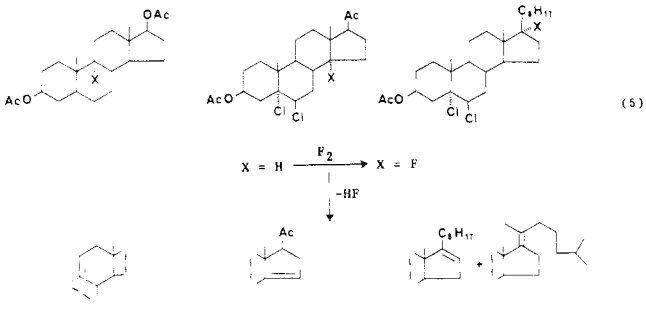


It was intriguing to use this route to try to prepare the yet unknown tetra-*tert*-butylethene (eq 4). The



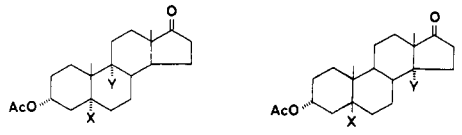
attempt, however, failed since the fluorine molecule has to approach the tertiary C–H bond with at least one molecule of solvent. The steric factor, which usually is not of dominant importance, proved in this extreme case to be insurmountable.

Fluorination of steroids demonstrates some subtle electronic and steric effects.[17] While four tertiary hydrogens are present in 5α-androstane-3β,17β-diol diacetate, only the remotest 9α-H was replaced by fluorine.[18] However, it is possible to substitute other tertiary hydrogens by attaching various deactivating groups on different sites of the steroidal skeleton.[19] In each case subsequent dehydrofluorination provides a good route for further chemical transformations[20] on sites that were previously completely inert (eq 5).[19,21]



(12) Rozen, S.; Gal, C.; Faust, Y. *J. Am. Chem. Soc.* **1980**, *102*, 6860.
(13) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769.
(14) Rozen, S.; Gal, C. *Tetrahedron Lett.* **1984**, *25*, 449.
(15) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 4928.
(16) Rozen, S.; Gal, C. *Tetrahedron Lett.* **1985**, *26*, 2793.
(17) Actually we started the research on steroidal tertiary fluorination using CF_3OF and F_2 while working at the Research Institute of Medicine and Chemistry in Cambridge, MA, under Profs. Barton, Hesse, and Pechet about 15 years ago. I would like to use this opportunity to thank them again for a great time.
(18) Barton, D. H. R.; Hesse, R. H.; Markwell, R. E.; Pechet, M. M.; Rozen, S. *J. Am. Chem. Soc.* **1976**, *98*, 3036.
(19) Alker, D.; Barton, D. H. R.; Hesse, R. H.; James, J. L.; Markwell, R. E.; Pechet, M. M.; Rozen, S.; Takashita, T.; Toh, H. T. *Nouv. J. Chim.* **1980**, *4*, 239.
(20) The synthesis of many steroidal drugs starts from the corresponding olefins. A $\Delta^{9,11}$ steroid provides a starting point for cortisone type drugs possessing the 9α-fluoro-11β-hydroxy moiety. A double bond at 14,15 can serve as a precursor for many cardenolides, most having a hydroxyl at 14, while cholesterol with a double bond at 17,20 is potentially an inexpensive starting material for the synthesis of many other expensive steroids.

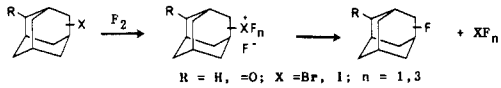
The less common 3α-acetoxy steroids allowed fluorination of the nearby 5-position (never observed in the 3β series), apparently by stabilizing the appropriate transition state.[22] With the 5β steroids the cis A/B arrangement prevented the fluorine from approaching the 9α-H (although electronically favored) and the fluorination took place always on the next most suitable tertiary site (eq 6).[22] These rigid and well-defined



(6)

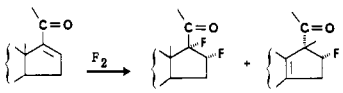
fluoro steroids presented a good opportunity for detailed ^{13}C NMR studies. From these it was concluded that in such systems all γ carbons in anti position were deshielded and frequently coupled by the fluorine atom, while the gauche γ carbons were shifted to higher field by up to 5 ppm.[23]

B. Reactions with Organic Halides. Fluorine when acting as an electrophile can attack the electrons of other elements in organic substances. No easy attack is observed on oxygen, chlorine, and fluorine atoms since their bonds with carbon are quite strong, but it can attach itself to the nitrogen lone pair, resulting in some cases in destruction of the original compound[24] while in others in the formation of new and useful fluorinating agents.[25] F_2 also reacts immediately with aliphatic bromides and iodides, which then decompose to the corresponding halogen fluorides and many undefined products. However, in cases where the resulting carbocations are highly stabilized as in adamantane derivatives, fluorine after an initial electrophilic attack on the halogen will eventually substitute it in excellent yields, forming the corresponding fluoroadamantanes. If sources of other nucleophiles such as Cl^- or RO^- are present, chloro- or alkoxyadamantane derivatives are also obtained (eq 7).[26]



(7)

C. Addition to Double Bonds. In contrast to the direct chlorination or bromination of olefins, the preparation of 1,2-difluoro derivatives was considered to be difficult, and ways of circumventing the use of the element itself have been developed.[27] The pioneering work of Merritt[28] has shown that it is possible to add fluorine to certain simple olefins, but his technique was quite unusual and inconvenient. Many years later fluorine was bubbled through a solution containing a steroidal enone, which resulted in the formation of the corresponding α,β-difluoro derivative. This was accompanied by a rearrangement product (eq 8),[29] showing that the addition is not a four-centered process, suggested previously as a possible mechanism.[28] Later we found that adding a proton donor to the solution (e.g., EtOH) helped produce the expected difluoro adduct in a cleaner and better yield reaction.[30] The stereoselectivity is usually very high and, contrary to other halogens, was found to be syn, characteristic of an addition process involving electrophilic fluorine (eq 9).[31] Similar additions were also obtained with some sugars[32] and heterocycles,[33] enabling the positron-emitting radioisotope ^{18}F to be introduced.



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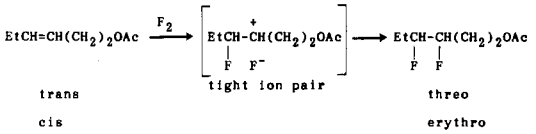
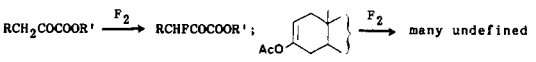


(9)

Fluorine was successfully added to the enolic forms of pyruvic acid derivatives (eq 10),[34] forming the corresponding fluoropyruvates. Addition to enols, however, did not prove to be a general reaction and when F_2 was passed through an electron-rich enol acetate, an instantaneous reaction took place with complete decomposition of the substrate. Is fluorine then limited in its reactions to tertiary H substitution and addition to a few olefins? The answer is definitely no, although somewhat indirect methods have to be used.



(10)

Indirect Fluorination

A. Using Perfluorinated Fluoroxy Compounds. Several compounds possessing the weak O–F bond are known. They can be grouped into two categories: one with the OF moiety bonded directly to some perfluorinated residue such as R_f or SF_5 and the other to a perfluoroacyl group—R_fCOOF. CF_3OF, the only compound produced commercially, received the most attention,[8] but its present price and availability have discouraged many from working with it. Most other fluoroxy compounds have been prepared mainly by inorganic chemists in order to measure physical constants, rather than for organic synthesis.[35] CF_3COOF, which

(21) It should be mentioned that the elegant radical "remote control" activation developed by Breslow has also led to tertiary halogenation and eventually to similar steroidal olefins; see, for example: Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

(22) Rozen, S.; Ben-Shoshan, G. *J. Org. Chem.* **1986**, *51*, 3522.

(23) Rozen, S.; Ben-Shoshan, G. *Org. Magn. Reson.* **1985**, *23*, 116.

(24) Rozen, S.; Gal, C., unpublished results.

(25) Purrington, S. T.; Jones, W. A. *J. Org. Chem.* **1983**, *48*, 761. Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452. Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465.

(26) Rozen, S.; Brand, M. *J. Org. Chem.* **1981**, *46*, 733.

(27) See, for example: Bornstein, J.; Borden, M. R.; Nunes, F.; Tarlin, H. I. *J. Am. Chem. Soc.* **1963**, *85*, 1609. Sket, B.; Zupan, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2169. Shellhamer, D. F.; Conner, R. J.; Richardson, R. E.; Heasley, V. L. *J. Org. Chem.* **1984**, *49*, 5015.

(28) Merritt, R. F.; Johnson, F. A. *J. Org. Chem.* **1966**, *31*, 1859. Merritt, R. F.; Steven, T. E. *J. Am. Chem. Soc.* **1966**, *88*, 1822. Merritt, R. F. *J. Org. Chem.* **1966**, *31*, 3871. Merritt, R. F. *J. Am. Chem. Soc.* **1967**, *89*, 609.

(29) Barton, D. H. R.; James, J. L.; Hesse, R. H.; Pechet, M. M.; Rozen, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1105.

(30) Rozen, S.; Brand, M. *J. Org. Chem.* **1986**, *51*, 3607.

(31) Barton, D. H. R.; Hesse, R. H.; Jackmann, G. P.; Ogunkoya, L.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 739.

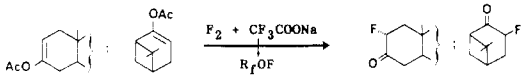
(32) Ido, T.; Wan, C. N.; Fowler, J. S.; Wolf, A. P. *J. Org. Chem.* **1977**, *42*, 2341. Diksic, M.; Jolly, D. *Carbohydr. Res.* **1986**, *153*, 17.

(33) Shiue, C. Y.; Wolf, A. P. *J. Labelled Compd Radiopharm.* **1980**, *18*, 1059.

(34) Tsushima, T.; Kawada, K.; Tsuji, T.; Misaki, S. *J. Org. Chem.* **1982**, *47*, 1107.

(35) Most of this work had been performed by Prager and Thompson in the mid 1960s. See, for example: Prager, J. H.; Thompson, P. G. *J. Am. Chem. Soc.* **1965**, *87*, 230. Thompson, P. G.; Prager, J. H. *J. Am. Chem. Soc.* **1967**, *89*, 2263. For a relevant review, see: Mukhametshin, F. M. *Usp. Khim.* **1980**, *49*, 1260.

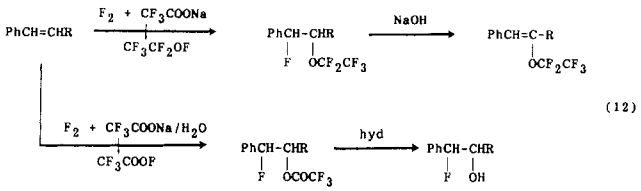
was prepared in a unique and difficult way,[36] is a typical example. Years later we passed dilute fluorine through a suspension of CF_3COONa in $CFCl_3$ and obtained an oxidizing solution.[37] The oxidative power was due to a mixture of several compounds, but a feature common to them all—the OF moiety—enabled us to regard it as a single homogeneous reagent. Thus, without any tedious isolation and purification steps, it was reacted with many types of electron-rich enol acetates, forming eventually the corresponding α-fluorocarbonyl derivatives (eq 11).[38] It should be noted that the reactions



(11)

are technically simple and the yields comparable to those obtained with the expensive CF_3OF, proving that after all, elemental fluorine is capable of reacting reasonably well with enols, if indirectly.

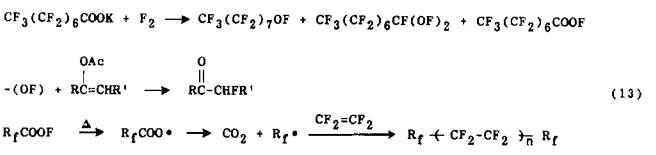
We found that under anhydrous conditions a large proportion of the above oxidizing mixture was CF_3CF_2OF, while in the presence of water or HF mostly CF_3COOF was formed. This presented an opportunity to introduce the perfluoroethoxy moiety into various systems[39] and increase their lipophilicity, an important factor in many potential drugs (eq 12). An interesting modification of the preparation of fluoroxypentafluoroethane containing ^{18}F has recently been published.[40]



(12)

Similarly, trifluoroacetyl hypofluorite (CF_3COOF) was added to alkenes, forming the corresponding fluorohydrin (eq 12),[41] an important moiety in many drugs. The reaction of both CF_3CF_2OF and CF_3COOF is fully regiospecific and has good stereoselectivity. The syn-mode addition, characteristic of electrophilic fluorination is dominant, with CF_3COOF giving better stereoselectivity than CF_3OF[42] or CF_3CF_2OF.[39] In both cases when the carbocation in the intermediate tight ion pair (eq 9) is stabilized more than usual, some of the stereoselectivity is lost, proving again that a four-centered reaction is not involved.

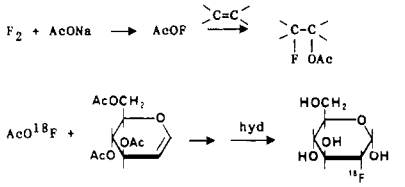
Fluorine can also react with salts of higher perfluorinated acids. The products are fluoroxy compounds of the type R_fOF and R_fCOOF, depending on the conditions.[43] The oxidizing components (either a mixture or a relatively pure species) are able to fluorinate enol acetates (eq 11), but their importance lies elsewhere. First, the oxidizing solution was found to be stable at 0 °C for at least a year, thus serving as a "shelf reagent" for electrophilic fluorinations. Second, and probably more important, is the fact that the higher hypofluorites are excellent radical initiators for the polymerization of tetrafluoroethene and other fluorine-containing olefinic monomers. Their unique advantage over other initiators is that no harmful end groups are formed, since the initiator decomposes to CO_2 and $R_f^{\bullet}$, the latter becoming an integral part of the polymer (eq 13).[43]



(13)

Up to that time all compounds with the OF moiety had a perfluoro residue. It was assumed that if this reactive moiety were bonded to an alkyl radical, an immediate HF elimination would take place, as theoretically predicted for the nonexistent CH_3OF.[44] As happened to many legends connected with F_2, this was also found to be of limited value. We were able to show that in acetyl hypofluorite, elimination is hindered by the interposed spacer between F and the adjacent alkyl hydrogens.

B. Acetyl Hypofluorite. When we passed dilute fluorine through a suspension of sodium acetate in $CFCl_3$, an oxidizing solution was obtained that reacted with olefins, adding the elements of AcOF (eq 14).[45]



(14)

Since there was a possibility that the reactions of this oxidizing solution did not originate from a single reagent, but rather from two or more consecutive steps providing the elements of AcO and F,[46] some of the molecule's physical constants and thermal characteristics were studied.[47] Eventually AcOF, the first member of a new oxidative family of acyl hypofluorites, was isolated in pure form by Appelman, proving its existence beyond any doubt.[48]

It became clear that the advantage of acetyl hypofluorite lies in its relative mildness. While the other fluoroxy reagents react cleanly only with benzylic or electron-rich double bonds, AcOF gives good results with most types of olefins.[49] Since the reactions are fast and proceed with good yields and syn stereospecificity, they were immediately mobilized also for the incorporation of the ^{18}F into biologically interesting compounds. For example, 2-deoxy-2-(^{18}F)fluoro-D-glucose was prepared (eq 14) and used for extensive brain studies by using positron emission transaxial to-

(36) Gard, G. L.; Cady, G. H. *Inorg. Chem.* **1965**, *4*, 594.
(37) Rozen, S.; Lerman, O. *J. Am. Chem. Soc.* **1979**, *101*, 2782.
(38) Rozen, S.; Menahem, Y. *J. Fluorine Chem.* **1980**, *16*, 19. For a review on the synthesis of α-fluorocarbonyl derivatives, see: Rozen, S.; Filler, R. *Tetrahedron Rep.* **1985**, *41*, 1111.
(39) Lerman, O.; Rozen, S. *J. Org. Chem.* **1980**, *45*, 4122.
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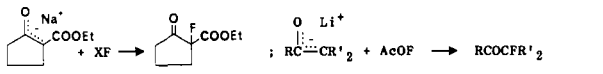
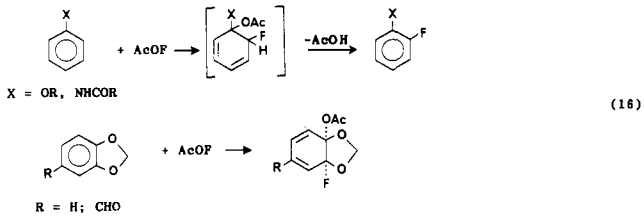
mography (PETT).[50] Because of the importance of AcOF, especially as an ^{18}F carrier, several variations for its preparation have been developed, the main one involving the passage of F_2 through a column packed with various salts of acetic acid.[51]

The mildness of AcOF is evident from its smooth reaction with 1,3-dicarbonyl compounds or their enolates.[52] What is more, even lithium enolates of monocarbonyl derivatives could be directly fluorinated,[53] eliminating the need to prepare the corresponding enol acetates, silyl enol ethers, and the like. The parallel reactions with F_2, CF_3OF, or CF_3COOF resulted only in tars or in very low yields of the expected monofluoro derivatives (eq 15).



X = CH_3COO: 92%
X = CF_3COO: 13%
X = F: 0% (15)

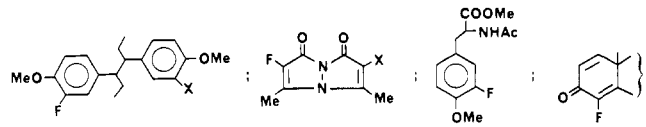
Though relatively mild in action, in absolute terms AcOF is a powerful reagent. One of the reactions emphasizing this fact is aromatic fluorination. The incorporation of a fluorine atom into a benzenoidic ring is achieved routinely only by the time-honored Balz–Schiemann reaction starting from the appropriate aniline derivative. There have been several attempts to fluorinate aromatic compounds with F_2 or fluoroxy compounds, but the conversions had to be kept unpracticably low if yields were not to drop drastically.[54] AcOF, however, could be reacted with many activated aromatic compounds to produce mainly the ortho fluoro derivatives in very good conversions and yields of up to 85%.[55] Several explanations have been offered for the dominant ortho substitution in similar reactions, including cyclic intermediates (for the reaction of PhOH and F_2[56]), but we have shown that AcOF is sufficiently powerful to add across the most electron-rich region of the aromatic ring in a fast reaction, suitable also for working with ^{18}F. A subsequent spontaneous elimination of AcOH restored the aromaticity, but in cases where this was not possible, the resulting cyclohexadiene reacted very rapidly with the reagent and tars were obtained. With careful monitoring, however, the corresponding adducts could in some cases be isolated (eq 16).[55] Acetyl hypofluorite, mainly with ^{18}F, was also used for cleavage of Ar–Sn, Ar–Si, and Ar–Hg



X = OR, NHCOR
R = H; CHO (16)

bonds forming the corresponding ArF compounds.[57]

After some of its fundamental reactions had been studied, only a short period elapsed before efforts were channeled toward using AcOF for electrophilic fluorinations of compounds with biological interest. Thus several fluoro sugars have been prepared,[58] the reactions of AcOF with uracil and cytosine were thoroughly studied,[59] and fluoroantipyrine[60] and fluorodopa[61] were obtained. Most of these compounds have been made with the ^{18}F radioisotope and hence on a small scale. Since we do not have the facilities for making and studying ^{18}F-containing compounds, we have restricted ourselves to the development of the chemical processes and to demonstrating that it is possible to make in good yields and on a larger scale, many types of biologically interesting derivatives, including fluorohexestrols, fluorotyrosine, various 4-fluoro steroidal enones, 6-fluoro steroids,[62] and fluorobimans, which are important fluorescent compounds with useful applications in biology (eq 17).[63]



X = H; F (17)

The free radical nature of fluorine reactions has been long known. We have demonstrated that the same element can also be a source for electrophilic fluorine. The versatility of this halogen is revealed in full by considering some new reactions in which this element can be an immediate source for nucleophilic fluorine as well, again without isolating or purifying the intermediate reagents.

C. Iodine and Bromine Monofluorides. Adding the elements of halogen fluorides across a simple double bond is a well-known procedure, achieved by a one-pot, two-step reaction using HF and an *N*-halo amide. This procedure, however, does not employ the actual halogen fluoride molecule, imposing quite a few limitations on the scope of the reaction. Fluorine, being an exceptionally active element, reacts with other halogens, producing the corresponding XF molecules. Among them ClF is a stable compound and so its chemistry has been considerably explored.[64] This is in contrast to the other two monofluoro interhalogens. IF has been described in only a few publications, most of them dealing with its thermal stability in the gas phase[65] and its

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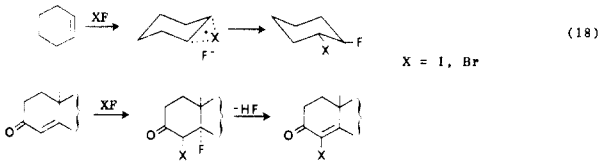
strong tendency to disproportionate to IF_3 and IF_5 in solution.[66] Practically no reactions of IF with organic compounds have been performed. Even less is known about BrF, since this molecule has never been isolated or fully characterized despite many efforts. It was concluded that it exists at low temperature, though its complex with pyridine can be isolated.[67] We have not made any attempt to isolate or purify the IF formed from the interaction of I_2 with F_2 in $CFCl_3$ and found that this was not necessary. The strongly polarized IF reacted quite efficiently with most types of olefins even at −78 °C with full regio- and stereoselectivity. The trans addition is characteristic of a nucleophilic attack by the fluoride (originated a step earlier from F_2) on the cyclic halonium ion.[68] While IF was added across π centers as expected, BrF, similarly obtained, proved to be uncontrollable and nonselective. When, however, a proton donor such as ethanol was added to the in situ generated reagent, a considerable taming effect was observed, and clean anti addition across most double bonds took place with a full stereoselectivity and good regioselectivity. When either IF or BrF was added to enones, HF elimination could easily be induced and the α-iodo or -bromo enones were formed (eq 18).[68]



(18)

An interesting reaction was found when iodine and bromine monofluorides were reacted with acetylenes. The first XF molecule can readily be added to form the fluoroiodo (or fluorobromo) olefin. In contrast to other methods, further addition of XF across the relatively unreactive halogenated olefin is possible. The addition is such that the most stable fluorocarbocation is initially formed, leading eventually to the corresponding *gem*-difluoro derivatives. Although an isolated acetylene reacts in a similar way with both IF and BrF, the latter is more active and capable of reaction also with ynones, which are not affected by IF. Even the triple bond in dimethyl acetylenedicarboxylate, which is most deactivated, is not resistant toward BrF and after 12 h at −75 °C dimethyl 2,3-dibromo-3,3-difluorosuccinate was obtained in good yield (eq 19).[69]

$$RC{\equiv}CR' \xrightarrow{XF} RCF{=}CXR' \xrightarrow{XF} RCF_2CX_2R'$$

$$MeOOC{-}C{\equiv}C{-}COOMe \xrightarrow{BrF} MeOOC{-}CF_2CBr_2{-}COOMe \text{ (no reaction with IF)} \qquad (19)$$

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While the above reaction offers a route to the important CF_2 moiety starting from an acetylene, the most desired transformation in this field is the conversion of a carbonyl into a CF_2 group. This is usually achieved by using the unpleasant and expensive SF_4[70] or its derivative (diethylamino)sulfur trifluoride (DAST).[71] We have adopted a different approach to this problem, involving converting a ketone to its hydrazone, DNP, or semicarbazone derivative. The basic nitrogen atoms in these are susceptible to attack from the electrophilic iodine in IF, allowing the nucleophilic fluorine to react with the developing positive charge on the carbon, leading eventually to the desired $CO \rightarrow CF_2$ transformation in reasonable yields (eq 20).[72]

$$R_2CO \rightarrow R_2C{=}NNR'_2 \xrightarrow{IF} R_2CF_2 \qquad (20)$$

Conclusion

Our main goal has been to demonstrate that elemental fluorine, a most neglected element in organic chemistry, is indeed a versatile reagent able to perform many selective reactions. During the 100 years since its discovery, this element has succeeded in being associated with frightening legends, which generated mythical fears and strong prejudice. Less than 20 years ago an article appeared in the *Journal of Chemical Education* stating that "fluorination by fluorine is unlikely to be used in normal organic synthesis".[73] We hope that the community of chemists will come to realize that this halogen has a great deal to offer to organic sythesis as well as toward constructing a wide variety of products with biological significance such as 2-deoxy-2-fluoro-D-glucose with or without the important ^{18}F radioisotope. Recently published reviews on the subject[74] are evidence that such a trend is indeed emerging.

I am deeply indebted to the graduate students who have brought life to the work described here. Their names are to be found in the appropriate references. I am also indebted to Professor D. H. R. Barton for his continuous interest in our work and to all fluorine chemists at E. I. du Pont de Nemours, Experimental Station, DE, for their support and hospitality. I also thank the Fund for Basic Research of the Israel Academy of Science and Humanities and Eli Lilly & Co., IN, for partial financial support.

Registry No. F_2, 7782-41-4.

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