Activating Unreactive Sites of Organic Molecules Using Elemental Fluorine

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Received February 3, 1987

Electrophilic substitution reactions on saturated carbons are extremely rare. Elemental fluorine, however, uses this pathway to replace tertiary unactivated hydrogens with great regio- and stereoselectivity, resulting in a full retention of configuration. In accordance with the proposed mechanism, the higher the contribution of p orbitals to the tertiary C–H bond, the easier the substitution process becomes. On the other hand, a low degree of p hybridization such as with cyclopropyl hydrogens, or due to the close proximity of an oxygenated function, does not allow any electrophilic substitution. Competitive reactions between tertiary hydrogens, either in different or in the same molecule, emphasize the electronic factors that govern this reaction. Oxygen- as well as nitrogen-containing molecules can participate in the reaction providing they are suitably protected. Chemically inert paraffins also react readily with fluorine in similar fashion producing monofluorinated derivatives. Methods for either acidic or basic dehydrofluorination were developed, resulting in double bond formation, thus opening an excellent route for further chemical transformations at sites where no chemical reactions were previously possible.

One of the most exacting challenges in organic chemistry is performing regio- and stereoselective reactions. This challenge is much greater when such reactions are aimed toward saturated and relatively sterically hindered sites in the target molecule, remote from any activating groups. Thus, for example, hundreds of reactions have been performed adjacent to the oxygen atom of the very simple molecule of 4-methylcyclohexanol and its derivatives, but practically none was recorded involving the tertiary unactivated C4. Occasionally a partially regioselective reaction of radical nature can be found as for example chlorination of some straight chain alcohols[1] or sterols,[2] ozone oxidation,[3] and the like. Another approach, which up to now has only limited success, is the hydroxylation of saturated centers with reagents possessing peroxy moieties.[4] In most cases the conversion, yield, and selectivity, especially in oxygen-containing compounds, are too low. Recently, serious efforts have been devoted to the problem of activating paraffins with soluble organometallic complexes of Ir, Rh, Re, and the like.[5] The reactions result mainly in activation of primary carbons, but their main disadvantage is the fact that they are not of catalytic nature. Some other unique reagents such as iodozil benzene together with tetraphenylporphyrin[6] or iodine tris(trifluoroacetate)[7] have also been used in a few special cases.

One of the most remarkable achievements in the area of activation of remote saturated sites is the "remote control" activation and its variations developed by Breslow.[8] Elegant as this approach is, it can be applied only on large rigid molecules such as steroids. There is a real need for a simple and yet a general and reliable method, which can substitute a tertiary unactivated hydrogen with a heteroatom, providing the opportunity for further chemical transformations on sites which are otherwise inaccessible. Despite the almost countless number of conventional agents in the organic chemist's arsenal, methods toward this goal are still not available, and it is clear that only an unusual reagent will be suitable for such a task.

Elemental fluorine, although known for a century, was practically in a state of hibernation as far as organic chemistry was concerned. Apart from a few sporadic publications,[9] organic chemists kept a safe distance. The ruling myth was that there is no point working with this element, because destruction of most organic substances is inevitable.[10] This situation however is changing rapidly. It has been shown that F_2 can indeed be used, either directly for monofluorination of some steroids and a few other special compounds such as uracil[11] or indirectly through various in situ generated carriers.[12] We have already communicated that this element can perform some surprisingly selective fluorinations,[13] a subject which we evaluate now in full.

The intensive destructiveness, which frequently is associated with this halogen, derives mainly from the ease of its homolytic cleavage to F radicals (39 kcal/mol). Since it is a very small atom and also the most electronegative one, it attacks organic molecules indiscriminately breaking almost any C–H and C–C bonds. This feature when appropriately tamed was used by Lagow[14] and later also by Adcock[15] for replacing all hydrogens in certain groups of

(1) See for example: Deno, N. C. *Methods in Free Radical Chemistry*; Huyser, E. S., Ed.; Marcel Dekker: New York, 1972; Vol. 3, p 135. Deno, N. C.; Meyer, M. D. *J. Org. Chem.* **1979**, *44*, 3383 and references therein.
(2) Mazur, Y.; Cohen, Z. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 281.
(3) Cohen, Z.; Mazur, Y. *J. Org. Chem.* **1979**, *44*, 2318 and references therein.
(4) Zadok, E.; Mazur, Y. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 303. Schneider, H. J.; Muller, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *21*, 146. Takaishi, N.; Takahashi, H.; Inamoto, Y. *Tetrahedron Lett.* **1985**, *26*, 2361.
(5) Parshall, G. W. *Catalysis* **1977**, *1*, 335. Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Paruell, C. A.; Quirk, J. M.; Morris, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 6994. Crabtree, R. H. *ChemTech* **1982**, 506. Bergman, R. G. *Science (Washington, D.C.)* **1984**, *223*, 902 and references therein.
(6) Groves, G. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243.
(7) Buddrus, J.; Plettenberg, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 436.
(8) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170. Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045. Breslow, R.; Mairta, U.; Heyer, D. *Tetrahedron Lett.* **1984**, *25*, 1123.
(9) Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, 1973.
(10) Sharts, C. M. *J. Chem. Educ.* **1968**, *45*, 3.
(11) (a) Alker, D.; Barton, D. H. R.; Hesse, R. H.; James, J. L.; Markwell, R. E.; Pechet, M. M.; Rozen, S.; Takeshita, T.; Toh, H. T. *Nouv. J. Chim.* **1980**, *4*, 239. (b) Barton, D. H. R.; Hesse, R. H.; Toh, H. T.; Pechet, M. M. *J. Org. Chem.* **1972**, *37*, 329. (c) Tsushima, T.; Kawada, K.; Tsuji, T.; Misaki, S. *J. Org. Chem.* **1982**, *47*, 1107. (d) Rozen, S.; Ben-Shushan, G. *J. Org. Chem.* **1986**, *51*, 3522.
(12) (a) Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* **1985**, *50*, 4753. (b) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342. (c) Rozen, S.; Lerman, O. *J. Org. Chem.* **1980**, *45*, 672. (d) Lerman, O.; Rozen, S. *J. Org.* Chem. **1980**, *45*, 4122.
(13) Rozen, S.; Gal, C.; Faust, Y. *J. Am. Chem. Soc.* **1980**, *102*, 6860. Gal, C.; Rozen, S. *Tetrahedron Lett.* **1984**, *25*, 449.
(14) Persico, D. F.; Gerhardt, G. E.; Lagow, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1197. Aikman, R. E.; Lagow, R. J. *J. Org. Chem.* **1982**, *47*, 2789.
(15) Adcock, J. L.; Robin, M. L. *J. Org. Chem.* **1984**, *49*, 1442 and references therein.

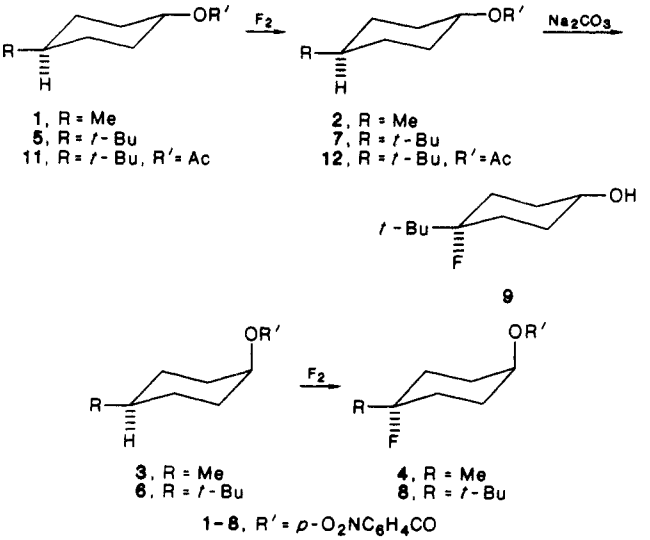
0022-3263/87/1952-2769$01.50/0

organic molecules, developing an impressive way for the synthesis of valuable perfluoro compounds. Fluorine radicals have also been reacted by Scherer with certain perfluoro olefins to form the most stable organic radicals known.[16] Outside the narrow context of these special compounds and techniques, when diluted fluorine (3–5% F_2 in N_2) is passed through a cold (–78 °C) $CFCl_3$ solution of *trans*-4-methylcyclohexyl *p*-nitrobenzoate (**1**), we witness the fast consumption of the starting material and at the same time the formation of a very complex mixture. A primary analysis of this mixture reveals an indiscriminate fluorination including an extensive fragmentation typical of radical fluorination. Similar results were obtained either with **1** or with any other compound described in this work, when other nonpolar solvents like hexane and heptane were used. If however the homolytical cleavage of the F–F bond were suppressed and some polarization achieved, an entirely different chemistry would be expected. Then the positive end of the F–F dipole, small as it is, will act as a very strong electrophile.

There is a very rich chemical literature dealing with various nucleophilic substitutions. Electrophilic substitutions on electron rich π regions such as olefins or benzenoidic rings have also been a subject for fertile research for generations. It is quite striking then to find that electrophilic substitutions on saturated carbons are practically unknown. Intuitively speaking, the electron density of a C–H bond will be higher when the carbon is more substituted and placed away from an electronegative moiety. As a result such a bond should be more reactive toward electrophilic attack. One of our goals in this work has been to define more exact criteria for the reactivity of the various saturated C–H bonds toward the extremely rare electrophilic substitution of such hydrogens.

When a cold (–78 °C) dilute solution of **1** in a 1:1 mixture of $CFCl_3/CHCl_3$ was treated with 3–4% fluorine in N_2 without a rigorous exclusion of oxygen, the results were different from those of the radical reaction described above. Chloroform, a good radical scavenger and a polar solvent, causes lowering of the energy of the wave function of the heterolytical cleavage below that of the homolytical one.[17] The disappearance of **1** was much slower than in the radical reaction (hours vs. minutes), and mainly a single product was formed and identified as *trans*-4-fluoro-4-methylcyclohexyl *p*-nitrobenzoate (**2**), in 60% yield. When *cis*-4-methylcyclohexyl *p*-nitrobenzoate (**3**) was similarly reacted with fluorine, *cis*-4-fluoro-4-methylcyclohexyl *p*-nitrobenzoate (**4**) was formed in 65% yield. Since **2** and **4** have different retention times in GC, it could be easily concluded that both products were free from each other, establishing a full retention of configuration during the substitution process of the C4 hydrogens. A simple radical pathway which would create a radical at C4 would cause, at least to some extent, an isomerization to the more stable **2** during the fluorination of **3**. A cage of radicals is also not likely because of the solvents' nature, the fluorine radicals reactivity and the fact that at higher temperatures, where such cages would be opened, the full stereoselectivity was still kept, although an inevitable drop in yields for the monofluorination took place.

Similar results were obtained when either *trans*- or *cis*-4-*tert*-butylcyclohexyl *p*-nitrobenzoate (**5** and **6**, respectively) were treated with fluorine. The tertiary hydrogen at C4 was stereoselectively substituted by fluorine, forming the corresponding fluoro derivatives **7** and **8** in



60% and 83% yield, respectively, which can be considered as excellent yields for such a reaction. It should be mentioned that the fluorinated *p*-nitrobenzoates can be hydrolyzed as demonstrated for **7**, by using sodium carbonate, to give *trans*-4-*tert*-butyl-4-fluorocyclohexanol (**9**) in 45% yield.

In order to prove the ionic nature of the substitution we have monitored the fluorination of an equimolar mixture of the *trans*-4-methyl- and *trans*-4-*tert*-butylcyclohexyl *p*-nitrobenzoates (**1** and **5**).[18] Despite the considerable steric hindrance of the bulky *tert*-butyl group, its geminal hydrogen at C4 was substituted by fluorine forming the fluorinated derivative **7**, faster than the corresponding hydrogen in **1**. Thus only after 70% conversion of **5** was achieved, the 4-methylcyclohexane derivative **1** started to react. Similar results were obtained from a competitive reaction using an equimolar mixture of the cis derivatives **3** and **6**.

It is evident that the electronic factors are at least as important as the steric ones and the bulky *t*-Bu group with the smaller σ value encourages the electrophilic substitution of the geminal tertiary hydrogen more then the methyl group. It should be remembered however, that although the reaction conditions do not encourage free radical reactions, they cannot be completely suppressed. At first, the slow ionic substitution indeed proceeds smoothly, but with time it slows down as the concentration of the starting material drops and the monofluorinated product is prevented from additional electrophilic reaction by the strong electron-withdrawing effect of the fluorine atom. Thus if the reaction is not monitored and stopped when the yield of the desired product reaches its maximum, the nonspecific radical side reactions continue to form fluorinated tars up to the point when the reactants as well as the products are destroyed.

Two main ionic mechanisms could be proposed for this unusual substitution. The first one calls for an hydride abstraction caused by the positive end of the fluorine dipole (eq 1). Apparently this mechanism is not the

$$R_3C\text{-}H + F_2 \xrightarrow{-H^-} R_3C^+ + HF \xrightarrow{+F^-} R_3C\text{-}F \qquad (1)$$

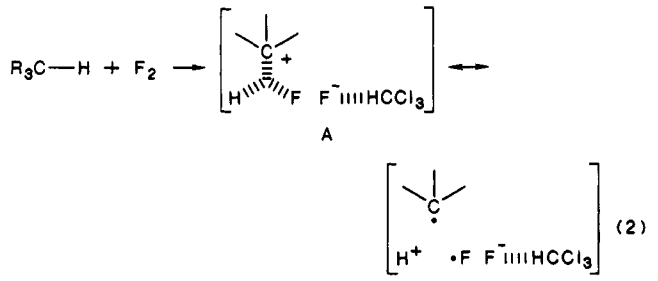
dominant one. The most hydride-like tertiary hydrogen is that α to an etheric oxygen and not the one farthest away

(16) Scherer, K. V., Jr.; Ono, T.; Yamanouchi, K.; Fernandez, R.; Henderson, P. *J. Am. Chem. Soc.* **1985**, *107*, 718.
(17) Pross, A. *Adv. Phys. Org. Chem.* **1985**, *21*, 99.

(18) It is very difficult to measure absolute rate constants since the reaction may be dependent on the rate of the fluorine flow, on the size of the gas bubbles, and on the solvent height through which these bubbles have to pass. Thus it is more meaningful to monitor the relative advance of a reaction of an equimolar mixture of two or more competing reactants.

from it. The fact that we have not observed reactions characteristic to carbocations, such as eliminations, rearrangements, and partial inversion of configuration, also stands against this type of mechanism. The hydride abstraction pathway, however, cannot be completely excluded especially when working with ethers which in a number of cases were oxidized by the fluorine to carbonyls.[19]

The most appropriate mechanism seems to be the attack of the electrons of the tertiary C–H bond on the positive pole of the fluorine molecule which leads to the fluorinated product through intermediate A,[20] inevitably with a full retention of configuration (eq 2). The chloroform plays



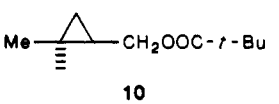
(2)

an important role in this reaction. It provides the necessary polar medium, acts as a radical scavenger and provides a somewhat acidic hydrogen which serves as an acceptor for the F^-, through hydrogen bonding, resulting in a lowering of the activation energy of the transition state. As stated before, solvents with no such acidic hydrogens, such as trichlorofluoromethane, pentane, or hexane cannot solvate the fluoride ion and therefore are not suitable for this reaction. The transition-state A can be considered as a resonant form in a charge-transfer process so fast as not to allow an inversion of configuration prior to radical recombination. Such a representation is in accordance with the fact that the farther the C–H bond is from an electron-withdrawing moiety, the easier the charge transfer will be.[21]

The usual electrophilic substitution processes in organic chemistry, as for example, in the aromatic field, proceed around regions rich in π electrons. The substitution on a saturated center bears some similarities. We have examined all the C–H bonds in most of the compounds described in this article using the CNDO and the more advanced PRDDO program.[22] In most cases the carbon–hydrogen bond with the highest p orbital contribution (the highest hybridization on p) is the one most successfully attacked by the fluorine.[23] Comparing for example the hybridization of the C–H bonds in 1 obtained by the PRDDO calculations, reveals that while all primary and secondary hydrogens have values of sp^x (x = 2.6–2.7) the C4-H has a value of x = 2.8. The differences are even greater in the case of **5**, where the hybridization for all primary and secondry C–H bonds is 2.6–2.8, while the tertiary C4–H bond has $sp^{3.0}$. A similar situation exists for the cis derivatives **3** and **6**. That hybridization is a dominant factor for a successful electrophilic substitution on a saturated center can also be demonstrated by the pivalic ester of 2-methylcyclopropanemethanol (**10**). This compound has a tertiary hydrogen separated by four bonds from the oxygen atom, not a prohibitive distance for electrophilic substitution as will be shown below. When, however, **10** was reacted with fluorine, even at concentrations as high as 20% F_2 in N_2, no selective electrophilic substitution took place, and only slow deterioration caused by a trace of fluorine radicals was observed. This result is in accordance with the fact that the hybridization of the tertiary hydrogens in the cyclopropyl ring is $sp^{2.1}$, far too low for a successful electrophilic attack.

It is clear that the alcoholic nuclei of all compounds with secondary hydroxyl groups have to be protected from the oxidative power of the fluorine, as indeed we have observed in a number of cases. Thus one can work with *p*-nitrobenzoates, acetates, or other esters without affecting the efficiency of the fluorination, providing the esters are soluble in the reaction solvent and do not contain reactive centers such as double bonds.[24]

Fluorination of *trans*-4-*tert*-butylcyclohexyl acetate (**11**) produced the corresponding 4-fluoro derivative **12** in 70% yield. When however the tertiary hydrogen was closer to the electronegative group as in *cis*-3-*tert*-butylcyclohexyl acetate (**13**), the yield of the substituted product **14** dropped to 50%. More significant still was the competitive fluorination carried on an equimolar mixture of **11** and **13**. The tertiary hydrogen of the latter was substituted much more slowly, and at the time a quantitative conversion of **11** was achieved, more than 30% of **13** still remained unreacted. When the tertiary hydrogen was placed as close as possible to the electronegative oxygen as in *trans*-2-*tert*-butylcyclohexyl acetate (**15**), even the strong electron-donating *tert*-butyl group could not activate the tertiary C–H bond toward electrophilic attack, resulting again in slow indiscriminating radical fluorination leading eventually to complete destruction of **15**.



10

13, X = H, R = *t*-Bu, R' = Ac
14, X = F, R = *t*-Bu, R' = Ac
16, X = H, R = Me, R' = *p*-$O_2NC_6H_4CO$
17, X = F, R = Me, R' = *p*-$O_2NC_6H_4CO$
18, X = H, R = Me, R' = $COCCl_3$
19, X = F, R = Me, R' = $COCCl_3$
20, X = F, R = Me, R' = H

15, R = *t*-Bu
21, R = Me

This trend was amplified when replacing the *t*-Bu group with the weaker electron releasing methyl one. Thus with *cis*-3-methylcyclohexyl *p*-nitrobenzoate (**16**) the tertiary hydrogen ($sp^{2.7}$–PRDDO calculations) was substituted in only 30% yield (**17**) and in much slower rate than the corresponding 4-methyl derivative **1**. Similar yield was obtained with *cis*-3-methylcyclohexyl trichloroacetate (**18**), which was fluorinated to give **19**. We used this protecting ester to demonstrate the readiness of its hydrolysis with

(19) Gal, C.; Ben-Shushan, G.; Rozen, S. *Tetrahedron Lett.* **1980**, *21*, 5067. See also ref 11a.

(20) A similar pentacoordinated carbonium ion for an electrophilic attack of H^+ or D^+ on C–H or C–C bonds was first proposed by Olah: Olah, G. A.; Halpern, Y.; Shen, Y.; Mo, Y. K. *J. Am. Chem. Soc.* **1973**, *95*, 4960. Olah, G. A.; Yoneda, N.; Parker, D. G. *J. Am. Chem. Soc.* **1977**, *99*, 483.

(21) We would like to thank Profs. G. A. Olah and A. Streitwieser, Jr., for valuable discussions concerning the mechanism of this reaction. Note that the charge-transfer process can be also described as a single electron shift from the electron-rich C–H bond, with the fluorine molecule serving as acceptor. This process will also lead to a full retention of configuration. Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212.

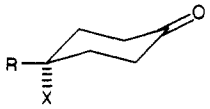
(22) Dixon, D. A.; Kleier, D. A., Lipscomb, W. N. *J. Am. Chem. Soc.* **1978**, *100*, 5681. The coordinates of the calculated molecules were obtained by using Alinger's MM1 and MM2 programs: Allinger, N. L. *Adv. Phys. Org. Chem.* **1976**, *13*, 1.

(23) The calculations were performed for the ground states. However, since the products are of great thermodynamic stability, the activation energies are quite low, so the transition states should strongly resemble the ground states of the reactants.

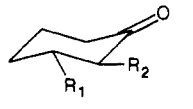
(24) The substitution reaction is one of the slowest reaction of fluorine with organic substrates. Double and triple bonds react much faster. Molecules containing aromatic rings, even when deactivated with a nitro or carbonyl group, cannot be present. Thus for example, when either 4-(*p*-nitrobenzyl)cyclohexyl acetate or bianthrone were treated with F_2, the aromatic rings were destroyed and only unidentified products were obtained.

Zn/ammonium acetate without affecting the fluorine atom. The 75% yield of *cis*-3-fluoro-3-methylcyclohexanol (**20**) thus obtained was considerably higher comparing to the basic hydrolysis already described for **7**. Here too, bringing the tertiary hydrogen closer to the oxygen atoms, as in *trans*-2-methylcyclohexyl acetate (**21**), completely deactivated the compound toward electrophilic reactions and again only slow deterioration was observed.

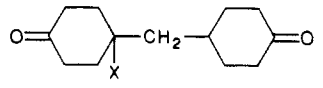
When the oxygen takes the form of carbonyl, the deactivating power is considerably stronger. Although 4-*tert*-butylcyclohexanone (**22**) was converted to 4-fluoro-4-*tert*-butylcyclohexanone (**23**) in 65% yield, it reacted much more slowly than the corresponding esters **5** and **6**. This phenomenon was even more noticeable when the *tert*-butyl group was replaced by a methyl as in 4-methylcyclohexanone (**24**), where the fluorination process became much more difficult and only 20% of 4-fluoro-4-methylcyclohexanone (**25**) was obtained. Adding an additional carbonyl, even far away from the tertiary center as in 4,4′-methylenebis(cyclohexanone) (**26**), further reduced the yield of **27** to only 10%. With 3-*tert*-butyl-, 3-methyl-, 2-*tert*-butyl-, and 2-methylcyclohexanones (**28–31** respectively) no selective electrophilic fluorination took place, and only very slow deterioration was observed even when higher than usual fluorine concentrations were employed.



22, R = *t*-Bu, X = H
23, R = *t*-Bu, X = F
24, R = Me, X = H
25, R = Me, X = F

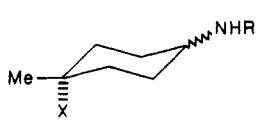


28, R_1 = *t*-Bu, R_2 = H
29, R_1 = Me, R_2 = H
30, R_1 = H, R_2 = *t*-Bu
31, R_1 = H, R_2 = Me

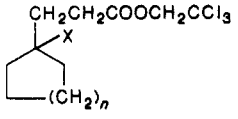


26, X = H
27, X = F

In order to find out if the oxygen in the electron-withdrawing moiety can be replaced with nitrogen, we attempted the fluorination of derivitized 4-methylcyclohexylamine (**32**). Neither the free amine, nor the acetamide **33** could be used because of the nitrogen's lone pair of electrons which reacts immediately with the electrophilic fluorine. The corresponding trifluoroacetamide **34**, on the other hand, was already too deactivated, and only (4-methylcyclohexyl)trichloroacetamide (**35**) produced the desired (4-fluoro-4-methylcyclohexyl)trichloroacetamide (**36**) in 70% yield.[25]

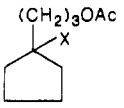


32, R = X = H
33, R = $COCH_3$, X = H
34, R = $COCF_3$, X = H
35, R = $COCCl_3$, X = H
36, R = $COCCl_3$, X = F

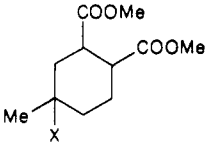


37, *n* = 2, X = H
38, *n* = 2, X = F
39, *n* = 1, X = H
40, *n* = 1, X = F

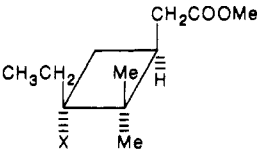
Another common functional group which was examined both for its influence on remote tertiary hydrogens and resistance to fluorine was the carboxylic acid. Usually this group, if not present as a salt,[26] is resistant to fluorine. However it is not suitable for work at low temperatures because of poor solubility and, as was found with alcohols, esters are the preferred derivatives. Thus reacting fluorine with the easily hydrolyzable 2,2,2-trichloroethyl 3-cyclohexylpropanoate (**37**) produced the corresponding 3-fluoro derivative **38** in 60% yield. The hybridization of the tertiary hydrogen in the parallel ester of the cyclopentane series **39** is lower ($sp^{2.8}$ vs. $sp^{2.9}$), reducing the yield of the 2,2,2-trichloroethyl 3-cyclopentyl-3-fluoropropanoate (**40**) to 40%. The carbomethoxy moiety is a weaker deactivating group than the hydroxyl, and while **40** was obtained in similar yield to **42**, it was formed much faster despite the three methylene groups in **41** separating the hydroxyl from the tertiary hydrogen compared to the two in the carboxylic derivative **39**.



41, X = H
42, X = F



43, X = H
44, X = F



45, X = H
46, X = F

The same trend was observed in the case of 1,2-dicarbomethoxy-4-methylcyclohexane (**43**), which was converted to the fluorinated derivative **44** in 25% yield. Both carbomethoxy groups have deactivated the tertiary hydrogen toward electrophilic fluorination with the same efficiency as a single hydroxyl has done for compound **16** or **18**.

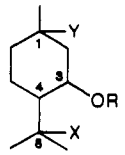
The hybridization of the tertiary hydrogen of a four-member ring such as *cis*-methyl 2,2-dimethyl-3-ethylcyclobutaneacetate (**45**) is $sp^{2.7}$, much higher than that of the cyclopropane hydrogens but still lower than that of the larger cyclic compounds. This is reflected in the experimental results, which produced *cis*-methyl 2,2-dimethyl-3-ethyl-3-fluorocyclobutaneacetate (**46**) in 30% yield. Again, a competitive reaction between **45** and the five-membered ring compound **41** was carried out, and although the acetate is a stronger deactivating group than the carbomethoxy one, the cyclobutane derivative **45** started to react only after more than 50% conversion of **40** was achieved. As in all other cases, a full retention of configuration was observed for **46** as evident from its ^1H NMR spectrum where the fluorine atom hardly affected the methyl group syn to the carbomethoxy moiety ($\Delta\delta$ −0.02) but strongly deshielded the one syn to itself ($\Delta\delta$ +0.1).

The fluorine, when acting as an electrophile is sensitive enough to differentiate between two or more tertiary hydrogens located on the same molecule. Menthyl *p*-nitrobenzoate (**47**) has three such hydrogens at C1, C4, and C8. It is easy to predict that the hydrogen at C1 will be the least activated toward an electrophilic displacement. According to the PRDDO calculations its hybridization is $sp^{2.7}$, considerably lower than the hybridization of C4-H and C8-H, both having the value of $sp^{2.9}$. The experimental results show that indeed no electrophilic monofluorination took place at C1 but rather at C8, producing the 8-fluoromenthyl *p*-nitrobenzoate (**48**) in 60% yield. This compound was accompanied by a small fraction, about 10% yield, isolated and identified as 1,8-difluoromenthyl

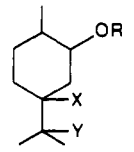
(25) The starting material in this case was commercial 4-methylcyclohexylamine (Aldrich) which is as a 1:3 mixture of cis/trans isomers. The fluorinated product **34** was a mixture of cis/trans isomers in the same 1:3 ratio. See Experimental Section.

(26) Salts of carboxylic acids do react with fluorine with results yet to be fully evaluated. Salts of acetic and perfluoroacetic acids give various fluoroxy derivatives depending on the reaction conditions. Rozen, S.; Lerman, O.; Kol, M. *J. Chem. Soc., Chem. Commun.* **1981**, 443. Hebel, D.; Lerman, O.; Rozen, S. *J. Fluorine Chem.* **1985**, *30*, 141. Appelman, E. H.; Mendelsohn, M. H.; Kim, H. *J. Am. Chem. Soc.* **1985**, *107*, 6515. Barnette, W. E.; Wealand, R. C.; Middleton, W. J.; Rozen, S. *J. Org. Chem.* **1985**, *50*, 3698.

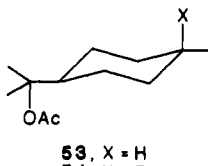
p-nitrobenzoate (**49**). The fact that no fluorine was found at C4 can be understood when we remember that the fluorine has to approach the reacting center with at least one molecule of chloroform. The C4 position is both the most hindered and the nearest to the oxygen atom whose nonbonding electrons will oppose any approach of the chlorinated solvent and possibly of the fluorine itself. These factors become more noticeable in carvomenthyl *p*-nitrobenzoate (**50**), where the oxygenated function is moved away from the immediate vicinity of C4 to C2. The electron density of both the C4–H and C8–H bonds is equally suitable for electrophilic attack, the coulombic repulsion is considerably weakened and the only difference is the higher sterical hindrance around C4. It is thus understandable that this time two isomeric compounds were formed, the major one proved to be the 8-fluorocarvomenthyl *p*-nitrobenzoate (**51**) in 35% yield, while the minor derivative was the 4-fluoro isomer **52** obtained in 15% yield. The identification of these two fractions was



47, X = Y = H
48, X = F, Y = H
49, X = Y = F



50, X = Y = H
51, X = H, Y = F
52, X = F, Y = H

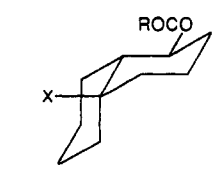


53, X = H
54, X = F

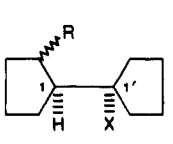
47–52, R = *p*-$COC_6H_4NO_2$

based, among other things, on the ^1H NMR of **51** which exhibits a doublet of 22 Hz for the isopropyl group which was also deshielded by 1.33 ppm. The paramagnetic shift of the same group in **52** was only 0.50 ppm (J = 7 Hz). The ^{13}C NMR spectra, especially when examining the α, β, and γ carbons (see below), is also fully supportive of the proposed structures. The deactivating effect on the immediate vicinity of the oxygen nonbonding electrons is emphasized again in *trans*-dihydroterpinyl acetate (**53**), where the oxygen is in the 8-position of the menthane skeleton. Although the hybridization of the C4 hydrogen is $sp^{2.9}$ vs. $sp^{2.7}$ of the C1 hydrogen, the fluorine substituted only the latter forming *trans*-1-fluorodihydroterpinyl acetate (**54**) in 37% yield.

Similar results were obtained with *cis*-1-decalyl *p*-nitrobenzoate (**55**) or acetate (**56**), where the tertiary hydrogen vicinal to the oxygen was not attacked and only the *cis*-5-fluoro-1-decalyl *p*-nitrobenzoate (**57**) or acetate (**58**) were obtained in 40% and 45% yield, respectively. The fluorine was very selective also in the case of a 1:1 mixture of *cis*- and *trans*-2-acetoxybicyclopentyl (**59**). In this case, however, the PRDDO calculations also clearly distinguish between the two hydrogens with hybridization of $sp^{2.8}$ for C1-H and $sp^{3.0}$ for C1′-H. Not surprisingly the last hydrogen was the only one substituted by fluorine producing a mixture of the corresponding trans and cis derivatives **60** and **61** isolated in 30% yield each.

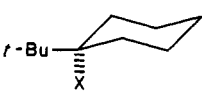


55, R = $C_6H_4NO_2$-*p*, X = H
56, R = CH_3, X = H
57, R = $C_6H_4NO_2$-*p*, X = F
58, R = CH_3, X = F

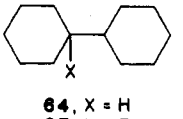


59, R = α- + β-OAc, X = H
60, R = α-OAc, X = F
61, R = β-OAc, X = F

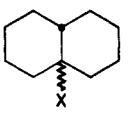
As we have seen, the electronegative group deactivates the nearby tertiary hydrogens, and this is one of the factors affecting the selectivity of the fluorination. It is thus of interest to define whether this group is essential for the reaction and for its remarkable regio- and stereospecificity. Paraffins are the ideal substrates for examining these points and for underlining the uniqueness of this reaction. Already the Latin name paraffin, which means "not enough affinity", suggests that usual chemical reactivity is not to be expected. But again of course, elemental fluorine is not a usual reagent. The reaction of *tert*-butylcyclohexane (**62**) with F_2, serves as an illuminating example. The tertiary carbon–hydrogen bond has the highest p character of all the C–H bonds in the molecule. It is therefore the most suitable for electrophilic substitution through the formation of a pentacoordinated carbonium ion and/or through the one-electron shift process via the radical carbocation. Indeed, the only product obtained in more than 1–3% yield was the 1-fluoro-1-*tert*-butylcyclohexane (**63**) isolated in 70% yield. Although this yield is comparable to the yields obtained for the oxygenated analogues **7** and **8**, the reaction of the paraffin with F_2 is much faster. Thus in order to reach the maximum yield of **7**, about 50 mole equiv of fluorine were bubbled through the reaction mixture while only 1.1 mole equiv were needed for the formation of **63**. Impressive yields were also obtained with bicyclohexyl (**64**) and *cis*- (**65**) and *trans*-decalin (**66**). These, in fast reactions, were converted to the corresponding monofluoro derivatives **67**, **68**, and **69** in 70%, 90%, and 80% yields respectively. Here too, when performing a competitive reaction between **65** and **55**, we saw that the paraffin was fully consumed, when less than 50% conversion for **55** had been achieved. Note that practically no difluorination of the last three compounds was detected, despite the two available tertiary hydrogens, since the first incorporated fluorine atom completely deactivated the adjacent second tertiary hydrogen toward any further electrophilic attack. The yields and the selectivity with the above paraffins were usually better than those of the corresponding oxygenated derivatives, since the electrophilic reaction is faster and leaves less time for the random slow fluorine radical attacks which consume both reactants and products.



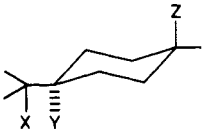
62, X = H
63, X = F



64, X = H
67, X = F



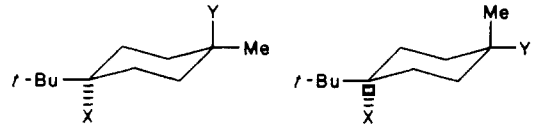
65, X = β-H (cis)
66, X = α-H (trans)
68, X = β-F (cis)
69, X = α-F (trans)



70, X = Y = Z = H
71, X = F, Y = Z = H
72, X = Y = H, Z = F
73, X = Z = H, Y = F

There are cases nevertheless where the deactivating electronegative moiety may play a positive role. As described above, we were able to substitute each of the tertiary hydrogens of the *p*-menthane skeleton by changing the site of the electronegative moiety. With *trans*-*p*-menthane (**70**), however, all three possible isomers (**71–73**) were obtained. We were unable to separate them by HPLC, but it was not difficult to conclude from the spectroscopic data, especially ^{19}F NMR, that as expected and for the same reasons outlined for the oxygenated derivatives, the yield of 8-fluoro-*p*-menthane (**71**) was 50% while the other two isomers were formed in 15% yield each.

An interesting intramolecular competitive reaction was carried on *trans*- and *cis*-1-*tert*-butyl-4-methylcyclohexane (**74** and **75**, respectively). In both cases PRDDO calculations indicated that the hydrogen geminal to the *tert*-butyl group has higher hybridization compared to the one geminal to the methyl group ($sp^{3.0}$ vs. $sp^{2.7}$). The trans derivative **74** gave *trans*-1-*tert*-butyl-1-fluoro-4-methylcyclohexane (**76**) in 60% yield along with an additional 10% of the isomeric **77**. The cis paraffin **75** similarly produced the *cis*-1-*tert*-butyl-1-fluoro-4-methylcyclohexane (**78**) in 50% yield accompanied by additional 15% of the 4-fluoro isomer **79**.



74, X = Y = H
76, X = F, Y = H
77, X = H, Y = F

75, X = Y = H
78, X = F, Y = H
79, X = H, Y = F

We have seen that the electrophilic substitution proceeds with full retention of configuration. Apart from ^{1}H and ^{19}F NMR spectra, which are of great help in evaluating the stereo- and regiospecificity, ^{13}C NMR serves also as an excellent probe for these purposes. The fluorine atom is unique among heteroatoms in that its similar dimensions to the hydrogen atom allow minimum distortion of the original molecule. Its high electronegativity, however, introduces considerable electronic changes that are responsible for many phenomena in this spectroscopy, originating from various long-range effects operating through either bonds or space. Together with the unique C–F coupling constant, these effects can potentially be of great help in structure elucidations. As expected, fluorine introduces an enormous paramagnetic shift on the α-carbon and a much more moderate one on the β ones. No general guidelines, however, were available for carbons in the various γ-positions. Eliel[27] pointed out that fluorine normally exerts a shielding effect on antiperiplanar γ-carbons, while Della[28] showed the reverse for some bridgehead fluorines. We have systematically studied this problem for tertiary fluoro steroids[29] and found that the γ-carbons gauche to the fluorine atom are always shifted to higher field by 1–5 ppm usually with small coupling constants of 0–6 Hz. On the other hand all the γ-carbons with an anti configuration to the fluorine atom have a paramagnetic shift of 2–4 ppm with coupling constants usually greater than these of the γ gauche carbons. These rules hold also for all other tertiary fluoro compounds studied by us[30] (see also Experimental Section). Because of the sensitivity of this test the ^{13}C NMR spectrum is a good criterion for establishing the practically absolute stereoselectivity and also for determining the configuration.

Fluorine is the only halogen able to substitute unactivated hydrogens by an electrophilic process. There are extremely few reports in the literature of attempts at such substitutions, and all of them concentrate on the polarization of the bromine or the chlorine molecule with the aid of strong Lewis acids such as $AgSbF_6$ or $AlCl_3$.[31] Such halogenations, which were applied only on very simple molecules, cannot be used for preparative purposes because of very low yields and lack of selectivity. We have experimented with a few substrates, such as **2** and 5α-androstane-3,17-diol diacetate[11a,d] and submitted them to reagents known to be good electrophilic halogenating sources. These compounds were treated in the dark at room temperature for at least 24 h with a large excess of bromine, NBS, $Br_2/AgSbF_6$, $Cl_2/SbCl_5$/*m*-dinitrobenzene (DNB, serving as a radical scavenger) or boiling SO_2Cl_2/DNB. In all these cases only the starting materials were isolated in practically quantitative yields. When, however, such reactions were repeated under radical conditions, either in the presence of light or peroxides, all the starting material was consumed, many products were obtained, and the main attack seemed to be on the secondary carbons. No product with a single tertiary bromine in yields higher than 1–2% was detected. It is thus quite clear that the special features of the fluorine molecule, which make this electrophilic substitution possible, are not present in the other halogens.

Electrophilic fluorination offers a special way to activate many "impossible sites" in organic molecules toward further chemical transformations. The main instrument for this purpose is dehydrofluorination, thus generating an olefin, one of the most reactive and versatile moieties in chemistry. Dehydrofluorination of tertiary fluorine can be achieved either by treatment with Lewis acids, such as BF_3·OEt_2, or by a reaction with bases.

When either one of the 4-fluoro-4-methylcyclohexanol esters **2** or **4** was treated with BF_3·OEt_2, 4-methyl-3-cyclohexenyl *p*-nitrobenzoate (**80**)[32] was obtained in 70% yield. Similar results were obtained with the *tert*-butyl analogues **7** or **8** forming the olefin **81** or with 3-fluoro-3-methyl derivative **17** which was converted to **82** in 60% yield.[33] When, however, two olefins with the same degree of substitution can potentially be formed, a mixture is usually obtained. Thus treating the ester derivative of fluoro-3-cyclohexanepropanoate **38** with boron trifluoride produced the exo- and endocyclic olefins **83** and **84** in 70% combined yield and in a corresponding ratio of 1:2.5. A mixture of olefins was also produced from the decalin derivative **57**, forming **85** and **86** in a 1:1 ratio, while with **44** the olefins **87** and **88** were formed in a ratio of 1:2.5 respectively, each reaction in 80% combined yield. It should be noted, however, that only the kinetically controlled isomer was obtained with the fluoromenthol derivative **48**, where one of the six available methyl protons was eliminated to form **89**.

When no hydrolyzable functions are present in the molecule, basic dehydrofluorination can also be employed. Such dehydrofluorination leads in most cases to a different distribution of olefins. When BF_3·OEt_2 or HF were employed the elimination proceeded through an E1 mechanism as evidenced by several rearrangements characteristic to carbocations which took place.[34] Such rearrangements were not found when bases were used. The elimination mechanism here is of E2 type, although the less common syn elimination, E_2B_H, seems to be dominant (see footnote 12d and references therein). The two basic agents which we have examined were NaOH and MeMgI. Reaction with the former is in ethylene glycol at high temperature while

(27) Eliel, E. L.; Bailey, W. F.; Kopp, L. D.; Willer, R. L.; Grant, D. M.; Bertrand, R.; Christensen, K. A.; Dalling, D. K.; Duch, M. W.; Wenkert, W.; Schell, F. M.; Cochran, D. W. *J. Am. Chem. Soc.* **1975**, *97*, 322.

(28) Della, E. W.; Cotsaris, E.; Hine, P. T. *J. Am. Chem. Soc.* **1981**, *103*, 4131.

(29) Rozen, S.; Ben-Shushan, G. *Magn. Reson. Chem.* **1985**, *23*, 116.

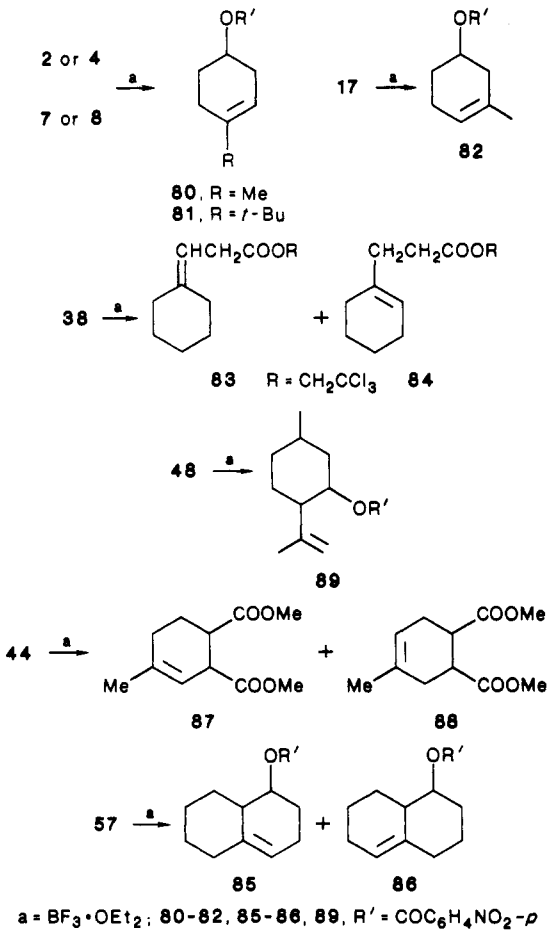
(30) The same ^{13}C NMR pattern was also found in other bicyclo fluorinated compounds, which will be described in the near future.

(31) Olah, G. A.; Renner, R.; Schilling, P.; Mo, Y. K. *J. Am. Chem. Soc.* **1973**, *97*, 7686. Olah, G. A.; Schilling, P. *J. Am. Chem. Soc.* **1973**, *97*, 7680.

(32) Braude, E. A.; Webb, A. A.; Sultanbawa, M. S. S. *J. Chem. Soc.* **1958**, 3328.

(33) Birch, A. J. *J. Chem. Soc.* **1946**, 593.

(34) Such a rearrangement was found, for example, when 14- and 17-fluorosteroids (ref 11a,d) were treated with BF_3·OEt_2. A migration of the 18-Me to these sites and other rearrangement products were accounted for most of the products (as yet unpublished results).

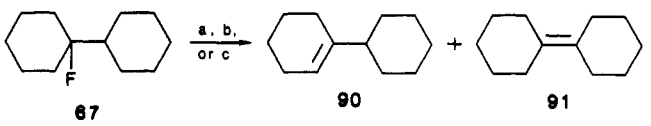


the Grignard reagent reacts at room temperature. Both these reagents give the same olefin distribution but the yields with the Grignard were usually considerably higher. Thus when 1-fluorobicyclohexyl **67** was treated with BF_3·OEt_2, NaOH, or MeMgI the two possible isomers **90**[35] and **91**[36] were obtained in more or less equal amounts (Table I). E1 and E_2B_H elimination mechanisms govern also the dehydrofluorination of *cis*- and *trans*-5-fluorodecalins (**68** and **69**) (Table II).

The carbocation formed from the cis derivative **68** when reacted with BF_3·OEt_2 collapses mainly to the more thermodynamically stable tertiary olefin **92**.[37] Notice that the carbocation formed from the *trans*-decalin **69** does not enjoy such a good overlap with the tertiary C–H orbital as in the cis isomer, explaining the relatively higher formation of **93**.[38] Where basic dehydrofluorination is concerned, it can be easily seen that there are several secondary hydrogens suitable for a syn elimination increasing the yield of **93** when compared to the E1 elimination. The differences in the ratios of the reactions of **68** and **69** can be understood too when noticing that in the cis **68** in addition to the secondary hydrogens, the tertiary one is also in a syn position to the fluorine atom, a situation not found in **69**.

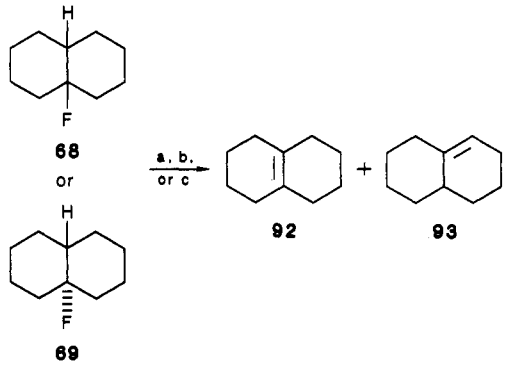
In conclusion this work shows that fluorine, which was discovered 100 years ago by Moisson and is still one of the most neglected of molecules as far as common organic chemistry is concerned, can in fact be a very selective reagent, doing chemistry that otherwise cannot be achieved and reacting with a variety of chemical families—paraffins

Table I



reagent	combined yield, %	90/91
(a) BF_3·OEt_2	85	1.5:1
(b) MeMgI	80	1:1
(c) NaOH	40	1:1

Table II



reagent	reactant	combined yield, %	92/93
(a) BF_3·OEt_2	**68**	75	27:1
(a) BF_3·OEt_2	**69**	70	8:1
(b) MeMgI[a]	**68**	80	5:1
(b) MeMgI	**69**	70	2:1

[a] NaOH (c) gave the same isomer distribution for **68** and **69** but with 40% yield only.

and oxygenated molecules. Apart from serving as a fluorinating agent it also offers excellent opportunities for chemical manipulations on sites that were hitherto inaccessible.

Experimental Section

^1H NMR spectra were recorded with a Bruker WH-90 and a Bruker WH-360 spectrometers at 90 and 360 MHz, respectively, with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 84.67 and 338.8 MHz respectively and are reported in parts per million upfield from $CFCl_3$, which also served as internal standard. The proton broad band decoupled ^{13}C NMR spectra were recorded on Bruker WH-90 and WH-300 spectrometers at 22.63 and 75.46 MHz, respectively. $CDCl_3$ served as a solvent and Me_4Si as internal standard. The ^{13}C NMR spectra of the parent compounds were also recorded, and the $\Delta\delta$ values were derived by comparing the latter spectra with those of the fluorinated compounds. $\Delta\delta$ is defined as the difference between the chemical shift of the relevant carbon atoms in the corresponding unfluorinated and fluorinated derivatives; "+" represents a deshielding effect and "–" a shielding one, both introduced by the fluorine atom; all coupling constants are C–F couplings. Mass spectra were measured with a Du Pont 21-491B spectrometer. IR spectra were recorded as neat films, in $CHCl_3$ solution or in KBr pellets on a Perkin-Elmer 177 spectrophotometer.

General Fluorination Procedure. Fluorine is of course a strong oxidizer and a very corrosive material. An appropriate vacuum line made from copper or monel in a well-ventilated area should be constructed for working with this element. Variations of such vacuum lines are described for example in Matheson Report No. G-115B or in a recent review.[39] The reactions themselves can be carried out in glass vessels. If elementary precautions are taken, work with fluorine is relatively simple, and we have had no bad experiences working with this element. The

(35) Pehk, T.; Lipmaa, E. *Org. Magn. Reson.* **1971**, *3*, 679.
(36) Krapcho, A. P.; Jahngen, E. G. E. *J. Org. Chem.* **1974**, *39*, 1650.
(37) Becker, K. B.; Boschung, A. F.; Geisel, M.; Grob, C. A. *Helv. Chim. Acta* **1973**, *56*, 2747.
(38) Becker, K. B. *Helv. Chim. Acta* **1977**, *60*, 68.
(39) Vyplel, H. *Chimia* **1985**, *39*, 305.

reactions were usually carried out at −75 °C on scales of 1–6 mmol of substrate dissolved in 400 mL of 1:1 $CFCl_3/CHCl_3$. The reactions were monitored by TLC and GC on 20% SE-30 or 10% OV-17 columns. They were usually stopped when the conversion reached about 90–95%. The fluorine concentration varied between 1% and 10% F_2 in N_2, and the gas mixture was prepared in a secondary container[40] before the reaction was started. This mixture was first passed through a dry NaF column serving as a HF scavenger (Matheson) and then in a slow stream of about 15 mL/min through a vigorously stirred solution of the substrate containing NaF. An efficient mixing, which is a very important factor especially for obtaining good yields, is achieved by using a vibromixer (Chemapec), which also ensures a fine dispersion of the gas bubbles. For compounds such as paraffins, which react fast and efficiently with fluorine, about 1 mole equiv of the halogen was bubbled through the solution in order to achieve a full conversion. Other compounds needed much more fluorine, and in certain cases up to 100 mole equiv was passed through. The unreacted fluorine was trapped by a soda lime trap, which was connected to the outlet of the reaction vessel. The term "worked up as usual" means stopping the reaction by pouring it into 500 mL water, washing the organic layer with $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent preferably at room temperature. The crude product was usually purified by vacuum flash chromatography using Silicagel 60-H (Merck) and if needed also by HPLC (Waters) on Merck's LiChrosorb Si-100. If the crude reaction mixture is not immediately purified, it is advisable to add a drop or two of pyridine or hexamethyldisilazane to capture the small amount of HF which may be formed with time. Without these bases the HF will autocatalyze additional elimination and the compounds will eventually decompose.

Alkylcyclohexyl *p*-nitrobenzoates were prepared from the commercial alcohols, which usually are mixtures of cis and trans isomers, and freshly prepared *p*-nitrobenzoyl chloride. The crude products were chromatographed on a short silica column with 2.5% EtOAc in petroleum ether (P.E.) as eluent. The cis and trans isomers were separated by HPLC using 2.5% EtOAc in cyclohexane, and their physical constants matched those of the literature.

Fluorination of *trans*-4-methylcyclohexyl *p*-nitrobenzoate (1)[41] was performed on 0.5 g (1.9 mmol) by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **2** was thus isolated in 60% yield: mp 115 °C (from MeOH); ^{1}H NMR δ 8.24 (Ar, 4 H, AB, J = 8 Hz), 4.95 (CHO, 1 H, m, $W_{h/2}$ = 24 Hz), 1.26 (CH_3CF, 3 H, d, J_{HF} = 21.4 Hz), 2.4–1.0 (8 H, m); ^{19}F NMR −151.3 (m, $W_{h/2}$ = 93 Hz); ^{13}C NMR 92.54 (C4 [α], d, J = 167.6 Hz, $\Delta\delta$ = +61.1), 26.60 (C7 [β], d, J = 19 Hz, $\Delta\delta$ = +4.9), 34.75 (C3, C5 [β], d, J = 22 Hz, $\Delta\delta$ = +3.31), 27.04 (C2, C6 [γ gauche], s, $\Delta\delta$ = −5.77), 73.5 (C1, s, $\Delta\delta$ = −1.61), 123.54, 130.76, 136.09, 150.58 (C_{arom}, s), 164.23 (CO, s); MS, m/e 281 (M^+), 261 [$(M - HF)^+$]. Anal. Calcd for $C_{14}H_{16}FNO_4$: C, 59.79; H, 5.69. Found: C, 59.73; H, 5.86.

Fluorination of *cis*-4-methylcyclohexyl *p*-nitrobenzoate (3)[42] was performed with the same quantities and conditions as for **1**. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **4** was thus isolated in 65% yield; mp 109 °C (from MeOH); ^{1}H NMR δ 8.20 (Ar, 4 H, AB, J = 8 Hz), 5.35 (CHO, 1 H, m, $W_{h/2}$ = 8 Hz), 1.38 (CH_3CF, 3 H, d, J_{HF} = 21.0 Hz), 2.4–1.0 (8 H, m); ^{19}F NMR −153.0 (m, $W_{h/2}$ = 86 Hz); ^{13}C NMR 93.32 (C4 [α], d, J = 167.3 Hz, $\Delta\delta$ = +61.9), 27.32 (C7 [β], d, J = 23.5 Hz, $\Delta\delta$ = +5.23), 31.84 (C3, C5 [β], d, J = 23.5 Hz, $\Delta\delta$ = +2.21), 25.80 (C2, C6 [γ gauche], s, $\Delta\delta$ = −3.83), 70.9 (C1, s, $\Delta\delta$ = −0.84), 123.61, 130.63, 136.22, 150.22 (C_{arom}, s), 164.05 (CO, s); MS, m/e 281 (M^+), 261 [$(M - HF)^+$]. Anal. Calcd for $C_{14}H_{16}FNO_4$: C, 59.79; H, 5.69. Found: C, 60.10; H, 6.05.

Fluorination of *trans*-4-*tert*-butylcyclohexyl *p*-nitrobenzoate (5)[43] was carried out on 0.5 g (1.64 mmol) by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **7** was thus isolated in 60% yield: mp 136 °C (from cyclohexane); ^{1}H NMR δ 8.22 (Ar, 4 H, AB, J = 8 Hz), 4.92 (CHO, 1 H, m, $W_{h/2}$ = 26 Hz), 0.99 (Me_3C, 9 H, s), 2.45–0.4 (8 H, m); ^{19}F NMR −172.1 (br t, J_{HF} = 40 Hz, $W_{h/2}$ = 80 Hz); ^{13}C NMR 97.58 (C4 [α], d, J = 180.0 Hz, $\Delta\delta$ = +49.9), 37.70 (C7 [β], d, J = 20 Hz, $\Delta\delta$ = +5.4), 28.53 (C3, C5 [β], d, J = 23 Hz, $\Delta\delta$ = +3.03), 26.97 (C2, C6 [γ gauche], s, $\Delta\delta$ = −5.19), 25.22 (Me_3C [γ], s, $\Delta\delta$ = −2.45), 74.15 (C1, s, $\Delta\delta$ = −1.42), 123.48, 130.76, 136.09, 150.58 (C_{arom}, s), 164.23 (CO, s); MS, m/e 323 (M^+), 303 [$(M - HF)^+$]. Anal. Calcd for $C_{17}H_{22}FNO_4$: C, 63.16; H, 6.81. Found: C, 63.31; H, 6.93. **7** (55 mg) was dissolved in 50 mL of aqueous MeOH-CH_2Cl_2 to which 28 mg of Na_2CO_3 was added. After 4 h at room temperature the reaction was acidified with HCl and worked up as usual. The crude product was chromatographed on silica gel column using 20% EtOAc in P.E. The alcohol **9** was thus isolated in 45% yield: mp 91 °C; ^{1}H NMR δ 3.56 (CHO, 1 H, m, $W_{h/2}$ = 22 Hz), 0.96 (Me_3C, 9 H, s) 2.3–0.6 (9 H, m); ^{19}F NMR −172.0 (br t, J_{HF} = 40 Hz, $W_{h/2}$ = 90 Hz); IR 3300 cm^{-1}; MS, m/e 174 (M^+), 154 [$(M - HF)^+$]. Anal. Calcd for $C_{10}H_{19}FO$: C, 68.96; H, 10.92. Found: C, 68.39; H, 10.44. Similarly, the oily **12** was obtained from the acetate **11** in 70% yield, after homogenation on HPLC using 5% EtOAc in cyclohexane: ^{1}H NMR δ 4.64 (CHO, 1 H, m, $W_{h/2}$ = 25 Hz), 2.04 (Ac, 3 H, s) 0.96 (Me_3C, 9 H, s), 2.20–0.8 (8 H, m); ^{19}F NMR −172.2 (br t, J_{HF} = 37 Hz); MS, m/e 196 [$(M - HF)^+$], 157 [$(M - OAc)^+$], 137 [$(M - HF - OAc)^+$]. Anal. Calcd for $C_{12}H_{21}FO_2$: C, 66.67; H, 9.72. Found: C, 66.94; H, 9.82.

Fluorination of *cis*-4-*tert*-butylcyclohexyl *p*-nitrobenzoate (6)[42] was carried out as for **5**. The pure **8** was thus isolated in 83% yield; mp 104 °C (from cyclohexane); ^{1}H NMR δ 8.25 (Ar, 4 H, AB, J = 8 Hz), 5.33 (CHO, 1 H, m, $W_{h/2}$ = 8 Hz), 1.03 (Me_3C, 9 H, s), 2.50–0.8 (8 H, m); ^{19}F NMR −175.2 (m, $W_{h/2}$ = 78 Hz) MS, m/e 323 (M^+), 303 [$(M - HF)^+$]. Anal. Calcd for $C_{17}H_{22}FNO_4$: C, 63.16; H, 6.81. Found: C, 63.71; H, 6.93.

Fluorination of *cis*-3-*tert*-Butylcyclohexyl Acetate (13). This compound was prepared from 3-*tert*-butylphenol, which was methylated and reduced by Birch's method followed by catalytic hydrogenation. The resulting 3-*tert*-butylcyclohexanone was further reduced by $NaBH_4$, and the crude alcohol was acetylated by Ac_2O–Py. The liquid cis acetate **13** was separated from the trans one by HPLC using 4% EtOAc in cyclohexane. The fluorination was carried on 0.5 g (2.50 mmol) by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 4% EtOAc in cyclohexane as eluent. The pure liquid **14** was thus isolated in 50% yield: ^{1}H NMR δ 4.98 (CHO, 1 H, m, $W_{h/2}$ = 25 Hz), 2.02 (Ac, 3 H, s), 0.97 (Me_3C, 9 H, s), 1.90–0.8 (8 H, m); ^{19}F NMR −169.5 (br t, J_{HF} = 40 Hz); ^{13}C NMR 100.92 (C3 [α], d, J = 175.6 Hz, $\Delta\delta$ = +54.3), 71.01 (C1 [γ gauche], s, $\Delta\delta$ = −3), 37.22 (C2 [β], d, J = 21.3 Hz, $\Delta\delta$ = +3.85), 35.44 (C7 [β], d, J = 22 Hz, $\Delta\delta$ = +3.5), 31.04 (C6, s, $\Delta\delta$ = −10.6), 28.69 (C4 [β], d, J = 23 Hz, $\Delta\delta$ = +2.52), 25.18 (Me_3C[γ], s, $\Delta\delta$ = −2.2), 21.21 (CH_3CO, s), 19.44 (C5 [γ], s, $\Delta\delta$ = −4.7) 169.95 (CO, s); MS, m/e 159 [$(M - t\text{-Bu})^+$], 157 [$(M - OAc)^+$], 139 [$(M - HF - t\text{-Bu})^+$]. Anal. Calcd for $C_{12}H_{21}FO_2$: C, 66.67; H, 9.72. Found: C, 66.23; H, 9.75.

Fluorination of *cis*-3-Methylcyclohexyl *p*-Nitrobenzoate (16). **16** was prepared from a mixture of cis and trans alcohols (Aldrich). The cis isomer[44] was isolated by HPLC using 2% EtOAc in cyclohexane. **16** (0.5 g) was fluorinated as described previously by using 6% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 4% EtOAc in cyclohexane as eluent. The pure oily **17** was isolated in 30% yield: ^{1}H NMR δ 8.23 (Ar, 4 H, AB, J = 8 Hz), 5.28 (CHO, 1 H, m, $W_{h/2}$ = 15 Hz), 1.42 (CH_3CF, 3 H, d, J_{HF} = 21.0 Hz), 2.4–0.7 (8 H, m); ^{19}F NMR −149.6 (m, $W_{h/2}$ = 62 Hz); ^{13}C NMR 95.10 (C3 [α], d, J = 167.3 Hz, $\Delta\delta$ = +63.65), 72.19 (C1 [γ gauche], s, $\Delta\delta$ = −2.97), 42.00 (C2 [β], d, J = 22.6 Hz, $\Delta\delta$ = +1.50), 35.86 (C4 [β], d, J = 23 Hz, $\Delta\delta$ = +1.83), 30.68 (C6, s, $\Delta\delta$ = −0.89), 27.69 (C7 [β], d, J = 24.8 Hz, $\Delta\delta$ = +5.4), 19.50 (C5 [γ gauche], s, $\Delta\delta$ = −4.5), 123.5, 130.7, 136.4, 150.5 (C_{arom}, s),

(40) Various mixtures of fluorine in inert gases such as N_2 or He are commercially available.

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164.10 (CO, s); MS, *m/e* 266 [(M – Me)$^+$], 150 [(OCOC$_6$H$_4$NO$_2$)$^+$]. Anal. Calcd for $C_{14}H_{16}FNO_4$: C, 59.79; H, 5.69. Found: C, 59.29; H, 5.63.

Fluorination of *cis*-3-Methylcyclohexyl Trichloroacetate (18). 18 was prepared from the corresponding mixture of cis and trans alcohols (Aldrich). The cis isomer was isolated by HPLC using 4% EtOAc in cyclohexane. 18 (0.5 g) was fluorinated as described previously by using 6% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure oily **19** was thus isolated in 35% yield: ^{1}H NMR δ 5.10 (CHO, 1 H, m, $W_{h/2}$ = 23 Hz), 1.40 (CH_3CF, 3 H, d, J_{HF} = 21.0 Hz), 2.8–0.7 (8 H, m); ^{19}F NMR –148.9 (m, $W_{h/2}$ = 90 Hz); MS, *m/e* 262.5 [(M – Me)$^+$], 115 [(M – OCOCCl$_3$)$^+$]. **19** (0.4 g), 1.0 g of Zn dust, and 1.7 g of ammonium acetate were refluxed in 30 mL of MeOH for 48 h. The solids were filtered, and the reaction mixture was worked up as usual and flashed chromatographed with 25% EtOAc in P.E. The oily alcohol **20** was thus isolated in 75% yield: ^{1}H NMR δ 3.92 (CHO, 1 H, m), 1.37 (MeCF, 3 H, d, J_{HF} = 21.4 Hz) 2.3–0.9 (8 H, m); ^{19}F NMR –148.9 (m, $W_{h/2}$ = 78 Hz); IR 3300 cm^{-1}.

Fluorination of 4-*tert*-butylcyclohexanone (22) was carried out on 0.5 g (3.2 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 2.5% EtOAc in cyclohexane as eluent. The pure **23** was thus isolated in 65% yield: mp 70 °C (from wet CH_2Cl_2); ^{1}H NMR δ 1.03 (Me_3C, 9 H, s), 2.80–0.9 (8 H, m); ^{19}F NMR –172.8 (tt, J_{H_aF} = 36.5 Hz, J_{H_eF} = 8 Hz); IR 1710 cm^{-1}; MS, *m/e* 172 (M$^+$), 152 [(M – HF)$^+$], 144 [(M – CO)$^+$]. Anal. Calcd for $C_{10}H_{17}FO$: C, 69.77; H, 9.88. Found: C, 69.73; H, 9.99.

Fluorination of 4-methylcyclohexanone (24) was performed on 0.60 g (5.35 mmol) by using 6.5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 10% EtOAc in cyclohexane as eluent. The pure liquid **25** was thus isolated in 20% yield: ^{1}H NMR δ 1.47 (CH_3CF, 3 H, d, J_{HF} = 21.4 Hz), 3.0–0.9 (8 H, m); ^{19}F NMR –154.9 (m, $W_{h/2}$ = 100 Hz); IR 1710 cm^{-1}; MS, *m/e* 130 (M$^+$), 110 [(M – HF)$^+$].

Fluorination of 4,4′-Methylenebis(cyclohexanone) (26). This compound was prepared from 4,4′-methylenebis(cyclohexylamine) following a known procedure,[45] mp 89 °C (from MeOH–H_2O). The fluorination was carried on 0.60 g (2.88 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 30% EtOAc in cyclohexane as eluent. The pure **27** was thus isolated in 10% yield: mp 35 °C (from MeOH–H_2O); ^{1}H NMR δ 2.7–2.3 (CH_2CO, 8 H, m), 1.71 (CH_2CF, 2 H, dd, J_{HF} = 24 Hz, J = 5.2 Hz), 2.3–1.2 (9 H, m); ^{19}F NMR –162.6 (quintet, J_{HF} = 24 Hz); IR 1690 cm^{-1}; MS, *m/e* 226 (M$^+$), 206 [(M – HF)$^+$]. Anal. Calcd for $C_{13}H_{19}FO_2$: F, 8.41. Found: F, 8.38.

Fluorination of *N*-(4-Methylcyclohexyl)trichloroacetamide (35). This was prepared from the 4-methylcyclohexyl amine (Aldrich) and trichloroacetic anhydride. Cis and trans isomers were obtained in the ratio of 1:3 as in the starting amine. The melting point of this mixture is 87 °C. A gram (3.86 mmol) of it was fluorinated by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. A mixture of cis and trans **36** was thus obtained in 1:3 ratio, respectively: yield 70%; mp 147 °C (from CH_2Cl_2–hexane); ^{1}H NMR δ 6.66 (c), 6.58 (t) (NH, 1 H, br s), 4.07 (c), 3.74 (t) (C*H*NH, 1 H, m), 1.41 (c), 1.36 (t) (CH_3CF, 3 H, d, J_{HF} = 22 (c), 21 Hz (t)), 2.1–1.0 (8 H, m); ^{19}F NMR –141.1 (c), –153.0 (t) (m, $W_{h/2}$ = 75 and 92 Hz); IR 3410, 1710, 1510 cm^{-1}; MS, *m/e* 138 [(M – HF – CCl$_3$)$^+$], 96 [(M – HF – NHCOCCl$_3$)$^+$]. Anal. Calcd for $C_9H_{13}Cl_3FNO$: C, 39.05; H, 4.70. Found: C, 39.16; H, 5.00.

Fluorination of 2,2,2-Trichloroethyl 3-Cyclohexylpropanoate (37). This ester was prepared from the corresponding acyl halide and trichloroethanol in pyridine; oil; 90% yield. **37** (0.9 g, 3.1 mmol) was fluorinated by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 8% EtOAc in cyclohexane as eluent. The pure oily **38** was thus isolated in 60% yield: ^{1}H NMR δ 4.75 (CH_2CCl_3, 2 H, s), 2.52 (CH_2CO, 2 H, t, J = 8 Hz), 2.01 (CH_2CF, 2 H, dt, J_{HF} = 20.0 Hz, J = 8 Hz), 2.1–1.1 (10 H, m); ^{19}F NMR –149.5 (m, $W_{h/2}$ = 90 Hz); MS, *m/e* 137 [(M – HF – OCH$_2$CCl$_3$)$^+$], 101 [(C$_6$H$_{11}$F)$^+$], 81 [(C$_6$H$_{10}$)$^+$]. Anal. Calcd for $C_{11}H_{16}Cl_3FO_2$: C, 43.21; H, 5.24. Found: C, 42.83; H, 5.01.

Fluorination of 2,2,2-Trichloroethyl 3-Cyclopentylpropanoate (39). This ester was prepared analogously to **37**: oil; 90% yield. One gram (3.65 mmol) of it was fluorinated by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure oily **40** was thus isolated in 40% yield: ^{1}H NMR δ 4.75 (CH_2CCl_3, 2 H, s), 2.63 (CH_2CO, 2 H, t, J = 8 Hz), 2.3–1.6 (10 H, m); ^{19}F NMR –146.0 (heptet, J_{HF} = 23 Hz); MS, *m/e* 271.5 [(M – HF)$^+$], 173 [(M – CCl$_3$)$^+$], 159 [(M – CH$_2$CCl$_3$)$^+$]. Anal. Calcd for $C_{10}H_{14}Cl_3FO_2$: C, 41.17; H, 4.80. Found: C, 40.84; H, 4.12.

Fluorination of 3-cyclopentylpropyl acetate (41) was carried as described before on 1.0 g (5.80 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure oily **42** was thus isolated in 40% yield: ^{1}H NMR δ 4.05 (CH_2O, 2 H, t, J = 6.6 Hz), 2.04 (Ac, 3 H, s), 2.26 ((C*H*$_2$)$_2$CF, 4 H, m), 2.12 (C*H*$_2$CF, 2 H, m), 1.89–1.73 (6 H, m); ^{19}F NMR –144.3 (m, $W_{h/2}$ = 65 Hz); ^{13}C NMR 106.50 (C1′ [α], d, J = 171.8 Hz, $\Delta\delta$ = +66.6), 37.58 (C3 [β], d, J = 24.8 Hz, $\Delta\delta$ = +5.23), 35.03 (C2′, C5′ [β], d, J = 24.8 Hz, $\Delta\delta$ = +7.08), 23.97 (C3′, C4′ [γ], s, $\Delta\delta$ = –1.25), 23.97 (C2 [γ], s, $\Delta\delta$ = –8.47), 20.91 (*C*H$_3$CO, s), 64.65 (C1, s), 171.09 (CO, s); MS, *m/e* 108 [(M – HF – AcOH)$^+$]. Anal. Calcd for $C_{10}H_{17}FO_2$: C, 63.83; H, 9.04. Found: C, 63.68; H, 8.66.

Fluorination of 1,2-Dicarbomethoxy-4-methylcyclohexane (43). This compound was prepared by methanolysis of hexahydro-4-methylphthalic anhydride (Aldrich). A mixture of two isomers was obtained in 90% yield. This mixture (0.6 g, 2.8 mmol) was fluorinated as described above by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 7% EtOAc in cyclohexane as eluent. A 1:1 mixture of two isomers of **44** was thus isolated as a liquid in 25% yield: ^{1}H NMR δ 3.69, 3.67 (MeO, 6 H, s) 3.20 (CHCO, 2 H, m), 1.34 (CH_3CF, 3 H, d, J_{HF} = 21.4 Hz), 3.1–1.3 (6 H, m); ^{19}F NMR –147.6 (m, $W_{h/2}$ = 69 Hz); MS, *m/e* 201 [(M – OMe)$^+$], 118 [(M – HF – OMe)$^+$], 114 [(M – 2COOMe)$^+$]. Anal. Calcd for $C_{11}H_{17}FO_4$: C, 56.89; H, 7.33. Found: C, 56.74; H, 7.11.

Fluorination of *cis*-Methyl 2,2-Dimethyl-3-ethylcyclobutaneacetate (45). This cyclobutane derivative was prepared from *cis*-pinonic acid (Aldrich), which was reduced by the Clemmensen method, followed by esterification with MeOH and sulfuric acid: liquid; overall yield 60%; ^{1}H NMR δ 3.64 (MeO, 3 H, s), 2.22 (CH_2CO, d, J = 2.2 Hz), 1.04 (Me syn to the carbomethoxy, 3 H, s), 0.87 (Me anti to the carbomethoxy, 3 H, s). One gram of **45** (5.4 mmol) was fluorinated by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure liquid **46** was thus isolated in 30% yield: ^{1}H NMR δ 3.65 (MeO, 3 H, s), 1.02 (Me syn to the carbomethoxy, 3 H, s), 0.97 (Me anti to the carbomethoxy, 3 H, s), 2.3–0.8 (10 H, m); ^{19}F NMR –166.5 (quintet, J_{HF} = 23 Hz); MS, *m/e* 182 [(M – HF)$^+$], 143 [(M – CH$_2$COOMe – H)$^+$]. Anal. Calcd for $C_{11}H_{19}FO_2$: C, 65.37; H, 9.40. Found: C, 65.33; H, 9.10.

Fluorination of menthyl *p*-nitrobenzoate (47) was performed on 0.5 g (1.64 mmol) by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. Two products were isolated. The less polar one proved to be **48**: 60% yield; ^{1}H NMR δ 8.24 (Ar, 4 H, AB, J = 8 Hz), 5.15 (CHO, 1 H, dt, J_1 = 10 Hz, J_2 = 5 Hz), 1.34 (Me_2CF, 6 H, d, J_{HF} = 23.0 Hz), 0.96 (C*H*$_3$CH, 3 H, d, J = 6 Hz), 2.2–0.65 (8 H, m); ^{19}F NMR –132.5 (d heptet, J_{MeF} = 23 Hz, J_{HF} = 9 Hz); MS, *m/e* 323 (M$^+$), 303 [(M – HF)$^+$]. Anal. Calcd for $C_{17}H_{22}FNO_4$: C, 63.16; H, 6.81. Found: C, 64.04; H, 6.72. The more polar fraction proved to be the difluoro **49**; 10% yield; ^{1}H NMR δ 8.23 (Ar, 4 H, AB, J = 8 Hz), 5.52 (CHO, 1 H, dt, J_1 = 10 Hz, J_2 = 5 Hz), 1.41 (MeCF, 3 H, d, J_{HF} = 22 Hz), 1.38 (Me_2CF, 6 H, d, J_{HF} = 23.0 Hz), 2.3–0.60 (7 H, m); ^{19}F NMR –132.6 (d heptet, J_{MeF} = 23 Hz, J_{HF} = 9 Hz), –151.2 (m, $W_{h/2}$ = 95 Hz); MS, *m/e* 341 (M$^+$). Anal. Calcd for $C_{17}H_{21}F_2NO_4$: C, 59.82; H, 6.15. Found: C, 59.58; H, 5.85.

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Fluorination of Carvomenthyl *p*-Nitrobenzoate (50). This was prepared by hydrogenation of dihydrocarvol (Aldrich) in MeOH using 10% Pd on carbon as a catalyst. Reaction with *p*-nitrobenzoyl chloride gives **50**, mp 67 °C.[46] The fluorination was performed on 0.5 g (1.64 mmol) by using 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. Two products were isolated. The less polar one proved to be **52**; 15% yield; mp 62 °C (from MeOH); ^{1}H NMR δ 8.25 (Ar, 4. H, AB, J = 8 Hz), 5.06 (CHO, 1 H, dt, J_1 = 10 Hz, J_2 = 5 Hz), 0.93 (3 Me, 9 H, d, J = 7 Hz) 2.2–0.7 (8 H, m); ^{19}F NMR −162.2 (br t, J_{HF} = 40 Hz, $W_{h/2}$ = 92 Hz); ^{13}C NMR 99.66 (C4 [α], d, J = 172.0 Hz, $\Delta\delta$ = +62.0), 37.27 (C3 [β], d, J = 22 Hz, $\Delta\delta$ = +2.0), 36.75 (C8 [β], d, J = 22 Hz, $\Delta\delta$ = +3.53), 31.0 (C5 [β], d, J = 24 Hz, $\Delta\delta$ = 2.18), 77.53 (C2 [γ gauche], s, $\Delta\delta$ = −2.2), 28.21 (C6[γ gauche], s, $\Delta\delta$ = −4.3), 16.9, 17.16 (C9, C10 [γ], s, $\Delta\delta$ = −2.8, −2.6), 37.04 (C1, s, $\Delta\delta$ = −5.80), 18.13 (C7, s, $\Delta\delta$ = −0.29), 123.61, 130.76, 136.15, 150.64 (C_{arom}, s), 164.16 (CO, s); MS, m/e 181 [(M − HF − $C_6H_4NO_2$)$^+$], 173 [(M − $COC_6H_4NO_2$)$^+$], 166[($OCOC_6H_4NO_2$)$^+$], 137 [(M − HF − $OCOC_6H_4NO_2$)$^+$]. Anal. Calcd for $C_{17}H_{22}FNO_4$: C, 63.16; H, 6.81. Found: C, 62.99; H, 6.75. The more polar fraction proved to be the isomeric **51**; 35% yield; mp 43 °C (from MeOH); ^{1}H NMR δ 8.25 (Ar, 4 H, AB, J = 8 Hz), 4.75 (CHO, 1 H, dt, J_1 = 10 Hz, J_2 = 5 Hz), 1.33 (Me_2CF, 6 H, d, J_{HF} = 22 Hz), 0.98 (CH_3CH, 3 H, d, J = 6 Hz), 2.1–0.9 (8 H, m); ^{19}F NMR −141.3 (m, $W_{h/2}$ = 64 Hz); ^{13}C NMR 96.62 (C8 [α], d, J = 169.4 Hz, $\Delta\delta$ = +63.4), 46.01 (C4 [β], d, J = 23 Hz, $\Delta\delta$ = +8.36), 24.60 (C9, C10 [β], d, J = 25 Hz, $\Delta\delta$ = +4.82), 26.36 (C3 [γ], s, $\Delta\delta$ = −8.9), 26.30 (C5 [γ], s, $\Delta\delta$ = −2.52), 32.74 (C6, s, $\Delta\delta$ = +0.18), 80.1 (C2, s, $\Delta\delta$ = −0.61), 37.42 (C1, s, $\Delta\delta$ = −5.42), 18.30 (C7, s, $\Delta\delta$ = −0.12), 123.57, 130.73, 136.15, 150.60 (C_{arom}, s), 164.4 (CO, s); MS, m/e 258 [(M − HF − 3Me)$^+$], 181 [(M − HF − $C_6H_4NO_2$)$^+$], 173 [(M − $COC_6H_4NO_2$)$^+$]. Anal. Calcd for $C_{17}H_{22}FNO_4$: C, 63.16; H, 6.81. Found: C, 62.54; H, 6.80.

Fluorination of Dihydroterpenyl Acetate (53). Compound **53** was obtained by hydrogenation of terpenyl acetate using 10% Pd on carbon as catalyst. After the usual fluorination procedure the trans fluoro isomer **54** was obtained after purification by HPLC using 5% EtOAc in cyclohexane as eluent, in 37% yield: oil; ^{1}H NMR δ 1.97 (Ac, 3 H, s), 1.41 (Me_2C, 6 H, s), 1.31 (MeCF, 3 H, d, J_{HF} = 21 Hz), 2.1–0.8 (9 H, m); ^{19}F NMR −153.5 (m, $W_{h/2}$ = 108 Hz); MS, m/e 157 [(M − OAc)$^+$], 137 [(M − HF − OAc)$^+$]. Anal. Calcd for $C_{12}H_{21}FO_2$: C, 66.67; H, 9.72. Found: C, 66.60; H, 9.63.

Fluorination of *cis*-1-decalyl *p*-nitrobenzoate (55) was performed on 1.0 g (3.3 mmol) by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **57** was thus isolated in 40% yield; mp 110 °C (from MeOH); ^{1}H NMR δ 8.20 (Ar, 4 H, AB, J = 8 Hz), 5.40 (CHO, 1 H, m, $W_{h/2}$ = 10 Hz), 2.5–0.8 (15 H, m); ^{19}F NMR −141.3 (br d, J_{HF} = 37 Hz, $W_{h/2}$ = 50 Hz); ^{13}C NMR 97.90 (C5 [α], d, J = 170.0 Hz, $\Delta\delta$ = +66.3), 28.92 (C4 [β], d, J = 23.5 Hz, $\Delta\delta$ = +3.0), 37.83 (C6 [β], d, J = 20.5 Hz, $\Delta\delta$ = +3.70), 44.84 (C10 [β], d, J = 18 Hz, $\Delta\delta$ = +4.70), 19.17 (C3 [γ gauche], s, $\Delta\delta$ = −6.80), 73.89 (C1 [γ gauche], s, $\Delta\delta$ = −3.8), 23.1 (C7 [γ anti], d, J = 7.3 Hz, $\Delta\delta$ = +2.9), 23.95 (C9 [γ anti], d, J = 10.2 Hz, $\Delta\delta$ = +2.6), 25.09 (C2, s, $\Delta\delta$ = −10.4), 25.09 (C8, s, $\Delta\delta$ = +0.6), 123.50, 130.60, 136.20, 150.50 (C_{arom}, s), 163.77 (CO, s); MS, m/e 301 [(M − HF)$^+$]. Anal. Calcd for $C_{17}H_{20}FNO_4$: C, 63.55; H, 6.23. Found: C, 63.15; H, 6.01. In a similar way the acetate **58** was obtained from **56**: liquid; 45% yield; ^{1}H NMR δ 5.20 (CHO, 1 H, m, $W_{h/2}$ = 11 Hz), 2.03 (Ac, 3 H, s), 2.0–0.9 (15 H, m); ^{19}F NMR −141.3 (br d, J_{HF} = 37 Hz, $W_{h/2}$ = 50 Hz); MS, m/e 171 [(M − Ac)$^+$]. Anal. Calcd for $C_{12}H_{19}FO_2$: C, 67.29; H, 8.88. Found: C, 66.96; H, 8.60.

Fluorination of 2-Acetoxybicyclopentyl (59). This compound was prepared by hydrogenation of 2-cyclopentylidenecyclopentanone (Aldrich) using Pd/C as a catalyst. The resulting ketone was reduced with $NaBH_4$ followed by acetylation to afford a 1:1 mixture of *cis*- and *trans*-**59** in a 60% overall yield. The mixture (0.5 g) was fluorinated by using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using 2% EtOAc in cyclohexane as eluent. Two fractions were thus isolated, and the less polar one proved to be the trans isomer **60**: 30% yield; oil; ^{1}H NMR δ 5.20 (CHO, 1 H, m, $W_{h/2}$ = 11 Hz), 2.02 (Ac, 3 H, s), 1.9–1.2 (15 H, m); ^{19}F NMR −152.2 (m, $W_{h/2}$ = 93 Hz); ^{13}C NMR 107.22 (C1′ [α], d, J = 175.4 Hz, $\Delta\delta$ = +63.3), 36.50 C2′ [β], d, J = 23.0 Hz, $\Delta\delta$ = +7.1), 36.83 (C5′ [β], d, J = 23.0 Hz, $\Delta\delta$ = +5.79), 52.87 (C1 [β], d, J = 23 Hz, $\Delta\delta$ = +2.17), 23.85 (C4′ [γ gauche], s, $\Delta\delta$ = −1.20), 24.11 (C3′ [γ gauche], s, $\Delta\delta$ = −1.06), 26.73 (C5 [γ], s, $\Delta\delta$ = −5.4), 77.74 (C2 [γ], s, $\Delta\delta$ = −3.04), 23.70 (C4, s, $\Delta\delta$ = +0.74), 33.70 (C3, s, $\Delta\delta$ = +0.98), 21.30 (CH_3CO, s), 170.45 (CO, s); MS, m/e 155 [(M − OAc)$^+$]. Anal. Calcd for $C_{12}H_{19}FO_2$: C, 67.28; H, 8.88. Found: C, 67.58; H, 9.11. The more polar fraction proved to be the cis isomer **61**: 30% yield; oil; ^{1}H NMR δ 5.35 (CHO, 1 H, m, $W_{h/2}$ = 8 Hz), 2.02 (Ac, 3 H, s), 1.95–1.2 (15 H, m); ^{19}F NMR −142.5 (m, $W_{h/2}$ = 76 Hz); ^{13}C NMR 106.39 (C1′ [α], d, J = 170.6 Hz, $\Delta\delta$ = +66.0), 36.87 (C2′ [β], d, J = 24.0 Hz, $\Delta\delta$ = +7.67), 37.67 (C5′ [β], d, J = 24.0 Hz, $\Delta\delta$ = +5.69), 51.00 (C1 [β], d, J = 24 Hz), 23.74 (C4′ [γ gauche], s, $\Delta\delta$ = −1.60), 24.33 (C3′ [γ gauche], s, $\Delta\delta$ = −1.09), 25.37 (C5 [γ], d, J = 3.3 Hz, $\Delta\delta$ = −6.86), 76.15 (C2 [γ], s, $\Delta\delta$ = −1.80), 21.97 (C4, s, $\Delta\delta$ = −0.41), 33.18 (C3, s), 21.41 (CH_3CO, s), 170.33 (CO, s); MS, m/e 194 [(M − HF)$^+$], 171 [(M − Ac)$^+$], 151 [(M − HF − Ac)$^+$]. Anal. Calcd for $C_{12}H_{19}FO_2$: C, 67.28; H, 8.88. Found: C, 67.10; H, 8.98.

Fluorination of *tert*-Butylcyclohexane (62). This alkane was prepared by Wolff–Kishner reduction of *tert*-butylcyclohexanone. The fluorination was carried out on 0.5 g (3.57 mmol) by using 1.3% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using cyclohexane as eluent. The pure **63** was thus obtained in 70% yield; liquid; ^{1}H NMR δ 0.95 (Me_3C, 9 H, s), 1.90–0.9 (10 H, m); ^{19}F NMR −172.8 (br t, J_{HF} = 40.0 Hz, $W_{h/2}$ = 85 Hz); MS, m/e 158 (M$^+$), 138 [(M − HF)$^+$], 101 [(M − t-Bu)$^+$], 57 (t-Bu$^+$).

Fluorination of bicyclohexyl (64) was carried on 0.8 g (4.8 mmol) by using 2.5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using cyclohexane as eluent. The fluorinated **67** was isolated in 70% yield: oil; ^{1}H NMR δ 1.8–0.88 (21 H, m); ^{19}F NMR −162.8 (t, J_{HF} = 35 Hz); ^{13}C NMR 97.36 (C1 [α], d, J = 168 Hz, $\Delta\delta$ = +53.86), 32.48 (C2, C6 [β], d, J = 24.0 Hz, $\Delta\delta$ = +2.26), 47.62 (C1′ [β], d, J = 21.0 Hz, $\Delta\delta$ = +4.12), 21.98 (C3, C5 [γ gauche], s, $\Delta\delta$ = −4.40), 27.13 (C3′, s), 26.84 (C4, C4′, s); MS, m/e 164 [(M − HF)$^+$], 82 ($C_6H_{10}^+$). Anal. Calcd for $C_{12}H_{21}F$: C, 78.26; H, 11.41. Found: C, 78.00; H, 11.43.

Fluorination of *cis*-decalin (65) was performed on 1.0 g (7.2 mmol) by using 1% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using cyclohexane as eluent. The pure liquid **68** was isolated in 90% yield; ^{1}H NMR δ 1.83–1.26 (17 H, m); ^{19}F NMR −140.6 (m, $W_{h/2}$ = 55 Hz); ^{13}C NMR 94.32 (C5 [α], d, J = 178.6 Hz, $\Delta\delta$ = +57.52), 37.27 (C6 [β], d, J = 22.6 Hz, $\Delta\delta$ = +7.57), 41.02 (C4 [β], d, J = 20.3 Hz, $\Delta\delta$ = +11.32), 43.34 (C10 [β], d, J = 22.6 Hz, $\Delta\delta$ = +6.54), 21.75 (C3 [γ gauche], s, $\Delta\delta$ = −5.38), 28.79 (C1 [γ gauche], s, $\Delta\delta$ = −0.92), 25.97 (C7 [γ anti], s, $\Delta\delta$ = +1.3), 30.55 (C9 [γ anti], s, $\Delta\delta$ = +0.86), 23.09 (C2, C8, s, $\Delta\delta$ = −1.4); MS, m/e 156 (M$^+$), 136 [(M − HF)$^+$]. Anal. Calcd for $C_{10}H_{17}F$: C, 76.92; H, 10.90. Found: C, 77.46; H, 11.14.

Fluorination of *trans*-decalin (66) was performed on 1.0 g (7.2 mmol) by using 1% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed, followed by HPLC using cyclohexane as eluent. The pure liquid **69** was isolated in 80% yield; ^{1}H NMR δ 1.80–0.95 (17 H, m); ^{19}F NMR −177.5 (br q, J_{HF} = 30 Hz, $W_{h/2}$ = 90 Hz); ^{13}C NMR 94.48 (C5 [α], d, J = 171.8 Hz, $\Delta\delta$ = +50.48), 37.21 (C4, C6 [β], d, J = 22.6 Hz, $\Delta\delta$ = +2.61), 43.35 (C10 [β], d, J = 23.6 Hz), 21.72 (C3, C7 [γ gauche], s, $\Delta\delta$ = −5.38), 28.79 (C1, C9 [γ gauche], s, $\Delta\delta$ = −5.81), 25.94 (C2, C8, s, $\Delta\delta$ = −1.16); MS, m/e 156 (M$^+$), 136 [(M − HF)$^+$]. Anal. Calcd for $C_{10}H_{17}F$: C, 76.92; H, 10.90. Found: C, 77.46; H, 11.14.

Fluorination of *trans*-*p*-Menthane (70). This compound was obtained by Clemmensen reduction of menthone followed by HPLC separation of the trans isomer from the small amount of the cis derivative, which was also formed. The *trans*-**70** was fluorinated as described above by using 1% F_2 in N_2. Three fluoro compounds could be detected, but we were not able to separate them with analytical purity. From GC and ^{1}H and ^{19}F NMR it could be concluded that the three fluoro derivatives were **71**: 50%

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yield; ^{19}F NMR −133.4 (m, $W_{h/2}$ = 110 Hz); **72**, 15% yield; ^{19}F NMR −153.7 (m, $W_{h/2}$ = 100 Hz); **73**, 15% yield; ^{19}F NMR −165.1 (br t, J_{HF} = 40 Hz).

Fluorination of *trans*- and *cis*-1-*tert*-Butyl-4-methylcyclohexane (74 and 75). These compounds were obtained from 4-*tert*-butylcyclohexanone treated with MeMgI. The resulting alcohol was dehydrated and the formed olefin dihydrogenated. A mixture of **74** and **75** was obtained in a corresponding ratio of 3:1 and separated by HPLC using cyclohexane as an eluent. Both isomers were separately fluorinated by using 1.5% F_2 in N_2. In both cases a mixture of two isomers were obtained which we were unable to completely separate. Thus **74** gave a mixture of **76** and **77** in 6:1 ratio: combined yield 70%; ^{19}F NMR (for **76**) −172.5 (m, $W_{h/2}$ = 90 Hz), (for **77**) −153.0 (m, $W_{h/2}$ = 95 Hz). The cis alkane **75** gave **78** and **79** in 65% combined yield in a 4.4:1 ratio. ^{19}F NMR (for **78**) −176.0 (m, $W_{h/2}$ = 88 Hz), (for **79**) −156.9 (m, $W_{h/2}$ = 96 Hz).

Dehydrofluorination Procedures. Three methods were employed for the described HF eliminations. Method A: 1.0 mmol of the corresponding fluoroderivative was dissolved under nitrogen in dry benzene and cooled down to about 10 °C. Freshly distilled BF_3·OEt_2 (8 mL) was added in one portion, the reaction mixture allowed to warm to room temperature and stirred for additional 4 h. Cold diluted HCl solution was added and the organic layer washed with bicarbonate and worked up as usual. The resulting olefins were usually chromatographed on HPLC. Method B: 1.0 mmol of the fluoro compound was dissolved in dry ether and cooled to 0 °C under nitrogen. About 3 mmol of MeMgI solution in ether was added, and the reaction mixture was stirred at room temperature overnight. Workup was as above. Method C: 1.0-mmol of the corresponding fluoride was dissolved in ethylene glycol to which 2 g of aqueous NaOH was added. The reaction mixture was stirred overnight at 105 °C, poured into water, extracted with several portions of CH_2Cl_2, and worked up as usual. The obtained olefins are known compounds, and their physical and spectroscopic data are in excellent agreement with the literature. When a mixture of olefins was obtained we have not separated them. In all cases, including the isomeric mixtures, the empirical formulas were established also by microanalysis fully confirming the purity and the assigned structure.

Acknowledgment. We thank the Fund for Basic Research, administered by the Israel Academy of Science and Humanities, for supporting this research. We also thank E. I. du Pont de Nemours and Co. for providing us with the opportunity to use the MM1 and PRDDO computational programs.

Registry No. **1**, 75350-69-5; **2**, 75350-71-9; **3**, 75350-73-1; **4**, 75350-75-3; **5**, 75350-70-8; **6**, 75350-74-2; **7**, 75350-72-0; **8**, 75350-76-4; **9**, 107742-88-1; **11**, 1900-69-2; **12**, 107742-89-2; **13**, 20298-72-0; **14**, 107742-90-5; **16**, 107742-91-6; **17**, 107742-92-7; **18**, 107742-93-8; **19**, 107742-94-9; **20**, 107742-95-0; **22**, 98-53-3; **23**, 107742-96-1; **24**, 589-92-4; **25**, 82953-31-9; **26**, 51113-52-1; **27**, 82953-32-0; *cis*-**35**, 107742-97-2; *trans*-**35**, 107742-98-3; *cis*-**36**, 107742-99-4; *trans*-**36**, 107743-00-0; **37**, 97865-17-3; **38**, 97845-33-5; **39**, 107743-01-1; **40**, 107768-21-8; **41**, 97845-31-3; **42**, 97845-32-4; **43**, 92709-07-4; **44**, 107743-02-2; **45**, 97845-29-9; **46**, 97845-30-2; **47**, 4277-14-9; **48**, 75350-80-0; **49**, 75350-81-1; **50**, 2225-93-6; **51**, 107743-04-4; **52**, 107743-03-3; **53**, 20777-41-7; **54**, 107743-05-5; **55**, 54289-26-8; **56**, 22222-30-6; **57**, 90304-28-2; **58**, 107768-22-9; α-**59**, 107743-06-6; β-**59**, 107743-07-7; **60**, 107743-08-8; **61**, 107743-09-9; **62**, 3178-22-1; **63**, 90304-26-0; **64**, 92-51-3; **65**, 493-01-6; **66**, 493-02-7; **67**, 107743-10-2; **68**, 90304-27-1; **69**, 82823-26-5; **70**, 1678-82-6; **71**, 107743-11-3; **72**, 107743-12-4; **73**, 107743-13-5; **74**, 4001-94-9; **75**, 3325-80-2; **76**, 90304-29-3; **77**, 65199-17-9; **78**, 107743-14-6; **79**, 65199-18-0; **80**, 75350-77-5; **82**, 107743-15-7; **83**, 107743-16-8; **84**, 107743-17-9; **85**, 107743-18-0; **86**, 107743-19-1; **87**, 58045-40-2; **88**, 86905-77-3; **90**, 3282-54-0; **91**, 4233-18-5; **92**, 493-03-8; **93**, 1194-95-2; F_2, 7782-41-4.

Methyl Viologen Neutral MV:. 1. Preparation and Some Properties

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Received September 18, 1986

The highest reduction product of 1,1′-dimethyl-4,4′-bipyridinium dichloride (methyl viologen dichloride, $MVCl_2$), methyl viologen neutral MV:, was obtained by magnesium reduction in acetonitrile and sodium reduction in tetrahydrofuran. The optical spectrum [λ_{max} 396 nm (ε 27 000 in MeCN)] and NMR spectra [δ 5.536 and 5.509 (H_2 H_6), 5.317 and 5.290 (H_3, H_5), 2.096 (CH_3)] were recorded. MV: was not found to be a diradical, nor was it found to possess a large dipole moment. It was found to undergo photoassisted reaction with water.

1,1′-Dimethyl-4,4′-bipyridinium dichloride (I), also known as methyl viologen (MV^{2+}) dichloride or paraquat, is an interesting and important member of the viologen family.[1] Some of the members of the family exhibit herbicidal activity.[2] Besides, these compounds have been investigated for electrochromic properties.[3] Methyl viologen dichloride itself has been used as a probe to investigate the structure and dynamics of clay and polymer electrodes, catalytic production of hydrogen, and micelle formation.[4]

Generally, investigations and studies have been confined to the first reduction product, the methyl viologen cation radical (eq 1). The higher reduction product (eq 2) was indicated by some workers,[1a,2c] but its importance was pointed out by Mohammad and co-workers,[5] and a sys-

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