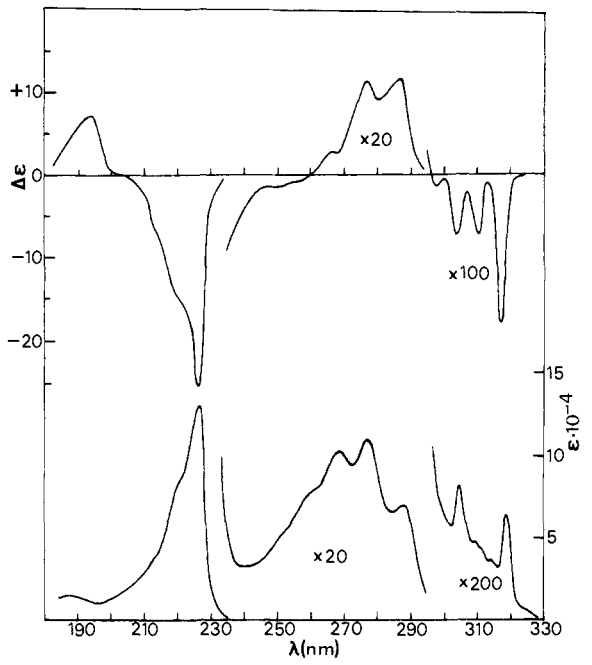

Figure 3. CD (upper) and UV (lower) spectra of II in *n*-heptane solution at room temperature. CD data are corrected for 100% optical purity of the sample.

degenerate transitions in benzene. Actually, the latter has been located by Klevens and Platt[5] at about 169–167 nm, but other authors place this band a few nm beyond the ^1B_b transition[6,9,10] toward shorter wavelengths. It is worth noting that the UV maximum of the main absorption in I (Figure 2) corresponds to the negative band at 225 nm in the CD spectrum, and this supports the ^1B_b assignment for this band.

Finally, the CD band at about 195 nm in II (Figure 3) corresponds to the UV maximum at 188 nm, and it could be due to the ^1C_b transition as suggested by Klevens and Platt[5] for naphthalene. In the CD spectrum of I, such a band could correspond to the shoulder at about 200 nm, overwhelmed by the relatively intense positive band at 211 nm due to the ^1B_a transition.

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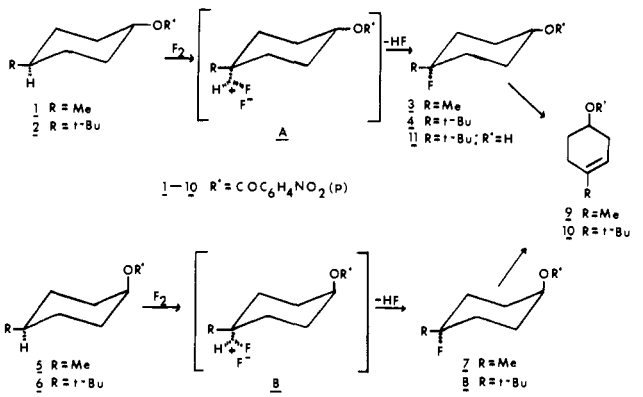
Remote and Selective Electrophilic Fluorinations at the Carbon–Hyrogen Single Bond

Sir:

Most of the organic syntheses performed today have one feature in common: they all require an anchor around which the reagents can group themselves. In fact, most organic chemical reactions are performed on, or around, functions such as carbonyl or hydroxyl groups, double bonds, heteroatoms, and so on. There are extremely few reactions on hydrogen atoms attached to an unactivated saturated carbon. It is even rarer for such reactions to be nonradical in character and to proceed with reasonable yield and high selectivity.[1]

Scheme I



In order to attack successfully an unactivated C–H bond, a very powerful electrophile has to be employed. However, this electrophile should be used in low concentration and low temperatures in order to take advantage of the differences in the electron density of the various covalent single hydrogen–carbon bonds, thus leading to regiospecific reactions. We have chosen for this purpose the most powerful electrophile, electrophilic fluorine. There are two main sources for such an unusual reactant: the first is already quite well-known and includes reagents with the fluoroxy function such as the commercial CF_3OF and SF_5OF[2] or such reagents which can be prepared in situ like CF_3CF_2OF and CF_3COOF.[3] The second and the more powerful source for an electrophilic fluorine seems to be elemental fluorine itself.[4,5]

We describe here a highly regiospecific and an absolutely stereospecific reaction on unactivated sites with this most reactive element of all. Scheme I, in which the starting materials are various 4-alkylcyclohexanol esters, can provide a good example of the synthetic potential of this fluorination reaction.

When 600 mg of *trans*-4-methylcyclohexanol *p*-nitrobenzoate (**1**) was treated with fluorine diluted with nitrogen (4%, v/v) at −70 °C, a single fluorinated product was obtained in 60% yield.[6] It was identified[7] as *trans*-4-methyl-4-fluorocyclohexanol *p*-nitrobenzoate (**3**), mp 115 °C. In a similar way, 700 mg of

(1) Representation of such reactions can be found in the works of N. C. Deno. Radical chlorination of certain straight chain alcohols in strongly acidic media shows a degree of perference for attack on sites remote from the hydroxyl group. The ionic hydroxylation of some hydrocarbons by trifluoroperoxyacetic acid is also able to functionalize positions remote from electronegative groups. These reactions, however, either radical or ionic, are also limited in scope, because complications arise with tertiary hydrogens. See: Frommer, U.; Ullrich, V. *Z. Naturforsch.* **1971**, *26B*, 322. Deno, N. C. "Methods in Free Radical Chemistry"; E. S. Huyser, Ed.; Marcel Dekker: N.Y., 1972; Vol. 3, p 135. Deno, N. C.; Eisenhardt, K. A.; Pohl, D. G.; Spinnelli, H. J.; White, R. C. *J. Org. Chem.* **1974**, *39*, 520. Deno, N. C.; Messer, L. A. *J. Chem. Soc., Chem. Commun.* **1976**, 1051. Deno, N. C.; Jedziniak, E. J.; Messer, L. A.; Meyer, M. D.; Stroud, S. G.; Tomezko, E. S. *Tetrahedron* **1977**, *33*, 2503. Deno, N. C.; Meyer, M. D. *J. Org. Chem.* **1979**, *44*, 3383.
(2) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60.
(3) (a) Rozen, S.; Lerman, O. *J. Am. Chem. Soc.* **1979**, *101*, 2782. (b) *J. Org. Chem.* **1980**, *45*, 672.
(4) There is one pioneering work in the whole chemical literature which deals with the functionalization of certain steroids with CF_3OF and F_2; see ref 5.
(5) Barton, D. H. R.; Hesse, R. H.; Markwell, R. E.; Pechet, M. M.; Rozen, S. *J. Am. Chem. Soc.* **1976**, *98*, 3036.
(6) The reactions were carried out in glass vessels with 2–4 mmol of substrate dissolved in 400 mL of $CHCl_3$–$CFCl_3$ (1:1). The mixtures of F_2 and N_2 were prepared in a vacuum line similar to the one described in the Matheson publication, report number G-115B. The fluorine gas as well as the gauges are also from Matheson. The delivery rate of the F_2/N_2 mixture was usually about 15 cm³/min, but changes in this rate are not of much importance since the solubility of fluorine is poor in the solvents we usually work with (see ref 3b). It is important, however, to ensure a good suspension of the gas bubbles in the solution. This can be achieved with an efficient vibromixer (Chemapec Inc., Hoboken, NJ). The progress of the reactions was monitored by GC (SE-30, 3%). Unless otherwise stated, the reactions were stopped after about 90–95% of the starting material was consumed, and in our case it required 3–6 h. The yields reported in this work are absolute.
(7) All new compounds had the correct composition established by microanalysis. Their spectral data (IR,[19] F and ^1H NMR, and mass spectra) are in excellent agreement with the assigned structures and stereochemistry.

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trans-4-*tert*-butylcyclohexanol *p*-nitrobenzoate (**2**) yields 50% of the trans-fluorinated derivative **4** (mp 136 °C); *cis*-4-methylcyclohexanol *p*-nitrobenzoate (**5**) (600 mg) produces the cis-fluoro compound **7** (mp 109 °C, yield 65%); and *cis*-4-*tert*-butylcyclohexanol *p*-nitrobenzoate (**6**) (700 mg) is converted to *cis*-4-*tert*-butyl-4-fluorocyclohexanol *p*-nitrobenzoate (**8**) in 83% yield, mp 104 °C.

An important feature in these reactions is the very high affinity of the fluorine toward the tertiary hydrogen atom. It is clear that the highest electron density lies at the carbon–hydrogen bond in the 4 position. The high yields and the failure to isolate a monofluoro compound in which the halogen is bonded to carbon other than in position 4 emphasize the high selectivity of this reaction. Even in the case of the bulky *tert*-butyl group, as in **2** and **6**, the fluorine prefers to replace the most sterically hindered hydrogen at the 4 position, stressing the improtance of the electronic factors over the steric ones. An additional important point in these reactions is their complete stereoselectivity. The fluorine atom replaces the tertiary hydrogen with full retention of configuration. Such a substitution might be viewed as a front side attack on the C–H bond, forming a pentacoordinated carbonium ion[8] (see structures A and B in Scheme I). Such transition states should inevitably lead to full retention of configuration, and, indeed, the absolute stereospecificity of our products confirms this mechanism.[9,10]

There has been some intense dispute over the question of whether fluorinations with R_fOF or F_2 are of ionic or radical character. Breslow et al.,[11] for example, suggested that a direct reaction between a hydrocarbon and F_2 generates a pair of radicals, and the product arises from a cage recombination of the carbon radical with the fluorine atom. If such a postulate were true, the respective radicals from the cis reactants **5** and **6** should isomerize, at least to some extent, to the more stable trans isomers, thus forming mixtures of the cis and trans fluoro compounds.

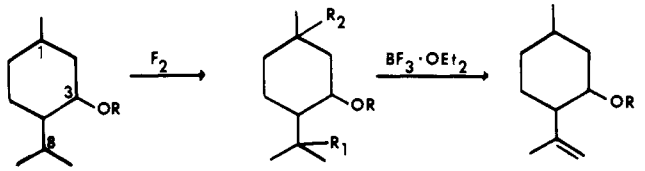
A second interesting observation was made when monitoring the fluorinations of equimolar mixtures of **1** and **2** or of **5** and **6**. The reaction between the *tert*-butyl compounds **2** or **6** and fluorine is much faster than that with the methyl derivatives **1** or **5**. These results, together with the fact that the σ value of the *tert*-butyl group is considerably lower than that of the methyl group, strongly support the ionic electrophillic mechanism for the above reaction. However, one cannot exclude entirely the existence of the radical pathway for reactions with elemental fluorine. When the solvent for the reaction is only trichlorofluoromethane (Freon-11), we are witnesses to a very rapid consumption of the starting material, resulting in the formation of an inseparable mixture of many randomly fluorinated and polyfluorinated products. It is true that at the beginning it is possible to detect the 4-monofluoro derivatives, but they disappear quite rapidly. Adding a small amount of nitrobenzene or performing the reaction in the dark has little effect. When, however, half or more of the Freon is replaced by $CHCl_3$, which substantially increases the polarity of the medium and also serves as a good radical scavenger, the reaction slows down considerably. First, the desired products are formed in increasing yields with little randomly fluorinated and polyfluorinated materials. Only after complete consumption of the starting material do the monofluorinated compounds begin to deteriorate slowly due to a random overfluorination. It seems that in a nonpolar solvent the radical pathway is the preferred mechanism by which the unselective fluorination occurs while in a more polar medium, which can also serve as a radical scavenger, the ionic, selective mechanism predominates. The fluoro derivatives which are thus formed are, of course, to a degree deactivated toward further electrophilic attack. However, reaction with the relatively low concentration of fluorine atoms present is still possible, leading to the already described deterioration.

The ability of the fluorine to react in an electrophilic mode with unactivated sites is unmatched by the other halogens. When suitable substrates, which react as described with F_2, are treated with an excess of Br_2, NBS, $AgSbF_6/Br_2$, $SbCl_5/Cl_2$, boiling SO_2Cl_2, and similar reagents under ionic conditions at room temperature, no reaction takes place, even after 72 h.

Under free-radical conditions (illumination and presence of benzoyl peroxide), 4-methylcyclohexanol *p*-nitrobenzoates (**1** and **5** for example), react slowly with Br_2 and NBS to give many bromine-containing products whose NMR spectra indicate the disappearance of the methyl group and incorporation of bromine mainly into the secondary carbons, resulting in various CHBr groups.

The reaction of fluorine with tertiary hydrogens provides a unique opportunity to introduce double bonds by dehydrofluorination, thus activating molecules toward further chemical transformation at sites which are very difficult, or even impossible, to activate by any other method. Thus, treatment of each of the isomeric fluoro compounds **3** and **7** with $BF_3{\cdot}OEt_2$ produces in about 70% yield the 4-methyl-3-cyclohexenol *p*-nitrobenzoate **9** (Scheme I; mp 87 °C) previously synthesized only by Birch reduction.[12] By the same treatment, and in similar yields, **4** and **8** are transformed to the unknown 4-*tert*-butyl-3-cyclohexenol *p*-nitrobenzoate **10**, mp 71 °C. It is worth noting that the fluorine at the 4 position is stable toward mild saponification (Na_2CO_3 in MeOH at room temperature) so if desired the free fluoro alcohols can be obtained. Thus, hydrolysis of **4** results in *trans*-4-*tert*-butyl-4-fluorocyclohexanol **11**, mp 91 °C.

Although this electrophilic fluorination is quite sensitive to small changes in the electron density of the C–H bond and prefers to attack the tertiary hydrogen which is farthest from an electron-withdrawing center,[5] it is possible to substitute such a hydrogen even if it is close to an electronegative group. This is demonstrated by the reaction of menthol *p*-nitrobenzoate (**12**) (700 mg) with F_2. The reaction is considerably slower in comparison with the 4-alkylcyclohexanols, but the eventual results are similar.



12 **13** $R_1 = F$; $R_2 = H$ **14** $R_1 = R_2 = F$ **15**

12 — **15** $R = COC_6H_4NO_2(P)$

The 8-fluoro derivative **13** was formed in 60% yield (oil), but when excess fluorine was applied again a slow deterioration takes place, and the yield of **13** drops gradually. Because of the presence of the second tertiary hydrogen at position 1, the 1,8-difuoromenthol *p*-nitrobenzoate **14** (mp 124 °C, 10% yield) can also be isolated from all the other randomly polyfluorinated compounds.

Treating **13** with $BF_3{\cdot}OEt_2$ products the *p*-nitrobenzoate of the known isopulegol **15** (40% yield, oil), thus activating the menthol in two steps, at a site that no other reagent is known to be capable of doing.

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(9) The only other example of fluorination with retention of configuration can be found in ref 5. However, the substrates there are steroids, and all the fluoro atoms possess the α configuration. One might have argued that strong steric hindrance from the 18 and 19 methyls controls the stereochemistry of the reactions.

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