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ACTIVATION OF TERTIARY PARAFFINS BY ELEMENTAL FLUORINE

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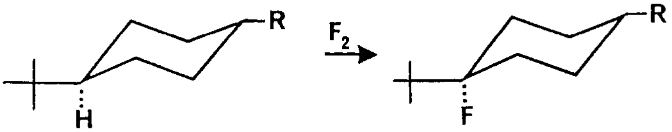
Abstract: Elemental fluroine was found to substitute, in a regio and stereospecific way, tertiary unactivated hydrogens in alkanes - the most unreactive family of organic compounds.

As the name indicates, paraffins[1] constitute a very unreactive class of compounds. They do not possess a single functional group around which reagents can regroup themselves preparatory to performing any of the numerous reactions known to organic chemistry. However, because of the enormous economical importance of the paraffins, large scale industrial reactions, mainly cracking and radical halogenations have been developed. In spite of the continuous challenge for milder regio and stereospecific activation of paraffins, very few new approaches have emerged in the last decade dealing with this problem. One of the directions taken has been radical and electrophilic oxidation with a variety of oxygen based oxidizing agents such as ozone and oxygen[2], peracids[3] and iodine tris (trifluoroacetate)[4]. Another, relatively new, and promising approach is the activation of certain paraffins by organometallic complexes[5,6].

We have found that elemental fluorine can be used for the preparation of various electrophilic fluorinating agents[7]. Contrary to the general belief, however, we have recently shown[8] that it can be used directly , to perform unique and specific electrophilic substitution of hydrogen atoms in some alcohol and carboxylic acid derivatives. We noticed that electronegative oxygenated functions deactivate nearby tertiary hydrogens, so that only those which were well separated from the electron withdrawing group were reactive[8]. It was of interest to see if paraffins, which do not benefit from the selectivity induced by electron withdrawing groups, could also be specifically fluorinated.

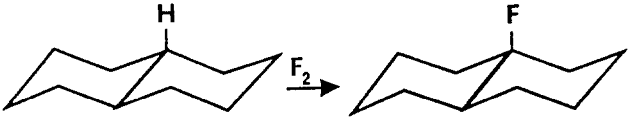
In a typical experiment[9], a stream of 1 to 2% fluorine in nitrogen was passed through a solution of 1 gr. of t-butylcyclohexane (1) in 400 cc of $CFCl_3/CHCl_3$ (1:1) at -75°C. The reaction was stopped when a conversion of about 95% was achieved resulting in a 70% yield of 1-t-butyl-1-fluorocyclohexane (2).



1 R = H 2

7 R = $OCOC_6H_4NO_2(p)$ 8

The reaction with paraffins, as with oxygenated compounds[8a,10], proceeds with a full retention of configuration, as is also evident from both isomers of decalin. Trans-decalin (3) was converted to trans-5-fluoro-decalin (4) in 80% yield, ^{19}F NMR: -177.5 ppm (q, J_{HaxFax} = 30 Hz). Similarly, cis-decalin (5) produced in 90% yield the corresponding cis-fluoro derivative 6, ^{19}F NMR = -140.6 ppm (m, W h/2 = 55 Hz).



3 4

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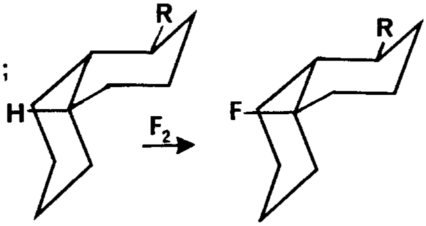
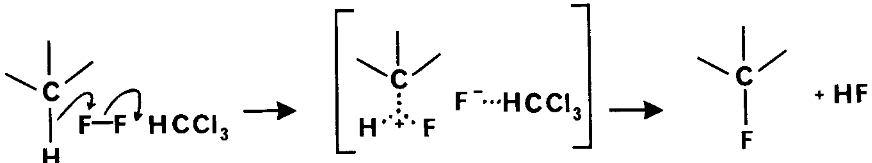


5 R = H 6

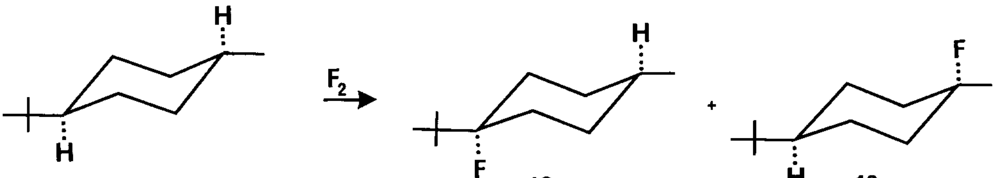
9 R = $OCOC_6H_4NO_2(p)$ 10

As with oxygenated derivatives[8], the fluorination performed under the above conditions is mainly of ionic character. When the medium of the reaction was nonpolar - $CFCl_3$, or pentane for example, an indiscriminate radical fluorination mainly took place and very complicated mixtures were obtained. The chloroform has several roles in determining the mode of the reaction. It increases the polarity of the medium, acts as a radical scavanger and serves as an acceptor, through hydrogen bonding, for the resulting F^- originating from the fluorine molecule. The results can be best explained by initial attraction of the positive end of the polarised F_2 by the tertiary carbon-hydrogen bond which has the highest electron density, resulting in insertion of fluorine into this σ bond through the pentacoordinated carbonium ion A. This intermediate is bound to lead to a product with retention of configuration. A similar mechanism can also be found in electrophilic oxygenations of alkanes, as described by Olah[11].



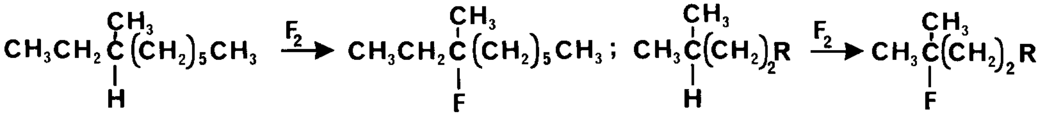
A

When an equimolar mixture of 1 and 7 or of 5 and 9, was treated with F_2, the paraffin reacted faster than the oxygenated compound. Less than 50% conversion of the esters, producing mainly 8 and 10[8a], was achieved when the alkanes had fully reacted. This is in accordance with the electrophilic character of the reaction since the electron withdrawing groups in 7 or 9 reduce the electron density of the tertiary C-H bond in question. A further example, emphasizing the electrophilic character of the reaction, is the fluorination of trans 4-t-butyl-1-methylcyclohexane (11) with F_2. Here again, the electron density of the tertiary C-H bond adjacent to the t-butyl group is higher than that vicinal to the methyl radical and indeed most of the fluorination occured at the former site. The main product was thus identified as 1-t-butyl-1-fluoro-4-methylcyclohexane (12), 60% yield, ^{19}F NMR:-172.5 ppm (t, J = 35 Hz) while the minor one proved to be 4-t-butyl-1-fluoro-1-methylcyclohexane (13), 10% yield, ^{19}F NMR: -153 ppm (m, W h/2 = 95 Hz). Very little difluorination was observed demonstrating again the ionic nature of the reaction, since the incorporation of the electronegative fluorine atom deactivates the second tertiary C-H bond toward further electrophilic attack.



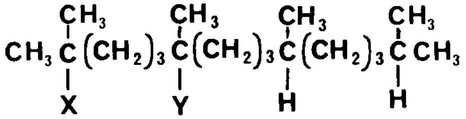
11 12 13

Open-chain paraffins are also suitable for selective fluorination. Although 3-methylnonane (14) has 22 hydrogens, the elemental fluorine when acting as an electrophile, substituted only the single tertiary hydrogen producing 3-methyl-3-fluorononane (15) in more than 60% yield, ^{19}F NMR = -146.1 ppm (octet, J = 21 Hz). As in the alicyclic field, a competitive reaction between 14 and the trichloroethyl ester of 2-methylpentanoic acid (16) was carried out. The tertiary carbon-hydrogen bond of the paraffin was attacked faster so that when all 14 was consumed, about a 50% yield of 17[8b] was obtained, but at 15% conversion only.



$$CH_3CH_2\overset{CH_3}{\underset{H}{C}}(CH_2)_5CH_3 \xrightarrow{F_2} CH_3CH_2\overset{CH_3}{\underset{F}{C}}(CH_2)_5CH_3\ ;\ CH_3\overset{CH_3}{\underset{H}{C}}(CH_2)_2R \xrightarrow{F_2} CH_3\overset{CH_3}{\underset{F}{C}}(CH_2)_2R$$

14 15 16 R=$COOCH_2CCl_3$ 17



$CH_3\overset{CH_3}{\underset{X}{C}}(CH_2)_3\overset{CH_3}{\underset{Y}{C}}(CH_2)_3\overset{CH_3}{\underset{H}{C}}(CH_2)_3\overset{CH_3}{\underset{H}{C}}CH_3$

18 X = Y = H

19 X = F ; Y = H

20 X = H ; Y = F

Only in the case of two different tertiary hydrogens with similar electronic properties, as in 2,6,10,14-tetramethylpentadecane (18), the two possible monofluorinated compounds 19 - NMR: 1.36 ppm (two outer methyls, d, J =22 Hz); ^{19}F NMR: -144.3 ppm, and 20 - NMR: 1.29 ppm (an inner methyl, d, J = 21 Hz); ^{19}F NMR: -143.8 ppm - were isolated in equal yield of 25% each.

It should be noted that in conditions favouring electrophilic reactions, radical fluorination still takes place although at a low rate. Thus if the reaction is not monitored properly, the products will eventually deteriorate and fluorinated tar will be obtained. On the other hand, in nonpolar solvents where the radical pathway is dominant, some specific mono fluorination can still be detected, although in very low yield.

In conclusion, this work presents a new route for regio- and stereospecific activation of branched paraffins by elemental fluorine. This element is not very violent when reacting in an electrophilic mode and is very sensitive to electronic differences in carbon hydrogen bonds. It is even capable of tracing minute differences existing between tertiary hydrogens, either in two different compounds or in the same molecule.

References and Notes

1. From Latin meaning: "not enough affinity".
2. See for example: Mazur, Y.; Zadok, E. Angew. Chem. Int. Ed. 1982, **21**, 303; Cohen, Z.; Mazur, Y. J. Org. Chem. 1979, **44**, 2318; Hellman, T.M.; Hamilton, G.A. J. Am. Chem. Soc. 1974, **96**, 1530; Barton, D.H.R.; Gastiger, M.J.; Mortherwell, W.B. J. Chem. Soc., Chem. Commun. 1983, 41.
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7. See for example: Rozen, S.; Lerman, O. J. Org. Chem. 1980, **45**, 672; Lerman, O.; Rozen, S. J. Org. Chem. 1980, **45**, 4122.
8. a) Rozen, S.; Gal, C.; Faust, Y. J. Am. Chem. Soc. 1980, **102**, 6860. b) Gal, C.; Ben-Shushan, G.; Rozen, S. Tet. Lett. 1980, 5067. c) Gal, C.; Rozen, S. J. Flu. Chem. 1982, **20**, 689.
9. More details about the experimental procedure and some words of caution about working with F_2, which is a very strong oxidising and corrosive material, can be found in references 7 and 8. The analytical data of the new fluorinated compounds described here are in excellent agreement with the assigned structures and stereochemistry. The ^{19}F NMR spectra were recorded with a Bruker WH-90 at 84.67 MHz, $CFCl_3$ serving as internal standard.
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