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PRELIMINARY NOTE

THE EFFECT OF TWO ELECTRON-WITHDRAWING GROUPS ON REMOTE
TERTIARY HYDROGENS SUSCEPTIBLE TO ELECTROPHILIC FLUORINATION
USING F_2

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SUMMARY

    The direct electrophilic fluorination of unactivated remote
tertiary hydrogens is effected by the number, nature and
distance of electron-withdrawing groups. The effect of these
groups on reducing electron density of the tertiary C-H bond
seems to be additive. The more remote these groups are from
the reaction center, the higher the yield of the fluorination.

    Reactions on remote tertiary unactivated hydrogens are
very rare and usually of radical nature. Recently, [1,2] we
have demonstrated that elemental fluorine can substitute such
tertiary hydrogens by the uncommon electrophilic attack on a
sp^3 carbon-hydrogen bond [3]. The presence of an electronega-
tive group in the molecule has an important role in the
reaction. The stronger the electron-withdrawing group is, or
the nearer it is to the tertiary hydrogen, the more difficult
the electrophilic fluorination becomes. These effects can be
impressively transferred through several single carbon-carbon
bonds. Therefore, it is of interest to determine the effect of
two electronegative groups on the unactivated tertiary
hydrogens. Will this affect or even prevent the reaction by
lowering the electron density of a distant tertiary C-H bond?

Between molecules containing one or two electronegative groups
at the same distance from the reacting center, EHT calculations
do not clearly indicate that there will be a considerable
difference in the net charge on the tertiary hydrogens.*

When there is only one methylene separating the tertiary
site from each electronegative group, as in dimethyl-3-methyl-
glutarate (I), the reaction was very slow. Eventually, only 2%
of the desired fluoro derivative II was detected, along with
much fluorinated tar. This lack of selectivity indicates that
fluorine was behaving in the radical mode, despite the
discouraging conditions for such radical reactions [1]. By
comparison, the mono functional molecule — 1,1,1-trichloro-
ethyl iso-valerate (III) gave about 30% of the expected
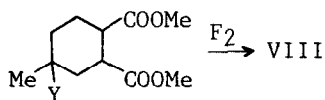fluorinated product IV [2].

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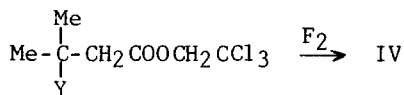\underset{\underset{Y}{\overset{\overset{Me}{|}}{|}}{\text{MeOOC(CH}_2)_m\text{C(CH}_2)_n\text{COOMe}} \xrightarrow{F_2} \text{II or VI}
$$
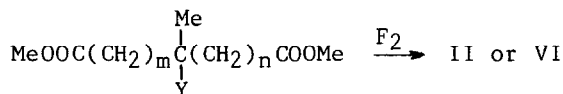
I.   Y=H; m=n=1
II. Y=F; m=n=1
V.   Y=H; m=1; n=2
VI. Y=F; m=1; n=2

VII. Y=H
VIII. Y=F

$$
\text{Me}-\underset{\underset{Y}{|}}{\overset{\overset{Me}{|}}{C}}-\text{CH}_2\text{COOCH}_2\text{CCl}_3 \xrightarrow{F_2} \text{IV}
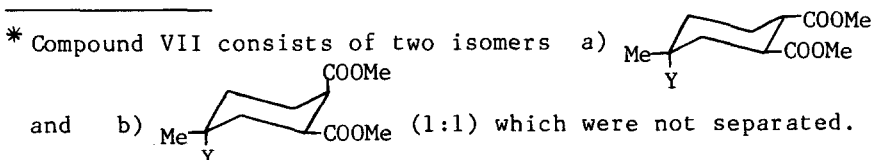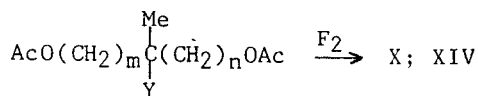$$

III. Y=H
IV. Y=F

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* The results of some MO calculations on compounds possessing
  remote tertiary hydrogens in connection with electrophilic
  fluorinations will be published elsewhere.

Placement of one of the electronegative groups one methylene
group further from the reaction center, as in the dimethyl
3-methyladipate (V), increases the yield of the corresponding
fluoro derivative VI to 10%. In 1,2-dicarbomethoxy-4-methyl
cyclohexane (VII)[*], the tertiary hydrogen is separated from
the two electronegative groups by the same number of bonds as
in the case of the adipic acid derivative V. The fluorination,
however, proceeds more readily and then the corresponding
fluorinated product VIII is obtained in 25% yield. Obviously,
not only electronic factors dominate this type reaction. The
practically unrestricted movement of the two electronegative
ends in compounds like I and V can hinder the tertiary C-H
bond; this decreases the rate of the selective electrophilic
fluorination and enables the slow radical reaction to take its
toll on the substrate, thereby lowering the yield.

Replacing the carbomethoxy group by a protected hydroxylic
one usually results in more difficult electrophilic fluorina-
tion and consequently lower yields [2]. Even so, increasing of
the distance between the reacting center and the electronega-
tive groups by one more methylene unit as in V → IX such as 1,5-
diacetoxy-3-methyl pentane (IX) (m=n=2) increases the yield of
the fluorinated product X to 37%. When IX is compared to a
molecule having only one electronegative group such as the
p-nitrobenzoate of 3-methyl-1-butanol (XI), the yield of the
tertiary fluorinated product XII increases from 37 to 60% [2].
Insertion of one additional methylene unit between the reacting
center and the electronegative ends, as in 1,6-diacetoxy-3-
methyl hexane (XIII) (m=2, n=3) further increases the yield of
the fluorination product XIV to 52%.

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* Compound VII consists of two isomers a) [structure: Me—(cyclohexane with Y)—COOMe, COOMe]

and b) [structure: Me—(cyclohexane with Y)—COOMe, COOMe] (1:1) which were not separated.

The tertiary axial hydrogen (Y=H) is substituted by fluorine
in the same rate for both isomers, so the fluorinated
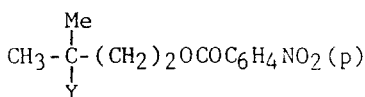product VIII also consists of the above 1:1 mixture (Y=F).

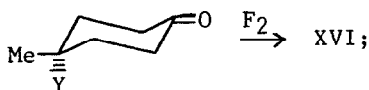$$AcO(CH_2)_m \overset{\overset{\displaystyle Me}{\displaystyle |}}{\underset{\underset{\displaystyle Y}{\displaystyle |}}{C}} (CH_2)_n OAc \overset{F_2}{\longrightarrow} X; \ XIV$$

IX. Y=H; m=n=2

X. Y=F; m=n=2

XIII. Y=H; m=2; n=3

XIV. Y=F; m=2; n=3

$$CH_3 - \overset{\overset{\displaystyle Me}{\displaystyle |}}{\underset{\underset{\displaystyle Y}{\displaystyle |}}{C}} - (CH_2)_2 OCOC_6H_4NO_2 \ (p)$$
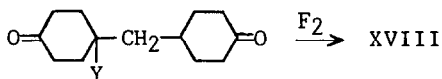
XI. Y=H

XII. Y=F

XV. Y=H

XVI. Y=F

XVII. Y=H

XVIII. Y=F

The electrophilic fluorination can also be performed in the presence of a ketone, although generally it seems that the yields are somewhat lower than in the case of the acid or the alcohol derivatives. This is demonstrated by the reaction of 4-methylcyclohexanone (XV) with elemental fluorine, producing the 4-methyl-4-fluorocyclohexane (XVI) in 20% yield. However, when a second carbonyl group is attached even far from the tertiary reaction site, as in 4,4'-methylene-bis(cyclohexanone) (XVII), the yield of the fluorinated product XVIII (m.p.=35°) is halved to only 10%.

It seems that this unique electrophilic fluorination is dependent on the nature, distance and the number of the electrophilic groups present in a given molecule.
All the fluorination reactions were carried out in glass vessels. About 5-7 mmol of the substrate were dissolved in 400 ml of $CHCl_3-CFCl_3$ (1:1) and cooled to -75°C. About 8-10% of HF-free fluorine, diluted with nitrogen, was passed through the reaction mixtures for the compounds with m,n<2 and 4-5% of HF-free F_2 in N_2 was used for the rest of the compounds. A good suspension of the gas bubbles was achieved with a vibromixer. The reactions were monitored by

GC and usually stopped when conversion of about 90-95% was achieved. All the fluorinated compounds are new liquids unless otherwise stated and, with the exception of II, which was not analytically purified, had the correct composition established by microanalysis. Their spectral data, IR, ^{19}F and ^{1}H NMR are also in excellent agreement with the assigned structures. The identification of compound X can serve as an example for the rest of the compounds: the ^{19}F NMR shows a signal at $\emptyset^* = 145.7$ ppm (octet, J = 21 Hz) while the tertiary methyl on the ^{1}H NMR spectrum is shifted by 0.45 ppm to lower field than in the starting material and characteristicly split by the vicinal fluorine ($\delta = 1.41$ ppm, d, $J_{FH} = 21$ Hz).

1   Rozen, S.; Gal, C.; Faust, Y. J. Am. Chem. Soc. 1980, 102, 6860.

2   Gal, C.; Ben-Shoshan, G.; Rozen, S. Tet. Lett. 1980, 21, 5067.

3   Protons from very strong acids or the hydroxyl moiety from aromatic peracids can, to some extent, also electrophil-ically attack a tertiary carbon hydrogen bond. See a) Olah, G. A.; Halpern, Y.; Shen, J.; Mo, Y. K. J. Am. Chem. Soc. 1971, 93, 1251.   b) Muller, W.; Schneider, H. J. Ang. Chem. (Int. Ed.) 1979, 18, 407.