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^{19}F NMR ANALYSES OF SOME CYCLOPROPANE DERIVATIVES*

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SUMMARY

Structural assignments of all possible diastereoisomers of 1-chloro-2-ethoxy-1-fluoro-alkylcyclopropanes have been achieved through their ^{19}F NMR spectra. The previously unreported effect of an ethoxyl group on the fluorine signal has been studied and found to promote in most cases a shielding effect in the vicinal cis-fluorine and a deshielding effect when trans to this halogen.

INTRODUCTION

Empirical structure-spectroscopic data correlations derived from the application of high resolution NMR spectroscopy have proved to be of great value in structural studies of organic molecules. In this context, during our recent work on fluorinated pheromone mimics of insect sex pheromones [1,2], several chlorofluorocyclopropane derivatives have been prepared and their ^{19}F NMR spectra recorded in order to 1) assign unequivocally the right structure to each of the diastereoisomers obtained in the synthesis, and 2) establish some possible structure-spectral parameters correlations. Assignment of the signals has been based on vicinal H-F coupling constant magnitudes [3,4] and chemical shifts reported in the literature [5].

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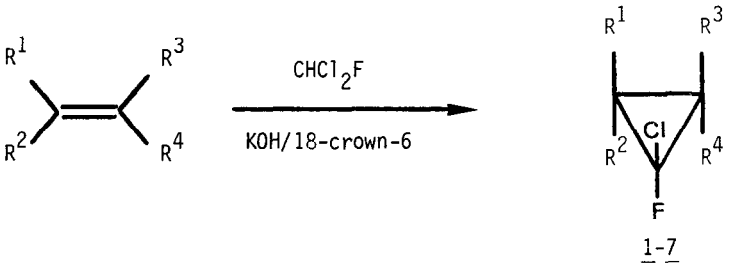
RESULTS AND DISCUSSION

The chlorofluorocyclopropanes (1-7) have been prepared in good yields by stereospecific addition of chlorofluorocarbene, generated in situ from dichlorofluoromethane and potassium hydroxide, to the corresponding vinyl ethers under PTC conditions [6] (Table 1). Starting vinyl ethers were used, generally, as mixtures of Z/E isomers; only entry 7 was repeated carrying out the reaction with the stereoisomerically pure E isomer in order to confirm the initial structural assignment of the diastereoisomers 7a-d. Most vinyl ethers have been prepared by dehydroethoxylation of the corresponding acetals in the presence of p-toluenesulfonic acid/quinoline [7]. 2-Ethoxyprop-1-ene was obtained by decarboxylation of 3-ethoxycrotonic acid [7] and immediately distilled into the cyclopropanation reaction mixture.



1-7

TABLE 1

Cyclopropane derivatives (1-7) prepared by cyclopropanation of vinyl ethers

Entry	Vinyl ether	Reaction time (h)	Reaction products	Yield (%)
1	ethyl vinyl ether	24	1a-b	76
2	2-ethoxyprop-1-ene	2	2a-b	64
3	1-ethoxy-2-methylprop-1-ene	3.5	3a-b	78
4	1-ethoxyprop-1-ene	5.5	4a-d	80
5	1-ethoxybut-1-ene	6	5a-d	80
6	1-ethoxydec-1-ene	7	6a-d	61
7	3-ethoxypent-2-ene	4	7a-d	82

TABLE 2

Assignment of the ^{19}F NMR parameters to compounds 1a-7d

Comp.	R^1	R^2	R^3	R^4	Chem. shift	Mult*	Coupling constants (Hz)
1a	H	H	OEt	H	62.0	ddd	18.4, 12.7, 7.6
1b	H	H	H	OEt	83.0	ddd	19.7, 9.3, 1.5
2a	H	H	OEt	Me	65.2	ddt	17.1, 7.9, 3.4
2b	H	H	Me	OEt	74.1	ddq	20.5, 9.0, 2.6
3a	Me	Me	OEt	H	68.8	dhept	14.0, 2.3
3b	Me	Me	H	OEt	85.1	b	
4a	Me	H	OEt	H	58.6	ddq	31.9, 18.4, 2.6
4b	H	Me	H	OEt	75.9	dm	13.3
4c	Me	H	H	OEt	76.4	dm	23.9
4d	H	Me	OEt	H	57.3	ddq	22.5, 13.1, 2.5
5a	Et	H	OEt	H	57.7	ddq	32.1, 17.7, 1.7
5b	H	Et	H	OEt	75.5	dm	13.3
5c	Et	H	H	OEt	75.0	dm	22.0
5d	H	Et	OEt	H	56.25	ddq	25.2, 12.6, 1.5
6a	Oct	H	OEt	H	58.2	ddt	31.9, 16.9, 1.5
6b	H	Oct	H	OEt	74.75	dm	13.6
6c	Oct	H	H	OEt	75.0	dm	23.1
6d	H	Oct	OEt	H	56.2	ddt	22.5, 13.1, 2.0
7a	Me	H	OEt	Et	62.25	dq	22.2, 2.6
7b	H	Me	Et	OEt	85.2	b	
7c	Me	H	Et	OEt	69.1	d	24.2
7d	H	Me	OEt	Et	79.8	b	

*dm stands for a doublet showing secondary splitting which could not be determined on a first order analysis.

Signals of the ^{19}F NMR spectra (referred to trifluoroacetic acid in an internal sealed capillary tube, positive values for upfield shifts) have been assigned (Table 2) on the basis of the following determining factors:

i) In 1-chloro-1-fluorocyclopropanes, methyl groups* in cis position relative to the fluorine exert a shielding effect (ranging from 8.5 to 12.5 ppm; estimated average 11 ppm), whereas in a trans relationship promote a deshielding effect (-3.6 to -10.5 ppm; estimated average -6 ppm) [5].

ii) In fluorocyclopropanes $^{3}J_{H-F}$ cis ($\phi \simeq 0°$) is generally larger than the corresponding $^{3}J_{H-F}$ trans ($\phi \simeq 120°$) [8], as a consequence of the known dependence of $^{3}J_{H-F}$ on the bond angle θ, the dihedral angle ϕ [3] and the electronegativity of substituents [4].

On the other hand, as shown in Scheme 1, from the average shielding increments promoted by alkyl groups derived from literature data [5] and the chemical shifts of chloro-fluoro-ethyl- and chloro-fluoro-dimethyl-cyclopropane, the previously unreported absorption for the parent 1-chloro-1-fluorocyclopropane (CFCP) can be estimated as 63.5 ppm.

Since the influence of an ethoxyl group on the ^{19}F absorption on 1-chloro-1-fluoro-alkylcyclopropanes has not been previously described, we have deduced the shielding effects for this group from our data of the pair of isomers 3, due to the possible unambiguous assignment in this case (Scheme 2). The low field absorption at δ 68.8 ppm was attributed to the cis isomer (F and EtO in trans relationship) on the basis of the coupling constants of 3a (14.0 Hz) and 3b (broad signal). Comparison of the chemical shift values of 3a and 3b with that of 1-chloro-1-fluoro-2,2-dimethyl-cyclopropane (65.5 ppm) indicates that substitution of ethoxyl for a cis H resulted in a shielding effect of 19.6 ppm, whereas for a trans H the effect is only 3.3 ppm. Further proof of the same effects can be found in other cases (see below).

Furthermore, from the chemical shifts comparison of the pair of isomers 1 with those of 3, configurational assignment to diastereoisomers 1a and 1b was made. From the absorptions of 1a and 1b and the CFCP calcula-

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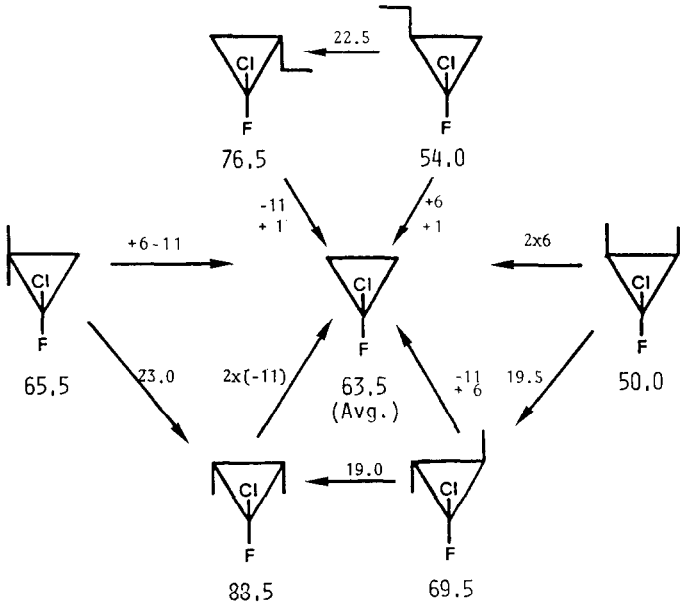
*From our results in Table 2 (cf. 4a-d and 5a-d) an average of 1 ppm deshielding effect is derived from substitution of a methyl for an ethyl group.

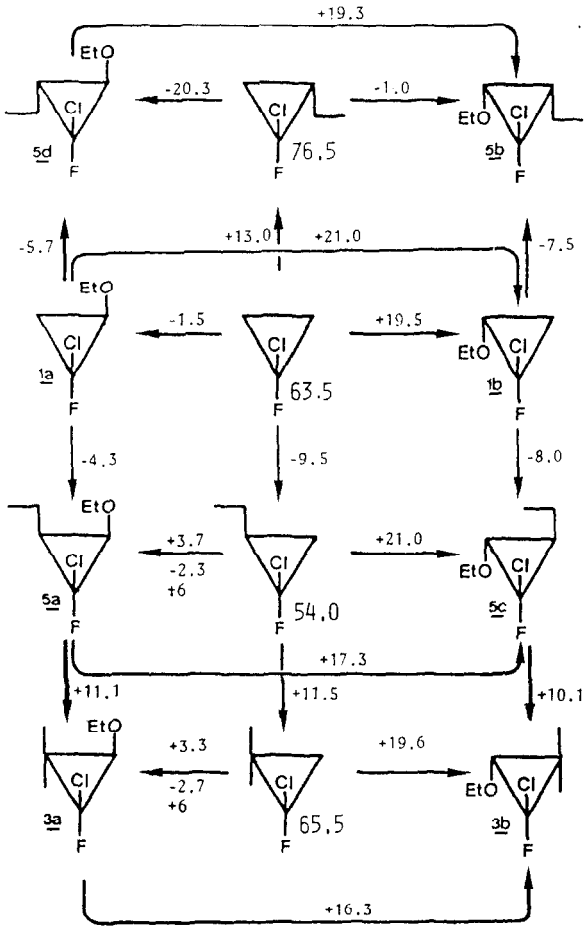


Scheme 1

ted value (63.5 ppm), a shielding increment of 19.5 ppm for introduction of an EtO group cis to the F and an almost negligible deshielding effect (-1.5 ppm), when both groups were in trans relationship, were inferred.

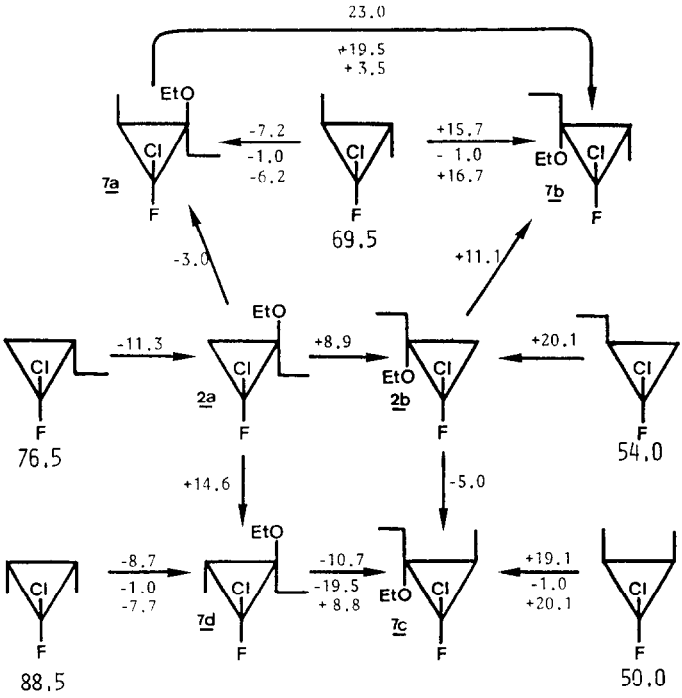
In the pair of isomers 2 (Table 2) the high field signal at δ 74.1 ppm was attributed to the trans isomer 2b (F and EtO in cis relationship) by comparison of the observed coupling constants with those of 1b, and the 65.2 ppm signal, showing coupling constants that suit better those of 1a, was assigned to 2a. As shown in Scheme 3, the results point out a ca. 20 ppm shielding effect for introduction of an EtO group in cis position relative to fluorine, in an alkyl substituted carbon (geminal substitution in the following discussion), an 11 ppm deshielding effect for trans geminal substitution, and a 9 ppm chemical shift difference (CSD) for the cis/trans interchange of substituents orientation (δ_{2b}-δ_{2a}).

For structural assignment of compounds 7a-d an independent synthesis of the pair 7c-d from pure (E)-3-ethoxypent-2-ene was undertaken [9]. The low field doublet at δ 69.1 ppm with a cis coupling constant ($^3J_{H-F}$ 24.2 Hz) was attributed to 7c and the high field broad absorption to 7d. By the



Scheme 2

same token, the 62.25 ($^3J_{H-F}$ 22.2 Hz) and 85.2 signals were assigned to 7a and 7b respectively. As in the previous case, chemical shift values for the pair of isomers 7c-7d point to effects of the same magnitude as those described above for 2a and 2b, taking into account the CSD for the methyl group (19.5 ppm) shown in Scheme 1. The CSD for ethoxyl/alkyl geminal inversion obtained for 2a-2b and 7c-7d (ca 9 ppm) would lead to a CSD for the pair 7a-7b of 28.5 ppm (9.0 plus 19.5 ppm effect due to the methyl group), whereas the observed experimental value is 23.0 ppm. We have



Scheme 3

rationalized this upfield shift (ca 6 ppm) as promoted by the simultaneous presence of the ethoxyl, chlorine and alkyl groups on the same side of the cyclopropane ring. In fact, the same effect was found in other compounds with the same substitution pattern (3a-6a). On the other hand, from the values depicted in Scheme 3, the average shielding effect for introduction of an EtO group in trans to the F, in an alkyl substituted carbon, may be estimated as -10 ppm.

As presented in Table 3, for compounds 4a-d we attributed, on the basis of the coupling constants, structure a (the most deshielded calculated signal) to the low field absorption with largest vicinal coupling constants (two cis $^{3}J_{H-F}$) and, conversely, b (the most shielded calculated signal) to the high field absorption with lower coupling constants (two trans $^{3}J_{H-F}$). On the other hand, the decrease of the coupling constants values induced by electronegative substituents, like ethoxyl, over geminal hydrogens [5], led us to assign the remaining high field absorption to

TABLE 3

Calculated and experimental absorptions for compounds 4

Isomer	Parent value	Substituent shielding effects*	Chemical shifts (calcd.)	(found)
a	63.5	- 6- 1 (- 7)	56.5	58.2
b	63.5	+11+20 (+31)	94.5	75.9
c	63.5	+20- 6 (+14)	77.5	76.4
d	63.5	+11- 1 (+10)	73.5	57.3

*cis-Me, +11; trans-Me, -6; cis-EtO, +20; trans-EtO, -1 (see text)

structure c and the low field signal to structure d. Structural assignments for the isomers of 5 and 6 were based on the direct correspondence of their practically identical chemical shifts and coupling constants with those of 4.

Examination of the CSD depicted in Scheme 2 pointed out a value of ca 20 ppm for introduction of an ethoxyl substituent in an unsubstituted carbon of the cyclopropane ring and in cis relationship to F (cf. 1b with the parent compound CFCP, 5c with 2-ethyl-CFCP and 3b with 2,2-dimethyl-CFCP), an identical value to that found in the previously discussed case of geminal substitution (see above). Similarly, the estimated effect for the corresponding trans relationship is ca -2 ppm, by taking into account the 6 ppm correction for the above mentioned steric arrangement (cf. 1a with CFCP, 5a with 2-ethyl-CFCP and 3a with 2,2-dimethyl-CFCP). Nevertheless, the chemical shifts of 5b and 5d give rise to a notorious deviation of the above pattern, when compared with the literature value for 2-ethyl-CFCP, although the CSD between 5b and 5d (19.3 ppm) is in good agreement with those found for the other pairs of isomers (21.0 ppm for compounds 1, 16.3 for 3 and 17.3 for 5a-5c).

In conclusion, we have found that the shielding effect generally promoted by the introduction of an ethoxyl group in 1-chloro--1-fluorocyclopropane derivatives in a cis relationship to the fluorine

amounts to ca 20 ppm. Conversely, the effect of the incorporation of an ethoxyl moiety trans to the fluorine depends on the presence of alkyl substituents in the cyclopropane ring. Deshielding effects of around 2 and 10 ppm were observed when that incorporation took place in vicinal and geminal positions to the alkyl groups, respectively. The simultaneous presence of ethoxyl, chlorine and alkyl substituents on the same side of the cyclopropane ring may require the introduction of a correction of ca 6 ppm, to account for the deviation observed from the estimated chemical shift values.

EXPERIMENTAL

Infrared spectra were obtained on a Perkin Elmer 257 spectrometer. ^{1}H NMR spectra were recorded on a Bruker WP80SY at 80 MHz using TMS as internal standard. ^{19}F NMR spectra were determined on a Bruker WP80SY or on a Varian XL200 operating at 75.39 and 188.15 MHz respectively, using trifluoroacetic acid as internal standard. Chemical shifts are reported in δ scale (ppm) and positive absorptions are upfield from the reference signal. Elemental analyses were measured on a Carlo Erba 1106.

General procedure for the preparation of 1-chloro-2-ethoxy-1-fluoro-3-alkyl cyclopropanes 1-7

Cyclopropanes 1-7 have been prepared by the cyclopropanation reaction described by Y. Bessière *et al.* [6] using longer reaction times depending on the substrate (see Table 1). Control of the extent of the reaction was carried out by NMR analyses.

1-Chloro-2-ethoxy-1-fluorocyclopropanes 1a-b

From ethyl vinyl ether, compounds 1a-b were prepared in 76% yield. B.p. 53-55°/120 Torr. IR (CCl_4) ν 1385 (C-F), 1210 (C-O) cm^{-1} ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J=7.02 Hz, 3H, $OCH_2\underline{CH}_3$), 1.1-1.9 (complex, 2H, $CH\underline{CH}_2C$), 3.3-3.9 (complex, 3H, $\underline{CH}O\underline{CH}_2CH_3$). Elemental analysis: Calcd. for C_5H_8ClFO: C, 43.47; H, 5.79. Found: C, 43.88; H, 5.99.

1-Chloro-2-ethoxy-1-fluoro-2-methylcyclopropanes 2a-b

3-Ethoxycrotonic acid (0.78 g, 6 mmole) was placed in a distilling flask and heated at 160°. After sublimation, the acid was decarboxylated to yield pure 2-ethoxy-prop-1-ene [7]. The enol ether was directly collected over a mixture of Freon 21 (5 ml), 55% KOH solution (9 ml) and 18-crown-6 (55 mg), previously cooled at 0°C. After 2 h reaction, water was added to dissolve the precipitate, the layers were separated and the organic phase distilled from potassium carbonate to yield 0.279 g (54% overall yield from the acid) of cyclopropanes 2a-2b. In another run a 64% yield of 2a-b was obtained from isolated vinyl ether. B. p. 65-67°/80 Torr. IR (CCl_4) ν 1385 (C-F), 1215 (C-O) cm^{-1} ^1H NMR ($CDCl_3$) δ 1.2 (t, J=6.6 Hz, 3H, $OCH_2\underline{CH_3}$), 1.6 (m, 3H, $CH_2\underline{CCH_3}$), 1.0-1.5 (m, $\underline{CH_2}C$).

1-Chloro-2-ethoxy-1-fluoro-3,3-dimethylcyclopropanes 3a-b [7]

Yield 78%. B. p. 67-70°/100 Torr. IR (CCl_4) ν 1395, 1120 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.25 (complex, 9H, $3x\underline{CH_3}$), 2.95 (s, 1H, $\underline{CH}$ of compound 3a), 3.1 (d, J=12.0 Hz, 1H, $\underline{CH}$ of compound 3b), 3.6 (q, J=6.8 Hz, 2H, $O\underline{CH_2}CH_3$).

1-Chloro-2-ethoxy-1-fluoro-3-methylcyclopropanes 4a-d

Yield 80%. B. p. 60-62°/60 Torr. IR (CCl_4) ν 1390, 1130 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.1 (complex, 3H, $\underline{CH_3}CH$), 1.2 (t, J=6.8 Hz, 3H, $CH_2\underline{CH_3}$), 1.6 (complex, 1H, $\underline{CH}$), 3.2-3.9 (complex, 3H, $\underline{CH_2}O$ and $\underline{CH}O$).

1-Chloro-2-ethoxy-1-fluoro-3-ethylcyclopropanes 5a-d

Yield 80%. B. p. 43-45°/65 Torr. IR (CCl_4) ν 1390, 1130 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.05 (t, J=7.2 Hz, 3H, $CCH_2\underline{CH_3}$), 1.23 (t, J=7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.5 (complex, 3H, $\underline{CH}$ and $CH\underline{CH_2}CH_3$), 3.25-3.9 (complex, 3H, $\underline{CH_2}O$ and $\underline{CH}O$). Elemental analysis: Calcd. for $C_7H_{12}ClFO$: C, 50.45; H, 7.20. Found: C, 50.19; H, 7.12.

1-Chloro-2-ethoxy-1-fluoro-3-octylcyclopropanes 6a-d

Yield 61%. B. p. 90-95°/0.55 Torr. IR (CCl_4) ν 2960, 2930, 2860, 1290 cm^{-1} ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, $CH_2\underline{CH_3}$), 1.02-1.7 (b, 21H, $CC\underline{H_2}C$, $OCH_2\underline{CH_3}$ and $C\underline{CH}CH_2$), 3.3-3.9 (complex, 3H, $\underline{CH_2}O$ and $\underline{CH}O$). Elemental analysis: Calcd. for $C_{13}H_{24}ClFO$: C, 62.40; H, 9.60. Found: C, 62.72; H, 9.91.

1-Chloro-2-ethoxy-2-ethyl-1-fluoro-3-methylcyclopropanes 7a-d

Yield 82%. B. p. 70-75°/80 Torr. IR (CCl_4) ν 2980, 2880, 1150, 1070 cm^{-1} ^1H NMR ($CDCl_3$) δ 0.85-1.30 (complex, 9H, 3xCH_3), 1.30-2.10 (complex, 3H, CCH_2CH_3 and $CHCH_3$), 3.35-3.80 (complex, 2H, OCH_2CH_3). Elemental analysis: Calcd. for $C_8H_{14}ClFO$: C, 53.31; H, 7.83. Found: C, 53.28; H, 7.81.

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