Conformational Studies on 2-Fluoro-1,2-disubstituted Ethanes by NMR Spectroscopy. Influence of Electronegativity on Vicinal Proton–Proton and Fluorine–Proton Coupling Constants

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The analysis of the ABKX spectra of thirteen compounds of the series RC(H-K)(F-X)C(H-A)(H-B)X gave the four vicinal proton–proton and fluorine–proton coupling constants. These coupling constants of conformationally mobile structures were used (i) to calculate the populations of the rotational states of the —CHF—CH$_2$— bond, (ii) to calculate the vicinal *trans* proton–proton $J(\mathrm{HH})^t$ and *gauche* and *trans* fluorine–proton coupling constants $J(\mathrm{FH})^g$ and $J(\mathrm{FH})^t$ and (iii) to give the unambiguous assignment of protons H-A and H-B. The dependence of the *gauche* and *trans* coupling constants with substituent electronegativity is explored. The results extend known correlations towards smaller electronegativity values. More quantitatively, the results and those in the literature, excluding those where deformations of torsional or bond angles occur, give a good fit of the data: a linear fit for $J(\mathrm{HH})^t = 15.0–0.77\ \Sigma\ (\Delta E)$, an exponential fit for $J(\mathrm{FH})^g = 15.35 \exp\ [-0.266\ \Sigma\ (\Delta E)]$ and a linear fit for $J(\mathrm{FH})^t = 65.75 - 7.52\ \Sigma\ (\Delta E)$, where $\Sigma\ (\Delta E)$ is the sum of the electronegativity difference between hydrogen and the six atoms or groups on the CH—CF fragment.

INTRODUCTION

Karplus's theoretical work[1] has established from valence bond calculations that vicinal proton coupling constants, $^3J(\mathrm{HH})$, in the unsubstituted ethane molecule depend mainly on the torsional angle between the coupled protons, according to the so-called Karplus equation (or trigonometrically related equations): $J = A \cos 2\phi - B \cos \phi + C$. It was also shown that the coupling constants of the H—C—C′—H skeleton in substituted ethanes depend on a variety of other molecular parameters: the electronegativity of the substituents attached to C and C′, the bond angles $\theta = \mathrm{HCC'}$ and $\theta' = \mathrm{CC'H}$, the CC′ bond lengths, molecular vibrations, etc.[1b] The electronegativity of the substituents is an important factor in determining the magnitude of vicinal coupling constants.[2] Most of the vicinal proton coupling constants, $^3J(\mathrm{HH})$, decrease with increasingly electronegative substituents.[2,3] Electronegative groups, when not in a *trans*-coplanar relationship with respect to the coupled protons, have been found to increase, rather than decrease, the magnitude of a vicinal *gauche* coupling.[2,4–6] In some cases (1,1,2-trisubstituted ethanes), the substituent effect has been described by distortions from regular geometry, which could result from steric effects between bulky groups or repulsion between the electric dipoles of polar groups.[7]

Populations of the three rapidly exchanging staggered rotamers around the C—C′ bond in conformationally mobile structures can be obtained from the *gauche* J^g ($\phi = 60°$) and *trans* J^t ($\phi = 180°$) coupling constants. These values were derived from the previously studied dependence of $^3J(\mathrm{HH})$ on the dihedral angle and the electronegativity.[6] For instance, for studies of rotamer distribution around the C-α,C-β bond (conformational states of the side-chain) in α-amino acids, RC-βH$_2$C-αH(NH$_3^+$)COO$^-$, several sets of J^g and J^t values were used, depending on the degree of reliability of the model chosen by the authors: 2.32 and 13.70,[8] 2.60 and 13.56,[9] 3.28 and 11.90,[10] 3.25 and 12.40,[11] 3.38 and 12.90[12] and 3.55 and 13.90.[13]

Empirical and theoretical evidence confirms that the guidelines previously proposed for $^3J(\mathrm{HH})$ apply equally well for vicinal F–H coupling constants, as follows.

(i) The dependence of $^3J(\mathrm{FH})$ on the electronegativities of the substituents on the CH—CF

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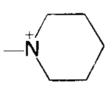
Table 1. ^1H **chemical shifts (δ), in ppm from TMS.** ^{19}F **chemical shifts (δ) in ppm from** $CFCl_3$ **(positive values are downfield from the reference) and coupling constants in Hz [vicinal** ^3J**(H-A, H-K) [*J*(AK)],** ^3J**(H-B, H-K) [*J*(BK)],** ^3J**(F, H-A) [*J*(AF)] and** ^3J**(F, H-B) [*J*(BF)], and geminal** ^2J**(H-A, H-B) [*J*(AB)] and** ^2J**(F, H-K) [*J*(KF)]]**

Compound	R	X	δ_A	δ_B	δ_K	$^3J(AK)$	$^3J(BK)$	$^2J(AB)$	δ_F	$^3J(AF)$	$^3J(BF)$	$^2J(KF)$
1	$p\text{-}CH_3C_6H_4$	Cl	3.73	3.63	5.52	8.0	3.7_2	−12.1	−177.8	15.2	26.2	47.1
2	C_6H_5	Cl	3.66	3.58	5.42	7.8_4	3.8	−12.1	−179.6	15.4_6	25.5_5	47.2
3	$p\text{-}FC_6H_4$	Cl	3.72	3.62	5.50	7.5	4.1	−12	−177.2	15.3	23.8_5	46.7
4	$p\text{-}ClC_6H_4$	Cl	3.69	3.62	5.51	7.4	4.1	−12.1	−179.6	16.0	24.1	46.7
5	$p\text{-}BrC_6H_4$	Cl	3.71	3.63	5.50	7.3	4.4	−12	−180.1	15.6_4	22.9_7	46.7
6	C_6H_5		3.72	3.49	6.20	10.3	1.7	−14.5	−176.4	13.8	35.6	49.6
7	$o\text{-}ClC_6H_4$	Br	3.73	3.57	6.00	7.6	2.9	−11.5	−182.6	19.0	27.6_8	46.0
8	$o\text{-}BrC_6H_4$	Br	3.75	3.56	5.90	7.6	2.5_6	−11.5	−184.3	19.0	28.1	46.5
9	CH_3	COOEt	2.71	2.52	5.10	7.7	4.8	−15.5	−173.5	16.0	26.5	47.0
10	COOEt	COOEt	2.95	2.95	5.30	6.5	5.0	−5.3	−191.8	24.0	24.0	47.4
11	C_6H_5	COOEt	3.01	2.77	5.90	9.0	4.5	−15.5	−174.2	15.5	30.5	46.0
12	COOH	CH_3	1.96	1.84	4.90	6.5	4.5	−7.5	−189.3	24.9	24.9	48.0
13	COOEt	C_6H_5	3.20	3.11	5.05	4.5	7.5	−14.5	−190.7	26.5	24.5	47.5

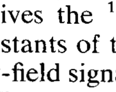
fragment measured in the series $CH_3CF{<}^{X}_{Y}$ and $CF_3\text{—}CH{<}^{X}_{Y}$ (where the average vicinal coupling constant $^3J(FH)^{av} = \frac{1}{3}[J(FH)^t + 2J(FH)^g]$ and X and Y are electronegative substituents) according to the equation $^3J(FH)^{av} = 29.05 - 3.38 \sum (\Delta E)$ where $\sum (\Delta E)$ is the sum of the Huggins[14] electronegativity difference between hydrogen and the six atoms or groups on the CH—CF fragment.[15] The $^3J(FH)$ values in these series are therefore approximately four times more sensitive to substituent effects than vicinal H—H couplings $[^3J(HH)^{av} = 7.4 - 0.8 \sum (\Delta E)]$. However, the problem seems to be more complex, since Hall and Jones[16] showed that a plot of $^3J(FH)$, particularly $J(FH)^{cis}$, of sixteen 1,2-disubstituted derivatives of acenaphthene against substituent electronegativity gives a better agreement with an exponential relationship than with a conventional linear relationship.

(ii) The dependence of $^3J(FH)$ on the dihedral angle, ϕ, in a series of rigid molecules (acenaphthenes and bicyclo[2.2.1]-2-heptenes) with a constant bond angle ϕ and having groups of similar electronegativity.[16–18]

(iii) Extended Hückel calculations of the stereochemical dependence of $^3J(FH)$ can be fitted to the equation $27 \cos 2\phi - 20 \cos \phi + 29$.[19,20] For an estimation of the populations of staggered rotamers around the C-α,C-β bond in β-fluoro-α-amino acids and related compounds we had to determine the variation of the *gauche* and *trans* couplings as a function of electronegativity. The already known values of $^3J(FH)$ are either a function of the dihedral angle at constant electronegativity[19] or a function of the electronegativity for constant dihedral angles other than 60° and 180°.[18]

The aim of this work was to study the dependence of $^3J(FH)^g$ and $^3J(FH)^t$ in the CHCF fragment in compounds of the series RC(H-K)(F)C(H-A)(H-B)X against the electronegativity of R and X through the four coupling constants ^3J(H-A, H-K) [J(AK)], ^3J(H-B, H-K) [J(BK)], ^3J(F, H-A) [J(AF)] and ^3J(F, H-B) J(BF)].

RESULTS

Thirteen compounds were studied, of formula $RCHFCH_2X$ with $R = 4\text{-}ZC_6H_4$ and X = Cl (Z = CH_3, **1**; H, **2**; F, **3**; Cl, **4** and Br, **5**); R = C_6H_5 and X = , **6**; R = $2\text{-}ZC_6H_4$ and X = Br (Z = Cl, **7**; Z = Br, **8**); R = CH_3 and X = COOEt, **9**; R = X = COOEt, **10**; R = C_6H_5 and X = COOEt, **11**; R = COOH, X = CH_3, **12** and R = COOEt, X = C_6H_5, **13**.

The ^1H and ^{19}F spectra are the ABK and the X part, respectively, of a four-spin system ABKX. Table 1 gives the ^1H and ^{19}F chemical shifts and coupling constants of the four spin systems of these series. The low-field signal of the methylene protons is termed A.

These four coupling constants can give, unambiguously, the fractional populations of the rotamers described as the staggered rotational states of the CC bond of the —CHF—CH_2— fragment, and the assignment of the CH_2 signals H-A and H-B to their respective protons (Fig. 1) and three vicinal coupling constants for a chosen dihedral angle, 60° (*gauche* conformation, g) and 180° (*trans* conformation, *t*) (i.e. $J(HH)^t$, $J(FH)^g$ and $J(FH)^t$) according to the following three-step treatment.

(i) Figure 1 shows the two hydrogens of the methylene group, numbered 1 and 2 in a clockwise sense when viewed in the direction —C(HF)CH_2—.[21] Assuming a normal dihedral angle in these acyclic compounds, rotamer populations I–III can be obtained

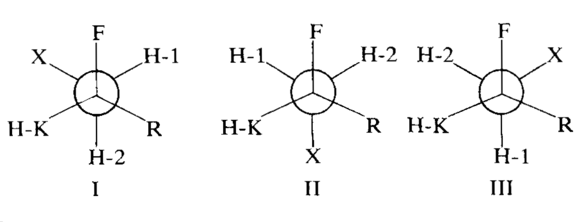


Figure 1. Newman projections of the staggered rotational states of the $RC(HF)C(H_2)X$ bond of compounds **1–15**, according to the IUPAC–IUB commission on Biochemical Nomenclature.[21]

as a function of $J(\mathrm{HH})^t$ from the measured proton–proton vicinal coupling constants $J(\mathrm{AK})$ and $J(\mathrm{BK})$. As an electronegative group has the maximum effect on *gauche* vicinal couplings when it is *trans*-coplanar to one of the coupled protons,[2] we used the Forrest equation:[6]

$$J(\mathrm{HH})^{g(1,2)} = (4.1+0.63\textstyle\sum \Delta E_i)(1-0.462\Delta E_1) \times (1-0.462\Delta E_2) \tag{1}$$

to calculate the *gauche* HH coupling constants $[J(\mathrm{HH})^g]$ from substituent electronegativity. In Eqn 1, $J(\mathrm{HH})^{g(1,2)}$ is the *gauche* HH coupling constant, with the superscript referring to the groups 1 and 2 *trans* to the coupled protons and ΔE_i is the electronegativity[14] difference between hydrogen and the atom (or group) *i*, 1 and 2. The electronegativity differences $\Delta E_X = E_X - E_H$ between the atom (or group) X substituting the studied bond and hydrogen ($E_H = 2.2$) was calculated from literature values generally obtained from the internal chemical shift ($\delta_{CH_2} - \delta_{CH_3}$) of the corresponding ethyl derivatives CH_3CH_2X: F = 1.7; Cl = 1.05; Br = 0.75; $\overset{+}{N}H_3 = 0.71$; COOH and COOEt = 0.40; $C_6H_5 = 0.55$;[22] *o*-ClC_6H_4 and *o*-$BrC_6H_4 = 0.63$[23] and $CH_3 = 0.05$.[24] The three equations relating the observed proton–proton vicinal coupling constants to the fractional populations of rotamers are

$$\left.\begin{aligned} J(1\mathrm{K}) &= x_I(J(\mathrm{HH})^t + x_{II}J(\mathrm{HH})^{g(\mathrm{H,R})} + x_{III}J^{g(\mathrm{F,X})} \\ J(2\mathrm{K}) &= x_IJ(\mathrm{HH})^{g(\mathrm{H,F})} + x_{II}J(\mathrm{HH})^t + x_{III}J^{g(\mathrm{R,X})} \\ 1 &= x_I + x_{II} + x_{III} \end{aligned}\right\} \tag{2}$$

where $J(1\mathrm{K})$ and $J(2\mathrm{K})$ are the experimental $^3J(\mathrm{HH})$ values from Fig. 1, [$J(\mathrm{AK})$ and $J(\mathrm{BK})$ or $J(\mathrm{BK})$ and $J(\mathrm{AK})$, depending on the assignment of the methylenic protons]. These three linear equations with the three unknown populations can be solved as a function of $J(\mathrm{HH})^t$.

(ii) Assuming that $J(\mathrm{FH})^t$ and $J(\mathrm{FH})^g$ depend only on the electronegativity of the substituent, without any influence from the orientation of the electronegative substituents, the experimental fluorine–proton coupling constants are related to the conformational populations according to the following equations, solutions of the three linear equations analogous to Eqns 2, with only one value for the $J(\mathrm{FH})^g$ coupling constants:

$$\left.\begin{aligned} x_I &= \frac{J(2\mathrm{F}) - J(\mathrm{FH})^g}{J(\mathrm{FH})^t - J(\mathrm{FH})^g} \\ x_{II} &= \frac{J(1\mathrm{F}) - J(\mathrm{FH})^g}{J(\mathrm{FH})^t - J(\mathrm{FH})^g} \\ x_{III} &= 1 - x_I - x_{II} \end{aligned}\right\} \tag{3}$$

where $J(1\mathrm{F})$ and $J(2\mathrm{F})$ are the experimental $^3J(\mathrm{FH})$ coupling constants from Fig. 1 [$J(\mathrm{AF})$ and $J(\mathrm{BF})$ or $J(\mathrm{BF})$ and $J(\mathrm{AF})$, depending on the assignment of the methylenic protons]. In these equations the population of the calculated conformer is that in which the coupled nuclei are in a *trans* conformation. The three unknown populations can be obtained as a function of $J(\mathrm{FH})^g$ and $J(\mathrm{FH})^t$.

(*iii*) The last step of the treatment is an iteration using $J(\mathrm{HH})^t$, $J(\mathrm{FH})^g$ and $J(\mathrm{FH})^t$ as adjustable parameters, to obtain coherent conformational populations.

The conformational populations calculated from $J(\mathrm{HH})^t$ (Eqns 2) and from $J(\mathrm{FH})^g$ and $J(\mathrm{FH})^t$ (Eqns 3) are shown in Table 2 and are in good agreement, within experimental error.

These calculations also give the assignment of the methylenic protons as A ≡ 1, i.e. the low-field signal is assigned to the first proton in a clockwise sense of the Newman projections of Fig. 1, except for **9** and **13**. Compounds of the same series already known in the literature, 1-bromo-2-fluoro-2-phenylethane (**14**)[25] and 2-fluoro-3-aminopropanoic acid in acidic, neutral and basic media **15a**, **15n**, **15b**, respectively,[26] can be treated by the same procedure. The calculated populations and the vicinal $J(\mathrm{HH})^t$, $J(\mathrm{FH})^g$ and $J(\mathrm{FH})^t$ coupling constants are given in Table 3. The assignment of the CH_2 signals agrees with those proposed by the authors (selective deuteriation for **14** or reliable proton and fluorine spectral analysis for **15**). The three $J(\mathrm{HH})^t$, $J(\mathrm{FH})^g$ and $J(\mathrm{FH})^t$ coupling constants were not derived in Ref. 25 and interest was focused on the $^3J(\mathrm{HH})$ coupling constants in Ref. 26.

Table 2. Conformational populations and $J(\mathrm{HH})^t$ calculated from Eqns 2 with $J(1\mathrm{K})$ and $J(2\mathrm{K})$ [correct assignment of $J(\mathrm{AK})$ and $J(\mathrm{BK})$] and $J(\mathrm{HH})^{g(\mathrm{X,Y})}$ evaluated from Eqn 1; conformational populations and $J(\mathrm{FH})^g$, $J(\mathrm{FH})^t$ and $J(\mathrm{FH})^{av} = \frac{1}{3}[J(\mathrm{FH})^g + 2J(\mathrm{FH})^t]$, from Eqns 3 with $J(1\mathrm{F})$ and $J(2\mathrm{F})$ [correct assignment of $J(\mathrm{AF})$ and $J(\mathrm{BF})$]; values of $\Sigma(\Delta E)$, sum of the electronegativity differences between hydrogen and the six atom (or group) substituents of the two carbons of the $>$CH—CF$<$ fragment

Compound	$J(1\mathrm{K})$	$J(2\mathrm{K})$	$J(\mathrm{HH})^{g(\mathrm{H,R})}$	$J(\mathrm{HH})^{g(\mathrm{F,X})}$	$J(\mathrm{HH})^{g(\mathrm{H,F})}$	$J(\mathrm{HH})^{g(\mathrm{R,X})}$	$J(\mathrm{HH})^t$	x_I	x_{II}	x_{III}	$J(1\mathrm{F})$	$J(2\mathrm{F})$	$J(\mathrm{FH})^g$	$J(\mathrm{FH})^t$	$J(\mathrm{FH})^{av}$	x_I	x_{II}	x_{III}	$\sum\Delta E$
1	8.0	3.7_2					12.5	0.55_5	0.19	0.25	15.2	26.2	6.0	42.0	18.0	0.56	0.18_5	0.25_5	
2	7.8_4	3.8					12.5	0.54	0.20	0.26	15.4_6	$25{,}5_5$	6.25	42.0	18.1_6	0.54	0.20	0.26	
3	7.5	4.1	4.61	0.65	1.33	2.24	12.3_7	0.51	0.22	0.27	13.3	23.8_5	6.0	41.0	17.6_6	0.51	0.22_5	0.26_5	3.3
4	7.4	4.1					12.2_5	0.50_5	0.23	0.27	16.0	24.1	6.5	41.5	18.1_6	0.50	0.22_5	0.27	
5	7.3	4.4					12.5	0.47_5	0.25	0.27_5	15.6_4	22.9_7	6.0	41.5	17.8_3	0.48	0.25	0.27	
6	10.3	1.7	4.45	0.62	1.28	3.00	12.5	0.81	(−0.005)	0.19	13.8	35.6	7.0	42.5	18.8	0.80_5	0.00_4	0.191	2.96
7	7.6	2.9	4.29	0.84_5	1.30	2.79	12.2_5	0.56	0.10	0.33_6	19.0	27.6_8	7.0	43.5	19.1_6	0.56_6	0.10	0.33	3.1
8	7.6	2.5_6					12.0	0.58_7	0.07	0.34	19.0	28.1	7.0	43.0	19.0	0.58_6	0.08	0.33	
9	4.8	7.7	5.32	0.95	1.17	4.34	14.0	0.16	0.40	0.44	26.5	16.0	9.5	49.0	22.6_6	0.16_5	0.40_5	0.43	2.15
10	6.5	5.0	4.62_5	0.99_5	1.22	3.77	13.5	0.38_5	0.23	0.38_5	24.0	24.0	8.0	49.0	21.6_5	0.39	0.22	0.39	2.5
11	9.0	4.5	4.30	1.01	1.24	3.50	13.5	0.58	0.23	0.19	15.5	30.5	8.0	47.0	21.0	0.57_7	0.23	0.19	2.65
12	6.5	4.5	4.44	1.14	1.17	4.34	12.7_5	0.41_6	0.17_5	0.41	24.9	24.9	8.0	49.0	21.6_6	0.41	0.18	0.41	2.15
13	7.5	4.5	4.70	0.92_5	1.24	3.50	14.5	0.43	0.18	0.39	24.5	26.5	9.0	49.0	22.3_3	0.44	0.17_5	0.38_5	2.65

Table 3. Conformational populations and $J(HH)^t$, $J(FH)^g$ and $J(FH)^t$ coupling constants from data published in Refs 25 and 26

Compound	R	X	$J(HH)^t$	$J(FH)^g$	$J(FH)^t$	x_I	x_{II}	x_{III}	$\sum \Delta E$
14	C_6H_5	Br	11.75	6.5	42.0	0.549	0.212	0.239	3.01
15a	COOH	NH_3^+	13.0	7.0	43.0	0.573	0.105	0.322	2.81
15n	COO^-	NH_3^+	13.5	6.5	43.0	0.587	0.102	0.311	2.81
15b	COO^-	NH_2	12.5	8.0	47.0	0.475	0.090	0.435	(2.81)[a]

[a] See text.

DISCUSSION

The first comparison with literature data is undertaken through $J(FH)^{av}$. These values can be calculated from our $J(FH)^g$ and $J(FH)^t$ measurements using the relationship $J(FH)^{av} = \frac{1}{3}[J(FH)^t + 2J(FH)^g]$.[27] A linear correlation of $J(FH)^{av}$ with electronegativity is found, $J(FH)^{av} = 30.8\text{–}3.9 \sum (\Delta E)$ for our series ($r = 0.92$ and 1.0 Hz as a mean deviation). This correlation agrees reasonably well with that obtained from Abraham and Cavalli's work, $J(FH)^{av} = 29.05\text{–}3.38\ (\pm 0.03) \sum (\Delta E)^{27}$ or from Harris *et al.*'s work, $J(FH)^{av} = 30.46 - 3.23\ (\pm 0.02) \sum (\Delta E)$.[28]

A more refined comparison with literature data can be made with $J(FH)^g$ and $J(FH)^t$.

Correlation of $J(FH)^g$ values versus electronegativity

$J(FH)^g$ values versus electronegativity differences $\sum (\Delta E)$ in the range 0.45–1.60 were obtained from our work. Other $J(FH)^g$ values can be added from analysis, according to our treatment, of published data[25,26] for substituted fluoroethanes, $RCHFCH_2X$, comparable (**14**, **15**) with those of our series. It is interesting to compare these data with those derived from Hall and Jones' work[16] in the $\sum (\Delta E)$ range 1.10–4.50 using the relationship $J(FH)^g = 0.25\ J(FH)^{cis}$[17,19,29] from the $J(FH)^{cis}$ of ten 1,2-substituted fluoro derivatives of acenaphthenes (*cis* means that the dihedral angle HCCF is zero). The exponential fit from our data and those obtained from the literature[16,25,26] for 22 compounds with $^3J(FH)^g$ from 9.50 to 3.20 and $\sum (\Delta E)$ from 2.15 to 6.20 is

$$J(FH)^g = 15.35 \exp[-0.266 \sum (\Delta E)] \tag{4}$$

with a correlation coefficient $r = 0.98$. The effect corresponding to this exponential fit can be described as follows: a substituent X with electronegativity E_x reduces J from J_0 to $J_0 - Y$, and a second similar substituent reduces J by the same fraction, i.e. from $J_0 - Y$ to $(J_0 - Y)/J_0 \cdot (J_0 - Y)$.

Various other data cannot be included in the correlation since there is evidence that these values show a dependence on both electronegativity and orientation of the electronegative substituent with respect to the interacting vicinal proton–fluorine, through blocked conformations (cf. Fig. 14 in Ref. 2). These data can be obtained from: (i) a fluorosteroid series,[30] the hexapyranosyl fluoride series[31,32] or difluorocyclohexane at low temperature[33] and (ii) the three blocked conformations of fluorohalogenoethanes at low temperatures.[34–36] For some compounds[30] our treatment is unsuccessful, since $^3J(HH)$ does not exist.

Correlation of $J(FH)^t$ values versus electronegativity

$J(FH)^t$ values versus electronegativity differences from compounds **1–13** can be compared with literature values [1-bromo-2-fluoro-2-phenylethane,[25] three 1,1,2,2-tetrahalogeno-1-fluoroethanes,[34,35] several fluorosteroids,[30] 1,1-difluorocyclohexane at low temperature[33] or derived from literature data through reliable calculations [from $J(FH)^{av}$[27] and the already described equation $J(FH)^t = 3J(FH)^{av} - 2J(FH)^g$ for the $CH_3CF\!<$, $CF_3CH\!<$ and $>\!CHCF\!<$ fragments].

An approximately linear correlation from our data and those obtained from the literature[25,27,30,33–35] for 31 compounds with $^3J(FH)^t$ from 56.0 to 4.6 Hz and $\sum (\Delta E)$ from 1.7 to 8.5, is observed, according to the equation

$$J(FH)^t = 65.75 - 7.52 \sum (\Delta E) \tag{5}$$

with a correlation coefficient $r = 0.98$.

Several other compounds are not included in the correlation since there are (i) electronegativity changes with pH[27,37] or (ii) deviations of the torsional angle from 180° in highly strained structures (acenaphthenes[16]), in ring A of fluorohydroxy steroids[30] or in the sugar ring.[31,38,39]

Correlation of $J(HH)^t$ values with electronegativity

An approximately linear correlation is observed for $J(HH)^t$ values versus electronegativity differences for our series, and for compounds from the literature [**14**, **15** and the α-amino acids, as $^3J(\text{H-}\alpha, \text{H-}\beta)^t$ is now well determined[13]], according to the following equation, for 16 compounds, with $^3J(HH)^t$ from 14.0 to 11.75 Hz and $\sum (\Delta E)$ from 1.25 to 3.3:

$$J(HH)^t = 15.0 - 0.77 \sum (\Delta E) \quad \text{(r.m.s. error 0.5 Hz)} \tag{6}$$

This variation is relatively low relative to the $J(FH)$ case, but is compatible with the variation of the *trans* coupling with electronegativity studied by Abraham and Gatti[4] in the *trans* isomer (J_t^t) according to the equation $J_t^t = 14.2 - 0.88 \sum (\Delta E)$.

Conformational populations around the $C(FH)—C(H_2)$ bond in compounds 1–13

Table 2 shows the conformational populations of compounds **1–13** obtained from Eqns 2 and 3.

Some values can be compared with those obtained from a completely different method, e.g. the analysis of the bending vibrational frequency obtained by IR spectroscopy at 1400–1500 cm^{-1}.[40] The conformational populations of the *trans* ($p_{\rm II}$) and *gauche* ($p_{\rm I}+p_{\rm III}$) conformers (defined with respect to the relative positions of the two highly electronegative atoms F and Cl) can be measured. The IR method gives $p_{\rm II}=0.21$ for **2** and 0.25 for **5**. The agreement with our results (0.20 and 0.25, respectively) is good.

Table 2 shows that, except for **9**, $p_{\rm I}$ (R and X antiperiplanar) is the most abundant conformational population. In most cases $p_{\rm II}$ is less than 0.25 (except for **9**). These $p_{\rm II}$ conformation population values are particularly small when large steric effects occur (**6** with a large X, **7** and **8** with *ortho* substituents in R) and decrease slightly when the electron-donating effect of Z increases with *para*-substituents in R (an electronic stabilizing effect seems to occur in conformation II between Cl and C_6H_5Z with an electron-withdrawing substituent, in opposition to the steric effect favouring conformation I). $p_{\rm III}$, always larger than 0.19, is moderate, corresponding to a conformation with all three large and electronegative groups, F, X and R being adjacent, as already observed in α-amino acids[41] and in β-fluoro-α-amino acids,[42] and contrary to that assumed in a description of rotational isomerism in several 1,1,2-trisubstituted ethanes.[7]

EXPERIMENTAL

Compounds **1–8** were prepared from the corresponding alcohols by dehydrofluorination using either HF–pyridine (70:30) for **1–5** as described previously,[43] or by using Yarovenko's reagent (FAR) for **6–8**.[44] These compounds were purified by vacuum distillation: **1**, b.p. (0.7) 75 °C; **2**, b.p. (16) 94 °C; **3**, b.p. (0.8) 54 °C; **4**, b.p. (1) 81 °C; **5**, b.p. (0.1) 80 °C; **6** b.p. (0.5) 95 °C; **7** b.p. (16) 145 °C or by recrystallization (from isopropyl alcohol), m.p. 216 °C. Compounds **9**, **10** and **12** were obtained by deaminofluorination of the corresponding α-amino acids or their ethyl esters, using the appropriate molar ratio of the HF–pyridine mixture,[45] giving β-fluorination (deaminofluorination with transposition) for **9** and **10** or α-fluorination for **12** using the original 70:30 HF:pyridine molar ratio.[46] Distillation gave: **9**, b.p. (12) 38 °C; **10**, b.p. (0.1) 45 °C and (0.3) 71 °C. **11** was obtained from the reaction of $C_6H_5PF_4$ on the silyl ether of the corresponding alcohol[47] and purified by silica gel chromatography (hexane–ethyl acetate, 9:1). **13** was prepared by catalytic hydrogenation (Pd/C in methanol) of ethyl α-fluorocinnamate,[48] b.p. (0.6) 67 °C.

^{1}H proton NMR spectra were obtained with a CAMECA 250 spectrometer operating at 250 MHz using the continuous wave mode.

^{1}H noise decoupled ^{19}F NMR spectra were obtained with a Bruker WP 100 spectrometer operating at 94.18 Hz using the Fourier transform mode. The spectra were recorded under the following conditions: pulse width 6 μs; flip angle 90°; spectral width from 3760 to 6000 Hz; data points 8K; accumulation number 200; relaxation delay. C_6F_6 was used as a secondary reference ($\phi_{C_6F_6}-\phi_{CFCl_3}=-163$).

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