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^{13}C NUCLEAR MAGNETIC RESONANCE—XIV

CARBON-FLUORINE COUPLING CONSTANTS AS PROBES FOR INTRAMOLECULAR SUBSTITUENT INTERACTIONS[1]

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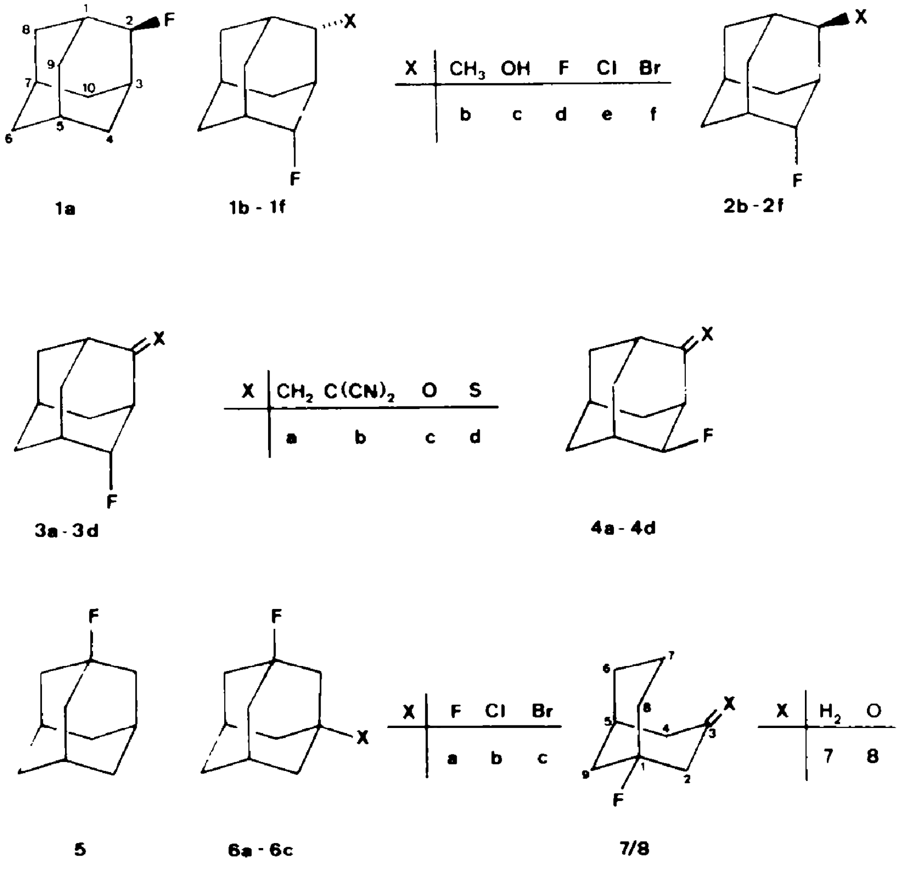
Abstract—It is shown that one-bond carbon-fluorine coupling constants sensitively reflect intramolecular n, σ^* interactions of substituents separated by four bond and being in W-arrangement (Fig.1).

In a series of publications[2-5] we rationalized observed non-additivities of substituent effects on chemical shifts of some C atoms of 2^e, 4^e-disubstituted adamantanes[4] (Fig. 1a and 1b), 4^e-substituted adamantanones[2,3,5] and corresponding thiones[5], methoximes[5] and olefins[5] (Fig. 1c) by assuming an intramolecular interaction between the substituents' lone pairs and the unoccupied σ^* orbitals of the C–X and C=X bonds, respectively, via an intervening C–C bond orbital. This interaction affects the γ-anti effects of the singly bonded substituents as well so that non-additivities are observed not only at the substituted C-2 and C-4 atoms but also at C-9.

The interaction is relatively weak so that other spectroscopic parameters as ^{1}H chemical shifts, IR wave numbers, UV wave lengths and others do not reflect it.[5]

Thus, we synthesized a series of fluorinated adamantane derivatives (**1**–**4**) and **8** (Scheme 1) in order to investigate the dependence of C–F coupling constants



Scheme 1.

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†For convenience reason the C atom bearing fluorine was given number 4 in all adamantanes **1b**-**1f**, **2b**-**2f**, **3a**-**3d** and **4a**-**4d**.

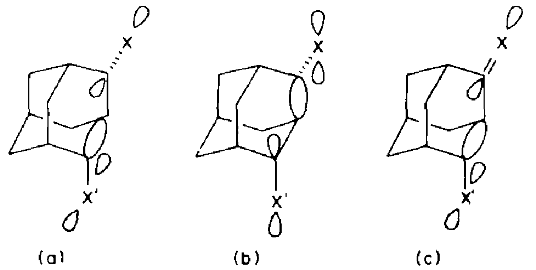

Fig. 1. n, σ^* orbital interactions in 2^e, 4^e-disubstituted adamantanes (a and b) and 4^e-substituted adamantanones and related thiones and olefins (c).

RESULTS AND DISCUSSION

In Tables 1 and 2 we present the ^{13}C chemical shifts and ^{13}C–^{19}F coupling constants of compounds **1**–**4**. The signal assignments are based on ^1H off-resonance decoupling experiments and on the evaluation of the $^nJ_{CF}$ values which depend on the number n of intervening bonds in a characteristic way:[6–8] n = 1: 178–191 Hz; n = 2: 17–25 Hz; n = 3: 7–13 Hz, if the observed nucleus is in antiperiplanar position to fluorine (C-2 and C-9 for **1**, **2** and **3**; C-6 and C-10 for **4**; C-3, C-5 and C-7 for **8**) and 0 – 2 Hz, if it is in gauche position (C-6 and C-10 for **1**, **2** and **3**; C-2 and C-9 for **4**). Thus, we obtained unambiguous assignments for all signals except for C-9 of **1d**; this signals could not be identified safely due to signal overlap.

All non-additivity effects fit the trends observed for other compounds of these types[2–5] and were also helpful in identifying the configurations at the substituted C-2 and C-4 atoms in the cases where epimeric mixtures were produced in the syntheses.

The intramolecular interaction of the substituents in molecules as depicted in Fig. 1 is of hyperconjugative nature and is reflected in non-additivities of the individual substituent effects ($\Delta\delta$) on the chemical shifts of

Table 1. ^{13}C Chemical shifts of 2-fluoroadamantane (**1a**) and 2-substituted 4-fluoroadamantane derivatives **1b**–**1f**, **2b**–**2f**, **3a**–**3d** and **4a**–**4d**; is ppm relative to internal tetramethylsilane

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1a[a]	32.9	95.6	32.9	31.5	27.7	37.3	27.3	35.8	31.5	35.8
1b[b]	32.9	36.8	38.3	96.4	32.7	32.3	27.3	31.0	36.6	25.4
1c	33.3	71.9	39.7	93.6	31.7	30.7	26.6	31.4	31.8	25.3
1d	31.3	92.2	37.7	92.2	31.3	31.0	26.2	31.0	–[c]	25.7
1e	34.4	62.8	40.4	93.4	31.5	31.6	26.5	30.6	33.5	25.3
1f	35.5	56.6	40.6	93.2	31.6	32.0	26.5	31.4	34.1	26.1
2b[d]	33.6	40.5	38.4	92.3	32.6	32.3	27.0	38.8	30.5	32.1
2c	33.6	76.0	39.5	92.2	32.6	31.3	26.1	35.9	29.7	30.5
2d	32.0	96.5	37.7	91.4	31.8	31.0	25.8	35.0	29.6[e]	29.8[e]
2e	34.9	67.2	40.1	91.1	32.9	31.4	25.8	37.7	29.9	32.5
2f	35.4	60.9	40.4	91.6	32.4	31.5	25.8	38.4	30.7	33.3
3a[f]	37.5	153.7	43.9	94.9	32.5	31.1	27.2	38.9	35.5	33.3
3b[g]	37.7	187.1	43.6	92.2	31.5	30.0	26.3	39.5	33.7	34.5
3c[h]	45.2	212.7	52.6	92.2	31.8	30.1	26.6	38.9	30.9	33.9
3d	56.0	262.0	62.2	93.2	31.8	30.6	26.7	40.8	33.5	35.9
4a[i]	38.2	152.8	43.8	96.0	32.8	35.4	26.9	39.0	33.4	37.7
4b[k]	38.2	188.5	43.7	96.4	32.9	34.1	25.8	39.1	33.7	38.0
4c[h]	46.4	214.0	52.2	95.7	32.4	35.7	26.1	38.8	32.4	38.8
4d	56.8	263.9	61.4	98.0	32.0	34.9	26.4	40.9	34.4	40.0

[a] See also refs. 5, 7 and 8.

[b] CH_3: 17.6

[c] Could not be identified safely due to signal overlap.

[d] CH_3: 18.5

[e] May be interchanged.

[f] CH_2: 104.7

[g] =C : 80.6; CN: 111.1/111.2

[h] See also ref. 5.

[i] CH_2: 104.9

[k] =C : 81.1; CN: 111.3

Table 2. ^{13}C-^{19}F Coupling constants of compounds **1a**–**1f**, **2b**–**2f**, **3a**–**3d**, **4a**–**4d** and **8**; in Hz[a]

	$^{1}J_{CF}$	$^{2}J_{CF}$			$^{3}J_{CF}$(anti)		
1a[b]	178.8		17.8			8.9	
	C-4:	C-3:	C-5:		C-2:	C-9:	
1b	179.0	17[c]	17 - 18[c]		8.3	9.5	
1c	180.3	17.8	18.2		11.4	10.5	
1d	182.0	17 - 19[c]	17 - 19[c]		12.5	-[d]	
1e	184.1	19.5	18.1		11.2	10.3	
1f	184.6	19.5	18 - 19[c]		10.7	9.8	
2b	175.8	19.8	17 - 18[c]		9.5	9.3	
2c	175.5	18.0	18 - 19[c]		9.8	9.2	
2d[e]	176.9	16.5	17.7		9.9	9.6	
2e	176.8	20.5	18.1		9.8	9.3	
2f	176.9	21.0	18.0		9.6	9.2	
3a	183.4	19.8	17.9		9.4	8.0	
3b	190.4	24.4	18.5		9.2	8.3	
3c	187.4	19.2	18.4		9.9	9.8	
3d	189.1	20.6	18.5		8.5	8.5	
	C-4:	C-3:	C-5:		C-6:	C-10:	
4a	180.7	18.9	17.7		8.9	8.2	
4b	185.0	18.7	20.0		8.1	7 - 8[c]	
4c	181.2	21.0	17.6		8.3	8.8	
4d	183.4	19.6	17.4		8.4	7.6	
	C-1:	C-2:	C-9:	C-8:	C-3:	C-5:	C-7:
8	181.5	21.2	17.4	20.9	13.7	10.5	11.1

[a] Absolute values; accuracy ± 0.2 - 0.3 Hz.

[b] See also refs. 7 and 8.

[c] Exact value unknown due to signal overlap.

[d] Owing to signal overlap of the C-9 signal of 1d could not be identified safely.

[e] Couplings to the fluorine atom at C-2: $^{1}J_{CF}$ = 179.4 Hz; $^{2}J_{C1_{F}}$ = 18.4 Hz; $^{2}J_{C3_{F}}$ = 16.5 Hz; $^{3}J_{C8_{F}}$ = 8.8 Hz; $^{3}J_{C10_{F}}$ = 8 - 10 Hz[c].

the substituted C-2 and C-4 atoms as well as of the unsubstituted C-9 atoms[2–5] (Table 3). In Fig. 2 the one-bond coupling constants $^{1}J_{CF}$ are correlated with the $\Delta\delta$-values of the signals of the C-4 atoms involved in the coupling:

As can be seen from the good correlation the direct coupling is a parameter which reacts sensitively upon the hyperconjugative interaction; there is a rather larger range of about 12 Hz. Slight changes in the molecular geometries cannot be held responsible. In the compounds **2** and **4** with one axial substituent, effects of this kind are supposed to be even more likely, but the changes of the one-bond coupling constants are definitely smaller in these compounds than in those where the hyperconjugative interaction is operative, e.g. there is an increase of 5.8 Hz comparing **1f** and **1a**, but a decrease of 1.9 Hz for **2f**.

Recently, Pincock *et al.* reported among other data carbon–fluorine coupling constants of 1-fluoroadamantane **5** and 3-substituted 1-fluoroadamantanes **6a**–**6c**.[7] In the latter compounds the relative position and the configuration of the substituents is very similar to those in **1d**–**1f**; the substituents being in a coplanar W-arrangement in both cases. Pincock's derivatives, however, are bridgehead substituted. They also find an increase in $^{1}J_{CF}$ from **5** (184 Hz) to **6a** (188.0 Hz), **6b** (188.5 Hz) and **6c** (188.7 Hz)[7] which can be explained in analogous terms as has been done in Fig. 1a and 1b by an intramolecular interaction. This is also shown by the non-additivity effects for C-1, C-3 and C-5 signals of **6a**–**6c** which are very similar in their trend compared with those of **1d**–**1f** though not identical.[7]

The increase of $^{1}J_{CF}$ by the presence of a CO in the suitable configuration is not restricted to adamantane derivatives. We can also observe it in the 1-fluorobicyclo-[3.3.1]nonan-3-one (**8**) (181.5 Hz) compared with 1-fluorobicyclo[3.3.1]nonane (**7**) (175.0 Hz[9]). The non-additivity effects of **8** have been discussed in a previous publication.[5]

The two-bond coupling constants ($^{2}J_{CF}$) of **1b**–**1f** and

Table 3. Non-additivities of substituent effects (Δδ)[a] of **1b**–**1f** and **3a**–**3d**; in ppm

	C-2	C-4	C-9
1b	−0.4	−1.0	−1.0
1c	−0.8	−0.9	−2.9
1d	−2.1	−2.1	–[b]
1e	−3.3	−2.7	−2.8
1f	−5.1	−3.4	−2.7
3a	−2.5	−2.8	−2.4
3b	−3.5	−5.3	−4.0
3c	−1.9	−4.8	−6.3
3d	−2.4	−5.3	−5.2

[a] Δδ = δ(experimental) − δ(calculated)[5]; the calculated values are obtained assuming additivity of the individual substituent effects[2,3].

[b] Owing to signal overlap the C-9 signal of 1d could not be identified safely.

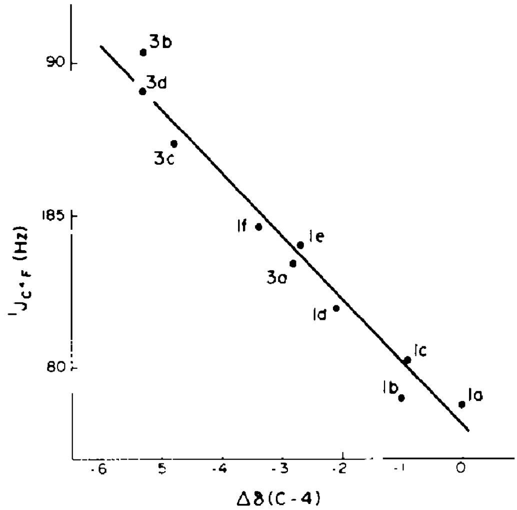

Fig. 2. Non-additivity effects at C-4 signals vs. direct C-4–F coupling constants for **1a**–**1f** and **3a**–**3d**.

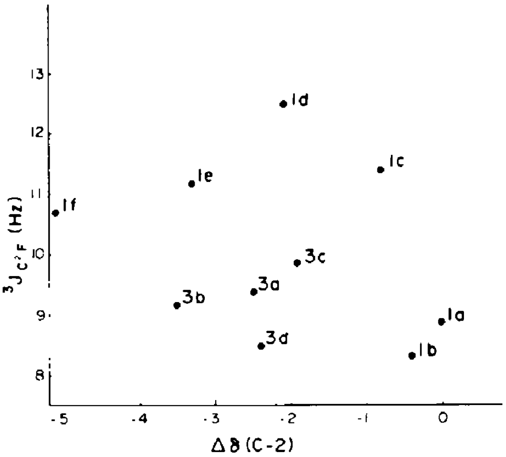

Fig. 3. Non-additivity effects at C-2 signals vs three-bond C-2–F coupling constants for **1a**–**1f** and **3a**–**3d**.

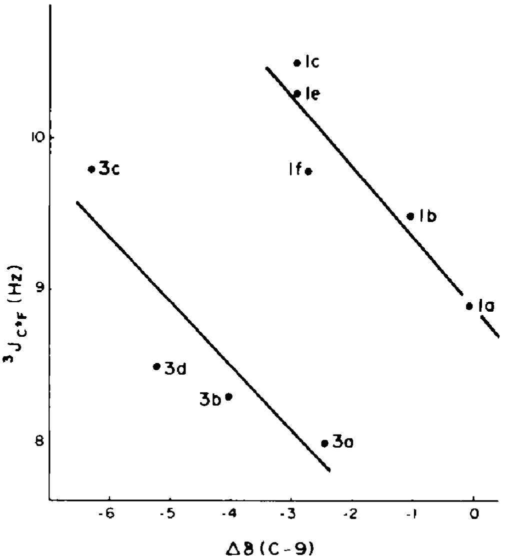

Fig. 4. Non-additivity effects at C-9 signals vs three-bond C-9–F coupling constants for **1a**–**1f** and **3a**–**3d**.

3a–**3d** can be partitioned into two groups: If C-5 is involved, they are essentially unchanged compared to $^2J_{CF}$ in 2-fluoroadamantane (**1a**). For the signals of C-3, however, which is lying between the two substituted carbon atoms the values of $^2J_{CF}$ can be enhanced substantially up to 24.4 Hz (**3b**).

There are two different antiperiplanar γ-C atoms with respect to the fluorine atom at C-4 (C-2 and C-9), both signals of which reveal non-additivities of the substituent effects. There is no correlation between the three-bond couplings and the non-additivity effects for the substituted C-2 (Fig. 3), whereas rough correlations of the $^3J_{CF}$ and the Δδ-values for C-9 do exist (Fig. 4). In this case, however, there are two plots: one for the compounds of type **1** and another for those of type **3**. Analogously, the $^3J_{CF}$ at C-5 of **8** is nearly 2 Hz larger than the corresponding value of **7**.[9] The $^3J_{CF}$ values of C-5 of Pincock's compounds, however, do not show a significant alteration. Thus, in contrast to the $^1J_{CF}$-values the three-bond coupling constants cannot be regarded as safe probes for the detection of substituent interactions, since their substituent dependence is small in magnitude and may vary from one molecular system to another. More experimental evidence is desirable.

EXPERIMENTAL

Measurements. The ^{13}C NMR spectra were recorded in the PFT mode (16 K data points for the FID) at ambient temp with internal D lock using a Bruker WH-90 spectrometer (22.64 MHz). The samples were recorded in $CDCl_3$ soln with concentrations of 0.05 – 0.2 M. The chemical shifts were determined on the δ-scale relative to internal TMS. The coupling constants are accurate to 0.2–0.3 Hz in all cases.

Syntheses

Compounds **1a**[8] and **3c**[10] were obtained according to known procedures; **3b** was prepared by treating **3c** with malodinitrile[11] in quantitative yield. Reaction of **3c** with P_2S_5[12] gave **3d** in 67% yield as a pink oily liquid which is stable for several months at −20°. The olefin **3a** was made from **3c** by Wittig reaction and yielded **1b** after hydrogenation along with the other epimer **2b**. Both isomers could not be separated by column chromatography; the ^{13}C signal assignments, however, could be achieved, since the ratio of the epimers **1b** and **2b** in the mixture was about 3:2. The compounds **4a** – **4d** which are isomers of **3a** – **3d** were prepared by analogous reactions. Reduction of **3c** with zinc borohydride[13,4] produced **1c** along with the other epimer **2c** in a 2:1 mixture; again the mixture was not resolved. **1e**, **2e**, **1f** and **2f** were prepared from the mixture of **1c** and **2c** with thionyl chloride- or PBr_3/PBr_5 at 0°, respectively. In both cases the resulting epimers were separated by column chromatography. **1d** and **2d** were obtained from the mixture of **1c** and **2c** with NaF in HF/pyridine soln[14] along with 2^a, 4^a-difluorodamantane. The three isomers could not be separated from each other completely. The fluoroketone **8**[5] was obtained from 1-hydroxy-bicyclo[3.3.1]-nonan-3-one[15] by the same procedure in 28% yield.

All samples were purified (if possible) by column chromatography under normal or medium pressure (silica gel and ligroin/acetone mixtures as eluants) followed by sublimation and in some case recrystallisation. Owing to the volatility of the compounds some yields are not satisfactory. The compounds were identified by IR, ^{1}H NMR[16] and mass spectra. Further details about preparations and other spectroscopic data will be published later and are available on request.

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