Journal of Fluorine Chemistry, *48* (1990) 281–292

Received September 28, 1989, accepted February 18, 1990

THE RELATIONSHIPS BETWEEN ^{19}F SUBSTITUENT CHEMICAL SHIFTS AND ELECTRON POPULATIONS IN PARA AND META SUBSTITUTED α-FLUORO-Z-CINNAMIC ESTERS

ROGER ARNAUD, ROBERT SUBRA

Université Joseph Fourier (Grenoble I), LEDSS VII, CNRS UA 332,
301 rue de la Chimie, BP 53, F-38041 Grenoble (France)

CLAUDE G. BEGUIN*

Université Joseph Fourier (Grenoble I), Laboratoire de Cinétique et
Dynamique Moléculaires, CNRS SDI 5196, 301 rue de la Chimie, BP 53,
F-38041 Grenoble (France)

ELIAS ELKIK and CHARLETTE FRANCESCH

Laboratoire de Chimie de l'E.N.S., CNRS UA 1110, 24 rue Lhomond,
F-75231, Paris Cédex 05 (France)

SUMMARY

The ^{19}F substituent chemical shifts (SCS) of *para* and *meta* substituted α-fluoro-Z-cinnamic esters (α-fluoro-*trans* -cinnamic esters) correlate well with the electron populations of the fluorine atom obtained from STO-3G calculations. The slope of the relationship between $\Delta q_{\pi}{}^{F}$ and the fluorine chemical shifts is 2000 ppm/electron in the *para* series (1600 for *meta*) showing a sensitivity of the fluorine atom to electron density of the same order of magnitude as in other related series. The analysis in terms of inductive and resonance substituent effects shows that the main contribution to the inductive component of fluorine SCS is from a π inductive mechanism.

0022-1139/90/$3 50

INTRODUCTION

The fluorine atom, specially in aromatic compounds, can be considered as a structural probe, using ^{19}F NMR spectroscopic studies, in Chemistry [1] and Biochemistry [2, 3, 4].

There have been many reports on ^{19} F substituent chemical shifts (SCS) in several series. In one group (substituted fluorobenzenes 2 [5] difluorostyrenes [6], fluoroanthracenes [7], fluoronaphtalenes [8, 9], benzoyl fluorides 3 [10] and phenacyl fluorides [11] donor substituents cause upfield shifts. In another group (substituted benzylfluorides [12,13,14], phenethyl fluorides [12], and phenylfluoroethanols [15] and other fluorocompounds [16] donor substituents cause downfield shifts. For the first group, there have been several attempts to rationalize ^{19}F shifts in terms of electron distributions. In the *para*-substituted fluorobenzene system, the π electron density (calculated at *ab initio* STO-3G levels of approximation) gives a reasonably linear correlation with ^{19}F SCS with a slope of 2100 ppm/electron [1]. For the *para* - benzoyl fluoride series the slope of the relationship between $\Delta q_{\pi}{}^{F}$ (π electron density of fluorine atom relative to the unsubstituted compound), and ^{19}F SCS is 5000 ppm/electron [10] with the same theoretical method. All these results indicate the great sensitivity of the fluorine atom to small changes in electron density.

Recently [17], two of us, synthesized substituted α-fluoro-Z-cinnamic esters 1 (named also α-fluoro-*trans*-cinnamic esters) and observed a direct fluorine SCS effect (i.e donor substituents giving upfield shifts).

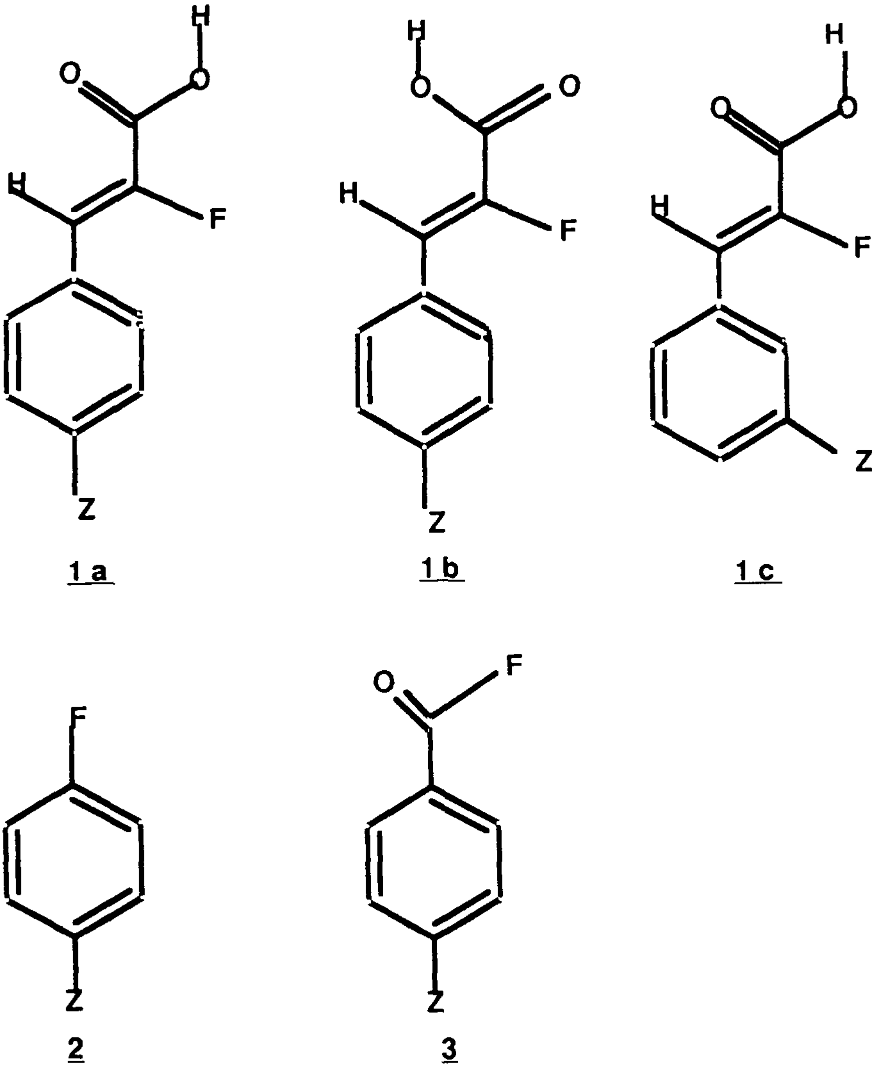
For comparison with series of compounds showing the same direct fluorine SCS effect, we examined the relationship between electron populations and ^{19}F chemical shifts in this series.

THEORETICAL METHOD AND RESULTS

Para-compounds

As no information is known about the conformation of the C(F)-C(OOEt) bond, we examined for the calculation of electron populations the structures 1a and 1 b shown in Figure 1.

The calculations have been performed at the *ab initio* STO-3G [18] level using the GAUSSIAN 80 program [19]. A recent study on the basis set dependency of molecular electronic structures shows that the STO-NG with N =3,4,5,6, give well-balanced wave functions [20] and give almost the same total charges, in the Mulliken sense, independently of the contraction number N.



1a 1b 1c

2 3

FIG. 1.

The optimizations were performed by the Murtaugh-Sargent procedure [20] We have undertaken a complete optimization of Z and Y monosubstituted benzenes (Z = OCH_3, CH_3, F, H, Cl, CN) , the Y substituent being - CH = CF - CO_2CH_3), the CH lengths of the benzene ring being taken as 108.1 pm throughout and we deduced the optimized geometries of the disubstituted Z- C_6H_4-Y compounds by means of the 'superimposition' hypothesis [21,22]. We checked on the Z=H compound that non-planar conformations gave higher energies. When doing the electron population calculations on disubstituted compounds, the GAUSSIAN 80 program limits the size of the problem to 80 A O's. So we had to substitute the methyl group of CO_2CH_3 by an H atom, lying in the direction of the missing CH_3 group, with an optimized OH length of 98.24 pm. This substitution doesn't change significantly the electron populations on fluorine. As we will examine only the variation of the electron populations (and of the chemical shifts) between a substituted compound and the unsubstituted one, this replacement (methyl to hydrogen) does not affect the comparison. We performed the complete set of electron population calculations on the geometrically optimized disubstituted system ZC_6H_4Y with six representative Z substituents . OCH_3, CH_3, F, H, Cl, CN and Y being -CH = CHF - CO_2H.

We used the Mulliken population analysis [23]. The calculated changes in electron populations relative to the unsubstituted compound (Z = H) for the fluorine atom F (Δq_π, Δq_t and $\Delta q_\sigma = \Delta q_t - \Delta q_\pi$) of a series of disubstituted benzenes are defined as follows :

$$\Delta q_\pi F = q_\pi F(Z) - q_\pi F \quad (Z = H)$$

$$\Delta q_t F = q_t F(Z) - q_t F \quad (Z = H)$$

where $q_\pi{}^F(Z)$ is the gross charge on atom F of the Z-substituted molecule and $q_\pi{}^F(Z{=}H)$ is the gross charge obtained from the unsubstituted molecule. The gross charges $q_\pi{}^F$ and $q_t{}^F$ are defined in the Mulliken sense [23] from the following equations :

$$q_\pi F = N^\circ{}_\pi(F) - N_\pi(F)$$

$$q_t F = N^\circ(F) - N(F)$$

where N°_{π} (F) is the number of electrons in the atomic orbital $2p_z$ (called π) on fluorine (N°_{π} (F)=2) and N°(F) is the total number of electrons in the ground state of the free neutral atom F (N°(F) = 9). The total gross population N_{π} (F) on the π atomic orbitals of atom F and the total gross populations N (F) on atom F are defined as "gross orbital charges" and "total atomic charges" in the GAUSSIAN 80 package and are given by the following equations :

$$N_{\pi}(F) = \sum_{i} n(i)\left(c^2_{i\pi} + \sum_{q \in B} c_{i\pi} c_{iq} S_{\pi q}\right)$$

$$N(F) = \sum_{p \in F} N_p(F)$$

where i runs over the entire set of molecular orbitals $\phi_i = \sum c_{iq}\, \chi_q$, each of them containing n (i) electrons (n (i) = 2 or 0), $S_{\pi q}$ is the overlap integral between the A.O.'s : χ_{π} and χ_q , B stands for the entire set of atoms different from fluorine and F stands for all A.O. of fluorine atom.

We have found that the calculated energy differences between the two *para* conformations (**<u>1a</u>** and **<u>1b</u>**) for a given substituent are relatively small (< 1.5 $kJ.mol^{-1}$), and hence we put down the electron populations for the conformations corresponding to the minimum of energy (very close of the averaged values of these populations) without specification of the involved conformation.

The total gross population on the π atomic orbitals of atom F, $N_{\pi}(F)$, the corresponding gross charge, q_{π}^{F}, the total gross population on atom F, N(F), and the corresponding gross charge, q_t^{F}, for the unsubstituted α-fluoro-Z-cinnamic esters, are respectively 1.92 957, 0.07 043, 9.12 390 and -0.12 390.

The calculated change in electron populations relative to the unsubstitued compound (Z = H) for the fluorine atom, Δq_t, Δq_{π} and Δq_{σ}, for the series of five substituents (OCH_3, CH_3,F,Cl and CN) are given in Table 1.

TABLE 1

Substituent chemical shifts and electron densities in *para* α-fluoro-Z-cinnamic esters with optimized geometries (see text)

Z	Δq_t (a)	Δq_π (a)	Δq_σ (a)	$\Delta\delta$(b)
OCH_3	- 22	- 12	- 10	- 3.41
CH_3	- 7	- 4	- 3	- 1 18
F	- 7	- 2.4	- 4.5	- 1.13
Cl	+ 22	+ 16	+ 6.6	+ 0.89
CN	+ 34	+ 26	+ 8	+ 5.13

a) Electron densities ($\times 10^4$) expressed relative to the unsubstituted compound. Negative values denote an increase in electron density.

b) ^{19}F chemical shifts measured in $CDCl_3$ [17] expressed in ppm, relative to the unsubstitued compound. Positive values are downfield. α-fluoro-Z-cinnamic ethyl ester has a ^{19}F chemical shift of - 125.93 ppm from $CFCl_3$ (highfield from reference)

Meta compounds

The same type of calculations were made on the *meta* compounds **1c**. As only small effects were observed between the two conformations **1a** and **1b** in the *para* series, the geometry used for all Z substituents in the *meta* series was the optimized one with Z = H (as shown in Formula **1c** in Figure 1).

We recalculated the change in electron population in the *para* series in the same conditions and the results are given in the first part of Table 2. The modification is sensible but small and does not change the general trend.

The calculated change in electron populations relative to the unsubstituted compound for the fluorine atom Δq_t, Δq_π, Δq_σ in the *meta* series are given in the second part of Table 2.

TABLE 2

Substituent chemical shifts in ppm and electron densities ($x10^4$) in *para* and *meta* α-fluoro-Z-cinnamic esters with optimized geometry obtained for Z=H

		Δq_t	Δq_π	Δq_σ	$\Delta\delta$
p-Z	OCH3	-24	- 9	-15	-3.41
	CH3	- 9	- 6	- 3	-1.18
	F	- 6	- 2	- 4	-1.13
	Cl	+23	+16	+ 7	+0.89
	CN	+34	+25	+ 9	+5.13
m-Z	OCH_3	+ 21	+ 9.4	+ 11.6	+ 0,67
	CH_3	- 3	- 1	- 2	- 0.03
	F	+ 17.5	+ 11	+ 6.5	+ 2.11
	Cl	+ 37.5	+ 20	+ 17.5	+ 2.37
	CN	+ 31	+ 19	+ 12	+ 3.85

DISCUSSION

Para compounds

A multiple linear correlation of the type :

$$\delta F = \delta F_0 + \rho_I \sigma_I + \rho_R \sigma_{R^\circ}$$

where σ_I is the substituent inductive constant (determined from rigid cyclic systems), the substituent resonance constant defined by $\sigma_{R^\circ} = \sigma^\circ - \sigma_I$ where σ° is the whole substituent constant on a well chosen set of reactions [24, 25]. The susceptibilities of the fluorine chemical shift to σ_I and σ_{R° are respectively ρ_I and ρ_R. The dual substituent parameters analysis (DSP) calculated with the ^{19}F SCS of the 11 synthesized compounds <u>1</u> versus σ_I and σ_{R° indicates the sensitivity of fluorine to substituent effects in our series according to the following equation .

$$\delta F = -0.26 + 6.34\,\sigma_I + 11.6\,\sigma_R^\circ$$

with 0.990 as the coefficient of correlation [26]. This equation shows that both inductive and resonance effects contribute to fluorine substituent chemical shifts. We compared the corresponding values for p-fluorobenzenes (δ (ZPhF) = 7.0 σ_I + 30.6 σ_R°) and for p-benzoylfluorides (δ (ZPhCOF) = 3.3 σ_I + 6.0 σ_R°) [10]. The ρ_I values are nearly the same for 2 and 1 and larger than for 3. As the distance between the fluorine atom and the substituent in our system is larger than in 2, the similar magnitude of the ρ_I values in 1 and 2 indicates that the inductive effect on fluorine substituent chemical shifts is a π inductive effect [27], likely due to the vinylogous relationship between the two series. A comparison of the ρ_{R° values for the three systems shows that resonance effects decrease from 2 to 1 and to 3. Morever, the major resonance interactions of the substituent Z in our series are shared between the fluorine atom and the carboxyl group. This was also the case in benzoyl fluorides between the substituent and the oxygen atom [10].

A more quantitative comment can be made through the relationship between the fluorine SCS values and the electron density. Donating substituents increase the total π and σ electron densities about the fluorine whilst they are decreased by the withdrawing substituents. Because the π electron densities were found to be the best parameter of choice for correlating fluorine SCS values in fluorobenzenes, we have plotted the fluorine SCF for 1 versus Δq_π^F :

$$\delta F = -0.87 + 0.198\,\Delta q_\pi F$$

(with 0.951 as the coefficient of correlation) i.e with a slope of 2000 ppm/electron (almost the same value in fluorobenzenes (2100) and smaller than in benzoyl fluorides (5000). The correlations of Δqt^F and Δq_σ^F are almost the same (coefficient of correlation 0.948 and 0.943 respectively).

Comparison of the Δq_π electron charges and the fluorine SCS in the three series is shown in Table 3. The range in Δq_π^F values for 1 is intermediate between **2** and **3**. It can be related to the sharing of resonance interaction between fluorine and the oxygen atom in **3** or the carboxyl group in **2**, and the vinylogy relationships of **1** versus **2**. It is interesting to observe almost the same value of the slopes in ppm/electron (2000) between **1** and **2**.

TABLE 3
Comparison of substituent chemical shifts in ppm and π electron densities ($\times 10^4$) in the *para* substitued compounds of the series **1**, **2**, **3**, with the same units as in Table 1.

	Δq_π			$\Delta\delta$		
Z	**1**	**2**	**3**	**1**	**2**	**3**
OCH_3	- 12	- 44	- 4	- 3.41	- 11.54	- 2.15
CH_3	- 4	- 15	- 2	- 1.18	- 5.46	- 0.67
F	- 2.4	- 18	- 1	- 1.13	- 6.70	- 0.10
CN	+ 26	+ 54	+ 4	+ 5.13	+ 9.11	+ 2.09

Meta compounds

For the smaller range of shifts in the *meta* compounds of the series (8 compounds **1c** [17]) the DSP analysis gives the following equation:

$$\delta Fm = 0.30 + 5.62\sigma_I + 2.88\,\sigma_R^\circ$$

with 0.994 as the coefficient of correlation [26]. For *meta* compounds in systems **1**, **2**, **3** the ρ_I, values are respectively : 5.6, 5.3 and 2.5 and the ρ_R values are 2.9, 0.8 and - 0.3.

The ratio of resonance to inductive effects ρ_R (*meta*) /ρ_I (*meta*) is higher for **1** (0.5) than for series **2** (0.15) and **3** (0.12) and smaller than the corresponding ratio for the para compounds **1** (1.84). The ratio of *meta/para* inductive effects are almost the same (0.75-0.88) for the three series, suggesting a strong analogy in the transmission of inductive effect . This can be interpreted [10] as a π inductive effect mechanism for the main contribution to the inductive component of fluorine SCS values in the three series.

A plot of ^{19}F SCS values for the *meta* compounds versus the $\Delta q_{\pi}{}^{F}$ values gives the following equation :

$$\delta m^{F} = - 0\ 02 + 0.156\ \Delta q_{\pi}{}^{F}$$

with 0.91 as the coefficient of correlation.

The plot is less satisfactory than that for the *para* compounds, but the slope of 1600 ppm/electron is not too far from the 2000 ppm/electron obtained for the *para* compounds. These two slopes are in the vicinity of those of the corresponding fluorobenzenes, giving justification to the vinylogy relationship between structures 1 and 2.

CONCLUSION

The fluorine chemical shift in *meta* and *para* substituted α-fluoro-Z-cinnamic esters is a sensitive probe for substituent effects. A good correlation (2000 ppm/electron in the *para* series) between this SCS and the change in the π gross charge on the fluorine atom relative to the unsubstitued compound ($\Delta q_{\pi}{}^{F}$) is observed. The susceptibility ρ_R of SCS to the substituent resonance constant σ_{R°, is correlated to the fluorine π gross charge as it describes the resonance effect. The susceptibility ρ_I of SCS to the substituent inductive effect σ_I, is therefore related to this fluorine π gross charge, showing the π inductive mechanism of this inductive effect.

EXPERIMENTAL

The *ab initio* calculations were performed on a I.B.M. 3090 computer at the CNUSC (Montpellier) using a version of the GAUSSIAN-80 program [21].

REFERENCES

1 W.J. Hehre, R.W. Taft and R.D. Topsom, Prog. Phys. Org. Chem., 12 (1976) 159.

2 J.T. Gerig in 'Biomedicinal Aspects of Fluorine Chemistry', R. Filler and Y. Kobayashi. Eds. Elsevier N-Y (1982) pp. 163-189.

3 A. Dahbi, S. Hamman and C.G. Béguin, Bull. Soc. Chim. Fr., (1986) 916.

4 F. Tetaz, Thèse Université de Grenoble I (1988).

5 R.W. Taft, E. Price, I.R. Fox, I. C. Lewis, K. K. Andersen and G.T. Davis, J. Am. Chem. Soc., 85 (1963) 709 and 3146 .

6 D.R. Strobach, J. Org. Chem., 36 (1971) 1438 .

7 W. Adcock, M.J.S. Dewar, R. Golden and M.A. Zeb, J. Am. Chem. Soc., 97 (1975) 2198 .

8 W. Adcock, J. Alste, S.Q.A. Ruzvi and M. Aurangzeb, J. Am. Chem. Soc., 98 (1976) 1701 .

9 E.A. Dixon, A. Fischer and F.P. Robinson, Can. J. Chem., 59 (1981) 2642.

10 R.T.C. Brownlee and D.T. Craik, Org. Magn. Reson., 14 (1980) 186.

11 R.T.C. Brownlee and D.J. Craik, Org. Magn. Reson., 15 (1981) 248.

12 C. Beguin, Bull. Soc. Chim. Fr. (1967) 4214.

13 R.T.C. Brownlee and D.J. Craik, Tetrahedron Lett., (1980) 1681.

14 T. Schaefer, W.P. Niemczura, R. Sebastian, L.J. Kruczynski, and W. Danchura, Can. J. Chem., 58 (1980) 1178.

15 G. Aranda and H. de Luze, Org. Magn. Reson., 4 (1972) 847.

16 W. Adcock, A.N. Abeywickrema and G.B. Kok, J. Org. Chem., 49 (1984) 1387 and references cited therein.

17 E. Elkik and C. Francesch, Bull. Soc. Chim. Fr., (1986) 423.

18 W.J. Hehre, R.F. Stewart and J.A. Pople, J. Chem., Phys., 51 (1969) 2657.

19 J.S. Binkley, R.A. Whiteside, R. Krishnam, R. Seeger, D.J. Defrees, H.B. Schlegel, S.Topiol,L.R. Khan and J.A. Pople Gaussian 8O, Department of Chemistry, Carnegie-Mellon Univ., Pittsburg, Penn., U.S.A., 198O).

20 H.Ichikawa, K.Sameshima and Y.Ebisawa, Chem. Soc.Japan, 59 (1986) 2729.

21 P. George, C.W. Bock and M. Trachtman, J. Mol. Struct. (Theochem), 137 (1986) 387.

22 The complete set of geometrical parameters will be sent by the authors on request.

23 R.S. Mulliken, J. Chem. Phys., 23 (1955) 1833.

24 R.W. Taft, J. Phys. Chem., 64 (1960) 1805.

25 P.R. Wells, S. Ehrenson and R.W. Taft, Prog. Org. Chem., 6 (1968) 147.

26 The coefficient of correlation is the square root of the coefficient of determination which is the ratio of the regression explained varianceto the total variance (N.R. Draper and H. Smith (1980) Applied Regression Analysis, 2nd Ed. Wiley, New York).

27 D.F. Ewing and K.J. Toyne, J. Chem. Soc. Perkin Trans. 2 (1979) 243.