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An NMR Study of Halogenated 1,4-Dihydro-1-ethyl-4-oxoquinoline-3-carboxylates

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Ethyl 1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylate and 29 of its mono-, di- and tri-fluoro and/or -chloro derivatives were synthesized and their ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded. ^{1}H, ^{13}C and ^{19}F chemical shifts, J_{HH}, J_{FH}, J_{CF} and J_{FF} coupling constants are reported. The ^{13}C substituent chemical shift values of the chloro and fluoro substituents were calculated by linear multiple regression.

KEY WORDS NMR; ^{1}H NMR; ^{13}C NMR; ^{19}F NMR; J_{CF}; quinolinones; substituent chemical shifts

INTRODUCTION

The clinical success[1] of the third generation of nalidixic acid[2] and its congeners[3] (so-called fluoroquinolines[4]) against Gram-negative and Gram-positive bacteria-caused urinary tract and systemic infections has generated intense international competition to synthesize more effective agents with a broader activity spectrum.[5] The key intermediates for the synthesis of these congeners are usually 6-fluoro-7-chloro and other halo derivatives of 1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylic acid or ester (Fig. 1) from which these compounds are obtained by regioselective nucleophilic substitution of the 7-halogen atom by cyclic amines.

However, an unfavourable side reaction, the nucleophilic substitution of the 6-fluoro atom, can also take place.[6] To increase the selectivity of the required reaction, borate complexes were formed.[7] To understand the factors affecting the regioselectivity of the two competing reactions, first the electronic structure of the starting quinolones has to be known. NMR spectroscopy proved to be a useful method for monitoring the electronic structures of molecules, and NMR parameters have often been succesfully correlated with reactivity.[8] Therefore, in this work we studied the ^{1}H, ^{13}C and ^{19}F NMR spectra of ethyl 1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylate (**1**), its monochloro and monofluoro derivatives (**2–9**), difluoro derivatives (**10–15**), dichloro derivatives (**20–25**), several of its chlorofluoro derivatives (**16–19**) and a few trihalo derivatives (**26–30**) (see Scheme 1 and compounds **III** in Table 1).

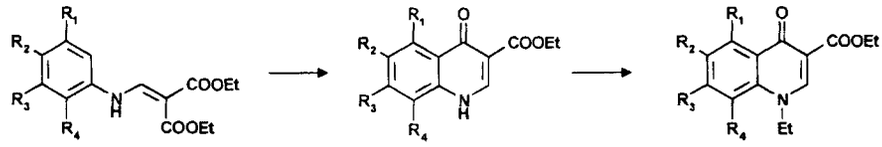
EXPERIMENTAL

Preparation of compounds

Compounds **III** (**1–30**) were prepared by the synthetic route shown in Scheme 1. The respective aniline was condensed[9] with diethyl ethoxymethylenemalonate and the resulting *N*-arylaminomethylenemalonate (**I**) was cyclized[10] thermally or by the action of polyphosphoric acid (PPA) ethyl ester, and finally the quinolone (**II**) was *N*-alkylated[11] by heating with triethyl phosphate in the presence of potassium carbonate.

The melting points of the intermediates **I** and **II** and of the final products **III** are presented in Table 1. The general synthetic procedure is described below:

Diethyl (*halo-substituted*-phenyl)aminomethylenemalonates of general formula I. A 10 mmol amount of the appropriate halo-substituted aniline and 10 mmol (2.16 g) of diethyl ethoxymethylenemalonate were heated and stirred at 115–120 °C for 30–60



I II III (1-30)

Scheme 1. Preparation of compounds **1–30**.

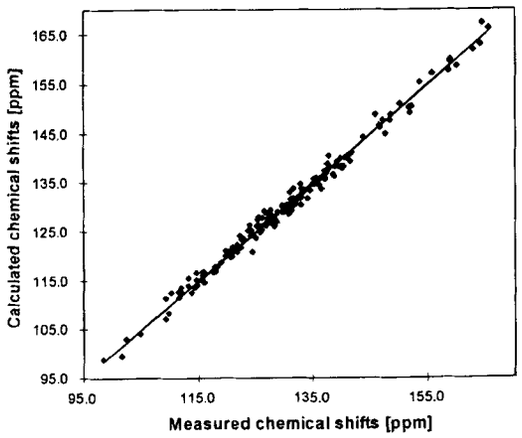


Figure 1. Calculated *vs* measured ^{13}C chemical shifts.

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Table 1. Structures and melting points of compounds I, II and III

				Intermediate I				Intermediate II				Product III		
R_1	R_2	R_3	R_4	M.p. (°C)	Lit. m.p. (°C)	Ref.	Method of ring closure	M.p. (°C)	Lit. m.p. (°C)	Ref.	Compound No.	M.p. (°C)	Lit. m.p. (°C)	Ref.
H	H	H	H	47–49	48–49	18	A	280	271–273	20	**1**	106–107	109	32
F	H	H	H	I (R_1 = F) = I (R_3 = F)			B	[a]			**2**	115–118		
H	F	H	H	71–72	69–70	19	A	288–289	313–314	26	**3**	183–184		
H	H	F	H	44–47	47–48	20	A	301	308–309	20	**4**	128–129		
H	H	H	F	81–82	77	21	A	214–216	214	21	**5**	120–122		
Cl	H	H	H	I (R_1 = Cl) = I (R_3 = Cl)			B	[b]	284–285	28	**6**	118–120		
H	Cl	H	H	88–89	82–83	18	A	300	303	29	**7**	160–162	184–185	33
H	H	Cl	H	56–57	56–57	20	A	>300	321–222	28	**8**	163–165		
H	H	H	Cl	90–92	92–93	22	A	254–256	256	29	**9**	122–124		
F	F	H	H	I (R_1 = R_2 = F) = I (R_2 = R_3 = F)			B	298			**10**	206–208		
F	H	F	H	103–105			A	313			**11**	134–136		
F	H	H	F	89–92			A	218–222			**12**	134–135		
H	F	F	H	80–83	77–79	19	A	322			**13**	155–156		
H	F	H	F	78–81	75–77	23	A	277–278			**14**	152–153	168–170	23
H	H	F	F	96–98			A	262–263			**15**	176–177	164–166	34
Cl	F	H	H	I (R_1 = Cl, R_2 = F) = I (R_2 = F, R_3 = Cl)			B	[c]			**16**	179–183		
H	F	Cl	H	73–76	58–60	19	A	312	302–304	30	**17**	165–167	171	32
H	F	H	Cl	82–83			A	310–313			**18**	124–129[*]		
H	Cl	H	F	93–94			A	284			**19**	143–144		
Cl	Cl	H	H	I (R_1 = R_2 = Cl) = I (R_2 = R_3 = Cl)			B	[d]			**20**	148–150		
Cl	H	Cl	H	87–89	92	24	A	306	326–328	24	**21**	162–163		
Cl	H	H	Cl	119–120	119–120	25	A	317–319	203–205	25	**22**	148–150		
H	Cl	Cl	H	84–86	76–77	26	A	335	335–337	26	**23**	174–176		
H	Cl	H	Cl	106–110	107–109	27	A	290	305	27	**24**	126–127		
H	H	Cl	Cl	99–100			A	290	288–290	6	**25**	122–125		
F	F	H	F	91–93			A	265			**26**	148–150		
H	F	F	F	92–93	89–91	19	A	273–274	280–283	31	**27**	205–206		
Cl	Cl	Cl	H	92–93	91–92	27	A	319–320	318	27	**28**	170–173		
Cl	Cl	H	Cl	104–106	114–115	27	A	268–270	273–275	27	**29**	154–155		
H	Cl	Cl	Cl	130–132			A	314–316			**30**	150–151		

[a] Isomeric mixture with II (R_3 = F).
[b] 60 : 40 ratio isomeric mixture of II (R_1 = Cl) and II (R_3 = Cl).
[c] Isomeric mixture with II R_2 = F, R_3 = Cl).
[d] Isomeric mixture with II (R_2 = R_3 = Cl).
[*] 96% purity.

min, while the ethanol formed in the reaction was distilled off. The reaction mixture was cooled to room temperature and diluted with 70% aqueous methanol (5 ml). The precipitated crystals were collected, washed with 70% aqueous methanol and dried. Yields varied between 77 and 95%, depending on the substituent.

Ethyl *halo-substituted*-1,4-dihydro-4-oxoquinoline-3-carboxylates of general formula II. *Method A: thermal ring closure of compounds I in Dowtherm A.* Dowtherm A (53 ml) was pre-heated to 250 °C and the malonate **I** (10 mmol) was added. The mixture was stirred at 250 °C for 1 h, while the ethanol, formed in the reaction, was distilled off. The reaction mixture was cooled to room temperature and the precipitated crystals were collected, washed with light petroleum. To the raw material, five volumes of absolute ethanol were added, the suspension was stirred under reflux conditions for 30 min, cooled to room tempetature and the crystals were collected and dried. Yields varied between 55 and 95%, depending on the substituent, but in most cases exceeded 80%.

Method B: ring closure of compounds I (R_1 = Cl; R_1 = F; R_1 = R_2 = Cl; R_1 = R_2 = F; and R_1 = Cl, R_2 = F) in PPA ethyl ester. A 10 mmol of the malonate **I** in 45 ml of PPA ethyl ester were heated and stirred at 100–110 °C for 3 h. The resulting thick reaction mixture was cooled to room temperature and poured on to 75 ml of ice–water mixture. The precipitated crystals were collected, washed consecutively with water and ethanol and dried. The raw materials were obtained in yields 82–95% depending on the substituent. They were isomeric mixtures, as shown in Table 1. The mixtures were reacted further without separation.

Ethyl *halo-substituted*-1,4-dihydro-1-ethyl-4-oxoquinoline-3-carboxylates of general formula **III**. To 10 mmol of the ring-closed product **II**, triethyl phosphate (7.28 g, 40 mmol) and anhydrous potassium carbonate (1.38 g, 10 mmol) were added and the mixture was heated and stirred at 190 ° for 1.5 h, then cooled to 100 °C and poured on to ice–water mixture (80 ml). The precipitated crystals were collected, washed consecutively with

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Table 2. ^{1}H NMR chemical shifts for compounds 1–30

Compound	2-H	5-H	6-H	7-H	8-H
1	8.55	8.57	7.45	7.71	7.48
2	8.41	—	7.04	7.59	7.22
3	8.55	8.21	—	7.46	7.54
4	8.49	8.56	7.15	—	7.11
5	8.42	8.37	7.37	7.42	—
6	8.40	—	7.40	7.51	7.34
7	8.55	8.51	—	7.65	7.43
8	8.56	8.50	7.42	—	7.48
9	8.46	8.54	7.34	7.73	—
10	8.41	—	—	7.50	7.19
11	8.39	—	6.81	—	6.91
12	8.32	—	6.99	7.34	—
13	8.52	8.32	—	—	7.28
14	8.42	8.06	—	7.22	—
15	8.41	8.35	7.26	—	—
16	8.38	—	—	7.45	7.35
17	8.50	8.27	—	—	7.54
18	8.45	8.21	—	7.51	—
19	8.40	8.33	—	7.42	—
20	8.37	—	—	7.70	7.28
21	8.37	—	7.40	—	8.37
22	8.34	—	7.33	7.54	—
23	8.46	8.58	—	—	7.57
24	8.43	8.48	—	7.71	—
25	8.46	8.43	7.55	—	—
26	8.32	—	—	7.32	—
27	8.41	8.19	—	—	—
28	8.35	—	—	—	7.48
29	8.31	—	—	7.77	—
30	8.44	8.57	—	—	—

water and ethanol and dried. Yields of the raw products varied between 45 and 99% depending on the substituent, but in most cases exceeded 90%. The raw products were purified as specified below.

Compounds **2**, **4**, **6**, **10**, **20** and **25** were purified by column chromatography using a silica gel 60 column. From 1.0 g of the respective raw product were obtained 0.56 g of **2** [eluent toluene–methanol (8:1)], 0.88 g of **4** [eluent toluene–methanol (99:1)], 0.2 g of **6**, besides 0.42 g of the isomeric **8** [eluent toluene–methanol (6:1); 0.1 g of **10**, besides 0.84 g of the isomeric **13** [eluent ethyl acetate–methanol (12:1)], 0.12 g of **20** [eluent toluene–methanol (6:1)], and 0.54 g of **25** [eluent toluene–methanol (4:1)].

In case of **11**, the aqueous mother liquor of the precipitated raw product was extracted with chloroform and the organic layer was separated, evaporated, triturated with water, to obtain pure **11** in 19% yield.

In the case of **30**, the raw product was crystallized from ethanol and then purified by preparative TLC on pre-coated silica gel 60 F-250 plates using benzene–methanol 5:1 as the eluent.

The raw product of **1** was crystallized from ethyl acetate–light petroleum (2:1), that of **9** from 50% aqueous ethanol, that of **16** four times from ethyl-acetate and that of **21** and **28** from ethanol–DMF (3:1). In all remaining cases, the raw products were crystallized from ethanol.

NMR spectra

^{1}H and ^{13}C NMR spectra were recorded on a Bruker WP-80 spectrometer at 80 and 20.1 MHz, on a Bruker AC-250 spectrometer at 250 and 62.1 MHz or on a Bruker AC-400 spectrometer at 400.13 and 100.62 MHz, respectively. Internal TMS was used as the chemical shift reference. Selective INEPT spectra[12] were measured with delays optimized for 7 Hz couplings (Δ_1 = 46 ms, Δ_2 = 56 ms) using 10 ms selective 90° proton pulses. ^{19}F NMR spectra were measured on a JEOL FX-100 spectrometer at 94 MHz or on a Bruker AC-400 spectrometer at 376 MHz. External trifluoroacetic acid was used as the chemical shift reference. The chemical shift of its signal was assigned to −77 ppm.

RESULTS

The structures of compounds **1**–**30** and their physical constants are presented in Table 1.

Table 3. J_{HH}, J_{FH} and J_{FF} coupling constants (Hz) in compounds 1–27[a]

Compound	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$^4J_{5,7}$	$^4J_{6,8}$	$^5J_{5,9}$
1	8.1	7.0	8.7	1.7	1.1	0.5
2	*11.2*	8.1	8.7	*5.0*	1.0	*1.0*
3	*8.9*	*7.2*	9.2	2.8	*4.4*	
4	8.9	*7.9*	*10.4*	*6.6*	2.3	0.5
5	+8.1 ± 0.1	+7.9 ± 0.1	*14.7 ± 0.1*	+1.6 ± 0.1	*+4.3 ± 0.1*	*−0.8 ± 0.1*
6	—	7.8	8.4	—	1.3	—
7	—	—	9.1	2.5	—	0
8	9.4	—	—	—	1.7	0
9	7.8	7.8	—	1.9	—	—
10	**18.9**	*9.4*	9.4	*7.5*	*3.8*	*2.2*
11	*11.1*	*8.8*	*10.3*	**13.5**	2.3	*1.8*
12	*10.4*	9.0	*14.0*	*4.3*	*3.4*	**19.8**
13	*10.4*	**22.0**	*11.2*	*8.9*	*6.0*	
14	*8.5*	7.5	*14.0*	3	**6.3**	*1.5*
15	9.1	*9.2*	**14.8**	*6.0*	*6.8*	*2.2*
16	—	*7.7*	9.4	—	*4.4*	—
17	*9.1*	—	—	—	*5.6*	0
18	*8.3*	*7.3*	—	3.2	—	—
19	—	—	*13.8*	2.5	—	*1.3*
20	—	—	9.2	—	—	—
21	—	—	—	—	1.9	—
22	—	8.5	—	—	—	—
23	—	—	—	—	—	0
24	—	—	—	2.6		
25	8.7	—	—	—	—	—
26	**19.5**	*9.4*	*13.8*	6.6	**1.5**	**17.5**
27	*10.6*	**22.6**	**17.0**	*8.3*	**4.9**	*2.4*

[a] J_{FH} values in italics; J_{FF} values in bold.

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Table 4. ^{13}C Chemical shifts (ppm) of compounds 1–30[a]

Compound	C-4a	C-5	C-6	C-7	C-8	C-8a
1	129.6	128.3	125.1	132.7	115.7	138.9
2	118.9	162.8	112.0	132.9	111.4	140.8
3	131.1	113.0	159.9	120.9	117.9	135.1
4	126.1	131.3	113.6	165.5	102.2	140.5
5	132.0	124.0	125.2	119.6	151.8	128.1
6	125.4	135.8	128.3	131.6	114.6	141.0
7	130.4	127.5	131.6	133.0	117.5	137.3
8	127.9	130.0	125.7	139.3	115.6	139.7
9	132.9	127.8	125.5	136.4	121.6	137.0
10	120.5	150.0	147.1	121.2	111.3	136.2
11	115.9	164.0	101.4	164.3	98.3	141.8
12	120.5	158.6	111.8	119.7	147.6	129.7
13	126.5	115.8	148.4	153.6	104.7	135.6
14	133.0	109.1	158.8	109.1	152.1	125.0
15	126.9	124.2	114.1	153.6	140.3	129.6
16	126.4	122.1	155.6	120.0	115.4	137.0
17	129.8	114.5	155.7	127.3	118.2	135.7
18	134.1	113.0	158.7	124.4	122.8	133.5
19	132.4	123.5	130.9	120.3	151.6	126.9
20	126.5	133.4	131.5	132.8	115.2	139.4
21	123.8	137.1	128.1	137.6	114.5	141.5
22	128.7	134.6	128.7	134.8	120.8	139.8
23	128.8	129.5	130.1	137.6	117.8	137.8
24	131.1	127.0	133.2	135.8	122.4	135.3
25	130.8	127.4	127.0	140.1	120.4	138.7
26	121.6	146.5	145.9	109.6	146.6	125.7
27	126.0	110.0	148.5	143.6	141.5	125.8
28	125.3	136.1	130.7	137.5	115.5	139.1
29	129.7	132.5	131.6	135.2	120.9	138.4
30	130.5	127.5	131.3	138.6	122.3	137.1

[a] Shift ranges for C-2, 147.4–152.1; C-3: 110.8–113.3; C-4, 171.5–174.4; COO, 164.9–166.0 OCH_2, 60.8–61.3; CH_3, 14.1–14.5; NCH_2, 48.8–53.6; CH_3, 14.1–16.4 ppm.

^1H NMR spectra of compounds **1–30** were measured in 0.05 M $CDCl_3$ solution. The assignment of the spectra was straightforward in most cases, but strongly coupled spin systems were observed with compounds **5** and **8** at 250 MHz. The chemical shifts and the coupling of these derivatives were obtained from spectral simulation using the PANIC program. The simulation was strongly dependent on the relative sign of the J_{FH} coupling constants so these were also obtained from the calculation. Unequivocal assignments of 6-H and 8-H in **5** were based on DNOE measurements; irradiation of the N-CH_2 signal resulted in intensity enhancement of 8-H. Similarly, DNOE measurements were used to assign 5-H and 2-H in compound **30**, NOE interaction was detected between NCH_2 and 2-H. Characteristic chemical shifts are summarized in Table 2 and the coupling constants obtained are listed in Table 3.

^{13}C NMR spectra of compounds **1–30** were measured in 0.2 M $CDCl_3$ solution. Unequivocal spectral assignment was achieved in most compounds based on general considerations of substituent effects on ^{13}C chemical shifts and based on the expected magnitude of J_{CF} coupling constants. The remaining uncertainties were resolved in compounds **6** and **15** by a DEPT experiment that determined the multiplicities of the signals, and in compounds **21**, **25** and **28–30** by proton coupled ^{13}C NMR spectra. Semi-selective INEPT spectra of compound **20** were measured by irradiating the two neighbouring aromatic protons selectively. The obtained correlations transferred by long-range carbon–proton couplings rendered unambiguous the assignment of C-5 and C-6 as the two aromatic protons. Unambiguous proton assignment was transferred to the protonated carbons by HETCOR 2D measurement in compound **25**. The chemical shifts of compounds **1–30** are summarized in Table 4 and J_{CF} coupling constants are listed in Table 5.

The chemical shifts of carbons C-4a, C-5, C-6, C-7, C-8 and C-8a were calculated for compounds **2–18**, adding the substituent effects of Cl and F (determined in benzene derivatives)[13] to the chemical shifts of compound **1**. The measured and the calculated shifts were compared. These values, together with the substituent chemical shifts (SCS) used, and the largest deviations obtained are summarized in the first column of Table 6. The predicted chemical shifts were plotted as a function of the measured shifts and the function $y = ax$ was fitted to the data. The slope of the straight line, the square of the regression coefficient (r^2) and the root mean square error of the prediction are also shown in the first column of Table 6.

The differences between measured and calculated chemical shifts are up to 5 ppm, and

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Table 5. J_{CF} **coupling constants (Hz) in compounds 2–5, 10–19, 26 and 27**

J	2	3	4	5	10	11	12	13	14	15	16	17	18	19	26	27
$^1J_{C5,F}$	265.9	—	—	—	267.4	268.8	262.9	—	—	—	—	—	—	—	264.8	—
$^1J_{C6,F}$	—	247.6	—	—	248.2	—	—	251.2	250.1	—	246.4	250.8	250.7	—	251.0	252.9
$^1J_{C7,F}$	—	—	252.7	—	—	252.7	—	256.1	—	253.6	—	—	—	—	—	257.5
$^1J_{C8,F}$	—	—	—	249.4	—	—	245.7	—	253.6	251.7	—	—	—	254.0	249.9	254.8
$^2J_{C4a,5F}$	7.0	—	—	—	1.8	6.9	7.6	—	—	—	—	—	—	—	3.8	—
$^2J_{C5,6F}$	—	23.0	—	—	13.0	—	—	18.6	22.7	—	18.1	22.6	23.4	—	12.7	18.6
$^2J_{C6,5F}$	21.8	—	—	—	12.6	25.6	24.6	—	—	—	—	—	—	—	14.4	—
$^2J_{C6,7F}$	—	—	22.6	—	—	25.6	—	13.6	—	18.7	—	—	—	—	—	11.0
$^2J_{C7,6F}$	—	25.1	—	—	19.8	—	—	15.3	28.3	—	25.4	20.7	27.3	—	29.1	17.2
$^2J_{C7,8F}$	—	—	—	23.2	—	—	26.0	—	26.8	13.5	—	—	—	26.6	22.7	16.1
$^2J_{C8,7F}$	—	—	26.9	—	—	26.2	—	22.4	—	16.7	—	—	—	—	—	14.2
$^2J_{C8a,8F}$	—	—	—	6.8	—	—	8.0	—	7.0	4.0	—	—	—	6.9	7.6	5.4
$^3J_{C4a,6F}$	—	6.9	—	—	0	—	—	4.7	7.6	—	—	6.1	~6	—	0	3.6
$^3J_{C4a,8F}$	—	—	—	0	—	—	0	—	0.9	0	—	—	—	0	0	2.5
$^3J_{C5,7F}$	—	—	10.4	—	—	14.9	—	2.4	—	8.3	—	—	—	—	—	3.4
$^3J_{C6,8F}$	—	—	—	8.5	—	—	8.3	—	11.9	0	—	—	—	10.3	12.0	2.2
$^3J_{C7,5F}$	12.0	—	—	—	1.8	14.9	10.7	—	—	—	—	—	—	—	0	—
$^3J_{C8,6F}$	—	7.9	—	—	6.3	—	—	0	10.8	—	8.0	0	9.0	—	9.2	2.3
$^3J_{C8a,5F}$	3.3	—	—	—	0	5.1	2.6	—	—	—	—	—	—	—	3.1	—
$^3J_{C8a,7F}$	—	—	11.6	—	—	13.1	—	9.1	—	2.5	—	—	—	—	—	2.2
$^4J_{C4a,7F}$	—	—	2.5	—	—	2.9	—	2.1	—	1.6	—	—	—	—	—	1.1
$^4J_{C5,8F}$	—	—	—	3.3	—	—	2.8	—	3.9	4.7	—	—	—	3.6	4.5	0
$^4J_{C8,5F}$	4.4	—	—	—	6.3	4.9	4.4	—	—	—	—	—	—	—	5.6	—
$^4J_{C8a,6F}$	—	1.8	—	—	—	—	—	2.0	3.0	—	2.0	0	2.6	—	0	0

the mean error of the prediction is about 2 ppm; therefore, multilinear regression calculation was performed to obtain the optimal SCS of the two halogen substituent applying the simple additive model of chemical shifts. The SCS values and their errors obtained in the regressional analysis are listed in the second column of Table 6. The value of 0.9805 was obtained for r^2 of the multiple regression. The differences between the calculated and the measured shifts decreased. The calculated chemical shifts were plotted as a function of the measured shifts and the straight line $y = ax$ was fitted to the data again. The parameters of this fit are listed in the second column of Table 6.

We found that the largest deviations between the measured and the calculated

Table 6. SCS values and statistical parameters of the predictions

	I	II	III
ipso-F	35.1	33.9 ± 0.3	33.5 ± 0.3
ortho-F	−14.3	−11.9 ± 0.2	−12.8 ± 0.2 (p)[e]
			−10.9 ± 0.3 (q)[e]
meta-F	0.9	1.2 ± 0.2	1.1 ± 0.2
para-F	−4.4	−4.2 ± 0.3	−4.2 ± 0.3
ipso-Cl	6.4	6.1 ± 0.3	6.7 ± 0.3
ortho-Cl	0.2	−0.2 ● 0.2	1.1 ± 0.2 (p)
			−1.5 ± 0.3 (q)
meta-Cl	1.0	0.9 ± 0.2	1.0 ± 0.2
para-Cl	−2.0	−1.6 ± 0.3	−1.6 ± 0.3
R^2 (m)[a]		0.9805	0.9903
D (m)[b]		1.7	1.3
D_{max}[c]	+5.8 to 4.8	+3.9 to −4.2	+3.4 to −3.1
estimated/predicted $y = ax$ linear regression			
a	0.99636	0.9996	0.9997
r^2	0.97688	0.9850	0.9900
D [d]	2.08	1.58	1.29

[a] Square of regression coefficient of the multiple regression.
[b] Root mean square of the error of estimation of the multiple regression (ppm).
[c] Maximum deviations between the measured and predicted shifts (ppm).
[d] Standard error of estimation (ppm).
[e] (p) SCS for carbons bearing hydrogen; (q): SCS for quaternary carbon

shifts are observed for those quaternary carbons which are in an *ortho* position to a chloro or a fluoro substituent. Therefore, the multiple regression was repeated introducing two new parameters: different SCS values were used for quaternary and methine carbons. The results are summarized in the third column of Table 6. A value of 0.9899 was obtained for the r^2 of the multiple regression. The maximum deviation between the measured and predicted chemical shifts further decreased. The calculated chemical shifts are plotted as a function of the measured shifts in Fig 1. The straight line shown the $y = ax$ fit of the data; the parameters of this linear regression are listed in the third column of Table 6.

^{19}F NMR spectra of compounds containing fluorine were measured in 0.2 M $CDCl_3$ solutions. Assignment of the spectra of di- and trifluoro derivatives were unambiguous knowing the chemical shifts of the monofluoro derivatives, and knowing the J_{FH} values from the ^1H NMR spectra. The ^{19}F NMR chemical shifts are summarized in Table 7 and the J_{FF} values are listed in Table 3.

DISCUSSION

Deviations of the SCS values from true additivity have been thoroughly studied for 1,4- and 1,3-disubstituted benzene derivatives,[14] but the calculated chemical shift based on simple additivity is still an important method of spectral assignment. The breakdown of the simple additivity rules due to the interaction of substituents in *ortho* positions has been known for a long time,[15] but to our knowledge no efforts have been made to introduce correction terms. The SCS values were found to be different in chlorinated naphthalenes when the halogen atom is connected to C-1 or C-2, and upfield deviations of the measured shifts from the calculated values were observed for *ortho*-disubstituted derivatives.[16] These effects were interpreted in terms of steric hindrance. The inspection of the reported chemical shifts revealed that a 2–3 ppm upfield deviation of the calculated chemical shifts from the measured values occurs in all cases at quaternary carbons. This is in agreement with our data, the *ortho* SCS values of chlorine are −1.5 and +1.1 ppm for quaternery and methine carbons, respectively.

The statistical analysis of the three different procedure used for the calculation of chemical shifts (Table 6) clearly shows that the simple method suggested for the correction of the *ortho* effect substantially increases the quality of the prediction.

The large set of carbon-fluorine coupling constants in Table 5 permits us to investigate the effect of substitution on this parameter. Substituent-induced changes in these coupling constants closely follow the trends observed earlier by Weigert and Roberts.[17]

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Table 7. ^{19}F Chemical shifts (ppm) of compounds 2–5, 10–19, 26 and 27[a]

Compound	5-F	6-F	7-F	8-F
2	−34.08	—	—	—
3	—	−39.13	—	—
4	—	—	−28.04	—
5	—	—	—	−47.10
10	−61.59	−64.96	–	—
11	−103.34	—	−100.67	—
12	−111.53			−126.45
13	—	−62.44	−51.04	—
14	—	−111.35	—	−117.77
15	—	—	−128.98	−149.78
16	—	-39.11	—	—
17	—	−41.58	—	—
18	—	−113.65	—	—
19	—	—	—	−119.98
26	−141.69	−136.71	—	−122.98
27	—	−58.86	−74.01	−68.10

[a] $\delta_{CFCl_3} = 0.00$ ppm

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Received 16 April 1996; accepted (revised) 20 June 1996