Proton, Carbon-13 and Fluorine-19 NMR Studies of N-Alkyl-8-fluoroquinolinium Halides: Relative Signs of Through-space ¹H-¹⁹F and ¹³C-¹⁹F Coupling Constants

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Because of experimental and theoretical interest in long-range ${}^{1}H^{-19}F$ and ${}^{13}C^{-19}F$ coupling constants between proximate atoms, a series of N-alkylfluoroquinolinium compounds was synthesized and the NMR parameters were accurately measured. By means of spin tickling and selective population inversion difference spectroscopy, the ${}^{5}J(HF)$ and ${}^{4}J(CF)$, which are associated with the proximate fluorine and methyl groups, were shown to be of the same (positive) sign as the directly bonded ${}^{13}C^{-1}H$ and vicinal ${}^{1}H^{-1}H$ coupling constants. In N-methyl-8-fluoroquinolinium iodide (1a) and chloride (1b) ${}^{5}J(HF) = +8.8$ and ${}^{4}J(CF) = +16.3$ Hz, and in N-ethyl-8-fluoroquinolinium iodide ${}^{5}J(HF) = +3.0$, ${}^{6}J(HF) = +1.5$, ${}^{4}J(CF) = (+)$ 15.8 and ${}^{5}J(CF) = \pm 5.2$ Hz. Calculated molecular orbital results, which were based on the INDO-FPT method and a molecular geometry from the x-ray diffraction data for 1b, were in reasonable agreement with the ${}^{4}J(CF)$ values, but the ${}^{5}J(HF)$ values were of the wrong sign and magnitude.

It has been suggested^{1,2} that long-range hydrogenfluorine coupling constants (LRHFC) exhibit a complex dependence on proximity and bond orientation effects. Semi-empirical molecular orbital (MO) results for the Fermi contact contribution to LRHFC usually led to large negative values in those cases in which the two nuclei were spatially proximate. However, large positive values were found when the C-H bond was directed away from the fluorine atom. In the latter case it was noted that substantial contributions to the LRHFC arose from the non-bonded interactions associated with the orbitals of the fluorine and those of the carbon atom to which the proton is bonded. Recent results^{3,4} have emphasized that non-bonded interactions are pervasive in providing mechanisms for 'relaying' nuclear spin-spin coupling involving ¹³C and ¹⁹F.

An experimental criterion for the importance of the non-bonded interactions for long range H–F coupling is provided by the substantial (8.8 Hz; a preliminary value of 8.3 Hz was given in Ref. 1) coupling between the N-methyl hydrogens and the fluorine atom in N-methyl-8-fluoroquinolinium iodide (1a), since this coupling is too small to be measured over the same number of bonds in the 3-fluoro derivative 2.

Based on the literature data for the geometry of the quinoline ring,^{1,5} the calculated INDO-FPT molecular orbital results for LRHFC to the three *N*-methyl



hydrogens in **1a** were -17.3, -17.3 and 30.6 Hz for the orientation depicted in Fig. 1a.¹ It seemed likely that the disparity between the average of these three values (-1.3 Hz) and the experimental value of ± 8.8 Hz was due to inappropriate structural data, as well as the cancellation between large terms of opposite sign and possible influences of the solvent. Accordingly, this study presents detailed NMR studies of



Figure 1. (a) Specifications of the dihedral angle ϕ , measured about the N---C-9 bond, for the lowest energy conformation of the *N*-methyl-8-fluoroquinolinium cation **1**. (b) In the *N*-ethyl-8-fluoroquinolinium cation **3**, the dihedral angle is measured clockwise from the quinolinium plane, but it is measured to the C---H bond which lags the methyl group by 120°. The calculated lowest energy conformation is that for which $\phi = 160^\circ$.

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the ${}^{1}H{-}{}^{19}F$ and ${}^{13}C{-}{}^{19}F$ coupling constants, including sign determinations, in the non-aromatic parts of the series of molecules **1**-**3**, and a comparison with theoretical results.



EXPERIMENTAL

Syntheses

N-Methyl-8-fluoroquinolinium iodide (1a). The synthesis of 8-fluoroquinoline by Roe and Hawkins⁶ was modified using the method of Fletcher and Namkung⁷ to prepare the fluoroborate salt. To an ice-cold, mechanically stirred solution of 8-aminoquinoline (10.0 g, 0.069 mol) in tetrahydrofuran (30 ml) was added 40% fluoroboric acid (60 ml, 0.36 mol) and water (30 ml). After 10 min a chilled solution of sodium nitrite (6.0 g, 0.087 mol) in water (10 ml) was added dropwise. The suspension was stirred at 0 °C for 10 min and then the orange precipitate was collected by filtration, washed with ice-cold ether (4×10 ml) and air-dried overnight to afford 15.6 g (93%) of crude diazonium fluoroborate, m.p. 144 °C (dec.).

The diazonium salt was decomposed in an efficient hood by adding the salt (15 g, 0.062 mol) gradually and with magnetic stirring through a large-bore air condenser to refluxing xylene (350 ml). After the addition was complete, most of the xylene was removed by distillation. The residue was extracted with hydrochloric acid which was neutralized with aqueous sodium carbonate and extracted with diethyl ether. The ether extract was dried over sodium sulfate and concentrated *in vacuo* to afford 3.4 g (37%) of a brown oil. Distillation gave 2.7 g (30%) of 8-fluoroquinoline as an oil, b.p. 70 °C/0.3 mmHg;lit.,⁶ b.p. 148 °C/30 mmHg. The picrate has m.p. 172–173 °C (ethanol); lit.,⁶ 170– 172 °C.

The methiodide **1a** was prepared by refluxing 8fluoroquinoline (0.52 g, 0.0035 mol) and iodomethane (2.5 g, 0.0175 mol) in benzene (10 ml) for 2 h. The resulting solid was crystallized from ethanol to give **1a** as yellow needles, m.p. 193 °C. Analysis: calculated for $C_{10}H_9NFI$, C 41.55, H 3.14, N 4.84; found, C 41.51, H 3.09, N 4.73%.

 $N-(^{13}C-Methyl)-8$ -fluoroquinolinium iodide (1c). This was prepared by the same method, except that equimolar quantities of 8-fluoroquinoline and $^{13}CH_3I$ were used in the last step.

N-Methyl-8-fluoroquinolinium chloride (1b). A solution of **1a** (2.0 g, 0.0069 mol) and freshly prepared silver chloride (3.5 g, 0.024 mol) in dry ethanol (120 ml) was stirred at 20 °C for 24 h. The mixture was filtered and the filtrate concentrated to afford a white solid.

Crystallization from ethanol-diethyl ether gave **1b** (1.37 g, 100%) as a white powder, m.p. 186-189 °C.

N-Methyl-3-fluoroquinolinium iodide (2). The synthesis of 3-fluoroquinoline⁶ was modified⁷ as described above for 8-fluoroquinolinium iodide. Thus, the diazonium fluoroborate was obtained from 3-aminoquinoline (Pfaltz and Bauer) in 87% yield, m.p. 89 °C (dec.) [lit.,⁶ m.p. 95 °C (dec.)]. The fluoroborate salt was decomposed in refluxing toluene to give 3-fluoroquinoline in 72% yield, b.p. 72 °C/0.8 torr (lit.,⁶ b.p. 102 °C/15 torr). The picrate had m.p. 185–186 °C (ethanol) (lit.,⁶ m.p. 183–185 °C).

The methiodide was prepared in the manner described above and was crystallized from ethanol to give N-methyl-3-fluoroquinolinium iodide (2) as yellow needles, m.p. 191 °C. Analysis: calculated for $C_{10}H_9NFI$, C 41.55, H 3.14, N 4.84; found, C 41.56, H 3.14, N 4.82%.

N-Ethyl-8-fluoroquinolinium iodide (3). A solution of 8-fluoroquinoline (1.16 g, 0.00789 mol) and ethyl iodide (2.1 g, 0.013 mol) in benzene (20 ml) was refluxed for 24 h. The resulting solid was collected and crystallized from ethanol-diethyl ether to give **3** (0.96 g, 40%) as yellow needles, m.p. 170-172 °C. Analysis: calculated for $C_{11}H_{11}NFI$, C 43.59, H 3.66, N 4.62; found, C 43.55, H 3.59, N 4.60%.

NMR spectra

Proton, ¹³C and ¹⁹F NMR spectra were recorded at 250.13, 62.90 and 235.39 MHz, respectively, on a Bruker Instruments WM-250 FT NMR spectrometer. (On the WM-250 spectrometer it is essential to ensure that the ¹⁹F spectra are plotted in the same sense as the spectra for the other nuclei). Several ¹³C NMR spectra were also recorded at 22.63 MHz on a Bruker Instruments WH-90 FT NMR spectrometer. Either DMSO- d_6 or acetone- d_6 was used as solvent and internal ²H lock materials. Chemical shifts are referenced downfield from internal tetramethylsilane (TMS). In all cases the digital resolution, as determined by spectral widths and computer memory size, was better than the estimated errors.

Relative signs were determined by spin tickling⁸ and selective population inversion (SPI) difference spectroscopy.^{9,10} The pulse sequence used to apply a selective 180° pulse while observing ¹³C or ¹⁹F is given in Fig. 2. The first half of the pulse sequence is the SPI experiment, and the second half (starting at the memory inversion) subtracts a normal ¹³C spectrum (for example) from the SPI data. The selective 180° proton pulse is a long (0.3–1.5 s), low intensity pulse generated using an external 20–67 db attenuator and the low power range proton decoupler channel NMR hardware. Thirty milliseconds after the selective 180° pulse, an intense non-selective 90° ¹³C pulse is applied using the usual ¹³C observation channel hardware. After the 90° pulse, the data acquisition period was 12.5 s. To subtract the normal ¹³C NMR data from the SPI data to form SPI-difference data, the SPI free induction decay signal is inverted before the normal



Figure 2. Pulse sequence for SPI difference spectra.

free induction decay is added to the memory and then, after the addition, the computer memory was inverted again. The normal ¹³C NMR data were collected with a non-selective 90° pulse and a 12.5 s data acquisition period. The entire pulse sequence was repeated until an adequate signal-to-noise ratio of the SPI-difference data was achieved.

Analyses of proton NMR spectra

N-Methyl-8-fluoroquinolinium iodide (1a) and chloride (1b). The initial proton chemical shift assignments were made with data from a series of homonuclear decoupling experiments. Then, a complete secondorder iterative fit of the seven spin system, including the six hydrogens of the quinolinium ring and the fluorine, was performed using Bruker Instruments PANIC.80 NMR simulation program.¹¹ In the proton NMR spectra of 1a the methyl hydrogens were decoupled to eliminate the 0.70 and 0.62 Hz couplings to H-2 and H-4, respectively. The agreement between

the simulated and experimental spectra was excellent, with a root-mean-square error in the peak positions of 0.064 Hz.

The proton chemical shift assignments for 1a and 1b are given in Table 1. Inter-proton coupling constants are given in Table 2. The 14.62 Hz coupling constant to the fluorine identifies H-7. The 8.01 and 8.21 Hz vicinal proton-proton couplings link H-7 to H-6 and H-6 to H-5. The four-bond 0.52 Hz coupling links H-5 to H-4 and the 8.50 and 5.84 Hz vicinal coupling constants, respectively, complete the assignments by linking H-4 to H-3 and H-3 to H-2. The large downfield chemical shift of C-2 caused by the nitrogen is additional confirmation of the identity of H-2.

To analyze the proton spectrum of 1a, it was necessary to understand the spectrum of the impurity in the The impurity was identified as sample. Nmethylquinolinium iodide.

N-Methyl-3-fluoroquinolinium iodide (2). The proton chemical shift assignments in Table 1 were made using several types of decoupling experiments and the coupling constants. Homonuclear proton decoupling experiments and selective proton decoupling while observing fluorine allowed most of the coupling constants to be deciphered. The proton spectra were then fitted with Bruker Instruments PANIC.80 NMR simulation program.¹¹ An iterative seven-spin simulation of the six aromatic hydrogens and fluorine produced good agreement between the experimental and calculated line positions, with a root-mean-square error of 0.070 Hz.

Chemical shift assignments for H-2, H-4 and the methyl hydrogens were clear. The assignments of H-2 versus H-4 could be made from the downfield shift of H-2 and the lack of coupling from H-2 to the hydrogens in the other aromatic ring (see Table 2). The assignments for H-5 and H-8 were based on their 0.55 and 0.92 Hz coupling constants. In 1b the coupling

Table	1. Pro	ton chemical	shifts	and ¹ H- ¹⁹ F	couplin	ig constants	for con	npounds 1–3		
	1a [*]		1b*			2 ⁶		3 ⁶		
	δ	J(HF) ^d	δ	J(HF) ^d	δ°	J(HF) ^d	δ	J(HF) ^d		
H-2	9.52	<0.3	9.77	<0.	10.15	4.8(5)	10.10	<0.3		
H-3	8.22	()0.3(1)°	8.23	0.6			8.46	<0.3		
H-4	9.33	2.23(10)	9.39	2.1(2)	9.33	7.76(9)	9.59	2.18(3)		
H-5	8.31	-0.73(4) ^f	8.36	-0.73º	8.58	<0.2	8.57	-0.82(2) ^f		
H-6	8.01	4.36(2)	8.01	4.36(8)	8.19	1.0(2)	8.24	4.28(3)		
H-7	8.14	14.62(2)	8.14	14.64(8)	8.37	0.61(5)	8.30	15.00(3)		
H-8	—				8.73	<0.3	—			
H-9	4.75	8.79(3)	4.80	8.81(9)	5.00	<0.2	5.54	3.03(6)		
		[8.59(4)] ^b					[5.16]ª	[3.20(8)]*		
H-12 ⁱ				<u></u>	_		1.95	1.47(1)		
							[1.63]*	[1.59(8)] ^a		

^e In DMSO-d_e.

^b In acetone- d_6 . ^c In ppm from TMS.

^d In hertz; values in parentheses are errors in the last significant figure cited.

* A negative sign was assumed in the iterative NMR computer simulation.

^f The symmetry of the spectrum indicates that the coupling is negative.

⁹ This value was fixed in the iterative NMR computer simulation.

^h H-9—H-11 are the equivalent hydrogens of the methyl group of 1a, 1b, and 2; H-9 and

H-10 are the equivalent hydrogens of the methylene group in 3. ¹ H-12 is one of the hydrogens of the methyl group in 3.

Table 2. Inter-proton coupling constants in 1a, 1b, 2 and 3 ^a								
Coupled			-0	-0	-h			
nuclei	18	165	2	3~	35			
2,3	5.84(4)	5.82(2)		5.69(8)	5.82(8)			
2,4	1.46(5)	1.46 ^d	2.68	1.39(3)	1.42(5)			
2,5	<0.3	<0.6	<0.3	0.09(2)	0.09 ^d			
2,6	<0.3	<0.3	<0.3	0.16(3)	0.16 ^d			
2,7	<0.3	<0.3	<0.3	0.25(3)	0.25(6)			
2, 8	_		<0.3					
2, CH ₂			_	(-)0.40(6)°	<0.5			
2, CH ₃	(-)0.70(5)°	-0.7(2)	0.71(5)	<0.2	<0.5			
3, 4	8.50(3)	8.45(8)	—	8.45(4)	8.29(6)			
3, 5	(-)0.15(9)*	-0.15 ^d		(-)0.23(2)°	-0.23 ^d			
3, 6	<0.2	<0.2		0.18(3)	0.18 ^d			
3,7	<0.2	<0.2		0.25(3)	0.25(6)			
3, CH ₂		—	_	0.20(6)	<0.5			
3, CH ₃	<0.2	<0.5		<0.2	<0.5			
4,5	(-)0.52(9) ^e	-0.52 ^d	()0.55(9)	(-)0.45(2)°	–0.45 ^d			
4,6	<0.2	<0.2	<0.6	0.15(3)	0.15 ^d			
4,7	<0.2	<0.2	<0.6	<0.2	0.00 ^d			
4, 8		—	0.9(2)					
4, CH ₂	_			(-)0.20(6)°	<0.5			
4, CH3	(-)0.62(5)*	(-)0.7(2)*	<0.2	<0.4	<0.5			
5,6	8.21(2)	8.16(8)	8.31(9)	8.25(2)	8.28(4)			
5,7	1.35(2)	1.31(8)	1.39(9)	1.34(2)	1.35(4)			
5,8			0.7(2)	_	_			
5, CH,				<0.1	<0.5			
5, CH	<0.2	<0.5	<0.1	<0.2	<0.5			
6,7	8.01(2)	8.01(8)	7.09(9)	7.98(3)	7.98(3)			
6,8	_		0.86(20)) —				
6, CH,		—	_	<0.1	<0.5			
6, CH	<0.2	<0.5	<0.1	<0.2	<0.5			
7,8		<u> </u>	9.07(9)	_	_			
7, CH,				<0.1	<0.5			
7, CH,	<0.2	<0.5	<0.1	<0.2	<0.5			
8, CH		_	<0.1	_	_			
CH₂CH₃	_			7.20(1)	7.19(6)			

^a All values in Hz. Values in parentheses are uncertainties in the last significant figure.

^b DMSO-d₆ solvent.

^c Acetone-d₆ solvent.

^d This value was assumed in the iterative NMR simulation.

• Negative sign obtained in the iterative analysis, or assumed by analogy to similar compounds.¹⁹

between H-4 and H-5 is also 0.52 Hz, and several similar compounds have been reported with J(45) of about 0.5 Hz and J(48) of about 0.9 Hz.¹²

N-Ethyl-8-fluoroquinolinium iodide (3). Table I shows that the proton chemical shifts for **3** are very similar to those for *N*-methyl-8-fluoroquinolinium chloride and iodide. Seven-spin iterative fits of the aromatic hydrogens and the fluorine gave the hydrogen-fluorine and hydrogen-hydrogen coupling constants listed in Tables 1 and 2. The experimental peak positions for **3** in both acetone- d_6 and DMSO- d_6 were in excellent agreement with the simulated peak positions, with a root-mean-square error of 0.028 Hz.

Analysis of ¹³C NMR spectra

N-Methyl-8-fluoroquinolinium iodide (1a) and chloride (1b). Chemical shift assignments for **1a** were also

complicated by the presence of the impurity Nmethylquinolinium iodide. The unfortunate ratio of two parts **1a** and one part impurity caused each fluorine split carbon resonance from **1a** to have the same intensity as the impurity peaks. The mixture was divided into **1a** and impurity peaks by taking carbon spectra at two fields (5.9 and 2.1 Tesla). Running the sample at more than one field identified the carbon resonances which are coupled to fluorine, and since fluorine NMR spectra showed that the impurity did not contain fluorine, all fluorine coupled carbons belong to **1a**. The resulting division of peaks was later confirmed by the carbon spectra of the relatively pure N-methyl-8-fluoroquinolinium chloride (**1b**).

The carbon chemical shifts for **1a** and **1b** in Table 3 are unambiguous. The five carbon assignments of the methyl carbon, C-2, C-4a, C-8a, and C-8 were relatively simple. The off-resonance decoupled spectra identified the methyl carbon and separated quaternary from methine carbons. The 1 Hz nitrogen broadening identified the methine carbon C-2 and differentiated the two quaternary carbons C-4a and C-8a. The large directly bonded fluorine coupling of 256 Hz identified C-8.

The remaining five carbon assignments were much more difficult. The proton spectra of **1a** permitted the assignments of the carbons. Each hydrogen was selectively irradiated while observing the carbon spectra to assign the attached carbon resonance. The ¹³C NMR parameters are consistent with those for fluoropyridinium ions and fluoroquinolines.¹³

The chemical shift assignments for the iodide **1a** were then used to assign the carbon resonances in the chloride **1b**. Changing the anion from iodide to chloride did not significantly change the chemical shifts of the carbon resonances (see Table 3).

N-Methyl-3-fluoroquinolinium iodide (2). Chemical shift assignments in Table 3 for half of the carbons in **2** were relatively easy. The large 246 Hz directly bonded fluorine coupling identifies C-3. An incompletely proton decoupled carbon spectrum allowed the quaternary carbons C-4a and C-8a to be found, and nitrogen broadening helped assign C-8a and C-2. Once C-2 was identified, C-4 was assigned by its large 17.3 Hz fluorine coupling constant. The very different chemical shift of the methyl carbon from the aromatic carbons, as well as off-resonance decoupled spectra, made this assignment obvious. The remaining four carbons (C-5–C-8) were assigned by selectively decoupling the proton resonances while observing the 13 C NMR spectra.

N-Ethyl-8-fluoroquinolinium iodide (3). The aromatic carbon chemical shift assignments for **3** are the same as for **1a** and **1b** in Table 3. The assignments of the carbons of the ethyl group were confirmed by off-resonance decoupling.

Measurements of the ¹⁹F NMR spectra

The ¹⁹F chemical shifts of **1a**, **2** and **3** measured in acetone- d_6 and DMSO- d_6 are given in Table 4.

	DMSC	-a ₆						
	1a		1ь		2		3	
	δ	J(CF) ^b	δ	J(CF) ^b	δ	J(CF) ^b	δª	J(CF) ^b
C-2	152.3	1.50(9)	152.6	1.54(7)	142.3	40.7(2)°	151.7	1.6(1)
C-3	122.8	1.54(7)	122.7	1.49(4)	154.0	246.4(1)	123.0	1.38(6)
C-4	146.9	2.50(6)	147.0	2.50(4)	130.2	17.3(1)	147.2	2.4(1)
C-4a	131.3	0.51(7)	131.3	0.50(2)	129.0	8.4(1)	131.7	0.66(6)
C-5	126.8	4.55(7)	126.8	4.57(2)	129.8	5.5(1)	127.3	4.34(6)
C-6	130.3	8.66(7)	130.2	8.64(4)	130.6	1.0(1)	130.2	8.96(6)
C-7	121.2	22.30(7)	121.1	22.36(4)	134.5	2.4(1)	121.6	23.15(6)
C-8	152.2	255.80(6)	152.1	255.73(2)	119.1	1.2(1)	151.3	255.0(1)
C-8a	128.6	8.14(5)	128.5	8.07(7)	136.3	1.3(1)	127.3	7.86(6)
C-9°	49.9	+16.31(4)	49.6	16.34(7)	45.7	<0.6	57.7	15.75(6)
		[17.2(3)] ^d						[16.2(2)] ^d
C-10 ^e		—	—	_	_		16.2	5.20(4)
								[5.7(2)] ^d

Table 3. Carbon-13 chemical shifts and ¹³C-¹⁹F coupling constants for compounds 1-3 in DMSO-d.

* In parts per million to high frequency of TMS.

^b In hertz; except for coupling to C-9 in 1a, signs were not determined. Values in parentheses are uncertainties in the last place.

^e Methyl carbon in 1a, 1b and 2, methylene in 3.

^d Value measured in acetone-d₆.

^e Methyl carbon of 3.

iorine-19 m from C	chemical FCl ₃	shifts in		
1a	2	3		
-112.5	-122.5	115.2		
-113.3	-122.1	-114.7		
	iorine-19 m from C ^{1a} –112.5 –113.3	and the second state and the s	accine-19 chemical shifts in m from CFCl ₃ 1a 2 3 -112.5 -122.5 -115.2 -113.3 -122.1 -114.7	

Signs of ${}^{4}J({}^{13}CF)$ and ${}^{5}J(HF)$ in N-(${}^{13}C$ -methyl)-8-fluoroquinolinium iodide (1c).

To determine the relative signs of the long-range coupling constants in 1, the ¹³C-labeled *N*-methyl compound 1c was prepared. The five-spin subsystem consisting of the ¹⁹F, ¹³C and methyl hydrogens gives a spectrum of the AMX₃ type. The ¹H NMR spectrum of the methyl group consists of a doublet of doublets; the ¹³C NMR spectrum is a quartet which is split into doublets by both the ¹⁹F and H-2 of the ring; the ¹⁹F signal is a complex multiplet due to additional coupling with the aromatic protons.



The method of selective population inversion $(SPI)^{9,10}$ was used to determine the signs of ${}^{4}J({}^{13}C^{19}F)$ and ${}^{5}J({}^{1}H^{19}F)$ relative to the (positive) directly bonded ${}^{13}C^{-1}H$ coupling constant of the methyl group. In the SPI scheme, long selective 180° pulses are applied to invert the populations of the two associated energy levels, followed by observation of the changes in the transitions which share one of the perturbed energy

levels. Energy level diagrams (in the form of Castellano tables¹⁴) were constructed for all possible sign combinations for comparison with the experimental results. To eliminate the transitions which are not affected by the population inversion, the normal spectrum is subtracted from the SPI spectrum. The pulse sequence, which was used to perform the SPI difference experiments, is depicted in Fig. 2.

Two experiments were required to establish the relative signs of ${}^{5}J(\text{HF})$ and ${}^{4}J(\text{CF})$; in the first of these the ¹³C NMR spectra of the labeled methyl were examined while irradiating each of the proton transi-tions. The proton-coupled ¹³C NMR spectrum of the methyl group is shown in Fig. 3a (each of the ¹³C transitions is further split into doublets due to coupling with the aromatic hydrogen H-2). The doublets labeled C2 and C4 are obscured by overlap with lines from the impurity N-(¹³C-methyl)quinolinium iodide. These caused no difficulty, however, as the impurity lines cancelled out in the SPI difference spectra depicted in Fig. 3b and c. These were obtained, respectively, by applying selective 180° pulses to the H1 and H2 transitions of the methyl group protons. In each group the transitions are numbered in order of increasing frequency. The ¹H NMR spectrum of the methyl group in 1c consists of a doublet of doublets. The four transitions are labeled H1-H4 in order of increasing frequency. The progressively and regressively connected transitions lead to lines with positive and negative intensities, respectively. The patterns of the ¹³C SPI difference spectra in Fig 3b and 3c show clearly that ${}^{4}J(CF)$ and ${}^{5}J(HF)$ are of the same sign. Long-range H-F and C-F coupling constants were both positive or both negative. The ¹⁹F NMR spectrum of 1c is shown in Fig. 4a; it is complicated by substantial coupling from the aromatic protons as well as the spins of the ¹³CH₃ group. The ¹⁹F SPI difference spectra arising from the application of selective 180 pulses to the H1, H3 and H2 transitions of the



Figure 3. (a) Coupled ¹³C NMR spectrum of the methyl group of N-(¹³C-methyl)-8-fluoroquinolinium iodide (1c). The C2 and C4 doublets are obscured by doublets from the impurity, ¹³C-methylquinolinium iodide. Each line is split into a doublet by the aromatic proton H-2. (b) SPI difference spectrum resulting from the application of a selective 180° pulse to the proton transition H1. (c) SPI difference spectrum resulting from the application of a selective 180° pulse to the proton transition H2. (d) Simulated ¹³C spectrum of the methyl group of 1c, assuming a 4.45 Hz coupling to the aromatic proton H-2. The eight doublets are numbered in order of increasing frequency.

protons are depicted in Fig. 4b, c and d, respectively. In order to understand these SPI difference spectra, a simulated ¹⁹F (stick) spectrum is given in Fig. 4e. For simplicity, couplings to the aromatic protons were ignored so the spectrum consists of a doublet of quartets and the transitions are designated F1-F8 in Fig. 4e. From the Castellano tables for the AMX₃ spin system, those ¹⁹F transitions which are progressively (P) and regressively (R) connected to the proton transitions for both the +++ and +-- sign combinations are listed in Table 5. The SPI difference spectra in Fig. 4b, c and d are only consistent with + + +. For example, a selective 180° pulse at the H1 proton transition shifts the spectrum to low frequency because of the disappearance of the high-frequency quartet. On irradiation of H3 the spectrum is shifted by an equal amount in the opposite direction.

Signs of ${}^{5}J(FCH_{2})$ and ${}^{6}J(FCH_{3})$ in 3

The non-aromatic atoms in **3** can be viewed as an A_3M_2X spin system composed of three equivalent methyl hydrogens and two equivalent methylene hydrogens coupled to the fluorine atom. At 250 MHz the proton NMR spectrum of the ethyl group of **3** is a first-order pattern with the couplings ${}^{3}J(CH_2CH_3) = +7.20 \text{ Hz}$, ${}^{5}J(FCH_2) = \pm 1.47 \text{ Hz}$ and ${}^{6}J(FCH_3) = \pm 3.03 \text{ Hz}$. Spin tickling the fourth downfield peak of the methyl group triplet of doublets splits or attenuates the second, fourth and sixth peaks in the quartet of doublets associated with the methylene hydrogens. This shows that the signs of ${}^{5}J(FCH_2)$ and ${}^{6}J(FCH_3)$ are the same. Further irradiations of the ${}^{1}H \text{ NMR}$ resonance were performed to verify this result.



Figure 4. (a) The proton-coupled ¹⁹F NMR spectrum of 1c is a broad multiplet due to coupling with the ¹³C-methyl group as well as the aromatic protons. (b) SPI difference spectrum resulting from a selective 180° pulse applied to the proton transition H1. (c) SPI difference spectrum resulting from a selective 180° pulse applied to the proton transition H3. (d) SPI difference spectrum resulting from a selective 180° pulse applied to the proton transition H2. (e) Simulated ¹⁹F spectrum of 1c assuming that there is no coupling to the aromatic protons. The transitions are numbered in order of increasing frequency.

The SPI difference method was used¹⁵ to show that the signs of ${}^{5}J(FCH_{2})$ and ${}^{6}J(FCH_{3})$ are the same as the positive vicinal H–H coupling constant. The arguments are more complicated than those in the previous section, and are not reproduced here.

Table 5. Tabulation of progressive (P) and regressive (R) ¹⁹ F(A) trans- itions on irradiation of the ¹ H(X) transitions for the + + + and + sign combinations in an AMX, spin system								
Proton	+ -	+ +	+-					
transitions	Ρ	к	P	н				
H1	F4, F6	F1, F2	F7, F8	F3, F5				
H2	F1, F2	F4, F6	F3, F5	F7, F8				
НЗ	F7, F8	F3, F5	F4, F6	F1, F2				

F7, F8

F1, F2

F4 F6

F3. F5

H4

RESULTS AND DISCUSSION

In the course of this study an x-ray diffraction examination of N-methyl-8-fluoroquinolinium chloride (1b) was performed^{15,16} and the structure is depicted in Fig. 5. The results show the importance of steric repulsions anticipated in the previous study¹; the F—C-8—C-8a angle is 5.6° larger than the F—C-8—C-7 angle and the C-9—N—C-8a angle is 2.9° larger than the C-9—N—C-2 angle. Also, the $F \cdots C$ -9 interatomic distance is 0.34 Å greater than the value based on structural data for the quinoline molecule.^{1,5} However, the x-ray data indicate that the planarity of the quinolinium ring is not significantly distorted by these steric interactions; taking the least-squares plane to be the ten non-hydrogen atoms in the quinolinium ring, the fluorine is also in the plane and C-9 is 0.085 Å out of the plane. Molecular orbital calculations based on the INDO¹⁷ and MINDO/3¹⁸ approximations of selfconsistent-field MO theory also showed that the lowest energy conformation for the methyl group of the N-methyl-8-fluoroquinolinium cation conforms to that depicted in Figs 1a and 5.

In the absence of x-ray structural data for 3, our initial guess was that the CH₃ group of the N-ethyl group would replace the H-b hydrogen atom in the conformation depicted in Fig. 1a. However, a series of MO calculations^{17,18} indicated that the lowest energy conformation is one in which the CH₃ group is very nearly perpendicular to the plane, as depicted in Fig. 1b. Calculations for the cation carried out at 10° intervals of the dihedral angle ϕ lead to a minimum at $\phi = 160^{\circ}$, i.e. the methyl group is situated closer to the fluorine atom.¹⁵ Experimental verification for a nearly perpendicular methyl group is to be found in the long range interproton coupling constant data in Table 2. An expression has been derived¹⁹ relating orthobenzylic, ${}^{4}J(ob)$, coupling constants to mutual atomatom polarizabilities $\pi_{pp'}$ and dihedral angles ϕ ,

$$J(ob) = 7.04 \pi_{pp'} \sin^2 \phi - 0.28 \cos^2 \phi \qquad (1)$$

The $\pi_{pp'}$ for the N—C-2 bond can be inferred from the -0.20 Hz value for ${}^{4}J(CH_{3}, H-2)(ob)$ in **1a**. Substituting this value into Eqn 1, and the dihedral angle for the perpendicular orientation in Fig. 1b, yields ${}^{4}J(ob) = -0.49$ Hz in comparison with the experimental value of -0.40 ± 0.06 Hz. If the methyl group were in the plane, Eqn 1 gives -0.91 Hz, which is substantially larger in magnitude than the experimental value.

The ¹H and ¹³C chemical shifts and coupling constants for compounds 1–3 are given in Tables 1–3. Extensive tabulations and theoretical discussions of the ¹³C-¹⁹F coupling constants involving the aromatic carbons of fluoroquinolines,¹³ fluoroaromatics^{1,13} and carbocations²⁰ have been given previously. In the aromatic systems the calculated INDO–FPT results for ¹³C-¹⁹F coupling constants are in disagreement with the experimental data. It has been suggested that it will be necessary to improve the quality of the wavefunctions and/or include orbital and dipolar contributions as well as the Fermi contact terms.^{13,21} It is interesting that in saturated fluorocarbons vicinal ¹³C-¹⁹F coupling constants appear to be dominated by the contact mechanism.^{4,22}



Figure 5. The N-methyl-8-fluoroquinolinium cation x-ray diffraction structure. The thermal ellipsoids are drawn to enclose 50% of the probability distribution.¹⁶

In Tables 1 and 3 the long-range hydrogen-fluorine coupling (LRHFC) and carbon-fluorine coupling (LRCFC) between the N-alkyl group and the proximate fluorine on C-8 are substantial in comparison with coupling over a similar number of bonds in 2. To investigate the electronic factors influencing these types of coupling, molecular orbital calculations of the Fermi contact term were performed. All calculations were based on the finite perturbation theory (FPT) formulation for coupling constants in the INDO (intermediate neglect of differential overlap) approximation of unrestricted SCF MO theory.^{17,23} Molecular geometries were based on the x-ray diffraction data for the cation of **1b**.^{15,16} However, C—H and C—C bond distances and bond angles in the methyl and ethyl groups were assumed to conform to the standard geometrical model.²⁴ To maintain symmetry and reduce the number of computations required, the fluoroquinolinium ring and all atoms bonded to it were assumed to lie in a plane. This change is so small that the calculated values would be affected to a negligible extent. All calculations were performed with a Control Data Corp. CYBER 175 digital computer.

Molecular orbital results for the Fermi contact contributions to the LRHFC and LRCFC involving the fluorine and the N-methyl and N-ethyl groups of **1** and **3** are entered in Table 6 at 30° intervals of the dihedral angle ϕ . This angle is measured from the plane of the aromatic rings as depicted in Fig. 1.

The lowest energy conformation for the N-methyl-8-fluoroquinolinium cation according to the MO results corresponds to $\phi = 60^{\circ}$, which is in conformity with the x-ray structural data. However, in Table 6 the calculated INDO minimum in the energy for the Nethyl-8-fluoroquinolinium cation occurs for the conformation in which the methyl group is almost perpendicular to the plane of the quinolinium ring ($\phi = 160^{\circ}$). To be consistent with the definition of the dihedral angle, the perpendicular arrangement corresponds to $\phi = 150^{\circ}$ (see Fig. 1b).

As expected from previous studies¹ of proximity and bond orientation effects on LRHFC, ${}^{4}J(CF)$ and ${}^{5}J(HF)$ assume their maximum magnitudes for $\phi = 0^{\circ}$, i.e. in those cases in which the hydrogens of the methyl or methylene are in closest proximity to the fluorine atom. In both cations the calculated ${}^{5}J(HF)$

Table 6.	Calculated INDO-FPT values for ${}^{5}J(HF)$, ${}^{4}J(CF)$, ${}^{5}J(CF)$, ${}^{6}J(HF)$ and energies
	in N-methyl- and N-ethyl-8-fluoroquinolinium cations at 30° intervals of the
	dihedral angle ϕ^*

ф	N-Methyl-8-fluoroquinolium cation			N-Ethyl-8-fluoroquinolinium					
Deg.	⁵ J(HF) (Hz)	⁴ J(CF) (Hz)	$\Delta \varepsilon^{b}$ (a.u. × 10 ³)	⁵ J(HF) (Hz)	⁴ J(CF) (Hz)	⁶ J(HF) ^c (Hz)	⁵ J(CF) (Hz)	Δε ^{b,d} (a.u.×10 ³)	
0	53.96	43.57	2.071	-57.03	42.51	2.77	-2.22	2.488	
30	-21.84	17.42	0.994	-22.90	17.11	1.37	0.16	5.292	
60	-1.51	3.48	0.000°	-1.52	3.38	0.38	0.84	3.773	
90	-1.82	17.42	0.994	1.91	17.11	1.37	-0.16	5.292	
120	-1.69	43.57	2.071	-1.44	42.51	2.77	-2.22	2.488	
150	1.53	17.42	0.994	0.83	16.24	1.97	-0.13	0.439	
180	2.56	3.48	0.000 ^e	4.13	-1.06	-26.18	85.03	7.259	
210	1.53	17.42	0.994	f	f	f	f	731.9	
240	-1.69	43.57	2.071	f	f	f	f	268.4	
270	-1.82	17.42	0.994	f	f	f	f	731.9	
300	-1.51	3.48	0.000 ^e	-1.48	-1.06	-26.18	85.03	7.259	
330	-21.84	17.42	0.994	-22.54	16.24	1.97	-0.13	0.439	
$\langle J(XF) \rangle_{av}^{9}$	-5.04	12.41		-11.78	17.57	1.99	-0.21		
$\langle J(XF) \rangle_{expt.}^{h}$	8.79	16.31	(1a)	3.03	(+)15.75 [;]	1.47	±5.20	(3)	
	8 8 1	16.34	(1h)						

* The dihedral angle ϕ is measured from the plane of the ring as depicted in Fig. 1.

^b Energies are measured relative to the lowest calculated value.

° Entries in this column are averages over the three hydrogens of the methyl group.

^d The calculated INDO value for the energy is -121.183408 a.u. corresponding to $\phi = 160^{\circ}$.

^e The calculated INDO value for the energy is -112.743717 a.u. ^f Because of the exceedingly high values of the energies arising from the methyl-fluorine interaction, the calculated coupling constants are not thought to be meaningful and would not contribute to the average in Eqn 2.

⁹ Average values of coupling constants obtained from Eqn 2 using Simpson's rule numerical integration.

h This work; see Experimental.

Assumed to be positive by analogy.

values in Table 6 have their maximum (negative) magnitudes in this orientation and become most positive for $\phi = 180^\circ$. The calculated ⁴J(CF) values are also quite sensitive to the orientation of the hydrogens, and in the N-methyl cation 1 there is a 120° periodicity. A simple average of the calculated values for 60°, 180° and 300° in Table 6 yields the values of $\langle {}^{5}J(\text{HF}) \rangle = -0.15 \text{ Hz} \text{ and } \langle {}^{4}J(\text{CF}) \rangle = 3.48 \text{ Hz}.$ These values do not agree with the experimental values of +8.8 Hz and +16.3 Hz, respectively. However, the relatively low height of the barrier, which is here approximated by the calculated INDO energies $\Delta \varepsilon(\phi)$ in Table 6, precludes a simple average. It is essential to weight the calculated values with the barrier hindering internal rotation.

$$\langle J(XF) \rangle = \int J(XF)(\phi) \exp^{-\Delta\varepsilon(\phi)} d\phi / \int \exp^{-\Delta\varepsilon(\phi)} d\phi$$
(2)

The calculated MO results for ${}^{4}J(CF)$ and ${}^{6}J(HF)$ are in reasonable conformity with the experimental results, but the calculation of an incorrect sign for ${}^{5}J(\text{HF})$ is a major inadequacy of the theoretical methods. At the outset of this study it was thought that the major inadequacy of previous calculations¹ was due to poor geometrical data and the use of a very simplistic averaging procedure. It now appears that the theoretical methods for nuclear spin-spin coupling are not adequate to describe coupling between certain proximate nuclei. Similar difficulties have been noted²⁵ in a recent study of the signs of proximate ³¹P-¹⁹F and ¹⁹F-¹⁹F coupling constants.

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