# SPIN-SPIN COUPLING BETWEEN FLUORINE AND AROMATIC PROTONS OF 3-FLUOROQUINOLINE: DEPENDENCE ON THE ELECTRONIC STRUCTURE OF THE RING NITROGEN

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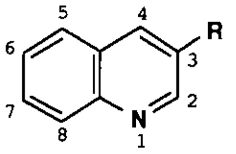
**Abstract** The spin-spin coupling constant, $J_{2H\text{-}3F}$, of 3-fluoroquinoline was strongly dependent on the electronic structure of the ring nitrogen. $J_{2H\text{-}3F}$ measured in $CDCl_3$ was almost null and increased as the acidity of solvent increased, reaching 2.8 *Hz* in 10% $D_2SO_4$. The J values of its methiodide and *N*-oxide were 3.1-3.3 and 3.8-4.6, respectively, which were not appreciably dependent on the acidity of the solvent for measurement.

In the course of our serial studies on the genotoxicity of quinoline derivatives, we found an interesting feature of the spin-spin interaction between the fluorine nucleus and a ring proton located in its ortho positions of the 3-fluoroquinoline molecule. The present paper concerns dependence of $J_{2H\text{-}3F}$ on the electronic structure of the ring nitrogen of 3-fluoroquinoline.

## RESULTS AND DISCUSSION



R=H : Quinoline
R=F : 3-Fluoroquinoline

Proton magnetic resonance spectra of 3-fluoroquinoline (pKa of its conjugate acid, 2.7) were measured with a 400 *MHz* spectrometer in various solvents; $CDCl_3$, $D_2O$ adjusted at appropriate pH's, and 10% $D_2SO_4$. Coupling constants were read by first-order analysis of the spectra with the help of a decoupling technique. The coupling constants between all the pairs of ortho nuclei are shown in Table I. It is apparent that $J_{2H\text{-}3F}$ is strongly depndent on the electronic structure of the ring nitrogen. Figure 1 shows the dependence of $J_{2H\text{-}3F}$ on the solvent acidity for measurement, along with that of $J_{3F\text{-}4H}$ which can be seen in the figure to be not appreciably dependent on the solvent acidity. Such a characteristic dependence observed in the coupling between F and the *o*-proton is not found in the spectrum of 5- or 6-fluoroquinoline, as shown in Figure 2. On the assumption that structural changes in the ring nitrogen of quinoline might be responsible for this feature of the coupling, we prepared the methiodide (*N*-methylquinolinium iodide) and the *N*-oxide of 3-fluoroquinoline and compared their nmr spectra with that of 3-fluoroquinoline. The results are shown in Table I. When one compares the $J_{2H\text{-}3F}$ values of these derivatives in $CDCl_3$ or $D_2SO_4$, the order of the magnitude is outlined as follows:

Table I. Spin coupling constants (*Hz*) between nuclei in the ortho position of 3-fluoroquinoline

| Structure | Solvent | $J_{2H\text{-}3F}$ | $J_{3F\text{-}4H}$ | $J_{5H\text{-}6H}$ | $J_{6H\text{-}7H}$ | $J_{7H\text{-}8H}$ |
|---|---|---|---|---|---|---|
| \\ N / | (CDCB) | ~0 | 9.0 | 8.1 | 6.9 | 8.4 |
| \\ N···H— / (H-bonded) | ($D_2O$) | 1.0 | 8.7 | 8.2 | 6.9 | 8.8 |
| | (>pH 3.5) | 1.0-1.7 | 8.9 | 8.2-8.4 | 6.9-7.3 | 8.1-8.6 |
| \\ $N^{+}$- H / | (pH 1.93) | 2.6 | 7.9 | 8.6 | 6.9 | 8.5 |
| | (10%$D_2SO_4$) | 2.8 | 7.9 | 7.9 | 6.9 | 7.9 |
| \\ $N^{+}$- $CH_3$ / | ($D_2O$) | 3.3 | 7.4 | 8.3 | 7.6 | 9.2 |
| | (10%$D_2SO_4$) | 3.1 | 7.4 | 8.6 | 8.0 | 8.9 |
| \\ $N^{+}$-$O^{-}$ / | (CDCB) | 4.6 | 7.6 | 7.6 | 7.0 | 8.6 |
| | ($D_2O$) | 4.3 | 6.8 | 7.6 | 7.4 | 8.6 |
| \\ $N^{+}$- OH / | (10%$D_2SO_4$) | 3.8 | 8.1 | 8.3 | 7.5 | 9.1 |

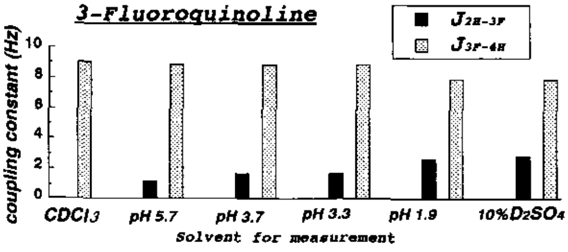
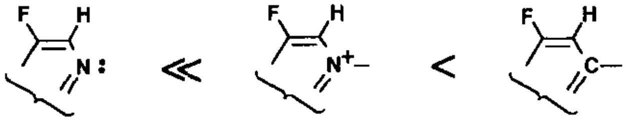


**Figure 1.** Solvent Effects on $J_{2H\text{-}3F}$ and $J_{3F\text{-}4H}$

**$J_{H\text{-}F}$**



It is worth emphasizing that the structure carrying a cationic nitrogen, regardless of $NH^+$, $N^+\text{-}CH_3$, $N^+\text{-}O^-$, or $N^+\text{-}OH$, affects the $J_{2H\text{-}3F}$ to a similar extent to give coupling constants (2.8–4.6 *Hz*) that amount to about 1/2 to 1/3 of the J values given by ordinary spin-spin coupling between fluorine and its ortho protons (8–10 *Hz*) in aromatic rings.

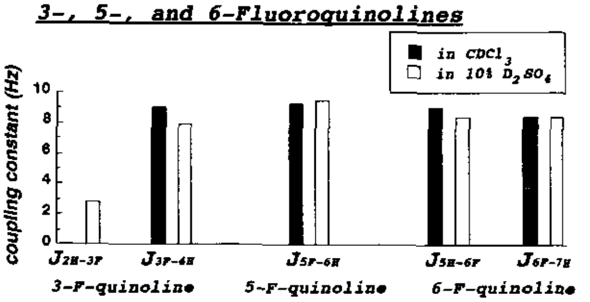


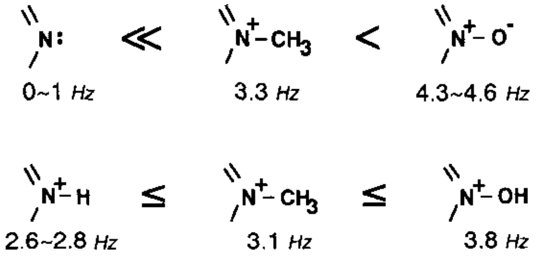
**Figure 2.** Solvent Effect on Spin Couplings between F and Its ortho Protons in Fluoroquinolines

*It is further noted that the nitrogen carrying a non-bonded electron-pair (in free base) gives the* most profound decreasing effect on the spin interaction between 2H and 3F, resulting in almost nullifying the coupling constant.

**$J_{2H\text{-}3F}$**

*In $CDCl_3$ or $D_2O$*

*In 10%$D_2SO_4$*



Significant contribution of the electronic structure of the ring nitrogen to the spin couplings of neighboring nuclei was previously reported for the spin couplings between $^{15}N$ and 2H,[1] $^{15}N$ and 3H,[1] 2H and 3H, F and $2^{13}C$,[2] or F and $3^{13}C$.[2] These coupling constants were changed by shifting the solvent from a neutral to an acidic one, as shown in Table II. Although the theory of the spin coupling has been well developed,[3] it seems that no rationale for these observations has been successfully provided.

Table II. *N*-Protonation effect on absolute values of the spin coupling constant between nuclei involved in quinoline derivatives

| | Coupling constant *(Hz)* | | Protonation effect |
|---|---|---|---|
| | in aprotic medium | in acidic medium | |
| ***Quinoline (R=H)*** | | | |
| $J_{N(15)\text{-}2H}$ | **11.1** | **2.0** | ⇓ |
| $J_{N(15)\text{-}3H}$ | **1.4** | **4.5** | ⇑ |
| $J_{2H\text{-}3H}$ | **4.2±0.2** | **5.5±0.1** | ⇑ |
| ***3-Fluoroquinoline (R=F)*** | | | |
| $J_{2H\text{-}3F}$ | **<0.1** | **2.8** | ⇑ |
| $J_{3F\text{-}4H}$ | **9.0** | **7.9** | ⇓ |
| *Other pairs of o-protons* | | | |
| J's | **7.5—9.0** | **7.5—9.0** | ⇒ |

## EXPERIMENTAL

MATERIALS Fluoroquinolines were synthesized from the corresponding aminoquinolines, via diazonium fluoroborates according to the Schieman reaction.[4] 3-Fluoroquinoline methiodide[3] and *N*-oxide[5] were prepared by previously reported methods.

NMR MEASUREMENTS $^1$H-Nmr spectra were recorded with a JMN-GSX 400 FT-NMR spectrometer operating at 400 *MHz*. The deuterium signal of the solvent, $CDCl_3$ or $D_2O$, was used as the internal lock signal. Chemical shifts were referred to the signal of internal tetramethylsilane or 3-trimethylsilylpropionic acid-$d_4$ sodium salt.

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