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Note

^{13}C NMR studies of fluoroflavones

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ABSTRACT: ^{13}C NMR chemical shifts were measured in DMSO-d_6 for fluorocarbonyl compounds. Sulfonic derivatives display ^4J(C,F) coupling constants for carbonyl groups which are also obtained from non-sulfonic derivatives when they are recorded in acidic solution. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{13}C NMR; fluoroflavonesulfonic acid; C–F coupling constants

INTRODUCTION

Flavones **Ib** and **IIb** are new compounds synthesized in these laboratories as possible anti-HIV molecules (**Ia** without fluorine has been found to have activity at a concentration of 10 μmol l^{-1}). Sulfonated dyes are of considerable interest because of their pharmaceutical properties. For examples, Evans Blue, which has anti-viral activity, has been examined as a potential anti-HIV agent[1] and sulfonated azo dyes have been shown to inhibit HIV-protease.[2]

EXPERIMENTAL

Materials

Perchloric acid (76%, $d = 1.67$) was obtained from Prolabo and 5′-fluoro-2′-hydroxyacetophenone from Aldrich. Fluoromethoxyflavones were synthesized from the corresponding methoxybenzoic acids and the above acetophenone.[3] Fluoroflavonesulfonic acids were obtained by boiling fluoromethoxyflavones in sulfuric acid (98%) for 5 h at 85 °C.

6-Fluoro-2′,3′-dimethoxyflavone (Ia). M.p. 126 °C (EtOH). IR (KBr): 1648, 1602, 1566, 1460, 1438, 1344, 1256, 1106, 1028, 992 cm^{-1}. ^{1}H NMR: δ 7.64–7.82 (m, 3H, H-5,7,8), 7.17–7.37 (m, 3H, H-4′, 5′, 6′), 6.76 (s, 1H, H-3), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3). Analysis: calculated for $C_{17}H_{13}O_4F$, C 68.00, H 4.33; found, C 68.13, H 4.26%.

6-Fluoro-2′,3′,4′-trimethoxyflavone (IIa). M.p. 148 °C (EtOH). IR (KBr): 1644, 1622, 1594, 1580, 1562, 1480, 1416, 1290, 1176, 1130, 1076, 1006 cm^{-1}. ^{1}H NMR: δ 7.64–7.83 (m, 3H, H-5,7,8), 7.57–7.61 (d, 1H, J = 8.9 Hz, H-6′), 6.96–7.00 (d, 1H, J = 8.9 Hz, H-5′), 6.77 (s, 1H, H-3), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). Analysis: calculated for $C_{18}H_{15}O_5F$, C 65.45, H 4.54; found, C 65.50, H 4.62%.

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6-Fluoro-2′-hydroxy-3′-methoxyflavone-5′-sulfonic acid (Ib). IR (KBr): 3416, 3136, 1628, 1608, 1568, 1558, 1490, 1414, 1258, 1240, 1166, 1056, 1032 cm^{-1}. ^{1}H NMR: δ 10.11 (s, 1H, OH), 7.68–7.85 (m, 4H, H-5,6′,7,8), 7.33–7.34 (d, 1H, J = 1.88 Hz, H-4′), 7.11 (s, 1H, H-3), 3.88 (s, 3H, OCH_3).

6-Fluoro-2′,3′,4′-trihydroxyflavone-5′-sulfonic acid (IIb). IR (KBr): 3416, 3112, 1618, 1570, 1482, 1464, 1372, 1240, 1178, 1142, 1068, 1036 cm^{-1}. ^{1}H NMR: δ 7.78–7.85 (m, 2H, H-5,7), 7.64–7.69 (dd, 1H, J = 8.8, 2.2 Hz, H-8), 7.61 (s, 1H, H-6′), 7.13 (s, 1H, H-3).

Ib and **IIb**, hygroscopic, were characterized as their *p*-toludinium salts. The sulfonic acid (500 mg) was dissolved in the minimum volume of boiling water and a satured aqueous solution of *p*-toluidine hydrochloride (500 mg) was added. The mixture was cooled and the precipitate was filtered and recrystallized from hot water.

p-Toluidinium salt of **Ib**, $C_{16}H_{10}O_7FS^-C_7H_{10}N^+ \cdot 2H_2O$, m.p. 270 °C. Analysis: calculated for $C_{23}H_{24}O_9FNS$, C 54.22, H 4.71, N 2.75; found, C 54.47, H 4.21, N 2.58%.

p-Toluidinium salt of **IIb**, $C_{15}H_8O_8FS^-C_7H_{10}N^+ \cdot H_2O$, m.p. 244 °C. Analysis: calculated for $C_{22}H_{20}O_9FNS$, C 53.54, H 4.05, N 2.84; found, C 53.41, H 4.11, N 2.76%.

NMR measurements

The ^{13}C NMR spectra were obtained at 25 °C on a Bruker AC-200 spectrometer operating at 50.32 MHz using 0.5 M
solutions in DMSO-d_6. The ^{1}H and ^{13}C chemical shifts of the solvent were used as a secondary reference and referred to the TMS signal using the usual relationships.[4]

Resonance multiplicities of carbon were obtained using DEPT pulse sequence. For the DEPT spectra the width of a ^{13}C 90° pulse was 6 μs, the width of a ^{1}H 90° pulse was 5.5 μs and the $(2J)^{-1}$ delay was set equal to 3.1 ms. Typical experimental conditions for ^{13}C spectra recording were as follows: spectral width, 12 kHz; pulse width, 4 μs; acquisition time, 0.68 s; number of transients, 200–500; number of data points, 16K; ^{1}H CPD decoupling; no zero filling.

RESULTS AND DISCUSSION

The ^{13}C–^{19}F coupling constants were obtained from the coupled ^{13}C NMR spectra of **Ia** and **IIa** (Fig. 1). The

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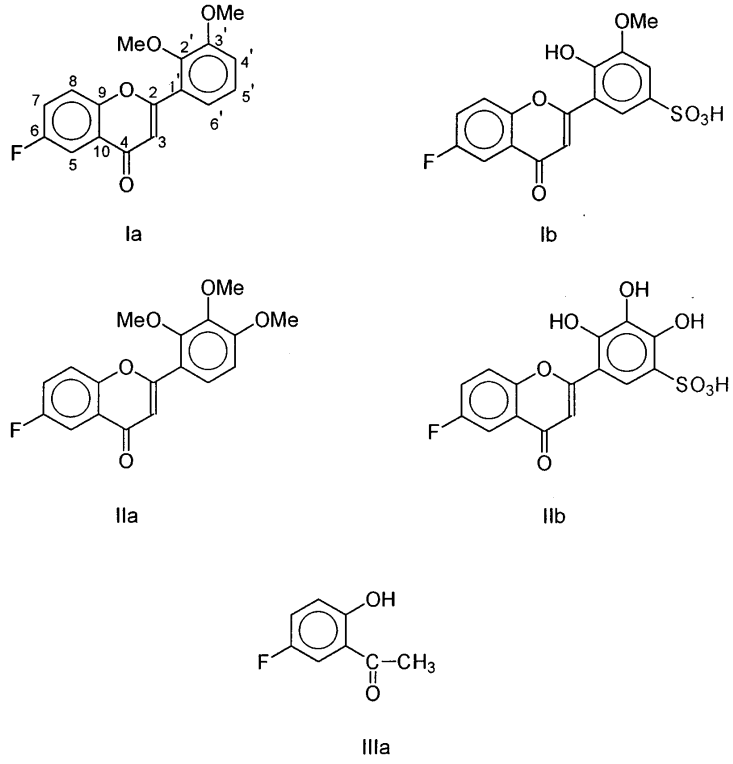

Ia Ib

IIa IIb

IIIa

Figure 1. Structures and numbering of the compounds investigated.

coupling constants from *ipso*, *ortho* and *meta* carbon atoms are entered in Tables 1 and 2. Coupling constants are greatest close to the site of substitution and attenuate rapidly with increasing distance.[5] In the spectra of **Ib** and **IIb**, recorded under the same experimental conditions, the carbonyl carbon in a *para* exocyclic position split in two signals with $J = 3$ Hz. Coupling to the C-9 carbon was not observed. Presumably, the splitting of the signal of the carbonyl carbon is related to the protonation of the carbonyl oxygen. The structure of the molecule **Ib**, without a fluorine atom (Fig. 2), has been solved by x-ray crystallography. In the solid state, the molecule has a zwitterionic structure.[6] It can reasonably be supposed that in solution the zwitter-

Table 1. Carbon-13 spectral data for **Ia**, **Ia** + $HClO_4$ and **Ib**[a]

Carbon	Ia	Ia + $HClO_4$	Ib
C-2	161.8	162.0	160.9
C-3	110.4	110.6	110.0
C-4	176.2	176.58–176.52 (3 Hz)	176.78–176.72 (3 Hz)
C-5	109.5–109.0 (25 Hz)	109.7–109.2 (25 Hz)	109.8–109.3 (25 Hz)
C-6	161.36–156.51 (−242.5 Hz)	161.54–156.69 (−242.5 Hz)	161.59–156.74 (−242.5 Hz)
C-7	122.5–122.0 (25 Hz)	122.7–122.2 (25 Hz)	122.8–122.3 (25 Hz)
C-8	121.33–121.16 (8.5 Hz)	121.51–121.34 (8.5 Hz)	121.50–121.33 (8.5 Hz)
C-9	152.2	152.4	152.5
C-10	124.28–124.13 (7.5 Hz)	124.45–124.31 (7.5 Hz)	124.60–124.45 (7.5 Hz)
C-1′	124.4	125.7	116.8
C-2′	147.1	147.3	146.9
C-3′	152.9	153.1	147.6
C-4′	115.9	116.1	111.5
C-5′	124.4	124.6	139.0
C-6′	120.5	120.7	117.2
2′-OMe	60.5	60.7	
3′-OMe	55.98	56.1	56.5

[a] Coupling constants [J(C,F)] are given in parentheses.

Table 2. Carbon-13 spectral data for IIa, IIa + $HClO_4$ and IIb[a]

Carbon	IIa	IIa + $HClO_4$	IIb
C-2	161.4	161.6	161.3
C-3	109.3	109.4	109.1
C-4	176.2	176.52–176.46 (3 Hz)	176.66–176.61 (2.5 Hz)
C-5	109.50–109.02 (24 Hz)	109.64–109.17 (23.5 Hz)	109.72–109.21 (25.5 Hz)
C-6	161.28–156.45 (−241.5 Hz)	161.45–156.60 (−242.5 Hz)	161.45–156.60 (−242.5 Hz)
C-7	122.35–121.85 (25 Hz)	122.55–122.03 (26 Hz)	122.43–121.91 (26 Hz)
C-8	121.19–121.03 (8 Hz)	121.39–121.22 (8.5 Hz)	121.25–121.08 (8.5 Hz)
C-9	152.2	152.3	152.3
C-10	124.28–124.14 (7 Hz)	124.40–124.25 (7.5 Hz)	124.54–124.40 (7 Hz)
C-1′	117.78	117.9	109.2
C-2′	152.2	152.3	146.0
C-3′	142.18	142.3	132.9
C-4′	156.2	156.4	147.6
C-5′	108.2	108.4	123.7
C-6′	124.28	124.48	116.9
2′-OMe/3′-OMe	61.04, 60.46	61.22, 60.63	
4′-OMe	56.07	56.25	

[a] Coupling constants [J(C,F)] are given in parentheses.

ionic character is maintained since sulfonic acids are strong acids. Moreover, flavones are weak bases and protonation of the carbonyl oxygen is possible by perchloric acid[7] or trifluoracetic acid.[8,9]

To confirm this idea, the spectra of **Ia** and **IIa** were recorded in DMSO-d_6 with a drop of concentrated perchloric acid. The splitting of the carbonyl carbon appeared under such conditions.

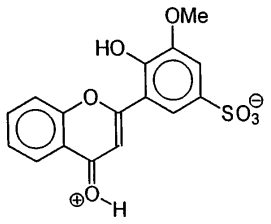

Figure 2. Zwitterionic structure of sulfoflavones.

We also recorded the spectrum of 5′-fluoro-2′-hydroxy-acetophenone (**IIIa**) in DMSO-d_6 and we repeated the experiment with a drop of concentrated perchloric acid (5′-fluoro-2′-hydroxyacetophenone is used as a starting material in the synthesis of **Ia** and **IIa**). A possible intramolecular hydrogen bond can be considered for this molecule. However, in DMSO-d_6 this hydrogen bond is broken.[10] The hydroxyl group binds preferentially to DMSO. Since the oxygen carbonyl is free to be protonated, the carbonyl carbon was split.

Protonation of the carbonyl oxygen can involve a deshielding for C-4 as noted for coumarins in sulfuric acid.[11] This is indicated by a slight downfield chemical shift of C-4 for the fluoroflavone sulfonic acids or non-sulfonic compounds in acidic solution. In the zwitterionic structure,[6] and other structures,[12,13] the widening of C-10—C-4—C-3 bond angle is correlated with a shortening of the C-4—C-10 bond distance. This may

Table 3. Carbon-13 spectral data for IIIa and IIa + $HClO_4$ [a]

Carbon	IIIa	IIIa + $HClO_4$
C-1	120.73–120.62 (5.5 Hz)	120.96–120.85 (5.5 Hz)
C-2	156.81	157.79
C-3	119.14–118.96 (9 Hz)	119.95–119.80 (7.5 Hz)
C-4	123.42–122.94 (25 Hz)	124.42–123.96 (23 Hz)
C-5	156.81–152.12 (−234.5 Hz)	157.55–152.84 (−235.5 Hz)
C-6	116.3–115.8 (25 Hz)	117.12–116.66 (23 Hz)
C=O	203.0	204.44–204.38 (3 Hz)
CH_3	28.0	28.3

[a] Coupling constants [J(C,F)] are given in parentheses.

increase the overlap of C-4 and C-10 orbitals. As C–F coupling is transmitted effectively through the π-systems, perturbation of the electronic system changes the coupling constant.

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