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Synthesis and NMR studies of 2- and 3-fluorosubstitued five-membered heterocycles

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Abstract

A set of 2-fluoro- and 3-fluoro-substituted thiophenes, pyrroles and furans has been synthesized by a treatment of the corresponding lithio derivatives with *N*-fluorodibenzenesulfonamide. For all these compounds, $^1J_{CC}$ and $^1J_{CH}$ coupling constants and ^{19}F NMR chemical shifts have been measured. In all cases, a dramatic increase of the $^1J_{C_2C_3}$ couplings has been observed in 2-fluoro- and 3-fluoro-substituted compounds in comparison with those measured for the parent compounds. The same is valid for $^1J_{C_3C_4}$ measured in 3-fluoro derivatives.

The DFT calculations performed for 2- and 3-fluoro-substituted compounds reproduce very well the experimental coupling values and show that the Fermi contact contribution is the main factor determining their magnitude. Also the trends observed in the ^{19}F NMR shieldings are well reflected in the calculated DFT data.

Keywords: 2- and 3-Fluoro derivatives; Thiophene; Pyrrole; Furan; $^1J_{CC}$ couplings; DFT calculations

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1. Introduction

During our studies on the substituent effects on one-bond carbon–carbon spin–spin couplings, $^1J_{CC}$, we became interested in substituted furans, pyrroles and thiophenes. Our recent studies have shown that in these compounds [1], similarly to other systems such as substituted acetylenes [2], ethylenes [3], benzenes [4] or pyridines and their *N*-oxides [5], the influence of the substituent electronegativity on the magnitude of $^1J_{CC}$ is dramatic. An especially strong influence on the coupling value is exerted by the lithio substituent which causes a strong decrease of the coupling value. The coupling constants across the C_2C_3 bond found in 2-lithiofuran, 2-lithiopyrrole and 2-lithiothiophene are of ca. 30 Hz only [1]. For comparison, the corresponding couplings in the parent systems are 69.1, 66.3 and 64.2 Hz, respectively. It was of great interest to determine $^1J_{CC}$ couplings for the corresponding fluoro-substituted compounds in which a dramatic increase of the coupling value is expected.

Our work consists of two parts: one is devoted to synthesis of the 2- and 3-fluoro-substituted furans, pyrroles and thiophenes, in the other the experimental and theoretical NMR results are presented and discussed. A special attention is paid to one-bond carbon–carbon and carbon–proton spin–spin coupling constants, as well as to the fluorine NMR shieldings and to relationship between these parameters and the aromaticity of the compounds studied.

2. Results and discussion

2.1. Synthesis of the compounds

In spite of the fact that many methods of synthesis for the fluoro-substituted heterocycles have already been published in the literature, the preparation of the model compounds which would not contain substituents other than alkyls, proved to be rather difficult. Some procedures require expensive and/or hazardous reagents such as, for example, perchloryl fluoride, others are difficult to repeat and/or are of limited applicability. Most of the papers published so far have been devoted to variously substituted fluorothiophenes [6–17], considerably fewer to pyrroles [16–22], and only a few to

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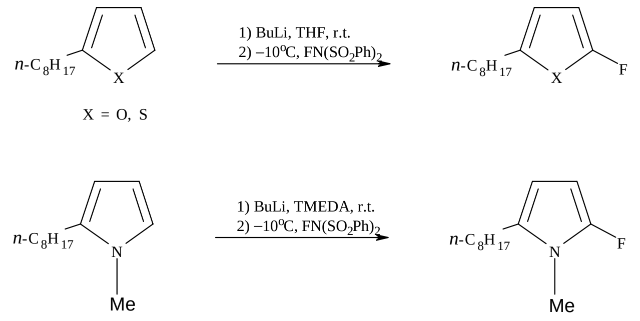


Scheme 1. Synthesis of 2-fluoro-5-*n*-octylthiophene, **1**, 2-fluoro-5-*n*-octyl-*N*-methylpyrrole, **6**, and 2-fluoro-5-*n*-octylfuran, **12**.

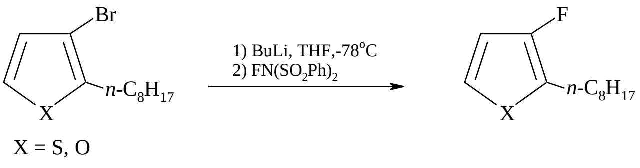
furans [16,17,23,24]. Though the methods of the synthesis of the fluoro-substituted heterocycles were not our primary goal, we had to check and/or modify the procedures chosen in order to synthesize the required model compounds.

Two approaches seemed to be the most promising. One of them involved the regiospecific lithiation of the starting heterocycle followed by a treatment of the corresponding lithio derivative with *N*-fluorodibenzenesulfonimide [25]. This reagent has been successfully applied by Taylor and Zhou [14] in order to obtain 3-fluorothiophene-2-carboxylic acid and by Barnes et al. [19], who synthesized 3-fluoro-*N*-(tri-*iso*-propyl)silylpyrrole. Using this method we synthesized 2-fluoro-5-*n*-octylthiophene (**1**), 3-fluoro-2-*n*-octylthiophene (**2**), 2-fluoro-5-*n*-octyl-*N*-methylpyrrole (**6**), 2-fluoro-5-*n*-octylfuran (**12**), and 3-fluoro-2-*n*-octylfuran (**13**). In the case of 2-fluoro-substituted compounds, the intermediate lithio derivatives were obtained by a direct lithiation of the corresponding parent compounds using butyllithium (Scheme 1).

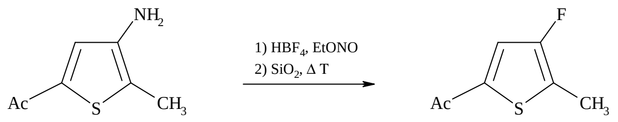
3-Fluoro-substituted derivatives were obtained starting from the corresponding 3-bromoheterocycles and butyllithium as a lithiating reagent (Scheme 2).

All the compounds synthesized are stable enough to allow measurement of INADEQUATE NMR spectra. However, there is a distinct difference between derivatives of thiophene **1** and **2** and furan **12** and **13**, and pyrrole **6**. Whereas fluorothiophenes and fluorofurans do not show any sign of decomposition when left for several days at room temperature, fluoropyrrole **6** slowly undergoes a dimerization process, an elimination of hydrogen fluoride being obviously the first step. We did not study this reaction in detail; only the structure of the 2,2-dimer has been confirmed by the use of NMR and MS.

Another method chosen by us involved a thermal decomposition of a diazonium salt as a key step (a Schiemann reaction) which has been used successfully in the synthesis of a variety of fluorobenzenes. The first and so far the only successful application of that approach to the thiophene ring was reported by Kofarbard et al. [15], who obtained 3-fluorothiophene by heating a mixture of the corresponding diazonium salt and sand at 160 °C under vacuum (0.1–1 Torr) distillation conditions. We modified this procedure by the use of ethyl nitrite in the synthesis of the diazo compound. The reaction was carried out in very carefully dried ethyl ether and the starting tetrafluoroborane salt of 5-acetyl-3-amino-2-methylthiophene was also obtained in ether solution (Scheme 3).



Scheme 2. Synthesis of 3-fluoro-2-*n*-octylthiophene, **2**, and 3-fluoro-2-*n*-octylfuran, **13**.



Scheme 3. Synthesis of 5-acetyl-3-fluoro-2-methylthiophene, **3**.

Decomposition of the diazo compound obtained was conducted under rather mild conditions and the product was immediately distilled off under vacuum (ca. 11 Torr). This allowed us to obtain a reasonable amount of 5-acetyl-3-fluoro-2-methylthiophene (**3**), though the yield was not especially high. To the best of our knowledge, this is the second successful application of the Schiemann reaction to the thiophene system.

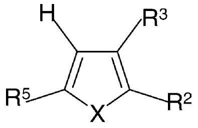
2.2. The NMR data

The compounds studied represent a full set of 2- and 3-fluoro derivatives of three basic heterocycles, i.e. thiophene (compounds **1**, **2** and **3**) pyrrole (compounds **6**, **8** and **10**) and furan (compounds **12**, **13** and **14**). The experimental one-bond carbon–carbon and carbon–proton coupling constants measured for them are presented in Tables 1 and 2, respectively; in these Tables also the $^1J_{CC}$ and $^1J_{CH}$ values for the relevant heterocycles not bearing the fluorine substituent are included for comparison (compounds **4**, **5**, **7**, **9**, **11** and **15**). Tables 3 and 4 contain the DFT calculated $^1J_{CC}$ and $^1J_{CH}$ couplings, respectively. In order to save computing time the calculations were performed for the corresponding ethyl derivatives denoted as compounds **a**. This, however did not influence the values of the calculated parameters. The ^{13}C NMR chemical shifts and carbon–fluorine couplings are presented in Table 5. In Table 6, the experimental and DFT calculated fluorine NMR shieldings are given. The ^{13}C and ^{19}F NMR data are complemented by the ^{1}H NMR data which are shown in Table 7.

An inspection of the data presented in Tables 1 and 2 reveals that the introduction of the fluoro substituent strongly influences the couplings only across the bonds directly involved, i.e. the $^1J_{C_2C_3}$ and $^1J_{C_3C_4}$ couplings in the 3-fluoro derivatives and the $^1J_{C_2C_3}$ couplings in 2-fluoro-substituted compounds. The $^1J_{C_3C_4}$ couplings increase in order 3-fluoro-2-*n*-octylfuran (**13**) 3-fluoro-*N*-(tri-*iso*-propyl)silylpyrrole

Table 1

Experimental $^1J_{CC}$ couplings (in Hz) in 2- and 3-fluoro-substituted thiophenes, pyrroles and furans, and in the corresponding parent compounds[a]



Compound no.	X	R^1	R^2	R^3	R^5	$^1J_{C_2C_3}$	$^1J_{C_3C_4}$	$^1J_{C_4C_5}$	$^1J_{C_2C_{2'}}$[b] or $^1J_{C_5C_{5'}}$
1	S		F	H	n-C_8H_{17}	81.8	58.8	65.2	47.8
2	S		n-C_8H_{17}	F	H	84.2	73.8	66.1	[c]
3	S		CH_3	F	CH_3CO	81.3	74.5	64.6	47.0
4	S		n-C_8H_{17}	H	H	65.2	56.8	63.0	47.5
5	S		CH_3	H	CH_3CO	62.1	57.1	61.6	46.6
6	N	CH_3	F	H	n-C_8H_{17}	89.1	53.3	68.4	[c]
7	N	CH_3	n-C_8H_{17}	H	H	68.2	51.9	66.2	51.3[d]
8	N	H	F	H	CHO	83.4	54.8	66.8	[c]
9	N	H	H	H	CHO	62.3	54.5	64.4	65.5[e]
10	N	Si(i-Pr)$_3$	H	F	H	89.0	68.6	67.4	[c]
11	N	Si(i-Pr)$_3$	H	H	H	65.8	[f]	65.8	[c]
12	O		F	H	n-C_8H_{17}	96.3	52.2	71.7	55.1
13	O		n-C_8H_{17}	F	H	98[g]	67.1	71.5	[c]
14	O		C_2H_5	F	Ph	94.9	68.7	74.5	55.1
15	O		n-C_8H_{17}	H	H	71.8	50.4	69.5	54.1

[a] R^1 concerns the pyrrole derivatives only.

[b] Concerns alkyl groups if not otherwise stated.

[c] Could not be determined or not concerns.

[d] Measured for 1,2-dimethylpyrrole.

[e] Corresponds to $^1J_{C_5CHO}$.

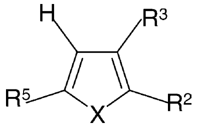
[f] The coupling could not be determined because the nuclei involved are magnetically equivalent.

[g] Accuracy ±1 Hz.

(**10**) and 3-fluoro-2-n-octylthiophene (**2**) 67.1 (50.4), 68.6 (51.9) and 73.8 (56.8) Hz, respectively; in parentheses, the $^1J_{C_3C_4}$ values in the corresponding parent octyl derivatives **15**, **7** and **4** are shown. Thus, the magnitude of the I increment, defined as the difference between the $^1J_{CC}$ coupling measured for the fluoro-substituted compound and for the corresponding molecule without the fluoro substituent, is of ca. 17 Hz in all three heterocyclic systems. The trends observed for the $^1J_{C_2C_3}$ couplings are opposite. First of all, the smallest $^1J_{C_2C_3}$ couplings of 81.8 and 84.2 Hz have been

Table 2

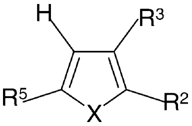
$^1J_{CH}$ couplings (in Hz) in 2- and 3-fluoro-substituted thiophenes, pyrroles and furans[a]



Compound no.	X	R^1	R^2	R^3	R^5	$^1J_{C_2H_2}$	$^1J_{C_3H_3}$	$^1J_{C_4H_4}$	$^1J_{C_5H_5}$
1	S		F	H	n-C_8H_{17}	–	169.6	166.7	–
2	S		n-C_8H_{17}	F	H	–	–	170.4	187.9
3	S		CH_3	F	CH_3CO	–	–	171.8	–
4	S		n-C_8H_{17}	H	H	–	163.8	167.3	185.3
5	S		CH_3	H	CH_3CO	–	166.6	167.0	–
6	N	CH_3	F	H	n-C_8H_{17}	–	174.8	170.5	–
7	N	CH_3	n-C_8H_{17}	H	H	–	167.7	169.2	181.9
8	N	H	F	H	CHO	–	179.3	171.5	–
9	N	H	H	H	CHO	185.6	173.9	171.5	–
10	N	Si(i-Pr)$_3$	H	F	H	185.3	–	173.0	184.3
11	N	Si(i-Pr)$_3$	H	H	H	181.0	168.7	168.7	181.0
12	O		F	H	n-C_8H_{17}	–	180.1	174.1	–
13	O		n-C_8H_{17}	F	H	–	–	176.3	204.6
14	O		C_2H_5	F	Ph	–	–	176.3	–
15	O		n-C_8H_{17}	H	H	–	172.2	173.8	200.7

[a] R^1 concerns the pyrrole derivatives only.

Table 3
DFT $^1J_{CC}$ couplings (in Hz) in six basic 2- and 3-fluoro-substituted thiophenes, pyrroles and furans[a]



Compound no.	X	R^2	R^3	R^5	$^1J_{C_2C_3}$				$^1J_{C_3C_4}$				$^1J_{C_4C_5}$			
					FC	PSO	DSO	SUM	FC	PSO	DSO	SUM	FC	PSO	DSO	SUM
1a	S	F	H	Alk	84.3	−6.9	0.3	77.7	57.5	−4.5	0.3	53.3	69.3	−8.0	0.3	61.6
2a	S	Alk	F	H	87.1	−7.4	0.4	80.1	76.5	−5.0	0.3	71.8	70.7	−7.5	0.2	63.4
6a	NMe	F	H	Alk	92.1	−6.1	0.3	86.3	56.2	−4.9	0.2	51.5	72.8	−7.4	0.3	65.7
10a	$NSiH_3$	H	F	H	93.6	−6.9	0.3	87.0	70.4	−5.1	0.3	65.6	72.8	−5.1	0.3	65.8
12a	O	F	H	Alk	98.6	−6.4	0.3	92.5	55.6	−4.3	0.2	51.5	75.2	−8.1	0.3	67.4
13a	O	Alk	F	H	99.5	−7.5	0.4	92.4	69.7	−4.6	0.3	65.4	75.6	−7.6	0.3	68.3

[a] R^1 concerns the pyrrole derivatives only; Alk: ethyl.

found for 2-fluoro-5-*n*-octyl (**1**) and 3-fluoro-2-*n*-octylthiophene (**2**), respectively, the largest $^1J_{C_2C_3}$ of 96.3 and 98 Hz for 2-fluoro-5-*n*-octylfuran (**12**) and 3-fluoro-2-*n*-octylfuran (**13**), respectively. A comparison of the data obtained for 2- and 3-fluoro-substituted compounds shows that the position of the fluoro substituent is of no significance as far as the $^1J_{C_2C_3}$ values are concerned. The $I_{C_2C_3}$ values are 19, 23 and 26 Hz for thiophene, pyrrole and furan, respectively. It is worth mentioning that the I_{CC} increment in fluorobenzene is of 16 Hz [4] and in fluoroethene of 23 Hz [3].

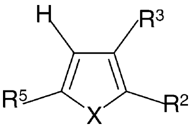
The $^1J_{C_2C_3}$ couplings measured for the fluoro-substituted compounds studied in the present work are the largest determined so far for the substituted five-membered heterocycles. The smallest ones of ca. 30 Hz only have been determined recently by us for all three 2-lithio substituted compounds, i.e. 2-lithiothiophene, 2-lithio-*N*-methylpyrrole and 2-lithiofuran [1]. Thus, the total range covered by $^1J_{CC}$ couplings varies from ca. 50 Hz in substituted thiophenes up to ca. 70 Hz in substituted furans showing the magnitude of the changes occurring in the electronic structure of these compounds upon substitution.

The DFT ^1J couplings calculated for 2-and 3-fluoro-substituted compounds as well as for the parent systems using the deMon program recently developed by Malkin et al. [26], reflect very well all the trends observed for the experimental $^1J_{CC}$ data (compare data in Tables 1 and 3). Moreover, also the absolute $^1J_{CC}$ values are reproduced within 1–2 Hz. The Fermi contact contribution is always the main factor determining the ^1J magnitude which should be interpreted in terms of the increase of the s-electron density on the carbon atoms involved. The PSO term is about ten times smaller and negative. The DSO contribution is almost negligible, of ca. 0.4 Hz.

The influence of the fluoro substituent on the $^1J_{CH}$ couplings is dramatically less pronounced than in the case of $^1J_{CC}$ and the changes observed are less characteristic. An increase of several Hz takes place for all the C–H couplings present in the studied molecules, the largest one being observed for $^1J_{CH}$ in 2-fluoro-substituted compounds. All the $^1J_{CH}$ couplings are dominated by the Fermi contact term, the remaining contributions being almost negligible, ca. 1 Hz only, and therefore only the total $^1J_{CH}$ values are displayed in Table 4.

The $\delta(^{13}C)$ chemical shift data obtained in our work allow one to elucidate the F substituent chemical shift (SCS) values in three basic heterocyclic systems studied in our

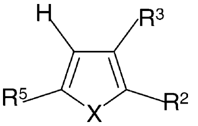
Table 4
DFT $^1J_{CH}$ couplings (in Hz) in six basic 2- and 3-fluoro-substituted thiophenes, pyrroles and furans[a]



Compound no.	X	R^2	R^3	R^5	$^1J_{C_2H_2}$ (total)	$^1J_{C_3H_3}$ (total)	$^1J_{C_4H_4}$ (total)	$^1J_{C_5H_5}$ (total)
1a	S	F	H	Alk	–	165.8	161.6	–
2a	S	Alk	F	H	–	–	166.5	185.2
6a	NMe	F	H	Alk	–	173.0	167.4	–
10a	$NSiH_3$	H	F	H	184.2	–	171.5	183.8
12a	O	F	H	Alk	–	176.2	168.8	–
13a	O	Alk	F	H	–	–	173.6	201.0

[a] R^1 concerns the pyrrole derivatives only; Alk: ethyl.

Table 5
$\delta(^{13}C)$ chemical shifts (in ppm) in 2- and 3-fluoro-substituted thiophenes, pyrroles and furans, and in the corresponding parent compounds; $^{n}J_{CF}$ for compounds **1**–**3**, **5**, **7**, **9** and **11**–**13** (in Hz, $n = 1$–4) are given in parentheses[a]



Compound no.	X	R^1	R^2	R^3	R^5	$\delta(^{13}C)$ chemical shifts and $^{n}J_{CF}$ couplings ($n = 1$–4)			
						C$_2$	C$_3$	C$_4$	C$_5$
1	S		F	H	n-C$_8$H$_{17}$	163.3 (−286.9)	105.7 (10.2)	119.4 (3.9)	142.8 (0)
2	S		n-C$_8$H$_{17}$	F	H	121.4 (18.7)	154.2 (−252.9)	116.7 (27.3)	119.5 (10.1)
3	S[b]		CH$_3$	F	CH$_3$CO	126.5 (17.9)	152.7 (−257.8)	121.0 (24.7)	126.8 (5.3)
4	S		n-C$_8$H$_{17}$	H	H	145.4	123.7	126.4	122.4
5	S[c]		CH$_3$	H	CH$_3$CO	149.5	132.8	126.5	142.1
6	N	CH$_3$	F	H	n-C$_8$H$_{17}$	146.4 (−256.8)	82.7 (10.3)	101.2 (4.8)	124.2 (1.5)
7	N	CH$_3$	n-C$_8$H$_{17}$	H	H	132.4	104.9	105.9	119.9
8	N	H	F	H	CHO	153.7 (−271.5)	90.9 (13.1)	123.5 (0)	125.9 (0)
9	N	H	H	H	CHO	132.5	122.2	110.0	123.6
10	N	Si(i-Pr)$_3$	H	F	H	106.0 (26.5)	154.0 (−240.7)	99.5 (18.0)	121.3 (8.1)
11	N	Si(i-Pr)$_3$	H	H	H	123.6	110.0	110.0	123.6
12	O		F	H	n-C$_8$H$_{17}$	156.5 (−272.6)	80.5 (12.7)	105.6 (0)	146.2 (1.2)
13	O		n-C$_8$H$_{17}$	F	H	138.6 (25.6)	148.6 (−244.6)	102.8 (20.4)	138.5 (8.8)
14	O		C$_2$H$_5$	F	Ph	139.1 (25.6)	149.3 (−244.6)	97.8 (20.4)	149.1 (8.8)
15	O		n-C$_8$H$_{17}$	H	H	156.6	104.6	109.9	140.5

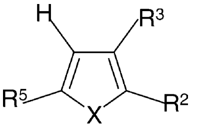
[a] R^1 concerns the pyrrole derivatives only; δ values are relative to TMS; the negative sign of $^{1}J_{CF}$ assigned by analogy to that reported in [27].

[b] CO 188.9 (2.1); CH$_3$ at C$_2$ 10.1 (10.0); CH$_3$ at CO 25.3.

[c] CO 190.0; CH$_3$ at C$_2$ 15.6; CH$_3$ at CO 26.1.

work. Thus, the SCS values, $\Delta\delta_F$, calculated for carbon C$_2$ in 2-fluorothiophene (**1**), 2-fluoropyrrole (**6**), and 2-fluorofuran (**12**) are 40.9, 26.5 and 16.0 ppm, respectively and for carbon C$_3$ −20.7, −23.2 and −29.4 ppm, respectively. They indicate that the deshielding of carbon C$_2$ decreases dramatically in this order, whereas the shielding of carbon C$_3$ increases. It is worth noting that the SCS effects found for 2-fluoro-substituted thiophene are very similar to those reported for

Table 6
Experimental and DFT calculated fluorine NMR shieldings (in ppm) in 2- and 3-fluoro-substituted thiophenes, pyrroles and furans[a]



Compound no.	X	R^1	R^2	R^3	R^5	$\sigma(^{19}F)_{exp}$	Reference	$\sigma(^{19}F)_{DFT}$
1[b]	S		F	H	n-C$_8$H$_{17}$	133.7	This work	280.9
2[b]	S		n-C$_8$H$_{17}$	F	H	136.6	This work	293.0
16			F	H	H	134.7	[8]	285.7
17			H	F	H	131.0	[8]	284.6
18	S		F	F	H	156.6, 149.6	[7]	307.7, 304.7
3	S		CH$_3$	F	CH$_3$CO	131.3	This work	
6[b]	N	CH$_3$	F	H	n-C$_8$H$_{17}$	142.7	This work	303.7
8	N	H	F	H	CHO	130.3	[c]	
10	N	Si(i-Pr)$_3$	H	F	H	166.5	[d]	317.7
12[b]	O		F	H	n-C$_8$H$_{17}$	118.0	This work	275.8
13[b]	O		n-C$_8$H$_{17}$	F	H	176.1	This work	333.8
14	O		C$_2$H$_5$	F	Ph	172.4	[e]	329.1
19	O		F	F	H	130.1, 187.8	[24]	284.8, 346.0

[a] R^1 concerns the pyrrole derivatives only.

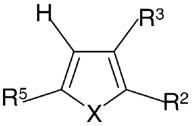
[b] Calculated for the corresponding ethyl compound (compounds **1**, **2**, **6**, **12** and **13**).

[c] 126.6 ppm reported in [20].

[d] 165.4 ppm reported in [19].

[e] 172.7 ppm reported in [23].

Table 7
$\delta(^1H)$ chemical shifts (in ppm), $^nJ_{HH}$ and $^nJ_{HF}$ coupling constants (in Hz) in 2- and 3-fluoro-substituted thiophenes, pyrroles and furans[a]



Compound no.	X	Substituents				$\delta(^1H)$				$^nJ_{HH}$		$^nJ_{HF_2}$		$^nJ_{HF_3}$		Reference
		R^1	R^2	R^3	R^5	H_2	H_3	H_4	H_5	H_3H_4	H_4H_5	H_3F_2	H_4F_2	H_4F_3	H_5F_3	
1	S		F	H	*n*-Octyl		6.42	6.53		3.8		1.9	3.2			[8]
16	S		F	H	H		6.35	6.54	6.74	3.9		1.6	3.1			This work
2	S		*n*-Octyl	F	H			6.74	6.93		5.4			<0.5[b]	3.9	This work
17	S		H	F	H	6.51		6.69	7.01		5.4			−0.8	3.3	[8]
3	S		CH_3	F	CH_3CO			7.15						<0.5[b]		This work
6[c]	N	CH_3	*n*-Octyl	H	F		5.27	5.56		3.9		3.9	4.6			This work
8	N	H	F	H	CHO		5.81	6.96		4.1		4.1	4.2			This work
20	N	CH_3	F	H	H		5.39	5.82	6.23	3.8		4.2	5.0			[17]
21	N	CH_3	H	F	H	6.51		5.79	6.44		2.9			<0.4[b]	4.5	[17]
12	O		F	H	*n*-Octyl		5.26	5.87		3.2		7.1	3.2			This work
13	O		*n*-Octyl	F	H			6.23	7.05		2.2			0.5[b]	3.6	This work

[a] Measured in $CDCl_3$ if not otherwise stated.

[b] The sign has not been determined.

[c] $\delta(NCH_3) = 3.37$ ppm, $^4J_{2FCH_3} = 0.8$ Hz; measured in acetone-d_6.

benzene [27]. The SCS_F effects in 3-substituted compounds are different from those found for the 2-substituted ones. The corresponding $\Delta\delta_F$ values for directly F-substituted carbon C_3 are 30.5 ppm for the thiophene derivative **2** and 44.0 ppm for both pyrrole **10** and furan **13** derivatives. The β-SCS effects in this group of compounds are ca. −20 Hz for the C_2 carbon and only ca. −10 Hz for the C_4 one.

Let us now consider the trends observed in the shielding or deshielding of the fluorine nuclei in particular compounds studied. By analogy to the presentation of the nitrogen data applied by Witanowski in his numerous papers [28,29], we will present our results in terms of $\Delta\sigma$, which represents the differences in the fluorine nuclear shielding constants of the compounds studied and that of fluorotrichloromethane used as reference. Thus, we use the expression "fluorine shielding" for $\Delta\sigma$, since the positive sign corresponds to an increase in magnetic shielding. Hence, $\Delta\sigma = -\delta$, where the latter is commonly termed as the chemical shift. Consequently, "fluorine shieldings" and "fluorine chemical shifts" differ only in their sign.

An analysis of the data obtained shows that the most shielded is the fluorine nucleus in position 3 of 3-fluoro-2-*n*-octylfuran (**13**) and the most deshielded the fluorine nucleus in position 2 of 2-fluoro-5-*n*-octylfuran (**12**) 176.1 and 118.0 ppm, respectively. The difference between the shielding of these two nuclei attains then 58.1 ppm. In the case of pyrrole, this difference decreases to 23.8 ppm, the fluorine nucleus at C_3 being still more shielded than that at C_2; the corresponding shielding values are 166.5 and 142.7 ppm, respectively. Further significant decrease of $\Delta\sigma$ occurs when we pass to fluorothiophenes, **1** and **2**, where the difference between the shielding of fluorine at C_3 and fluorine at C_2 is of 2.9 ppm only. A similar difference but of the opposite sign, of ca. −4 ppm, has been observed by Gronowitz and coworkers [8] for 2- and 3-fluorothiophene, which do not bear any other substituent.

Several interesting papers have been recently published on the theoretical calculations of the ^{19}F shieldings [30–35], and the authors indicated that the ab initio calculated ^{19}F NMR shieldings can be of great help in the assignment and prediction of the ^{19}F signals in the spectra of a variety of compounds. It was therefore of considerable interest to find out if the trends observed experimentally in the compounds studied by us would be reproduced by the DFT calculations. Indeed, a very good linear correlation with a correlation coefficient r of 0.986 was obtained when the experimental fluorine shieldings measured in the present work were plotted against the corresponding DFT values calculated by the use of the deMon program [26] (Fig. 1); a standard deviation is of 3.7 ppm, which amounts to about 5.3% of the total range of the fluorine shieldings considered (70 ppm):

$$\sigma(^{19}F)_{exp} = 0.94 \times \sigma(^{19}F)_{DFT} - 135.55 \qquad (1)$$

$$r = 0.986; \quad S.D. = 3.7; \quad n = 13$$

Finally, it is worth mentioning that some time ago Witanowski and Biedrzycka [36] suggested that the difference $|^1J_{C_2C_3} - {}^1J_{C_3C_4}|$ can be applied as an indicator of the aromaticity of five-membered heterocycles. Their observation that this difference decreases with the increasing aromaticity of the compound has been supported by our recent results [1] and it is further corroborated by the data of the present work. The resonance energies calculated for furan, pyrrole and thiophene are 67, 88 and 121 kJ/mol, respectively [37], and the difference between the $^1J_{C_2C_3}$ and $^1J_{C_3C_4}$ couplings in the 3-fluoro-substituted compounds, **13**, **10** and **2** decreases in the same order, 28.9, 20.4 and 8.4 Hz, respectively ($^1J_{C_2C_3}$ values in **2** and **13** corrected by 2 Hz

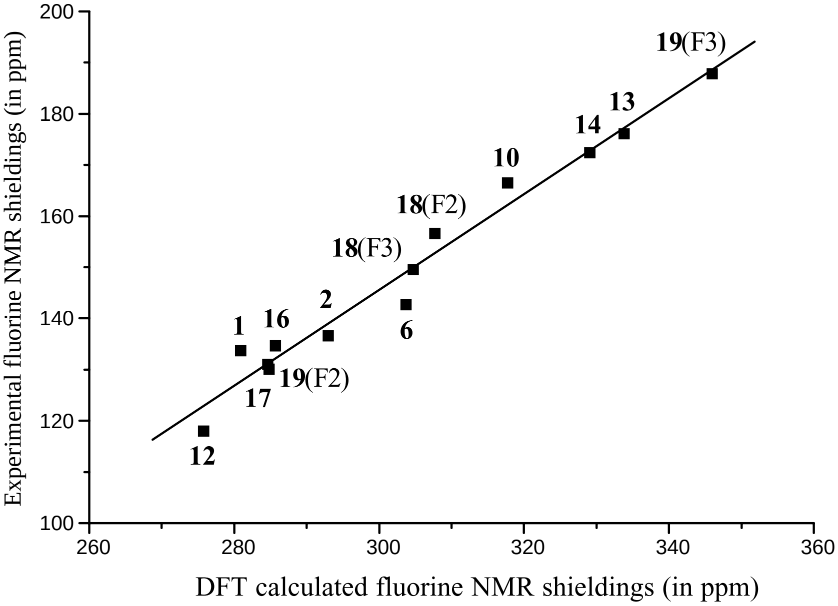


Fig. 1. A plot of experimental fluorine shieldings, referenced to $CFCl_3$, against DFT calculated absolute fluorine shieldings for 2- and 3-fluoro-substituted thiophenes, pyrroles and furans. The relevant values of the shieldings are reported in Table 6, and the linear regression concerned is represented by Eq. (1).

for the methyl substitution). Moreover, as was already shown above, the same trend is displayed by the differences between the shieldings of the fluorine nuclei at carbons C_2 and C_3: $|\sigma_{exp}(F_2) - \sigma_{exp}(F_3)| = 58.1$, 23.8 and 2.9 ppm, for fluorofurans, fluoropyrroles and fluorothiophenes, respectively. Thus, it can be concluded that both these parameters may be used as a measure of aromaticity of the compounds studied.

3. Conclusions

The results obtained show clearly that a significant increase of the s-electron density occurs on those carbon atoms to which the fluorine atom is attached. This is reflected in the experimental and DFT calculated $^1J_{CC}$ coupling constants which are dramatically larger than the coupling constants in the parent compounds. This observation is valid for C_2 and C_3 carbons. The inductive effect of the fluorine atom is the obvious cause of the re-distribution of the s-electron densities.

It has been confirmed that the differences $|^1J_{C_2C_3} - {}^1J_{C_3C_4}|$ and $|\sigma_{exp}(F_2) - \sigma_{exp}(F_3)|$ can be applied as indicators of the aromaticity of the five-membered heterocycles.

4. Experimental

4.1. Computational methods

Full density functional theory geometry optimizations were carried out using the TURBOMOLE program (BIOSYM/MSI) [38,39]. The gradient-corrected exchange-correlation energy functional employed consists of the exchange functional of Becke [40,41] and the correlation energy functional of Perdew [42]. Standard double ξ quality basis with polarization functions (DZVP) and a fine grid with 32 radial points for the numerical integrations were selected.

The DFT calculations were performed using the recent approach proposed by Malkin et al. and the deMon program developed by this group [26]. Within this methodology, three contributions are taken into account, i.e. the Fermi contact contribution (FC), the paramagnetic spin–orbit (PSO) and the diamagnetic spin–orbit (DSO) contributions. The spin–dipolar (SD) term is neglected. The FC term is calculated by the finite perturbation theory (FPT), the PSO contribution is obtained using the sum-over-states density functional perturbation theory (SOS-DFPT) and the DSO term is obtained by numerical integration. The spin–spin couplings were calculated using the correlation functional of Perdew [43,44] and the semilocal exchange of Perdew and Wang [45]. The basis set employed was the IGLO-III of Kutzelnigg et al. [46] and a fine grid with 64 radial points was used. The value of 0.001 was used for the perturbation parameter.

4.2. Measurement of the spectra

In most cases, NMR spectra were measured in 5 mm tubes in $CDCl_3$ solutions; only compounds **6** and **7** were dissolved in acetone-d_6. Standard ^1H, ^{13}C and ^{19}F NMR spectra were measured on a Varian Mercury-400 FT spectrometer. Tetramethylsilane (TMS) for ^1H (400.42 MHz) and ^{13}C (100.602 MHz), and $CFCl_3$ for ^{19}F NMR (376.398 MHz) spectra were used as standards. 1D INADEQUATE ^{13}C NMR spectra were measured on a Bruker DRX "Avance" spectrometer using the standard B microprogram (32-phase Freeman cycle with automatic data storage). Typical conditions were: acquisition time 2.4–6.2 s, digital resolution 0.16–0.25 Hz per point and 215 cycles within 12 h.

FT-IR spectra were measured on a Perkin-Elmer spectrophotometer Spectrum 2000 solid samples being examined as KBr discs and oil samples as films.

MS and HRMS spectra were measured using an Intectra GmbH AMD 604 mass spectrometer.

4.3. Preparation of the compounds

Syntheses of all the compounds were carried out under an argon atmosphere. This was particularly important in the case of the pyrrole derivatives which easily undergo oxidation. In the case of these compounds also the NMR tubes should be filled with argon. The structure of all compounds has been confirmed by the use of NMR, MS and IR measurements.

5-Fluoro-1*H*-pyrrole-2-carbaldehyde (**8**), 3-fluoro-*N*-(tri-*iso*-propyl)silylpyrrole (**10**), and *N*-(tri-*iso*-propyl)silylpyrrole (**11**) and 2-ethyl-3-fluoro-5-phenylfuran (**14**) were obtained as described in Refs [20], [19], [47] and [23], respectively.

2-*n*-Octylthiophene (**4**), 2-*n*-octyl-*N*-methylpyrrole (**7**) and 2-*n*-octylfuran (**15**) were obtained according to the procedures described in [48]. The relevant data for **7** (new compound) are (^{1}H NMR, 500 MHz, acetone-d$_6$, $\delta(^1\text{H})$ in ppm and $^nJ_{\text{HH}}$ in Hz) and IR ($\tilde{\nu}$, cm^{-1}): 5.88 (H-3), 6.05 (H-4), 6.53 (H-5), $^3J_{34} = 3.4$, $^3J_{45} = 2.7$, $^4J_{35} = 1.7$; $\tilde{\nu}$ (cm^{-1}) 2956, 2927, 2855, 2811, 1495, 1466, 1416, 1378, 1301, 1088, 766, 698; bp 140 °C/14 mmHg and GC–MS (EI 70 eV): *m/z* (%) 193 (18, M^+), 94 (100, $[M - \text{C}_7\text{H}_{15}^+]$). HRMS (EI): Calcd. for $\text{C}_{13}\text{H}_{23}\text{N}$: 193.18305. Found: 193.18312.

The remaining compounds were obtained according the following procedures.

*4.3.1. 2-Fluoro-5-n-octylthiophene (**1**)*

To a solution containing BuLi (5.6 mmol, 3.5 ml) and 15 ml of THF cooled to 0 °C, 2-*n*-octylthiophene (1 g, 5.1 mmol) was added by the use of a syringe. The temperature was allowed to rise to RT and the reaction mixture was left for 30 min with stirring. Subsequently the solution was cooled to −10 °C and powdered *N*-fluorodibenzenesulfonamide (1.77 g, 5.6 mmol) added by the use of a glass-finger. The slurry obtained was left with stirring at RT over 3 h, then 50 ml of pentane were added and stirring continued for 1 min. The reaction mixture was filtered through a small layer (2–3 cm, ca. 15 g) of neutral aluminum oxide placed on a Schott funnel in order to remove the precipitate of dibenzenesulfonamide. The organic solution obtained was washed five times with a small amount of water and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, 0.89 g of 2-fluoro-5-*n*-octylthiophene was obtained which contained some remaining 2-*n*-octylthiophene (ca. 25%). A pure sample of 2-fluoro-5-*n*-octylthiophene was isolated by the use of TL chromatography (silica gel plates, pentane as eluent). It is a colorless oil, stable at RT.

GC–MS (EI 70 eV): *m/z* (%) 214 (18, M^+), 115 (100, $[M - \text{C}_7\text{H}_{15}]^+$). HRMS (EI): Calcd. for $\text{C}_{12}\text{H}_{19}\text{SF}$: 214.11915. Found: 214.11836. IR ($\tilde{\nu}$, cm^{-1}): 2957, 2928, 2856, 1635, 1573, 1506, 1465, 1197, 783, 724, 705.

*4.3.2. 3-Fluoro-2-n-octylthiophene (**2**)*

To a pre-cooled (−78°) stirred solution containing *n*-BuLi (2 ml, 3.17 mmol) and tetrahydrofuran (10 ml) 3-bromo-2-*n*-octylthiophene (0.87 g, 3.17 mmol, obtained as described in [49]) was added by the use of a syringe. After the reaction mixture had been stirred for 20 min, powdered *N*-fluorodibenzenesulfonamide (1.0 g, 3.17 mmol) was added by the use of a glass finger. The reaction was stirred an additional 10 min at −78° and then the obtained red solution left at room temperature for 3 h. After that 50 ml of pentane were added and stirring continued for 1 min; then the reaction mixture was filtered through a small layer (2–3 cm) of neutral aluminum oxide (ca. 15 g) placed on a Schott funnel, the organic solution washed five times with a small amount of water and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure 0.67 g of pale yellow oil was obtained which contained some amount of 2-*n*-octylthiophene (ca. 25%). A pure sample of 3-fluoro-2-*n*-octylthiophene was isolated by the use of TLC (silica gel plates, pentane as eluent). The compound is colorless and stable at RT.

MS (EI 70 eV): *m/z* (%) 214 (23, M^+), 115 (100, $[M - \text{C}_7\text{H}_{15}]^+$). HRMS (EI): Calcd. for $\text{C}_{12}\text{H}_{19}\text{SF}$: 214.11915. Found: 214.11946. Anal. Calcd. for $\text{C}_{12}\text{H}_{19}\text{FS}$: C, 67.24; H, 8.93; S, 14.96. Found: C, 66.99, 66.97; H, 9.18, 9.21; S, 14.87, 14.83. IR ($\tilde{\nu}$, cm^{-1}): 3117, 2957, 2927, 2856, 1577, 1454, 1395, 1229, 700.

*4.3.3. 5-Acetyl-2-fluoro-2-methylthiophene (**3**)*

To a pre-cooled (10 °C) solution of 4.65 g (30 mmol) of 5-acetyl-3-amino-2-methylthiophene dissolved in 30 ml of anhydrous ethyl ether 60 ml of 2 M solution of HBF_4 in ethyl ether were added. Subsequently 5-acetyl-2-methyl-3-aminothiophene tetrafluoroborate precipitated, to which after cooling to 5 °C, 3 g of ethyl nitrite dissolved in 10 ml of Et_2O were added. The salt of the amine slowly dissolved and after a short time a resin-like diazonium salt separated. After 10 min the salt was decanted and washed out with dry ethyl ether. The 5-acetyl-2-methyl-3-thiophenediazonium tetrafluoroborate obtained was mixed with 10 g of silica gel and heated in a round-bottomed flask at 160 °C under vacuum distillation (water pump) conditions until diazonium salt decomposed. The distillate was dissolved in 20 ml of methylene chloride, washed out several times with water (pH = 7) and dried over magnesium sulfate. The crude 5-acetyl-3-fluoro-2-methylthiophene was purified by the use of TL chromatography (silica gel, hexane–methylene chloride 2:1 as eluent) which yielded 400 mg (9%) of white crystals. Melting point 97–99.5 °C. MS (EI 70 eV): *m/z* (%) 158 (45, M^+), 143 (100, $[M-CH_3]^+$), 115 (26, $[M-CH_3CO]^+$). HRMS (EI): Calcd. for C_7H_7OSF: 158.02016. Found: 158.02038. Anal. Calcd. for C_7H_7OSF: C, 53.15; H, 4.45; S, 20.27. Found: C, 53.14; H, 4.50; S, 20.11; IR ($\tilde{\nu}$, cm^{-1}): 3071, 3025, 2966, 2926, 1647, 1569, 1470, 1445, 1397, 1378, 1279, 1168, 1111, 931, 893, 870, 733, 611, 597.

4.3.4. 2-Fluoro-5-n-octyl-N-methylpyrrole (**6**)

To a solution containing BuLi (3.8 mmol, 2.4 ml) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (0.44 g, 3.8 mmol) 2-*n*-octyl-*N*-methylpyrrole (0.66 g, 3.4 mmol) was added by the use of a syringe at RT. The reaction mixture was left for 2 h with stirring, then cooled to −10 °C, 15 ml of THF added by the use of a syringe followed by powdered *N*-fluorodibenzenesulfonamide (1.2 g, 3.8 mmol) added by the use of a glass-finger. After 15 min, the cooling bath was removed and the slurry obtained was left with stirring at RT over 3 h, then 50 ml of pentane were added and stirring continued for 1 min. The reaction mixture was worked up as described for **1** and 0.65 g of the crude oil which contained (ca. 40%) of 2-*n*-octyl-*N*-methylpyrrole was obtained. A small amount of a pure sample of 2-fluoro-5-*n*-octyl-*N*-methylpyrrole was isolated by the use of TL chromatography (neutral aluminum oxide plates, pentane as eluent). It is a slightly yellow oil, significantly less stable in chloroform-d_1 solution than the derivatives of thiophene and furan, and therefore NMR measurements in this case were carried out in acetone-d_6.

GC–MS (EI 70 eV): *m/z* (%) 211 (15, M^+), 112 (100, $[M-C_7H_{15}]^+$), HRMS (EI): Calcd. for $C_{13}H_{22}FN$: 211.17363. Found: 211.17346. Anal. Calcd. for $C_{13}H_{22}FN$: C, 73.89; H, 10.49, N, 6.63. Found: C, 73.75, 73.70; H, 10.67, 10.57; N, 6.54, 6.46. IR ($\tilde{\nu}$, cm^{-1}): 2956, 2928, 2856, 1588, 1535, 1485, 1467, 1413, 1386, 1297, 1176, 1009, 726.

4.3.5. 2-Fluoro-5-n-octylfuran (**12**)

2-Fluoro-5-*n*-octylfuran (**12**) was synthesized as described for compound **1** using 1.9 ml (3.05 mmol) of BuLi, 0.5 g (2.77 mmol) of 2-*n*-octylfuran, 10 ml of THF and 1.31 g (4.16 mmol) of *N*-fluorodibenzenesulfonamide. After removal of the solvent under reduced pressure 0.54 g of pale yellow oil was obtained which contained some remaining 2-*n*-octylthiophene (ca. 20%). A very pure sample of 2-fluoro-5-*n*-octylfuran was isolated by the use of TL chromatography (silica gel plates, pentane as eluent). It is a colorless oil, stable at RT, bp 100 °C/14 mmHg.

GC–MS (EI 70 eV): *m/z* (%) 198 (12, M^+), 99 (100, $[M-C_7H_{15}]^+$); HRMS (EI): Calcd. for $C_{12}H_{19}OF$: 198.14199. Found: 198.14163. Anal. Calcd. for $C_{12}H_{19}FO$: C, 72.69; H, 9.66. Found: C, 72.43, 72.58; H, 9.53, 9.82. IR ($\tilde{\nu}$, cm^{-1}): 3145, 3118, 2957, 2929, 2858, 1640, 1592, 1466, 1378, 1263, 1201, 1004, 990, 946, 762.

4.3.6. 3-Fluoro-2-n-octylfuran (**13**)

To a pre-cooled (−78°) stirred solution containing *n*-BuLi (3.3 ml, 5.3 mmol) and THF (10 ml) 3-bromo-2-*n*-octylfuran (1.25 g, 4.8 mmol, obtained as described in [50]) was added by the use of a syringe. After the reaction mixture had been stirred for 20 min, powdered *N*-fluorodibenzenesulfonamide (1.67 g, 5.3 mmol) was added by the use of a glass finger. The reaction was stirred an additional 10 min at −78 °C and then the red solution obtained left at room temperature overnight. After that 50 ml of pentane were added and stirring continued for 1 min; then the reaction mixture was filtered through a small layer (2–3 cm, ca. 15 g) of neutral aluminum oxide placed on a Schott funnel, the organic solution was washed with a small amount of water and dried over anhydrous sodium sulfate. After removal of the solvents under reduced pressure 1.1 g of pale yellow oil was obtained which contained some 2-*n*-octylfuran (ca. 25%). A very pure sample of 3-fluoro-2-*n*-octylfuran (a colorless oil) was isolated by the use of TLC (silica gel plates, pentane as eluent).

GC–MS (EI 70 eV): *m/z* (%) 198 (10, M^+), 99 (100, $[M-C_7H_{15}]^+$). HRMS (EI): Calcd. for $C_{12}H_{19}FO$ 198.14199. Found: 198.14228. IR ($\tilde{\nu}$, cm^{-1}): 2957, 2928, 2857, 1653, 1466, 1440, 1428, 1271, 1145, 1070, 885, 720, 612.

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