Full Articles

Spin-spin coupling constant $^3J_{H,F}$ as a reliable criterion for recognition of individual regioisomeric and tautomeric pairs of $H(CF_2)_2$-containing isoxazoles and pyrazoles

V. Ya. Sosnovskikh

A. M. Gorky Ural State University,
51 prosp. Lenina, 620083 Ekaterinburg, Russian Federation.
Fax: +7 (343 2) 61 5978. E-mail: Vyacheslav.Sosnovskikh@usu.ru

The spin-spin coupling constant $^3J_{H,F}$ of the $H(CF_2)_2$ group varies within 1.6—3.5 Hz for 5-R^F- and 3.8—4.5 Hz for 3-R^F-isoxazoles and pyrazoles in $CDCl_3$ and can serve as a reliable criterion for recognition of regioisomeric and tautomeric structures of $H(CF_2)_2$-containing heterocyclic compounds.

Key words: spin-spin coupling constant $^3J_{H,F}$ of $H(CF_2)_2$ group, $H(CF_2)_2$-containing isoxazoles and pyrazoles, ^1H NMR spectroscopy, regioisomers, tautomers.

We have recently[1] shown that the spin-spin coupling constant $^3J_{H,F}$ of the $H(CF_2)_2$ group depends on the nearest environment of the carbon atom bonded to this group and is a helpful tool for the recognition of regioisomeric and tautomeric pairs of organofluorine compounds. It turned out that in molecules containing the HCF_2CF_2—C(X)=C fragment the $^3J_{H,F}$ value is much lower than that in the molecules with the HCF_2CF_2—C(C)=X fragment, where X = O, N. This observation allowed us to use the $^3J_{H,F}$ constant in the study of the regioisomeric and tautomeric structures of five-membered heterocycles, such as isoxazoles and pyrazoles.

In the previous reports, we described the syntheses of 3-(2-hydroxyaryl)-5-polyfluoroalkyl- and 5-(2-hydroxyaryl)-3-polyfluoroalkylisoxazoles[2] and pyrazoles[3] by the reactions of 2-hydroxy-2-polyfluoroalkylchroman-4-ones and 2-polyfluoroalkylchromones with hydroxylamine, hydrazine hydrate, and methyl- and phenylhydrazines. The structures of these compounds, including problems of regioisomerism and tautomerism, were proved on the basis of the ^1H, ^{19}F, and ^{13}C NMR spectroscopic data taking into account published data on related molecules.[4—9] In this work, using a series of regioisomeric $H(CF_2)_2$-containing isoxazoles **1—3** and pyrazoles **4—11** as examples, we studied a change in the $^3J_{H,F}$ constant at different positions of the $H(CF_2)_2$ group in the heterocycle and as a function of the nature of substituent, solvent polarity, and medium acidity.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 1977—1984, October, 2003.

1066-5285/03/5210-2087 $25.00

Experimental

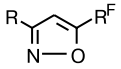
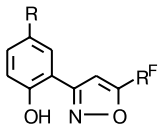
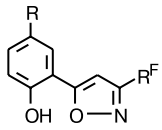
^{1}H NMR spectra were recorded on a Bruker DRX-400 instrument (400.1 MHz) using Me_4Si for solutions in $CDCl_3$ and DMSO-d_6 followed by the addition of CD_3CO_2D and CF_3CO_2H. The digital resolution in the spectra was 0.12—0.14 Hz per point. The $^3J_{H,F}$ and $^2J_{H,F}$ constants and chemical shifts of the terminal proton of the $H(CF_2)_2$ group and H(4) proton in isoxazoles **1**—**3** and pyrazoles **4**—**11** are presented in Tables 1 and 2.

Results and Discussion

Regioisomeric isoxazoles and *N*-substituted pyrazoles (neutral solutions). Prototropic tautomerism is absent in 5- and 3-R^F-isoxazoles **1**—**3** and *N*-substituted pyrazoles **7**—**10** (hereinafter $R^F = H(CF_2)_2$) and, as can be seen from the data in Tables 1 and 2, they can easily be distinguished by the $^3J_{H,F}$ value, being 1.6—3.5 Hz for 5-R^F- and 3.8—4.5 Hz for 3-R^F-regioisomeric isoxazoles and pyrazoles in $CDCl_3$.

The data on 3-Ar-5-R^F-isoxazoles **1** and **2** (see Table 1) show that the nature and position of the substituent in the aromatic ring exert a noticeable effect on $^3J_{H,F}$. For example, for solutions in $CDCl_3$ the introduction of the HO (**1b**) and MeO groups (**1c**) into the *para*-position of the phenyl substituent does not virtually change the $^3J_{H,F}$ constants, while the *o*-MeO group (**1d**) increases this value by 0.3 Hz, and the *o*-HO group (**2a**) decreases it by 0.3 Hz. In the series of 3-R^F-isoxazoles **3**, $^3J_{H,F}$ is 3.9—4.0 Hz, *i.e.*, by ~1.2 Hz higher than those of the corresponding 5-R^F regioisomers **2**. The replacement of $CDCl_3$ by DMSO-d_6 increases the constant by 0.6 Hz for 3-R^F-isoxazoles **3** ($^3J_{H,F}$ ~4.5 Hz) and by 0.7—1.4 Hz for

Table 1. Spin-spin coupling constants $^3J_{H,F}$, $^2J_{H,F}$ and chemical shifts of the terminal proton of the $R^F = H(CF_2)_2$ group and the H(4) proton in R^F-isoxazoles **1**—**3**

Compound[a]	Structure	R	Solvent	$^3J_{H,F}$	$^2J_{H,F}$	δ	
				Hz		$(CF_2)_2H$ (tt)	H(4) (t, J = 1.0—1.1 Hz)
1a		Ph	$CDCl_3$	3.1	53.1	6.12	7.01
			$CDCl_3$—TFA[b]	3.0	53.1	6.12	7.02
			DMSO-d_6	3.8	51.8	7.08	7.93
1b		4-HOC_6H_4	$CDCl_3$	3.1	53.1	6.12	6.95
1c		4-$MeOC_6H_4$	$CDCl_3$	3.2	53.1	6.12	6.95
			$CDCl_3$—TFA	3.1	53.1	6.12	6.98 (s)
			DMSO-d_6	3.9	51.8	7.05	7.85
1d		2-$MeOC_6H_4$	$CDCl_3$	3.4	53.1	6.12	7.23
			DMSO-d_6	4.0	51.7	7.08	7.55
1e		Bu^t	$CDCl_3$	3.3	53.1	6.08	6.61
			DMSO-d_6	4.0	51.8	6.99	7.36
2a		H	$CDCl_3$	2.8	53.1	6.13	7.11
			$CDCl_3$—DAA[c]	2.8	53.1	6.15	7.15
			$CDCl_3$—TFA	2.8	53.1	6.14	7.14
			DMSO-d_6	4.1	51.7	7.09	7.57 [d]
			DMSO-d_6—TFA	4.0	51.8	7.04	7.57 [d]
2b		Me	$CDCl_3$	2.9	53.1	6.12	7.11
2c		Cl	$CDCl_3$	2.6	53.1	6.14	7.12 (s)
			DMSO-d_6	4.0	51.7	7.08	7.60
3a		H	$CDCl_3$	4.0	53.1	6.18	7.00 (s)
			$CDCl_3$—DAA	4.0	53.0	6.20	7.07 (c)
			$CDCl_3$—TFA	3.4	53.1	6.16	7.05 (s)
			DMSO-d_6	4.5	51.8	7.03	7.19 (s)
			DMSO-d_6—TFA	4.5	51.8	7.01	7.20 (s)
3b		Me	$CDCl_3$	4.0	53.1	6.17	6.99 (s)
3c		Cl	$CDCl_3$	3.9	53.1	6.18	7.06 (s)
			$CDCl_3$—TFA	3.5	53.1	6.17	7.07 (s)
			DMSO-d_6	4.5	51.7	7.03	7.26 (s)

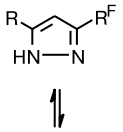
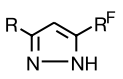
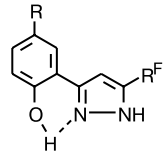
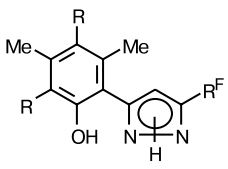
[a] The compounds were synthesized by described procedures.[2]

[b] Three drops of TFA and 10—15 mg of the substance in 0.5 mL of a solvent.

[c] DAA is deuterioacetic acid (3 drops of DAA and 10—15 mg of the substance in 0.5 mL of a solvent).

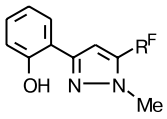
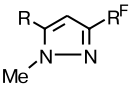
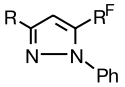
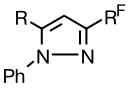
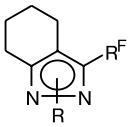
[d] Triplet with $^4J_{H,F}$ = 1.2—1.3 Hz.

Table 2. Spin-spin coupling constants $^3J_{H,F}$, $^2J_{H,F}$ and chemical shifts of the terminal proton of the $R^F = H(CF_2)_2$ group and the H(4) proton in R^F-pyrazoles **4—11**

Compound[a]	Structure	R	Solvent[b]	$^3J_{H,F}$	$^2J_{H,F}$	δ	
				Hz		$(CF_2)_2H$ (tt)	H(4) (s)
4a		Ph	$CDCl_3$	3.6	53.6	6.06	6.79
			$CDCl_3$—DAA	3.4	53.5	6.08	6.83
			$CDCl_3$—TFA	2.3	53.6	6.06	6.91
			DMSO-d_6	5.0	52.2	6.83	7.10 [c]
			DMSO-d_6—TFA	5.0	52.2	6.82	7.10
4b		2-HOC_6H_4	$CDCl_3$	2.8	53.7	6.09	6.96
			$CDCl_3$—DAA	3.2	53.6	6.07	6.91
			$CDCl_3$—TFA	2.0	53.6	6.07	7.04
			DMSO-d_6	5.0	52.2	6.82	7.03
4c		2-$MeOC_6H_4$	$CDCl_3$	4.3	53.5	6.17	6.89
			$CDCl_3$—DAA	3.2	53.6	6.07	6.93
			$CDCl_3$—TFA	2.5	53.6	6.05	6.97
			DMSO-d_6	5.1	52.2	6.83	7.03
			DMSO-d_6—TFA	5.1	52.2	6.81	7.03
4d		4-HOC_6H_4	$CDCl_3$	4.0	53.5	6.14	6.72
			$CDCl_3$—DAA	3.4	53.5	6.07	6.72
			$CDCl_3$—TFA	2.2	53.6	6.06	6.83
			DMSO-d_6	5.1	52.2	6.80	6.89
4e		4-$MeOC_6H_4$	$CDCl_3$	3.8	53.5	6.10	6.71
			$CDCl_3$—DAA	3.5	53.5	6.07	6.74
			$CDCl_3$—TFA	2.3	53.6	6.06	6.84
4f		4-MeC_6H_4	$CDCl_3$	3.8	53.5	6.07	6.75
			$CDCl_3$—TFA	2.3	53.6	6.04	6.85
4g		4-FC_6H_4	$CDCl_3$	3.4	53.6	6.06	6.75
			$CDCl_3$—TFA	2.2	53.6	6.05	6.85
4h		4-ClC_6H_4	$CDCl_3$	3.3	53.6	6.05	6.77
			$CDCl_3$—DAA	3.2	53.6	6.07	6.82
			$CDCl_3$—TFA	2.2	53.6	6.05	6.88
			DMSO-d_6	4.9	52.2	6.83	7.16
4i		Bu^t	$CDCl_3$	3.9	53.6	6.08	6.35
			$CDCl_3$—TFA	2.5	53.6	6.01	6.47
			DMSO-d_6	5.2	52.2	6.75	6.36 [c]
4j [d]		Et	$CDCl_3$	3.7	53.8	5.96	6.29
4k [d]		Me	$CDCl_3$	3.5	53.8	5.96	6.27
5a		Me	$CDCl_3$	2.9	53.7	6.10	6.95
			$CDCl_3$—TFA	2.8	53.6	6.08	6.95
5b		MeO	$CDCl_3$	2.9	53.7	6.10	6.92
			$CDCl_3$—TFA	2.8	53.6	6.08	6.91
5c		Cl	$CDCl_3$	2.1	53.7	6.08	6.98
			$CDCl_3$—DAA	3.0	53.6	6.06	6.91
			$CDCl_3$—TFA	2.2	53.6	6.05	6.98
			DMSO-d_6	5.0	52.2	6.82	7.12
5d		NO_2	$CDCl_3$	1.6	53.8	6.09	7.16
			$CDCl_3$—DAA	2.4	53.7	6.08	7.10
			$CDCl_3$—TFA	1.9	53.7	6.08	7.16
			DMSO-d_6	4.9	52.2	6.85	7.21
6a		H	$CDCl_3$	3.6	53.6	6.14	6.75
			DMSO-d_6	5.1	52.2	6.81	6.54
6b		NO_2	$CDCl_3$	2.8	53.6	6.14	6.82

(*to be continued*)

Table 2 (*continued*)

Compound[a]	Structure	R	Solvent[b]	$^3J_{H,F}$	$^2J_{H,F}$	δ	
				Hz		$(CF_2)_2H$ (tt)	H(4) (s)
7			$CDCl_3$	2.3	53.7	6.05	6.92
			$CDCl_3$—TFA	2.2	53.7	6.06	6.94
8a		Ph	$CDCl_3$	4.2	53.5	6.15	6.57
			$CDCl_3$—TFA	3.2	53.6	6.08	6.61
			DMSO-d_6	4.9	52.1	6.82	6.81
8b[e]		2-HOC_6H_4	$CDCl_3$	4.1	53.5	6.14	6.60
			$CDCl_3$—DAA	4.1	53.5	6.14	6.57
			$CDCl_3$—TFA	3.0	53.6	6.07	6.62
			DMSO-d_6	5.0	52.2	6.80	6.60
9a		Ph	$CDCl_3$	3.3	53.4	5.81	7.07
			DMSO-d_6	4.3	52.0	6.86	7.52
9b[e]		2-HOC_6H_4	$CDCl_3$	3.2	53.4	5.84	7.15
			$CDCl_3$—TFA	3.1	53.4	5.84	7.16
			DMSO-d_6	4.4	51.9	6.93	7.51
9c[d]		Et	$CDCl_3$	3.5	53.5	5.76	6.58
10a		Ph	$CDCl_3$	4.5	53.4	6.23	6.77
			DMSO-d_6	5.0	52.2	6.91	7.08
			CD_3COCD_3[f]	5.1	53.4	6.75	7.65
10b[e]		2-HOC_6H_4	$CDCl_3$	4.4	53.4	6.23	6.81
			$CDCl_3$—TFA	3.3	53.5	6.15	6.85
			DMSO-d_6	5.0	52.1	6.89	6.86
11a[g]		H	$CDCl_3$	3.7	53.6	6.00	—
11b[g]		Ph (3-R^F)	$CDCl_3$	4.8	53.5	6.25	—
11c[g]		Ph (5-R^F)	$CDCl_3$	3.4	53.8	5.63	—

[a] Compounds **4**—**6** were synthesized according to a described procedure.[3]
[b] DAA is deuterioacetic acid.
[c] Broadened doublet with $^4J_{H(4),NH}$ = 1.9—2.0 Hz.
[d] The data in Ref. 15.
[e] Described in Ref. 3.
[f] The data in Ref. 10.
[g] The data in Ref. 4.

5-R^F-isoxazoles **1** and **2** ($^3J_{H,F}$ ~4.0 Hz), which makes it possible to distinguish these regioisomers in both $CDCl_3$ and DMSO-d_6 solutions. The influence of substituents in the benzene ring on the $^3J_{H,F}$ value appears in DMSO-d_6 as well, although to a smaller extent than in $CDCl_3$.

The changes in the heterocycle structure that occur in the environment nearest to the $H(CF_2)_2$ group have the greatest effect on the $^3J_{H,F}$ constant value. For example, in solution of isoxazole **3a** and pyrazole **8b** in $CDCl_3$ ($^3J_{H,F}$ = 4.0 and 4.1 Hz, respectively), the transition from the O atom to the N—Me fragment in the series of 3-R^F isomers exerts almost no effect on the $^3J_{H,F}$ value, whereas a similar change in the series of 5-R^F isomers (**2a**, **7**) decreases this value by 0.5 Hz. The replacement of the methyl group at the N(1) atom by phenyl in 3-R^F-pyrazoles (**8b**, **10b**) increases $^3J_{H,F}$ by 0.3 Hz, whereas in 5-R^F-pyrazoles (**7**, **9b**) this replacement results in an increase by 0.9 Hz. The possibility of recognition of regioisomeric pyrazoles remains for both $CDCl_3$ and DMSO-d_6 solutions. The comparison of pyrazoles **9a**,**b** and **10a**,**b** shows that, as in the isoxazole series, the *o*-HO group decreases the $^3J_{H,F}$ value, and this occurs to a greater extent for the 5-R^F isomer.

The regularities related to a change in the constant on going from $CDCl_3$ to DMSO-d_6 in the isoxazole series are retained for *N*-phenylpyrazoles: the $^3J_{H,F}$ value increases by 1.0—1.2 Hz in 1-Ph-5-R^F-pyrazoles **9a**,**b** and by 0.5—0.6 Hz in 1-Ph-3-R^F-pyrazoles **10a**,**b**. Thus, the replacement of $CDCl_3$ by DMSO-d_6 has a greater effect on the $^3J_{H,F}$ value for the 5-R^F isomers, due to which their constants in DMSO-d_6 become equal to the constants of the 3-R^F isomers in $CDCl_3$. As a whole, in a

solution of DMSO-d_6 for 3-R^F-pyrazoles studied in this work, regardless of the substituent at the N(1) atom, $^3J_{H,F}$ ~5.0 Hz, while for 5-R^F-pyrazoles it is ~4.4 Hz, which is by 0.4—0.5 Hz higher than those for the corresponding isoxazoles in the same solvent.

Taking into account the $^3J_{H,F}$ value, we can easily establish the composition of a regioisomeric mixture. For example, we isolated[3] a product with m.p. 56—59 °C from the reaction of β-diketone $PhCOCH_2CO(CF_2)_2H$ with phenylhydrazine in an acidic medium in 8% yield. The ^1H NMR spectrum of this product contained two sets of signals corresponding to 1-Ph-5-R^F- and 1-Ph-3-R^F-pyrazoles. The main regioisomer (94%) in a DMSO-d_6 solution had $^3J_{H,F}$ = 4.3 Hz (3.3 Hz in $CDCl_3$), and the minor regioisomer (6%) was characterized by $^3J_{H,F}$ = 5.0 Hz (4.5 Hz in $CDCl_3$). These data make it possible to ascribe the structure of 5-R^F-pyrazole **9a** to the first of them, whereas the second regioisomer can be considered as 3-R^F-pyrazole **10a**. When this reaction has previously[10] been carried out under the basic conditions, a compound with m.p. 144—145 °C recognized as 5-R^F-pyrazole **9a** was obtained. However, according to the melting point and $^3J_{H,F}$ = 5.1 Hz in deuterioacetone, the structure of 3-R^F-pyrazole **10a** should be ascribed to the highly melting isomer. Compound **10a** is the predominant regioisomer in the reactions of phenylhydrazine with polyfluoroalkyl-containing β-diketones.[11]

***N*-Nonsubstituted pyrazoles (neutral solutions).** The substantial differences (1.2—1.8 Hz) between the $^3J_{H,F}$ values of the regioisomeric pairs of isoxazoles and *N*-substituted pyrazoles enable us to use the $^3J_{H,F}$ constant as a simple and reliable criterion for studying fast (in the NMR spectroscopy time scale) prototropic processes, namely, for the estimation of position of the tautomeric equilibrium in *N*-nonsubstituted pyrazoles **4**—**6** (see Table 2).

For the estimation of the prototropic equilibrium by the $^3J_{H,F}$ constant, let us consider 3(5)-(1,1,2,2-tetrafluoroethyl)-5(3)-phenylpyrazole (**4a**) for which $^3J_{H,F}$ = 3.6 Hz in $CDCl_3$ and 5.0 Hz in DMSO-d_6. In the latter solvent, the proton exchange rate is so retarded that allows one to observe the spin-spin coupling between the H(4) and NH protons, due to which the pyrazolic H(4) proton appears as a broadened doublet with $^4J_{H(4),NH}$ = 1.9 Hz ($^1HN—^{13}C$ splitting in 3-azido-1*H*-pyrazole has previously[12] been reported and ascribed to the absence of prototropism). When CF_3CO_2H is added to this solution, the exchange rate increases and the doublet signal of the H(4) atom is transformed into a singlet. No other changes in the spectrum were found, indicating the absence of pyrazole ring protonation under these conditions. Since in pyrazole **4a** the $^3J_{H,F}$ constant is 5.0 Hz and coincides with $^3J_{H,F}$ for 1-R-3-R^F-pyrazoles **8a**,**b** and **10a**,**b**, it is reasonable to assume that in DMSO-d_6 pyrazole **4a** exists predominantly, unless exclusively, as the more polar (calculation of the dipole moments by the semiempirical AM1 method[13]: 3-CF_3 tautomer **4a**, 5.58 D; 5-CF_3 tautomer **4a**, 1.30 D) and thermodynamically more stable[6] 1*H*-3-R^F tautomer. Similar conclusion can be made for other *N*-nonsubstituted pyrazoles **4b**—**k**, whose $^3J_{H,F}$ values are in a narrow region of 4.9—5.2 Hz, which agrees with the conclusion[3] based on the ^1H and ^{13}C NMR spectroscopic data.

In a $CDCl_3$ solution pyrazole **4a** exists as two tautomeric forms, between which the fast (in the NMR experiment time scale) proton exchange occurs, and the chemical shifts (CS) of spin-spin coupling constants are the weighted mean values according to the contributions of the 3-R^F and 5-R^F tautomers. For the estimation of these contributions, we used pyrazoles **7** and **8b** with $^3J_{H,F}$ = 2.3 and 4.1 Hz as model substances. We took into account that in the 5-R^F form the *o*-HO group decreases $^3J_{H,F}$ by 0.2—0.3 Hz (*cf.* **9a** and **9b**, **1a** and **2a**), and the N—Me group increases it by 0.1—0.2 Hz (see below). This makes it possible to accept $^3J_{H,F}$ = 4.0 Hz for 1*H*-5-aryl-3-R^F-pyrazoles, whereas for 1*H*-3-aryl-5-R^F-pyrazoles $^3J_{H,F}$ = 2.4 Hz can be accepted. Therefore, the value of $^3J_{H,F}$ = 3.6 Hz determined for pyrazole **4a** corresponds to ~75% of the 3-R^F form and ~25% of the 5-R^F form (method *A*, error ±5%, Table 3). Thus, in a solution of **4a** in $CDCl_3$ the prototropic equilibrium is shifted toward the 3-R^F tautomer, as it takes place in the case of pyrazole **11a** synthesized from cyclohexanone[4] and in the case of 3(5)-methyl-5(3)-trifluoromethylpyrazole.[14] It has been shown for the latter by the calculation methods[6] that the 3-CF_3 tautomer is by ~2.4 kcal mol^{-1} more stable than the 5-CF_3 tautomer.

In the series of pyrazoles **4b**—**h** monosubstituted in the benzene ring (see Table 2), the $^3J_{H,F}$ constant is lowest (2.8 Hz) for compound **4b** with the 2-hydroxyphenyl substituent. The calculation of the percentage content of the tautomers shows that for compound **4b** the 5-R^F tautomer stabilized by the intramolecular hydrogen bond

Table 3. Tautomeric composition of pyrazoles **4a**—**i**

Pyrazole	Content of tautomers (%)			
	Method *A*		Method *B*	
	3-R^F	5-R^F	3-R^F	5-R^F
4a	75	25	70	30
4b	40	60	45	55
4c	100	0	100	0
4d	100	0	100	0
4e	90	10	90	10
4f	85	15	85	15
4g	65	35	65	35
4h	55	45	60	40
4i	85	15	80	20

becomes predominant (~60% when $^3J_{H,F}$ of pyrazoles **7** and **8b** are used as standards with correction for the N—Me group for **7**, method *A*, Table 3). On going from compound **4b** in which the HO group is in the *ortho*-position to compound **4d** with the *para*-HO group, the $^3J_{H,F}$ constant increases by 1.2 Hz in $CDCl_3$ but remains virtually unchanged in DMSO-d_6; the greater increase (by 1.5 Hz) is observed when *o*-HO (**4b**) is replaced by the *o*-MeO group (**4c**). Such a substantial increase in the constant on going from **4b** to **4c**,**d** can be explained by the absence of the intramolecular hydrogen bond (IMHB) favoring the 5-R^F form in molecules **4c**,**d**, due to which the prototropic equilibrium is almost completely shifted toward the thermodynamically more stable 3-R^F tautomer. It can be seen from the data in Table 3 that electron-donating substituents (HO, MeO, Me) in the *para*-position of the benzene ring increase and electron-withdrawing substituents (F, Cl) decrease the content of the 3-R^F tautomer in an equilibrium mixture as compared to the content of pyrazole **4a**. It should be mentioned that, when estimating the tautomeric equlibrium in chloroform solutions of pyrazoles **4c**,**i**, the $^3J_{H,F}$ values should be decreased by 0.2—0.3 Hz, because the constant increases by precisely this value when the phenyl group is replaced by the 2-$MeOC_6H_4$ and Bu^t groups in isoxazoles **1d**,**e** incapable of prototropism.

Additional studies are needed to elucidate the influence of the second substituent in the benzene ring on the $^3J_{H,F}$ value in the series of disubstituted pyrazoles **5**. However, it is already clear that the constant depends strongly on the nature of the substituent in the *para*-position to the HO group. For example, the introduction of the chlorine atom into the benzene ring of isoxazole **2a** decreases $^3J_{H,F}$ by 0.2 Hz (**2c**), whereas the appearance of the same atom in the pyrazole series decreases this value by 0.7 Hz (*cf.* **4b** and **5c**). This can be explained by the shift of the prototropic equilibrium toward the 5-R^F tautomer caused by an increase in the acidity of the phenolic proton and IMHB enhancement. The stronger (by 1.2 Hz) decrease in the constant observed by the comparison of pyrazoles **4b** and **5d** is related to the specific influence of the NO_2 group on the $^3J_{H,F}$ constant rather than the shift of equilibrium toward the 5-R^F form. For example, in 6-R-2-R^F-chromones where tautomerism is absent and the R and R^F groups are remote at a distance of seven bonds, as in pyrazole **5d**, at R = NO_2 the $^3J_{H,F}$ value decreases by 0.4—0.5 Hz compared to R = Cl, H.[1] It is of interest that the introduction of the 5′-Me group into the benzene ring of pyrazole **4b** (**5a**) increases the constant by 0.1 Hz only, while the introduction of the 6′-Me group (**6a**) increases it by 0.8 Hz. This is related, most likely, to the violation of coplanarity of molecule **6a**, which weakens or completely cleaves the IMHB and, hence, shifts the tautomeric equilibrium toward the 3-R^F form.

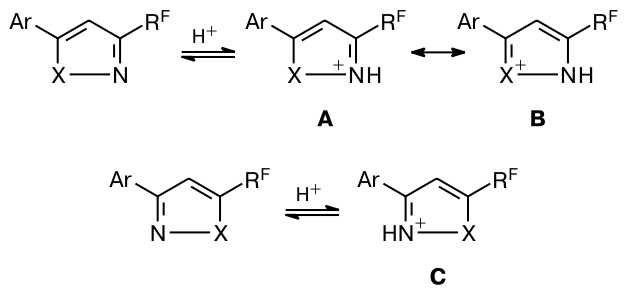
For solutions of pyrazoles **5c**,**d** in DMSO-d_6 compared to $CDCl_3$, the $^3J_{H,F}$ constant increases by 2.5—3 times and reaches ~5.0 Hz, which is characteristic of 1-R-3-R^F-pyrazoles. Therefore, in $CDCl_3$, due to the IMHB (O—H...N=C), pyrazoles **5a**—**d** exist mainly in the form of the 1*H*-5-R^F tautomer, while in DMSO-d_6, where intermolecular hydrogen (O—H...O=S) bonds are formed instead of IMHB, the prototropic equilibrium shifts toward the 1*H*-3-R^F tautomer. We have previously[1] observed a similar situation in the series of 5(7)-aryl-7(5)-polyfluoroalkyl-2,3-dihydro-1*H*-1,4-diazepines, which exist in $CDCl_3$ predominantly in the form of the 7-R^F tautomer if the HO group is in the *ortho*-position of the aryl substituent, and when this group is absent or in a DMSO-d_6 solution they exist in the form of the 5-R^F tautomer.

Regioisomeric isoxazoles and *N*-substituted pyrazoles (acidic solutions). An information helpful for structural studies can be obtained by comparison of the $^3J_{H,F}$ values in neutral and acidic media. For example, the addition of CF_3CO_2H to solutions of isoxazoles **2a** and **3a** and pyrazoles **4a**,**c** in DMSO-d_6 does not change their ^{1}H NMR spectra, including the $^3J_{H,F}$ constant, indicating that azoles are not protonated and, hence, their basicities are lower than that of DMSO-d_6. However, the situation becomes different in a less polar solvent $CDCl_3$. No substantial changes (except for the disappearance of the signal of the phenolic proton) occur in the spectra of compounds **2a** and **3a** in $CDCl_3$ in the presence of CD_3CO_2D, while the addition of CF_3CO_2H decreases $^3J_{H,F}$ by 0.6 Hz only for 3-R^F-isoxazole **3a** (ΔJ = $^3J_{H,F}$(neutr.) – $^3J_{H,F}$(acid.) = 0.6 Hz). For 5-R^F-isoxazoles **1a** and **2a**, the ΔJ value is only ~0.1 Hz (see Table 1). A similar pattern is observed in the series of isomeric pyrazoles, where ΔJ for 3-R^F-pyrazoles **8a**,**b** and **10b** is ~1.0 Hz, and for 5-R^F-pyrazoles **7** and **9b** it is ~0.1 Hz (see Table 2).

It is most likely that such a substantial difference in changing the $^3J_{H,F}$ constant for the 3- and 5-R^F regioisomers on going from the neutral to acidic media reflects the fact of the more drastic π-electron density redistribution in the cation formed from the 3-R^F isomer upon protonation of the iminic nitrogen atom geminal toward the R^F group. In this case, the R^F and C=N^+H groups consistently affect the π–electrons of the C=C bond and unshared electrons of the second X heteroatom (structure **A**), due to which the positive charge is delocalized between the N and X atoms, and the corresponding π-electron density redistribution decreases the C=N bond order (Scheme 1, structure **B**) and, as a consequence, decreases $^3J_{H,F}$.[1]

Since in 3-R^F-pyrazoles the ΔJ value is almost twice as large as that in 3-R^F-isoxazoles, we can assume that the contribution of structure **B** increases on going from O

Scheme 1



to N—R. This conclusion also agrees with the CS value of the terminal proton of the $(CF_2)_2H$ group, whose signal in 3-R^F-pyrazoles **8a**,**b** and **10b** exhibits an upfield shift by 0.07—0.08 ppm upon the addition of CF_3CO_2H but remains unchanged in 5-R^F-pyrazoles **7** and **9b**.

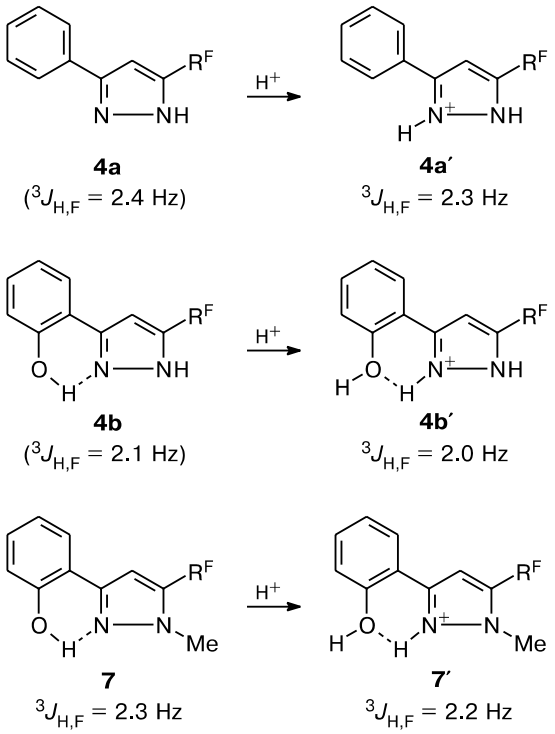
Protonation of the 5-R^F regioisomers also occurs at the iminic N atom, which is remote, in this case, from the R^F group, to form cation **C** in which charge delocalization is hindered due to the inconsistent (directed to opposite sides) influence on the π–electrons of the cationic center and R^F group. Thus, the structure of the cationic species formed from both 3-R^F- and 5-R^F-pyrazoles is most perfectly reflected by structure **B** with the remote iminic N atom and R^F group, which explains the substantial change in the $^3J_{H,F}$ constant only in the case of 3-R^F-pyrazoles.

***N*-Nonsubstituted pyrazoles (acidic solutions).** The change in the $^3J_{H,F}$ value in $CDCl_3$ in the presence of CF_3CO_2H (ΔJ) enables one to suggest belonging of azoles to the series of 3-R^F or 5-R^F regioisomers. These data can be helpful for the estimation of position of the tautomeric equilibrium in solutions of *N*-nonsubstituted pyrazoles, because the protonation of the 3-R^F form only should substantially change the $^3J_{H,F}$ constant. Indeed, the addition of CF_3CO_2H to solutions of pyrazoles **4a**,**c** in DMSO-d_6 does not change the $^3J_{H,F}$ constant, as it has already been mentioned for isoxazoles and *N*-substituted pyrazoles. However, in $CDCl_3$, where compounds **4a**—**k**, except for **4b**, exist predominantly in the form of the 3-R^F tautomer, the $^3J_{H,F}$ value decreases considerably (ΔJ = 1.1—1.8 Hz). The constant gains the value unchanged for most acidic solutions (2.2—2.3 Hz), which is almost independent of the nature of the substituent in the *para*-position of the benzene ring but decreases to 2.0 Hz in the presence of the *o*-HO group (**4b**) and increases to 2.5 Hz when the *o*-MeO group is introduced (**4c**) and the Ph group is replaced by the *tert*-butyl group (**4i**), *i.e.*, it changes in the same manner as for the above considered isoxazoles **2a** and **1d**,**e** compared to compound **1a**.

Since only the 3-R^F form is characterized by a decrease in $^3J_{H,F}$ in an acidic medium, we can conclude that the greater the contribution of the 3-R^F tautomer, the higher ΔJ. Considering that the maximum value ΔJ = 1.8 Hz observed for pyrazoles **4c**,**d** corresponds to the 100% 3-R^F tautomer, the percentage composition of a tautomeric mixture can be calculated from a change in the $^3J_{H,F}$ value after CF_3CO_2H addition (ΔJ). The calculations by the corrected $^3J_{H,F}$ constants of model pyrazoles **7** and **8b** (method *A*) and by ΔJ (method *B*) give very close results (see Table 3). For example, for pyrazole **4a** (~75% of the 3-R^F tautomer by method *A*) the calculation by method *B* (ΔJ = 1.3 Hz) gives ~70% of the 3-R^F tautomer, whereas for pyrazole **4i** method *A* ($^3J_{H,F}$ = 3.9 — 0.2 (correction for the Bu^t group) = 3.7 Hz) and method *B* (ΔJ = 1.4 Hz) give ~80% of the 3-R^F tautomer. Since appropriate model compounds are lacking, method *A* cannot be applied to pyrazoles **5** disubstituted at the benzene ring; however, the low ΔJ values indicate that the 5-R^F tautomer predominates.

The comparison of the $^3J_{H,F}$ values in the products of protonation of pyrazoles **4a**,**b** and **7**, whose structures are described best of all, as we believe, by the 5-R^F-cationic form (**4a´**, **4b´**, **7´**), shows that the introduction of the *o*-HO group into the benzene ring decreases the $^3J_{H,F}$ constant by 0.3 Hz (perhaps, due to IMHB formation), and the subsequent introduction of the Me group into position 1 of the pyrazole cycle increases the constant by 0.2 Hz (Scheme 2). The assumption about a similar change in $^3J_{H,F}$ in neutral forms **4a**,**b** and **7**, taking into account

Scheme 2



that the protonation of the 5-R^F regioisomer decreases the constant by 0.1 Hz (see above), gives $^3J_{H,F}$ = 2.4 and 2.1 Hz for 5-R^F tautomers **4a** and **4b**, respectively, which were used as standards in the calculation of tautomeric mixtures by method *A*.

When deuterioacetic acid is added to solutions of pyrazoles **4a**—**e**,**h** in $CDCl_3$, the $^3J_{H,F}$ values approach each other in a region of 3.2—3.5 Hz (*cf.*, *e.g.*, **4b** and **4c**), which is probably related to the shift of the prototropic equilibrium rather than protonation (in *N*-substituted pyrazole **8b**, under similar conditions, the constant remains virtually unchanged). The content of the 3-R^F tautomer increases in **4b** with the *o*-HO group, whereas it decreases in other cases, due to which the ratio of the 3-R^F and 5-R^F tautomers for all pyrazoles becomes equal to ~1 : 1. This can be explained by the equalization in energy of two tautomeric forms in this solvate environment.

It should be noted in conclusion that, unlike the $^3J_{H,F}$ constant, which in a $CDCl_3$ solution is very sensitive even to slight changes in the molecular structure, the $^2J_{H,F}$ constant value remains virtually unchanged in both $CDCl_3$ and DMSO-d_6. For example, in regioisomeric 3- and 5-R^F-isoxazoles its equals 53.1 Hz, whereas in pyrazoles it is 53.4—53.8 Hz (in $CDCl_3$). In a DMSO-d_6 solution all $^2J_{H,F}$ values for the azoles studied range from 51.7 to 52.2 Hz, and the $^3J_{H,F}$ constant depends slightly on the nature of the substituent in both the benzene ring and heterocycle, which makes it less informative in this solvent. The signal of the terminal proton of the $H(CF_2)_2$ group (triplet of triplets) in DMSO-d_6 experiences a downfield shift (compared to a solution in $CDCl_3$) by ~0.65—0.85 ppm for the 3-R^F regioisomers and by 0.95—1.10 ppm for the 5-R^F regioisomers. Isomeric *N*-phenylpyrazoles can easily be distinguished (only in a $CDCl_3$ solution) by the CS of the terminal proton: δ = 5.63—5.84 ppm for 1-Ph-5-R^F-pyrazoles and δ = 6.23—6.25 ppm for 1-Ph-3-R^F-pyrazoles. The CS value of the heterocyclic H(4) proton depends, to a considerable extent, on the conformation of the molecule, solvent, and nature of the substituent in positions 1, 3, and 5, which impedes its use in structural studies.

Thus, the $^3J_{H,F}$ constant is a reliable and simple tool that enables the easy recognition of regioisomeric pairs of $H(CF_2)_2$-containing organofluorine compounds and, which is especially important, can be used for studying fast (in the NMR time scale) tautomeric equilibria.

The author thanks M. I. Kodess (Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences) for measuring ^{1}H NMR spectra.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-32706) and partially by the US Civilian Research and Development Foundation (Grant REC-005).

References

1. V. Ya. Sosnovskikh, *Izv. Akad. Nauk*, *Ser. Khim.*, 2001, 1166 [*Russ. Chem. Bull.*, *Int. Ed.*, 2001, **50**, 1223].
2. V. Ya. Sosnovskikh, A. Yu. Sizov, and B. I. Usachev, *Izv. Akad. Nauk*, *Ser. Khim.*, 2002, 1175 [*Russ. Chem. Bull.*, *Int. Ed.*, 2002, **51**, 1270].
3. V. Ya. Sosnovskikh, M. A. Barabanov, and A. Yu. Sizov, *Izv. Akad. Nauk*, *Ser. Khim.*, 2002, 1184 [*Russ. Chem. Bull.*, *Int. Ed.*, 2002, **51**, 1280].
4. D. V. Sevenard, O. G. Khomutov, M. I. Kodess, K. I. Pashkevich, I. Loop, E. Lork, and G.-V. Röschenthaler, *Can. J. Chem.*, 2001, **79**, 183.
5. J. Elguero, G. I. Yranzo, J. Laynez, P. Jiménez, M. Menéndez, J. Catalán, J. L. G. de Paz, F. Anvia, and R. W. Taft, *J. Org. Chem.*, 1991, **56**, 3943.
6. J. Catalán, F. Fabero, R. M. Claramunt, M. D. Santa Maria, M. C. Foces-Foces, F. H. Cano, M. Martinez-Ripoll, J. Elguero, and R. Sastre, *J. Am. Chem. Soc.*, 1992, **114**, 5039.
7. C. P. Félix, N. Khatimi, and A. J. Laurent, *J. Org. Chem.*, 1995, **60**, 3907.
8. X.-Q. Tang and C.-M. Hu, *J. Fluorine Chem.*, 1995, **73**, 133.
9. J. Elguero, A. Fruchier, N. Jagerovic, and A. Werner, *Org. Prep. Proced. Int.*, 1995, **27**, 33.
10. K. I. Pashkevich, V. I. Saloutin, A. N. Fomin, V. V. Berenblit, V. S. Plashkin, and I. Ya. Postovskii, *Zh. Vsesoyuz. Khim. o-va im. D. I. Mendeleeva*, 1981, 105 [*Mendeleev Chem. J.*, 1981 (Engl. Transl.)].
11. J. L. Peglion, R. E. Pastor, and A. R. Cambon, *Bull. Soc. Chim. Fr.*, 1980, II-309.
12. M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R. M. Claramunt, J. Elguero, J. I. Garcia, C. Toiron, and P. Vedsø, *Magn. Reson. Chem.*, 1993, **31**, 107.
13. M. J. S. Dewar, E. G. Zoeblisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
14. J. L. Atwood, K. R. Dixon, D. T. Eadie, S. R. Stobart, and M. J. Zaworotko, *Inorg. Chem.*, 1983, **22**, 774.
15. K. I. Pashkevich, V. I. Filyakova, and O. A. Kuznetsova, *Izv. Akad. Nauk*, *Ser. Khim.*, 1996, 3019 [*Russ. Chem. Bull.*, 1996, **45**, 2868 (Engl. Transl.)].

Received February 19, 2003;
in revised form June 20, 2003