Spin-spin coupling constant $^3J_{H,F}$ of the 1,1,2,2-tetrafluoroethyl group as a useful tool for recognition of regioisomeric and tautomeric pairs of organofluoric compounds

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The spin-spin coupling constant $^3J_{H,F}$ of the $H(CF_2)_2$ group varies within 1.6—6.5 Hz (in $CDCl_3$) depending on the structure of the molecular fragment, which is linked with the group, and can be used for the recognition of regioisomeric and tautomeric pairs of organofluoric compounds.

Key words: spin-spin coupling constant $^3J_{H,F}$ of $H(CF_2)_2$ group, regioisomers, tautomers, O- and N-heterocycles.

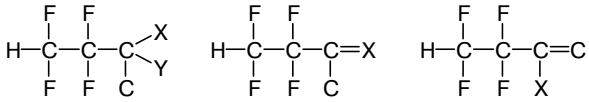
The spin-spin coupling constant $^3J_{H,H}$ of the H—C—X—H (X = O, N) fragment is widely used in studying tautomeric processes.[1—3] This work is devoted to the $^3J_{H,F}$ constant of the 1,1,2,2-tetrafluoroethyl group, which is of interest for revealing the structure of fluorine-containing organic compounds.

Results and Discussion

We examined the ^1H NMR spectra of more than 250 compounds of various classes containing $H(CF_2)_n$ (n = 1—3) and $H(CF_2)_2CH_2$ groups and found that at n = 2 the $^3J_{H,F}$ constant is very sensitive to the nearest environment of the C atom to which the $H(CF_2)_2$ group is linked and, depending on the structure of the molecular fragment, varies in a wide range, from 1.6 to 6.5 Hz. At the same time, the $^2J_{H,F}$ values of the $H(CF_2)_n$ (n = 1—3) groups and $^3J_{H,F}$ of the $H(CF_2)_3$ and $H(CF_2)_2CH_2$ groups are low informative and can be useful only in rare cases. More than 90% of all available data on the $^2J_{H,F}$ constant of the HCF_2 group range within 53.0—56.5 Hz,[4—7] and those for $^3J_{H,F}$ of the $H(CF_2)_3$ and $H(CF_2)_2CH_2$ groups are within 5.0—5.8 Hz.[5,8,9]

To exclude the influence of the solvent nature on the $^3J_{H,F}$ constant of the $H(CF_2)_2$ group, we considered only ^1H NMR spectra recorded in a solution of $CDCl_3$, although the main conclusions of this work do not contradict to the spectroscopic data for solutions in CCl_4, DMSO-d_6, and deuterioacetone. We analyzed the following classes of organic compounds containing the $H(CF_2)_2$ group: fluoro-containing β-hydroxy- and α,β-unsaturated carbonyl compounds, β-diketones, β-aminovinylketones, pyrazoles, pyrazolines, isoxazolines, imidazolidines, tetra- and dihydro-4-pyrones and -3-furanones, chromanones, chromones, 4-pyrones, 2*H*-pyranes, 2,3-dihydro-1*H*-1,4-diazepines, 3*H*-1,5-benzodiazepines, pyrimidines, and benzimidazoles.

It turned out that for the molecules containing the saturated fragments (**1a—d**) $^3J_{H,F}$ = 5.6—6.5 Hz, whereas for the molecules with the unsaturated fragments (**2a,b** and **3a—c**) it is 4.8—5.9 and 1.6—4.5 Hz, respectively, *i.e.*, transition from the sp^3- to sp^2-hybridized C atoms decreases $^3J_{H,F}$, and this is especially pronounced for the C=C bond next to the $H(CF_2)_2$ group.



1a—d **2a,b** **3a—d**

1a—d: X = C, Y = O (**a**); X = N, Y = O (**b**); X = Y = N (**c**); X = Y = O (**d**)
2a,b: X = N (**a**), O (**b**)
3a—c: X = C (**a**), N (**b**), O (**c**)

It has previously[10,11] been mentioned that the direct spin-spin coupling constant $^1J_{C,F}$ in the CF_3 group increases substantially on going from the CF_3—C=C fragment (~270 Hz) to CF_3—C=O (~285 Hz). We can speak about only the tendency and a 5—6% change in the $^1J_{C,F}$ constant, which do not allow reliable conclusions about the molecule structure. In our case, we revealed a pronounced regularity of a 50—70% and sometimes 2—3-fold increase in the $^3J_{H,F}$ constant on going from the **3a—c** to **2a,b** and **1a—d** fragments. The examples in Table 1 show a change in the $^3J_{H,F}$ and $^2J_{H,F}$ values with structural changes in the nearest environment of the C atom directly linked to the $H(CF_2)_2$ group and the chemical shift of the terminal proton.

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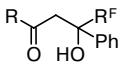
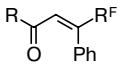
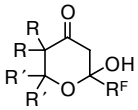
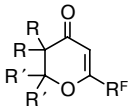
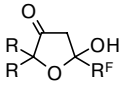
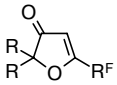
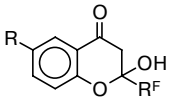
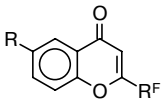
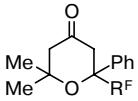
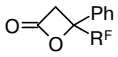
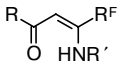
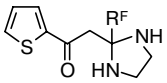
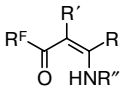
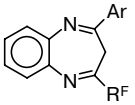
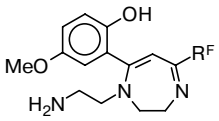
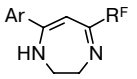
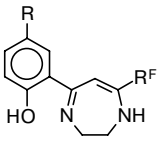
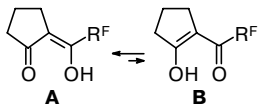
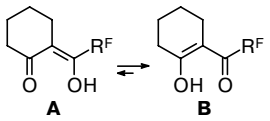
Table 1. Spin-spin coupling constants $^3J_{H,F}$, $^2J_{H,F}$ and chemical shift of a proton of the $R^F = H(CF_2)_2$ group in a solution of $CDCl_3$

Compound		Fragment	$^3J_{H,F}$	$^2J_{H,F}$	δ	Reference
			Hz			
	(**4**)	**1a**	6.3—6.5	53.0—53.2	5.90—6.05	12, 13
	(**5**)	**3a**	4.1—4.4	53.2—53.4	5.60—5.75	12, 13
	(**6**)	**1d**	6.1	53.0	6.10—6.15	14
	(**7**)	**3c**	4.3—4.5	53.0—53.1	5.95—6.00	14
	(**8**)	**1d**	5.9—6.0	52.8—52.9	6.10—6.15	4
	(**9**)	**3c**	3.7—3.8	52.8—52.9	6.00—6.05	4
	(**10**)	**1d**	5.7—5.9	52.8—52.7	6.20—6.30	4
	(**11**)	**3c**	3.0—3.8	52.8—53.2	6.05—6.20	4
	(**12**)	**1a**	6.3	53.1	6.00	12
	(**13**)	**1a**	5.6	52.3	5.63	13
	(**14**)	**3b**	2.5—3.8	53.3—53.6	5.85—6.05	4, 14
	(**15**)	**1c**	6.3	53.6	6.23	15
	(**16**)	**2b**	5.2—5.9	52.8—53.4	6.10—6.30	16—19
	(**17**)	**2a**	5.6—5.7	52.8—52.9	6.35—6.40	6, 20

(*to be continued*)

Table 1 (*continue*)

Compound		Fragment	$^3J_{H,F}$	$^2J_{H,F}$	δ	Reference
			Hz			
	(**18**)	**2a**	5.6	53.4	6.26	21
	(**19**)	**2a**	5.5—5.6	53.5—53.6	6.25—6.30	22—24
	(**20**)	**3b**	3.2—3.4	53.6—53.8	5.90—5.95	22, 23
	(**21**)	**3c**	4.6	53.0	6.05	25
	(**22**)	**2b**	5.6	52.7	6.20	18, 19

The dehydration of compounds **4** with the β-ketol fragment to the corresponding α,β-unsaturated carbonyl compounds **5** is accompanied by a decrease in $^3J_{H,F}$ by 2.0—2.4 Hz. A similar situation is also observed on going from cyclic semiketals **6**, **8**, and **10** to compounds **7**, **9**, and **11**, which can be used in analysis of mixtures of products. Tetra- and dihydropyrones **6** and **7** are close in the $^3J_{H,F}$ value to β-hydroxy- and α,β-unsaturated carbonyl compounds **4** and **5**, and tetra- and dihydrofuranones **8** and **9** are closer to chromanones and chromones **10** and **11**. It is noteworthy that $^3J_{H,F}$ decreases in chromones **11** (R = Me, H, Cl, NO_2) from 3.8 to 3.0 Hz, respectively. The lowest values in the series of oxygen-containing heterocycles were observed for 4-pyrones[26] and 2*H*-pyranes[4] ($^3J_{H,F}$ = 2.2—2.8 Hz). The replacement of the OH group by Ph at the saturated C atom (compounds **6** and **12**) increases $^3J_{H,F}$ only insignificantly (0.2 Hz), whereas transition from the six- to four-membered cycle (compounds **12** and **13**) decreases $^3J_{H,F}$ by 0.7 Hz, which is related, most likely, to an increase in the s-character of the C—R^F bond. These examples emphasize the priority character of the influence of the hybrid state of the C atom compared to its nearest environment on the $^3J_{H,F}$ value.

In the series of nitrogen-containing compounds, β-amino-β-(tetrafluoroethyl) vinyl ketones **14** (fragment **3b**) are characterized by low $^3J_{H,F}$ values. For them, depending on the structure of the radical at the carbonyl group, the $^3J_{H,F}$ constant changes within 2.5—3.5 Hz and can increase to 3.8 Hz for a substituent at the N atom. For example, in the reaction of aminoenone **14** (R is 2-thienyl, R′ = H) with ethylenediamine, which affords imidazolidine **15**, $^3J_{H,F}$ increases from 3.3 Hz (**14**) to 6.3 Hz (**15**), *i.e.*, almost twofold, and for imidazoline cycle opening in an acidic medium, it decreases to 3.8 Hz, which indicates the formation of *N*-substituted aminoenone.[15,22]

It is important that for regioisomeric aminoenones **16** with the $H(CF_2)_2$ group at the carbonyl (fragment **2b**) $^3J_{H,F}$ is much higher and ranges within 5.2—5.9 Hz. This fact can be used for revealing the routes of reactions of nonsymmetric fluorinated β-diketones with amines. For example, in the synthesis of 3*H*-1,5-benzodiazepine **17** (Ar = Ph) from the corresponding β-diketone and *o*-phenylenediamine, a precipitate is formed in the solution in 15 min after the dissolution of the reactants in alcohol in the presence of AcOH at ~20 °C. The precipitate is the intermediate aminoenone (the reaction product at one keto group of β-diketone), which then is cyclized within 2 days to form benzodiazepine **17** (Ar = Ph). In the ^{1}H NMR spectrum of the intermediate product, the terminal hydrogen of the $H(CF_2)_2$ group appears as a triplet of triplets with $^2J_{H,F}$ = 53.4 and $^3J_{H,F}$ = 5.2 Hz and, therefore, the structure of **16** (R = Ph, R′ = H, R″ = *o*-$H_2NC_6H_4$) should be ascribed to it. The spectrum in the re-

gion of aromatic protons of the phenyl substituent (7.27—7.40 ppm) also gives evidence for the $H(CF_2)_2$ group rather than Ph is next to the carbonyl group. Thus, in the formation of 3*H*-1,5-benzodiazepines **17** from $RCOCH_2COR^F$ and *o*-phenylenediamine, the reaction starts from the attack of the carbonyl remote from the R^F group, which agrees with published data on the interaction of amines with fluoro-containing β-diketones.[17,27]

The chemical shifts of a proton of the $H(CF_2)_2$ group can serve as an additional argument in favor of this or another structure. Analysis of the data in Table 1 shows that the transition from fragment **1** to fragment **3** is always accompanied by an upfield shift of the triplet of triplets of the terminal H atom by 0.1—0.3 ppm, and that from fragment **2** to fragment **3** is accompanied by the shift of 0.2—0.5 ppm and even more. For aminoenone prepared from $PhCOCH_2CO(CF_2)_2H$ and *o*-phenylenediamine, the proton of the $H(CF_2)_2$ group appears at 6.19 ppm, which corresponds to structure **16** (δ 6.10—6.30) rather than **14** (δ 5.85—6.05). As a whole, the following regularity is observed for aminoenones and nitrogen-containing heterocycles: at $^3J_{H,F}$ = 2.5—4.0 Hz the chemical shift of the proton of the $H(CF_2)_2$ group usually does not exceed 6.1 ppm and at $^3J_{H,F}$ = 5.0—6.3 Hz it is never lower than 6.1 ppm. In the series of β-ketols, α,β-unsaturated carbonyl compounds, β-diketones, and oxygen-containing heterocycles, a similar interrelation is not observed. However, in this case, as mentioned above, a decrease in $^3J_{H,F}$ is always accompanied by an upfield shift of the signal from the terminal hydrogen.

Especially valuable information, hardly accessible by other methods, is provided by taking into account the $^3J_{H,F}$ constant of the $H(CF_2)_2$ group linked to nitrogen-containing heterocycles existing in several tautomeric forms. We have recently[21] reported the constant $^3J_{H,F}$ = 5.6 Hz for *N*-substituted dihydrodiazepine **18**, whose structure is proved by XRD. This value agrees well with the data on 3*H*-1,5-benzodiazepines **17** and, hence, can serve as a guiding line for compounds containing fragment **2a**. Knowledge that for **2a** $^3J_{H,F} \approx$ 5.6 Hz and for **3b** $^3J_{H,F} \approx$ 3.3 Hz allows us to discuss the problem of prototropism in fluoro-containing 2,3-dihydro-1*H*-1,4-diazepines, which have previously[22—24] been described as tautomer **20** with the geminal arrangement of the amine N atoms and the R^F group, *i.e.*, in the form of 5-R-7-R^F-2,3-dihydro-1*H*-1,4-diazepines regardless of the nature of the second substituent. It is seen in Table 1 that for dihydrodiazepines **19** (Ar = Ph, 2-thienyl, 4-pyridyl) $^3J_{H,F}$ = 5.5—5.6 Hz, and for **20** (R = H, Me, MeO, Cl) $^3J_{H,F}$ = 3.2—3.4 Hz. Therefore, in a deuteriochloroform solution of dihydrodiazepines with aryl and hetaryl substituents, the prototropic equilibrium is almost completely shifted to tautomer **19**, whereas dihydrodiazepines with the 2-HO—5-RC_6H_3 substituents exist mainly as tautomer **20** stabilized by the formation of an intramolecular hydrogen bond between the phenol OH group and imine N atom. The chemical shifts of the proton of the $H(CF_2)_2$ group in the spectra of compounds **18** and **19** (fragment **2a**) are in a region of 6.25—6.30 ppm (see Table 1), and in the spectrum of compounds **20** (fragment **3b**) they are at 5.90—5.95 ppm, which additionally confirms the validity of the conclusion about the structure of dihydrodiazepines **19** and **20** in a solution of $CDCl_3$.

Thus, tautomeric form **20** with the geminal arrangement of the amine N atom and R^F group, which has been preferred previously,[22—24] is thermodynamically less stable and can exist only under additional stabilization provided by the intramolecular hydrogen O—H...N= bond. The higher stability of tautomer **19** is related, most likely, to the displacement of an unpaired electron pair of the amine N atom to the acceptor fragment $N{=}C{-}R^F$, which results in the formation of a more delocalized conjugated system and appears as shielding of the proton in position 6 of the cycle in compound **19** (δ 5.30—5.40) compared to a similar atom in molecule **20** (δ 5.60—5.80). Note that in a solution of DMSO-d_6 the vinyl proton of compound **20** (R = H) appears in the spectrum at 5.48 ppm, and the $^3J_{H,F}$ constant increases to 5.6 Hz, which is likely related to the cleavage of the intramolecular hydrogen bond by basic molecules of the solvent and the shift of the tautomeric equilibrium to the thermodynamically more stable form **19**. When CCl_4 is added to this solution, the prototropic process is retarded and signals of all protons are strongly broadened, which makes it impossible to calculate the $^3J_{H,F}$ constant.

The conclusion about a higher stability of tautomer **19** agrees with the results of earlier observations: aminovinyl ketones,[28] thiones,[28] and imines[21] with the α-arrangement of the amino and R^F groups are spontaneously isomerized to thermodynamically more stable analogs with the γ-arrangement of these groups. The recently described[29] R^F-containing enaminoimines also exist predominantly as tautomers with the γ-arrangement of the amine N atom and R^F group.

This approach can be used for the recognition of other tautomeric and regioisomeric pairs, for example, pyrazoles and isoxazoles. In addition, it can be fruitful to take into account the $^3J_{H,F}$ constant in studying intrachelate tautomerism in the series of unsymmetric fluoro-containing β-diketones. It has previously[10] been shown by spectral data that the tautomeric equilibrium in a $CDCl_3$ solution of 2-trifluoroacetylcyclopentanone is shifted to *exo*-tautomer **A**, and for 2-trifluoroacetylcyclohexanone it is shifted to *endo*-tautomer **B**. The $^3J_{H,F}$ values of their analogs **21** and **22** with the $H(CF_2)_2$ group are presented in Table 1 and represent weighted average mean (according to the contributions of tautomers **A** and **B**) correlating with the previously indicated[10] directions of enolization.

Thus, the spin-spin coupling constant $^3J_{H,F}$ of the $H(CF_2)_2$ group can be used as a criterion for the

recognition of regioisomeric and tautomeric pairs, which is fruitful for revealing the structure of fluoro-containing organic compounds.

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