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# Fluorinated nitroxide radicals

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**The current status, history, problems, structural aspects and ESR spectroscopy of fluorinated nitroxide radicals (FNRs), as well as the effect of their composition and structure, type of the radical ring on the redox properties of FNRs are considered. New pathways in synthesis of FNRs and their application in different areas of chemistry and molecular biology are discussed.**

The first articles on the preparation and spectroscopic behaviour of stable fluorinated nitroxide radicals (FNRs)[1,2] were published after the reports on stable free nitroxide radicals (NRs).[3,4] One of them was small bis(trifluoromethyl) nitroxide **1** $(CF_3)_2NO^{\bullet}$, which attracted attention in terms of its structure, quantum chemistry and spectroscopic properties.[1,5–10] Radical **1** was synthesised, isolated and characterised as a stable purple gas at ambient temperature, chemically inert (it did not react with water, air, copper, mercury, stainless steel, 10% aqueous sodium hydroxide, *etc*.). Its properties were compared with those of di-*tert*-butyl nitroxide synthesised by Hoffmann and Henderson.[11] NMR spectroscopy exhibited a single $^{19}F$ peak and confirmed the ESR spectrum with a pattern of nine lines for six equivalent fluorine atoms of two trifluoromethyl groups attached to the nitrogen $^{14}N–O^{\bullet}$ radical centre with $g = 2.0046$.[1] The published hyperfine splitting (hfs) constants are listed in Table 1.

Precise measurements and calculations allowed one to determine $a_F$ and $a_N$ parameters and to estimate the hfs $a_C^{CF_3}$ on $^{13}C$ atoms (Table 1).[7] It was concluded that **1** is close to planar in structure because of the best fitting of the experimental parameters to calculated ones, which were also compared with those for the $(CF_3)_2C^{\bullet}O^-$ radical dissolved in MeCN. The molecular structure of **1** was determined in a gas phase by an electron diffraction method.[10] The angle between the CNC plane and the N–O bond is equal to 22±3°. It is very close to 21° for the same angle in $HOR_6$ (see below) but noticeably larger than 0° (planar structure) measured in di-*tert*-butyl nitroxide and $(p\text{-}MeOC_6H_4)_2NO^{\bullet}$.[12,13] A theoretical analysis of the temperature dependence of the ESR spectrum of **1** was performed using self-consistent field calculations in the INDO approximation.[9] It was concluded that the increased amplitude of vibration of the molecule away from planarity with increased temperature was the only appropriate way to explain the temperature changes of the ESR spectrum of **1**. Indeed, anomalous temperature dependence ($–110 \le T \le 24$ °C) in ESR spectra of **1** for the hfs constants (in Gauss) has been observed and explained:[6]

$$a_N = 8.776 + 0.0023T;\ a_F = 9.327 - 0.0036T.$$

Several FNRs with fluorocarbon substituents have been synthesised, isolated and characterised by Blackley[5] [$(ClCF_2CF_2)_2NO^{\bullet}$ **2** ($g = 2.0074$), $(C_7F_{15})_2NO^{\bullet}$ **3**] and by Strom and Bluhm[14] ($MeOOCCF_2)_2NO^{\bullet}$ **4**). The dependence of β-fluorine ESR hfs constants in fluoro-substituted NRs was investigated in the temperature range $–90 \le T \le 40$ °C for $CF_3CF_2NO^{\bullet}Bu^t$ **5**, $PhCF_2NO^{\bullet}Bu^t$ **6** and $(CF_3)_2CFNO^{\bullet}Bu^t$ **7** (Table 1),[15] and explained by angular changes in the structure of these FNRs. These results allowed one to choose the most probable conformation for FNR derivatives, because the experimental data differed for each system studied, and the bridgehead fluorine coupling is appreciable.

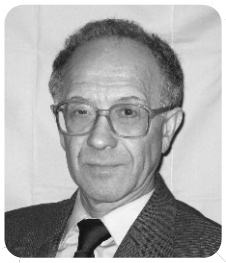
An interesting set of fluorinated nitroxides has been started by Rassat with co-workers: $p\text{-}FC_6H_4NO^{\bullet}Bu^t$ **8**, a typical representative of substituted aromatic NRs was obtained by the reaction[2]

$$p\text{-}FC_6H_4NO_2 + Bu^tMgCl \rightarrow p\text{-}FC_6H_4NO^{\bullet}Bu^t. \quad (1)$$

It was determined that $|a_{F^p}| \approx |2a_{H^0}| = |2a_{H^m}|$, and the spin density distribution in a phenyl ring was estimated. The measured hfs values of **8** were compared with parameters for other halogen analogous compounds (Cl, Br or I atoms in the *para*-position), and the effect of their electron-donor properties on ESR parameters was discussed.

This series was continued in $o\text{-}FC_6H_4NO^{\bullet}Bu^t$ **9**, $m\text{-}FC_6H_4NO^{\bullet}Bu^t$ **10** and $m\text{-}CF_3C_6H_4NO^{\bullet}Bu^t$ **11**.[16] The hfs constants measured with the use of ESR (Table 1) were in a good agreement with those obtained by NMR spectroscopy for $^{19}F$ and $^1H$ atoms in all positions of the phenyl ring. Since the latter also gives the absolute sign of the splitting constant, the fluorine hyperconjugation and spin transmission mechanisms were also investigated.

These studies were performed by Eberson.[17,18] FNRs $PhCHFNO^{\bullet}Bu^t$ **12**, $PhC(OH)FNO^{\bullet}Bu^t$ **13**, $PhC(CF_3CO_2)HNO^{\bullet}Bu^t$ **14**, $C_6F_5CHFNO^{\bullet}Bu^t$ **15** and **6** were synthesised by the inverted spin



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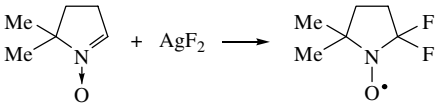
trapping: reactions between the radical cation of α-phenyl-*N*-*tert*-butylnitrone and ionic or neutral nucleophiles, using fluorinated agents such as $F_3NO$ or $AgF_2$:[19,20]

$$PhCH{=}NOBu^t + F_3NO \rightarrow PhCHFNO^{\bullet}Bu^t, \quad (2)$$

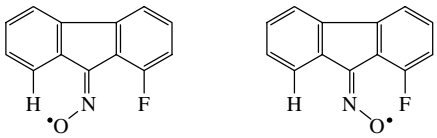
$$PhCH{=}NOBu^t + AgF_2 \rightarrow PhCF_2NO^{\bullet}Bu^t. \quad (3)$$

The properties of these FNRs in various chemical reactions have been investigated in detail. By the same procedure, the well-known spin trap 5,5-dimethyl-1-pyrroline 1-oxide (DMPO) gave corresponding difluoro compound **16**.[18] Two mechanisms of generating fluoro spin adducts from nitrones were characterised: (*a*) with the use of the strong oxidant $XeF_2$, which proceeded *via* formation of the nitrone radical cation, followed by reaction with the $F^-$ ion (inverted spin trapping[17]) and (*b*) with the use of the N-fluoro reagent $(PhSO_2)_2NF$, which is a weak oxidant and acts by oxidising the appropriate hydroxylamines.[18]




DMPO **16** (4)

Another type of fluorinated nitroxides has been performed by the ESR studies of two sets of fluorinated iminoxy radicals from 1-fluorofluorenone oximes.[21] The hfs constants for **17** ($g$ = 2.0061) and **18** ($g$ = 2.0059) are also given in Table 1. The hfs constants of the fluorine nuclei in these radicals were remarkably large and explained in terms of an interaction between the orbital of the unpaired electron and the fluorine atom in **18** and its analogues by a hyperconjugation mechanism.




**17** **18**

All of the above FNRs (except for **16**) were of the linear type, while a lot of fluorinated NRs belonged to F-substituted piperidine, pyrroline or imidazoline type radicals.[22–25] These compounds are important spin probes and labels for studying biological systems, the structure and function of enzymes, proteins, nucleic acids, biological and synthetic membranes, as well as for testing chemical and catalytic activity. These FNRs are mainly described below in comparison with their applications. The paramagnetic fragments $-R^x_n$ (nitroxide rings) will be marked as follows:

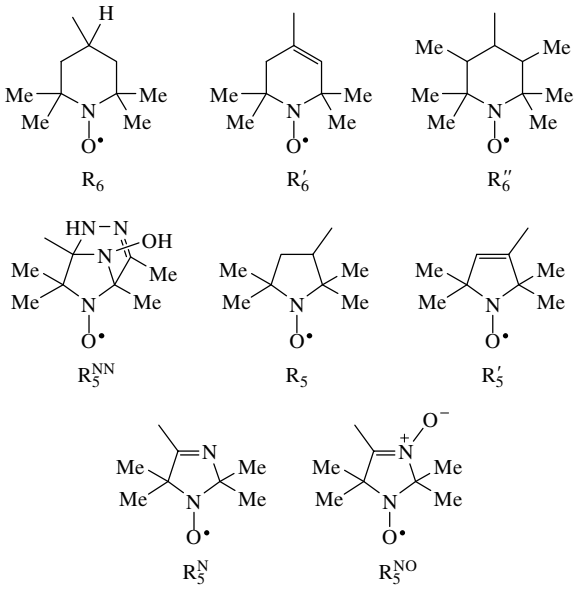



**Table 1** Hfs constants of FNRs at ambient temperature.

| Radical | Solvent | $\lvert a_N \rvert$/G | $\lvert a_H \rvert$/G | $\lvert a_F \rvert$/G | Ref. |
|---|---|---|---|---|---|
| **1** | $CFCl_3$ | 9.3 | — | 8.2 | 1 |
| **1** | $CFCl_3$ | 9.458±0.18 | — | 8.263±0.10 | 6 |
| **1** | $CFCl_3$ | 9.46 | $a_C$ = 5.1 | 8.26 | 7 |
| **2** | $CFCl_3$ | 9.3 | — | 10.1 | 5 |
| **4** | $CF_3Cl$ | 9.41±0.08 | $a_F^{\beta}$ = 0.53 | 13.79±0.08 | 14 |
| **5** | $CF_3Cl$ | 11.25 | $a_F^{\gamma}$ = 0.43 | 21.16 | 15 |
| **6** | $CF_3Cl$ | 11.66 | — | 19.26 | 15 |
| **6** | $CH_2Cl_2$ | 12.8 | — | 21.2 | 17 |
| **7** | $CH_2Cl_2$ | 12.11 | $a_F^{\gamma}$ = 2.27 | 2.27 | 15 |
| **8** | $C_6H_6$ | 13.7 | $a_H^{o}$ = 1.72 | 3.50 | 2 |
| **9** | $CH_2Cl_2$ | 14.2 | — | 1.35 | 16 |
| **10** | $(HOCH_2CH_2)_2O$ | 12.65 | 1.95 | 0.95 | 16 |
| **11** | $(HOCH_2CH_2)_2O$ | 12.5 | 2.0 | 0.7 | 16 |
| **12** | $CH_2Cl_2$ | 12.7 | 1.05 | 45.7 | 17 |
| **14** | $CH_2Cl_2$ | 8.1 | — | — | 17 |
| **15** | $CH_2Cl_2$ | 12.2 | 2.88 | 56.0 | 18 |
| **17** | $CH_2Cl_2$, $C_6H_6$ | 32.6 | 2.85 | 4.4 | 21 |
| **18** | $CH_2Cl_2$, $C_6H_6$ | 31.1 | 0.8 | 13.5 | 21 |
| **40** | Toluene | 10.51±0.15 | 3.65±0.05 | 7.40 | 38 |
| **41** | Toluene | 11.28±0.15 | 3.68±0.06 | 6.62 | 38 |
| **42** | Toluene | 11.6 | 2.93 | — | 43 |
| **60** | Toluene | 13.3±0.1 | — | 2.80±0.02 | 51 |
| **63** | $CCl_4$–$CH_2I_2$ (1:1) | 10.6 | 2.2; 0.8 (*m*) | 28.9 | 57 |

The following FNRs have been described by Morrisett[26] (see also refs. 27–37).

Berliner and co-authors have synthesised 15 *o*-, *m*-, and *p*-substituted fluoro-sulfonylated reagents for studying the active sites of trypsin and chymotrypsin:[30,31] *o*-$FSO_2C_6H_4NHCOR'_5$ **19**, *o*-$FSO_2C_6H_4SO_2OR_6$ **20**, *p*-$FSO_2C_6H_4NHCOR'_5$ **21**, *p*-$FSO_2C_6H_4SO_2OR_6$ **22**, *p*-$FSO_2C_6H_4COOR_6$ **23**, *p*-$FSO_2C_6H_4CONHR_6$ **24**, *p*-$FSO_2C_6H_4CONHR_5$ **25**, *m*-$FSO_2C_6H_4NHCOR_5{'}$ **26**, *m*-$FSO_2C_6H_4COOR_6$ **27**, *m*-$FSO_2C_6H_4CONHR_6$ **28**, *m*-$FSO_2C_6H_4CONHR_5$ **29**, *m*-$FSO_2C_6H_4NHCOOR_6$ **30**, *m*-$FSO_2C_6H_4NHCONHR_6$ **31**, *m*-$FSO_2C_6H_4NHCOR_5$ **32**, *m*-$FSO_2C_6H_4COOCH_2R_5$ **33**. Using these spin labels, Berliner and Wong obtained very valuable information concerning structural differences and functional dynamics of these two related enzymes.[30] An apolar binding site near the catalytic centre of human α-thrombin has been revealed with the use of **21**, **25**, and **33** spin labeled substrates.[30(*b*)]

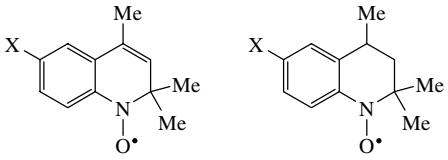
An interesting group of new phosphofluorinated NRs, F(Me)$POOR_6$ **34**, *N*-oxyl-4′,4′-dimethyloxazolidine of 5α-androstan-3-one-17β-methylphosphonofluoridate **35**, F(EtO)$POOR_6$ **36**, F(MeO)$POOR_6$ **37**, F($C_6H_{11}O$)$POOR_6$ **38**, F($Pr^iO$)$POOR_6$ **39** and the first biradical-type FNR $OPF(OR_6)_2$ **B1** have been synthesised and suggested as specific spin labels for the active sites of proteolytic enzymes and esterases (trypsin, α-chymotrypsin, cholin-esterase, *etc.*).[27–37]

Guanidine hydrochloride denaturation of the active site of spin-labeled α-chymotrypsin by **34** and hormone-like *N*-oxyl-4′,4′-dimethyloxazolidine of 5α-androstan-3-one-17β-methylphosphonofluoridate **35** has been carefully studied as a function of guanidine concentration and pH.[29] The ESR results were compared with those obtained by a circular dichroism method. The high field hfs constant position of α-chymotrypsin spin-labeled with **35** was measured as a function of solvent viscosity and used for the determination of the rotational correlation time of the enzyme in water.[33] A detailed investigation of trypsin spin labeled with **34**, **36** or **B1** has revealed that the enzyme was not irreversibly locked into a conformation dependent on its pH of inhibition.[34] This evidence against two 'pH-locked' conformations of phosphorylated trypsin was a strong argument in discussions with the results published earlier.[28,35]

FNR probes **37** and **B1** react with serine proteinases and esterases in a manner analogous to common active phosphate ester inhibitors.[35,36] A comparative study of the micro structure of the active sites has been done. The effect of various environmental perturbations on the conformation of the active sites has also been probed. It was shown that methionine 192 in α-chymotrypsin moved in response to the ionization of aspartic acid 194 and isoleucine 16, and the relationship of this fact to the crystal-

lographic model of the enzyme and its catalytic activity was discussed.[36] Studies of α-chymotrypsin and cholinesterase inhibited by spin labeling with **38**, **39** and **B1** indicated a variation of the structure of the active site in the area of the active serine.[37] It was suggested that such labels could be of great importance in studying the nature of active sites of such enzymes under catalytic conditions. Unfortunately, some changes in ESR spectra of **B1**-spin labeled cholinesterase were interpreted[37] as conformational changes and the decrease of the electron spin exchange efficiency, while these changes may be revealed to the partial decay of an unpaired electron (paramagnetic centre) in a biradical **B1** molecule.

Russian scientists also synthesised and investigated FNR compounds.[38–48] For evaluation of the spin density distribution and the role of hyperconjugation in NR derivatives of hydrated quinoline, radicals F-$RQ_1$ **40** and F-$RQ_2$ **41** were synthesised among other compounds.[38]



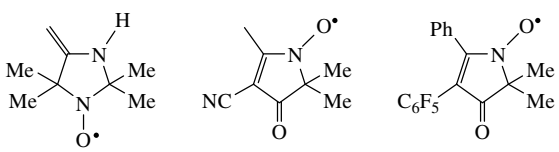
$RQ_1$ $RQ_2$

Parameters calculated from their ESR spectra are given in Table 1. In the original spectra reported,[38] one can see that the hyperfine splitting on the $^{14}N$ nucleus is masked by doublet splitting on the $^{19}F$ nucleus in the 6-position, as well as by splitting on $^{1}H$ in the 4- and 8-positions of the quinoline molecule. These two radicals are short-lived (minutes); this did not allow detailed studies of their properties. The FNR $(CF_3)_2COH$–$RQ_1$ **42** has been reported.[43]

Unique spin probes $C_6F_{13}COOR_6$ **43** and $C_6F_{13}COOR_6''$ **44** have been synthesised for testing fluorinated hydrocarbon media. These probes were successfully used in studies of structural transformations in the artificial blood Perftoran, its crystallization, regularities and peculiarities of its spatial distribution in the media, macromolecular dynamics at different temperatures in solutions; for measurements of Perftoran oxygenation and its capacity to molecular oxygen.[42]

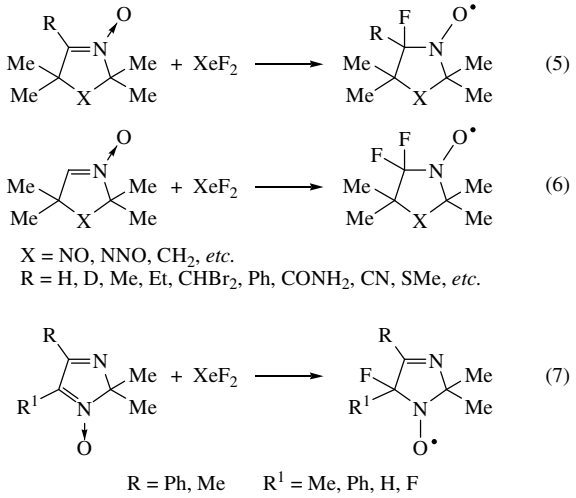
Fluorinated β-diketonates of piperidine nitroxide radicals $CF_3COH{=}CHCOR_6'$ **45** ($L^1H$) and $CF_3COH{=}CHCOR_6$ **46** ($L^2H$) were suggested as chelating agents for the synthesis of spin labeled transition metal complexes.[39] Such complexes with different metals ($CuL^1_2$, $NiL^1_2$, $CoL^1_2$, $MnL^1_2$, $EuL^1_3$, $PrL^1_3$ and $CuL^2_2$, $NiL^2_2$, $CoL^2_2$, $MnL^2_2$, $EuL^2_3$ and $PrL^2_3$) were prepared and characterised; their magnetic susceptibility was also measured and calculated theoretically. One more paramagnetic complexon of the same row, $CF_3COCH_2COR_5^N$, was described.[40]

The synthesis of two FNRs, $(CF_3)_2CHCF{=}NR_6$ **47** and $(CF_3)_2C{=}C{=}NR_6$ **48**, and their properties have been reported.[41] High electrophilic activity of these radicals allowed the use of them for investigating spin labeled bovine serum albumin. Two new FNRs, $p$-$FC_6H_4R_5^{NO}$ **49** and $p$-$FC_6H_4R_5^N$ **50**, were described.[44] Several FNRs based on the $R_5^{NH}$ and $R_5^N$ radical fragments were synthesised: $F_3CCOCH{=}R_5^{NH}$ **51**,[45,46] $C_6F_5CO$-$CH{=}R_5^{NH}$ **52** and $C_6F_5CH_2R_5^N$ **53**,[47] $CF_3COCCl{=}R_5^{NH}$ **54**, $C_6F_5COCCl{=}R_5^{NH}$ **55**, and $PhCOC(C_6F_5){=}R_5^{NH}$ **56**.[48] FNRs based on pyrroline were also reported: $F_3CR_5''$ **57**, $C_6F_5R_5''$ **58** and **59**.[48]



$R_5^{NH}$ $R_5''$ **59**

Fluorinated 3-imidazoline and 3-imidazoline-3-oxide derivatives have been prepared.[49,50] More than 30 FNRs were obtained by the reactions (5)–(7). For all of these FNRs, the



X = NO, NNO, $CH_2$, *etc.*
R = H, D, Me, Et, $CHBr_2$, Ph, $CONH_2$, CN, SMe, *etc.*



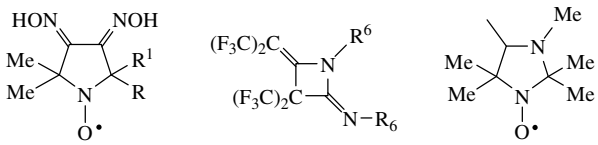
R = Ph, Me $R^1$ = Me, Ph, H, F

**Table 2** ESR parameters for $NiL_2$ complexes with ligands analogous to **60**.

| Ligand | $a_N$±0.1/G | $A_{\|}$±0.3/G | $\|J/a\|$ for $NiL_2$/G |
|---|---|---|---|
| $HL^1$, R = Me | 14.7 | 34.6 | 1.8±0.03 |
| $HL^2$, R = Ph | 14.6 | 33.8 | 8.1±0.2 |
| $HL^3$, R = $CF_3$ | 13.3 | 30.2 | > 22.5 |

spin-Hamiltonian parameters were measured by ESR spectroscopy.[49] Quantitative correlations between the hfs constants and various properties of the substituents were revealed, for example: $|a_N| < |a_F| < 2|a_N|$; $|a_F| \approx 2|a_N^1| = 4|a_N^3|$.

An interesting example of fluorinated chelating agents has been performed for the analysis of how various acceptor substituents in a pyrrolidone ring influence intramolecular spin exchange in nickel(II) complexes spin labeled with **60** ($R_1$ = Me, R = $CF_3$, $HL^3$).[51] Properties of **60** were compared with those for its analogues with $R^1$ = Me, R = Me, $HL^1$ or R = Ph, $HL^2$. The isotropic hfs constants of **60** are given in Table 1, and the spectroscopic parameters are listed in Table 2. The main result was that the absolute exchange integral value $|J|$ in biradical-type spin labeled metal complexes increases in parallel with the substitution of the methyl groups with stronger electron acceptor residues nearby the paramagnetic >N–O• fragment of the ligand.[51] Synthesis of two FNRs of such a type was described, **61**: $R^1$ = Ph, R = $CF_3$ and **62**: $R^1$ = Bu, R = $CF_3$.[52]



**60–62** **B2** $R_5^{NR}$

The second example of a fluorinated biradical was obtained by the dimerization reaction of **48** in the presence of CsF with producing only one isomer **B2**.[41] Its structure was proved by IR and ESR methods. It was shown that the average distance $r$ between >N–O groups in **B2** is equal to 9.5±0.3 Å in toluene solutions frozen at 77 K.[41] Toluene was carefully purified.[53] Radical concentration was ≤ $5\times10^{-4}$ mol dm$^{-3}$ to avoid intermolecular exchange broadening.[54] ESR spectra were recorded at $-40 \le T \le 75$ °C (Figure 1). By changes in the spectra, one can conclude that in **B2** the case of strong electron spin exchange occurs, and there are fast transitions between different effective conformations of the biradical.[55]

The ESR spectra of this type allow one to measure the average exchange integral value $|J^*|$.

$$J^* = (J_1\tau_1 + J_2\tau_2)/(\tau_1 + \tau_2).$$

Here, $|J_1| < |J_2|$ are the exchange integrals for two different effective conformations of the biradical, and $\tau_1$, $\tau_2$ are the characteristic lifetimes of these conformations.[55] Positions of the ESR lines are determined, according to the theory of fast

exchange between two conformations by the value $J^*$, while the line widths are determined by fluctuations of $J(t)$ around $J^*$.[55,56] Two parameters were experimentally measured: the hfs constant $a$ on $^{14}N$ nitrogen and the value of $|J^*/a|$, which were calculated in units of the hfs constant $a$, *i.e.* as $|J/a|$.[55,56] If a biradical exists in solution only in two different conformations, a linear Arrhenius plot of $|J^*/a|$ has to be valid in the whole temperature range. In the case of **B2** it is not the case (Figure 2), *i.e.*, we should conclude that **B2** is presented in a solution at least in three conformations, differed by the value of the exchange integral, with fast transitions between them. It is also seen in Figure 2 that the most thermodynamically stable conformation is that with $|J^*| < 1.4a$, which is stabilised at low temperatures with $r \approx 9.5$ Å.

The third asymmetric biradical $R^N_5CH_2(p\text{-}C_6F_4)COCH{=}R^{NH}_5$ **B3** was described but, unfortunately, its detailed ESR investigation was not performed.[47]

Recently, the characterization and NMR and ESR spectra of β-fluorinated nitroxides, which were synthesised by the reaction[57]

$$\begin{gathered} ArN{=}O + BrCH(COOR)_2 \rightarrow \\ Ar(O^-)N^+{=}C(COOR)_2 + XeF_2 \rightarrow ArNO^{\bullet}CF(COOR)_2, \end{gathered} \quad (8)$$

was considered.

In a first step, the N-alkylation of an appropriate nitroso compound using an alkoxy bromomalonate afforded a ketonitrone, which then reacted with $XeF_2$ to produce the nitroxide radical (Ar = Ph or $C_6D_5$, and R = Me or Et). The hfs constants of the radical $PhNO^{\bullet}CF(COOMe)_2$ **63** are shown in Table 1. These FNRs are described in detail elsewhere.[58]

Ristori *et al.*[59] prepared perfluoropolyether $CF_3O[CF_2CF(CF_3)O]_3CF_2CONHR_6$ **64**, which was used as a spin probe for

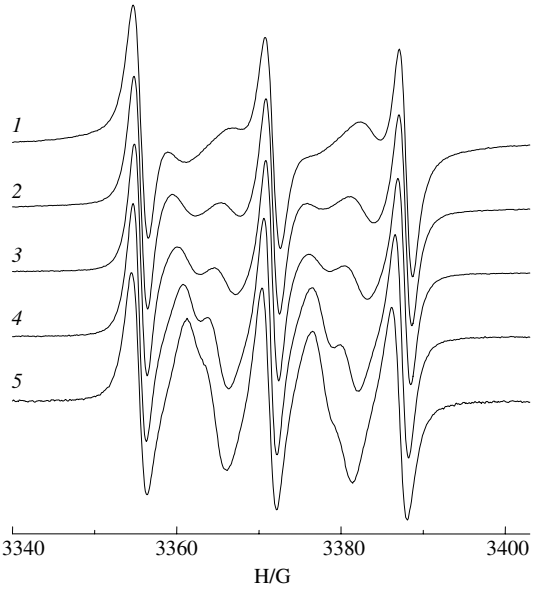



**Figure 1** ESR spectra of biradical **B2** in toluene at: (*1*) –40, (*2*) –20, (*3*) 20, (*4*) 40 and (*5*) 75 °C.

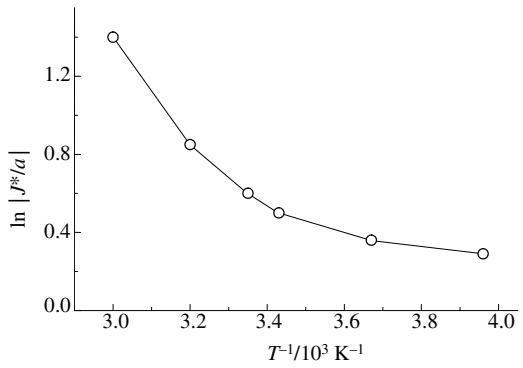



**Figure 2** $|J^*/a|$ values as a function of temperature for biradical **B2** in toluene.

**Table 3** Rate constants $k_1$ of the reaction between NR and diphenylhydrazine in *n*-hexane.[62]

| Radical | $k_1$/dm$^3$ mol$^{-1}$ s$^{-1}$ |
|---|---|
| $p\text{-}FC_6H_4R^N_5$ | 7.7 |
| $PhR^N_5$ | 4.9 |
| $p\text{-}FC_6H_4R^{NO}_5$ | 43.8 |
| $PhR^{NO}_5$ | 31.5 |
| $p\text{-}FC_6H_4R^{NN}_5$ | 37 |
| $Ph\text{–}R^{NN}_5$ | 32 |
| $p\text{-}FC_6H_4R^{NR}_5$ | 2.8 |
| $PhR^{NR}_5$ | 2.17 |
| $p\text{-}MeC_6H_4R^{NR}_5$ | 2.1 |
| $(CF_3)_2COHRQ_1$ | 3100 |

the characterization of betaine micelles and betaine–perfluoropolyether mixed vesicles. The results were compared with data obtained by NMR spectroscopy and light scattering.

A special use of FNRs was connected with their chemical activity.[60–63] It has been suggested to compare the redox properties of NRs by the rate constant $k_1$ of the reaction between NR and diphenylhydrazine in hexane solutions at ambient temperature:[60]

$$RNO^{\bullet} + PhNHNHPh \xrightarrow{k_1} RNOH + PhN^{\bullet}NHPh \quad (9)$$

$$RNO^{\bullet} + PhN^{\bullet}NHPh \longrightarrow RNOH + PhN{=}NPh \quad (10)$$

The $k_1$ values for more than 90 NRs have been compared, and the effects of different functional groups (substituents) in nitroxide radicals on their redox activity were analysed.[62] There were several fluorinated nitroxides among these NRs, including **42**, $p\text{-}FC_6H_4R^N_5$ **65**, $p\text{-}FC_6H_4R^{NO}_5$ **66**, $p\text{-}FC_6H_4R^{NN}_5$ **67**, $p\text{-}FC_6H_4R^{NR}_5$ **68**, whose parameters are given in Table 3 in comparison with $k_1$ values for analogous unfluorinated compounds. It is evident from Table 3 that the replacement of an H atom in the *para*-position of the phenyl ring with the F atom results in an approximately 1.5-fold increase of $k_1$, while changes in the nitroxide ring structure produce variations in $k_1$ values more than in an order.

Another chemical reaction in which FNRs were tested was hydrogen exchange:[57]

$$R_1NOH + R_2NO^{\bullet} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_1NO^{\bullet} + R_2NOH, \quad (11)$$

where $R_1$ and $R_2$ are cyclic, aliphatic or aromatic fragments. The rate constants $k_1$ and $k_{-1}$, as well as the equilibrium constant $K_{eq} = k_1/k_{-1}$ are listed in Table 4.[57,58] A fluorinated hydroxylamine, a reduced form of **42** ($R_1NOH$), reacted with various NRs. Table 4 indicates that variations in the type and structure of nitroxides resulted in noticeable changes of rate constants of the forward and back reactions. Indeed, changes in the equilibrium constant $K_{eq}$ exceed two orders. This fact opens a new way for the preparation of new FNRs.

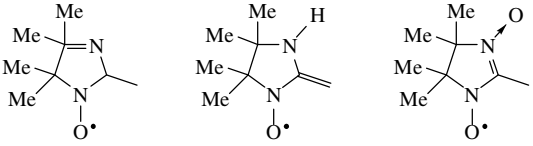
Interesting applications of FNRs are connected with their use as paramagnetic chelating agents for transition metal cations.[64–69] The main advantage of such chelating FNR complexes with paramagnetic metal ions is connected with the possibility to construct and design the molecular ferromagnets (a rapidly developing area of supramolecular chemistry). Such fluorinated NRs as **51**,[64,68] $CF_3COH{=}CHR^N_5$ **65**,[70] $CF_3COCH_2R^N_5$ **66**,[71–78] $CF_3COCH(Cl)R^N_5$ **67**[77,78] and $CF_3COCH(Me)R^N_5$ **68**[77] were used for the preparation and characterization of their complexes with nickel(II),[68,71,73–75,77] cobalt(II)[68,72,74,76,77] and copper(II).[64,65,68,78]

**Table 4** Rate constants $k_1$ and $k_{-1}$ and the equilibrium constant $K_{eq} = k_1/k_{-1}$ of reaction (11) between fluorinated hydroxylamine, a reduced form of **42**, and various NRs.[61–63]

| Radical | $k_1/10^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | $k_{-1}/10^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | $K_{eq}$ |
|---|---|---|---|
| $HOR_5$ | 0.73 | 16.2 | 0.046 |
| $H\text{–}R_6$ | 7.6 | 2.9 | 2.62 |
| $O{=}R_6$ | 6.4 | 0.74 | 8.87 |
| $MeR^{NR}_5$ | 0.5 | 14.0 | 0.036 |
| $PhR^{NR}_5$ | 0.97 | 15.2 | 0.064 |
| $PhR'_6$ | 4.3 | 3.0 | 1.43 |
| $Ph_3CRQ_2$ | 6.6 | 0.75 | 8.86 |

If instead of the $CF_3$ group (the acceptor of electron density) alkyl or aryl groups were used, the solid phase of complexes had molecular surrounding with a square planar or tetrahedral structure.[66] In the case of strong electron acceptors ($CF_3$ or COOEt groups), the coordination number of the central metal ion increased to six, and a layered-polymeric structure was formed.[71,79] Another way to increase the acceptor properties of the central metal ion is the insertion of acceptor atoms or groups (Cl, CN) to the chelating fragment, for example, **67** or $CF_3COCH(CN)R_5^N$ **69**.[66,68,78]

The synthesis of new fluorinated NRs has been continued.[67,69,80–83] New FNRs were obtained by the reaction of **54** with nucleophilic agents (Nu), such as $NCS^-$ (**a**), $NO_2^-$ (**b**), $OCN^-$ (**c**), $MeCO_2^-$ (**d**): $CF_3COC(Nu)=R_5^{NH}$ **70a–d**.[67] A new class of fluorinated enehydroxylamino ketones was performed and their chemical reactions analysed, as well as the X-ray diffraction structures.[69] It was noted that the magnetic susceptibility curve for $CF_3COC(CN)=R_5^{NH\alpha}$ **71** showed the presence of a strong intermolecular exchange interaction in the solid samples.[69]

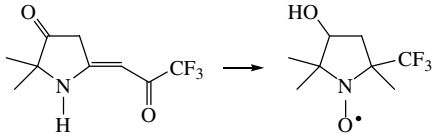


$R_5^{N\alpha}$ $R_5^{NH\alpha}$ $R_5^{NO\alpha}$

It should be mentioned that the synthesis of fluorinated NRs is in progress.[69,80–83] Special fluorinated spin probe $CF_3(CF_2)_6CH_2O$–$COR_5'$ **72** was used for magnetic resonance characterization of ordered systems, such as the hydrophobic perfluoro-rich domains inside macroaggregates of fluorinated polymers.[80] A new set of lipophilic pH-sensitive spin probes for measurements in biological membranes and tissues at different pH values has been suggested: **51**, **54**, $CF_3COC(CN)=R_5^{NH}$ **73**, and their analogues, in which one of the methyl groups in the imidazoline ring was substituted with $C_8H_{17}$ (**51a**, **54a**, **73a**).[81]

Fluorinated nitronyl nitroxide radicals 4-$CF_3C_6H_4R_5^{N\alpha}$ **74**, 2,6-$F_2C_6H_3R_5^{N\alpha}$ **75**, 4-$CF_3C_6H_4R_5^{NO\alpha}$ **76**, 2,6-$F_2C_6H_3R_5^{NO\alpha}$ **77** were used as the redox-sensitive probes of NO$^\bullet$ scavenging, recorded by ESR and $^{19}F$ NMR techniques.[82] ESR allowed one to observe NO-induced transformations of the paramagnetic traps to the corresponding iminonitroxides, while the diamagnetic hydroxylamine products were easily detected by $^{19}F$ NMR. The pH dependence of chemical shifts of the signals in NMR spectra was also recorded.[82] This approach is of importance for the understanding of the mechanism of NO$^\bullet$-radical reactions carried out in living organisms under normal conditions and in pathology. For example, the $^{19}F$ NMR measurements of NO$^\bullet$ production in highly sensitive rats of ISIAH and OXYS strains, which are common and adequate animal models of hypertension, as well as in normotensive Wistar rat strain were reported.[83] Significantly lower HIN/HNN ratios (HNN is the concentration of FNR **77**, and HIN is the concentration of its hydroxylamine) were measured in the blood of hypertensive rats *in vivo*. It was found that the NMR data positively correlate with the levels of nitrite/nitrate ratios and negatively correlate with the blood pressure.[83]

Fluorinated spin traps, such as 5,5-dimethyl-4-hydroxy-2-trifluoromethyl-1-pyrroline 1-oxide (F-DMPO) and *p*-$CF_3C_6H_4$–CH=NO–$CMe_3$ (F-PBN), are unique for *in vivo* studies of oxidative stress status.[84] Combination of $^{19}F$ NMR with ESR measurements showed new promising possibility of evaluating oxidative stress in living organisms in real time.



(12)

**78**

ESR and NMR spin trapping was used for the detection of free radical reactions with the use of a new fluorinated spin trap and new FNR **78**, which was synthesised by the reaction (12).[85] Radical **78** exists as two stereoisomers; this was confirmed by an NMR technique. The kinetic parameters of the fluorine- and phosphorus-containing analogues of DMPO in Fenton processes were measured and discussed as the appropriate models of antioxidants in biological systems and cells.

Thus, fluorinated nitroxide radicals are interesting for synthetic fluoroorganic chemistry and ESR studies. We would like to stress that (i) the reaction of nucleophilic substitution of the fluorine atom at α-carbon atom position of the radical centre in stable NRs[50] is unique and very promising for the synthesis of new FNRs by the reaction without touching the unpaired electron. (ii) Formation of spin adducts – FNRs, as a result of spin trapping of the free radicals by fluorinated nitrones, permitted to develop a new method for investigation of radical processes in biological systems and the analytical method of nitrogen oxide concentration measurements with the use of $^{19}F$ NMR. (iii) The cation-radical mechanism of nucleohilic addition to nitrones was convincingly proved by the results of transformation of different nitrones reacted with $XeF_2$ or $ArF_2$ into FNRs with F-atoms in α-carbon position to N–O$^\bullet$ group. (iv) FNRs as specific spin probes and labels are very promising tools for molecular and cell biology, biophysics, biological and enzyme chemistry and macromolecular chemistry.

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