Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2016, **26**, 24–25
Mendeleev Communications

Sensitivity of magnetic resonance imaging based on the detection of ^{19}F NMR signals

Mikhail V. Gulyaev,*[a] Nikolay V. Anisimov,[a] Nadezhda E. Ustyuzhanina,[b] Andrey S. Dmitrenok,[b] Alexander S. Shashkov,[b] Dmitry V. Yashunsky,[b] Lev L. Gervits,[c] Yury A. Pirogov[a] and Nikolay E. Nifantiev*[b]

[a] *Department of Fundamental Medicine, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: mihon-epsilon@yandex.ru*
[b] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 8784; e-mail: nen@ioc.ac.ru*
[c] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

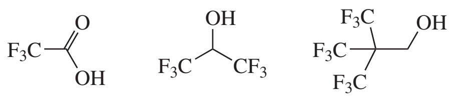
DOI: 10.1016/j.mencom.2016.01.010

The evaluation of the sensitivity of magnetic resonance tomography with a magnetic field of 7 T based on the detection of ^{19}F NMR signals was performed with the use of the solutions of trifluoroacetic acid, 1,1,1,3,3,3-hexafluoroisopropanol and *sym*-nonafluoroneopentanol, whose ^{19}F NMR spectra consist of single line signals. The scanning of a 12×12 cm zone with a resolution of 1.2 mm and a cut thickness of 4 mm for 10 min gave reliable images if the local concentration of ^{19}F atoms in the test zone exceeded 0.3–0.6%.

New versions of NMR spectroscopy can be used for the investigation of natural systems.[1] One of them is magnetic resonance imaging (MRI), which is typically based on the detection of ^1H NMR signals.[2] However, the use of other magnetic nuclei such as ^{19}F in MRI is of practical interest.[3,4] This is determined by a similarity of magnetic properties of ^1H and ^{19}F atoms: ^{19}F also has a large gyromagnetic ratio, which is only 6% smaller than that of a proton, and it has absolute (100%) natural abundance of fluorine. Interest in the development of ^{19}F MRI is stimulated by wide applications of synthetic fluorinated compounds in medicine, first of all, as therapeutic agents, blood substitutes[5,6] and cell labelling agents.[7,8] During the development and biomedical trials of such substances, ^{19}F MRI may give an opportunity for the monitoring of processes occurring after their application, including localization in target tissues, metabolism and clearance. Fluorine has very small presence in biological objects avoiding a risk to detect undesirable side signals and decreasing experimental noise, which causes problems in ^1H NMR based MRI. That is why another challenging application of ^{19}F MRI is connected with its use as a non-invasive 3D intracorporal medical diagnostic method to reveal and highlight the sites of disease.

To develop specific protocols of ^{19}F MRI, it is important to evaluate the level of sensitivity of this method under selected doses of a ^{19}F-containing contrasting agent and acceptable scanning time. For this purpose, it is not enough to detect a signal after applying a large amount of a fluorinated agent and having defined the signal-to-noise ratio, but also to calculate its decrease upon dissolution of a sample. Such an approach does not consider the possibility of a change of physical properties of the test substance (diffusive parameters and relaxation times) on its dissolution. It is also impossible to exclude the influence of technical factors, for example, hardware imperfections. Therefore, for assessment of the sensitivity of an MRI scanner, it is desirable to do test measurements with the use of a set of variously dissolved model contrasting agents containing different amounts of ^{19}F.

Here, we report the results of the sensitivity level evaluation of ^{19}F MRI with the use of a Bruker BioSpec 70/30 USR (7 T) MR scanner containing a modified ^{19}F probe head resonator. In these default settings, it was adjusted based on an ^1H NMR frequency of 300 MHz. After all performed technical modifications, the resonator was tuned to a ^{19}F NMR frequency of 283 MHz.[9]



1 **2** **3**

Trifluoroacetic acid **1** (Acros), 1,1,1,3,3,3-hexafluoroisopropanol **2** (P&M-Invest) and *sym*-nonafluoroneopentanol **3** (P&M-Invest) containing one, two and three CF_3 groups, respectively, were used for test measurements. After the dissolution of substances in chloroform, the samples with concentrations of 0.25 and 0.125 mmol cm^{-3} were subjected to ^{19}F MRI analysis in cylindrical 4.5 ml vials (Figure 1). Compounds **2** and **3** were also tested in a concentration of 0.0625 mmol cm^{-3}, while nonafluoroneopentanol **3** was also examined in a concentration of

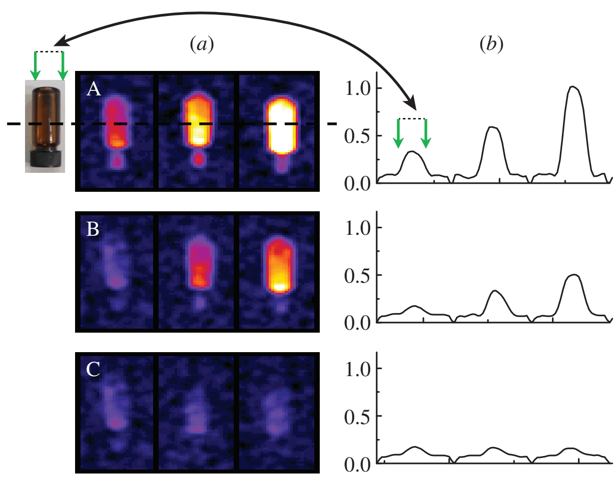


Figure 1 ^{19}F MR images of the test samples and graphics of brightness of pixels (NMR signal intensity) along a horizontal axis (dashed line) of the image. (*a*) (A) and (B) MR images for 0.25 and 0.125 mmol cm^{-3} solutions of compounds **1–3**, (C) MR images for 0.0625 mmol cm^{-3} solutions of compounds **2** and **3** and for 31.25 μmol cm^{-3} solution of compound **3**, respectively. (*b*) Integrated signal intensities along the horizontal line passing through the scanned zone (dashed line).

Table 1 Concentrations of ^{19}F atoms in the solutions of compounds **1**–**3**.

Concentration/mmol cm^{-3}	**1**	**2**	**3**
0.25	~1.0%	~1.8%	~2.45%
0.125	~0.5%	~0.9%	~1.2%
0.0625	n.a.	~0.45%	~0.6%
0.03125	n.a.	n.a.	~0.3%

31.25 μmol cm^{-3}. Table 1 shows the ^{19}F concentrations in the solutions.

The MRI scanning was carried out by a spin echo method during 10 min with the following parameters: TR/TE = 1000/8.2 ms at 6 signal accumulation with 96 kHz sampling. Radiofrequency pulses of a Hermite form by 1 and 1.5 ms duration, respectively, were applied to excite and refocus spin. A zone of 12×12 cm was scanned with a resolution of 1.2 mm at a slice thickness of 4 mm, which is equivalent to a voxel of 5.76 mm^3 in volume (1.2×1.2×4.0 mm). These parameters were selected by taking into account relaxation times T_1 and T_2^* of 2.8 and 0.1 s, respectively, for the prepared samples, which were measured on a Bruker AV 400 NMR spectrometer (^{19}F NMR frequency of 376.5 MHz). The T_1 and T_2^* values changed only slightly (about 10%) even at a tenfold dilution.

Figure 1 shows the MR images of tested samples (A–C) and ^{19}F NMR signal intensity along the horizontal line passing through the scanned zone (dashed line). The intensity of MR images decreased upon the dilution of test samples, but it can be integrated reliably if the local concentration of ^{19}F atoms in the test zone goes down to 0.3–0.6%, which is equivalent to 17–34 μg of ^{19}F per used voxel size of 5.76 mm^3 (see above). Lower concentrations of ^{19}F atoms are difficult for reliable detection under used conditions. Nevertheless, the determined threshold sensitivity of the MRI scanner forms the starting point to develop approaches to increase in the sensitivity of this version of ^{19}F NMR based tomography as a method for the invasive visualization of ^{19}F-containing biomolecular systems.[10] The results of our studies towards the development of highly fluorinated contrasting agents bearing biovector arms for tissue specific targeting of disease sites will be published elsewhere.

This work was supported by the Russian Science Foundation (grant no. 14-50-00126).

References

1 I. V. Koptyug, *Mendeleev Commun.*, 2013, **23**, 299.
2 E. M. Haacke, R. W. Brown, M. R. Thompson and R. Venkatesan, *Magnetic Resonance Imaging: Physical Principles and Sequence Design*, John Wiley & Sons, New York, 1999.
3 G. N. Holland, P. A. Bottomley and W. S. Hinshaw, *J. Magn. Reson.*, 1977, **28**, 133.
4 J. Ruiz-Cabello, B. P. Barnett, P. A. Bottomley and J. W. M. Bulte, *NMR Biomed.*, 2011, **24**, 114.
5 I. Tirotta, V. Dichiarante, C. Pigliacelli, G. Cavallo, G. Terraneo, F. Baldelli Bombelli, P. Metrangolo and G. Resnati, *Chem. Rev.*, 2015, **115**, 1106.
6 E. I. Maevsky and L. L. Gervits, *Chem. Today, Focus on Fluorine Chemistry*, 2008, **26**, 8.
7 S. K. Patel, J. Williams and J. M. Janjic, *Biosensors*, 2013, **3**, 341.
8 E. T. Ahrens and J. Zhong, *NMR Biomed.*, 2013, **26**, 860.
9 M. V. Gulyaev, L. L. Gervits, Yu. A. Ustynyuk, N. V. Anisimov, Yu. A. Pirogov and A. R. Khokhlov, *Zh. Radioelektroniki*, 2013, no. 8, http://jre.cplire.ru/win/aug13/11/text.html.
10 V. P. Ananikov, E. A. Khokhlova, M. P. Egorov, A. M. Sakharov, S. G. Zlotin, A. V. Kucherov, L. M. Kustov, M. L. Gening and N. E. Nifantiev, *Mendeleev Commun.*, 2015, **25**, 75.

Received: 25th August 2015; Com. 15/4716