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Spin Order Transfer from a Parahydrogen Molecule to the Counterion in the Iridium Complex under the SABRE Conditions

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Abstract—A possibility of generating spin polarization of ^{19}F nuclei in the counterions that form no covalent bond with the metal center is shown for the first time for new iridium complexes synthesized by reversible binding with the substrate (pyridine) and parahydrogen. This makes it possible to observe the integral polarization of ^{19}F nuclei in weakly coordinated tetrafluoroborate and hexafluorophosphate anions. The optimum parameters of the magnetic field strength for the maximum amplification of the ^{19}F signal in two fluorine-containing anions are determined from the dependences of the signal intensity in the NMR spectra on the magnetic field strength for two synthesized iridium complexes.

Keywords: NMR spectroscopy, parahydrogen, hyperpolarization, iridium complexes, carbene ligands, signal amplification, parahydrogen-induced nuclear hyperpolarization

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INTRODUCTION

NMR spectroscopy is one of the main methods for structure determination and, hence, finds wide use in various areas of chemistry [1], biology [2], and medicine [3]. In the last case, a possibility of noninvasive medical diagnostics of internal organs by magnetic resonance tomography (MRT) should surely be mentioned [4–6]. The major restriction of NMR spectroscopy for these applications is associated with its low sensitivity because of an exclusively low difference in occupancies of nuclear spin states at room temperature [7, 8]. As a result, the existing approaches to increasing sensitivity are based on a substantial increase in this difference in occupancies, i.e., achievement of hyperpolarization.

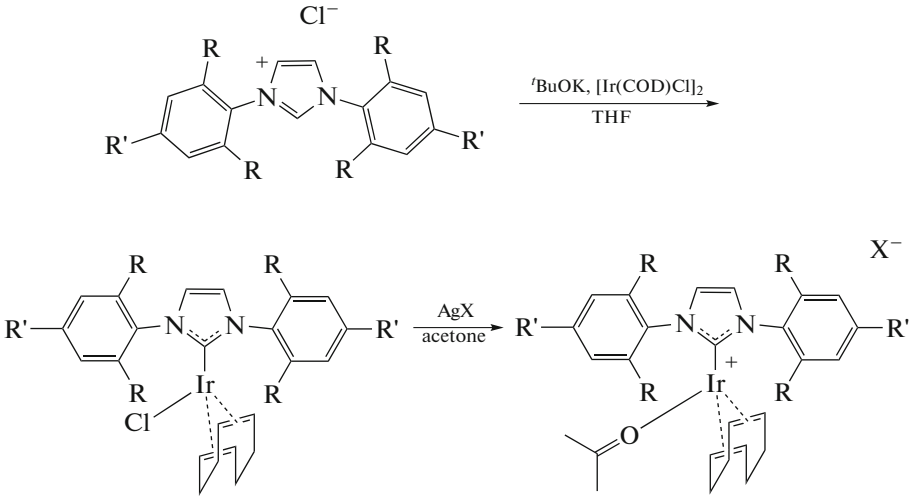
One of the breaking trends for the solution of this problem is related to the spin order transfer from a parahydrogen molecule to the studied molecule for the generation of nonequilibrium polarization of the studied nuclei, so-called parahydrogen-induced hyperpolarization (PHIP). Unlike the most part of other approaches aimed at generating nuclear hyperpolarization (such as optical pumping of noble gases [9–11] and dynamic nuclear polarization [12, 13]), PHIP demands no expensive equipment and is suitable for the generation of a broad class of polarized molecules, including contrast agents for MRT.

Parahydrogen is one of two spin isomers of molecular hydrogen that can easily be obtained by cooling gaseous hydrogen to temperatures of liquid nitrogen or helium in the presence of an appropriate paramagnetic catalyst. Although parahydrogen itself gives no signals in the NMR spectrum [14], the violation of magnetic equivalence of the atoms in a parahydrogen molecule upon their pairwise addition to a substrate leads to the reaction products in which the nonequilibrium distribution of occupancies of nuclear levels inherent in the pair of spins of parahydrogen protons is observed as an anomalous (sometimes by several orders of magnitude) increase in the signal intensity in the NMR spectrum [14].

In addition to classical PHIP effects related to the catalytic hydrogenation of unsaturated substrates in the presence of the homogeneous [15] or heterogeneous [16] catalysts, the SABRE (signal amplification by reversible exchange) approach has been proposed rather recently [17] to achieve a similar result. The approach is based on the reversible addition of molecular hydrogen containing a certain percent of parahydrogen and a substrate to a metal center of a homogeneous iridium-con-

taining catalyst. The polarization transfer from the hydride protons to other spins of the ligand nuclei [18, 19] occurs without chemical transformation (without hydrogenation reaction) due to magnetic interactions between spins in the obtained complex.

The predominant majority of the SABRE catalysts is presented by the charged iridium complexes containing a weakly coordinated counterion. However, we failed to find any data on the possibility of polarization transfer to the nuclei composing such a counterion. To fill this gap, in the present work we synthesized two iridium complexes with related carbene ligands (Scheme 1) and out-of-sphere tetrafluoroborate or hexafluorophosphate anions: [Ir(COD)-{acetone}(IPr)]BF_4 (tetrafluoroborate[1,3-bis[2,6-diidopropylphenyl]-2-imidazol-2-idene]-[(η4)-1,5-cyclooctadiene](2-propanone)iridium **(I)** and [Ir(COD){acetone}(IMes)]PF_6 (hexafluorophosphate[1,3-bis[2,4,6-trimethylphenyl]-2-imidazol-2-idene][(η4)-1,5-cyclooctadiene](2-propanone)iridium **(II)**. The magnetically active ^{11}B, ^{19}F, and ^{31}P nuclei of the latter allowed us to study the spin order transfer from a parahydrogen molecule under the SABRE conditions.



R = R' = Me; X = BS_4 **(I)**

R = ^{i}Pr, R' = H; X = PF_6 **(II)**

Scheme 1.

EXPERIMENTAL

All procedures associated with the synthesis and isolation of the complexes were carried out under a nitrogen atmosphere in a glove box. Compounds 1,3-bis(2,6-diisopropyl phenyl)imidazolium chloride (IPr·HCl) and 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl) were used as received (Sigma-Aldrich), and $(IrCODCl)_2$ was synthesized using a previously described procedure [20]. The earlier described compounds [IrCl(COD)(IPr)] and [IrCl(COD)(IMes)] [21, 22] were synthesized using a modified procedure of in situ generation of carbene. Elemental analyses to carbon, nitrogen, and hydrogen were carried out on a Carlo Erba (model 1106) analyzer.

Synthesis of complex [IrCl(COD)(IPr)]. Compounds $[IrCl(COD)]_2$ (537 mg, 0.80 mmol) and ^{t}BuOK (180 mg, 1.60 mmol) were mixed in a glove box, and anhydrous THF (10 mL) was added to the mixture. The resulting dark red solution was stirred at room temperature for 10 min. The addition of IPr·HCl (680 mg, 1.60 mmol) to the solution changed its color from dark red to dark yellow. The reaction mixture was stirred for 16 h. Then THF was removed in vacuo, and the residue was purified by column chromatography eluting the product with an EtOAc–petroleum ether (1 : 1) mixture. The yield was 799 mg (69%).

For $C_{35}H_{48}N_2ClIr$

Anal. calcd., %	C, 57.82	H, 6.80	N, 4.79
Found, %	C, 58.03	H, 6.68	N, 4.89

^{1}H NMR ($CDCl_3$; 400 MHz; δ, ppm): 0.85 (m, 2H, CH_2), 1.11 (d, 12H, CH_3), 1.54–1.11 (m, 16H, CH_2, CH_3), 1.64 (m, 2H, CH_2), 2.74 (m, 2H, CH), 2.85 (m, 2H, CH), 3.40 (m, 2H, CH), 4.14 (m, 2H, CH), 7.03 (s, 2H, IPr), 7.36 (m, 4H, IPr), 7.44 (t, 2H, IPr).

Synthesis of complex [IrCl(COD)(IMes)]. Compounds $[Ir(Cl)(COD)]_2$ (537 mg, 0.80 mmol) and ^{t}BuOK (180 mg, 1.60 mmol) were mixed in a glove box, anhydrous THF (10 mL) was added, and the resulting dark red solution was stirred at room temperature for 5 min. The addition of IMes·HCl (545 mg, 1.60 mmol) to the solution changed its color from dark red to dark yellow. The reaction mixture was stirred for 16 h. Then THF was removed in vacuo, and the residue was purified by column chromatography eluting the product with a dichloromethane–acetone (8 : 1) mixture. The yield was 875 mg (73%).

^{1}H NMR ($CDCl_3$; 400 MHz; δ, ppm): 1.24 (m, 4H, CH_2), 1.64 (m, 4H, CH_2), 2.10 (s, 6H, CH_3), 2.29 (s, 12H, CH_3), 2.90 (m, 2H, CH), 4.09 (m, 2H, CH), 6.97 (s, 2H, CH), 7.00 (s, 2H, CH), 7.03 (s, 2H, CH).

For $C_{29}H_{36}N_2ClIr$

Anal. calcd., %	C, 54.32	H, 5.80	N, 5.66
Found, %	C, 54.40	H, 5.67	N, 4.38

Synthesis of complex [Ir(COD){acetone}(IPr)]BF_4 (I). Compound $AgBF_4$ (1 equiv, 157 mg, 0.81 mmol) was added to a solution of [IrCl(COD)(IPr)] (586 mg, 0.81 mmol) in acetone (10 mL), and the mixture was stirred at room temperature in the dark for 30 min. The resulting suspension was filtered and evaporated to 0.5 mL, and diethyl ether was added to the residue. Then the precipitate was filtered off and dried in vacuo. The yield was 506 mg (75%).

^{1}H NMR (CD_2Cl_2; 400 MHz; δ, ppm): 1.14 (d, 24H, CH_3) 1.42 (d, 24H, CH_3), 2.11 (s, 6H, CH_3), 2.67 (m, 4H, CH), 3.04 (m, 4H, CH), 4.11 (m, 4H, CH), 7.16 (s, 2H, CH), 7.39 (d, 4H, IPr), 7.58 (t, 2H, IPr).

For $C_{38}H_{54}N_2OF_6Ir$

Anal. calcd., %	C, 54.65	H, 6.49	N, 3.25
Found, %	C, 54.73	H, 6.53	N, 3.36

Synthesis of complex [Ir(COD){acetone}-(IMes)]PF_6 (II). Compound $AgPF_6$ (1 equiv, 233 mg, 0.92 mmol) was added to a solution of IrCl(COD)(IMes)] (589 mg, 0.92 mmol) in acetone (10 mL), and the mixture was stirred at room temperature in the dark for 30 min. The obtained suspension was filtered and evaporated to 0.5 mL, and diethyl ether was added to the residue. The precipitate was filtered off and dried in vacuo. The yield was 531 mg (77%).

^{1}H NMR ($CDCl_3$; 600 MHz; δ, ppm): 1.56 (m, 4H, CH_2), 1.72 (m, 4H, CH_2), 2.18 (s, 12H, CH_3) 2.41 (s, 6H, CH_3), 2.46 (s, 6H, CH_3), 3.46 (m, 2H, CH), 4.01 (m, 2H, CH), 7.08 (m, 2H, CH), 7.12 (s, 4H, CH). ^{13}C{^{1}H} NMR ($CDCl_3$; 600 MHz; δ, ppm): 18.32 (CH_3), 21.13 (CH_3), 29.03 (CH_2), 32.79 ($CO\underline{C}H_3$), 33.22 (CH_2), 66.00 (CH), 82.61 (CH), 124.31 (CH), 129.34 (CH), 134.89 (C), 134.97 (C), 139.92 (C), 173.67 ($\underline{C}OCH_3$).

For $C_{32}H_{42}N_2OF_6PIr$

Anal. calcd., %	C, 47.91	H, 5.33	N, 3.36
Found, %	C, 47.58	H, 5.24	N, 3.47

NMR spectra under the SABRE conditions were recorded on a Bruker Ascend 400 MHz spectrometer (Larmor proton frequency 400.13 MHz) in methanol-d_4. In experiment parahydrogen was passed under a pressure of 4 bar for 10 s through the sample placed inside a standard cylindrical NMR tube (5 mm) using the automated gas system fabricated at the International Tomography Center (Siberian Branch, Russian Academy of Sciences). After bubbling in a specified magnetic field, the sample was rapidly transferred to the spectrometer sensor, and NMR spectra were recorded. The magnetic field strength was varied by mechanical positioning of the tube with the sample in the field of spectrometer cryomagnet scattering along its thermal hole using a stepper motor. A setup with fast magnetic field switching was described in detail [23, 24].

RESULTS AND DISCUSSION

The ^{1}H and ^{13}C NMR spectra of the synthesized iridium complexes [Ir(COD){acetone}(IPr)]BF_4 (**I**) and [Ir(COD){acetone}(IMes)]PF_6 (**II**) (Scheme 1) entirely corresponded to the expected spectra. To study the polarization transfer from a parahydrogen molecule under the SABRE conditions, the corresponding NMR spectra were recorded during parahydrogen bubbling through solutions of the indicated complexes in methanol-d_4 in the presence of pyridine. The appearance of intense signals of hydride intermediates was observed in the negative spectral range (Fig. 1) along with the intense signal of gaseous orthohydrogen (chemical shift δ = 4.57 ppm). In a strong magnetic field, the antiphase nature of the most part of the indicated signals is characteristic of the hydride intermediates obtained under the SABRE conditions [25, 26]. The observed change in the phase of signals

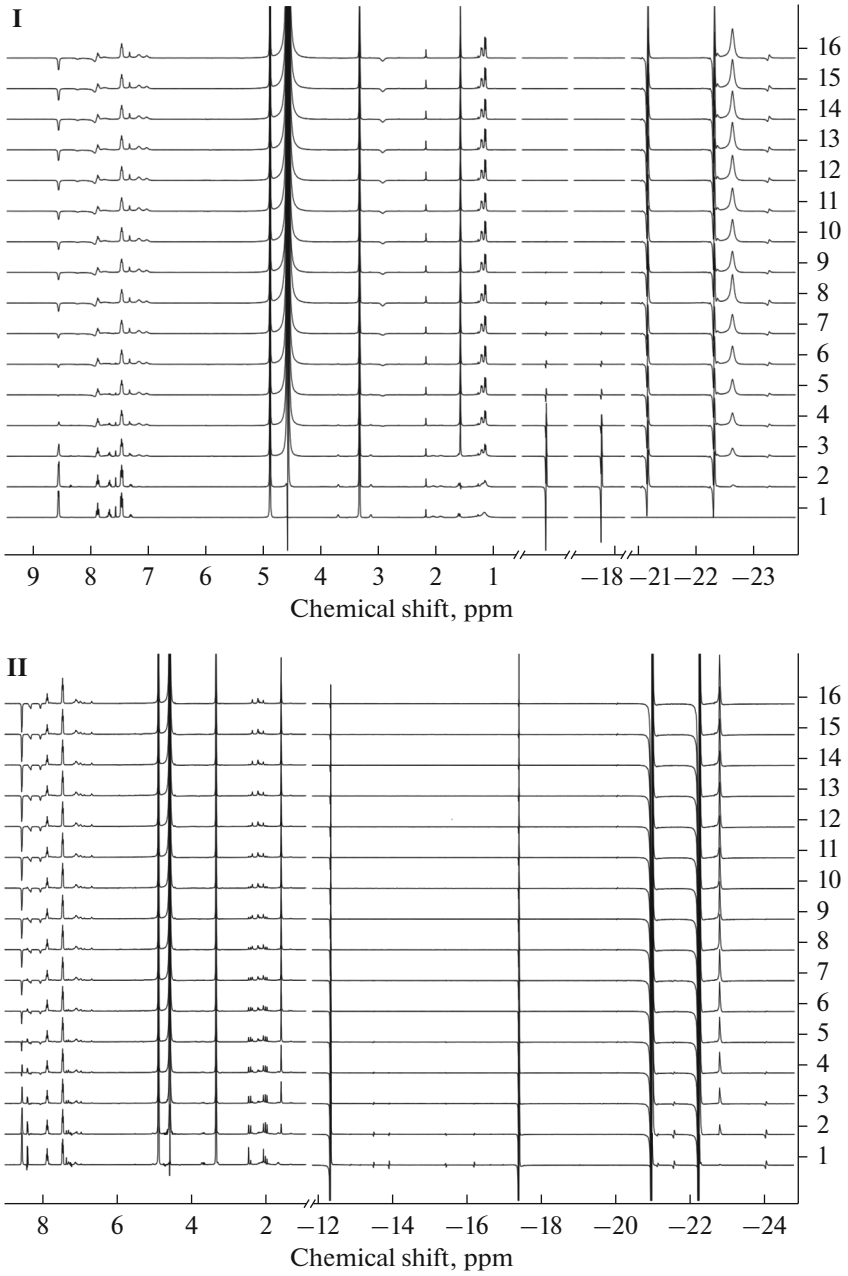
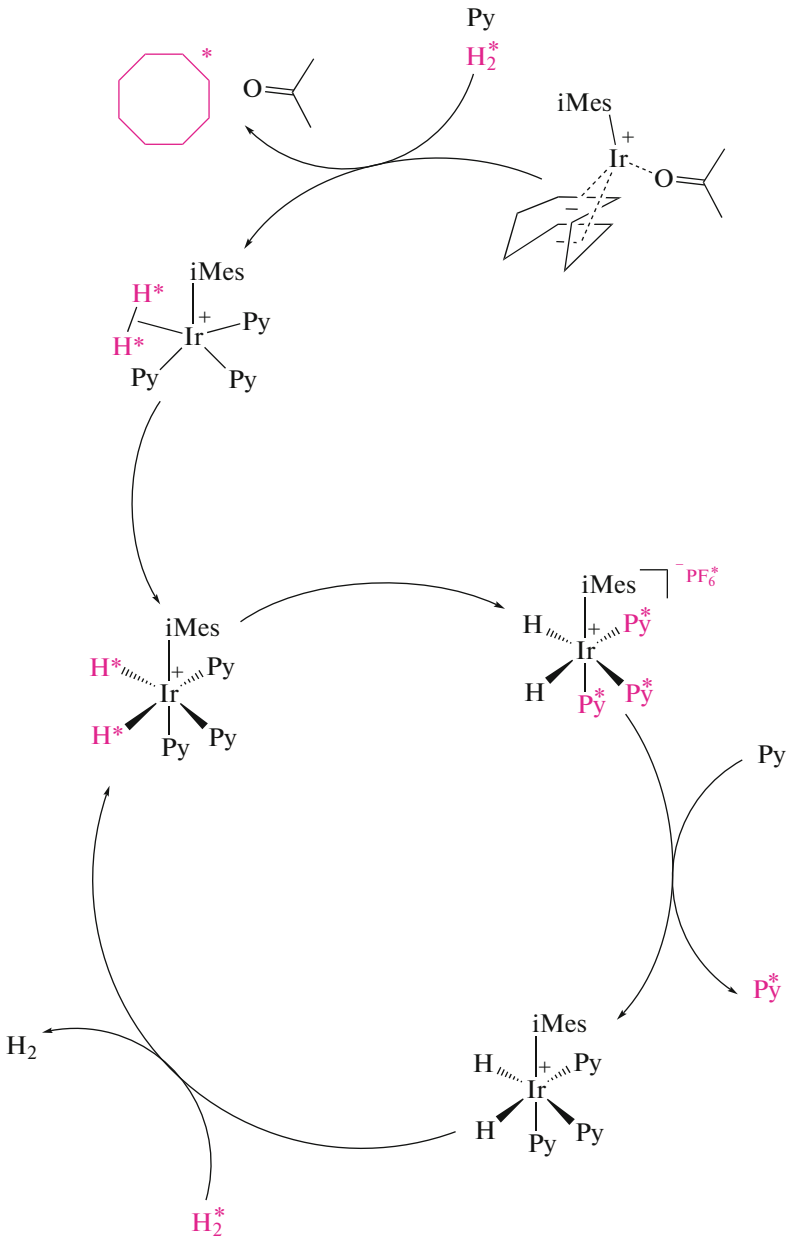


Fig. 1. ^{1}H NMR spectra of complexes **I** (1.2 mmol) and **II** (1.2 mmol) in deuterated methanol in the presence of pyridine (12.4 mmol) when passing parahydrogen (~95% para-H_2). Every subsequent spectrum was recorded after parahydrogen bubbling through the solution at an interval of 10 s.

from the pyridine protons should also be mentioned, indicating the successful polarization transfer from the parahydrogen molecule to this ligand (Fig. 1).

In fact, the catalytic cycle that occurs under the SABRE conditions is more complicated and includes the formation of more hydride intermediates with different degrees of solvation [27] than those shown in simplified Scheme 2. However, in the most part of cases, the polarization transfer to the nuclei of the catalyst and ligand themselves proceeds via the chain of chemical bonds due to the scalar spin–spin interaction. Nevertheless, the tetrafluoroborate or hexafluorophosphate anion that is not linked with the metal center can form a tight ion pair with the latter in an organic solvent due to which the polarization transfer to their nuclei is possible.



(polarized fragments are marked by color and sign *)

Scheme 2.

To establish possibilities of this polarization transfer from parahydrogen to the counterion, we studied the dependence of the amplification coefficients of ^{19}F signals in the indicated fluorine-containing counterions for the reaction in a magnetic field varied from 2 mT to 9 T (Fig. 2). Significant changes in the signal intensity were observed in the ^{19}F NMR spectra depending on the chosen magnetic field strength, which indicated the polarization transfer to the counterion that is not linked directly with the metal center of the complex (Figs. 2c, 2d). An increase in the signal intensity with an increase in the magnetic field strength higher than 0.2 T is induced by an increase in the thermal difference in spin level occupancies that are split by the magnetic field, while a maximum of ^{19}F polarization was observed in a weak magnetic field of 6.4 mT in the plots of the field dependences of both complexes. Since the probability of even a short-term formation of the direct Ir–F bond is very low, the polarization transfer to ^{19}F is achieved, most likely, due to the dipole–dipole mechanism.

Remarkably, we failed to detect the polarization transfer to ^{31}P and ^{11}B nuclei of the counterions, which can be related to both their higher remoteness from the metal center and shorter (especially for boron nuclei) magnetic relaxation times.

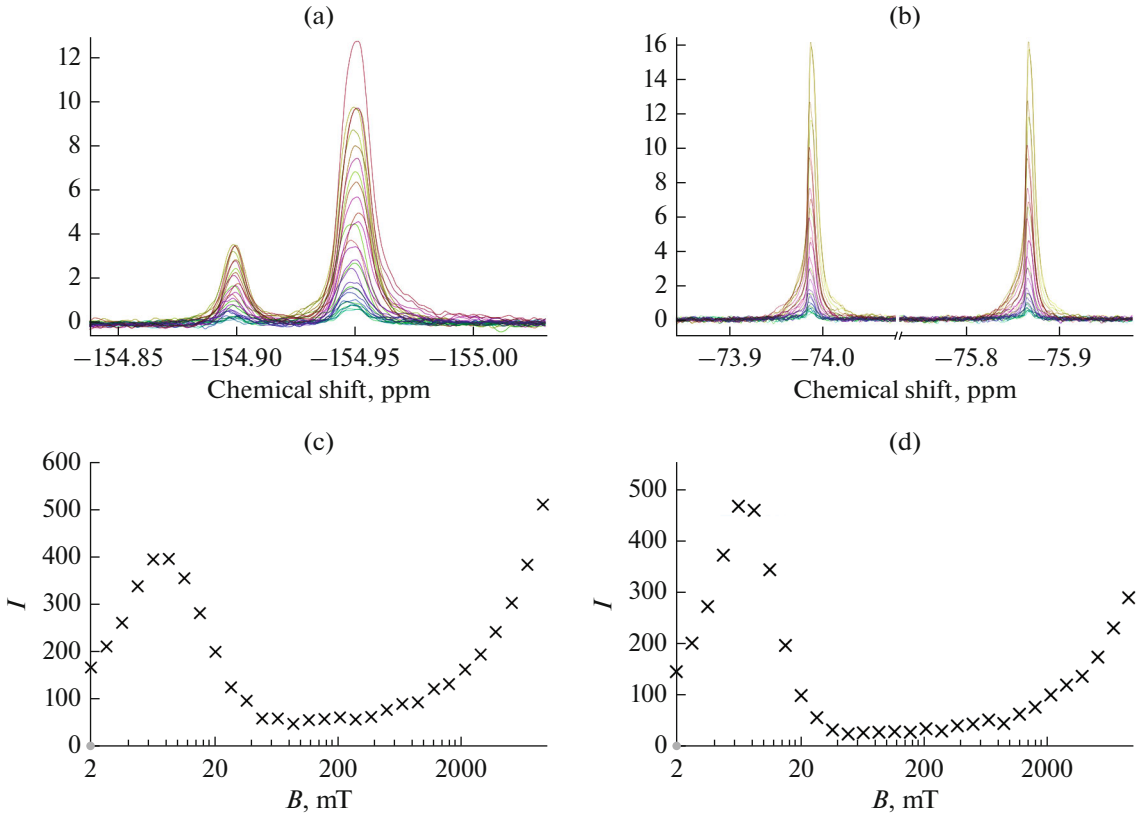


Fig. 2. ^{19}F NMR spectra of complexes **I** and **II** upon the polarization transfer to (a) tetrafluoroborate and (b) hexafluorophosphate anions for the SABRE reaction in the magnetic field from 2 mT to 9 T and the dependences of the ^{19}F NMR signals of (c) tetrafluoroborate and (d) hexafluorophosphate anions on the magnetic field strength.

To conclude, the spin polarization transfer from a parahydrogen molecule to organic molecules using the iridium-based catalysts under the SABRE conditions is a reliable method for enhancing sensitivity of NMR spectroscopy, including manufacturing hyperpolarized probes for functional MRT. Although the most part of the works is devoted to studying the polarization transfer to the nuclei of the exchanged ligand (e.g., pyridine), the presence of an unbound counterion, such as tetrafluoroborate and hexafluorophosphate anions, in the molecular complex can also result in the polarization transfer to its nuclei.

The present study of two iridium complexes [Ir(COD){acetone}(IPr)]BF_4 and [Ir(COD){acetone}(IMes)]PF_6 allowed us to demonstrate for the first time the spin order transfer from parahydrogen molecules to the ^{19}F nuclei of the weakly coordinated counterions under the SABRE conditions and to determine the optimum magnetic field strength providing a maximum increase in the intensity in the NMR spectra. The mechanism of the discovered effect remains insufficiently clear to date but has a presumably dipole–dipole nature. A logical further step of the investigation is the preparation of a SABRE catalyst in which the counterion, on the one hand, can coordinate to the metal ion to increase the degree of polarization and, on the other hand, is biologically compatible as, for example, pyruvate anion. These studies are presently being conducted in our research groups.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Atkinson, K.D., Cowley, M.J., Duckett, S.B., et al., *Inorg. Chem.*, 2009, vol. 48, p. 663.
2. Terreno, E., Castelli, D.D., Viale, A., and Aime, S., *Chem. Rev.*, 2010, vol. 110, p. 3019.
3. Bhattacharya, P., Ross, B.D., and Bünger, R., *Exp. Biol. Med.*, 2009, vol. 234, p. 1395.
4. Golman, K., in't Zandt, R., and Thaning, M., *Proc. Natl. Acad. Sci. U.S.A.*, 2006, vol. 103, p. 11270.
5. Ardenkjaer-Larsen, J., Boebinger, G., Comment, A., et al., *Angew. Chem., Int. Ed. Engl.*, 2015, vol. 54, p. 9162.
6. Larive, C.K. and Larsen, S.C., *Anal. Chem.*, 2017, vol. 89, p. 1391.
7. Natterer, J. and Bargon, J., *Prog. Nucl. Magn. Reson. Spectrosc.*, 1997, vol. 31, p. 293.
8. Hövener, J., Pravdivtsev, A.N., Kidd, B., et al., *Angew. Chem., Int. Ed. Engl.*, 2018, vol. 57, p. 11140.
9. Becker, J., Bermuth, J., Ebert, M., et al., *Nucl. Instrum. Methods Phys. Res. A*, 1998, vol. 402, p. 327.
10. Frossati, G., *Nucl. Instrum. Methods Phys. Res. A*, 1998, vol. 402, p. 479.
11. Bouchiat, M.A., Carver, T.R., and Varnum, C.M., *Phys. Rev. Lett.*, 1960, vol. 5, p. 373.
12. Ardenkjaer-Larsen, J.H., Fridlund, B., Gram, A., et al., *Proc. Natl. Acad. Sci. U.S.A.*, 2003, vol. 100, p. 10158.
13. Kaptein, R. and Oosterhoff, L.J., *Chem. Phys. Lett.*, 1969, vol. 4, p. 214.
14. Bowers, C.R. and Weitekamp, D.P., *Phys. Rev. Lett.*, 1986, vol. 57, p. 2645.
15. Bowers, C.R. and Weitekamp, D.P., *J. Am. Chem. Soc.*, 1987, vol. 109, p. 5541.
16. Kovtunov, K.V., Beck, I.E., Bukhtiyarov, V.I., and Koptyug, I.V., *Angew. Chem.*, 2008, vol. 120, p. 1514.
17. Adams, R.W., Aguilar, J.A., Atkinson, K.D., et al., *Science*, 2009, vol. 323, p. 1708.
18. Rayner, P.J. and Duckett, S.B., *Angew. Chem., Int. Ed. Engl.*, 2018, vol. 57, p. 6742.
19. Spiridonov, K.A., Kozinenko, V.P., Nikovsky, I.A., et al., *Mendeleev Commun.*, 2021, vol. 31, p. 475.
20. Shen, M.-H., Ren, X.-T., Pan, Y.-P., and Xu, H.-D., *Org. Chem. Front.*, 2018, vol. 5, p. 46.
21. Kownacki, I., Kubicki, M., Szubert, K., and Marciniec, B., *J. Organomet. Chem.*, 2008, vol. 693, p. 321.
22. Kelly, III R.A., Clavier, H., Giudice, S., et al., *Organometallics*, 2008, vol. 27, p. 202.
23. Hadjiali, S., Bergmann, M., Kiryutin, A., et al., *J. Chem. Phys.*, 2019, vol. 151, p. 244201.
24. Knecht, S., Kiryutin, A.S., Yurkovskaya, A.V., and Ivanov, K.L., *J. Magn. Reson.*, 2018, vol. 287, p. 10.
25. Knecht, S., Hadjiali, S., Barskiy, D.A., et al., *J. Phys. Chem.*, 2019, vol. 123, p. 16288.
26. Limbach, H.-H., Ulrich, S., Gründemann, S., et al., *J. Am. Chem. Soc.*, 1998, vol. 120, p. 7929.
27. Fekete, M., Bayfield, O., Duckett, S.B., et al., *Inorg. Chem.*, 2013, vol. 52, p. 13453.

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