Design Principles of Responsive Relaxometric $^{19}$F Contrast Agents: Evaluation from the Point of View of Relaxation Theory and Experimental Data

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ABSTRACT: $^{19}$F magnetic resonance imaging (MRI) is a promising tool in medical diagnostics. An important class of $^{19}$F MRI contrast agents is based on paramagnetic resonance enhancement. This effect allows an improvement in sensitivity by increasing the number of scans per unit of time or facilitates the development of responsive contrast agents that are based on changes in relaxation rates as a detection principle. In this work, Bloch–Redfield–Wangsness relaxation theory was used to predict the relaxation properties of existing lanthanoid and transition metal complexes of fluoroorganic ligands and to evaluate several design strategies for responsive contrast agents. Electron–nucleus dipole–dipole, Curie relaxation, and contact interactions were included in the model. Potential significance of chemical shift anisotropy–anisotropic dipolar shielding cross-correlation was discussed. The calculated and experimental results were well aligned. The presented model, along with the optimized field-dependent values of electronic relaxation times, could be used for the preliminary selection of the optimal metal ion for applications in $^{19}$F MRI. The results indicate potential advantages of other metal ions in addition to Gd$^{3+}$, particularly Cu$^{2+}$, Mn$^{2+}$, Ni$^{2+}$, Fe$^{3+}$, and other lanthanoids as a part of $^{19}$F contrast agents.

INTRODUCTION

The physical foundations of nuclear magnetic resonance (NMR) were established at the turn of the 1950s and 1960s. Since then, this technique has found widespread use in physics, chemistry, and biochemistry, especially for structural studies. In the 1970s, the use of MR as a safe, non-invasive imaging technique in medicine gained traction, and it is one of the leading techniques for the diagnosis of pathological changes in soft tissues. $^1$H magnetic resonance imaging (MRI) uses subtle differences in the relaxation of water protons in different tissues. To obtain more reliable results, allowing for unambiguous differentiation between normal organs and pathological changes, paramagnetic contrast agents are frequently used to affect the relaxation of protons present in their vicinity. Gd$^{3+}$, Mn$^{2+}$, and Fe$^{3+}$ are commonly used as paramagnetic ions, with gadolinium complexes being the largest group of commercial contrast agents. The potential accumulation of gadolinium ions in the body can lead, in some cases, to dangerous complications, such as nephrogenic fibrosing dermopathy.

Because fluorine is not present in soft tissues, $^{19}$F MRI is essentially a background-free technique since only fluorine atoms introduced with the contrast agent are visible. Typically, the $^{19}$F MR image is superimposed with the $^1$H anatomical images for precise localization of the injected fluorinated tracer.

An interesting class of contrast agents is responsive agents, sometimes referred to as "smart" agents, which are activated under the influence of a specific trigger in the environment. These triggers may be an enzyme, pH gradient, metal ions, or a change in the oxygen concentration. Due to many potential applications in medical diagnostics, the field of responsive contrast agents is a growing area of research. The detection principle generally relies on a chemical shift or changes in relaxation times due to paramagnetic relaxation enhancement (PRE) exerted by paramagnetic complexes. Relaxation rates can be affected by other stimuli such as self-assembly, disassembly, or conformational changes that...
lead to mobility changes manifested in $T_2$-weighted images. Such transformation may be irreversible or reversible. Because the $^{19}$F NMR signal is concentration-dependent, a means of calibration is required for practical applications. The PRE phenomenon is also important in the design of simple $^{19}$F contrast agents consisting of paramagnetic metal ion complexes with pendant fluoroorganic moieties. Similarly, the design of $^{19}$F contrast agents enables the tuning of relaxation times to maximize the number of scans per unit time and, consequently, improve the S/N ratio. There are several ions with constant magnetic moments which could be useful as PRE agents. These ions have one or several unpaired electrons.

Figure 1. Structures of ligands with available $^{19}$F relaxation data of corresponding paramagnetic metal ion complexes taken from the literature. Ligands L$^{11}$ and L$^{12}$ were obtained for the purpose of this work.
and are trivalent lanthanoids or transition metal ions such as Mn$^{2+}$, Cr$^{3+}$, Co$^{2+}$, Fe$^{2+}$, Fe$^{3+}$, Ni$^{2+}$, and Cu$^{2+}$. Metal-free paramagnetic labels such as nitroxide are another option.$^{24}$ Most of the $^{19}$F MRI contrast agents developed are predominantly Gd$^{3+}$ complexes with only several instances of Ni$^{2+}$, $^{25}$Co$^{2+}$, $^{26}$ and Fe$^{2+}$. $^{27}$ complexes used in standard contrast agents, while Eu$^{2+/3+}$, $^{19}$Mn$^{2+/3+}$, $^{28}$ and Co$^{2+/3+}$ $^{29}$ were proposed for smart contrast agents along with some investigations focused on other lanthanoids.$^{20,30}$ The research in this field is highly dependent on the experimental discovery of new agents, focusing on the structure of the ligand. Moreover, less attention is paid to the selection of a metal ion based on theoretical calculations for the prediction of relaxation properties. Because the design of new contrast agents must take into account a multitude of factors affecting the relaxation properties, such as the distance and relative position of $^{19}$F nuclei from the paramagnetic center,$^{31}$ temperature, strength of the magnetic field, and a wide range of possible paramagnetic ions, the use of a reliable theoretical approach is of great value.

Bloch–Redfield–Wangsness (BRW) $^{32}$ relaxation theory is well established and is extensively used for NMR structural studies in biochemistry and in other fields with great success.$^{33}$ Several authors used theoretical calculations to outline design principles of paramagnetic $^{19}$F contrast agents, especially with regard to the effect of the magnetic field on their properties.$^{20,27,34}$ for analysis of results in terms of contribution of different relaxation mechanisms$^{26}$ or to model experimental results.$^{32}$ BRW relaxation theory was also used in studies of paramagnetic proton NMR relaxation to model the field dependence.$^{35,36}$

In this work, we compared $^{19}$F experimental relaxation data with the predicted values based on BRW relaxation theory to evaluate the reliability of the theoretical calculation. Two series of isostructural complexes of two cyclen-derived ligands, L$^{11}$ and L$^{12}$, were obtained to complement the literature data. L$^{11}$ and L$^{12}$ differed in the number of groups that could participate in the coordination of the metal ion. Their structures are presented in Figure 1. Both ligands are of a similar structure to those most commonly found in the literature. However, they differ in terms of the distance between the fluorine nuclei and the paramagnetic center. In most cases described in the literature, the metal–fluorine (M–F) distances are in the range of 5–7.5 Å and greater than 9 Å. The M–F distances of the L$^{11}$ and L$^{12}$ complexes are 8–9 Å. The proposed structure of L$^{11}$ also allowed the assessment of the effect of chemical exchange on the observed relaxation times and the reliability of theoretical calculations under such conditions. In total, 217 and 143 instances of longitudinal and transverse $^{19}$F relaxation data, respectively, from the literature and experimental data were collected. The optimized electronic relaxation times and rotational correlation times allowed to further evaluate potential design strategies of various classes of contrast agents. The focus of this study was only on the relaxation rates. The changes in the chemical shift$^{19,20,27,34}$ were not investigated.

### EXPERIMENTAL SECTION

**Materials.** 1,4,7,10-Tetraazacyclododecane (95%) was supplied by ABCR GmbH (Karlsruhe, Germany). tert-Butyl bromoacetate (99%), 3-(trifluoromethyl)benzyl bromide (99%), and trifluoroacetic acid were supplied by Fluorochem (Glossop, UK). 3-(Trifluoromethyl)aniline (99%), neodymium(III) chloride (99.99%), erbium(III) nitrate pentahydrate (99.99%), and terbium(III) chloride hexahydrate (99.99%) were supplied by Sigma-Aldrich (Steinheim, Germany). Praseodymium(III) oxide (99.9%) was supplied by The British Drug Houses (Poole, UK). Manganese(II) chloride tetrahydrate (analytical grade), copper(II) sulfate pentahydrophilic and L$^{12}$, were obtained to complement the literature data. L$^{11}$ and L$^{12}$ differed in the number of groups that could participate in the coordination of the metal ion. Their structures are presented in Figure 1. Both ligands are of a similar structure to those most commonly found in the literature. However, they differ in terms of the distance between the fluorine nuclei and the paramagnetic center. In most cases described in the literature, the metal–fluorine (M–F) distances are in the range of 5–7.5 Å and greater than 9 Å. The M–F distances of the L$^{11}$ and L$^{12}$ complexes are 8–9 Å. The proposed structure of L$^{11}$ also allowed the assessment of the effect of chemical exchange on the observed relaxation times and the reliability of theoretical calculations under such conditions. In total, 217 and 143 instances of longitudinal and transverse $^{19}$F relaxation data, respectively, from the literature and experimental data were collected. The optimized electronic relaxation times and rotational correlation times allowed to further evaluate potential design strategies of various classes of contrast agents. The focus of this study was only on the relaxation rates. The changes in the chemical shift$^{19,20,27,34}$ were not investigated.
drate (reagent grade), nickel(II) chloride hexahydrate (reagent grade), cobalt(II) chloride hexahydrate (reagent grade), ammonium tetrafluoroborate (reagent grade), chromium(III) chloride hexahydrate, iron(II) chloride tetrahydrate (analytical grade), and potassium carbonate (analytical grade) were supplied by POCHE (Glówie, Poland). Cerium(III) nitrate hexahydrate (analytical grade) was supplied by ChemPur (Piekary Śląskie, Poland). DyCl₃, PdCl₂, and SmCl₃ were obtained from the respective oxides in a reaction with an aqueous 3 M HCl solution. Aqueous solutions were prepared using distilled water. 

Characterization Techniques. The products were characterized using ¹H and ¹³C NMR in CDCl₃, or dimethyl sulfoxide (DMSO), while ¹⁹F NMR spectra were recorded in an aqueous solution (10% D₂O). The spectra were referenced internally using residual protonated solvent resonances relative to tetramethylsilane (δ = 0 ppm), trifluoroacetic acid (¹¹F NMR, δ = −76.5 ppm), or ammonium tetrafluoroborate (δ = −151.5 ppm) as an internal standard. The T₁ and T₂ measurements were performed using inversion recovery and Carr–Purcell–Meiboom–Gill (CPMG) sequences, respectively. Samples of complexes for ¹⁹F NMR relaxation experiments were prepared by mixing 500 μL of aqueous solution (30 mmol dm⁻³) with 50 μL of 22 mmol dm⁻³ aqueous solution of ammonium tetrafluoroborate and 50 μL of D₂O. An Agilent 400 MR instrument was used for all NMR experiments. High-resolution mass spectrometry studies were performed using an Xevo G2 QToF instrument (Waters) equipped with an electrospray ionization (ESI) source.

DFT Calculations. All density functional theory (DFT) calculations were performed using Orca 4.2.1 software. Full geometry optimizations of the Gd⁺ complexes of all investigated ligands were performed in aqueous solution using the hybrid meta-generalized gradient approximation, with the TPSSh exchange correlation functional. In these calculations, an energy-consistent large-core quasirelativistic effective core potential and its associated [5s4p3d]-Gaussian type orbital valence basis set for lanthanoids were employed, whereas the ligand atoms were described using the standard 6-31G(d) basis set. Hyperfine coupling tensors (Asso) for all NMR-active ¹⁹F nuclei were also calculated in Orca 4.2.1. with a series of hybrid Perdew–Burke–Ernzerhof functionals with the Hartree–Fock exchange set at 30%. The input files and molecular plots were prepared using Avogadro software. Rotation correlation times were calculated using HYDRONMR on the previously optimized structures of Gd⁺ complexes for all investigated ligands. 

General Synthesis Method. The synthesis of the complexes was carried out according to Scheme 1.

4,7,10-Tri(tert-butoxycarbonylmethyl)-1,4,7,10-tetraazaacyclododecane, Hydrobromide Salt (1). 40 mL of anhydrous acetonitrile, 2.77 g (33 mmol) of sodium bicarbonate, and 1.72 g (10 mmol) of 4,7,10-tetraazaacyclododecane were mixed in a 100 mL round bottom flask in an ice bath under argon. Then, 4.81 mL (33 mmol) of tert-butyl bromoacetate was slowly added dropwise. The reaction was carried out for 48 h at room temperature and monitored by ultra-performance liquid chromatography (UPLC)-MS. After completion of the reaction, the mixture was filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash silica gel chromatography. The product was obtained (3.01 g, 45%). ESI-MS: m/z calculated for C₃H₃₆N₉O₇F₃⁺ [M + H]⁺, 673.4152; found, 673.4140.

2-Chloro-N-(3-trifluoromethylphenyl)-acetamide (2). 0.65 g, 4.03 mmol) and Et₂N (0.49 g, 4.84 mmol) in anhydrous CH₂Cl₂ (10 mL) were added to a 25 mL round bottom flask and placed in an ice bath under argon. Next, chloroacetyl chloride (0.55 g, 4.84 mmol) was added slowly to the solution. The reaction was stirred for 12 h and monitored by thin layer chromatography. After the substrates were completely consumed, the solution was washed with 1 M HCl (3 × 10 mL), followed by H₂O (3 × 10 mL). The organic phase was dried over MgSO₄, and the solvent was removed under reduced pressure. The crude product was purified using flash silica gel chromatography (CH₂Cl₂). The product was obtained as a pale-yellow solid (0.83 g, 87%). mp 73–74.5 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.38 (s, 2H), 7.85 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.47 (dd, J₁ = 17 Hz, J₂ = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H) 4.21 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 164.25, 137.35, 131.73, 129.86, 125.18, 123.31, 121.96 (q, J = 3.8 Hz, 2H), 117.01 (q, J = 3.9 Hz, 9H), 42.92.

2-Chloro-N-(3-trifluoromethylphenyl)-acetamide (3). 0.167 g, 0.91 mmol) was added to a stirred solution of 1,4,7,10-tris(tert-butoxycarbonylmethyl)-1,4,7,10-tetraazaacyclododecane (1) (0.30 g, 0.58 mmol), K₂CO₃ (0.80 g, 0.58 mmol) in anhydrous CH₂CN (20 mL) under argon. The mixture was left to boil under reflux for 15 h. The precipitate was removed by filtration, and the residue was washed with CH₂Cl₂ (2 × 15 mL). The solvent was removed under reduced pressure, and the resulting solid was purified by silica gel column chromatography (eluents: gradient, 100% CH₂Cl₂ to 5% CH₂OH/CH₂Cl₂ to give a pale-orange solid (5), which was used in the next step. ESI-MS: m/z calculated for C₃H₃₆N₉O₇F₃⁺ [M + Na]⁺, 738.4030; found, 738.4010.

2.5 mL of CH₂Cl₂ and 0.2 g (0.28 mmol) of 1,4,7-tris(tert-butoxycarbonylmethyl)-1,4,7,10-tetraazaacyclododecane (3) were added to a 10 mL round bottom flask. The solution was stirred for 5 min. Next, 2.5 mL of concentrated trifluoroacetic acid was added dropwise. The reaction was carried out for 24 h and was monitored by UPLC-MS. After reaction completion, the solvent was evaporated under reduced pressure. The residue was dissolved in a minimal amount of methanol temperature and monitored by UPLC-MS. After completion of the reaction, the mixture was filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash silica gel chromatography (eluents: gradient, 100% CH₂Cl₂ to 5% CH₂OH/CH₂Cl₂ to give a pale-orange solid (5), which was used in the next step. ESI-MS: m/z calculated for C₃H₃₆N₉O₇F₃⁺ [M + Na]⁺, 738.4030; found, 738.4010.

2.5 mL of CH₂Cl₂ and 0.2 g (0.28 mmol) of 1,4,7-tris(tert-butoxycarbonylmethyl)-1,4,7,10-tetraazaacyclododecane (3) were added to a 10 mL round bottom flask. The solution was stirred for 5 min. Next, 2.5 mL of concentrated trifluoroacetic acid was added dropwise. The reaction was carried out for 24 h and was monitored by UPLC-MS. After reaction completion, the solvent was evaporated under reduced pressure. The residue was dissolved in a minimal amount of methanol
and precipitated with ethyl ether. The orange precipitate was dissolved in H₂O. The solution was centrifuged, and the supernatant was lyophilized to yield a pale-yellow solid (0.13 g, 65%). ESI-MS: m/z calculated for C₆H₁₃NO₃⁻ [M + H]⁺, 548.2332; found, 548.2331. ¹H NMR (400 MHz, DMSO-d₅): δ 12.81 (br s, 3H), 8.29 (s, 1H), 8.1–7.3 (br m, 4H), 4.52 (s, 2H) 4.1–3.0 (br m, 22H). ¹³F NMR (376 MHz, DMSO-d₅): δ −64.08 (s, CF₃).

**Synthesis of L¹⁴ and L¹² Complexes.** ⁰² g of L¹¹ or L¹² was dissolved in 10 mL of water/methanol 1:1 solution. A 0.1 M NaOH solution was then added until the pH was ~7. Then, 2 mol % aqueous solution of a metal salt chloride (Nd³⁺, Tb³⁺, Sm³⁺, Dy³⁺, Eu³⁺, Gd³⁺, Ho³⁺, Er³⁺, Tm³⁺, Yb³⁺, Y³⁺), nitrate (Er³⁺, Ce³⁺, and Y³⁺), trifluoromethanesulfonate (Yb³⁺), or sulfate (Cu²⁺) was added to the solution. The reaction was carried out for 24 h at 60 °C, and the pH was adjusted to ~7 if needed. The progress was monitored by the UPLC-MS method. After the completion of the reaction, the pH was adjusted to ~10 with excess NaOH. The precipitated hydroxide was then separated by centrifugation, and the pure complex was obtained by lyophilization.

**Relaxation Data of ¹⁹F NMR.** Relaxation data were also taken from the literature and ML complexes, especially when isostructural series or multiple field data were available. Relaxation data were also taken from the literature data. The Curie-Weiss relaxation is typically treated as isotropic, but lanthanoid-induced nuclear relaxation is anisotropic. The relaxation theory is briefly discussed in this section.

### RESULTS AND DISCUSSION

**Relaxation Theory.** According to BRW theory, ⁰¹⁹F nuclei in the presence of paramagnetic species in non-viscous solutions occurs mainly due to five distinct mechanisms. The most important mechanisms are the electron–nucleus dipole–dipole (DD) interaction and Curie (Cur) relaxation given by

\[
R_{\text{DD}}^{\text{Cur}} = \frac{2}{15} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{\alpha_2^2 R_e^2}{d^6} \left( 1 + \omega_e^2 R_e + \frac{3\tau_R + \omega_e^2 R_e}{1 + \omega_e^2 R_e} \right)
\]

\[
R_{\text{DD}}^{\text{Cur}} = \frac{2}{15} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{\alpha_2^2 R_e^2}{d^6} \left( 1 + \omega_e^2 R_e + \frac{3\tau_R + \omega_e^2 R_e}{1 + \omega_e^2 R_e} \right)
\]

The Curie relaxation is typically treated as isotropic, but lanthanoid-induced nuclear relaxation is anisotropic. The

#### Table 1. Physical Constants Used for Relaxation Data Analysis

| Parameter | Value | Unit |
|-----------|-------|------|
| µ₀ | 1.25663706212 × 10⁻⁶ | [H m⁻¹] |
| γᵣ | 251.8148 | [rad s⁻¹ T⁻¹] |
| h | 1.054571813131 | [J s] |
| k₀ | 1.38065 × 10⁻²³ | [J K⁻¹] |
| T | 300 | [K] |
| ζᵣ | 2.00232 | electron g-factor |
| µᵣ | 9.2740 009 994 × 10⁻²⁴ | [T⁻¹] |

#### Table 2. Literature Data Concerning ¹⁹F Relaxation and the Properties of Paramagnetic Ions

| Metal ion | µᵣ/µ₀ | S | T₁ₑ | Data source |
|-----------|-------|---|-----|-------------|
| Ce⁺ | 2.55 | 5/2 | 1 × 10⁻¹³ | 7–11.7 | 25, 51 |
| Gd³⁺ | 4.7 | 3/2 | 10⁻¹⁹ to 10⁻¹⁵ (HS) | 1.4–9.4 | 46 |
| Cr³⁺ | 3.8 | 3/2 | 5 × 10⁻⁹ to 1 × 10⁻¹⁰ | 9.4 | a |
| Cu²⁺ | 1.9 | 1/2 | (1–5) × 10⁻⁹ | 9.4–11.7 | 25 |
| Dy³⁺ | 10.3 | 15/2 | 10⁻¹⁰ to 10⁻⁸ | 4.7–16.5 | 19, 20, 25, 27, 30, 47, 51 |
| Eu³⁺ | 9.4 | 15/2 | 10⁻¹⁰ | 4.7–16.5 | 20, 25, 27, 30, 48 |
| Fe³⁺ | 3.5 | 7/2 | 10⁻¹⁰ | 5.7–11.7 | 25, 27, 49, 53 |
| Fe⁵⁺ | 5.4 | 2 | 10⁻¹⁰ to 10⁻¹⁵ (HS) | 1.4–9.4 | 27, 46 |
| Gd⁵⁺ | 7 | 5/2 | 10⁻¹⁰ to 10⁻¹⁵ (LS) | 9.4–11.7 | 25 |
| Ho³⁺ | 7.63 | 7/2 | 10⁻¹⁰ | 5.9–11.7 | 25, 27, 49, 53 |
| Mn²⁺ | 10.4 | 8 | 10⁻¹⁰ | 4.7–16.5 | 19, 20, 25, 27, 30, 48, 50, 51 |
| Nd³⁺ | 5.8 | 5/2 | 10⁻¹⁰ | 9.4 | a |
| Ni²⁺ | 3.69 | 9/2 | 10⁻¹⁰ to 10⁻⁸ | 9.4–11.7 | 25 |
| Pm⁵⁺ | 3.5 | 1 | 10⁻¹⁰ to 10⁻¹² | 9.4–11.7 | 25, 45, 46, 56 |
| Sm²⁺ | 3.47 | 4 | 10⁻¹⁰ to 10⁻¹⁵ | 9.4–11.7 | 25 |
| Tb⁵⁺ | 1.58 | 5/2 | 10⁻¹⁰ to 10⁻⁸ | 4.7–11.7 | 19, 20, 25, 27, 30, 47, 49, 53 |
| Tm³⁺ | 9.8 | 6 | 10⁻¹⁰ | 4.7–16.5 | 19, 20, 27, 30, 48, 49, 51 |
| Yb³⁺ | 7.6 | 6 | 10⁻¹⁰ to 10⁻¹⁵ | 4.7–11.7 | 19, 25, 27, 51 |

“ML¹¹ and ML¹² data obtained based on our study (Table S2). µᵣ—effective magnetic moment, S—spin–spin coupling, T₁ₑ—electronic relaxation time, LS—low spin, and HS—high spin.”
effect is more significant for $^{13}$C and $^{15}$N compared to that for $^1$H or $^{19}$F, and these contrast agents strongly affect the relaxation rates of nuclei less than 4 Å away from the paramagnetic ion.60–62 Because the M–F distance in all of the investigated ligands was greater than 5 Å, the anisotropy was not factored into the calculations. Potentially, the significance of anisotropy can be identified if the distance calculated from relaxation data substantially deviates from the DFT or X-ray distances. However, in PRE measurements, these deviations are not typically observed.62,63

The third mechanism of $^{19}$F nucleus relaxation is based on contact interactions (Con) which may be significant in the case of transverse ($T_2$) relaxation of fluoroorganic complexes of d-elements. Con is given by

$$R_{1\text{Con}} = \frac{S(S + 1)\alpha_{\text{HFC}}^2}{3} \cdot \frac{2T_{ie}}{1 + \alpha_i^2 T_{ie}}$$

$$R_{2\text{Con}} = \frac{S(S + 1)\alpha_{\text{HFC}}^2}{3} \cdot \left( T_{ie} + \frac{T_{ie}}{1 + \alpha_i^2 T_{ie}} \right)$$

In the specific case of $^{19}$F relaxation in the lanthanoid complexes, $R_{1\text{f}}$ and $R_{2\text{Con}}$ contributions may safely be ignored.30 Fermi contact hyperfine coupling constants ($\alpha_{\text{HFC}}$) can be obtained from quantum chemistry calculations if a structure of a complex is known.27 It is worth noting that $\alpha_{\text{HFC}}$ in rad$^{-1}$ is used in eqs 5 and 6. In the case of d-metals, this mechanism usually contributes 1–2 Hz in relaxation rates and is often ignored. The significance of Con relaxation can be easily identified if predicted $R_2$ is strongly underestimated compared to accurately predicted $R_1$. This is because of the greater impact of the contact mechanism on $R_{2\text{Con}}$ than on $R_{1\text{Con}}$ (eq 7, Table 3).

$$\frac{R_{2\text{Con}}}{R_{1\text{Con}}} = \frac{2 + \alpha_i^2 T_{ie}^2}{2}$$

### Table 3. Ratio of Transverse and Longitudinal Contact Relaxation Rates (Eq 7) in the d-Metal Complexes Assuming Non-Zero $\alpha_{\text{HFC}}$

| metal ion | $\frac{R_{2\text{Con}}}{R_{1\text{Con}}}$ (1 T) | $\frac{R_{2\text{Con}}}{R_{1\text{Con}}}$ (9.4 T) |
|-----------|----------------------------------|----------------------------------|
| Cr$^{3+}$ | $2.5 \times 10^3$ | $2.2 \times 10^3$ |
| Mn$^{2+}$ | $1.8 \times 10^4$ | $4.2 \times 10^3$ |
| Fe$^{3+}$ | 27 | $2.3 \times 10^3$ |
| Fe$^{2+}$ | 1.3 | 106 |
| Co$^{2+}$ | 1.8 | 68 |
| Ni$^{2+}$ | 1.3 | $6.0 \times 10^3$ |
| Cu$^{2+}$ | $3.9 \times 10^3$ | $3.4 \times 10^3$ |

*aElectronic relaxation times were taken from Table 4.*

The remaining two mechanisms, chemical shift anisotropy and internuclear dipole–dipole interaction, are minor contributors to BRW theory and can be ignored in most $^{19}$F PRE applications.20 Special attention should be paid to cross-correlation effects that are ignored by BRW theory. These cross-correlation effects occur due to the simultaneous presence of multiple relaxation mechanisms such as dipolar, Curie spin, and chemical shift anisotropy relaxations. The importance of cross-correlation effects can be estimated from various two-dimensional NMR experiments64 or observed in relaxation rate measurements in solution structure refinement of proteins.65 The greatest cross-correlation effects can be expected when the Curie spin relaxation mechanism plays a dominant role. This is the case of paramagnetic ions with rapidly relaxing electronic spins (i.e., Dy$^{3+}$ and Yb$^{3+}$).66 Transverse relaxation times are affected more than the longitudinal relaxation times by cross-correlation effects and are both distance- and angular-dependent. Overall, experimental $R_1$ can differ from predicted values depending on the relative position of the paramagnetic center and particular nucleus.65

The chemical shift anisotropy—anisotropic dipolar shielding cross-correlation (CSA × DSA) is the most important one, especially when rotational correlation times are greater than 1–5 ns. In the case of low-molecular weight complexes of $r_t$ $\approx$ 0.25 ns, relaxation rates $R_1$ and $R_2$ arising from CSA × DSA were estimated for a series of putative lanthanoid complexes using eqs S2–S5 assuming an anisotropy of the chemical shift tensor $\Delta e^{eff}$ of 100 ppm.66 The CSA × DSA cross-correlation effect is negligible at 1–3 T, but its importance increases with the magnetic field. The results at 9.4 T (Tables S3 and S4) indicate that depending on the angle between the principal axes of chemical shift anisotropy and dipolar shielding anisotropy tensors ($\theta_{\text{CSA,DSA}}$), the cross-correlation effect can be responsible for the increase or the decrease in longitudinal and transverse relaxation rates by up to 7 Hz for ions having a small effective magnetic moment (Ce$^{3+}$, Pr$^{3+}$, Nd$^{3+}$, Sm$^{3+}$, and Eu$^{3+}$). In the case of ions exerting strong PRE (Tb$^{3+}$, Dy$^{3+}$, Ho$^{3+}$, Er$^{3+}$, and Tm$^{3+}$), the effect is higher and can reach 40 and 60 Hz for longitudinal and transverse relaxation rates, respectively. Comparing with the contribution of contact and Curie spin relaxation (Table S5), this means that the CSA × DSA cross-correlation effect can dominate at large distances (10 Å) between the paramagnetic ion and fluorine nuclei regardless of the metal ion. At short, typically observed, distances (6 Å), the effect can contribute at most 10% in the case of Tb$^{3+}$, Dy$^{3+}$, Ho$^{3+}$, Er$^{3+}$, and Tm$^{3+}$. Such high contributions are possible only for $\theta_{\text{CSA,DSA}}$ close to 0 or 90° with zero contribution at 54.7°. For this reason, the cross-correlation effects were not considered in this work. Additionally, relaxation data of a single $^{19}$F resonance do not allow deconvolution of potential cross-correlation effects from the dipolar and Curie spin relaxation rate enhancements if the distance, correlation time, and $\theta_{\text{CSA,DSA}}$ must be found by data fitting.

The relaxation rates resulting from various relaxation mechanisms are additive

$$R_{1\text{f}} = R_{1\text{DD}} + R_{1\text{Cur}} + R_{1\text{Con}}$$

$$R_{2\text{f}} = R_{2\text{DD}} + R_{2\text{Cur}} + R_{2\text{Con}}$$

The remaining variables are given by:

$$\alpha_k = \frac{e_k \mu_B}{h} B_0$$

$$\omega_F = \gamma_F B_0$$

$$R_i = R_{i\text{f}} + R_{i\text{diamagnetic}}$$

$$\tau_{R^{-1}} = \tau_{R^{-1}} + T_{ie}^{-1}$$
\[ \mu_{\text{eff}} = \sqrt{4S(S + 1)} \]  
\[ T_1 = \frac{1}{s_0} \left( \frac{1}{1 + \omega^2 \tau_e^2} + \frac{4}{1 + 4 \omega^2 \tau_e^2} \right) \]

where \( T \) is the temperature, \( \omega_e \) and \( \omega_L \) are the electron and nuclear Larmor angular frequencies, respectively, and the physical constants have their usual meaning. \( R_i \) _diamagnetic_ (eq 12) are the relaxation rates observed for complexes containing nonparamagnetic metals such as La \(^{3+}\) or Y \(^{3+}\). These rates can be directly measured or extrapolated from relaxation rates in a series of isomeric complexes of different paramagnetic ions, and they are typically 1 and 2 Hz or greater for \( R_1 \) and \( R_2 \), respectively. When the effect of PRE is significantly large (\( R_2 > 50 \text{ Hz} \)), then the diamagnetic contribution can be ignored.

Equation 13 defines correlation time (\( \tau_{\text{corr}} \)) and is valid in solution in the absence of chemical exchange. Note that this equation was frequently missprinted in the literature without the multiplicative inverse of the left side.

The effective magnetic moment (\( \mu_{\text{eff}} \)) can be calculated based on eq 14. However, such approximation is not generally valid because strong ligand field effects exist.\(^{25,33,34,61}\) Effective magnetic moments are usually determined experimentally using the Evans method\(^{60}\) or SQUID magnetometry\(^{70}\) for a given compound. Most authors use tabularized data (Table 2) obtained from the measurements of various macrocyclic complexes of paramagnetic ions. The same approach was used here. In this way, the ligand effects were at least partially included in magnetic moment calculations. The use of tabularized data is also justified due to great structural similarities between investigated fluoroorganic ligands. The remaining parameters that are necessary to predict relaxation rates are the following: electronic relaxation time (\( T_{1e} \)), rotational correlation time (\( \tau_R \)), and metal–nucleus distances (\( d \)). These parameters are usually obtained during independent experiments or derived from relaxation data.

**Fitting of the Experimental Relaxation Data to BRW Theoretical Equations.** An iterative fitting procedure of the experimental relaxation data was performed using BRW theoretical eqs 1–4. \( T_{1e} \), \( \tau_0 \), and \( d \) were allowed to change. An agreement between experimental and predicted log \( R_1 \) and log \( R_2 \) with equal weighting was sought (eq S1). The boundaries of \( T_{1e} \) were 0.1–9 times the literature values. \( \tau_0 \) values ranged from 0.1 to 0.9 ns, and \( d \) was \( \pm 1 \text{ Å} \) of the expected M–F distance (calculated using DFT for Gd \(^{3+}\) complexes or taken from X-ray data). In the case of ligands where the data did not produce well defined minima during the fitting procedure, \( \tau_0 \) was fixed at 0.25 ns, or the exact distance was taken from X-ray data when available. This occurred in the absence of field-dependent data when only a single metal complex was investigated with a particular ligand. In the second step, resulting \( T_{1e} \) was fitted to eq 15. In this equation, the correlation time (\( \tau_e \)) indicated the field dependency, whereas \( \tau_0 \) was the correlation time under the zero field.\(^{71}\)

\[ \frac{1}{T_{1e}} = \frac{1}{5s_0} \left[ \frac{1}{1 + \alpha_e^2 \tau_e^2} + \frac{4}{1 + 4\alpha_e^2 \tau_e^2} \right] \]

The field dependence of \( T_{1e} \) was determined for Dy \(^{3+}\), Er \(^{3+}\), Tm \(^{3+}\), Tb \(^{3+}\), Ho \(^{3+}\), Ce \(^{3+}\), Ni \(^{3+}\), Co \(^{3+}\), and Fe \(^{3+}\). For other metals, single \( T_{1e} \) was obtained as an estimate within 4.7–11.7 T (Table 4). In the next iteration, only \( \tau_R \) and \( d \) were optimized again. Finally, \( d \) was allowed to vary by \( \pm 0.5 \text{ Å} \) from the average distance for each individual complex. For selected complexes displaying significantly greater observed \( R_2 \) compared to the calculated value, contact interaction (\( a_{\text{HPC}} \)) was determined by data fitting (Table S6). There was no systematic deviation between the observed and predicted data for any metal ion or ligand. However, the \( R_2 \) data were predicted with lower precision overall.

**Electronic Relaxation times.** It is necessary to emphasize that transverse and longitudinal relaxation times are field- and ligand-dependent.\(^{72–74}\) Ligand dependence was ignored, and only the average values of \( T_{1e} \) suitable for predicting the properties of typical fluoroorganic complexes were calculated. The theoretical expressions (eqs 1–6) given above are more complicated if \( T_{1e} \neq T_{2e} \). However, the existence of a single (average) electronic relaxation time was assumed. In the literature, only approximate values of \( T_{1e} \) are often presented for a given metal ion. Otherwise, \( T_{1e} \) values are calculated based on BRW equations for each case to achieve the best fit between observed and predicted relaxation rates. The most precise values can be determined from nuclear magnetic relaxation dispersion data\(^{72}\) or from relaxation studies using several instruments encompassing a wide range of magnetic fields. For most of the collected literature regarding \( ^{19}\text{F} \) relaxation data, the effect of the magnetic field on \( T_{1e} \) could be ignored. However, in the case of Ni \(^{2+}\) complexes,\(^{52}\) no reasonable agreement between the predicted and experimental values could be achieved without taking into account the field dependency of \( T_{1e} \). Based on the \( \tau_0 \) and \( \tau_e \) values (Table 4), the electronic relaxation time (\( T_{1e} \)) can be calculated for any field strength. On average, resultant \( T_{1e} \) at 1 and 16.5 T is about 20 and 250% of the value at 9.4 T, respectively.

**Rotation Correlation Times.** \( \tau_R \) is associated with the rotation of a molecule and is dependent on the size, shape, and molecular dynamics. \( \tau_R \) is often estimated using the Stokes–Einstein–Debye equation,\(^{75}\) and one may add an appropriate shape correction factor\(^{76}\) for non-spherical molecules. More sophisticated hydrodynamic calculations based on the bead model (implemented in the HYDROMR program) have

| metal | \( \tau_0 \) [ps]\(^a\) | \( \tau_e \) [ps]\(^a\) | \( T_{1e} \) (9.4 T) [s] |
|-------|------------------|------------------|------------------|
| Cr\(^{3+}\) | 395 ± 50 | 4 × 10\(^{-10}\) |  |
| Mn\(^{2+}\) | 55000 ± 5000 | 5.5 × 10\(^{-4}\) |  |
| Fe\(^{3+}\) | 39 ± 1 | 3.9 × 10\(^{-11}\) |  |
| Fe\(^{2+}\) | 1.9 ± 0.06 | 1.0 ± 0.03 | 1.6 × 10\(^{-11}\) |
| Co\(^{2+}\) | 0.9 ± 0.03 | 0.5 ± 0.03 | 2.5 × 10\(^{-12}\) |
| Ni\(^{3+}\) | 1.7 ± 0.06 | 3.8 ± 0.08 | 1.7 × 10\(^{-10}\) |
| Cu\(^{2+}\) | 5000 ± 100 | 5 × 10\(^{-9}\) |  |
| Ca\(^{3+}\) | 0.1 ± 0.03 | 0.7 ± 0.2 | 5.4 × 10\(^{-13}\) |
| Pr\(^{3+}\) | 0.1 ± 0.01 | 9.9 × 10\(^{-14}\) |  |
| Nd\(^{3+}\) | 0.3 ± 0.01 | 2.8 × 10\(^{-13}\) |  |
| Sm\(^{3+}\) | 0.09 ± 0.01 | 9 × 10\(^{-14}\) |  |
| Eu\(^{3+}\) | 0.1 ± 0.01 | 1 × 10\(^{-14}\) |  |
| Gd\(^{3+}\) | 10000 ± 5000 | 1 × 10\(^{-8}\) |  |
| Tb\(^{3+}\) | 1.4 ± 0.03 | 0.5 ± 0.05 | 4.3 × 10\(^{-12}\) |
| Dy\(^{3+}\) | 1.2 ± 0.06 | 0.7 ± 0.03 | 5.6 × 10\(^{-12}\) |
| Ho\(^{3+}\) | 0.2 ± 0.01 | 1.4 ± 0.04 | 2.9 × 10\(^{-12}\) |
| Er\(^{3+}\) | 0.2 ± 0.04 | 1.4 ± 0.07 | 3.5 × 10\(^{-12}\) |
| Tm\(^{3+}\) | 0.5 ± 0.05 | 0.9 ± 0.06 | 3.5 × 10\(^{-12}\) |
| Yb\(^{3+}\) | 0.3 ± 0.01 | 2.6 × 10\(^{-12}\) |  |

\(^a\) Missing \( \tau_e \) values indicate the lack of data for the calculation of field dependency of electronic relaxation time. \(^b\) Uncertainties correspond to the maximal change of the loss function of 1% resulting from changes in \( \tau_0 \) or \( \tau_e \).
become popular recently.\textsuperscript{39} Another approach for calculating $\tau_R$ relies on field-dependent relaxation data that enable experimental determination of $\tau_R$ for a given compound by fitting the data to BRW theoretical equations.\textsuperscript{20} This approach was used here. In the absence of such data, $R_1$ and $R_2$ results measured in a single magnetic field, especially from a series of isostructural complexes, still enable sufficient estimates of $\tau_R$. If only the $R_1$ data are available, the fitting procedure is not reliable without knowledge of $T_1e$ and $d$. This is illustrated in Figure 2. Typically, there are two values of $\tau_R$ with the same predicted longitudinal relaxation rate, but $R_2$ data show a monotonous increase in $R_2$, whereas the increase in $R_2$ is in the 0.1–1 ns range. The pattern is strongly field-dependent.

Unfortunately, $\tau_R$ obtained from HYDRONMR is always greater than values calculated using the Stokes–Einstein–Debye equation, and even lower values are obtained by fitting the $^{19}$F relaxation data for the same molecule (Table S1). One can determine $\tau_R$ from $^1$H NMR relaxation dispersion (NMRD) data, but this procedure is known to underestimate its value.\textsuperscript{20} For low-molecular weight dodecane tetraacetic acid (DOTA) Gd complexes, correlation times near 0.1 ns are typically reported from $^1$H NMRD data.\textsuperscript{77} Other heteronuclear NMR measurements can also be used, but the resulting values would likely be different due to differences in mobility between functional groups. For example, from the field variable $^{31}$P relaxation data of complexes of a comparable structure, $\approx 0.3$ ns correlation times were identified,\textsuperscript{32} whereas rather high values (1–2 ns) were determined for a Gd$^{3+}$ complex with a molecular weight of 454 g mol$^{-1}$ from $^{13}$C relaxation data.\textsuperscript{78}

When analyzing the results of $^{19}$F relaxation data fitting to the theoretical equations for DOTA-type paramagnetic complexes, the average value of the rotational correlation time was 0.25 ns regardless of the type of $-\text{CF}_3$ group (aromatic or aliphatic) or the size of the complex (Table S1). This rotational correlation time value could be used for prediction of relaxation rates for all investigated complexes leading to sufficient agreement between the predicted and experimental data. However, an exception was the macro-molecular Ho$^{3+}$ [L$^3$-chitosan] complexes\textsuperscript{50} which exhibited a longer correlation time (3.8 ns). Interestingly, in the case of similar Dy$^{3+}$ complexes of [L$^3$-chitosan], the calculated correlation time was 0.2 ns (Table S1).

**Metal–Nucleus Distances.** The metal–nucleus distance ($d$) is the most important factor that affects the relaxation properties. This distance can be determined from the quantum chemistry calculations, but such data should be treated with caution because of the potential existence of a conformer that is different, more stable than the one identified by DFT calculations. X-ray data lack this shortcoming, but in both cases, the observed M–F distances of different fluorine atoms of a CF$_3$ group must be averaged. The correct approach is to average the calculated d$^{-6}$ values. Otherwise, the distance can be overestimated because fluorines closer to the paramagnetic center have a greater impact on the observed relaxation rates. This is especially evident for the complex developed by Yu et al.\textsuperscript{36} where the average metal–nucleus distance calculated from the DFT-optimized structure for the Gd$^{3+}$ complex was 8.4 Å, whereas the average of (d$^{-6}$)$^{-1/6}$ was 7.8 Å. For comparison, the distance calculated from BRW equations was 7.3 Å ([L$^3$]—Table S1). In most investigated cases, the difference was less than 0.5 Å. The average distances can also be determined from relaxation data in a series of isostructural complexes, but the M–F distances vary considerably between metals. For example, in a complex [L$^{2b}$],\textsuperscript{36} the DFT distances were between 6.1 Å (Gd$^{3+}$) and 6.7 Å (Fe$^{3+}$) (6.3–6.4 Å on average for other metals). The distances obtained using DFT (using Gd$^{3+}$ as the model) were within 1 Å of those calculated by fitting relaxation data to theoretical equations (Figure S6).

![Figure 2](https://doi.org/10.1021/acs.inorgchem.2c03451)
During the fitting procedure, the assumption of a constant distance in a series of complexes was initially assumed, leading to sufficient agreement between the predicted and experimental data. When the assumption was dropped and the distances were allowed to vary by ±0.5 Å from the mean value, the accuracy further improved (Figure 3A).

**Fermi Contact Hyperfine Coupling Constants \( a_{\text{IFC}} \).** Among the published \(^{19}\text{F}\) relaxation data, the contact mechanism was explicitly identified for some \( \text{Co}^{2+} \) complexes.\(^{26}\) Examining all available data with respect to the differences between predicted and experimental relaxation rates indicated that the contact mechanism was potentially significant in the case of several complexes of \( \text{Cu}^{2+} \) (L\(^{12}\) and FC-Cu\(^{2+}\)), \(^{25}\text{Fe}^{3+}\) (FC–Fe\(^{3+}\))\(^{25}\), \( \text{Co}^{2+} \) (L\(^{11}\)), and \( \text{Mn}^{2+} \) (L\(^{12}\)). The resulting \( a_{\text{IFC}} \) values from the fitting procedure were only partially confirmed by DFT calculations (Table S6), but in most cases, DFT yielded \( a_{\text{IFC}} \approx 0 \). These results could be a consequence of higher uncertainties of \( R_2 \) data or a contribution of other mechanisms of relaxation such as chemical exchange line broadening\(^{29}\), which was significant in the case of L\(^{11}\) complexes.

The practical significance of the contact mechanism in the design of contrast agents is illustrated in Table 3 which was based on eq 7 and the optimized electronic relaxation times (Table 4). In the case where field-dependent data were missing, \( T_{1e} \) at 1 T was assumed to be \( \approx 20\% \) of the value at 9.4 T. Because the transverse contact relaxation rate can be several orders of magnitude greater than the longitudinal relaxation rate, this mechanism should be especially considered for \( \text{Mn}^{2+} \), \( \text{Cr}^{3+} \), and \( \text{Cu}^{2+} \) and to a lesser extent for \( \text{Ni}^{2+} \), \( \text{Fe}^{3+} \), \( \text{Fe}^{3+} \), and \( \text{Co}^{2+} \). The field dependence of the contact mechanism is also evident, which should be considered during the development of new contrast agents. Overall, the contribution of the contact mechanism is comparable to the diamagnetic contribution in \( R_2 \) rates, but the contact mechanism is not significant in the case of \( R_1 \) rates. In most of the investigated cases, the dipolar and Curie mechanisms dominate and are responsible for at least 90% of PRE. However, a greater contribution of the contact mechanism in \( R_2 \) relaxation was found in the case of \( \text{Cu}^{2+} \), \( \text{Ni}^{2+} \), and \( \text{Mn}^{2+} \) complexes (Figure S5).

**Agreement between Predicted and Observed Results.** The reliability of the theoretical calculations for \( R_2 \) and \( R_1 \) is presented in Figure 3. The calculated data were generally consistent with experimental values regardless of the metal or ligand type. The deviations of \( R_1 \) were typically ±25% (Figure S3A) with several instances where the deviations reached ±125 or −40%. In the case of \( R_2 \), the consistency was lower. However, in most cases, the \( R_2 \) values were within the ±50% range.

It is worth noting that many of the investigated complexes displayed relaxation rates similar to their respective diamagnetic references. Additionally, even small absolute differences between the calculated and observed rates resulted in large relative deviations. The highest discrepancies of \( R_2 \) occurred in the cases of \( \text{Gd}^{3+} \), \( \text{Fe}^{3+} \), and \( \text{Mn}^{2+} \). In the case of \( \text{R}_{2} \), \( \text{Pr}^{3+} \) and \( \text{Nd}^{3+} \) had the highest discrepancies. In the case of \( \text{Gd}^{3+} \), these discrepancies were due to a very strong PRE effect and frequent difficulties in measuring very short relaxation times (<1 ms). Therefore, even a small underestimation or overestimation of relaxation times translates into significant differences between calculations and observed values. The case of iron is more complex due to the two possible oxidation and spin states with different properties that might coexist in the sample. An analogous situation can occur in europium complexes. The contamination with ferrimagnetic \( \text{FeO}_{\text{Fe}} \text{O}_{\text{3}} \) may form during complexation under basic conditions, is another possibility that contributes to measurement uncertainty and higher experimental relaxation rates. Another potential factor is the high contribution of other relaxation mechanisms, especially the chemical exchange line broadening\(^{79}\). This is in agreement with the short relaxation times observed by Jiang et al. in complexes of several diamagnetic ions (\( \text{Bi}^{3+} \), \( \text{Pb}^{2+} \), and \( \text{Hg}^{2+} \))\(^{25}\). This is particularly visible in the case of our data for the DO3A-based ligand L\(^{11}\). In this case, the diamagnetic reference showed the highest observed \( R_2 \) value (19 Hz, Table S2) indicating strong line broadening due to the free coordination site of the metal. The reliability of the calculations was also much lower compared to that of the corresponding complexes of the L\(^{12}\) ligand (Figure S4). Another potential factor is the contribution of chemical shift anisotropy—anisotropic dipolar shielding cross-correlation that may lead to either over- or underestimation of the calculated relaxation rates. Quantification of this effect would require the estimation of at least one additional variable (\( \delta (\text{CSA,DSA}) \)) from only \( ^{19}\text{F} \) \( R_1 \) and \( R_2 \) experimental data. This would require prior knowledge of \( \tau_0 \) or the F-metal distance in particular complex or multiple magnetic field relaxation data. Such data were not available for most complexes.

**Uncertainties of Predicted and Experimental Data.** The uncertainties of the relaxation rate measurements are typically 5% when INVERC or CPMG sequences are used. This translates into 0.1 Å uncertainty of \( d \) if it is calculated from relaxation data assuming that \( T_{1e} \) and \( \tau_0 \) values are known. Conversely, the knowledge of \( d \) is critical for the
accurate prediction of relaxation rates which are impacted by $T_{1e}$, $\tau_R$, or $\mu_{\text{eff}}$ to a lesser degree. This is illustrated in Table 5 for a series of model lanthanoid complexes wherein the $M$–F distance was 6 Å. In all cases, even a small, 2% difference (0.1 Å) can be the sole factor contributing to observed uncertainty despite much larger assumed uncertainties of $T_{1e}$ or $\tau_R$. The magnetic moment is also potentially important if actual $\mu_{\text{eff}}$ is different from the assumed one.

As a practical conclusion, the two-significant digit precision of $T_{1e}$ and $\tau_R$ is sufficient for the calculation of $R_i$. Such limits are justified by the predicted impact of changes in $T_{1e}$ and $\tau_R$ on relaxation times over a broad range of fields and effective magnetic moments (Figure 2). In the case of varying $T_{1e}$, the relaxation rates (at 9.4 T) are only minimally affected if $T_{1e}$ is either greater than $10^{-9}$ s or less than $10^{-11}$ s which is true for most of the paramagnetic ions except for Fe$^{2+}/3+$ and Ni$^{2+}$ (Table 4). The impact of rotational correlation time and field strength on the calculated relaxation times determined for a broad range of metals is illustrated in Figure 2. The results indicate that 50% changes in rotational correlation time translate into at least 20% changes of the resulting theoretical $R_1$ and $R_2$ but only under high field strength or when a paramagnetic ion with high effective magnetic moments is used regardless of the field strength. The data fitting procedure indicated that the 0.01 ns change of $\tau_R$ usually translated into 1% of the change in the loss function, and very narrow minima were observed, especially when multiple field relaxation data were available. Similarly, 0.01 Å changes in $d$ produced a similar 1% change of the loss function (Table S1, eq S1). If such precision is used instead of the assumptions in Table 5, the uncertainty of $R_i$ would be 5–6 times lower, and the contribution of distance to the overall uncertainty of $R_i$ would only be 8–50% depending on the metal.

**Potential Design Strategies for Relaxometric Contrast Agents.** The optimization procedure produced $\tau_{v}$, $\tau_{s0}$, and $\tau_R$ values that could be used to predict the properties of any contrast agent if the structure does not deviate significantly from the typical DOTA-type and contains the $-\text{CF}_3$ group as a tag. For such compounds, constant $\tau_R$ (0.25 ns) can be reasonably expected, and the field dependence of $T_{1e}$ should be considered. Weaker and stronger magnetic fields were studied

### Table 5. Contribution of the Main Factors to the Overall Uncertainty of the Predicted Relaxation Rates from BRW Theoretical Equations

| ion   | distance [Å] | $\mu_{\text{eff}}/\mu_B$ | $\tau_R$ [ns] | $T_{1e}$ [s] | calculated $R_i$ |
|-------|--------------|---------------------------|---------------|--------------|-----------------|
| Gd$^{3+}$ | 6.0          | 7.6                       | 0.25          | $1 \times 10^{-8}$ | 58,000 ± 600 |
|       | assumed uncertainty | 2%                        | 2%            | 40%          | 50%             |
|       | contribution to the error of $R_i$ | 99.9%                    | <0.1%         | <0.1%        | <0.1%           |
| Ho$^{3+}$ | properties | 6.0                       | 10.4          | 0.25         | $1.5 \times 10^{-12}$ | 1891 ± 20 |
|       | assumed uncertainty | 2%                        | 2%            | 40%          | 50%             |
|       | contribution to the error of $R_i$ | 99.7%                    | 0.3%          | <0.1%        | <0.1%           |
| Nd$^{3+}$ | properties | 6.0                       | 3.7           | 0.25         | $2.5 \times 10^{-15}$ | 72 ± 1 |
|       | assumed uncertainty | 2%                        | 2%            | 40%          | 50%             |
|       | contribution to the error of $R_i$ | 99.9%                    | <0.1%         | <0.1%        | <0.1%           |
Figure 5. Theoretical relationship between the metal–fluorine nucleus distance and the transverse relaxation time \( T_1 \) and \( T_2 \). Relaxation times of diamagnetic references: \( T_1 = 1 \) s and \( T_2 = 0.5 \) s, \( T = 300 \) K, \( \tau_R = 0.25 \) ns. \( T_{1e} \) values were calculated from Table 4. Mathematical model encompasses eqs 1–4, 12, and 15.

separately because they reflect the conditions in medical and research-based MR scanners, respectively.

**Effect of Metal Ions on**. \(^{19}F\) **Relaxation at a Fixed Distance.** To evaluate the suitability of various paramagnetic ions as components of \(^{19}F\) contrast agents, the first set of calculations aimed to demonstrate the impact of the ion type and distance on the relaxation time of the \(^{19}F\) nuclei due to the PRE effect. No further assumptions were made about the structure of the ligand. The literature values for the diamagnetic \( \text{Y}^{3+} \) or \( \text{La}^{3+} \) complexes were in the range of 0.5–1.5 s and 0.25–0.8 s for \( T_1 \) and \( T_2 \), respectively, and the mean values of 1 s and 0.5 s for \( T_1 \) and \( T_2 \), respectively, were used for the preparation of Figures 3 and 4. The results were intended to be a guide for ion selection or for design purposes, where only the distance needs to be determined.

All metal ions with sufficiently high effective magnetic moments and electronic relaxation times were used for the calculations. Some ions can have high- or low-spin states and different oxidation states that differ in PRE. In the case of iron and manganese, high-spin (HS) \( \text{Fe}^{2+} \) and HS and low-spin (LS) \( \text{Mn}^{2+} \), \( \text{Mn}^{3+} \), and \( \text{Fe}^{3+} \) are paramagnetic. Both \( \text{Eu}^{2+} \) and \( \text{Eu}^{3+} \) are paramagnetic with multiple LS states at room temperature for \( \text{Eu}^{3+} \) and a single LS state for \( \text{Eu}^{2+} \). Similarly, \( \text{Co}^{2+} \) is paramagnetic in both spin states, whereas \( \text{Co}^{3+} \) is diamagnetic. Copper has several oxidation states and single-spin states, but only \( \text{Cu}^{2+} \) is paramagnetic. In Figures 4 and 5, only HS states of \( \text{Fe}^{3+} \) and \( \text{Co}^{2+} \) are presented. In the case of \( \text{Eu}^{2+} \), the results are identical to those of \( \text{Gd}^{3+} \). Only the results for \( \text{Gd}^{3+} \) were presented. The results for all spin and oxidation states of \( \text{Co}, \text{Eu}, \) and \( \text{Fe} \) are presented in Figure S2. The field dependence was considered according to the data from Table 4. The data were presented as relaxation times.

In the case of the relaxation time \( T_1 \) and \( T_2 \) (Figures 4 and 5), the greatest reduction in relaxation time was observed for the \( \text{Gd}^{3+} \) ion. Upon assuming a minimal \( T_2 \) relaxation time that enables signal acquisition in a typical MRI/NMR instrument of 10 ms, the complete blanking of the NMR signal occurs at \( \approx 14 \) Å for \( \text{Gd}^{3+} \), \( \approx 12.5 \) Å for \( \text{Mn}^{2+} \), and \( \approx 8.5 \) Å for \( \text{Cu}^{2+} \) in a 9.4 T magnetic field. If 1 ms is assumed to be minimal, then the distances are 9.5 Å for \( \text{Gd}^{3+} \), 8.5 Å for \( \text{Mn}^{2+} \), and 6 Å for \( \text{Cu}^{2+} \). If a minimal \( T_1 \) of 10 ms is assumed, the corresponding distances are shorter because of the accompanying line broadening associated with \( T_2 \). Changing the magnetic field strength does not significantly affect the point where the signal is blanked. However, the use of a weaker magnetic field can slightly extend the working M–F distance, where the PRE effect is still significant. Even at a relatively large distance from fluorine of 25 Å, a gadolinium ion can halve the relaxation time of \(^{19}F\) compared to a diamagnetic compound. In the case of \( \text{Mn}^{2+} \), this occurs around 23 Å. At such large distances, the remaining paramagnetic ions do not show a significant PRE effect. Most ions exert significant PRE at a maximum distance of 5–6 Å. Samarium shows the weakest effect, where blanking can only be observed at short distances of 2 Å which are unlikely in typical fluoroorganic complexes where the distance is 5 Å or more (Table 2). If the distance of the paramagnetic ion from fluorine nuclei is within 5–15 Å, then the appropriate ion can be selected to fine-tune the desired relaxation rate.

The results indicate that several ions other than \( \text{Gd}^{3+} \), such as \( \text{Mn}^{2+} \), \( \text{Cu}^{2+} \), \( \text{Cr}^{3+} \), \( \text{Fe}^{3+} \), \( \text{Cr}^{3+} \), \( \text{Dy}^{3+} \), \( \text{Ho}^{3+} \), \( \text{Er}^{3+} \), and \( \text{Sm}^{3+} \), could be used as components of \(^{19}F\) contrast agents. However, they have rarely been used in practice. These ions exhibit a large effective magnetic moment \( \mu_{eff} \times \mu_B > 7 \) or long electronic relaxation time \( >10^{-9} \) s. In the case of \( \text{Gd}^{3+} \) and \( \text{Eu}^{2+} \), both criteria are met.

Special attention should be paid to copper, manganese, and iron because of their presence in organisms as micronutrients and lower potential toxicity compared with that of exogenous metals. Although chromium and other lanthanoids might be
The lanthanoids and transition metals were presented separately for two field strengths. The results indicate that the $T_2/T_1$ ratio either increases or decreases with the M–F distance depending on $B_0$ and the metal. Only Gd$^{3+}$ exhibits an increase in $T_2/T_1$ with increasing distance regardless of the external field, whereas the reverse is true for most other metals and fields. Interestingly, there is a strong dependence between the field and the maximal $T_2/T_1$ ratio. For most d-metals, the ratio is strongly reduced at 9.4 T compared to that in 1 T fields, whereas lanthanoids are less sensitive to the magnetic field. This has strong implications for the utility of the PRE effect, an appropriate paramagnetic ion at a carefully selected distance should be used to obtain an appropriate shortening of $T_1$ relaxation time. An important concern is the excessive broadening of the signal due to the simultaneous shortening of $T_2$. In the case of a short $T_1$, but relatively long $T_2$, it is possible to maximize the sensitivity of detection, but $T_2/T_1$ is always less than 1. $T_2$ values of 1 and 0.5 s, respectively, for a diamagnetic complex, the relationship between the $T_2/T_1$ ratio and the M–F distance was calculated for all paramagnetic ions (Figure 6).

The lanthanoids and transition metals were presented separately for two field strengths. The results indicate that the $T_2/T_1$ ratio either increases or decreases with the M–F distance depending on $B_0$ and the metal. Only Gd$^{3+}$ exhibits an increase in $T_2/T_1$ with increasing distance regardless of the external field, whereas the reverse is true for most other metals and fields. Interestingly, there is a strong dependence between the field and the maximal $T_2/T_1$ ratio. For most d-metals, the ratio is strongly reduced at 9.4 T compared to that in 1 T fields, whereas lanthanoids are less sensitive to the magnetic field. This has strong implications for the design of contrast agents and the translation of these results into medical practice. First, one must investigate the relative suitability of a particular metal if only the $T_2/T_1$ ratio is considered. For magnetic fields 1 T or slightly greater, the order is constant for lanthanoids and does not depend on the distance. Knowing the order may greatly simplify the design of new agents. However, at strong field strengths ($B_0 = 9.4$ T), the order of metal ions with respect to the $T_2/T_1$ ratio strongly depends on the M–F distance, especially within the 5–10 Å range typical for most fluoroorganic ligands. Because most of the research is currently done using 9–11 T NMR instruments or 1–3 T medical scanners, it is difficult to assess the suitability of contrast agents under different field strengths than that of initially used. Another concern is the contact interaction that may greatly decrease the $T_2/T_1$ ratio in the case of d-metals. This is especially important in the case of Mn$^{2+/3+}$ (Table 3).

**Figure 6.** Relationship between the M–F distances in the $T_2/T_1$ ratio [(A,B)–1 T and (C,D)–9.4 T]. Relaxation times of diamagnetic references: $T_1 = 1$ s and $T_2 = 0.5$ s, $T = 300$ K, $\tau_H = 0.25$ ns, $a_{\text{HFC}} = 0$. $T_1$, values were calculated from Table 4. Mathematical model encompasses eqs 1–4, 12, and 15.

**Paramagnetic, Metal-Based Smart Contrast Agents.** Another possible application of the PRE effect is in so-called smart or responsive contrast agents. Most contrast agents of this type use paramagnetic ions to completely turn off the $^{19}$F MRI signal when the paramagnetic ion is in the proximity of fluorine. As the distance between the paramagnetic ion and the fluorine increases, the $^{19}$F NMR signal increases. Cleavable linkers are the most popular approach to develop responsive contrast agents. These contrast agents will decompose under certain conditions such as a desired pH range or enzyme presence. The length of the cleavable linkers typically does not exceed 10 Å, and gadolinium is the most commonly used metal in these contrast agents due to its very strong PRE. After the linker is cleaved, the M–F distance increases to 50–1000 Å depending on the concentrations of the agent which is typically in the concentration range of 0.1–10 mM. However, this strategy is limited by the necessity for an internal standard for $^{19}$F signal quantification to avoid confounding the progress of activation with the concentration of the contrast agent. Redox-sensitive contrast agents can behave in a similar way. In such a case, the PRE effect can be switched on or off by means of metal ion oxidation/reduction which is tantamount to an increase in the distance between the paramagnet and fluorine to infinity if only one oxidation state is paramagnetic. Cu$^{2+/1+}$, Mn$^{2+/3+}$, Co$^{2+/3+}$, and Eu$^{2+/3+}$ were proposed as redox-sensitive contrast agents due to their significant PRE and low redox potential achievable under in vivo conditions. When selecting a paramagnet for a contrast agent containing a cleavable linker, the linker length must be considered. Too long a linker in combination with a...
weak paramagnet will have a small impact on the image contrast because relaxation times will not significantly change.

The effect of $M-F$ distance on relaxation times is presented in Figures 7 and 8. Assuming that the distance after a 50 Å linker ($\approx 10$ mM solution) is cleaved, most of the paramagnetic ions could be used to turn off the $^{19}$F MRI signal as long as the initial distance is relatively short ($<10$ Å). Tb$^{3+}$, Dy$^{3+}$, Ho$^{3+}$, Fe$^{3+}$, Cr$^{3+}$, Co$^{2+}$, and Cu$^{2+}$ provided an $\approx 1000\%$ increase in relaxation times upon dissociation of a putative smart contrast agent if the initial distance was less than 10 Å. For longer initial distances, only Gd$^{3+}$ and Mn$^{2+}$ can be effectively used. This is reflected in the literature since Gd$^{3+}$ was almost exclusively proposed as a paramagnetic ion for smart contrast agents.

Figure 7. Change in fluorine longitudinal relaxation times during the activation of a hypothetical smart contrast agent with a cleavable linker. The horizontal axis represents the initial distance. The final distance was fixed at 50 Å [(A,B) $\approx 1$ T and (C,D) $\approx 9.4$ T]. Relaxation times of diamagnetic references: $T_1 = 1$ s, $T = 300$ K, $\tau_R = 0.25$ ns. $T_{1e}$ values were calculated from Table 4. Mathematical model encompasses eqs 1–4, 12, and 15.

Figure 8. Change in fluorine transverse relaxation times during the activation of a hypothetical smart contrast agent. The horizontal axis represents the initial distance. The final distance was fixed at 50 Å [(A,B) $\approx 1$ T and (C,D) $\approx 9.4$ T]. Relaxation times of diamagnetic references: $T_2 = 0.5$ s, $T = 300$ K, $\tau_R = 0.25$ ns. $T_{1e}$ values were calculated from Table 4. Mathematical model encompasses eqs 1–4, 12 and 15.
However, Mn$^{2+}$ and other transition metals demonstrate potential for use in novel, smart contrast agents.

**Contrast Agents That Utilize the Variation of the Metal–Fluorine Distance as a Result of Isomerization or Conformational Changes.** Another type of smart contrast agent uses non-destructive phenomena leading to more subtle changes in the M–F distance.$^{23,25,89}$ An example of such a system is fluoroorganic paramagnetic complexes in which the M–F distance is dependent on the presence of target ions such as Ca$^{2+}$.$^{90}$ A possible design approach could be based on the selection of the rate of the change of the PRE effect within a particular distance range. This is presented in Figures 9 and 10 by calculating the first derivative of Figures 4 and 5. The best ion can be selected based on the average distance between a paramagnetic ion and fluorine atoms in the on and off states.

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**Figure 9.** First derivatives of the longitudinal relaxation times from Figure 4 depending on the M–F distance [(A,B) = 1 T and (C,D) = 9.4 T]. Relaxation times of diamagnetic references: $T_1 = 1$ s, $T = 300$ K, $\tau_R = 0.25$ ns. $T_{1e}$ values were calculated from Table 4. Mathematical model encompasses eqs 1–4, 12, and 15.

**Figure 10.** First derivatives of the transverse relaxation times from Figure 5 depending on the M–F distance [(A,B) = 1 T and (C,D) = 9.4 T]. Relaxation times of diamagnetic references: $T_2 = 0.5$ s, $T = 300$ K, $\tau_R = 0.25$ ns. $T_{1e}$ values were calculated from Table 4. Mathematical model encompasses eqs 1–4, 12, and 15.
Generally, the most suitable ions for initial experiments can be selected based on the position of the maxima in Figures 9 and 10. For example, if the observed changes are between 9 and 11 Å, the highest relative changes in relaxation times are observed for Co\(^{2+/3+}\), Ni\(^{2+/3+}\), Fe\(^{2+/3+}\), Fe\(^{3+/4+}\), and Tm\(^{3+}\) at 1 T. In all cases, the potential response is slightly lower at 9.4 T compared to that in 1 T magnetic fields. Alternatively, relaxation rates for a range of metal ions can be calculated for expected distances using data from Table 4 and eqs 1–4, 12, and 15.

**Redox Contrast Agents.** An interesting phenomenon is the change in the magnetic properties of metal ions with a change in the oxidation state. For \(^{19}\)F MRI, the most attractive contrast agents are low-molecular weight compounds whose metal ions change their oxidation state in a reducing or oxidizing environment. Consequently, these smart contrast agents can be used to track redox activity in living organisms using MRI.\(^{7,91}\) For example, in the pair of Mn\(^{2+}\) and Mn\(^{3+}\), the former oxidation state exerts much greater PRE effect than the latter.\(^{28,91}\) As a result, the \(^{19}\)F signal will change due to increased or decreased relaxation rates. In a similar way, other metal ion pairs can be utilized including Eu\(^{2+/3+}\), Mn\(^{2+/3+}\), Co\(^{2+/3+}\), \(^{57}\)Cu\(^{2+/3+}\), and Fe\(^{2+/3+}\).\(^{94}\) The changes in redox states are also applicable for \(^{1}\)H MRI.\(^{95}\) The changes in relaxation rates were different for each metal ion, and the calculated effects are presented in Figure 11.

As the M–F distance increases, the results from changing the oxidation state gradually decrease. If the adopted criterion for selecting the appropriate pair is a 30-fold change in relaxation (Figure 11), Eu\(^{2+/3+}\) and Mn\(^{2+/3+}\) are the most favorable metal ion pairs. Moreover, Eu\(^{2+/3+}\) and Mn\(^{2+/3+}\) are suitable over a wide range of M–F distances (5–15 Å). In the case of Cu\(^{2+/3+}\) and Co\(^{2+/3+}\), these ranges were shorter (5–10 Å and 5–7 Å for Cu\(^{2+/3+}\) and Co\(^{2+/3+}\), respectively). Changes in relaxation time are more complicated for Fe\(^{2+/3+}\) because of the two possible spin states for Fe\(^{2+}\) and Fe\(^{3+}\). Both HS and LS states of Fe\(^{3+}\) are paramagnetic, but the LS state of Fe\(^{2+}\) is diamagnetic. For this reason, changes in the relaxation time induced by changes in the oxidation state are smaller and do not exceed 10-fold (Figure 11). The most suitable metal ion pairing for redox contrast agents would be the transition between LS Fe\(^{3+}\) (diamagnetic) and HS Fe\(^{3+}\) (30-fold change at 10 Å). The impact of the magnetic field is negligible in the case of \(T_1\), but the field strength does have a small effect on \(T_2\) as is evident in the case of the Co\(^{2+/3+}\) pair. The actual response may vary if contact relaxation mechanism plays a significant role.

**Spin Cross-Over Agents.** Spin cross-over is a transition between the LS and HS states of some metal complexes. This phenomenon may be induced by changes in temperature or pressure or may be caused by radiation.\(^{96}\) The possibility of modulating the spin state of a given metal ion theoretically allows one to obtain a new type of relaxometric contrast agent. A single contrast agent based on this mechanism has been described, but the detection was based on a change in the chemical shift and not a change in the relaxation time of fluorine.\(^{97}\) Metal ions with potential applications in such a system are Fe\(^{2+}\), Fe\(^{3+}\), and Co\(^{2+}\). The results of the prediction of their relaxation properties are shown in Figure 12.
Fe³⁺ had the greatest effect on relaxation times. Therefore, Fe³⁺ spin cross-over-based contrast agents would be feasible for fluorine–iron distances ranging from 5 to 15 Å regardless of the external field.

## CONCLUSIONS

Theoretical calculations of the relaxation rates for fluoroorganic complexes can aid in the design of new ¹⁹F contrast agents. Knowing the distance between the fluorine and paramagnetic ions is required to predict the extent of the PRE effect. Considering dipolar and Curie relaxation mechanisms leads to the correct predictions (eqs 1–4) of relaxation times. However, in some cases, Fermi contact interaction should also be considered. The predictions are fairly accurate in terms of the order of magnitude of the $T_1$ and $T_2$ reduction. These predictions are sufficient estimates for practical purposes, especially in the case of very short relaxation times. The prediction power of the model could be improved if field-dependent relaxation data were available for a wider range of fluoroorganic paramagnetic complexes that would allow more precise determination of $\tau_{e0}$ and $\tau_r$. Furthermore, more precise $\tau_{e0}$ and $\tau_r$ measurements are especially important for the translation of new contrast agents into medical practice where low-field instruments are dominant compared to the high-field strength (9.4–16.1 T) instruments used in research. Such data would also allow for precise calculation of correlation times and M–F distances and a better understanding of the behavior of new contrast agents, especially in terms of the significance of the different relaxation mechanisms. Multiple-field relaxation data would also allow the inclusion of chemical shift anisotropy–anisotropic dipolar shielding cross-correlation in the model with further improvement in accuracy. The presented results offer some general guidance for the selection of paramagnetic ions at the design stage of a contrast agent. Field strength and M–F distance are among the crucial factors. In the case of $T_1$, Gd³⁺ shows great potential as a contrast agent because it reduces the relaxation time by several orders of magnitude compared to non-paramagnetic $Y^{3+}$ in a broad range of distances up to 20 Å. However, fluorine relaxation times are extremely short for Gd³⁺ ions when M–F distances are shorter than 10 Å, thus rendering the contrast agent invisible in ¹⁹F MRI. This phenomenon is convenient for responsive contrast but not in the case of other types of contrast agents. For complexes where the M–F distance is less than 8 Å, the use of other ions, such as Co²⁺ (in the range of 5–7 Å) or Fe³⁺ and Ni²⁺ (in the range of 7–8 Å), is also warranted. Moreover, due to their common occurrence in the body, Co²⁺, Ni²⁺, and Fe³⁺ pose less of a toxicity risk compared to Gd³⁺. Depending on the field strength and the intended application, the suitable ions that enable a sufficient change in relaxation properties compared to diamagnetic compounds are presented in Table 6. Among the transition metals, Mn²⁺ has the greatest potential as a component in various types of contrast agents, which is not yet reflected in the literature. Unfortunately, the presence of significant contact interaction might preclude the use of this metal in some cases. Ce³⁺ demonstrates potential for standard contrast agents where the M–F distance is in the range of 9–11 Å. A considerable limitation of Ce³⁺ is the toxicity concern. Other lanthanoids, particularly Yb³⁺, could be used at short M–F distances of 4–5 Å, regardless of the magnetic field. Lanthanoids such as Ho³⁺, Er³⁺, Dy³⁺, and Tb³⁺ are also potentially useful and should be considered during the development of new paramagnetic contrast agents. However, these metals unfortunately suffer from the same potential side effects as those of Gd³⁺. The utility of paramagnetic ions with a small magnetic moment might be in nanoparticle contrast agents where the distance between ¹⁹F and the paramagnetic center is much shorter than that in typical fluoroorganic complexes. Potential design strategies could also take into consideration changes in the chemical shift of ¹⁹F induced by the paramagnetic ion in order to improve contrast quality.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.2c03451.

NMR and MS spectra, DFT structural coordinates, additional figures, raw relaxation data, calculated cross-correlation, and rotational correlation time data (PDF)

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**Table 6. Suitable Paramagnetic Ions for Different Types of ¹⁹F MRI Contrast Agents at Various Field Strengths**

| type of contrast | field strength | 1 T | 9.4 T | 16.5 T |
|-----------------|----------------|-----|-------|--------|
| smart with a cleavable linker, initial distance 10 Å, after cleavage 50 Å | Mn²⁺, Gd³⁺ | Ce³⁺, Mn²⁺, Fe³⁺, Gd³⁺ | Ce³⁺, Mn²⁺, Ni²⁺, Fe³⁺, Tb³⁺, Dy³⁺, Ho³⁺, Gd³⁺ |
| smart of variable distance, initial distance 7 Å, after isomerization 14 Å | Mn²⁺, Cu²⁺, Fe³⁺, Dy³⁺, Tb³⁺, Gd³⁺ | Ce³⁺, Mn²⁺, Ni²⁺, Fe³⁺, Tb³⁺, Er³⁺, Tb³⁺, Dy³⁺, Ho³⁺, Gd³⁺ | Ce³⁺, Mn²⁺, Ni²⁺, Fe³⁺, Tb³⁺, Er³⁺, Tb³⁺, Dy³⁺, Ho³⁺, Gd³⁺ |
| standard contrast agent, fixed distance 5 Å | Er³⁺, Ho³⁺, Tb³⁺, Dy³⁺, Tb³⁺, Gd³⁺ | Er³⁺, Ho³⁺, Tb³⁺, Tb³⁺, Dy³⁺, Ho³⁺, Gd³⁺ | Er³⁺, Ho³⁺, Tb³⁺, Tb³⁺, Dy³⁺, Ho³⁺, Gd³⁺ |
| standard contrast agent, fixed distance 10 Å | Mn²⁺, Ni²⁺, Fe³⁺, Fe³⁺ | Mn²⁺, Mn²⁺, Mn²⁺, Mn²⁺ | Mn²⁺, Mn²⁺, Mn²⁺, Mn²⁺ |
| spin cross-over pair | Mn²⁺, Mn²⁺ | Mn²⁺, Mn²⁺, Mn²⁺, Mn²⁺ | Mn²⁺, Mn²⁺, Mn²⁺, Mn²⁺ |

| Redox pair⁶ | Mn²⁺-(5–15 Å), Cu²⁺-(5–10 Å), Co²⁺-³/²⁺(5–7 Å) | Fe³⁺-(5–15 Å), Co²⁺(5–8 Å) |

⁴The criteria of selection. ⁵At least 3000% increase in relaxation time due to cleavage or isomerization of a contrast agent. ⁶Reduction in relaxation time down to 1–10 ms.
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Notes

The authors declare no competing financial interest.

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