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Transition metal complexes of the (2,2,2-trifluoroethyl)phosphinate NOTA analogue as potential contrast agents for $^{19}$F magnetic resonance imaging†

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A new hexadentate 1,4,7-triazacyclononane-based ligand bearing three coordinating methylene-(2,2,2-trifluoroethyl)phosphinate pendant arms was synthesized and its coordination behaviour towards selected divalent (Mg$^{2+}$, Ca$^{2+}$, Mn$^{2+}$, Fe$^{2+}$, Co$^{2+}$, Ni$^{2+}$, Cu$^{2+}$, Zn$^{2+}$) and trivalent (Cr$^{3+}$, Fe$^{3+}$, Co$^{3+}$) transition metal ions was studied. The ligand forms stable complexes with late divalent transition metal ions (from Co$^{2+}$ to Zn$^{2+}$) and the complexes of these metal ions are formed above pH $\sim$ 3. A number of complexes with divalent metal ions were structurally characterized by means of single-crystal X-ray diffraction. The complex of the larger Mn$^{2+}$ ion adopts a twisted trigonally antiprismonic geometry with a larger coordination cavity and smaller torsion of the pendant arms, whereas the smaller ions Ni$^{2+}$, Cu$^{2+}$ and Zn$^{2+}$ form octahedral species with a smaller cavity and larger pendant arm torsion. In the case of the Co$^{2+}$ complexes, both coordination arrangements were observed. The complexes with paramagnetic metal ions were studied from the point of view of potential utilization in $^{19}$F magnetic resonance imaging. A significant shortening of the $^{19}$F NMR longitudinal relaxation times was observed: a sub-millisecond range for complexes of Cr$^{3+}$, Mn$^{2+}$ and Fe$^{3+}$ with symmetric electronic states ($t_{2g}^3$ and HS-d$^5$), the millisecond range for the Ni$^{2+}$ and Cu$^{2+}$ complexes and tens of milliseconds for the Co$^{2+}$ complex. Such short relaxation times are consistent with a short distance between the paramagnetic metal ion and the fluorine atoms ($\sim$ 5.5–6.5 Å).

Among the redox-active complexes (Mn$^{3+}$/Mn$^{2+}$, Fe$^{3+}$/Fe$^{2+}$, Co$^{3+}$/Co$^{2+}$, Cu$^{2+}$/Cu$^{+}$), the cobalt complexes show sufficient stability and a paramagnetic–diamagnetic changeover with the redox potential lying in a physiologically relevant range. Thus, the Co$^{3+}$/Co$^{2+}$ pair can be potentially used as a smart redox-responsive contrast agent for $^{19}$F MRI.

Introduction

Magnetic Resonance Imaging (MRI) is one of the most powerful imaging methods in current medicine. Compared to the classical radiological methods utilizing ionizing radiation such as Computed Tomography (CT), Single-Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET), MRI utilizes the nuclear magnetic resonance effect and uses non-ionizing radiation for detection which brings a strong benefit to the patients. Classical MRI utilizes the detection of the NMR effect of water $^1$H nuclei and distinguishes the different tissues according to the water content and/or signal relaxation times (longitudinal, $T_1$, and transversal, $T_2$). The image contrast can be further improved by the application of contrast agents (CAs) which influence the water proton relaxation times, and a suitable experimental setup selectively increases or decreases the water $^1$H signal according to the CA distribution in the tissue. Other MRI techniques have been developed, including the detection of $^1$H signals of compounds other than water (e.g. fat) or utilization of responsive (“smart”) contrast agents which change their properties according to the surrounding conditions. In addition, other NMR active nuclei such as $^{13}$C, $^{19}$F or $^{31}$P can also be detected by MRI. Among them, fluorine is of special
interest, as it is a monoisotopic element with a high gyromagnetic ratio which provides a very high sensitivity towards the NMR effect. The gyromagnetic ratio of $^{19}$F is very close to that of $^1$H which enables the detection of the $^{19}$F NMR signal with the use of standard MRI scanners with only small hardware and software modifications. Furthermore, fluorine has almost no abundance in living organisms and, thus, it has no natural background in the imaging experiments. This fact predisposes the $^{19}$F nuclei for “hot-spot” imaging where only the externally supplied xenobiotic contrast agent molecules provide the $^{19}$F MRI signal. As both $^1$H and $^{19}$F MRI experiments can be performed on the same hardware, the need to overlay $^{19}$F “hot-spots” with the anatomical image can be elegantly solved by $^1$H + $^{19}$F tandem MRI. Such an imaging method could be especially useful for example for following the fate of labelled cells after transplantation.

The compounds first tested as $^{19}$F NMR contrast agents were usually highly fluorinated hydrocarbons and their derivatives (for simplicity called perfluorocarbons, PFCs). The design of fluorinated contrast agents takes advantage of the generally high stability of the C-F bond towards hydrolysis which makes these compounds inert and non-biodegradable. Highly fluorinated organic compounds therefore usually exhibit a low acute toxicity, and some of the PFCs have been already studied for a long time as potential blood substitutes due to the high solubility of molecular oxygen$^{8-11}$ or as materials in vitreo-retinal surgery due to their optical properties.$^{12,13}$ Although some adverse health effects have been reported in the latter application,$^{14}$ they have been attributed mainly to the presence of trace toxic impurities like non-fully substituted hydrocarbons and other derivatives.$^{15,16}$ However, although PFCs show high stability, it was recently found that they cause some environmental risks.$^{17}$

The compounds originally used for $^{19}$F MRI are not water-soluble and have been used in the form of nano- or micro-emulsions which complicates some applications (e.g. cellular labelling). Further complication arises from a generally long $T_1$ relaxation time of the $^{19}$F nucleus in the PFC (order of seconds). Therefore, a signal is acquired for several seconds, a long delay between excitation pulses is needed and it prolongs the whole experiment. To solve this problem, complexes of fluorine-containing ligands with some paramagnetic metal ions were introduced, as the presence of a paramagnetic metal ion strongly influences the NMR relaxation times of nuclei in the vicinity.$^{18}$ The concentration of the contrast agents must be relatively high (on a millimolar scale) to achieve a reasonable signal-to-noise ratio. Therefore, the complexes must exhibit exceptional kinetic inertness as the free metal ions are frequently toxic and, in addition, the contrast agent loses convenient relaxation properties after the dissociation of the complexes. Therefore, the ligands are often based on a macrocyclic scaffold, mostly on 1,4,7-triazacyclononane (tacn), 1,4,7,10-tetraazacyclododecane (cyclen) or 1,4,8,11-tetraazacyclotetradecane (cyclam), Fig. 1, with suitably chosen coordinating pendant arms or substituents which contain fluorine atoms. The first explored groups were derivatives and analogues of its transition metal complexes were reported.$^{21,25,31}$ Recently, the same pendant arm has been utilized in the cyclam-based ligand $H_4$dotp[t]$^16$ (Fig. 1) containing twelve fluorine atoms and we studied its Ln$^{3+}$ complexes. For complexation of transition metal ions, $H_4$dota derivatives have also been used$^{28,34,35}$ but hexadentate derivatives of tacn and cyclam are generally more suitable for this purpose.$^{16}$ Therefore, several tacn derivatives with three coordinating pendant arms containing fluorine were prepared and studied.$^{27-30}$ Similarly, cyclam-based ligands with two coordinating groups have also been studied.$^{41-47}$

In our previous contributions, we showed that (2,2,2-trifluoroethyl)phosphinic acid is a suitable synthon for the introduction of the fluorine atoms into a ligand molecule. We used this coordinating pendant arm in the synthesis of the cyclam-based ligand $H_4$dotp[t]$^16$ (Fig. 1) which contains twelve fluorine atoms and we studied its Ln$^{3+}$ complexes.$^{31}$ Recently, the same pendant arm has been utilized in the cyclam-based ligand 1,8-H$_2$te$H_2$te$^{16}$ (Fig. 1) containing six fluorine atoms and a study of its transition metal complexes was reported.$^{47}$ The results showed that such a concept is viable and brought promising data especially for the Co$^{2+}$ complex.$^{47}$

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![Fig. 1](Image) Ligands mentioned in the text.
To extend our work in this field, we designed a new tacn-based ligand containing three [methylene-(2,2,2-trifluoroethyl) phosphinic acid] pendant arms, H₃notp (Fig. 1). It increases the number of fluorine atoms in one small molecule to nine. It would potentially increase the visibility of the contrast agents during the imaging experiment. In this manuscript, we report on the synthesis of the designed ligand and the results of its coordination study with selected first-row transition metal ions.

**Experimental**

**General**

Commercial chemicals (Fluka, Aldrich, CheMatech, Lachema, Fluorochem) were used as obtained. Anhydrous solvents were obtained by established procedures.⁴⁶ 2,2,2-Trifluoroethyl-tosylate and 2,2,2-trifluoroethylbromide⁵⁰ were prepared according to published procedures with slight modifications. (2,2,2-Trifluoroethyl)phosphinic acid was prepared analogously as reported earlier⁴⁷ but 2,2,2-trifluoroethylbromide was used instead of iodide and the workup was modified. Analytical HPLC-MS experiments were carried out on a Waters ACQUITY QDa system (detection: MS – electrospray ionization under atmospheric pressure, m/z 100–1250; UV-Vis – λ 210–800 nm, diode array) equipped with an RP column (Cortecs C18 2.7 μm, 4.6 × 50 mm) using a mixture of water with 0.1% trifluoroacetic acid (TFA) and MeCN with 0.1% TFA; for details on the

**Chemical shifts of paramagnetic compounds were corrected for a bulk magnetic susceptibility effect as described previously (difference of the ¹⁹F signals of 2,2,2-trifluoroethanol between the paramagnetic sample and the insert, Table S1),⁴⁷ the corrected values are presented throughout the text. The T₁ relaxation times of the nucleus were measured using the Inversion Recovery sequence. The ¹⁹F T₂ relaxation times of diamagnetic compounds were measured from the CPMG sequence on a Varian Inova 400 MHz and Bruker III 600 MHz; the measurement is not accessible on VNMRS300 as the probe used does not provide accurate 180° pulses for the ¹⁹F nuclei. For all paramagnetic complexes, T₁* relaxation times were calculated from half-widths of their NMR signals.

**Ligand synthesis**

2,2,2-Trifluoroethyl-tosylate. 2,2,2-Trifluoroethanol (30.0 g, 300 mmol, 1.0 equiv.) was poured into a 1000 ml round-bottomed flask and was diluted with dichloromethane (DCM, 300 ml). Triethylamine (84 ml, 600 mmol, 2.0 equiv.) was added and the mixture was cooled in a bath with a water–ice mixture. To this mixture, a solution of tosylchloride (54.3 g, 285 mmol, 0.95 equiv.) in DCM (150 ml) was added dropwise. After the addition was completed, the cooling bath was removed and the reaction mixture was allowed to warm up to room temperature and was stirred for 18 h. Thereafter,aq. HCl (6 M, 150 ml) was added and the mixture was transferred into a separation funnel. The organic layer was separated, washed with brine (3 × 200 ml) and dried over anhydrous MgSO₄. Volatiles were evaporated on a vacuum rotary evaporator. The pale orange oil remaining was poured onto an evaporating dish. The white solid product crystallized in the fridge overnight. Yield 68.5 g (95%).

Elem. anal.: found (calc. for C₉H₉F₃O₃S, Mᵣ 254.22) C: 42.44 (42.52), H: 3.43 (3.57), F: 21.27 (22.42), S: 12.10 (12.61).

NMR (CDCl₃): ¹H: 2.47 (s, 3H, CH₃); 4.34 (q, 2H, J₃HF 8.0, CH₂); 7.38 (d, 2H, JHH 8.2, arom.); 7.81 (d, 2H, JHH 8.2, arom.). ¹³C{¹H} (CH₃): 21.8 (CH₃); 64.7 (q, JCF 38.1, CH₂); 122.7 (q, JCF 277, CF₂); 128.2, 130.3, 132.0, 146.1 (4 × arom.). ¹⁹F: –74.2 (t, J₉HF 8.0, CF₂).

Recrystallization from boiling 96% aq. EtOH afforded single-crystals suitable for determination of the crystal structure by X-ray diffraction. The crystal structure is the same as that already reported,⁵¹ but with significantly better parameters of refinement (see the ESI, Table S4 and Fig. S34).

2,2,2-Trifluoroethylbromide. The non-trivial apparatus is shown in Fig. S2. The 2,2,2-Trifluoroethyl-tosylate (105 g, 413 mmol), diethyleneglycol (250 ml), KBr (75.0 g, 630 mmol, 1.5 equiv.) and a few ceramic boiling chips were added into a 1000 ml three-necked round-bottomed flask in a heating mantle. The flask necks were equipped with a stopcock connected to a N₂ (g) source, a Dimroth condenser and a stopper. The Dimroth condenser was connected to an adapter with a thermometer and a low-temperature side condenser which was filled with ethanol. The temperature in the low-temperature condenser was maintained around –70 °C by periodic addition of liquid N₂. A 100 ml round-bottomed receiving flask was con-
nected to the low-temperature condenser and cooled in a Dewar vessel which was filled with ethanol and N₂ (l). Water for the Dimroth condenser was pre-heated to 35 °C (the boiling point of the product is approx. 26 °C). The reaction mixture was heated to reflux diethylenglycol (245 °C) and 2,2,2-trifluoroethyl-tosylate and KBr fully dissolved at this high temperature. The product was distilled as a colourless high-density liquid. The yield was 65.9 g (98%).

NMR (20% v:v solution in CH₂Cl₂, 20 °C): ¹H: 3.72 (q, 2H, ³JHF 8.9, CH₃). ¹³C{¹H}: 26.4 (q, ³JCP 37.8, CH₂); 123.7 (q, ³JCP 274, CF₃). ³¹P: −69.6 (t, ³JFP 8.9, CF₃).

(2,2,2-Trifluoroethyl)phosphinic acid and ammonium salt. Under a stream of argon, crystalline hypophosphorous acid (5.00 g, 75.8 mmol) in a three-necked 250 ml flask was dissolved in anhydrous DCM (50 ml). The flask was immersed in a water–ice cooling bath and anhydrous N,N-diisopropyl-ethylamine (DIPEA, 29.4 g, 227 mmol, 3.0 equiv.) was added. Afterwards, trimethylsilyl chloride (TMS-Cl, 24.7 g, 227 mmol, 3.0 equiv.) was added dropwise; the rate of addition was kept slow to prevent a white haze from flowing away from the apparatus. After addition of the whole amount of TMS-Cl, the reaction mixture was stirred at room temperature for 3 h. Formation of bis(trimethylsilyloxy)phosphine was confirmed by ³¹P NMR (141 ppm, d, ³JFP 177).

Then, 2,2,2-trifluoroethylbromide (13.6 g, 83.5 mmol, 1.1 equiv.) dissolved in anhydrous DCM (20 ml) was added dropwise to the reaction mixture; the rate of the addition was slow enough to prevent haze formation. The mixture was stirred at room temperature overnight. Then, the reaction mixture (0.1 ml) was hydrolysed in 96% ETOH (1 ml) and ³¹P NMR of the hydrolysed sample revealed ca. 72% conversion; the main impurity was H₃PO₃. The whole reaction mixture was hydrolysed by dropwise addition of 96% ETOH (60 ml). The hydrolysed mixture was evaporated on a rotary evaporator at the bath temperature of 50 °C. The residue was dissolved in water (30 ml) and the solution was poured onto a column of a strong cation exchange resin (Dowex 50, H⁺-form, 400 ml). Elution with water a...
as an eluent; TFA is eluted off slightly earlier than H₃notptfe which is thus enriched in the later fractions. The fractions were analysed by ¹⁹F NMR spectroscopy and combined according to their purity. After repeated procedures, some amount of pure H₃notptfe was isolated as a colourless thick oil containing only some small amount of water as an impurity.

### Preparation of solutions of the complexes for NMR studies

The ligand stock solution was prepared by dissolving H₃notptfe (600 mg, TFA-free) in water into a 25 ml volumetric flask. The exact ligand concentration (38.3 mM) was determined by ¹⁹F NMR using standardized aq. solution of TFA similarly as described previously.⁴⁷

For determination of magnetic moments, the samples were prepared by mixing exactly the measured volume (200–300 µl) of the aq. ligand stock solution, the appropriate amount of the aq. stock solution of the metal ion salts (MnCl₂, NiCl₂, FeCl₃, CoCl₂, CuCl₂; 0.95 equiv., concentration determined by chelatometry), appropriate amount of 1.50 M aq. NaOH (2.90 equiv.) and exactly measured volume (200–300 µl) of aq. HEPES buffer (0.1 M) with pH 7.4. The solutions of the Mn⁺, Fe⁺, and Cu⁺ complexes were measured immediately (a fast complex formation) and the solutions of the Co⁺ and Ni⁺ complexes were equilibrated at 50 °C in a tightly closed vial overnight. To prepare the Cr⁺ complex, the mixture of the weighed solid CrCl₃·6H₂O and the ligand stock solution (1.05 equiv.) with pH adjusted to ca. 9 (in the case of the Fe⁺ complex, exactly 1.000 ml) and the corresponding solid metal salt (CrCl₃, FeCl₃, MnCl₂, NiCl₂, CuCl₂ and ZnCl₂). These stock solutions were prepared by dissolution of 9 equiv. of the respective metal salts in water (100 ml). The pH of the mixtures was carefully adjusted by stepwise addition of diluted aq. NaOH to ca. 7 (in the case of the Fe⁺ complex, diluted aq. NH₃ was used). Then, the vials were closed and the mixtures were heated overnight at 50 °C (in the case of the Cr⁺ and Fe⁺ complexes, the mixtures were heated at 90 °C for 5 d). After cooling, pH was adjusted to 7.4 by diluted aq. NH₃ (7.5 in the case of the Mg⁺–H₃notptfe system).

Successful formation of the complexes was seen from the colour change (Cr⁺, Fe⁺, Co⁺, Ni⁺ and Cu⁺) and was confirmed by NMR spectroscopy (Tables S1 and S2†) and mass spectrometry. The NMR and UV-Vis spectra of the complexes are shown in Fig. S8–S25.†

[Mg(I)(notptfe)]: colourless. NMR (H₂O, pH 7.5): ¹⁹F: –57.2 (35%, broad, q, ⁴JFH = ⁴JFP ~10); –57.0 (65%, free ligand, dt). MS-ESI (–): m/z 630.1 ([M⁺], calc. 630.1).

[Cr(II)(notptfe)]: deep purple. NMR (H₂O, pH 7.4): ¹⁹F: –46.0 (extremely broad). MS-ESI (+): m/z 669.1 ([M + H⁺], calc. 669.0).

[Mn(I)(notptfe)]: colourless. NMR (H₂O, pH 7.4): ¹⁹F: –41.8 (extremely broad). MS-ESI (–): m/z 662.2 ([M⁺], calc. 661.0).

[Fe(II)(notptfe)]: yellow. NMR (H₂O, pH 7.4): ¹⁹F: –31.0 (very broad). MS-ESI (+): m/z 663.1 ([M + H⁺], calc. 663.0).


[Ni(II)(notptfe)]: light blue. NMR (H₂O, pH 7.4): ¹⁹F: –48.1 (91%, broad); –45.4 (9%, broad). MS-ESI (–): m/z 664.9 ([M⁺], calc. 664.0).

[Cu(II)(notptfe)]: deep blue. NMR (H₂O, pH 7.4): ¹⁹F: –54.2 (broad). MS-ESI (–): m/z 669.1 ([M⁺], calc. 669.0).

[Zn(II)(notptfe)]: colourless. NMR (D₂O, pD 7.4, evaporated to dryness and re-dissolved in D₂O): ¹H: 2.87 (broad s, 10H); 3.12 (broad s, 14H).¹H: 5.54 (dt, ⁴JCP 102, N₃H₂P); 126.2 (q, ¹JCP 89.8, ²JCP 28.5, PCHA₃F); 53.11 and 57.05 (2 × broad s, NCH₂CH₂N); 60.0 (d, ¹JCP 102, NCH₂P); 126.2 (q, ²JCP 274, ³JCP 1.5, CF₃); 34.21.¹F: –57.21 (pseudo-q, ⁴JFP ~10.5, ³F = 29.02 (m, ⁴JFP ~10.5, ³F = 29.02 (q, ⁴JFP 10.5). MS-ESI (+): m/z 670.1 ([M⁺], calc. 670.0).

### Electrochemical study

The stock solutions of the H₃notptfe complexes for electrochemical experiments were prepared analogously as solutions for NMR studies but starting from the ligand stock solution (exactly 1.000 ml) and the corresponding solid metal salt (exactly 0.9 equiv.; CrCl₃·6H₂O, MnCl₂·4H₂O, FeCl₃·6H₂O, CoCl₂·6H₂O, NiCl₂·6H₂O, CuCl₂·2H₂O). The pH of the solutions was adjusted to 7.4.

The H₃not complexes for the electrochemical experiments with the same metal ions were prepared and isolated in the solid form as described in the literature (or by analogous procedures).³² The solids were dissolved in water before the measurement.

Cyclic voltammetry was performed using a potentiostat Polarographic analyzer PA 3 equipped with an XY writer (Laboratorium přístroje Praha). A three-electrode setup was used. Working electrodes were a hanging mercury drop electrode (HMDE) or platinum disc electrode; a saturated calomel electrode (SCE) was used as the reference electrode. Platinum wire with a plate was used as the auxiliary (counter) electrode. Among the several aqueous supporting electrolytes tested (0.1 M NaH₂PO₄/Na₂HPO₄ buffer with pH 7.4, 0.05 M LiClO₄, 0.05 M (NH₄)ClO₄, 0.05 M (NET₃)ClO₄, 0.05 M aq. LiClO₄ was chosen due to the widest measurement window [+0.4 (–2.2) V]
and +1.5–(−0.9) V for the HMDE and Pt electrode, respectively, vs. SCE. For each measurement, 0.05 M aq. LiClO₄ (10 ml) was deoxygenated by bubbling argon through the solution in the measuring cell for several minutes; the absence of dissolved oxygen was confirmed by the measurement of a blank scan. Then, an appropriate volume of the stock solution of the studied H₃notptfe complex or weighed amount of the solid H₃nota complex was added to reach a concentration of 1–4 mM for the complexes, and the solution was shortly deoxygenated again before the start of the electrochemical experiment.

Spectro-electrochemical experiments were performed using an optically transparent thin-layer electrochemical cell (OTTL cell) assembled from a Pt mesh working electrode, Pt mesh auxiliary electrode and Ag wire as the reference electrode (in a 1:1:1 system). The titrations of the free ligand and H₃notptfe complex or weighed amount of the solid H₃nota complex was added to reach a concentration of 1–4 mM for the complexes, and the solution was shortly deoxygenated again before the start of the electrochemical experiment.

Electrosynthesis of the [Co^{III}(notptfe)] complex was performed in an H-shaped electrochemical cell with a fine frit placed in the middle of the horizontal part connecting two vertical tubes. One tube was equipped with the auxiliary electrode (Pt wire with a plate) and was filled with 0.05 M LiClO₄. The second tube contained the working electrode (Pt wire with a plate). The experiment was performed starting from 5 mM solution of the [Co^{II}(notptfe)]⁻ complex in 0.05 M LiClO₄.

**Potentiometric study**

The methodology of potentiometric titrations and processing of the experimental data were analogous to those previously reported. The ligand stock solution was prepared by dissolution of TFA-free H₃notptfe (600 mg) in a 50 ml volumetric flask. The exact ligand concentration (19.2 mM) was determined by 19F qNMR using standardized aq. solution of TFA before the solvent was evaporated. The titrations were performed using a 1:1:1 system. The concentration of the ligand was 19.38 mM, diatomic tubes were used in a common titration (and a slow concentration in air). The concentration of the ligand in the titration vessel was ca. 0.004 M, ligand-to-metal ratio 1 : 0.95, ionic strength 0.1 M (NMe₄)Cl and starting volume ca. 5 ml. An equilibrium in the systems Co^{II}–H₃notptfe and Ni^{II}–H₃notptfe was established slowly and, therefore, the out-of-cell method was used in these cases. Each solution corresponding to one titration point was prepared in a tube with a ground joint (pH 1.6–6.5, three titrations with 15 points, starting volume ca. 1 ml, the same concentrations as used in a common titration) and the solutions were left to equilibrate at room temperature for one week. The overall protonation constants \( \beta_h \) are concentration constants and are defined by \( \beta_h = [H_hL]/([H]^h[L]) \) (stepwise protonation constants are defined as \( K_i = \log \beta_i; \log K_h = \log \beta_h - \log \beta_{h-1} \)). The overall stability constants are defined by the general equation \( \beta_{hml} = [M_{hml}][L]^h[L]^l \). Here, the formation of only M : L 1 : 1 complexes \((m = l = 1)\) was considered. The water ion product, \( K_w \) (13.81), and stability constants of M^{2+}–OH⁻ systems were taken from the literature. The constants (with their standard deviations) were calculated with program package OPIUM (Table S3†).

**Single-crystal X-ray diffraction study**

**Preparation of single crystals.** The single crystals of \([\text{NH}_4]_3[\text{Mn}(\text{notptfe})]_2\text{Cl}_3\cdot3\text{H}_2\text{O}\) and \([\text{NH}_4]_2[\text{Cu}(\text{notptfe})]_2\text{Cl}_3\cdot3\text{H}_2\text{O}\) were prepared by neutralization of an aq. solution containing equimolar amounts of the ligand and MCl₂ (M = Mn, Cu) with diluted aq. NH₃ to pH ca. 7 followed by a slow evaporation. Single crystals of \([\text{Mn}(\text{H}_2\text{O})_6][\text{Mn}(\text{notptfe})]_2\cdot18\text{H}_2\text{O}\) were obtained by similar procedure but an excess of MnCl₂ was used and some Mn(OH)₂ was filtered off before the solvent was evaporated. The crystals of \([\text{NH}_4]_3[\text{Co}(\text{notptfe})]_3\cdot3.5\text{H}_2\text{O}\), \([\text{NH}_4]_2[\text{Cu}(\text{notptfe})]_3\cdot3.5\text{H}_2\text{O}\) and \([\text{Mg}(\text{H}_2\text{O})_6][\text{Ni}(\text{notptfe})]_2\cdot12\text{H}_2\text{O}\) were prepared from the corresponding aq. solutions of the \([\text{NH}_4]_2[\text{M}(\text{notptfe})]_2\) complexes by the slow vapour diffusion of EtOH. The ammonium salts \([\text{NH}_4][\text{M}(\text{notptfe})]_2\) (M = Co, Cu) were obtained by reaction of the ligand with a slight excess of freshly precipitated M(OH)₂ followed by chromatography of the formed complex on silica using aq. NH₃·EtOH in a 1 : 10 mixture as an eluent; under these conditions, the excess of free M^{2+} was kept at the top of the column. In the case of \([\text{Mg}(\text{H}_2\text{O})_6][\text{Ni}(\text{notptfe})]_2\cdot12\text{H}_2\text{O}\) the ammonium salt obtained by chromatography was crystallized by concentration of the aq. solution in the presence of an excess of MgCl₂ (10 equiv.). The single crystals of \([\text{Co}(\text{H}_2\text{O})_6][\text{Co}(\text{notptfe})]_2\cdot14.25\text{H}_2\text{O}·0.75\text{MeOH}\) were prepared by saturation of the ligand solution with an excess of freshly precipitated Co(OH)₂, filtration, concentration and a slow vapour diffusion of MeOH into the complex solution. The single crystals of Na₃[Co(notpffe)]Br·3Me₂CO were prepared by neutralization of an equimolar aq. solution of the ligand and CoBr₂ with NaOH to pH ca. 7, concentration and a slow vapour diffusion of acetone. The single crystals of \([\text{ZnCl}(\text{H}_2\text{O})_6][\text{Zn}(\text{notptfe})]_2\cdot2\text{H}_2\text{O}\) were obtained by mixing the ligand and an excess of ZnCl₂, neutralization with diluted aq. NH₃ to pH ca. 5, and a slow concentration in air.

**General procedure for data acquisition and treatment.** The diffraction data were collected using a Bruker D8 VENTURE Duo diffractometer with an IμS micro-focus sealed tube using Cu-Kα radiation (λ 1.54178 Å) or Mo-Kα radiation (λ 0.71073 Å). Data were analysed using the SAINT software package (Bruker AXS Inc., 2015–2019). Data were corrected for absorption effects using the multi-scan method (SADABS). All structures were solved by direct methods (SHELXT2014) and refined using full-matrix least-squares techniques (SHELXL2017). The details of the structure refinements are given in the ESI.† For overview of the experimental crystallographic data, see Table S4.† The cif-files of all structures reported here have been deposited in the Cambridge Crystallographic Data Centre (CCDC 2327147–2327158†).
Results and discussion

Synthesis of the ligand H₃notptfe

Synthesis of the studied ligand H₃notptfe (H₃L) was performed as shown in Scheme 1.

The synthesis of the starting (2,2,2-trifluoroethyl)phosphinic acid was reported previously;⁴⁷ however, the use of commercial 2,2,2-trifluoroethyl iodide for an Arbuzov-type reaction with bis(trimethylsilyl)hypophosphite resulted in the presence of hydroiodic acid in the final mixture that complicated further purifications.⁴⁷ Therefore, we optimized the synthesis using 2,2,2-trifluoroethylbromide. This compound was prepared by reaction of 2,2,2-trifluoroethyl-tosylate⁴⁹ with KBr in boiling anhydrous diethyleneglycol (boiling point 244 °C).⁵⁰ However, the synthesis needs non-trivial apparatus as the product is volatile (boiling point 26 °C) (see Experimental and Fig. S2†).

A Mannich-type reaction between tacn, (2,2,2-trifluoroethyl) phosphinic acid and paraformaldehyde was performed in a strong acid solution (50% v/v aq. TFA) at 40 °C. It was found that only a slight excess of (2,2,2-trifluoroethyl)phosphonic acid (3.1 equiv.) and paraformaldehyde (3.5 equiv.) is sufficient to reach almost quantitative conversion according to the ¹⁹F and ³¹P NMR spectra. Only a small extent of oxidation of (2,2,2-trifluoroethyl)phosphonic acid to (2,2,2-trifluoroethyl) phosphonic acid and formation of hydroxymethyl-(2,2,2-trifluoroethyl)phosphonic acid were observed under these conditions. The ligand H₃notptfe behaves as a strong acid and can be eluted from a strong cation exchange resin using water. However, its elution is only slightly slowed down compared to the simple acids present in the mixture [TFA, (2,2,2-trifluoroethyl)phosphonic acid, hydroxymethyl-(2,2,2-trifluoroethyl) phosphonic acid, an excess of starting (2,2,2-trifluoroethyl) phosphonic acid]. Traces of macrocyclic by-products with two phosphinic acid, an excess of starting (2,2,2-trifluoroethyl)phosphinic acid and paraformaldehyde was performed in a strong acid solution (50% v/v aq. TFA) at 40 °C. It was found that only a slight excess of (2,2,2-trifluoroethyl)phosphonic acid (3.1 equiv.) and paraformaldehyde (3.5 equiv.) is

Equilibrium studies

To study the acid–base behaviour of H₃notptfe and the stability of its complexes, potentiometric titrations were employed. Two protonation constants were calculated from the titration data acquired in the pH range 1.6–12.1. Tables 1 and S3† list the results together with data reported for related ligands. The observed protonation steps correspond to the protonations of the amino groups of the tacn skeleton. Going from the fully deprotonated species, the first protonation proceeds in the alkaline region (log K₁ > 10) as it is common for other tacn-based ligands; the observed value falls into a range of values for other tacn-tris(phosphonic acid) derivatives (Table 1).⁶⁰–⁶² Compared to the acetate (H₃nota) and phosphonate (H₆notp) derivatives (Fig. 1), the basicity of H₃notptfe is lower due to the electron-withdrawing characteristic of the phosphinate groups.⁶³ The protonation constant describing the second protonation step also corresponds well to those of other tacn-tris (phosphonic acid) derivatives (Table 1). Further protonations lay below the pH range accessible by potentiometry pointing to the strong acidity of the phosphinic acid groups. The calculated distribution diagram of differently protonated H₃notptfe species is shown in Fig. S26†.

The thermodynamic stabilities of the complexes with selected alkaline earth (Mg²⁺, Ca²⁺) and transition (Mn²⁺, Co²⁺, Ni²⁺, Cu²⁺, Zn²⁺) metal ions were studied in the M²⁺–H₃notptfe systems using a slight ligand excess. Except for Co²⁺ and Ni²⁺, complexation of all metal ions was fast enough for conventional potentiometry. The systems containing Co²⁺/Ni²⁺ ions were studied by the out-of-cell method. The system containing Fe³⁺ cannot be studied by this method as some precipitate is irreversibly formed during the titration. In general, besides formation of the [M(notptfe)³⁻] complexes, the formation of hydroxido-complexes [M(notptfe)⁻(OH)²⁻] was observed in strongly alkaline solutions pointing to the weak nucleophilicity of the pendant arm oxygen atoms which are replaced by the hydroxido ligand in a strongly alkaline solution (Table 1). It should be noted that potential formation of the hydroxido complexes of Co²⁺ and Ni²⁺ ions cannot be confirmed as the out-of-cell titration used to study the systems cannot be reliably performed up to the alkaline region. Stability constants of [M (notptfe)³⁻] complexes are similar to those found for other phosphinic acid derivatives and are significantly lower in compari-
Magnetic properties of the complexes in solution

As the value of magnetic moment plays a significant role in the paramagnetic relaxation enhancement mechanism, we son with those of H3nota and H6notp as a result of a generally lower overall basicity of the donor sites in the phosphinate ligands.63 The ligand H3notp16e shows a slight selectivity for Mg2+ over Ca2+ analogously to other related derivatives; however, these biogenic ions are not fully complexed even in the strongly alkaline region (see Fig. 2 and S27†).

The complexes with the transition metal ions are much more stable than those of alkaline earth ions; the Mn2+ complex has the lowest stability among the studied transition metal ions and is fully formed above pH 7 (Fig. 2 and S28†). Complexes with Co2+–Zn2+ have comparable stability and the ligand shows almost no selectivity for the Cu2+ ion; so, the effect of Williams–Irving ordering is negligible. These metal ions are fully complexed at pH > 3; an illustrative distribution diagram is shown in Fig. 2 and S29†.

The observed non-selectivity for the Cu2+ ion is consistent with the non-selectivity of other phosphorus-containing tacn-based ligands but it is in contrast to the selectivity observed for H3nota (Table 1). Overall, the ligand H3notp16e binds paramagnetic transition metal ions into stable complexes with a high selectivity over biogenic alkaline earths ions which is promising for potential in vitro/in vivo use.

Table 1  Logarithms of ligand protonation constants (log Kp), stability constants of the studied metal complexes (log β011) and protonation constants of hydroxidocomplexes (log β011 – log β−11) of H3notp16e, and comparison with related ligands. Charges of the species are omitted for clarity; "L" means fully deprotonated form of the ligand.

<table>
<thead>
<tr>
<th>Equilibrium</th>
<th>H3notp16e</th>
<th>H3notp16e</th>
<th>H3notpMe</th>
<th>H3nota</th>
<th>H3notp</th>
</tr>
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<tbody>
<tr>
<td>H+ + L = HL</td>
<td>10.23</td>
<td>10.16b</td>
<td>10.92d</td>
<td>13.17e</td>
<td>12.17f</td>
</tr>
<tr>
<td>H+ + HL = H2L</td>
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<td>3.13b</td>
<td>3.97d</td>
<td>5.74f</td>
<td>9.44f</td>
</tr>
<tr>
<td>H+ + H2L = H3L</td>
<td>—</td>
<td>—</td>
<td>2.09d</td>
<td>3.22f</td>
<td>7.55f</td>
</tr>
<tr>
<td>H+ + H2L = H3L</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.96e</td>
<td>5.99f</td>
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<tr>
<td>H+ + H2L = H3L</td>
<td>—</td>
<td>—</td>
<td>0.70f</td>
<td>2.9f</td>
<td>2.7h</td>
</tr>
</tbody>
</table>

---

† This work, 0.1 M (NMe4)Cl. 6 0.1 M KNO3, ref. 66.
65. g 0.1 M KNO3, ref. 60.
63. g 0.1 M (NMe4)Cl, ref. 61.
62. g 0.1 M (NMe4)Cl, ref. 64.
61. g 0.1 M (NMe4)Cl, ref. 65.
60. g 0.1 M (NMe4)Cl, ref. 66.
59. g 0.1 M KNO3, ref. 67.
determined the magnetic moments of the studied paramagnetic complexes in solution. As the Mn$^{2+}$/Cu$^{2+}$–H$_3$notptfe complexes are formed quickly (see Potentiometric study section), they were prepared by mixing the metal salt and ligand (in a slight excess) stock solutions, and adjusting the pH to 7.4. Solutions of the Co$^{2+}$ and Ni$^{2+}$ complexes were prepared analogously but the solutions were heated to 50 °C overnight to ensure full complexation. In the system containing Fe$^{2+}$, some colloidal precipitate was continuously formed; therefore, measurement of the magnetic moment was performed immediately after preparation of the solution under argon and filtration through a microfilter.

Solutions of the Cr$^{3+}$ and Fe$^{3+}$ complexes were prepared by the reaction of CrCl$_3$·6H$_2$O (solid) or Fe(NO$_3$)$_3$ (stock solution), respectively, with a slight excess of H$_3$notptfe after neutralization to pH 5–6 and heating at 90 °C for 5 d (Cr$^{3+}$) or overnight (Fe$^{3+}$). Surprisingly, attempts to prepare a solution of the Co$^{3+}$ complex by reaction of the ligand with Na$_3$[Co(CO$_3$)$_3$] (a kinetically labile precursor commonly used for a direct preparation of trivalent cobalt complexes) failed; the Co$^{2+}$ complex was formed instead as identified by UV-Vis and $^{19}$F NMR spectroscopies.

Magnetic moments were determined using Evans’ method from the chemical shift difference of t-BuOH present in the solution of the complex with a known concentration and aq. solution in the insert cuvette and are listed in Table 2.

The values of $\mu_{\text{eff}}$ clearly show that the complexes of Mn$^{2+}$, Fe$^{2+}$/Fe$^{3+}$ and Co$^{2+}$ are high-spin and, thus, an overall ligand field induced by the (notptfe)$^{3-}$ anion is relatively small.

### Redox properties of the complexes

The redox behaviour of transition metal complexes of the "parent” H$_3$nota is well documented in the literature. Redox potentials of the M$^{2+}$/M$^{3+}$–H$_3$notptfe systems are reported for M = Cr, Mn, Fe, Co and Ni, and values of some of them fall into a biologically relevant range (Table 3). The change of oxidation state governs electronic and magnetic properties of the ions, and can significantly alter the chemical shift of the $^{19}$F NMR signal and its relaxation properties. If the redox change can occur under in vivo conditions, the complex can be utilized as a redox-responsive probe. Therefore, electrochemical studies of H$_3$notptfe complexes and analogous H$_3$nota complexes were performed to obtain directly comparable data as data reported in the literature were sometimes acquired under different or unspecified conditions (electrode material, supporting electrolyte). Besides the metal ions mentioned above, we also studied the Cu$^{2+}$ complex as the Cu$^{2+}$/Cu$^{+}$ pair can also be employed as a redox probe.

<table>
<thead>
<tr>
<th>Complex</th>
<th>$\mu_{\text{eff}}$ (B.M.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Cr$^{III}${notptfe$^{16}$}]</td>
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</tr>
<tr>
<td>[Mn$^{II}${notptfe$^{16}$}]</td>
<td>5.75</td>
</tr>
<tr>
<td>[Fe$^{II}${notptfe$^{16}$}]</td>
<td>5.29</td>
</tr>
<tr>
<td>[Fe$^{III}${notptfe$^{16}$}]</td>
<td>6.16</td>
</tr>
<tr>
<td>[Co$^{II}${notptfe$^{16}$}]</td>
<td>4.98</td>
</tr>
<tr>
<td>[Ni$^{II}${notptfe$^{16}$}]</td>
<td>2.77</td>
</tr>
<tr>
<td>[Cu$^{II}${notptfe$^{16}$}]</td>
<td>1.86</td>
</tr>
</tbody>
</table>

### Table 3 Redox potentials of [M$^{III}$\{L\}]$/[M^{II}$\{L\}]$ pairs of the transition metal ion complexes of L = H$_3$notptfe and H$_3$nota, obtained by CV (0.05 M aq. LiClO$_4$, ambient temperature, values are given in V vs. SCE)

<table>
<thead>
<tr>
<th>Redox pair</th>
<th>M–H$_3$notptfe</th>
<th>M–H$_3$nota</th>
</tr>
</thead>
<tbody>
<tr>
<td>This work</td>
<td>This work</td>
<td>Literature$^{52}$</td>
</tr>
<tr>
<td>Cr$^{3+}$/Cr$^{2+}$</td>
<td>−1.32$^a$</td>
<td>−1.39$^a$</td>
</tr>
<tr>
<td>Mn$^{III}$/Mn$^{II}$</td>
<td>0.67$^b$</td>
<td>0.56$^b$</td>
</tr>
<tr>
<td>Mn$^{IV}$/Mn$^{III}$</td>
<td>0.96$^b$</td>
<td>1.02$^b$</td>
</tr>
<tr>
<td>Fe$^{III}$/Fe$^{2+}$</td>
<td>−0.02$^b$</td>
<td>−0.035$^b$</td>
</tr>
<tr>
<td>Co$^{III}$/Co$^{2+}$</td>
<td>0.95$^a$</td>
<td>−0.23$^a$</td>
</tr>
<tr>
<td>Ni$^{III}$/Ni$^{II}$</td>
<td>−c</td>
<td>0.95$^b$</td>
</tr>
</tbody>
</table>

$^a$ Hanging mercury drop electrode. $^b$ Platinum electrode. $^c$ No electrochemical process was observed.

0.05 M aq. LiClO$_4$ solution was chosen as the supporting electrolyte due to a wide measurement window [−1.04—(−2.2)] and 1.5—(−0.9) V using the HMDE and Pt electrode, respectively, vs. SCE, and the complexes were studied by cyclic voltammetry (CV). The reversible behaviour of the M$^{2+}$/M$^{3+}$–H$_3$notptfe and M$^{2+}$/M$^{3+}$–H$_3$nota pairs was found for M = Cr, Mn, Fe and Co (Table 3). In contrast to the [Ni$^{II}$\{nota$^{−}$\}]$^{−}$ complex, [Ni$^{III}$\{notptfe$^{16}$\}$^{−}$] cannot be oxidized to the [Ni$^{IV}$\{notptfe$^{16}$\}]$^{2−}$ complex in the accessible potential range.

In the case of the Mn-systems with both ligands, a further reversible process was observed which is attributable to the [Mn$^{IV}$\{L\}$^{2−}$/[Mn$^{II}$\{L\}]$^{−}$ redox pair. This behaviour was reported for the Mn$^{2+}$–H$_3$nota complex previously but the reported potentials of 0.30 and 0.68 V for the [Mn$^{III}$\{nota$^{−}$\}]$^{−}$/[Mn$^{II}$\{nota$^{−}$\}]$^{−}$ and [Mn$^{IV}$\{nota$^{−}$\}]$^{2−}$/[Mn$^{III}$\{nota$^{−}$\}]$^{−}$ pairs, respectively, are not consistent with other literature data and with our value; probably, the reported potentials were wrongly corrected for the SCE potential. To identify the species and to study their stabilities, a spectro-electrochemical study was performed. If the potential was increased in the range from 0.5 to 1.0 V, a d–d transition band centred at 470 nm gradually appeared (Fig. S30†), attributable to Mn$^{3+}$ due to the one-electron oxidation of [Mn$^{III}$\{L\}]$^{−}$ and the formation of [Mn$^{IV}$\{L\}]$^{2−}$, consistent with the results obtained by the CV study. Further oxidation (applied potential up to 1.8 V) led to a gradual increase in absorbance over the whole spectral range, with no distinguished absorption band (Fig. S31†). It was probably caused by the formation of a colloidal precipitate. Thus, one can conclude that the oxidation of [Mn$^{III}$\{L\}]$^{−}$ to [Mn$^{IV}$\{L\}]$^{2−}$ is pseudo-reversible on the short CV timescale but the formed Mn$^{IV}$ species decomposes and colloidal MnO$_2$–H$_2$O is formed during the longer spectro-electrochemical timescale.

The spectro-electrochemical reduction (applied potential from 0.5 to −0.8 V) of the [Fe$^{III}$\{notptfe$^{16}$\}]$^{−}$ complex led to the formation of [Fe$^{II}$\{notptfe$^{16}$\}]$^{2−}$ as documented by the gradual spec-
tral change (Fig. S32†). The [FeII(noptfp)]− species was found to be stable on the given timescale (order of seconds); however as observed earlier, it decomposes on longer standing (see the Magnetic properties section).

The electro-synthetic oxidation (applied potential 1.1 V) of the [CoIII(L)] complex (characterized by three close low-intensity absorption bands centred around 520 nm) revealed the formation of the [CoIII(nptf)] complex (the appearance of two new intense d–d bands at 394 and 557 nm, as shown in Fig. S33†) which is stable in solution for at least several days.

The Cu2+ complexes of both H3nptfe and H3nota underwent irreversible two-electron reduction on HMDE as proved by the anodic peak corresponding to the oxidation of metallic copper; no electrochemical changes were observed using the Pt electrode. According to the measured values, the [CrII(L)] complex is a very strong reduction agent similar to [CrIII(nota)]+, and its potential lies close to the reduction edge of HMDE; such a value cannot be practically utilized in biological systems. However, the potentials of [MIII(L)]/ [MII(L)]− pairs with M = Mn, Fe and Co lie in the biologically relevant range. Among them, the stability of the Mn2+ complex is not sufficient for utilization in biological systems (full complexation at pH > 7, see Potentiometric study section) and the [FeII(noptfp)]− species was found to be kinetically labile, so only the Co2+/Co2−/H3nptfe redox pair is suitable for in vitro/ in vivo utilization. Furthermore, the [CoIII(nptf)]− complex is a high-spin paramagnetic species but the oxidized form [CoIII(noptf)]− is a low-spin diamagnetic complex, which induces a very significant change in the 19F NMR spectra (see below). Therefore, we studied the corresponding redox process using chemical oxidizing/reducing agents. The [CoIII(nptf)]− species can be prepared by chemical oxidation of [CoII(nptf)]− with K2S2O8 or H2O2 (Fig. S33†). The [CoIII(nptf)]− species can be reduced back to the [CoII(nptf)]− complex using NaBH4; other reducing agents tested = N2H4, NH2OH, Na2S2O4 caused no reaction. It should be further highlighted that the reaction of H3nptfe with Na2[CoII(CO3)3] afforded [CoII(nptf)]− and not the expected [CoIII(nptf)]− complex. Therefore, although the [CoIII(nptf)]− species is a relatively strong oxidation agent (E0 + 0.95 V vs. SCE, Table 3), some kinetic barrier plays a role in the tested chemical reductions, probably due to a full wrapping of the central metal ion with the ligand which prevents a close contact with a reduction agent. A comparison of the scaled UV-Vis spectra of [CoIII(nptf)]− and [CoIII(nptf)]− is shown in Fig. 3.

Solid-state structures of the complexes

The H3nota-like ligands usually wrap the metal ions in a hexadentate fashion. Three nitrogen atoms of the tacn skeleton form a basal N3-plane making one face of the coordination polyhedron, and the oxygen atoms of three pendant arms form a parallel upper O3-plane. Formation of the chelate rings upon a coordination of the tacn unit results in a clock-wise or anti-clock-wise torsion on the ethylene groups connecting the coordinated nitrogen atoms (i.e., in the Newman projection of

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**Figure 3** Comparison of the UV-Vis spectra of [CoIII(nptf)]− and [CoIII(nptf)]− complexes. Spectra are arbitrarily scaled. Extinction coefficients in dm3 mol−1 cm−1: [CoIII(nptf)]−: ε(502 nm) 16, ε(520 nm) 17, ε(541 nm) 16; [CoIII(nptf)]−: ε(394 nm) 68, ε(557 nm) 92.
R/S-isomerism give rise to a number of isomers (Fig. 4), similarly as observed for the phosphinate analogues of H$_2$doタ.81–83

Two Mn$^{2+}$ phases were obtained where the central Mn$^{2+}$ ion has the TTA coordination sphere. The absolute configuration on a phosphorus atom of all coordinated pendant phosphinate groups in the complex molecule is the same (in the latter compound forced due to the crystallographic trigonal symmetry of the space group, R3), resulting in the presence of the enantio-

meric pair $\Delta\delta$-SSS and $\Lambda\delta$-RRR in both structures. Selected relevant geometric parameters are listed in Tables 4 and S5† and molecular structures of the complex species are shown in Fig. 5 and 6.

The coordination cages are relatively large compared to other complexes (see below) as evidenced by the distance between the N$_5^-$ and O$_2^-$ planes (2.9 and 2.8 Å, respectively). It is caused by the long length of the N–Mn coordination bonds. The large separation of the planes leads also to a relatively small twist angle between the planes (i.e. pendant arm rotation, ca. 8° and 24° for the complex anions in [NH$_4$]$_6$[Mn (notp$^{16}$)]Cl$_2$3H$_2$O and [Mn(H$_2$O)$_6$][Mn(notp$^{16}$)]$_2$18H$_2$O phases, respectively). In the crystal structure of [Mn(H$_2$O)$_6$][Mn (notp$^{16}$)]$_2$18H$_2$O, two [Mn(notp$^{16}$)$^-_1$] anions are head-to-head connected to the central [Mn(H$_2$O)$_6$]$_{18}^2^-$ cation through hydrogen bonds (Fig. 6); a similar structural motif was also found in some other crystal structures (see below).

Several Co$^{2+}$-containing phases were obtained and, surprisingly, different diastereoisomers of the [Co(notp$^{16}$)$^-_1$] anion were found. In the crystal structure of [NH$_4$]$_6$[Co (notp$^{16}$)]3.5H$_2$O, the $\Delta\lambda$-SSS and $\Lambda\delta$-RRR enantiomers with the OC geometry were found (Fig. 7 and S37†). In the structure of [Co(H$_2$O)$_6$][Co(notp$^{16}$)]$_2$14.25H$_2$O·0.75MeOH the $\Delta\delta$-SSS and $\Lambda\delta$-RRR enantiomeric pairs with TTA geometries were found; for an example, see Fig. 8. These complex anions are connected to the [Co(H$_2$O)$_6$]$_{2}^2^-$ through the hydrogen bonds (Fig. S38†) similarly as it was observed in the crystal structure of [Mn(H$_2$O)$_6$][Mn(notp$^{16}$)]$_2$18H$_2$O discussed above, although the compounds are not isostructural. In contrast to the structures of the other Co$^{2+}$ phases, the sodium salt Na$_6$[Co(notp$^{16}$)]Br-3Me$_2$CO presents a TTA enantiomeric $\Delta\delta$-RRR/$\Lambda\delta$-SSS pair (Fig. 8 and S39†). Selected relevant geometric parameters for the structures are listed in Tables 4 and S5†.

The Ni$^{2+}$ complex was successfully crystallized as [Mg (H$_2$O)$_6$][Ni(notp$^{16}$)]$_2$12H$_2$O in the space group R3 and with the lattice parameters close to those of [Mn(H$_2$O)$_6$][Mn (notp$^{16}$)]$_2$18H$_2$O; however, the compounds are not isostructural. As in the [Mn(H$_2$O)$_6$][Mn(notp$^{16}$)]$_2$18H$_2$O and [Co (H$_2$O)$_6$][Co(notp$^{16}$)]$_2$14.25H$_2$O·0.75MeOH phases, two [Ni (notp$^{16}$)$^-_1$] anions are head-to-head connected to the central hexaaqua unit via hydrogen bonds (Fig. S40†). The [Ni (notp$^{16}$)$^-_1$] species form an octahedral $\Lambda\delta$-RRR/$\Lambda\delta$-SSS pair (Fig. 9). For geometric parameters, see Tables 4 and S5†.

In the case of the Cu$^{2+}$ complex, two different phases were isolated in the solid state. The compound [NH$_4$]$_6$[Cu (notp$^{16}$)]3.5H$_2$O is isostructural with [NH$_4$]$_6$[Co (notp$^{16}$)]3.5H$_2$O and even an analogous disorder was found (see the ESI†). The $\Delta\delta$-SSS/$\Lambda\delta$-RRR enantiomers with the octahedral geometry were found (Fig. S41 and S42†). In the other phase composition (NH$_4$)$_6$[Cu(notp$^{16}$)]Cl·3H$_2$O, only two pendant arms are coordinated and they are turned in mutually opposite directions (Fig. 10). Centrosymmetry of the space group (P1) leads formally to $\Delta\Lambda\delta$-SSR/$\Lambda\delta$-SSS enantiomers. Very similar pentacoordinated geometry was previously reported for the Cu$^{2+}$ complexes of H$_2$notp and H$_2$notp$^{6}$. 

![Fig. 4](image-url) Possible diastereoisomers of H$_2$notp$^{16}$ complexes; only one of the enantiomers of each diastereoisomer is shown. All shown enantiomers have the $\Delta\delta$-SSS conformations of the macrocycle, the other enantiomers have the $\Delta\lambda$-SSR conformations. Left column: the OC species; right column: the TTA species. Colour code: metal ion – magenta, phosphorus – orange, oxygen – red, nitrogen – light blue, carbon – dark grey.
Selected geometric parameters found in the crystal structures of the studied complexes [L²⁻ = (notptfe)₃]

<table>
<thead>
<tr>
<th>Geometry</th>
<th>(NH₄)₃[Mn(L)]Cl₃·3H₂O</th>
<th>[Mn(H₂O)₆][NH₄][Co(NO₃)₂]Cl₂·3H₂O</th>
<th>[NH₄][Co(L)]Cl₂·3H₂O</th>
<th>Na₃[Co(L)]Br·3Me₂CO·(NH₄)₃[Mn(L)]Cl₂·3H₂O</th>
<th>[Ni(NO₃)₂]·2H₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-N1</td>
<td>2.360(1)</td>
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<tr>
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<td>6.310(2)</td>
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<td>M--F₁</td>
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Dihedral angles (°)

| N1-NQ-OOQ-O11 | 6.76(7) | 24.38(9) | 46.8(1) | 33.43(8) | 33.03(8) | 29.08(8) | 35.99(9) | 34.7(4) | 33.4(3) | 44.82(6) | 50.39(4) | 43.0(2) |
| N4-NQ-OOQ-O21 | 6.65(6) | 24.38(9) | 49.6(1) | 32.27(8) | 33.45(8) | 29.08(8) | 35.99(9) | 33.2(3) | 33.2(3) | 53.7(6)  | 50.39(4) | 43.0(2) |
| N7-NQ-OOQ-O21 | 8.79(6) | 24.38(9) | 46.0(1) | 31.28(8) | 32.00(8) | 29.08(8) | 35.99(9) | 34.2(4) | 34.7(4) | 45.56(6) | 50.39(4) | 43.0(2) |

The complex molecule possesses trigonal symmetry, F₁ = F₄ = F₇, F₂ = F₅ = F₈, F₃ = F₆ = F₉. NQ and OQ are centroids of the Nₓ and Oₓ planes, respectively. Formal numbering: fluorine atoms F₁-3 belong to the pendant arm attached to N₁, fluorine atoms F₄-6 to the pendant arm attached to N₄, and fluorine atoms F₇-9 to the pendant arm attached to N₇. More abundant position of the disordered trifluoroethyl group.
Selected geometric parameters are listed in Tables 4 and S5.† Octahedral species with $\Lambda\delta$-RRR and $\Delta\lambda$-SSS geometry were also observed in the crystal structure of the Zn$^{2+}$ complex, [ZnCl(H$_2$O)$_3$][Zn(notptfe)]·2H$_2$O (Fig. S43†). Here, the counterion [ZnCl(H$_2$O)$_3$]$^+$ is formed from the excess of ZnCl$_2$ used in the reaction. For geometric parameters, see Tables 4 and S5.†

The critical parameter influencing the relaxation rates of the $^{19}$F nuclei is the distance between the paramagnetic ion and the fluorine atoms. Therefore, this parameter is compiled in Table 4 together with selected geometric parameters of the coordination cages. It can be seen that the exact geometry of the coordination sphere influences the M⋯F distance only negligibly – in the TTA species, the distances are only slightly longer (ca. 5.6–6.7 Å) when compared to the OC isomers (ca. 5.5–6.5 Å). Such distances fall in the range suggested to be relevant for a significant influence on the $^{19}$F NMR relaxation times.89 Very similar mean M⋯F lengths were observed also in the complexes of 1,8-H$_2$te$_2$ptfe (cyclam-based ligand with the same pendant arms, Fig. 1) which were studied previously.47

**Fig. 5** Molecular structure of the [Mn(notptf)${\text{III}}$]$^-$ anion with the $\Delta\delta$-SSS TTA geometry found in the crystal structure of (NH$_4$)$_3$[Mn(notptfe)]Cl$_2$·3H$_2$O. Hydrogen atoms are omitted for clarity.

**Fig. 6** Molecular structure of [Mn(H$_2$O)$_6$][Mn(notptfe)]$^{1-}$ fragment found in the crystal structure of [Mn(H$_2$O)$_6$][Mn(notptfe)]$^{1-}$·18H$_2$O. Intermolecular hydrogen bonds connecting two [Mn(notptfe)]$^{1-}$ anions to the central [Mn(H$_2$O)$_6$]$^{2+}$ cation are shown in turquoise. Individual [Mn(notptfe)]$^{1-}$ species adopt the $\Delta\delta$-SSS and $\Lambda\lambda$-RRR TTA geometries. Carbon-bound hydrogen atoms are omitted for clarity.

**Fig. 7** Molecular structure of the [Co(notptf)${\text{III}}$]$^-$ anion with the $\Delta\lambda$-SSS OC geometry found in the crystal structure of (NH$_4$)$_3$[Co(notptfe)]$^-$·3.5H$_2$O. More abundant part of the disordered pendant arm (P3A and related atoms) is shown; for the disorder, see Fig. S37†. Hydrogen atoms are omitted for clarity.
To study the solution structures of the complexes, the NMR spectra of diamagnetic (Mg\(^{2+}\), Zn\(^{2+}\)) complexes also were acquired. The \(^{19}\)F NMR spectrum of the Mg\(^{2+}\)–H\(_3\)notptfe system at pH 7.5 fully agrees with the results of potentiometry – the spectrum revealed the presence of the well resolved signals of the free ligand and the complex in ca. 65:35 ratio (Fig. S8†).

Besides these two species, some very minor signals were also observed, probably belonging to the complex species with different R/S configurations of the phosphinate pendant groups or to some species in which some of the pendant arms are uncoordinated. It indicates that the ligand and complex species are not in chemical exchange with respect to the NMR time scale, and, very probably, the major complex species has the C\(_3\)-symmetry. In the case of the Zn\(^{2+}\)–H\(_3\)notptfe system, a full complexation of the metal ion was expected on the basis of potentiometry. It was confirmed by the \(^{19}\)F and \(^{31}\)P NMR spectra (Fig. S23–S25†) where observation of only one symmetric signal points to the presence of only one enantiomeric pair of a single diastereoisomer (one combination of \(\Delta/\Lambda + \delta/\lambda\).

Fig. 8 Molecular structures of the [Co(notptfe\(^{18}\)])\(^{-}\) anion with the \(\Lambda\Lambda\Lambda\)-RRR TTA geometry found in the crystal structure of [Co(H\(_2\)O)\(_6\)][Co(notptfe\(^{18}\)])\(_2\).14.25H\(_2\)O.0.75MeOH (left) and that with the \(\Lambda\Lambda\Lambda\)-SSS TTA geometry found in the crystal structure of Na\(_3\)[Co(notptfe\(^{18}\)])\(_2\)Br.3Me\(_2\)CO (right). Hydrogen atoms are omitted for clarity.

Fig. 9 Molecular structure of the [Ni(notptfe\(^{16}\)])\(^{-}\) anion with the \(\Lambda\Lambda\Lambda\)-RRR OC geometry found in the crystal structure of [Mg(H\(_2\)O)\(_6\)][Ni(notptfe\(^{16}\)])\(_2\).12H\(_2\)O. Hydrogen atoms are omitted for clarity.

Fig. 10 Molecular structure of the pentacoordinated [Cu(notptfe\(^{16}\)])\(^{-}\) anion adopting the \(\Delta\Lambda\Lambda\Lambda\Lambda\Lambda\)-SR geometry found in the crystal structure of (NH\(_4\))\(_2\)[Cu(notptfe\(^{16}\)])Cl.3H\(_2\)O. Hydrogen atoms are omitted for clarity.
Table 5  Longitudinal relaxation times $T_1$ (ms) of the $^{19}$F NMR signals of H$_3$notptfe$^{16}e$ and its complexes. Estimated deviation (based on repeated measurements) is generally < 5%

<table>
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<tr>
<th>$^{19}$F Larmor frequency/MHz</th>
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<th>376</th>
<th>282</th>
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<td>Temperature/°C</td>
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<td></td>
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<tr>
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<td>$H_3$notptfe$^{16}e$</td>
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<td>$0.85 \times 10^3$</td>
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<tr>
<td>$[Cr^{III}(notptfe)^{16}e]$</td>
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<td>$2.0^b$</td>
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<td>$0.76 \times 10^3$</td>
</tr>
</tbody>
</table>

$^a$ Only a rough estimate due to the very fast relaxation. $^b$ Spectra cannot be successfully phased.

Table 6  Transversal relaxation times $T_2$ (ms, diamagnetic compounds, measured with the CPMG sequence) and effective transversal relaxation times $T_2^*$ (ms, paramagnetic compounds, calculated from the half-widths) of the $^{19}$F NMR signals of H$_3$notptfe and its studied complexes. Estimated deviation (based on repeated measurements) is generally < 5%

<table>
<thead>
<tr>
<th>$^{19}$F Larmor frequency/MHz</th>
<th>565</th>
<th>376</th>
<th>282</th>
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<td>$0.69 \times 10^3$</td>
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<td>$[Mn^{II}(notptfe)^{16}e]$</td>
<td>−46.0</td>
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<td>$[Zn^{II}(notptfe)^{16}e]$</td>
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<td>2.1</td>
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$^a$ Measurement of $T_2$ was not possible on a Varian VNMR300 with an accessible probe. $^b$ Only a rough estimate due to the extreme broadness of the signal. $^c$ Spectra cannot be successfully phased.

Fig. 11  Visual comparison of $^{19}$F NMR spectra of the studied transition metal complexes of H$_3$notptfe$^{16}e$ and free ligand. The inset shows spectra of diamagnetic H$_3$notptfe$^{16}e$ and [Zn(notptfe)$^{16}e$].
kHz at 565 MHz) and can be easily measured. However, the longitudinal relaxation of the $^{19}$F NMR signals of all these complexes is extremely fast ($T_1 < 1$ ms, Tables 5 and 6).

In contrast to the paramagnetic complexes discussed above, all $^1$H, $^{13}$C, $^{19}$F and $^{31}$P NMR spectra could be observed for the [Co$^{III}$(notptfe)]$^\text{−}$ complex. As several geometries of the complex were found in the solid state (see above), some dynamic equilibrium between the arrangements can be expected in the solution. However, there is only one symmetric (although broad) peak in the $^{1}H/^{13}C$ NMR spectra and only one set of a $^1$H/$^{13}$C ($^1$H) signal. Thus, fluxionality of the [Co$^{III}$(notptfe)]$^\text{−}$ complex species is probably very fast. In the $^1$H NMR spectra spreading over 200 ppm, 7 of the expected 8 signals were found (Fig. 12 and S13†) as the last signal was very close to the signal of the solvent (water/HDO) and overlapped; it was found by measuring the temperature dependence of the spectra (Fig. S13†). In the $^{13}$C($^1$H) NMR spectra, all of the expected 5 signals were found in the range from −500 to +200 ppm (Fig. 12 and S14†). A similar very large spectral $^{13}$C NMR range was observed previously for the Co$^{2+}$ complex of the N-(2,2,2-trifluoroethyl) cyclam derivative.45

In the $^{19}$F NMR spectrum of [Co$^{II}$(notptfe)]$^\text{−}$, one broad signal centred at −50.5 ppm is present (Fig. S15†) which shows optimally fast longitudinal relaxation in order tens of milliseconds ($T_1 ~ 40$–80 ms, dependent on the external magnetic field strength and temperature, Table 5), although its transversal relaxation is very fast (Table 6). This compound also shows a broad $^{31}$P($^1$H) NMR signal at ca. 200 ppm (Fig. S16†). When the [Co$^{II}$(notptfe)]$^\text{−}$ complex is oxidized with K$_2$S$_2$O$_8$ or H$_2$O$_2$, a set of multiplets (pseudo-quartets due to similar values of $J_{FH}$ and $J_{FP}$) of [Co$^{III}$(notptfe)]$^\text{−}$ gradually appears in the $^{19}$F NMR spectrum (Fig. 13). It is consistent with the data from spectro-electrochemical experiments (Fig. S33†). The signals are narrow and their relaxation is slow. Thus, the formed [Co$^{III}$(notptfe)]$^\text{−}$ complex is obviously diamagnetic with a low-spin $^a$d$^9$ arrangement. Several close and hardly separable $^{19}$F NMR signals of [Co$^{III}$(notptfe)]$^\text{−}$ appear which can be explained by the presence of isomers with different R/S configurations on the phosphinate groups. These isomers are not exchanged due to kinetic inertness and non-fluxionality of the Co$^{3+}$ complexes, and each affords individual signal(s).

The $^{19}$F NMR spectrum of the [Ni$^{II}$(notptfe)]$^\text{−}$ complex contains two broad $^{19}$F NMR signals separated by ca. 3 ppm, with a relative intensity ca. 10:90% (Fig. S18†). In the case of [Cu$^{II}$(notptfe)]$^\text{−}$, only one broad signal was observed (Fig. S20†). The signals of both complexes relax very fast with $T_1$ in the range of ca. 3–5 ms and $T_2$ ca. 2 ms (Tables 5 and 6).

Overall, the observed relaxation times are consistent with those found previously for the complexes of the related cyclam-based ligand 1,8-H$_2$te$_2$ptfe (Fig. 1) with the same pendant arm.47 Fast movement of the 2,2,2-trifluoroethyl group effectively averages the distances; however, the mean value cannot be reliably calculated as it strongly correlates with electronic relaxation times whose exact values are not known and, for individual metal ions, can cover a wide range.47 However, the [Cr$^{III}$(notptfe)], [Mn$^{II}$(notptfe)]$^2$ and [Fe$^{III}$(notptfe)] complexes cannot be utilised in $^{19}$F MRI as they show very broad signals which relax too fast and, therefore, are not reliably detectable. The relaxation characteristics of the [Ni$^{II}$(notptfe)]$^\text{−}$ and [Cu$^{II}$(notptfe)]$^\text{−}$ complexes are more suitable but their potential use in the imaging experiments would need special ultrafast measurement techniques,90,91 due to too short relaxation times (few milliseconds). In this respect, the most promising is the [Co$^{II}$(notptfe)]$^\text{−}$ complex showing optimally fast longitudinal relaxation ($T_1$ in order of tens of milliseconds) which is suitable for standard MRI hardware. Furthermore, the redox potential of the [Co$^{II}$(notptfe)]$^\text{−}$/[Co$^{III}$(notptfe)]$^\text{−}$ pair has physiologically relevant value making the compound potentially employable as a redox probe.

**Conclusions**

A new 1,4,7-triazacyclononane-based ligand substituted with three (2,2,2-trifluoroethyl)phosphinate pendant arms was studied with respect to its potential use in contrast agents for $^{19}$F Magnetic Resonance Imaging ($^{19}$F MRI). With a large metal ion Mn$^{2+}$, the ligand forms complexes with twisted-trigonal-
antiprismatic geometry, whereas with the smaller ions Ni$^{2+}$, Cu$^{2+}$ and Zn$^{2+}$, complex species with an octahedral geometry are formed. With the Co$^{2+}$ ion, both environments were observed. Complexes of Co$^{3+}$, Ni$^{2+}$, Cu$^{2+}$ and Zn$^{2+}$ are very stable and are fully formed at pH > ~3. Paramagnetic metal ion complexes show very short relaxation times of the $^{19}$F NMR signal due to a short distance between the paramagnetic metal ion and the fluorine atoms (values found in the crystal structures are ~5.5–6.5 Å). Most of the studied complexes show too fast longitudinal relaxation for the application ($T_1$ of the Cr$^{3+}$, Mn$^{2+}$ and Fe$^{3+}$ complexes in the sub-millisecond range; the Ni$^{2+}$ and Cu$^{2+}$ complexes ~4 ms), but $T_1$ of [Co$^{3+}$(notp)Fe]$^-$ (40–80 ms) falls in a range suitable for easy exploitation. Electrochemical studies revealed the formation of a stable diamagnetic Co$^{3+}$ complex ([$E_1$ 0.95 V vs. SCE]). Together with a suitable relaxation time, it makes the [Co$^{III}$(notp)Fe]/[Co$^{III}$(notp)Fe]$^-$ pair potentially useful as a redox-responsive contrast agent in $^{19}$F MRI.

Author contributions

FK – investigation, methodology, validation, visualization, and writing – original draft; TD – investigation and writing – original draft, JK – conceptualization, investigation, methodology, validation, visualization, and writing – original draft, review and editing, IC – investigation, JH – investigation, AL – investigation, VK – investigation, PH – conceptualization, funding acquisition, and writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

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