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4,4′-Bis(trifluoromethyl)-2,2′-bipyridine – a multipurpose ligand scaffold for lanthanoid-based luminescence/^{19}F NMR probes†

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The tetradentate ligand 4,4′-bis(trifluoromethyl)-2,2′-bipyridine-6,6′-dicarboxylic acid (H_2**1**) and three corresponding anionic rare earth complexes [RE(**1**)$_2$]$^-$ (RE = Y, Tb, Dy) were synthesized. The terbium and dysprosium complexes show lanthanoid-centered luminescence in aqueous solution, as well as paramagnetically enhanced longitudinal magnetic relaxation of the ^{19}F nuclei.

Introduction

Molecular lanthanoid complexes are very attractive for the development of bioanalytical probes because of the unique photophysical and magnetic properties that these building blocks can provide. In this context, ^{1}H MRI contrast agents based on gadolinium are nowadays one of the most widely used classes of metal complexes in clinical diagnosis,[1] while complexes with a variety of lanthanoids (*e.g.* Eu, Tb) have made considerable progress as luminescent probes in a great number of bioanalytical settings.[2] Every method has advantages but also specific intrinsic limitations. The use of analytical probes, however, which can be addressed by two different modalities in one molecular entity, is therefore potentially of great value. In the optimal case, these bimodal probes allow the synergistic combination of all the advantages of the individual methods while alleviating the disadvantages.[3] One very attractive possibility is the combination of magnetic and photophysical properties. Not surprisingly, several examples of such molecular, bimodal ^{1}H MRI/optical probes have been reported recently.[4] In almost all instances, however, bimodality is only achieved by the application of a mixture of different lanthanoids (*e.g.* Gd/Eu) with one ligand architecture. In addition, for this particular combination the requirements for both modalities are mutually detrimental. While Gd-based contrast agents need to have at least one water molecule bound to the metal center, luminescence is severely quenched by inner-sphere H_2O. A potentially very attractive alternative, which could be helpful to avoid this problem, is the use of ^{19}F (instead of ^{1}H) nuclei, which have a number of favorable NMR characteristics (*e.g.* 100% natural abundance, spin 1/2 and high gyromagnetic ratio). While the great potential of ^{19}F MRI has been recognized for quite some time, the remaining challenges (high probe concentrations/long acquisition times necessary) have to date precluded its wider application.[5] Parker *et al.* have recently introduced the idea of paramagnetic relaxation enhancement in fluorinated lanthanoid complexes in order to enhance the sensitivity of ^{19}F MRI/MRS probes.[6] According to their concept, fluorine nuclei are positioned within a distance of *ca.* 7.5 Å to a paramagnetic lanthanoid. This substantially decreases the longitudinal relaxation time T_1, making more scans per time interval possible. Provided that the signal broadening associated with concomitant shortening of the transverse relaxation time T_2 is not too severe, signal enhancement of one order of magnitude or more has been shown with this approach.[6] Some of the lanthanoids suitable for use in ^{19}F MRI are potentially also good candidates for the development of luminescence probes. The two most promising lanthanoids in this respect are the highly paramagnetic Tb ($\mu_{\text{eff}} = 9.7\ \mu_B$) and Dy ($\mu_{\text{eff}} = 10.6\ \mu_B$), which exhibit emission in the visible spectral region upon photoexcitation. The structural and electronic requirements for the realization of both modalities in a single ligand architecture are not easy to fulfill, especially if some generality with respect to the lanthanoid used is to be achieved. On the one hand, for maximum sensitivity, one would ideally like to have as many chemically and magnetically equivalent ^{19}F nuclei present, which also have to be positioned within a certain distance range from the lanthanoid center. On the other hand, the electronic structure of the ligand must be appropriate for the sensitization of lanthanoid luminescence by the antenna effect. As a promising candidate for the development of such ligands,

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†Electronic supplementary information (ESI) available: Calculation of weighted terbium–fluorine distances in **Tb-7**, determination of T_1 relaxation times of **RE-7** (RE = Y, Tb, Dy). CCDC 920406 (**4**) and 920407 (**Tb-7**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3dt50842k

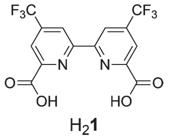


Fig. 1 Ligand H_2**1** based on a 4,4′-bis(trifluoromethyl)-2,2′-bipyridine scaffold.

we envisioned the simple model system H_2**1** (Fig. 1) featuring six equivalent fluorine nuclei and a 2,2′-bipyridine moiety, the latter being among the most commonly used synthetic platforms in lanthanoid coordination chemistry.[7]

In addition, it is known that 2,2′-bipyridine-6,6′-dicarboxylic acid can act as an antenna for the sensitization of Tb luminescence.[8] Here, we show in a proof-of-concept study that the 4,4′-bis(trifluoromethyl)-2,2′-bipyridine scaffold in H_2**1** is indeed suitable for the implementation of both modalities (^{19}F NMR and lanthanoid luminescence) in a single lanthanoid complex.

Results and discussion

Ligand synthesis

The ligand H_2**1** was synthesized in a linear sequence over five steps starting from 2-bromo-6-methyl-4-trifluoromethyl-pyridine (**2**) (Scheme 1). Nickel(0)-mediated coupling of **2** to the corresponding bipyridine **3** was rather efficiently achieved using the conditions developed by Furue *et al.* for electron-poor pyridines.[9] Oxidation of the benzylic methyl groups directly to H_2**1** proved to be impractical because of very low yields and the formation of mixtures of different species that were difficult to separate. Instead, we used another sequence involving oxidation to the corresponding *N*,*N*′-dioxide **4** (crystal structure in Fig. 2), Boekelheide rearrangement to **5**, saponification to **6**, and oxidation of bis(alcohol) **6** to cleanly give the desired ligand H_2**1**. Complexation with the rare earths Dy, Tb, and Y (as a diamagnetic, photoinactive reference) yielded the analytically pure complexes **RE-7**.

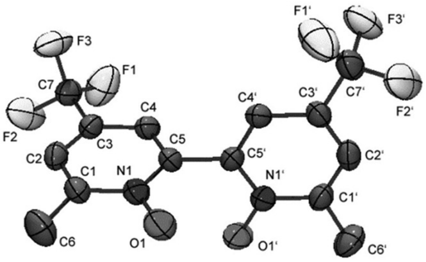
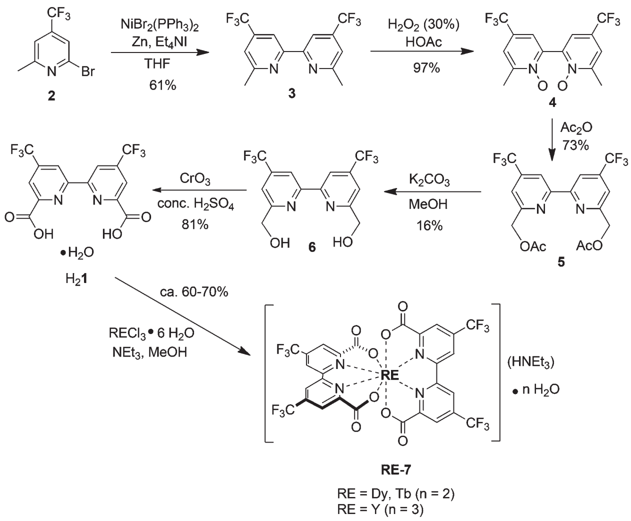


Fig. 2 Thermal ellipsoid plot for **4** (Ortep 3 for Windows,[10] 50% probability level). The hydrogen atoms are omitted for clarity.

The structure of the complexes was confirmed by X-ray analysis on single crystals of **Tb-7**, featuring two deprotonated ligands binding to the eight-coordinate metal center in an almost ideal trigonal-dodecahedral coordination geometry (idealized symmetry D_{2d}) (Fig. 3) with all four CF_3 groups being essentially equivalent. The complexes in the solid state are anionic with triethylammonium as the countercation. Importantly, the distances r_{Tb-F} are between 7.25 Å and 7.43 Å reflecting the possible range upon rotation of the CF_3 groups. The weighted, average distance is r_{mean} = 7.35 Å (weighting by r^{-6}, see the ESI†). This distance is rather long but would still be within the potentially useful range for ^{19}F NMR probes.[6]

Preliminary ^{19}F NMR measurements of **RE-7** (RE = Y, Tb, Dy) in D_2O showed only a single fluorine resonance in every case suggesting that the complex stayed intact upon dissolution. Expectedly, however, this simple model system is not stable enough under more demanding conditions such as a challenge with high-denticity competing ligands. For example, a 1.5 mM solution of **Y-7** (10 mM HEPES, pH 7.4) shows complete decomplexation upon the addition of 10 equivalents of Na_2H_2EDTA.



Scheme 1 Synthesis of ligand H_2**1** and the complexes **RE-7**.

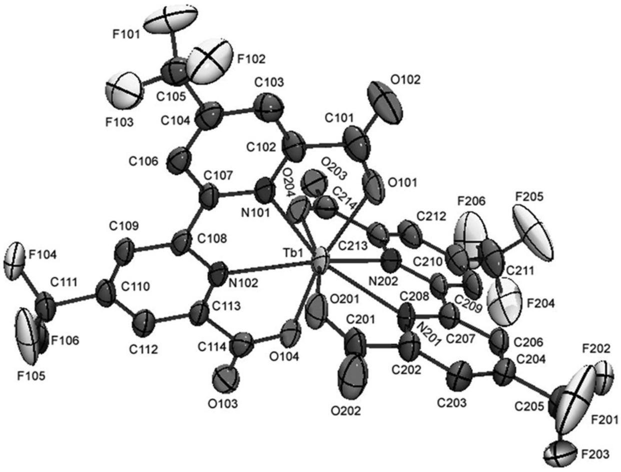


Fig. 3 Thermal ellipsoid plot for **Tb-7** (Ortep 3 for Windows,[10] 50% probability level). The hydrogen atoms and the isolated Et_3NH^+ cation are omitted for clarity.

Luminescence spectroscopy

The energy of the ligand-centered triplet state in the complexes **RE-7** was estimated from the low-temperature phosphorescence spectra of **Y-7** (Fig. 4). Fitting of the band structure yielded a zero-phonon transition energy (excited triplet → ground state singlet) of 22 700 cm^{-1}. This relatively high value, while above the emitting states of Tb ($^5D_4$ at *ca.* 20 500 cm^{-1})[11] and Dy ($^4F_{9/2}$ at *ca.* 21 100 cm^{-1}),[11] is very likely to be not sufficient to avoid problems of thermally activated back energy transfer associated with energy gaps smaller than *ca.* 2000 cm^{-1} between the triplet state of the antenna moiety and the corresponding accepting lanthanoid state. This phenomenon is likely to be responsible for the relatively small quantum yields of **Tb-7** and **Dy-7** (*vide infra*) and has also been observed previously for terbium in the non-fluorinated complex analogue with the ligand 2,2′-bipyridine-6,6′-dicarboxylic acid.[8]

Steady state luminescence spectra of **Tb-7** and **Dy-7** in aqueous solution show the typical emission bands for both lanthanoids (Fig. 5). Quantum yield measurements gave values of 0.9% for Tb and 0.7% for Dy (Table 1). The value for **Dy-7** is quite respectable since dysprosium complexes usually show quantum yields in aqueous systems well below 5% even for optimized systems.[12] On the other hand, the relatively poor luminescence efficiency of **Tb-7** is rather surprising, but in the light of the previously reported value of only 6.3% for the terbium complex with the ligand 2,2′-bipyridine-6,6′-dicarboxylic acid, is not entirely unexpected.[8] The low overall efficiencies for both complexes, however, are more than enough to ensure straightforward luminescence detection, keeping in mind that the concentrations for ^{19}F NMR measurements would be in the mM range which is much higher than usually necessary for luminescence probes.

Table 1 ^{19}F NMR data (5.87 T, 298 K) and quantum yields for **Tb-7** and **Dy-7** (10 mM HEPES buffer, pH 7.4)

Complex	δ_F [a] [ppm]	R_1 [a,b] [Hz]	$\Delta\omega_{1/2}$ [Hz]	Φ [d] [%]
Tb-7	−72.5	63.8(1.8)	41[c]	0.9
Dy-7	−74.8	99.5(2.1)	82[c]	0.7

[a] **Y-7**: δ_F = −64.7 ppm; R_1 = 1.18(0.04) Hz. [b] Sample standard deviation in parentheses (with Bessel correction). [c] In CD_3OD (see text). [d] ±10%, measured relative to quinine sulfate in 0.5 M H_2SO_4 (Φ = 54.6%) as the standard.[13]

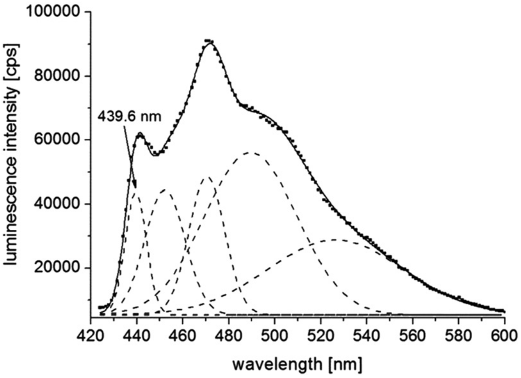


Fig. 4 Low-temperature (77 K) steady state emission spectrum of **Y-7** in MeOH–EtOH (1 : 1, v/v) after excitation at λ_{exc} = 310 nm (solid line: cumulative fit function; dashed lines: individual Gaussians).

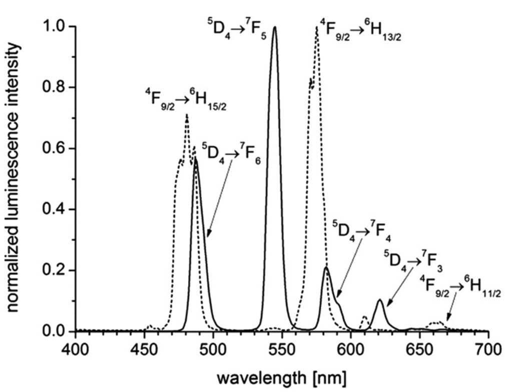


Fig. 5 Steady state emission spectrum of **Tb-7** (solid line) and **Dy-7** (dashed line) in H_2O after excitation at λ_{exc} = 306 nm.

^{19}F NMR spectroscopy

^{19}F NMR measurements in aqueous buffer solutions showed moderate paramagnetic shifts of *ca.* 8–10 ppm for **Tb-7** and **Dy-7** relative to the diamagnetic **Y-7** (Table 1). Measurements of the longitudinal relaxation rates R_1 (B = 5.87 T, T = 298 K) gave values of 63.8 Hz for **Tb-7** and 99.5 Hz for **Dy-7** (Table 1). These rates are rather high for fluorine nuclei at a distance of *ca.* 7.35 Å from the lanthanoid and high enough for potential paramagnetic ^{19}F probes. The signals of **Tb-7** and **Dy-7** in aqueous solution, however, are rather broad (with signal widths at half height $\Delta\omega_{1/2}$ > 350 Hz). This, however, is not an intrinsic property of the 2,2′-bipyridine unit. In CD_3OD, the signals are relatively sharp (Tb: $\Delta\omega_{1/2}$ = 41 Hz, Dy: $\Delta\omega_{1/2}$ = 82 Hz) in a similar range compared to previously reported successful examples of ^{19}F MRI probes,[6] indicating that the broadening in aqueous solution is due to exchange processes rather than paramagnetic acceleration of the transverse relaxation.

Conclusions

In conclusion, we have synthesized a model ligand H_2**1** that is based on the new 4,4′-bis(trifluoromethyl)-2,2′-bipyridine scaffold. We have shown that lanthanoid complexes based on this molecular entity could in principle be used simultaneously in paramagnetically enhanced ^{19}F NMR and in Tb/Dy luminescence measurements. The incorporation of this new building block into more elaborate ligand architectures promises great potential for the development of practical bimodal ^{19}F MRI/optical imaging probes.

Experimental section

Chemicals were purchased from commercial suppliers and used as received unless stated otherwise. NMR solvents had deuterium contents >99.8% D. Other solvents were dried by standard procedures (EtOH: Mg/I_2). Air-sensitive reactions were carried out under a dry, dioxygen-free atmosphere of N_2 using the Schlenk technique. Column chromatography was performed with silica gel 60 (Merck, 0.063–0.200 mm). Analytical thin layer chromatography (TLC) was done on silica gel 60 F_{254} plates (Merck, coated on aluminium sheets).

ESI mass spectrometry was done using Bruker Daltonics Esquire6000. NMR spectra were measured using Bruker DPX-250 (^{1}H: 250 MHz, ^{13}C: 62.9 MHz, ^{19}F: 235 MHz) and Bruker DPX-200 (^{1}H: 200 MHz, ^{13}C: 50.3 MHz). UV/vis spectra were recorded on a Jasco-670 spectrophotometer using 1.0 cm quartz cuvettes.

3-Cyano-6-methyl-4-trifluoromethyl-2-pyridone

1,1,1-Trifluoroacetylacetonate (100.23 g, 650.5 mmol, 1.0 equiv.) and cyanoacetamide (60.16 g, 715.5 mmol, 1.1 equiv.) were suspended in EtOH (400 mL, technical grade) and the mixture was heated to gentle reflux. Diethylamine (74.3 mL, 52.33 g, 715.5 mmol, 1.1 equiv.) was added dropwise over 60 min. Stirring and heating were continued for an additional 90 min and the dark brown solution was allowed to come to ambient temperature. The solid was broken up, the mixture was immersed in an ice-bath, and 1 M HCl (800 mL) was added slowly with stirring. After 30 minutes of stirring, the suspension was stored at 4 °C overnight. The precipitate was collected, washed with water, and dried under reduced pressure (1 mbar) at 60 °C (bath temperature) to yield the product as a light-yellow solid (117.74 g, 90%). The analytical data agree with previously reported literature data.[14]

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.63 (s, 1 H), 2.38 (s, 3 H) ppm. Anal. Calcd for $C_8H_5F_3N_2O$ (M_r = 202.13): C, 47.54; H, 2.49; N, 13.86. Found: C, 47.85; H, 2.65; N, 14.04.

6-Methyl-4-trifluoromethyl-2-pyridone[15]

3-Cyano-6-methyl-4-trifluoromethyl-2-pyridone (31.90 g, 157.9 mmol, 1.0 equiv.) was added in portions to 50% H_2SO_4 (300 mL). The suspension was heated to 150 °C (bath temperature) for 20 h. The resulting yellow solution was cooled, cautiously diluted with cold water to a volume of *ca.* 1.6 L, and neutralized with solid Na_2CO_3. The resulting colorless precipitate was collected, washed with cold water, and dried *in vacuo* (50 °C, 0.5 mbar, 4 h). The product was obtained as a colorless solid (24.99 g, 89%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.67 (s, 1 H), 6.22 (s, 1H), 2.42 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 165.5, 148.2, 143.7 (q, $^2J_{C-F}$ = 33 Hz), 122.4 (q, $^1J_{C-F}$ = 274 Hz), 114.2 (q, $^3J_{C-F}$ = 4.0 Hz), 101.8 (q, $^3J_{C-F}$ = 3.0 Hz), 19.3 ppm. Anal. Calcd for $C_7H_6F_3NO$ (M_r = 177.12): C, 47.47; H, 3.41; N, 7.91. Found: C, 47.51; H, 3.21; N, 7.95.

2-Bromo-6-methyl-4-trifluoromethylpyridine (2)

Under N_2, PBr_3 (37.2 mL, 107.1 g, 395.7 mmol, 3.2 equiv.) was added to 6-methyl-4-trifluoromethyl-2-pyridone (21.90 g, 123.6 mmol, 1.0 equiv.) and the light-yellow suspension was heated to 160 °C (bath temperature). After three hours, the reaction was discontinued, at room temperature the colorless sublimate that had formed was mechanically pushed down into the reaction phase, and heating was continued for an additional 4 h at 160 °C. After cooling to ambient temperature, the orange solution was poured onto crushed ice (*ca.* 250 g) and the resulting aqueous phase was treated cautiously with solid Na_2CO_3 until pH 5 was reached. The voluminous precipitate was filtered off with suction. The filtrate was extracted with $CHCl_3$ (4 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The remaining orange oil was distilled under reduced pressure (p = 72 mbar, bp 96–97 °C) to yield a light-yellow liquid (12.63 g, 43%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 7.34 (s, 1 H), 2.65 (s, 3 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 161.6, 141.9, 140.7 (q, $^2J_{F-C}$ = 32.2 Hz), 122.0 (q, $^1J_{F-C}$ = 274 Hz), 121.1 (q, $^3J_{F-C}$ = 3.6 Hz), 118.0 (q, $^3J_{F-C}$ = 3.4 Hz), 24.3 ppm.

6,6′-Dimethyl-4,4′-bis(trifluoromethyl)-2,2′-bipyridine (3)

Under N_2, a two-necked Schlenk flask was charged with [$NiBr_2(PPh_3)_2$] (4.46 g, 6.00 mmol, 0.30 equiv.), zinc powder (1.96 g, 30.0 mmol, 1.5 equiv.), and Et_4NI (5.14 g, 20.0 mmol, 1.0 equiv.). Dry, degassed THF (40 mL, three freeze–pump–thaw cycles) was added by a syringe and the suspension was stirred at ambient temperature for 30 min. A solution of 2-bromo-6-methyl-4-trifluoromethylpyridine (2) (4.80 g, 20.0 mmol, 1.0 equiv.) in dry, degassed THF (20 mL) was added and the dark-brown suspension was heated to 55 °C (bath temperature) for 24 h. At ambient temperature, aqueous ammonia (2 M, 200 mL) and CH_2Cl_2 (200 mL) were added, stirring was continued for 10 min, and the mixture was filtered. The aqueous layer of the filtrate was extracted with CH_2Cl_2 (2 × 200 mL), the combined organic phases were dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography (SiO_2, hexanes–$CHCl_3$ 5 : 1 → 1 : 1, preloading onto SiO_2). The product was obtained as colorless needles (1.94 g, 61%).

Mp 153–156 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.52 (s, 2 H), 7.41 (s, 2 H), 2.73 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 159.8, 156.0, 139.8 (q, $^2J_{C-F}$ = 34 Hz), 123.2 (q, $^1J_{C-F}$ = 273 Hz), 119.4 (q, $^3J_{C-F}$ = 3.5 Hz), 114.3 (q, $^3J_{C-F}$ = 3.6 Hz), 24.8 ppm. ^{19}F NMR (235 MHz, $CDCl_3$): δ = −64.7 ppm. MS (ESI+): m/z (%) = 342.9 (100, $[M + Na]^+$). Anal. Calcd for $C_{14}H_{10}F_6N_2$ (M_r = 320.23): C, 52.51; H, 3.15; N, 8.75. Found: C, 52.73; H, 2.83; N, 8.72. TLC: R_f = 0.14 (SiO_2, hexanes–$CHCl_3$ 5 : 1, detection: UV).

6,6′-Dimethyl-4,4′-bis(trifluoromethyl)-2,2′-bipyridine-*N*,*N*′-dioxide (4)

6,6′-Dimethyl-4,4′-bis(trifluoromethyl)-2,2′-bipyridine (3) (3.19 g, 10.0 mmol, 1.0 equiv.) was suspended in glacial acetic acid

(70 mL) and aqueous hydrogen peroxide (30%, 5.0 mL, 1.65 g, 45.8 mmol, 4.6 equiv.) was added dropwise. The mixture was heated at 80 °C (bath temperature) for 20 h. Another aliquot of aqueous hydrogen peroxide (30%, 4.0 mL, 1.32 g, 36.6 mmol, 3.7 equiv.) was added at ambient temperature and the reaction was heated at 80 °C for an additional 24 h. The clear solution was cooled down and immersed in an ice-bath, and the mixture was treated with sodium thiosulfate pentahydrate (*ca.* 2 g) in portions. After stirring for 10 min, an aqueous solution of NaOH (50 g in 250 mL H_2O) was added dropwise over the course of *ca.* 40 min, and the resulting suspension was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The product was obtained as a colorless solid (3.41 g, 97%) and was used in the next step without further purification. Crystals suitable for X-ray analysis were obtained by slow evaporation of methanolic solutions of the title compound.

Mp 204–206 °C. ^{1}H NMR (200 MHz, CD_3OD): δ = 8.06 (s, 2 H), 8.03 (s, 2 H), 2.65 (s, 6 H) ppm. ^{13}C NMR (62.9 MHz, CD_3OD): δ = 152.4, 144.7, 128.0 (q, $^2J_{C-F}$ = 35 Hz), 124.0 (q, $^1J_{C-F}$ = 272 Hz), 125.5 (q, $^3J_{C-F}$ = 3.7 Hz), 124.0 (q, $^3J_{C-F}$ = 3.9 Hz), 30.7, 22.4, 17.8 ppm. MS (ESI+): *m*/*z* (%) = 374.9 (100, $[M + Na]^+$). TLC: R_f = 0.23 (SiO_2, CH_2Cl_2–MeOH 24 : 1, detection: UV).

6,6′-Bis(acetoxymethyl)-4,4′-bis(trifluoromethyl)-2,2′-bipyridine (5)

Under N_2, 6,6′-dimethyl-4,4′-bis(trifluoromethyl)-2,2′-bipyridine-*N*,*N*′-dioxide (**4**) (3.41 g, 9.68 mmol, 1.0 equiv.) was dissolved in Ac_2O (50 mL) and the solution was heated to 120 °C (bath temperature) for 14 h. After cooling to room temperature, volatiles were removed under reduced pressure and the resulting brown oil was purified by column chromatography (SiO_2, CH_2Cl_2–MeOH 200 : 1, detection: UV). The product was obtained as a light-yellow solid (3.07 g, 73%).

Mp 88–90 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.63 (s, 2 H), 7.62 (s, 2 H), 5.39 (s, 4 H), 2.23 (s, 6 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 170.5, 157.6, 155.6, 140.6 (q, $^2J_{C-F}$ = 34 Hz), 123.0 (q, $^1J_{C-F}$ = 274 Hz), 117.7 (q, $^3J_{C-F}$ = 3.6 Hz), 116.4 (q, $^3J_{C-F}$ = 3.6 Hz), 66.3, 21.0 ppm. MS (ESI+): *m*/*z* (%) = 458.9 (100, $[M + Na]^+$). Anal. Calcd. for $C_{18}H_{14}F_6N_2O_4$ (M_r = 436.31): C, 49.55; H, 3.23; N, 6.42. Found: C, 49.69; H, 2.90; N, 6.75. TLC: R_f = 0.85 (SiO_2, CH_2Cl_2–MeOH 24 : 1, detection: UV).

6,6′-Bis(hydroxymethyl)-4,4′-bis(trifluoromethyl)-2,2′-bipyridine (6)

6,6′-Bis(acetoxymethyl)-4,4′-bis(trifluoromethyl)-2,2′-bipyridine (**5**) (3.04 g, 6.97 mmol, 1.0 equiv.) was dissolved in MeOH (100 mL) and K_2CO_3 (4.81 g, 34.8 mmol, 5.0 equiv.) was added. The yellow suspension was stirred at ambient temperature for 12 h. The solvent was removed, water (100 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The resulting brown oil was purified by column chromatography (SiO_2, CH_2Cl_2–MeOH 24 : 1, detection: UV, preloading onto SiO_2). The product was obtained as a colorless solid (0.40 g, 16%).

Mp 176–178 °C. ^{1}H NMR (200 MHz, CD_3OD): δ = 8.66 (s, 2 H), 7.90 (s, 2 H), 4.94 (s, 4 H) ppm. ^{13}C NMR (50.3 MHz, CD_3OD): δ = 165.0, 156.7, 141.2 (q, $^2J_{C-F}$ = 33 Hz), 124.6 (q, $^1J_{C-F}$ = 273 Hz), 117.7 (q, $^3J_{C-F}$ = 3.6 Hz), 116.1 (q, $^3J_{C-F}$ = 3.6 Hz), 65.7 ppm. MS (ESI+): *m*/*z* (%) = 374.9 (100, $[M + Na]^+$). Anal. Calcd. for $C_{14}H_{10}F_6N_2O_2$ (M_r = 352.23): C, 47.74; H, 2.86; N, 7.95. Found: C, 47.25; H, 3.14; N, 7.79. TLC: R_f = 0.39 (SiO_2, CH_2Cl_2–MeOH 9 : 1, detection: UV).

4,4′-Bis(trifluoromethyl)-2,2′-bipyridine-6,6′-dicarboxylic acid monohydrate ($H_2$1)

6,6′-Bis(hydroxymethyl)-4,4′-bis(trifluoromethyl)-2,2′-bipyridine (**6**) (323 mg, 917 μmol, 1.0 equiv.) was added in portions to conc. H_2SO_4 (4 mL) and the mixture was heated to 65 °C (bath temperature). CrO_3 (367 mg, 3.67 mmol, 4.0 equiv.) was added at a certain rate so that the internal temperature did not rise above 70 °C. After complete addition, the dark solution was heated at 70 °C (bath temperature) for an additional 60 min. The mixture was poured onto crushed ice (*ca.* 350 g), and the precipitate was collected on a filter, washed with cold water, and dried under reduced pressure at 100 °C for several hours. The product was obtained as an off-white solid (295 mg, 81%).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 9.01 (d, *J* = 0.9 Hz, 2 H), 8.40 (d, *J* = 0.9 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 164.5, 154.8, 150.0, 140.0 (q, $^2J_{C-F}$ = 34 Hz), 122.5 (q, $^1J_{C-F}$ = 273 Hz), 121.2 (q, $^3J_{C-F}$ = 3.0 Hz), 119.6 (q, $^3J_{C-F}$ = 3.8 Hz) ppm. ^{19}F NMR (235 MHz, DMSO-d_6): δ = −63.4 ppm. MS (ESI−): *m*/*z* (%) = 378.8 (100, $[M - H]^-$). Anal. Calcd for $C_{14}H_6F_6N_2O_4 \cdot H_2O$ (M_r = 398.21): C, 42.23; H, 2.02; N, 7.03. Found: C, 42.72; H, 2.08; N, 7.12.

Yttrium complex $[Y(\mathbf{1})_2](HNEt_3)\cdot 3H_2O$ (Y-7)

4,4′-Bis(trifluoromethyl)-2,2′-bipyridine-6,6′-dicarboxylic acid monohydrate (H_2**1**) (53.2 mg, 134 μmol, 2.0 equiv.) was suspended in dry MeOH (6 mL), and a solution of $YCl_3\cdot 6H_2O$ (20.3 mg, 66.8 μmol, 1.0 equiv.) in dry MeOH (2 mL) was added. The cloudy solution was stirred at ambient temperature for 15 min and concentrated to dryness under reduced pressure, and the remaining residue was resuspended in H_2O (8 mL). After the addition of NEt_3 (93 μL, 67.6 mg, 668 μmol, 10 equiv.), the mixture was heated to reflux and filtered hot, and the filtrate was concentrated to a volume of *ca.* 5 mL. The suspension was cooled in an ice-bath for 1 h, and the light-yellow solid was collected on a membrane filter (nylon, 0.45 μm) and washed with a minimum of ice-cold water. The pasty solid was transferred to a sublimation apparatus and heated at 70 °C (bath temperature) under reduced pressure ($p \approx 0.3$ mbar) for *ca.* 1 h. The sublimate (triethylammonium chloride) was discarded. The title compound was obtained as the remaining colorless solid (40 mg, 60%).

^{1}H NMR (200 MHz, CD_3OD): δ = 9.41 (s, 2 H), 8.53 (s, 2 H), 3.23 (q, 3 H, *J* = 7.3 Hz), 1.34 (t, 4 H, *J* = 7.3 Hz) ppm. ^{19}F NMR (235 MHz, D_2O): δ = −64.8 ppm. MS (ESI−): *m*/*z* (%) = 844.70 (100, $[Y(\mathbf{1})_2]^-$). Anal. Calcd for $C_{34}H_{24}F_{12}N_5O_8Y\cdot 3H_2O$ (M_r =

1001.52): C, 40.77; H, 3.02; N, 6.99. Found: C, 40.85; H, 3.38; N, 6.92.

Terbium complex $[Tb(\mathbf{1})_2](HNEt_3)\cdot 2H_2O$ (Tb-7)

4,4′-Bis(trifluoromethyl)-2,2′-bipyridine-6,6′-dicarboxylic acid monohydrate ($H_2\mathbf{1}$) (96.4 mg, 242 μmol, 1.9 equiv.) was suspended in dry MeOH (10 mL) and a solution of $TbCl_3\cdot 6H_2O$ (47.3 mg, 127 μmol, 1.0 equiv.) in dry MeOH (3 mL) was added. The cloudy solution was stirred at ambient temperature for 15 min and concentrated to dryness under reduced pressure, and the remaining residue was resuspended in H_2O (*ca.* 80 mL). After the addition of NEt_3 (177 μL, 128 mg, 1.27 mmol, 10 equiv.), the mixture was heated to reflux and filtered hot, and the filtrate was concentrated to a volume of *ca.* 5 mL. The suspension was cooled in an ice-bath for 1 h, and the light-yellow solid was collected on a membrane filter (nylon, 0.45 μm) and washed with a minimum of ice-cold water. The pasty solid was transferred to a sublimation apparatus and heated at 70 °C (bath temperature) under reduced pressure ($p \approx 0.3$ mbar) for *ca.* 1 h. The sublimate (triethylammonium chloride) was discarded. The title compound was obtained as the remaining yellow solid (75 mg, 59%). Crystals suitable for X-ray analysis were obtained by slow evaporation of methanolic solutions of the title compound.

^1H NMR (250 MHz, CD_3OD): δ = 20.9 (br, 4 H), 5.13 (br, 6 H), 3.00 (br, 9 H), −66.2 (br s, 4 H) ppm. ^{19}F NMR (235 MHz, CD_3OD): δ = −76.2 ppm. MS (ESI−): *m*/*z* (%) = 914.94 (100, $[Tb(\mathbf{1})_2]^-$). Anal. Calcd for $C_{34}H_{24}F_{12}N_5O_8Tb\cdot 2H_2O$ (M_r = 1053.52): C, 38.76; H, 2.68; N, 6.65. Found: C, 38.95; H, 2.35; N, 6.58.

Dysprosium complex $[Dy(\mathbf{1})_2](HNEt_3)\cdot 2H_2O$ (Dy-7)

4,4′-Bis(trifluoromethyl)-2,2′-bipyridine-6,6′-dicarboxylic acid monohydrate ($H_2\mathbf{1}$) (67.7 mg, 170 μmol, 2.0 equiv.) was suspended in dry MeOH (7 mL) and a solution of $DyCl_3\cdot 6H_2O$ (32.0 mg, 85.0 μmol, 1.0 equiv.) in dry MeOH (2 mL) was added. The cloudy solution was stirred at ambient temperature for 15 min and concentrated to dryness under reduced pressure, and the remaining residue was resuspended in H_2O (8 mL). After the addition of NEt_3 (118 μL, 86.0 mg, 850 μmol, 10 equiv.), the mixture was heated to reflux and filtered hot, and the filtrate was concentrated to a volume of *ca.* 5 mL. The suspension was cooled in an ice-bath for 1 h, and the light-yellow solid was collected on a membrane filter (nylon, 0.45 μm) and washed with a minimum of ice-cold water. The pasty solid was transferred to a sublimation apparatus and heated at 70 °C (bath temperature) under reduced pressure ($p \approx 0.3$ mbar) for *ca.* 1 h. The sublimate (triethylammonium chloride) was discarded. The title compound was obtained as the remaining colorless solid (61 mg, 68%).

^1H NMR (250 MHz, CD_3OD): δ = 19.9 (br, 4 H), 5.02 (br, 6 H), 2.99 (br, 9 H), −107.1 (br s, 4 H) ppm. ^{19}F NMR (235 MHz, CD_3OD): δ = −85.8 ppm. MS (ESI−): *m*/*z* (%) = 919.28 (100, $[Dy(\mathbf{1})_2]^-$). Anal. Calcd (Found) for $C_{34}H_{24}DyF_{12}N_5O_8\cdot 2H_2O$ (M_r = 1057.09): C, 38.63; H, 2.67; N, 6.63. Found: C, 38.51; H, 2.80; N, 6.57.

X-ray crystallography

Crystals were mounted on glass fibers using perfluoropolyether oil. The measurement was carried out on a RIGAKU XtaLAB mini diffractometer using monochromated Mo-K_α radiation (λ = 0.71075 Å). Data were collected at a temperature of 173(2) K. Frames corresponding to an arbitrary hemisphere of data were collected using ω scans. An empirical absorption correction based on the comparison of redundant and equivalent reflections was applied. The structure was solved within the Wingx[16] package by direct methods (SIR92[17]) and expanded using Fourier techniques (SHELXL-97[18]) on F^2. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included but not refined. They were positioned geometrically, with distances C–H = 0.93 Å for aromatic hydrogens, C–H = 0.97 Å for CH_2 moieties, and C–H = 0.96 Å for methyl groups. For the methyl groups in **4**, the rotation around the corresponding C–C bond was refined (HFIX 137). All hydrogens were constrained to ride on their parent carbon atoms. $U_{iso}(H)$ values were set at 1.2 times $U_{eq}(C)$. In **Tb-7**, the triethylammonium cation shows considerable disorder resulting in rather high U_{eq} or U_{iso} parameters for all carbon and connected hydrogen atoms, respectively.

Crystallographic data for **4** (CCDC 920406): $C_{14}H_{10}F_6N_2O_2$, M_w = 352.24 g mol^{-1}, colorless plate (0.20 × 0.10 × 0.10 mm^3), T = 173(2) K, tetragonal, space group $P4_12_12$, $a = b$ = 11.873(5) Å, c = 9.961(6) Å, $\alpha = \beta = \gamma$ = 90°, V = 1404.2(12) Å^3, Z = 4, 12 062 reflections measured, 1235 unique (R_{int} = 0.0700), $R(F_o)$ = 0.0573 (observed 983 reflections, $I > 2\sigma(I)$), $R_w(F_o^2)$ = 0.1352 (all data), GoF = 1.108, the largest peak and hole: 0.164 e Å^{-3} and −0.211 e Å^{-3}.

Crystallographic data for **Tb-7** (CCDC 920407): $[Tb(C_{14}H_4F_6N_2O_4)_2](HNEt_3)$, M_w = 1017.29 g mol^{-1}, colorless plate (0.31 × 0.16 × 0.15 mm^3), T = 173(2) K, triclinic, space group $P\bar{1}$, a = 10.18(1) Å, b = 11.59(1) Å, c = 16.46(2) Å, α = 78.15(3)°, β = 85.49(3)°, γ = 84.13(3)°, V = 1887(4) Å^3, Z = 2, 19 245 reflections measured, 8479 unique (R_{int} = 0.0542), $R(F_o)$ = 0.0718 (observed 7024 reflections, $I > 2\sigma(I)$), $R_w(F_o^2)$ = 0.207 (all data), GoF = 1.088, the largest peak and hole: 3.367 e Å^{-3} and −1.847 e Å^{-3} (both close to Tb).

Luminescence spectroscopy

Steady state emission spectra were acquired on a PTI Quantamaster QM4 spectrofluorimeter using 1.0 cm quartz cuvettes at RT. The excitation light source was a 75 W continuous xenon short arc lamp. Emission was monitored at 90°. Spectral selection was achieved using single grating monochromators (excitation: 1200 grooves per mm, blazed at 300 nm; emission: 1200 grooves per mm, blazed at 400 nm). Quantum yields were determined in HEPES buffer (10 mM, pH 7.4) using quinine sulfate in sulfuric acid (Φ_{abs} = 54.6%)[13] as the quantum yield standard after excitation at λ_{exc} = 315 nm for **Tb-7** and at λ_{exc} = 313 nm for **Dy-7**. Quantum yields were measured by the optically dilute method using the following equation:

$$\Phi_x = \Phi_r\ (\mathrm{Grad}_x/\mathrm{Grad}_r)\ (n_x^2/n_r^2)$$

where n is the refractive index and Grad is the linearly fitted slope from the plot of the integrated luminescence intensity *versus* the absorbance at the excitation wavelength. The subscripts 'x' and 'r' refer to the sample and the reference, respectively. The estimated uncertainties in Φ are ±10%.

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