Synthesis of Amino-Bridged 6,6′-Disubstituted-2,2′-Bipyridine Ligands for Lanthanide Coordination Chemistry

Samir Mameri, Loïc J. Charbonnière,* Raymond F. Ziessel*

Laboratoire de Chimie Moléculaire, associé au CNRS, ECPM, 25, rue Becquerel, 67087 Strasbourg Cedex 02, France
Fax +33(3)90242689; E-mail: ziessel@chimie.u-strasbg.fr

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Abstract: Three cognate ligands containing bipyridine carboxylic frameworks were readily prepared under mild conditions from a pivotal 6-bromo-6′-bromomethyl-2,2′-bipyridine building block and a primary amine as starting materials. In one case, the amine was adequately functionalised with a nitro group. Transformation of the resulting bromo derivatives to the corresponding ethyl esters was made possible by the use of a carboethoxylation reaction promoted by palladium(0), while further hydrolysis afforded the targeted acids after protonation. Corresponding europium complexes show interesting luminescence properties in water at biological pH values.

Key words: bromination, carboalkoxylation, bipyridine-carboxylate, Eu complexes, luminescence

For the last decade or so, there has been a steady and progressive interest in the production of novel lanthanide (Ln) complexes and an impressive number of such substances have now been documented.[1] The interest in the synthesis of lanthanide complexes has driven researches into finding new and improved species to label bioorganic molecules,[2] to perform biomedical analysis,[3] and as the basis for anion sensors.[4] Due to the specific coordination features of lanthanide cations, the engineering of the ligand is an essential part of these molecular architectures. These trivalent cations impose a dominant control over both the chemical and the physical properties of the resulting compounds. Therefore, it comes as no surprise that ligand design and engineering became central themes in the development of the chemistry of lanthanide complexes, particularly in terms of their optical properties.[5] Due to the very weak absorption coefficients of lanthanide salts, the use of chromophores such as oligopyridinic ligands has long been an ubiquitous component of highly luminescent lanthanide complexes, in order to benefit from the so-called antenna effect.[6]

Many research groups argued the case that relatively efficient energy transfer processes from the singlet and/or triplet excited states of such framework to the emissive states of the lanthanides is feasible. Relaxation to the ground state allows light to be emitted in a wide range of wavelengths spanning from visible to near infra red. In most cases a large number of emission lines are observed ($^5D_0 \rightarrow {}^7F_J$ with J = 0 to 6 for Eu) which allows some spectral discrimination.[7] The merit of these bipyridyl based ligands has been scrutinised previously[8] and it is only after our successful synthesis of α-substituted 2,2′-bipyridine (bipy) moieties with carboxylic acid groups that we were able to examine these complexes in water.[9] Subsequent variations of the nature and structure of the anchoring bipyridine arms and bridging groups provide many new types of ligands which are extremely useful for the production of stable lanthanide complexes. In most of these cases, the first coordination sphere of the lanthanide is almost saturated resulting in a very efficient shielding of the metal towards detrimental vibronic deactivation processes with the surrounding solvent.[10]

Recently, we have synthesised hybrid ligands bearing a P=O hook and two neutral substituted bipy arms.[11] Our initial idea was to avoid the saturation of the first coordination sphere of the lanthanide cation in order to provide some open coordination sites for sensing the arrival of some anions via fluorescence and time-resolved luminescence spectroscopy. Unfortunately, the resulting complexes were not sufficiently stable and soluble for the sensing of chemical species (e.g. biological anions) in aqueous solutions. The aim of the present research program is to construct novel artificial platforms able to strongly bind lanthanide cations which are soluble in various solvents including water, with very good photophysical properties (such as strong absorption in the near UV, long living excited states, efficient energy transfer from the peripheral ligands to the central Ln, high quantum yield of light emission, etc.), with the view to produce efficient sensors for the detection of oxophilic anions.

This manuscript describes the preparation and full characterisation of novel ligands bearing a *n*-butylamino group as pivotal fragment to anchor two or three bipyridine based pendant arms providing respectively a tertiary amine **A** and a quaternary ammonium salt **B** (Figure 1). The introduction of a nitrobenzoyl function (illustrated as Y in Figure 1), on the alkyl chain is also described together with a brief survey of the photophysical properties of the complexes formed with europium (III).

Access to this family of ligands requires the synthesis of the key building block **2**, itself prepared from 6-bromo-6′-methyl-2,2′-bipyridine (**1**) by a radical bromination reaction induced by AIBN, heat and light (Scheme 1). Derivative **1** was prepared in three steps from 2-amino-6-methypyridine according to literature procedure.[12–14]

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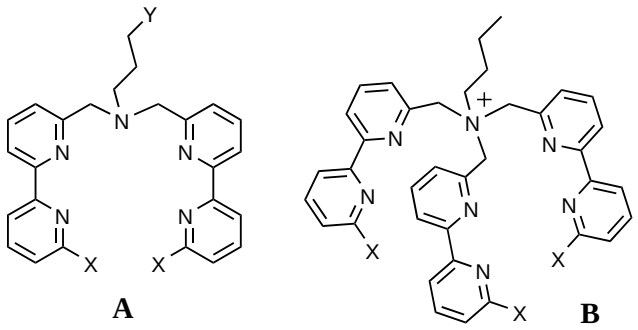
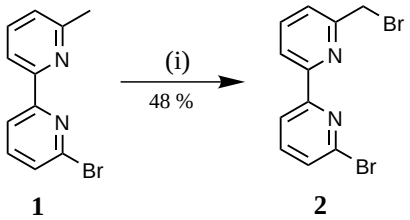


Figure 1 Structures of ligands **A** and **B** bearing an *n*-butylamino group

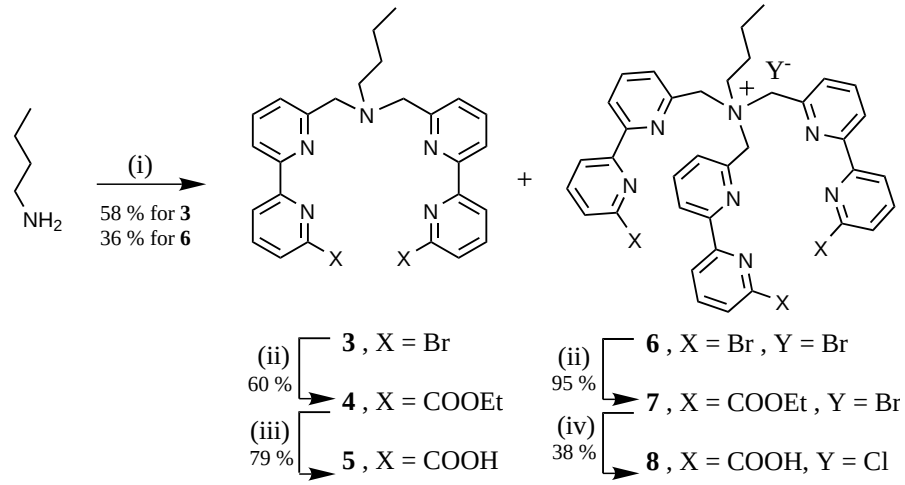


Scheme 1 (i) Benzene, AIBN, NBS, reflux, hν

The synthesis of molecules involving several 6-bromo substituted subunits grafted to a central nitrogen group remains challenging due to the presence of a reactive C_{arom}–Br bond. After some experimentation we were pleased to find quite a selective double alkylation of *n*-butylamine affording compound **3**, which was carried out in anhydrous acetonitrile using dry K_2CO_3 as base. The choice of *n*-butylamine was motivated by its high boiling point compared to related primary amines and its easy purification by distillation. Keeping in mind the need to solubilise the resulting lanthanide complexes in water, the use of longer amine chains was prohibited. The isolated yield for **3** was notably improved when an excess of the alkylating reagent **2** was used. However, we also noticed that in all cases the triply alkylated ammonium derivative **6** was formed and was isolated using chromatographic separation (Scheme 2). Different attempts to direct the selectivity towards the ammonium derivative were run and the best yield of **6** was found to be 36% with the use of four equivalents of derivative **2**. It is likely that the alkylation of compound **3** leading to **6** is much slower compared to the two first alkylation steps, which might also lead to the degradation of the alkylating agent **2**. In some cases 6-bromo-6′-hydroxymethyl-2,2′-bipyridine is isolated resulting from a hydrolysis process.

By analogy to our previous work,[15] the preparation of the target carboxylic acids **5** and **8** was achieved in parallel using the bromo derivatives **3** and **6** as starting materials, respectively. The synthesis of the esters according to a carboethoxylation reaction is promoted by low valent palladium catalyst under a continuous stream of carbon monoxide at atmospheric pressure in the presence of ethanol as nucleophile, and triethylamine was used to quench the nascent acid.[16,17] In fact, while the preparation of derivative **4** gave satisfactory results (60%), the synthesis of the triester **7** gave lower yields (10%) under the standard conditions using carbon monoxide with a gas purity of 99%. A tentative rationale considers the hydrolysis of the ammonium salts to its tertiary amine **4** by a nucleophilic attack of OH^- at the methylenic bridge of one of the bipy arms. Indeed, in all cases it was possible to isolate the derivative **4** during the carboethoxylation of **6** and some 6-carboethoxy-6′-hydroxymethyl-2,2′-bipyridine compound as by-product. The use of dry carbon monoxide gas (less than 5 ppm water, gas purity higher than 99.995%) significantly decreases the hydrolysis leading to an isolated yield of 95% for **7**.

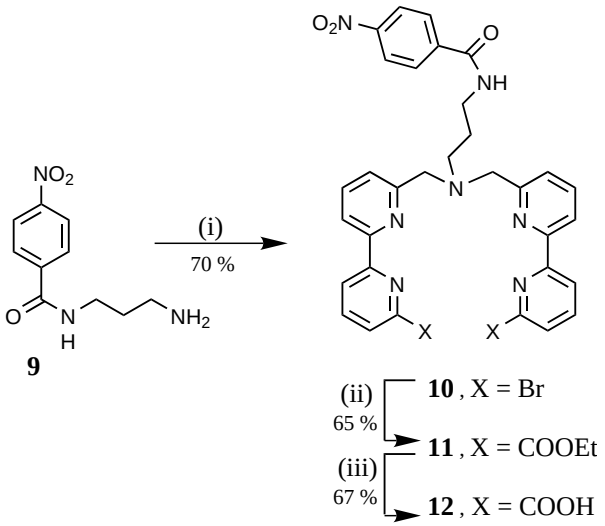
The conversion of the esters to the acids was realised for compounds **4** and **7** by a basic or an acidic hydrolysis, respectively. The target derivatives **5** and **8** were isolated as their hydrochloride salts after protonation with dilute HCl and pH control in the case of derivative **5**. Interestingly,



Scheme 2 (i) **2** (4 equiv), K_2CO_3, MeCN, 85 °C; (ii) $Pd(PPh_3)_2Cl_2$, EtOH, Et_3N, CO, 70 °C; (iii) 1. MeOH–H_2O, NaOH, reflux, 2. dil. HCl; (iv) HCl, H_2O, 70 °C

the hydrolysis of the ammonium salt to side products was not observed.

The success achieved by this convenient and versatile protocol prompted us to evaluate its potential for increasing molecular complexity and the tolerance of chemical functions which might be useful to anchor such labels to more complex structures such as proteins, antibodies or nanostructured surfaces. The synthesis of bis-bipy compounds bearing a 4-nitrobenzamide side chain is straightforward and proceeds via a sequence of reaction similar to the one previously described (Scheme 3).



Scheme 3 (i) 2 (2.3 equiv), K_2CO_3, MeCN, 85 °C; (ii) $Pd(PPh_3)_2Cl_2$, EtOH, Et_3N, CO, 70 °C; (iii) EtOH–H_2O, NaOH, 75 °C

Derivative **9** was prepared according to a literature procedure[18] and during the alkylation reaction of compound **9** with **2**, the formation of the ammonium salt was not observed. It is likely that the bulkiness of the amine substituent disfavours the polyalkylation process. However, the use of compound **10** in the sequence of reaction involving (i) carboalkoxylation in 65% yield, and (ii) hydrolysis afforded the bis-acid **12** in 67% yield.

The potential of these cognate ligands **5**, **8** and **12** bearing deprotonable functional groups has been investigated in lanthanide coordination chemistry. The resulting europium complexes have been investigated in aqueous solution by steady-state and time-resolved emission spectroscopy and selected data are collected in Table 1. The preparation of the europium complexes of ligands **5** and **8** is straightforward and easily feasible by mixing the acid form of the ligands in the adequate solvents with $EuCl_3 \cdot 6H_2O$. Deprotonation of the acid is ensured by the use of triethylamine.

This data is particularly informative on the coordination behaviours of these different ligands. For ligand **5**, the calculated number of water molecules directly coordinated in the first coordination sphere of the metal is ca. two, in good agreement with the expectation that **5** behaves as an heptadentate ligand in which the central nitrogen atom is coordinated. A coordination number of nine is then obtained for europium, which is a common value for such complexes.[5] This europium complex displayed non-negligible life-time (τ_{lum} 0.36 ms) and quantum yield (ϕ_{lum} 4.6%) values in water, despite the presence of these two water molecules in the first coordination sphere. In the case of ligand **8**, one would expect that the podand type structure displayed by the ligand would allow for a good complexation of the europium in the center of the molecular pocket formed by three bipy pendent arms. In such cases, the shielding of the metal from interactions with water molecules would dramatically decrease the non-radiative deactivation pathways with a concomitant increase of the luminescence lifetimes and quantum yields.[9] As anticipated, the values obtained for τ and ϕ are different to those obtained with ligand **5**. A calculated number of ca. 3 water molecules in the first coordination sphere are obtained. It is surmised that only two bipy strands are coordinated to the europium with ligand **8** and that the bridging nitrogen atom being charged in its ammonium form does not coordinate to the metal center. A further important point observed in the luminescence experiments is the presence in the emission spectrum of the complex of a broad emission band, centered around 410 nm (24400 cm^{-1}). Upon insertion of a delay (from 10 μs to 20 μs) between excitation and integration of the luminescence signal, this emission did not completely vanish, pointing to a localised ligand-centered $^3\pi\pi^*$ state. The presence of this excited state in the luminescence spectrum indicates that the ligand to metal energy process is not as efficient as it is in the previous case and could explain the decrease observed in the luminescence quantum yield determined with ligand **8** compared to the europium complex of ligand **5**. It is surmised that ligand **8** is not coordinated in a clipped podand type structure, presumably because of the methylene bridges linking the tridentate units and the podand nitrogen atom is too short.[20,21] For solubility reasons, the complexation of **12** could not be studied in pure water, which discarded the comparison

Table 1 Luminescence Properties of the Europium Complexes with Ligands **5**, **8**, and **12** in Aqueous Solution[a]

Ligand	λ_{em} (nm)[b]	$\tau(H_2O)$ (ms)[c]	$\tau(D_2O)$ (ms)[c]	$\Phi(H_2O)$ (%)[d]	$\Phi(D_2O)$ (%)[d]	q[e]
5	617	0.36	1.75	4.6	-	2.3
8	617	0.33	2.24	0.4	2.4	2.8
12	618	0.39	–	0.5	–	–

[a] Measured on the isolated complexes with ligands **5** and **8**. Measured with an equimolar amount of $EuCl_3 \cdot 6H_2O$ and **12**, in a 4:1 H_2O–MeOH mixture for solubility reasons.
[b] Maximum of emission corresponding to the $^5D_0 \rightarrow {}^7F_2$ transition centered on europium.
[c] Luminescence lifetime measured on the maximum of emission.
[d] Absolute quantum yield determined using $[Ru(bipy)_3]Cl_2$ in water as reference [$\Phi(H_2O) = 2.8\%$[19]].
[e] Number of water molecules in the first coordination sphere of the europium determined using the relationship,[10c] $q = 1.2 \times [1/\tau(H_2O) - 1/\tau(D_2O) - 0.25]$, estimated error ± 0.5 molecule.

with heavy water data. The presence of the hydrophobic nitrobenzoyl group is probably responsible for this lack of solubility. The measured excited state lifetime obtained in the 1:4 methanol–water mixture is very close to that measured for ligand **5**. One can anticipate that the coordinations of **5** and **12** are similar, both acting as heptadentate ligands with coordination of the two tridentate bipyridylcarboxylate fragments and of the bridging nitrogen atom. Nevertheless, the emission quantum yield is one order of magnitude smaller in the case of **12**. The loss of emission may be rationalised by the availability of the proximal nitrobenzoyl fragment to act as a luminescence quencher through the occurrence of electron transfer to the lanthanide centre.[22]

In summary, we have shown that employment of a 6-bromo-6′-bromomethyl-2,2′-bipyridine skeleton can provide an easy entry to N-substituted molecules with two or three chelating arms. The basic architecture of the target molecules is the presence of various number of anionic N,N,O donor fragments which is an ideal situation for complexation of trivalent lanthanide salts. The presence of an additional pendant arm carrying a potentially activated function ($NO_2 \rightarrow NH_2$) is especially appealing for conjugation to biological material. The utility of the ligands prepared during this study as auxiliaries in the preparation of luminescent lanthanide complexes has been demonstrated. The prospects of these complexes for anion detection at physiological pH, such as adenosine triphosphate (ATP) is currently under investigation and results will be shared in the scientific literature in due course.

The 200.1 (^{1}H) and 50.3 MHz (^{13}C) NMR spectra were recorded at r.t. on a Bruker AC 200 spectrometer, using perdeuterated solvents with internal standard: δ (H) in ppm relative to residual protiated solvent; δ (C) in ppm relative to the solvent. FT-IR spectra were recorded as KBr pellets on a Nicolet 210 spectrometer or as liquid (solvent CH_2Cl_2) on a Perkin Elmer Spectrum One spectrometer. Chromatographic purification was conducted using 40–63/63–200 μm silica gel or aluminum oxide 90 standardised obtained from Merck. TLC was performed on silica gel or aluminum oxide coated plates (Merck) with fluorescent indicator. All mixtures of solvents are given in v/v ratio.

2-Bromo-6-methylpyridine[12], 2-tributylstannyl-6-methylpyridine[13] and 6-bromo-6′-methyl-2,2′-bipyridine (**1**)[14] were synthesised according to literature procedure. 2-Amino-6-methylpyridine (Fluka), 4-nitrobenzoyl chloride (Acros) and $Pd(PPh_3)_2Cl_2$ (Aldrich) were used as purchased. *n*-Butylamine was distilled over KOH prior to use. *N*-(3-Aminopropyl)-4-nitrobenzamide (**9**) was synthesised according to Ref.[18]

Standard CO gas of 99% purity was used to carry out the carboalkoxylation reactions, except in the case of compound **7**, where a high purity CO (99.995%) was supplied.

Luminescence spectra were recorded on a Perkin Elmer LS50 spectrofluorimeter. Absolute quantum yields were measured relative to $[Ru(bipy)_3]Cl_2$ in nondegassed H_2O ($\Phi = 2.8\%$[19]) in the phosphorescence mode. Luminescence lifetimes were determined on a PTI QuantaMaster spectrophotometer. Deconvolution of the decay curves were obtained by fitting with mono and bi-exponential decays. In all cases, data were perfectly fitted with a mono-exponential decay curve.

6-Bromo-6′-bromomethyl-2,2′-bipyridine (2)

A solution of **1** (1.5 g, 6.0 mmol), AIBN (66 mg, 0.40 mmol) and NBS (1.3 g, 7.3 mmol) in benzene (90 mL) was refluxed, simultaneously illuminating with a standard 100 W halogen lamp, for 2.5 h. The solvent was then removed under reduced pressure and the residue, consisting of a mixture of **1**, the monobromo derivative **2**, and the corresponding *gem*-dibrominated analogue was purified by column chromatography [SiO_2, CH_2Cl_2–hexane, 50:50 to 100:0; R_f 0.42 (SiO_2), CH_2Cl_2]; yield: 942 mg (48%); white crystals.

IR (CH_2Cl_2): 2918 (w), 1574 (m), 1548 (s), 1424 (s), 630 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 4.61 (s, 2 H), 7.48 (d, 1 H, ^3J = 7.5 Hz), 7.50 (d, 1 H, ^3J = 7.5 Hz), 7.68 (t, 1 H, ^3J = 8.0 Hz), 7.83 (t, 1H, ^3J = 8.0 Hz), 8.33 (d, 1 H, ^3J = 8.0 Hz), 8.44 (d, 1 H, ^3J = 8.0 Hz).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 34.0, 120.1, 120.7, 124.0, 128.2, 138.1, 139.3, 141.6, 154.3, 156.4, 156.9.

MS (FAB$^+$): *m*/*z* (%) = 247 ([M – Br], 30), 249 ([M – Br], 30), 327 ([M + H]$^+$, 50), 329 ([M + H]$^+$, 100), 331 ([M + H]$^+$, 50).

Anal. Calcd for $C_{11}H_8Br_2N_2$: C, 40.28; H, 2.46; N, 8.54. Found: C, 40.12; H, 2.34; N, 8.44.

Bis[(6′-bromo-2,2′-bipyridine-6-yl)methyl]butylamine (3)

Compound **2** (400 mg, 1.22 mmol) was added to a stirred solution of anhyd *n*-butylamine (55 μL, 0.55 mmol) and K_2CO_3 (230 mg, 1.66 mmol) in anhyd MeCN (30 mL) in a Schlenk tube under argon. The resulting mixture was heated at 80 °C during 18 h. The MeCN was removed under reduced pressure resulting in the recovery of a yellowish solid. The solid was partitioned between H_2O (20 mL) and CH_2Cl_2 (60 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated to dryness and the resulting solid was purified by column chromatography (Al_2O_3 previously deactivated with H_2O; CH_2Cl_2–hexane, 20:80) to give compound **3** [R_f 0.38, (Al_2O_3), CH_2Cl_2–hexane: 60:40]; yield: 180 mg (58%); colourless crystalline powder.

IR (CH_2Cl_2): 2922 (w), 1574 (s), 1548 (s), 1420 (s), 629 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 0.87 (t, 3 H, ^3J = 7.3 Hz), 1.34 (m, 2 H), 1.59 (m, 2 H), 2.62 (t, 2 H, ^3J = 7.3 Hz), 3.92 (s, 4 H), 7.46 (dd, 2 H, ^3J = 7.8 Hz, ^4J = 0.9 Hz), 7.58 (t, 2 H, ^3J = 7.5 Hz), 7.63 (d, 2 H, ^3J = 7.7 Hz), 7.77 (t, 2 H, ^3J = 7.8 Hz), 8.25 (d, 2 H, ^3J = 7.7 Hz), 8.39 (dd, 2 H, ^3J = 7.7 Hz, ^4J = 0.9 Hz).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 14.0, 20.5, 29.6, 54.3, 60.5, 119.5, 119.7, 123.4, 127.7, 137.2, 139.1, 141.5, 153.6, 157.6, 159.9.

MS (FAB$^+$): *m*/*z* (%) = 509.3 ([M – C_4H_9 + H], 10), 511.3 ([M – C_4H_9 + H], 20), 513.2 ([M – C_4H_9 + H], 10), 566.2 ([M + H]$^+$, 50), 568.2 ([M + H]$^+$, 100), 570.3 ([M + H]$^+$, 50).

Anal. Calcd for $C_{26}H_{25}Br_2N_5$: C, 55.05; H, 4.44; N, 12.34. Found: C, 54.77; H, 4.30;, N, 12.16.

Bis[(6′-carboethoxy-2,2′-bipyridine-6-yl)methyl]butylamine (4)

A solution of **3** (180 mg, 0.32 mmol) and $Pd(PPh_3)_2Cl_2$ (22 mg, 0.032 mmol) in a mixture of EtOH (10 mL) and Et_3N (10 mL) was heated at 70 °C for 15 h under a CO atmosphere. The resulting solution was evaporated to dryness, the residue was dissolved in CH_2Cl_2 (15 mL), filtered and extracted by addition of H_2O (5 mL). After extracting the aqueous layer with CH_2Cl_2 (10 mL), drying the combined organic layers ($MgSO_4$), filtration and evaporation to dryness, afforded a yellowish residue, which after purification by column chromatography (Al_2O_3 previously deactivated with H_2O; CH_2Cl_2–hexane, 70:30), gave **4** [R_f 0.73 (Al_2O_3), CH_2Cl_2–MeOH, 99:1]; yield: 105 mg (60%); oil.

IR (CH_2Cl_2): 3061 (w), 2957 (w), 2928 (w), 1719 (s), 1580 (s), 1466 (m), 1439 (s), 1078 (s), 1024 cm^{-1} (s).

^{1}H NMR ($CDCl_3$): δ = 0.83 (t, 3 H, ^3J = 7.3 Hz), 1.33 (m, 2 H), 1.44 (t, 6 H, ^3J = 7.2 Hz), 1.60 (m, 2 H), 2.61 (t, 2 H, ^3J = 7.2 Hz), 3.92 (s, 4 H), 4.46 (q, 4 H, ^3J = 7.2 Hz), 7.60 (dd, 2 H, ^3J = 7.7 Hz, ^4J = 0.9 Hz), 7.80 (t, 2 H, ^3J = 7.7 Hz), 7.90 (t, 2 H, ^3J = 7.8 Hz), 8.10 (dd, 2 H, ^3J = 7.5 Hz, ^4J = 1.1 Hz), 8.40 (dd, 2 H, ^3J = 7.7 Hz, ^4J = 0.8 Hz), 8.60 (dd, 2 H, ^3J = 7.9 Hz, ^4J = 1.1 Hz).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 13.9, 14.2, 20.4, 29.5, 54.2, 60.4, 61.6, 119.6, 123.2, 124.0, 124.6, 137.1, 137.5, 147.7, 154.2, 156.5, 159.6, 165.2.

MS (FAB$^+$): *m*/*z* (%) = 480.2 ([M – CO_2Et], 10), 554.2 ([M + H]$^+$, 100).

Anal. Calcd for $C_{32}H_{35}N_5O_4$: C, 69.42; H, 6.37; N, 12.65. Found: C, 69.17; H, 6.14; N, 12.44.

Bis[(6′-carboxy-2,2′-bipyridine-6-yl)methyl]butylamine (5)

Compound **4** (136 mg, 250 μmol) was dissolved in a mixture of EtOH (25 mL) and H_2O (18 mL) containing NaOH (40 mg, 1.0 mmol) and the solution was refluxed overnight. After cooling to r.t., dil. HCl was slowly added until the mixture reached pH 3–4, resulting in the precipitation of a white solid. The solid was isolated by centrifugation, washed with H_2O (5 mL), isolated by centrifugation, and dried under vacuum to give compound **5**; yield: 103 mg (79%); white solid.

IR (KBr): 3446 (s), 2966 (w), 2926 (w), 1716 (s), 1541 cm^{-1} (s).

^{1}H NMR (CD_3OD): δ = 0.97 (t, 3 H, ^3J = 7.7 Hz), 1.45 (m, 2 H), 1.97 (m, 2 H), 3.51 (t, 2 H, ^3J = 8.4 Hz), 4.8 (s, 4 H), 7.5 (d, 2 H, ^3J = 7.7 Hz), 7.7 (t, 2 H, ^3J = 7.8 Hz), 8.0 (t, 2 H, ^3J = 7.8 Hz), 8.1 (d, 2 H, ^3J = 7.7 Hz), 8.5 (d, 2 H, ^3J = 8.0 Hz), 8.6 (d, 2 H, ^3J = 8.0 Hz).

^{13}C{^{1}H} NMR (CD_3OD): δ = 13.9, 21.0, 27.1, 57.1, 58.9, 123.1, 125.2, 125.3, 126.2, 139.4, 140.2, 150.5, 151.6, 156.2, 156.5, 168.7.

MS (FAB$^+$): *m*/*z* = 498.2 ([M + H]$^+$, 100%).

Anal. Calcd for $C_{28}H_{27}N_5O_4$·HCl·2H$_2$O: C, 59.00; H, 5.66; N, 12.29. Found: C, 58.91; H, 5.39; N, 12.09.

Tris[(6′-bromo-2,2′-bipyridine-6-yl)methyl]butylammonium Bromide (6)

Compound **2** (600 mg, 1.83 mmol) was added to a stirred solution containing freshly distilled *n*-butylamine (46 μL, 0.46 mmol) and K_2CO_3 (345 mg, 2.5 mmol) in anhyd MeCN (35 mL) in a Schlenk tube under argon. The mixture was heated at 85 °C during 44 h. The MeCN was distilled under reduced pressure resulting in the isolation of an orange solid. The solid was partitioned between H_2O (20 mL) and CH_2Cl_2 (40 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated to dryness, and the resulting solid was purified by column chromatography (Al_2O_3 previously deactivated with H_2O; CH_2Cl_2–hexane, 20:80) to give compound **6** [R_f 0.32 (Al_2O_3), CH_2Cl_2–MeOH, 95:5]; yield: 150 mg (36%); white solid.

IR (CH_2Cl_2): 2906 (w), 1653 (s), 1541 (s), 1123 (m), 785 cm^{-1} (w).

^{1}H NMR ($CDCl_3$): δ = 0.78 (t, 3 H, ^3J = 7.5 Hz), 1.19 (m, 2 H), 2.04 (m, 2 H), 4.01 (t, 2 H, ^3J = 7.5 Hz), 5.50 (s, 6 H), 7.38–7.52 (m, 6 H), 7.75 (t, 3 H, ^3J = 8.0 Hz), 8.0 (t, 6 H, ^3J = 7.5 Hz), 8.25 (d, 3 H, ^3J = 8.0 Hz).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 13.5, 14.9, 25.3, 61.7, 63.9, 119.3, 122.3, 128.5, 128.6, 138.6, 139.0, 142.0, 149.6, 154.5, 155.9.

MS (FAB$^+$): *m*/*z* (%) = 814.2 ([M – Br]$^+$, 95), 816.2 ([M – Br]$^+$, 100).

Anal. Calcd for $C_{37}H_{33}Br_4N_7$: C, 49.64; H, 3.72; N, 10.95. Found: C, 50.14; H, 3.95; N, 11.36.

Tris[(6′-carboethoxy-2,2′-bipyridine-6-yl)methyl]butylammonium Bromide (7)

A solution of **6** (121 mg, 135 μmol) and $Pd(PPh_3)_2Cl_2$ (12 mg, 0.017 mmol) in a mixture of EtOH (10 mL) and Et_3N (10 mL) was heated at 70 °C for 20 h under a CO atmosphere. After the solution had cooled to r.t., the solvents were removed under vacuum and the resulting solid was dissolved in CH_2Cl_2 (30 mL), and the CH_2Cl_2 layer was washed with aq NaOH (pH 10, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was dissolved in a minimum amount of CH_2Cl_2, and Et_2O was added until a white precipitate forms. The solid was filtered off and the mother liquor was evaporated to dryness and the residue was dried under vacuum to give **7**; yield: 112 mg (95%, using CO of 99.995% purity); 12 mg (10% using standard CO of 99% purity) as an orange oil.

IR (CH_2Cl_2): 3063 (w), 2959 (m), 2925 (s), 2854 (m), 1739 (s), 1721 (s), 1581 (s), 1465 (m), 1441 (s), 1082 (m), 1024 cm^{-1} (m).

^{1}H NMR ($CDCl_3$): δ = 0.75 (t, 3 H, ^3J = 7.5 Hz), 1.20 (m, 2 H), 1.45 (t, 9 H, ^3J = 7.0 Hz), 1.92 (m, 2 H), 4.02 (m, 2 H), 4.48 (q, 6 H, ^3J = 7.0 Hz), 5.61 (s, 6 H), 7.83 (t, 3 H, ^3J = 8.0 Hz), 7.93 (t, 3 H, ^3J = 8.0 Hz), 8.11 (d, 3 H, ^3J = 7.5 Hz), 8.19 (d, 3 H, ^3J = 7.5 Hz), 8.31 (d, 3 H, ^3J = 7.5 Hz), 8.58 (d, 3 H, ^3J = 7.5 Hz).

^{13}C{^{1}H} NMR ($CDCl_3$): δ = 13.5, 13.6, 20.0, 25.5, 31.0, 62.1, 64.0, 122.8, 123.7, 125.4, 128.8, 138.0, 138.9, 148.3, 149.7, 155.3, 155.6, 165.0.

MS (FAB$^+$): *m*/*z* (%) = 704.2 ([M – $C_4H_{10}O_2$], <5),749.2 ([M – C_2H_5O], 20), 794.3 ([M – Br]$^+$, 100).

Anal. Calcd for $C_{46}H_{48}BrN_7O_6$: C, 63.16; H, 5.53; N, 11.21. Found: C, 62.83; H, 5.20; N, 10.88.

Tris[(6′-carboxy-2,2′-bipyridine-6-yl)methyl]butylammonium Chloride (8)

Compound **7** (112 mg, 128 μmol) was suspended in a mixture of conc. HCl (0.5 mL) and H_2O (3.5 mL) and the solution was heated at 70 °C overnight. After the mixture had cooled to r.t., the solvents were evaporated under reduced pressure. Recrystallisation from MeOH–Et_2O gave compound **8**; yield: 44 mg (38%); white solid.

IR (CH_2Cl_2): 3421 (s), 3098 (w), 1717 (s), 1633 (m), 1618 (m), 1580 cm^{-1} (m).

^{1}H NMR (CD_3OD): δ = 0.93 (t, 3 H, ^3J = 7.0 Hz), 1.3–1.4 (m, 2 H), 2.3–2.4 (m, 2 H), 3.6–3.7 (m, 2 H), 5.5 (s, 6 H), 7.7–7.8 (br s, 3 H), 7.8–8.0 (m, 6 H), 8.0–8.1 (m, 3 H), 8.31 (t, 3 H, ^3J = 7.0 Hz), 8.55 (d, 3 H, ^3J = 8.0 Hz).

^{13}C{^{1}H} NMR (CD_3OD): δ = 13.9, 27.1, 53.4, 57.4, 60.2, 109.4, 123.0, 125.0, 125.9, 127.9, 140.7, 147.2, 147.6, 148.6, 159.1, 166.5.

MS (FAB$^+$): *m*/*z* = 710.2 ([M – Cl]$^+$, 100%).

Anal. Calcd for $C_{40}H_{36}ClN_7O_6$·3HCl·2H$_2$O: C, 53.88; H, 4.86; N, 11.00. Found: C, 53.73; H, 4.52; N, 10.88.

***N*-(3-Aminopropyl)-4-nitrobenzamide (9)[18]**

IR (KBr): 2976 (m), 2921 (m), 1638 (s), 1597 (s), 1548 (s), 1516 (s), 1352 cm^{-1} (s).

^{1}H NMR (DMSO-d_6): δ = 1.60 (q, 2 H, ^3J = 7.0 Hz), 2.60 (t, 2 H, ^3J = 7.0 Hz), 3.34 (br t, 2 H, ^3J = 7.0 Hz), 8.02–8.09 (m, 2 H), 8.29–8.33 (m, 2 H), 8.88 (br t, 1 H).

^{13}C{^{1}H} NMR (CD_3OD): δ = 28.7, 37.3, 51.2, 123.4, 128.5, 140.1, 148.8, 164.5.

MS (FAB$^+$): *m*/*z* = 224.1 ([M + H]$^+$, 100%).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.72; H, 5.75; N, 18.69.

N-3-{N′,N′-Bis[(6′-bromo-2,2′-bipyridine-6-yl)methyl]aminopropyl}-4-nitrobenzamide (10)

A mixture of **9** (187 mg, 0.84 mmol), **2** (638 mg, 1.95 mmol) and K_2CO_3 (347 mg, 2.51 mmol) was heated in MeCN (20 mL) for 22 h at 85 °C under argon. The solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (25 mL). The H_2O layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by column chromatography (SiO_2 flash, CH_2Cl_2–MeOH, 100:0 to 99:1) to give **10** [R_f 0.28, (SiO_2), CH_2Cl_2–MeOH, 95:5]; yield: 420 mg (70%); white powder.

IR (CH_2Cl_2): 2925 (w), 1735 (w), 1651 (w), 1574 (s), 1550 (s), 1524 (m), 1420 (s), 1126 (m), 764 cm^{-1} (w).

^1H NMR ($CDCl_3$): δ = 1.94 (m, 2 H), 2.88 (t, 2 H, ^3J = 6.0 Hz), 3.57 (dt, 2 H, ^3J = 6.0 Hz, ^3J = 5.5 Hz), 3.98 (s, 4 H), 7.36–7.58 (m, 8 H), 7.72 (t, 2 H, ^3J = 7.5 Hz), 7.90 (d, 2 H, ^3J = 8.0 Hz), 8.09 (br t, 1 H, ^3J = 5.5 Hz), 8.18–8.24 (m, 4 H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 25.5, 40.1, 53.3, 59.8, 119.5, 120.0, 123.2, 124.0, 127.8, 127.9, 137.4, 138.9, 140.0, 141.6, 148.9, 154.2, 156.9, 158.0, 165.1.

MS (FAB^+): *m/z* = 718.4 ($[M + H]^+$, 100%).

Anal. Calcd for $C_{32}H_{27}Br_2N_7O_3$: C, 53.57; H, 3.79; N, 13.67. Found: C, 53.20; H, 3.46; N, 13.32.

N-3-{N′,N′-Bis[(6′-carboethoxy-2,2′-bipyridine-6-yl)methyl]-aminopropyl}-4-nitrobenzamide (11)

A solution of **10** (300 mg, 420 μmol) and $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol) in a mixture of EtOH (60 mL) and Et_3N (60 mL) was heated at 70 °C overnight under a stream of CO. After the solution had cooled to r.t., the solvents were removed under vacuum. The residue was purified by column chromatography (SiO_2, CH_2Cl_2–MeOH–Et_3N, 100:0:0, 99:5:0, then 94:5:1) to give **11** [R_f 0.43 (SiO_2), CH_2Cl_2–MeOH, 90:10); yield: 193 mg (65%); beige powder.

IR (CH_2Cl_2): 3059 (w), 2969 (w), 2925 (w), 1713 (s), 1653 (m), 1421 (s), 1365 (s), 1224 (s), 1093 cm^{-1} (m).

^1H NMR ($CDCl_3$): δ = 1.41 (t, 6 H, ^3J = 7.0 Hz), 1.93 (br t, 2 H), 2.83 (t, 2 H, ^3J = 6.0 Hz), 3.54 (br m, 2 H), 3.94 (s, 4 H), 4.42 (q, 4 H, ^3J = 7.0 Hz), 7.38 (d, 2 H, ^3J = 8.0 Hz), 7.63 (t, 2 H, ^3J = 8.5 Hz), 7.71–7.85 (m, 6 H), 7.99 (dd, 2 H, ^3J = 8.0 Hz, ^4J = 0.5 Hz), 8.19 (br t, 1 H), 8.32 (d, 2 H, ^3J = 8.0 Hz), 8.40 (dd, 2 H, ^4J = 0.5 Hz, ^3J = 8.0 Hz).

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.4, 25.8, 40.0, 53.3, 60.0, 61.9, 120.3, 123.2, 124.0, 124.1, 124.9, 128.1, 137.5, 137.7, 140.2, 147.9 (br), 149.0, 155.0, 156.2, 158.3, 165.2.

MS (FAB^+): *m/z* = 704.2 ($[M + H]^{+\cdot}$, 100%).

Anal. Calcd for $C_{38}H_{37}N_7O_7$: C, 64.85; H, 5.30; N, 13.93. Found: C, 64.51; H, 4.94; N, 13.58.

N-3-{N′,N′-Bis[(6′-carboxy-2,2′-bipyridine-6-yl)methyl]aminopropyl}-4-nitrobenzamide (12)

Compound **11** (140 mg, 0.20 mmol) and NaOH (32 mg, 0.80 mmol) were dissolved in a mixture of H_2O (10 mL) and EtOH (10 mL) and heated at 75 °C overnight. The solution was evaporated to dryness, the solid residue was dissolved in a minimum of H_2O and acidified to pH 2–3 with dil. HCl. The precipitate that formed was collected by centrifugation and dried under reduced pressure; yield: 93 mg (67%); pale orange powder.

IR (KBr): 3348 (s), 2974 (w), 2924 (m), 1735 (s), 1639 (m), 1598 (m), 1523 (m), 1444 (m), 1322 (s), 1270 (m), 1200 (m), 1084 cm^{-1} (m).

^1H NMR ($CDCl_3$): δ = 2.36 (br t, 2 H), 3.59 (br t, 2 H), 3.74 (t, 2 H, ^3J = 7.5 Hz), 4.82 (s, 4 H), 7.51 (d, 2 H, ^3J = 7.5 Hz), 7.77 (t, 2 H, ^3J = 7.5 Hz), 7.85 (d, 2 H, ^3J = 9.0 Hz), 7.93 (t, 2 H, ^3J = 8.0 Hz), 8.08 (dd, 2 H, ^3J = 7.5 Hz, ^4J = 1.0 Hz), 8.20 (d, 2 H, ^3J = 9.0 Hz), 8.51 (d, 2 H, ^3J = 8.0 Hz), 8.63 (dd, 2 H, ^3J = 8.0 Hz, ^4J = 0.5 Hz).

$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 26.1, 37.6, 54.6, 59.2, 123.1, 124.6, 125.7, 125.8, 126.4, 129.6, 139.6, 140.1, 140.2, 149.1, 151.1, 151.3, 156.2, 156.3, 167.8, 168.7.

MS (FAB^+): *m/z* = 603.2 ($[M - CO_2H + H]$, <5), 648.2 ($[M + H]^{+\cdot}$, 100).

Anal. Calcd for $C_{34}H_{29}N_7O_7 \cdot 2HCl$: C, 56.67; H, 4.34; N, 13.61. Found: C, 56.61; H, 4.60; N, 13.49.

Bis[(6′-carboxy-2,2′-bipyridine-6-yl)methyl]butylamine Europium Complex

A solution of $EuCl_3 \cdot 6H_2O$ (13.0 mg, 35 μmol) in MeOH (10 mL) was added to a solution of ligand **5** (17.5 mg, 35 μmol) in MeOH (10 mL). The resulting mixture was stirred for 1 h at 70 °C. After addition of Et_3N (19 μL, 141 μmol) and an additional 1 h stirring at r.t., the solution was concentrated in vacuo. Precipitation with Et_2O gave a white crystalline product, which was recrystallised from MeOH–DMSO–THF mixture; yield: 21 mg (80%); white powder.

IR (CH_2Cl_2): 3448 (s), 2913 (w), 2853 (w), 1637 (s), 1364 (m), 1010 (m), 765 cm^{-1} (m).

MS (FAB^+): *m/z* = 648.2 ($[M + H]^+$, 100%).

Anal. Calcd for $C_{28}H_{25}ClEuN_5O_4 \cdot DMSO \cdot 2H_2O$: C, 45.20; H, 4.43; N, 8.79. Found: C, 45.10; H, 4.28; N, 8.53.

Tris[(6′-carboxy-2,2′-bipyridine-6-yl)methyl]butylammonium Europium Complex

A solution of $EuCl_3 \cdot 6H_2O$ (8.2 mg, 22 μmol) in MeOH (5 mL) was added to a solution of compound **8** (20 mg, 22 μmol) in MeOH (5 mL). The resulting mixture was then stirred at reflux for 1 h. Et_3N (20 μL 148 μmol) was added to the hot solution, which was cooled to r.t., and further stirred for 30 min. The solution was concentrated in vacuo and addition of Et_2O led to the precipitation of the desired complex, which was isolated by centrifugation and dried under vacuum; yield: 9.8 mg (48%); white powder.

IR (KBr): 3447 (s), 1646 (s), 1633 (s), 1560 (m), 1507 (m), 1023 (m), 771 cm^{-1} (m).

MS (FAB^+): *m/z* (%) = 804.2 ($[M - C_4H_9 + H]$, 25), 860.3 ($[M - Cl]^+$, 80).

Anal. Calcd for $C_{40}H_{33}ClEuN_7O_6 \cdot 3H_2O$: C 50.62, H 4.14, N 10.33. Found: C 50.48, H 3.85, N 10.13.

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