An efficient synthesis of pyridine containing triaza-macrocyclic triacetate ligand and luminescence properties of its europium(III) complex

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Abstract

Reaction of diethylenetriamine with 2-nitrobenzenesulfonyl chloride leads to an activated and protected compound that could be cyclized to *N*-protected aza-macrocycle. After a smooth deprotection step, the macrocycle was alkylated with chloroacetic acid leading to the pyridine containing triaza-macrocycle **1** in good yield. The luminescence properties of its Eu^{3+} complex were examined in aqueous solution. © 2000 Elsevier Science Ltd. All rights reserved.

Aza-macrocyclic ligands are known for their ability to complex transition and non-transition metallic cations and some of their lanthanide complexes have found application in the medical area.[1] However, the challenge in macrocyclic ligand design remains the obtention of lanthanide chelates that are both thermodynamically stable and kinetically inert. This is complicated by the fact that neither the complexation mechanisms nor the factors determining the complex stability have been fully understood. So, as part of our research on the complexation of f-elements, we report on the synthesis of the aza-macrocycle **1**. In addition, the luminescence properties of its Eu^{3+} complex were studied.

The synthesis of 12-membered Pyridine Containing TriAza-macrocyclic (PCTA) triacetate ligands has been previously described[2,3] and it appears that the building of the aza-macrocyclic ring is the crucial step. It is usually performed in anhydrous DMF or CH_3CN by reaction of the dianion of a bis-toluenesulfonamide derived from diethylenetriamine with a 2,6-bis(halomethyl)pyridine.[2] In these reactions, the *p*-toluenesulfonamide group serves a dual

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purpose. It not only increases the acidity of the secondary NH proton but it also acts as a temporary nitrogen-protecting group by controlling the monoalkylation of the amine function. However, the deprotection of the resulting macrocycle is often a low yielding reaction since it requires drastic conditions.[4,5] So, in order to increase the overall yield of the process, we decided to employ a new protecting/activating group that could be removed using smoother methods. In addition, a further functionalization of the 2,6-bis(halomethyl)pyridine moiety would thus be allowed.

Fukuyama and co-workers[6] have introduced the 2-nitrobenzenesulfonyl group as a new amine protecting/activating group. Since then, such derivatives have successfully been used for the synthesis of a variety of secondary amines,[6,7] as well as natural products.[8] It appears, therefore, that the 2-nitrobenzenesulfonyl group should be a protective group of choice to increase the overall yield of the synthesis of PCTA ligands, as it can be removed by a smooth method (PhSH, Na$_2$CO$_3$, room temperature).[6–8] Here we report on an efficient synthesis of PCTA ligand **1** employing a 2-nitrobenzenesulfonamide intermediate.

The tris(2-nitrobenzenesulfonyl)-protected compound **2** was prepared by reaction of 2-nitrobenzenesulfonyl chloride **3** with diethylenetriamine **4** (Scheme 1). The use of the heterogeneous NaHCO$_3$/THF system instead of the homogeneous Et$_3$N/CH$_2$Cl$_2$ system[7] avoids the purification by flash chromatography, as the desired product **2** is readily obtained by recrystallization in CH$_2$Cl$_2$.[9] Condensation of **2** with 2,6-bis(bromomethyl)pyridine **5** in DMF in the presence of Na$_2$CO$_3$ gives the aimed macrocyclic product **6** in a 76% yield.[10]
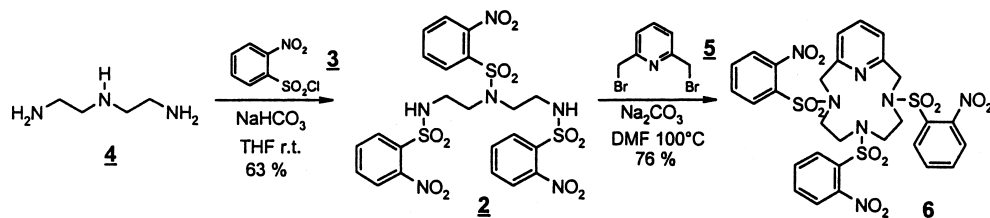
Scheme 1.

Compound **6** was readily deprotected with thiophenol at room temperature to produce the macrocycle **7**, which was isolated as its trihydrochloride salt in a 72% yield[11] (Scheme 2). Alkylation of **7** was performed by reaction with chloroacetic acid in the presence of potassium hydroxide at 80°C by maintaining the pH of the solution at 10. The targeted macrocycle **1** was isolated in a 78% yield as a white powder by purification by ion-exchange chromatography on DOWEX 1X8 (formate form, elution with dilute formic acid).[11]
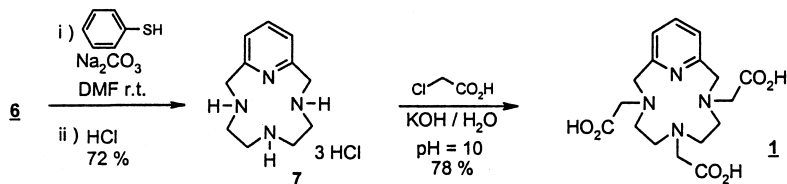
Scheme 2.

This procedure thus affords a very convenient and effective approach for the synthesis of a PCTA ligand, as the deprotection step was completed after a night at room temperature. This smooth step would allow further functionalization of the 2,6-bis(halomethyl)pyridine moiety in order to prepare a PCTA compound targeted to specific bio-receptors.[1]

The Eu^{3+} complex formed with the PTCA macrocycle **1** was characterized in aqueous medium by UV-light induced Eu^{3+} luminescence measurements. As a result of the low extinction coefficients associated with Laporte-forbidden lanthanide f–f transitions, direct excitation of lanthanide ions is only practicable with laser beams.[12,13] For practical reasons, it could be more convenient to use a complexant that incorporates a sensitizing chromophore. Indeed, the UV-light absorbed by the ligand could thus be transformed into visible lanthanoid emission via an intramolecular energy transfer.[12] In our case, the presence of a pyridine moiety in macrocycle **1** should provide an efficient through-space energy transfer from the excited chromophore to the proximate lanthanide.

The absorbance of an aqueous solution of equimolar quantities of EuCl$_3$ and macrocycle **1** at pH 7 was monitored by UV–visible spectroscopy and exhibited a maximum absorption at the 269 nm wavelength (Fig. 1). Moreover, the excitation of this solution at 269 nm gave rise to the well-known structured emission spectrum of the Eu^{3+} ion, thus being evidence of the formation of an Eu^{3+} complex together with the occurrence of a through-space energy transfer from the ligand to the proximate Eu^{3+}. The use of sensitized emission led to a large Stokes shift (>250 nm) such that it is unlikely that there was any overlap between the emission bands and the strong absorbance band.
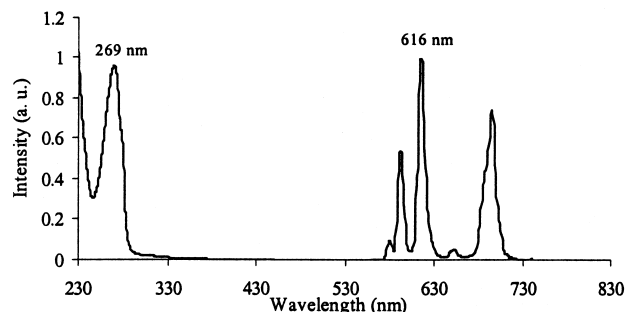

Figure 1.

As expected, all emission bands of Eu^{3+} arose from the $^5D_0$ state. The most intense bands corresponding to the $^5D_0 \rightarrow {}^7F_j$ ($J = 0, 1, 2, 3, 4$) transitions were observed with 37% of the total emission light centred on the 616 nm peak ($^5D_0 \rightarrow {}^7F_2$). The study of the thermodynamic properties of such complexes was thus made possible by Eu^{3+} luminescence experiments induced by a through-space energy transfer.

The complexation of Eu^{3+} with PCTA ligand **1** leads to an ion-exchange process with the carboxylic protons of the ligand so that the thermodynamic formation constant is a function of the pH. The stoichiometry of the Eu^{3+} complex formed with ligand **1** was determined by monitoring the luminescence at 615 nm as the function of Eu^{3+} added to aqueous solutions of **1** (5×10^{-5} M) at a pH such that the competition of protons is negligible (pH 7.0).[14] A 1:1 complex stoichiometry was disclosed. The luminescence lifetimes of this complex were measured in H$_2$O ($\tau_{H_2O} = 0.37$ ms) and D$_2$O ($\tau_{D_2O} = 2.12$ ms).† Such measurements allow the estimation of the number of coordinated water molecules (η_{H_2O}) by the use of the well-known empirical relation proposed by Horrocks and Sudnick.[13] The formula is reported to be accurate up to 0.5 water molecules. The presence of 2.3 coordinated water molecules is in agreement with the

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† Experimental uncertainty 5%.

expected seven-coordinating nature of compound **1** since Eu^{3+} prefers a coordination number of 8–9.[15] In water solution a luminescence quantum yield ($\Phi = 2.9\%$)[‡] for [Eu ⊂ **1**] was found. An evaluation of the association constant of macrocycle **1** with Eu^{3+} will be disclosed in due course.

Acknowledgements

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9. A solution of **3** (13.3 g, 60 mmol) in 150 mL of THF was added dropwise in 1 hour to a stirred suspension of **4** (2.06 g, 20 mmol) and $NaHCO_3$ (10.1 g, 120 mmol) in 150 mL of THF at 0°C under argon. The resulting reaction mixture was allowed to warm to room temperature and stirred for a further 96 hours. The inorganic salts were filtered and washed with THF. The filtrate was concentrated and the solid obtained was recrystallized in CH_2Cl_2 affording the pure compound **2** as a white solid: 8.25 g (63%); ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 3.06 (t, 4H, $J = 7$ Hz), 3.38 (t, 4H, $J = 7$ Hz), 7.80–8.21 (m, 12H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 41.2, 47.9, 124.4, 129.3, 130.9, 132.5, 134.0, 147.4.
10. A solution of **5** (2.65 g, 10 mmol) in anhydrous DMF (50 mL) was added dropwise in 1 hour to a stirred suspension of **2** (6.58 g, 10 mmol) and Na_2CO_3 (4.24 g, 40 mmol) in anhydrous DMF (50 mL) at 100°C under an argon atmosphere. The reaction was heated overnight. The solvent was evaporated and the residue was taken up in CH_2Cl_2. The organic phase was washed with aqueous sodium hydroxide (0.1 M), then dried over sodium sulfate and concentrated to give a solid, which was recrystallized from acetone to give **6** as a white product (5.8 g, 76%); ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 3.53 (t, 4H, $J = 6$ Hz), 3.77 (t, 4H, $J = 6$ Hz), 4.62 (s, 4H), 7.34 (d, 2H, $J = 8$ Hz), 7.82–8.06 (m, 13H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 46.1, 49.2, 54.9, 124.3, 129.4, 130.4, 132.3, 134.5, 138.4, 147.1, 147.7, 155.7. The purity of **6** was determined by HPLC analysis, Hypersil column (CH_2Cl_2 35/EtOAc 35/heptane 30).
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[‡] Experimental uncertainty 10%.