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Phloroglucinol based podands, versatile tripodal ligands

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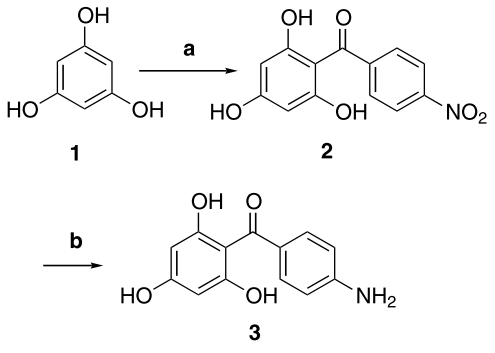
Abstract—The synthesis of four phloroglucinol based podands is described. Ligands **4** and **5** have three bipyridine arms and an induced octahedral cavity ideal for transition metal complexation. The iron(II) complex of **4** is described. Tripodes **6** and **7** possess three bipyridine-carboxylate arms, and are designed for the encapsulation of luminescent lanthanide salts. Some preliminary optical properties of the corresponding Eu^{3+} and Tb^{3+} are presented.

A constant effort has been made, during the last 20 years, to synthesize polypyridine ligands[1] in the hope of complexing various metals from transition ones to lanthanides. One strategy used to build covalent assemblies, having bipyridine subunits, was to graft bipyridine pendant arms on a molecular platform. The choice of the central molecule allows the control of the podand's cavity geometry. Numerous molecular frameworks were used to synthesize podands bearing three or more bipyridine units, such as polyamines,[2] polyamides,[3] or calixarenes.[4] Cage-type polypyridine podands consisting of three covalently linked bipyridines provide an ideal octahedral environment for the encapsulation of transition metal such as Ru(II).[5] Substituted bipyridines possessing a carboxylate function at the α position from one nitrogen atom were shown to generate a cavity with nine coordination sites. Such a configuration seems ideally appropriate for an efficient encapsulation of luminescent lanthanide salts.[6] We present now the synthesis of podands with three bipyridine arms derived from phloroglucinol (**1**), by alkylation of the hydroxyl groups with two differently substituted bipyridines bearing a benzylic bromide.

The first step to be achieved is the trialkylation of phloroglucinol with a good yield. The classical bases such as sodium carbonate or triethylamine did not lead to complete alkylation of the three hydroxyl groups. Moreover, some degradation of the phloroglucinol is observed, probably due to a partial oxidation. As previously described, Cs_2CO_3 is the appropriate base[7] in anhydrous degassed DMF, to obtain satisfactory results. Two central structures were chosen for our study; the free phloroglucinol (**1**), as a model compound, and a functionalized phloroglucinol specially designed to further link the resulting podand on a solid support or on a biomolecule.

The phloroglucinol was mono functionalized using a typical Friedel–Crafts reaction, with one equivalent of *p*-nitrobenzoyl chloride in presence of $AlCl_3$ as Lewis acid, in nitrobenzene (Scheme 1).[8] Compound **2** is obtained after steam extraction of the nitrobenzene and recrystallization in boiling water with 12% yield. The nitro group is quantitatively reduced to the corresponding aromatic amine **3**, with hydrogen in ethanol, in the presence of Pd/C as a catalyst.

The two central structures **1** and **3** (obtained by reduction of **2** and evaporation of the solvent, with no



Scheme 1. *Reagents and conditions*: (a) $AlCl_3$, CS_2, $PhNO_2$, $ClCOPhNO_2$, reflux, 12%; (b) H_2, Pd/C, EtOH, quant.

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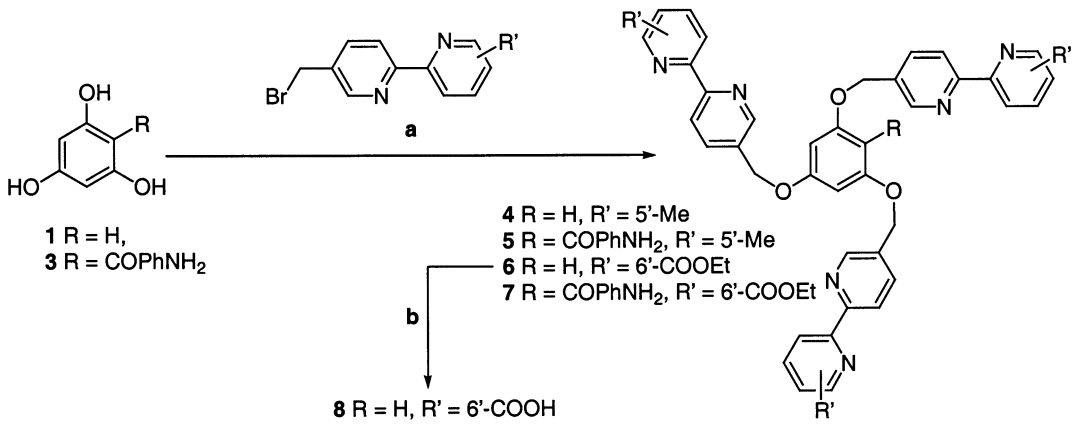

Scheme 2. *Reagents and conditions*: (a) Cs_2CO_3, 5-bromomethyl-R′-(2,2′-bipyridine) (3 equiv.), DMF, rt, 2–7 days, 30–83%; (b) i. NaOH, $MeOH/H_2O$, ii. HCl, 90%.

additional purification), were alkylated with 3 equiv. of 5-bromomethyl-5′-methyl-2,2′-bipyridine,[2] with cesium carbonate (5 equiv.) as base, in anhydrous degassed DMF, at room temperature during two days.[7] After chromatography on alumina, **4** and **5** were obtained with a respective yields of 30 and 42% (Scheme 2).

The complexation abilities of these tripodal podands were demonstrated by the synthesis of an iron(II) complex using the highly symmetrical model podands **4**.[†] To a solution of **4** (1 equiv.) in CH_2Cl_2 was added a methanolic solution of $FeSO_4$. The counter ion SO_4^{2-} was exchanged by using a saturated aqueous solution of KPF_6.[2] Purification by chromatography over Al_2O_3, with a standard eluent (CH_2Cl_2/MeOH, 95:5) led to [Fe(**4**)]$(PF_6)_2$[‡] with a good yield (51%), despite the possibility of polymerization reactions. This complex is clearly characterized by a well defined and intense metal-to-ligand charge transfer UV–vis absorption band at low energy $\lambda_{max} = 527$ nm ($\varepsilon = 6{,}400$ M^{-1} cm^{-1}), and by a clear ^1H NMR spectrum (Fig. 1). This spectrum shows a nice C_3 symmetry in the molecule and a clear AB system centered at 5.09 ppm for the methylene bridge, due to the rigid structure. A strong shielding from 8.70 to 6.52 ppm of the H^6 of the bipyridine can be noted, the three H^6 protons being blocked in the shielding cone of the benzene ring. The model compound **4** demonstrates that the phloroglucinol is indeed a good candidate for the effective preparation of podands with a three bipyridine coordination cavity. These ligands (**4**, **5**) are expected to be good candidates for the preparation of long life luminescent $Ru(bpy)_3^{2+}$ type complexes, in regard to the good results obtained with the mesitylene based analogous products.[5]

The present study was continued with the synthesis of phloroglucinol derivatives bearing three tritopic arms, to form nonadentate cavity designed for lanthanide complexation.[6] For our purpose, we used the same conditions for the nucleophilic substitution: Cs_2CO_3 as base in DMF, at room temperature, 3 equiv. of ethyl 5′-methyl-6-(2,2′-bipyridine)-carboxylate,[9] during two days to obtain **6** with a 50% yield,[10] and during 1 week

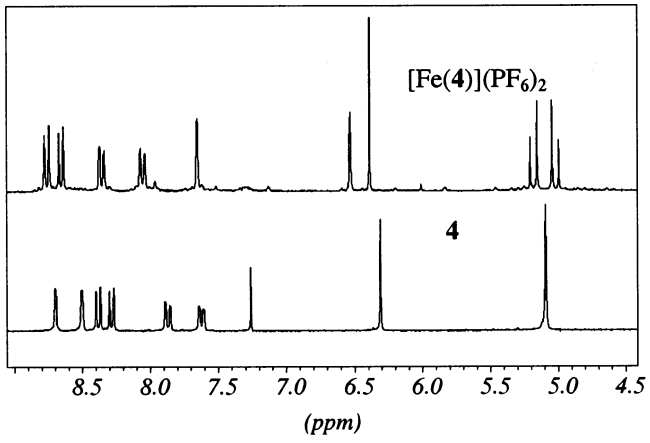

Figure 1. ^1H NMR spectra of **4** (in $CDCl_3$) and [Fe(**4**)]$(PF_6)_2$ (in CD_3COCD_3).

[†] [1,3,5-Tri[(5′-methyl-2,2′-bipyridin-5-yl)methoxy] benzene. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.40$ (s, 9H), 5.09 (s, 6H), 6.31 (s, 3H), 7.62 (dd, 3H, ^3J = 8.1 Hz $^4J = 1.7$ Hz), 7.87 (dd, 3H, $^3J = 8.2$ Hz $^4J = 2.4$ Hz), 8.29 (d, 3H, $^3J = 8.2$ Hz), 8.38 (d, 3H, $^3J = 8.2$ Hz), 8.50 (d, 3H, $^4J = 1.7$ Hz), 8.70 (d, 3H, $^4J = 1.7$ Hz). $^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $CDCl_3$): $\delta = 18.4$ (CH_3), 67.7 (CH_2), 95.2 (CH), 120.6 (CH), 120.7 (CH), 131.8 (Cq), 133.6 (Cq), 136.3 (CH), 137.5 (CH), 148.3 (CH), 149.6 (CH), 153.3 (Cq), 156.2 (Cq), 160.4 (Cq). IR (KBr): 1594 (s), 1470 (s), 1155 (s) cm^{-1}. UV–vis (CH_2Cl_2, 23°C): λ_{max} (ε, M^{-1} cm^{-1}) = 291 (88000). MS (FAB$^+$, *m*NBA): *m*/*z* (%) = 673 (100) [M+H$^+$], 695 (9) [M+Na$^+$].

[‡] {1,3,5-Tri[(5′-methyl-2,2′-bipyridin-5-yl)methoxy]benzene} iron(II) hexafluorophosphate. ^1H NMR (250 MHz, $(CD_3)_2CO$): $\delta = 2.21$ (s, 9H), 5.10 (AB sys, 6H, $\Delta\nu = 38.4$ Hz, $J_{AB} = 12.7$ Hz), 6.39 (s, 3H), 6.53 (d, 3H, $^4J = 1.5$ Hz), 7.65 (s, 3H), 8.05 (d, 3H, $^3J = 8.5$ Hz), 8.36 (d, 3H, $^3J = 8.2$ Hz, $^4J = 1.5$ Hz), 8.66 (d, 3H, $^3J = 8.2$ Hz), 8.77 (d, 3H, $^3J = 8.2$ Hz). $^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $(CD_3)_2CO$): $\delta = 18.6$ (CH_3), 71.3 (CH_2), 111.0 (CH), 124.6 (CH), 124.9 (CH), 135.5 (Cq), 139.6 (Cq), 140.3 (CH), 141.4 (CH), 154.0 (CH), 155.3 (CH), 157.0 (Cq), 159.5 (Cq), 160.5 (Cq). IR (KBr): 1649 (s), 1443 (m) cm^{-1}. UV–vis (CH_2Cl_2, 23°C): λ_{max} (ε, M^{-1} cm^{-1}) = 304 (6800), 527 (6400). MS (ES$^+$, CH_3CN): *m*/*z* (%) = 873.2 [{L+Fe}PF_6]$^+$, 364.2 [L+Fe]$^{2+}$.

Table 1. Selected photophysical data for the lanthanide complexes

Comp.	λ_{max}[a] (nm)	ε[a] $M^{-1}cm^{-1}$	τ_{H2O}[b]	τ_{D2O}[b]	nH_2O[c]	ϕ[d]
[Eu(**8**)]	309	37000	1.95	2.80	0.2	0.10
[Tb(**8**)]	309	38000	1.27	1.69	0.8	0.12

[a] Measured in water at 300 K.
[b] At 300 K.
[c] Calculated from Horrock's equation.[11]
[d] Calculated with $Ru(bpy)_3Cl_2$ as reference for Eu^{3+} complex and quinine sulfate for Tb^{3+} complex.

to give **7**[§] with a yield of 83% (Scheme 2). The substitution process is slow, and the yields can be increased by lengthening the reaction time. Compound **6** was saponified with NaOH in a $MeOH/H_2O$ mixture, and the corresponding triacid **8** was recovered by precipitation at pH 4.[6] Preliminary photophysical measurements were performed on the in situ generated complexes of **8** with Eu^{3+} and Tb^{3+}. Upon formation, the complexes induce a small bathochromic shift of the π–π^* band of the bipyridine core in the UV spectra, from 291 to 309 nm, in water. The [Eu(**8**)] model complex exhibits a very long-lived emission of 1.8 ms, a quantum yield in water of 10%, and no water molecule is present in the first coordination sphere (Table 1). In the case of the Tb^{3+} complex, the emission lifetime is shortened, probably by the presence of a water molecule. These results confirm the ability of the phloroglucinol based podands to encapsulate efficiently lanthanide salts.

The complexation studies of **7** with Eu(III) and Tb(III) and the optical properties of the corresponding complexes are in progress. Investigations for an optimal method to link these new podands on a biomolecule, using the residual amino function, are also under way.

In conclusion, we have shown that phloroglucinol is a good candidate for the efficient preparation of podands bearing three coordinating arms capable of inducing a coordination cavity. Moreover, the easy functionalization of the aromatic ring opens up new horizons for further functionalizations of the podands or their metal complexes.

[§] (4-Aminophenyl)(2,4,6-tri[(6′-ethoxycarbonyl-2,2′-bipyridin-5-yl) methoxy] phenyl) methanone. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.44–1.50 (m, 9H), 4.44–4.54 (m, 6H), 5.10 (s, 4H), 5.13 (s, 2H), 6.34 (s, 2H), 6.61 (d, 2H, ^3J = 8.5 Hz), 7.57 (dd, 2H, ^3J = 8.2 Hz ^4J = 2.4 Hz), 7.66 (d, 2H, ^3J = 8.5 Hz), 7.89–8.00 (m, 4H), 8.10 (dd, 2H, ^3J = 7.7 Hz, ^4J = 0.8 Hz), 8.40 (d, 2H, ^3J = 8.2 Hz), 8.51–8.62 (m, 7H), 8.73 (d, 1H, ^4J = 1.8 Hz).$^{13}C\{^1H\}$ JMOD NMR (62.5 MHz, $CDCl_3$): δ = 14.3 (CH_3), 61.9 (CH_2), 67.7 (CH_2), 68.0 (CH_2), 94.0(CH), 97.5 (CH), 113.7 (CH), 121.4 (CH), 121.5 (CH), 124.1 (CH), 124.8 (CH), 125.0 (CH), 128.3 (Cq), 131.9 (CH), 132.5 (Cq), 132.6 (Cq), 135.8 (CH), 136.3 (CH), 137.8 (CH), 137.9 (CH), 147.6 (CH), 147.65 (Cq), 147.7 (Cq), 148.2 (CH), 152.1 (Cq), 154.6 (Cq), 155.0 (Cq), 155.9 (Cq), 156.0 (Cq), 156.9 (Cq), 160.5 (Cq), 165.2 (C=O), 192.3 (C=O).IR (KBr): 3440 (m), 1740 (m), 1715 (m), 1644 (sh), 1595 (s) cm^{-1}. MS (FAB^+, *m*NBA): *m*/*z* (%) = 966 (100) [M+H$^+$], 988 (25) [M+Na$^+$].

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