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Aminomethyl bi- and terpyridines as luminescent probes for Zn^{2+} ions

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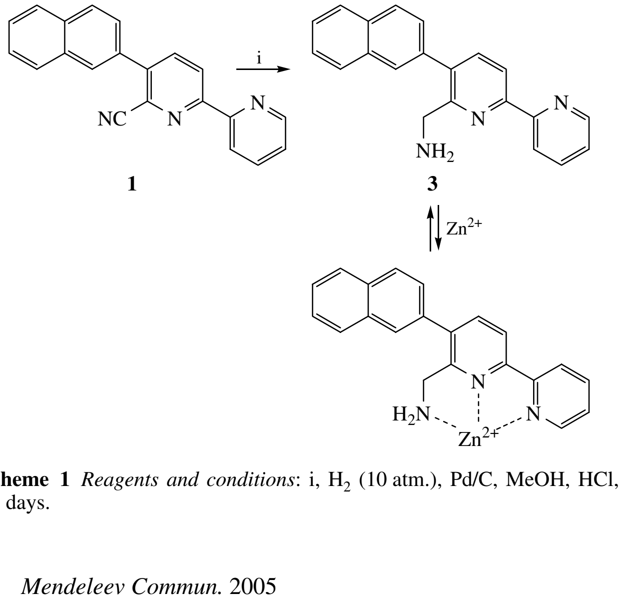
2,2′-Bi- and 2,2′:6′,2″-terpyridines, bearing aminomethyl and aryl substituents, show a significant increase in emission intensity and bathochromic emission wavelength change upon the addition of zinc ions in aqueous solution, and they can be used as luminescent probes for zinc ions in physiological media.

Selective and sensitive fluorescent probes for the *in vitro* and *in vivo* monitoring of metal ions are valuable tools for medical diagnostics. Probes for zinc ions are of increasing interest because a large number of cellular functions have been identified for zinc.[1,2] Several fluorescent probes based on substituted bi- and terpyridines have been reported recently.[3,4] The receptors are usually composed of a binding site, which is an oligopyridine as a well known ligand for transition metal ions, and a fluorescent unit.[5,6] Communication between the two units leads to changes in the emission properties upon analyte binding.

We report new fluorescent probes for zinc ions, in which a bi- or terpyridine moiety is both receptor and signalling unit. We used 2,2′-bi- and 2,2′:6′,2″-terpyridines with aryl substituents in the β-position of a terminal pyridine ring, which exhibited the highest emission quantum yields (80–90%) in comparison with α- and γ-substitution.[7] 5-Aryl-6-cyano-2,2′-bipyridines, such as **1**, and 5,5″-diaryl-2,2′:6′,2″-terpyridines, such as **2**, are readily accessible by a recently published synthetic route.[8,9] Reduction of the cyano moiety in 5-naphthyl-6-cyano-2,2′-bipyridine **1** yields 6-aminomethyl-5-naphthyl-2,2′-biypridine **3** (Scheme 1).[†] The emission of the naphthyl-bipyridine chromophore (the emission quantum yield of parent **1** is 0.58)[8] is now quenched by the well known PET mechanism of the amine lone pair.[10]

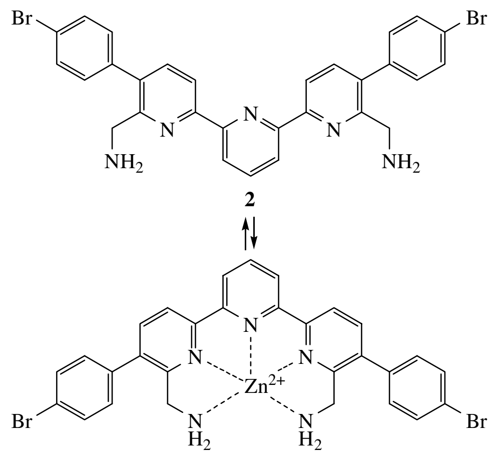
Upon metal cation coordination, which utilizes the amine beside the 2,2′-bipyridine binding site, the quenching is intercepted. The addition of zinc(II) to a buffered aqueous solution of **3** (10^{-5} M) at pH 8 results in a fivefold increase in the emission intensity with a bathochromic shift of maximum of emission from 460 to 480 nm (Figure 1). A correlation between the intensity of emission and the concentration of Zn^{2+} in solution was linear in the concentration range 0–2 μmol dm^{-3} (Figure 1). A bathochromic shift (25 nm) was observed in the electronic spectra of **3**.

We studied the response of 6,6″-bis(aminomethyl)-5,5″-bis-(4-bromophenyl)-2,2′:6′,2″-terpyridine **2** to the addition of Zn^{2+}. The ligand was prepared using a published procedure.[9] In a buffered aqueous solution (pH 8, TRIS buffer), it exhibited a weak emission at 355 nm. Upon addition of $Zn(ClO_4)_2$, a



Scheme 1 *Reagents and conditions*: i, H_2 (10 atm.), Pd/C, MeOH, HCl, 14 days.

[†] *6-Aminomethyl-5-(2-naphthyl)-2,2′-bipyridine hydrochloride* **3**. 6-Cyano-5-(2-naphthyl)-2,2′-bipyridine **1** (620 mg, 2.02 mmol) was hydrogenated for two weeks at 10 atm. in 10 ml of methanol with 1 ml of concentrated hydrochloric acid and 100 mg of 10% palladium on charcoal. The charcoal was filtered off and the solvent was evaporated. To the residue 2 ml of ethanol was added and the precipitate was separated by filtration to give **3** (575 mg, 82%); mp 273–274 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 4.37 (br. s, 2H, CH_2), 7.62 (m, 2H), 7.70 (m, 1H), 7.89 (br. t, 1H, *J* 5.6 Hz), 8.10 (m, 4H), 8.20 (d, 1H, *J* 8.1 Hz), 8.46 (br. t, 1H, 5.6 Hz), 8.63 (d, 1H, *J* 8.1 Hz), 8.90 (m, 5H). EI MS (70 eV), *m/z* (%): 311 (88%) [M^+], 310 (100), 295 (15), 294 (50), 293 (39), 283 (19), 282 (11), 281 (19), 279 (12), 154 (28).



Scheme 2

strong increase of the emission intensity was observed (Figure 2). The coordination of zinc ions (Scheme 2) is accompanied by a bathochromic shift of emission ($\lambda_{\max}$ 390 nm). The protonation of amino moieties also leads to an increase in emission, but the emission wavelength remains unchanged.

The addition of nickel(II), cobalt(II) or copper(II) results in an emission decrease due to quenching by energy transfer from the fluorophore to the paramagnetic metal ion.

In summary, available aminomethyl-substituted 2,2′-bi and 2,2′:6′,2″-terpyridines show a significant increase in emission intensity and bathochromic emission wavelength change upon addition of zinc ions. Protonation also leads to an emission increase, but without changes in the emission wavelength. Other transition metal ions quench the emission. The application of compounds **2**, **3** or their derivatives as luminescent probes for zinc ions in physiological media can therefore be clearly envisaged.

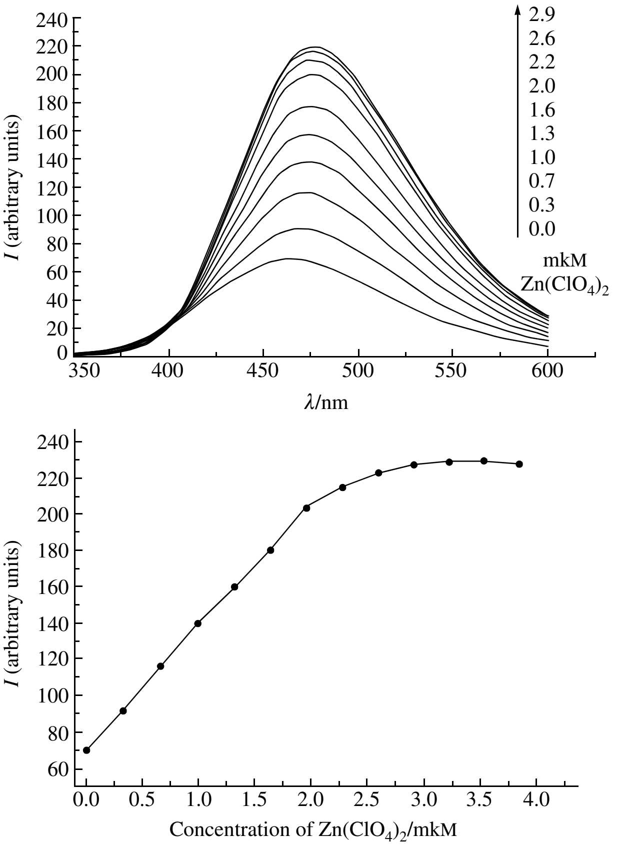


Figure 1 Fluorescence spectra and fluorescent titration curve of **3** (10 µM) upon the addition of $Zn(ClO_4)_2$: $[Zn^{2+}]$ = 0, 3.3, 6.6, 9.9, 13.2, 16.4, 19.6, 22.8, 26.0, 29.1 µM. The spectra were measured in aqueous solutions (TRIS buffer, 10 mM, pH 8) with excitation at an isosbestic point at 306 nm.

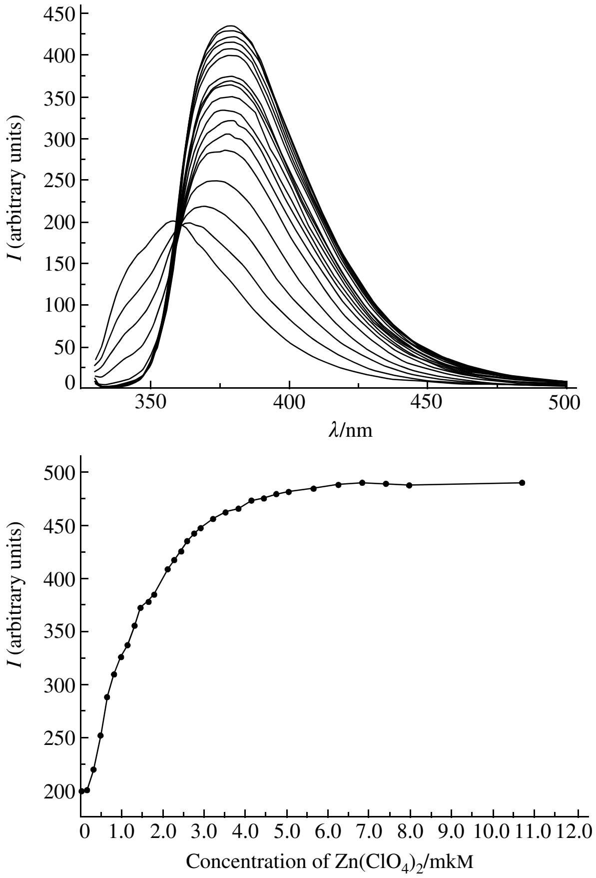


Figure 2 Fluorescence spectra and fluorescent titration curve of **2** (10 µM) upon the addition of $Zn(ClO_4)_2$. The spectra were measured in aqueous solutions (TRIS buffer, 10 mM, pH 8) with excitation at an isosbestic point at 325 nm.

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