Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 64 (2008) 2184–2191
Tetrahedron
www.elsevier.com/locate/tet

Bis(indolyl)methane derivatives as highly selective colourimetric and ratiometric fluorescent molecular chemosensors for Cu^{2+} cations

Rosario Martínez, Arturo Espinosa, Alberto Tárraga*, Pedro Molina*

Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, E-30100 Murcia, Spain

Received 6 November 2007; received in revised form 5 December 2007; accepted 10 December 2007
Available online 15 December 2007

Abstract

New probes based on bis(indolyl)methane derivatives only sense Cu^{2+} among other heavy and transition metal (HTM) ions through two different channels: the colourless to orange or purple colour change, that is visible to the naked eye, and a remarkable enhancement of the fluorescence along with a large red-shift in emission, in a water containing medium (CH_3CN/H_2O).

1. Introduction

The development of fluorescent molecular sensors for metal ions, especially for cations with biological interest, has always been of particular interest.[1] More specifically, molecular sensors directed towards the detection and measurement of divalent copper ions have enjoyed particular attention. The soft transition metal ion Cu^{2+} is third in abundance (after Fe^{2+} and Zn^{2+}) amongst the essential heavy metal ions in the human body and plays a pivotal role in a variety of fundamental physiological processes in organisms ranging from bacteria to mammals.[2] On the other hand, Cu^{2+} can be toxic to biological systems, alterations in its cellular homeostasis are connected to serious neurodegenerative diseases, including Menkes and Wilson diseases,[3] familiar amyotropic lateral sclerosis,[4] Alzheimer's disease[5] and prion diseases.[6] In this regard, copper binding studies in β-amyloid peptide,[7] human- and bovine-serum albumins[8] have been actively reported. The serum iron transport protein is known to bind Cu^{2+} and also the residues 135–155 of the cysteine-rich domain of APP (amyloid precursor protein), a protein highly implicated in Alzheimer's disease, are participating as Cu^{2+} binding site.[7]

Thus, copper, on one hand, is important for life but, on the other hand, is highly toxic to organism. For these reasons, the past few years have witnessed a number of reports on the design and synthesis of chromogenic[9] and fluorescent chemosensors for the detection of divalent copper ions. For most of the reported Cu^{2+} fluorescent chemosensors, the binding of the metal ion causes a quenching of the fluorescence emission.[10] In contrast, a few chemosensors in which the binding of a Cu^{2+} ion causes an increase in the fluorescence have been reported.[11] However, the low sensitivity and high order of interference by chemically closely related metal ions have necessitated the development of new highly selective and sensitive Cu^{2+} fluoroionophores.[12] Among these chemosensors, unfortunately, those that can be applied in aqueous solutions at neutral pH are still rare mainly because of the strong hydration ability of Cu^{2+} in water. Actually, chemosensors of this kind are always considered to be much more attractive and efficient in the respect that most copper-containing samples are near-neutral aqueous systems.[13]

Cu^{2+} metal ion is a paramagnetic ion with an empty d shell and can strongly quench the emission of a fluorophore via a photoinduced metal-to-fluorophore electron or energy transfer mechanism.[9c,14] Fluorescence quenching is not only disadvantageous for a high signal output upon recognition but also hampers temporal separation of spectrally similar complexes with time-resolved fluorometry.[15] Thus, it is of interest that the recognition of Cu^{2+} by the chemosensor does not quench the fluorescence.

* Corresponding authors. Tel.: +34 968 367 496; fax: +34 968 364 149 (P.M.); tel.: +34 968 367 499; fax: +34 968 364 149 (A.T.).
E-mail addresses: atarraga@um.es (A. Tárraga), pmolina@um.es (P. Molina).

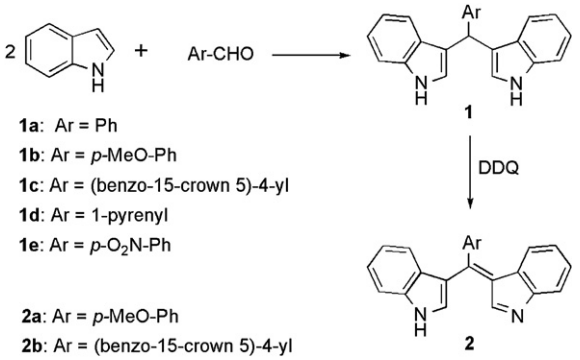
0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.12.025

Current interest in different heterocyclic ring systems containing a pyrrolic NH group is mostly related to their ability to act as molecular receptors for anions.[16] In this context, indole derivatives have been reported as anion chemosensors.[16e,17] Very recently, the first cation receptor making use of the pyrrolic NH group has been reported.[18]

We wish to report here that by using a structurally simple motif, *meso*-arylbis(indolyl)methane, highly selective Cu^{2+} sensing can be achieved through two different channels, colourimetric and fluorescent, in aqueous CH_3CN.

2. Results and discussion

The receptors **1a–e** were prepared in 89–95% yields by condensation of indole with the appropriate aryl aldehyde in methanol in the presence of potassium hydrogensulfate[19] (Scheme 1). These compounds were isolated as solids and were stable both in solid state and in solution.



Scheme 1.

The UV–vis absorption spectra of receptors **1a–e** in CH_3CN and CH_3CN/H_2O (70/30, v/v) are dominated by two strong absorption bands at 224 and 274–282 nm, respectively, and a less strong shoulder peak at 290 nm. In addition, receptor **1d** shows the typical pyrene absorption bands[20] in the region 241–344 nm. These receptors exhibit a very weak fluorescence in CH_3CN ($c=2.5\times10^{-5}$ M), the excitation spectrum revealing a $\lambda_{max}=350$ nm as an ideal excitation wavelength (ESI). Their emission spectra show two structureless bands at 404 and 424 nm, with rather low quantum yield ($\Phi=0.004-0.021$).[21]

The chemosensor behaviour of receptors **1a–e** with several metal cations (Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Sm^{3+}, Eu^{3+}, Yb^{3+} and Lu^{3+}),[22] in CH_3CN or CH_3CN/H_2O (70/30, v/v), was investigated by UV–vis and fluorescence measurements. All titration studies carried out in CH_3CN/H_2O (70/30, v/v) were conducted at pH 7 (0.1 M HEPES), and the titration experiments were analyzed using a computer program.[23]

Studies in the presence of the above-mentioned set of metal ions indicated that only Cu^{2+} ions promoted a notable response in their absorption spectra, and all other metal ions tested induced negligible responses, allowing unmistakable identification and quantification. Notably, stepwise addition of Cu^{2+} ions induced the appearance of a new and strong absorption band at 484–518 nm in CH_3CN and at 485–517 nm in CH_3CN/H_2O (70/30, v/v), reaching its maximum in intensity when 1 or 2 equiv of Cu^{2+} ions, respectively, were added (Tables 1 and 2, Fig. 1).

For these receptors **1a–e**, the low energy (LE) band was red-shifted, upon addition of Cu^{2+} ions, which is responsible for the change of colour from colourless to orange or purple. This fact can be used for a 'naked-eye' detection of Cu^{2+} ions. Simultaneously, well-defined isosbestic points were also observed, which indicate that a neat interconversion between the uncomplexed and complexed species occurs. The resulting titrations fitted nicely to a 1:1 binding model, and the corresponding K_{as} and detection limits were calculated both in CH_3CN and CH_3CN/H_2O solutions, respectively (Tables 1 and 2).

Assessments of the cation affinities also came from observing the extent to which the fluorescence intensity of receptors **1a–d** was affected in the presence of cations. Upon addition of small amounts of Cu^{2+} to a solution of receptors **1a–d** in CH_3CN, a remarkable intensity enhancement of the emission bands was observed (Fig. 2). It is worth mentioning that ligand **1d** also exhibits an additional band, corresponding to the pyrene excimer, at $\lambda=478$ nm, which does not increase during the process of addition of the metal cation (ESI).

The final fluorescence enhancement factors (FEFs) were up to 1000, as the quantum yields resulted in a notable increase (60-fold in the case of **1b**), and the Stokes shift being evaluated as 3819 cm^{-1} (Table 3). Such a remarkable shift is useful

Table 1
Data obtained from the UV–vis spectra upon titration of ligands **1a–e** with $Cu(OTf)_2$ in CH_3CN[a]

Ligand	L	L·Cu^{2+}	Isosbestic points/nm	K_{as}/M^{-1}	Detection limit/M
	λ/nm ($\varepsilon\times10^{-3}$ [M^{-1} cm^{-1}])	λ/nm ($\varepsilon\times10^{-3}$ [M^{-1} cm^{-1}])			
1a	224 (29.17), 282 (5.55), 290 (sh)	285 (5.58), 398 (2.86), 497 (5.24)	218, 232	1.3×10^5	4.54×10^{-6}
1b	224 (73.30), 282 (14.10), 290 (sh)	269 (sh), 284 (17.05), 332 (2.89), 438 (sh), 484 (15.36)	219, 235	1.9×10^5	3.54×10^{-6}
1c	224 (67.06), 282 (14.99), 290 (sh)	207 (100.08), 275 (18.50), 286 (sh), 488 (21.06), 667 (1.25)	221, 232	7.8×10^5	2.69×10^{-6}
1d	224 (80.66), 241 (65.29), 266 (33.06), 276 (44.81), 329 (25.23), 344 (34.87)	223 (88.30), 240 (sh), 265 (sh), 276 (39.04), 314 (sh), 329 (22.52), 344 (26.17), 512 (10.03), 590 (sh), 730 (1.77)	272, 281, 324, 351	1.2×10^5	4.99×10^{-6}
1e	224 (65.40), 274 (27.00), 290 (sh)	285 (26.48), 384 (6.16), 518 (17.52)	219, 229, 264, 281	1.3×10^5	3.28×10^{-6}

[a] $c=2.5\times10^{-5}$ M.

Table 2
Data obtained from the UV–vis spectra upon titration of ligands **1a–e** with $Cu(OTf)_2$ in CH_3CN/H_2O (7/3)[a]

Ligand	L	$L \cdot Cu^{2+}$	Isosbestic points/nm	K_{as}/M^{-1}	Detection limit/M
	λ/nm ($\varepsilon \times 10^{-3}$ [$M^{-1}\,cm^{-1}$])	λ/nm ($\varepsilon \times 10^{-3}$ [$M^{-1}\,cm^{-1}$])			
1a	224 (29.57), 282 (6.54), 290 (sh)	205 (sh), 295 (sh), 496 (2.27)	217, 231, 271, 295	3.9×10^{4}	1.13×10^{-5}
1b	224 (69.10), 282 (14.54), 290 (sh)	222 (sh), 262 (sh), 284 (sh), 418 (4.44), 488 (5.07)	219, 232, 277, 294	1.7×10^{4}	1.13×10^{-5}
1c	224 (76.53), 282 (19.76), 290 (sh)	204 (81.73), 226 (sh), 261 (19.50), 286 (sh), 485 (7.59)	215, 234, 272, 296	2.6×10^{4}	7.03×10^{-6}
1d	224 (74.20), 242 (64.12), 266 (33.72), 277 (43.60), 316 (sh), 329 (24.68), 346 (33.00)	223 (68.48), 241 (57.44), 266 (25.96), 276 (30.16), 315 (sh), 329 (18.52), 345 (22.52), 509 (5.28)	221, 354	4.0×10^{4}	6.11×10^{-6}
1e	224 (70.80), 282 (23.44), 290 (sh)	220 (sh), 264 (20.12), 517 (1.32)	213, 231, 265, 302	1.2×10^{4}	1.31×10^{-6}

[a] $c=2.5\times10^{-5}$ M.

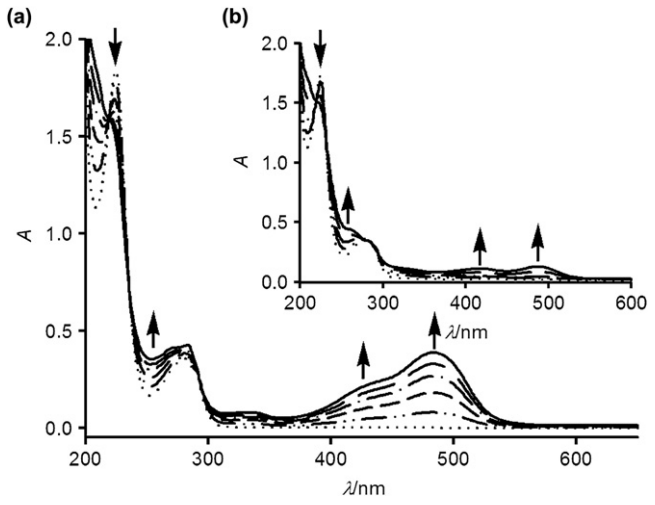


Figure 1. Variation of the UV–vis spectra of ligand **1b** ($c=2.5\times10^{-5}$ M) upon addition of increasing amounts of $Cu(OTf)_2$ in (a) CH_3CN (0, 0.2, 0.4, 0.6, 0.8 and 1 equiv of Cu^{2+}) and (b) CH_3CN/H_2O (7/3), (0, 0.5, 1.0, 1.5 and 2.0 equiv of Cu^{2+}); arrows indicate the absorptions that increase (up) and decrease (down) during the experiments.

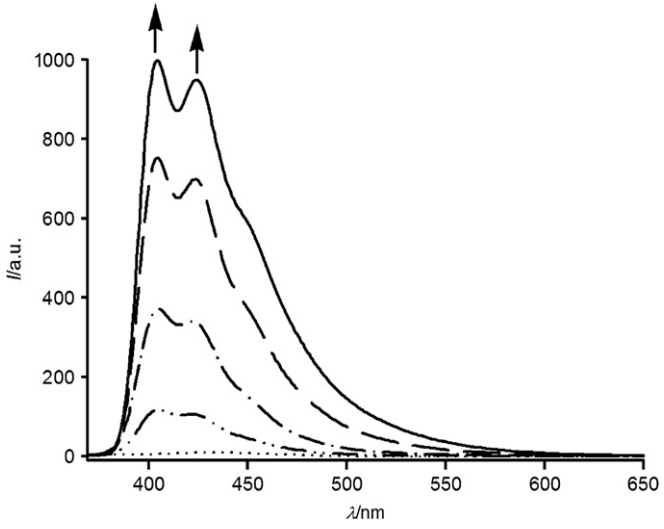


Figure 2. Variation of the fluorescence spectra of ligand **1c** ($c=2.5\times10^{-5}$ M in CH_3CN) upon addition of increasing amounts (0, 0.25, 0.5, 0.75 and 1 equiv) of $Cu(OTf)_2$; arrows indicate the emissions that increase during the experiments.

for various studies that require clear-cut differences between wavelengths for excitation and emission.

The values of the association constants and detection limits[24] were calculated and are summarized in Table 3. It is noticeable that only Cu^{2+} from all other metal ions tested is able to produce a drastic change in the emission spectrum, indicating that this enhancement of the fluorescence is highly specific for Cu^{2+} cations.

The response of the fluorescence of receptors **1a–d** towards a set of metal cations (see above) was also studied in CH_3CN/H_2O (70/30, v/v). Under these conditions, **1a–d** display two weak emission bands ($\lambda_{exc}=350$ nm) at 391–412 and 436 nm, respectively, with a low quantum yield ($\Phi=0.009$–0.011). Titration experiments demonstrate that only Cu^{2+} metal cations yielded progressively a significant decrease in the 391–412 and 436 nm emission bands and at the same time, a new emission band centred at 454–516 nm is developed. In compound **1c**, a clear isoemissive point at 454 nm indicates that only one type of complexing mechanism is involved (Fig. 3). It is noticeable that compound **1d** also presents an additional band at 494 nm, which upon addition of Cu^{2+} is blue-shifted at 454 nm. The final fluorescence enhancement factors (FEFs) were up to 60 (Table 4), and the quantum yields resulted in a two- to three-fold increase compared to those of the free receptors. The Stokes shift was evaluated to be 6545–9191 cm^{-1} (Table 4). As Figure 3 shows, the ratio of the long-wavelength emission at 516 nm to the short wavelength at 436 nm (I_{516}/I_{435}) in compound **1c** increases with the addition of increasing amounts of Cu^{2+}, achieving its maximum when 2 equiv of Cu^{2+} was added. The red-shifts make the ratiometric measurement possible. The ratio of the fluorescence intensities of two appropriate

Table 3
Data obtained from the fluorescence spectra upon titration of ligands **1a–d** with $Cu(OTf)_2$ in CH_3CN[a]

Ligand	L	$L \cdot Cu^{2+}$	$\Delta\Phi$ (FEF)	K_{as}/M^{-1}	Detection limit/M	Stokes shift/cm^{-1}
	λ_{em}/nm	λ_{em}/nm				
1a	404, 424	404, 424	18 (263)	2.5×10^{6}	3.86×10^{-6}	3819
1b	404, 424	404, 424	60 (935)	3.1×10^{6}	2.91×10^{-6}	3819
1c	404, 424	404, 424	30 (1000)	3.5×10^{6}	4.42×10^{-6}	3819
1d	391, 478	404, 424	4 (14)	1.3×10^{6}	3.36×10^{-6}	3819

[a] $c=2.5\times10^{-5}$ M.

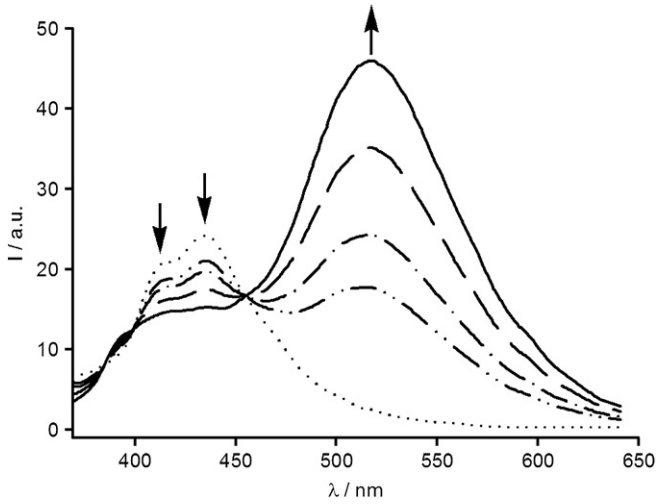


Figure 3. Variation of the fluorescence spectra of ligand **1c** ($c=2.5\times10^{-5}$ M) in CH_3CN/H_2O (7/3) upon addition of increasing amounts (0, 0.5, 1.0, 1.5 and 2 equiv) of $Cu(OTf)_2$; arrows indicate the emissions that increase (up) and decrease (down) during the experiments.

emission wavelengths provides a more reliable measurement of the concentration.

The fluorescence titration data indicate an empirical 1:1 stoichiometry for the complexes formed, the estimated association constants being 1.0×10^5–1.9×10^5 M^{-1} and the calculated detection limit being 2.43×10^{-6}–9.17×10^{-6} M. The difference in the association constants obtained from absorbance and emission titration is not surprising. While the former shows binding of the receptor in the ground state, the latter reflects binding in the excited electronic state.[25]

The Stokes shift value in acetonitrile is consistent with fluorescent arising from a charge transfer state, which is confirmed by solvatochromic measurements. The unresolved vibronic structure of the red-shifted emission bands and the large Stokes shift in acetonitrile/water of the complexes suggest that the excited states possess charge transfer character, although the formation of an excimer species in the presence of water must not be ruled out.[26]

In order to demonstrate that the sensing event is not based on the formation of **2** by oxidation of the receptor **1b** with Cu^{2+} [27] we have carried out two experimental tests. In the first one, a CH_3CN solution of the complex **1b**·Cu^{2+} was concentrated to dryness and the residue was washed several times with water. After filtration the remaining solid was found to be identical to the receptor **1b**. Furthermore, the addition of Cu^+ or Cu^{2+} to a CH_3CN solution of compound **2a** or **2b**, readily prepared from **1b** or **1c**, respectively, by oxidation with DDQ, does not induce neither fluorescence nor optical changes at all.

A general principle in designing fluorogenic and chromogenic chemosensors is based on analyte coordination events, therefore, both the interaction with the analyte and the change in colour or fluorescence should be reversible. Then, we have proved the reversibility of the recognition process by carrying out an experimental test: to a solution of **1b**, in CH_2Cl_2, 1 equiv of copper(II) triflate was added to obtain the complexed species, and the UV–vis spectrum was recorded. The CH_2Cl_2 solution of the complex was washed several times with water until the colour of the solution changed from orange to colourless. The organic layer was dried and the optical and ^1H NMR spectra were recorded, and they were found to be the same than those of the free receptor **1b**. This experiment was carried out over several cycles, the optical spectrum was recorded after each step and found to be recovered on completion of the step, thus demonstrating the high degree of reversibility of the sensing process (Fig. 4), inset.

The other metal ions studied exhibited basically no discernible changes at all. So, this fluorescence change can be possibly utilized in devices for the measurement of Cu^{2+} concentrations even in the presence of other cations.

The interference in the selective response of **1a–d** in the presence of Cu^{2+}, from the other metal cations tested, was also studied by using cross-selectivity experiments based on the comparison of the fluorescence results obtained by addition to the free ligand or to the complex **1a–d**·Cu of the other metals tested (Fig. 4).

The stoichiometry of the complex was determined by the changes in the fluorogenic response of **1a–d** in the presence

Table 4
Data obtained from the fluorescence spectra upon titration of ligands **1a–d** with $Cu(OTf)_2$ in CH_3CN/H_2O (7/3)[a]

Ligand	L	L·Cu^{2+}	ΔΦ (FEF)	K_{as}/M^{-1}	Detection limit/M	Stokes shift/cm^{-1}
	λ_{em}/nm	λ_{em}/nm				
1a	391, 436	400, 503	3 (34)	1.3×10^5	7.49×10^{-6}	8691
1b	391, 436	391, 513	3 (60)	1.0×10^5	9.17×10^{-6}	9078
1c	412, 436	412, 436, 516	2 (46)	1.9×10^5	6.06×10^{-6}	9191
1d	391, 494	391, 454	2 (3)	1.0×10^5	2.43×10^{-6}	6545

[a] $c=2.5\times10^{-5}$ M.

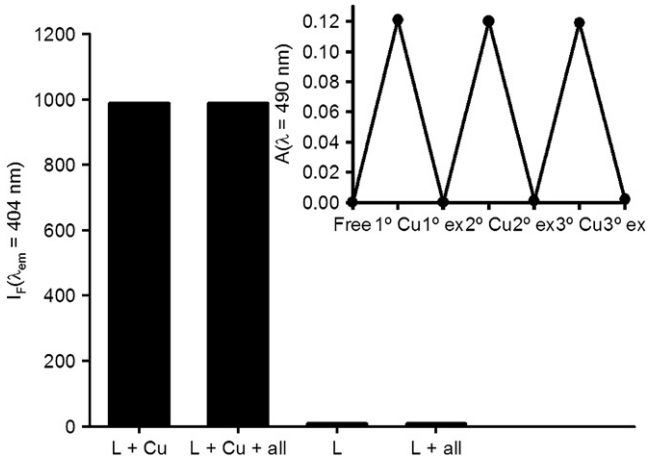


Figure 4. Changes in the fluorescence intensity of **1b**·Cu^{2+} even when there are other different cations. The term 'all' include Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Sm^{3+}, Eu^{3+}, Yb^{3+} and Lu^{3+}. Inset: stepwise complexation/decomplexation cycles, using water as decomplexation agent, carried out by UV–vis analysis.

of varying concentrations of Cu^{2+}. The results obtained confirmed an empirical 1:1 stoichiometry, which is also in agreement with the results obtained from the corresponding Job's plots resulting for the complexation processes (Fig. 5). The nature of the complexes formed has been also studied by the FABMS spectra of the isolated solid complexes, because all attempts to obtain suitable crystals for X-ray analysis were unsuccessful. This result confirms a real [2+2] nature stoichiometry for the complex formed.

Binding of Cu^{2+} by the simplest receptor **1a** has also been investigated by quantum chemical calculations at the DFT level (ESI). In the rather rigid free ligand, the quite separated and highly divergent NH functionalities (d_{NN}=5.985 Å, angle$_{HN\cdots NH}$=91.3°, dihedral$_{HN\cdots NH}$=48.1°, calculated at B3LYP/6-31G*) preclude the formation of a 1:1 (ligand/metal) stoichiometry. Instead, assuming tetracoordination around Cu^{2+} ions, stable $[\mathbf{1a}\cdot CuL_2]_2$ structures (2:2 stoichiometry) have been encountered for the calculated complexes (L: TfO^-, NCMe).

The calculated (B3LYP/6-31G*/Lanl2DZ-ECP) centrosymmetric geometry for the most representative $[\mathbf{1a}\cdot Cu(MeCN)_2]_2$ complexes (Fig. 6) consists of two separated Cu^{2+} ions ($d_{Cu\cdots Cu}$=7.485 Å) in a distorted tetrahedral environment (NCuN angle 119.3°; improper torsion angles NNLCu 19.5° and 33.2°) connected by two deprotonated bisindole ligands with typical covalent N–Cu bond distances (2.033 and 2.034 Å). Deprotonation of NH-containing ligands such as amides or pyrrole rings is a common feature in the coordination chemistry of Cu^{2+} ions.[28]

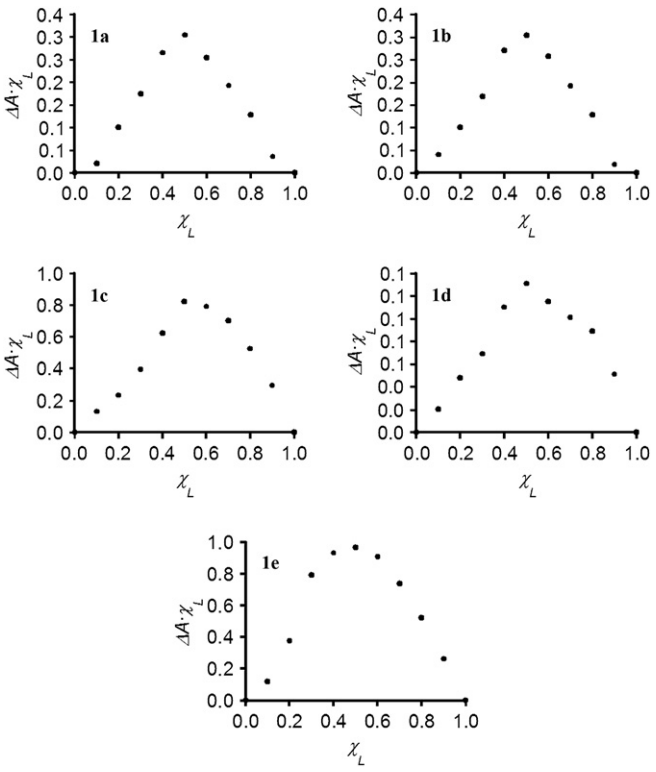


Figure 5. Job's plots for the complexation of ligands **1a–e** with Cu^{2+}, illustrating the 1:1 stoichiometry of the complexes formed.

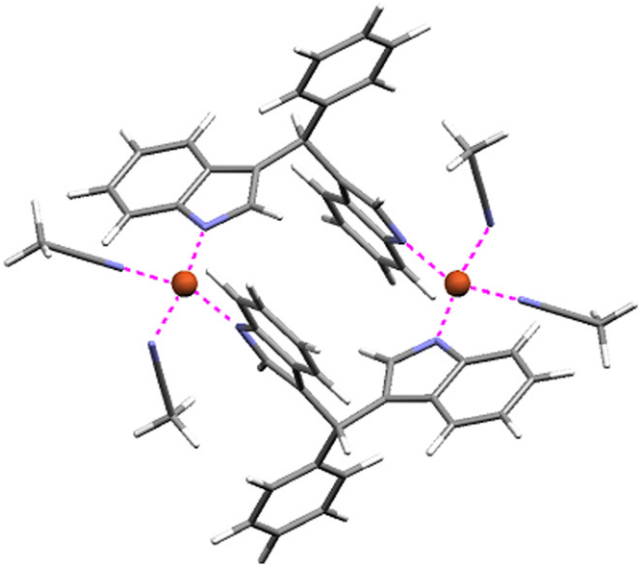


Figure 6. Calculated (B3LYP/6-31G*/Lan12DZ-ECP) geometry for the $[\mathbf{1a}\cdot Cu(MeCN)_2]_2$ complex.

3. Conclusions

We have designed highly selective and sensitive dual chromo- and fluorogenic chemosensor molecules for the ratiometric determination of Cu^{2+}. The receptors show either a remarkable fluorescence enhancement or red-shift of the emission band with high Stokes shift values and concomitant absorption changes. The recognition of the ion gave rise to major colour changes from colourless to orange or purple that is clearly visible to the naked eye (Fig. 7).

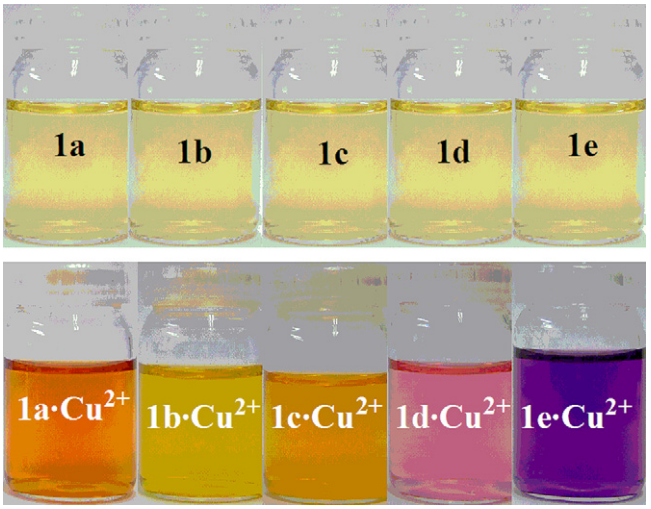


Figure 7. Colour of the different free ligands and the corresponding complexes in CH_3CN.

4. Experimental

4.1. General comments

Melting points were determined on a hot-plate melting point Reichert apparatus and are uncorrected. IR spectra

were determined as Nujol emulsions or films in a Nicolet impact 400 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 400 MHz in a Bruker Advance spectrometer. Chemical shifts refer to signals of tetramethylsilane. Carbon atom types (C, CH, CH_2, CH_3) were determined with the DEPT pulse sequence.

Quantum yield values were measured with respect to anthracene as standard (Φ=0.27±0.03), using the equation $\Phi_x/\Phi_s=(S_x/S_s)[(1-10^{-As})/(1-10^{-Ax})]$,[23] where x and s indicate the unknown and standard solutions, respectively, Φ is the quantum yield, S is the area under the emission curve and A is the absorbance at the excitation wavelength (λ_{exc}=350 nm).

4.1.1. General procedure for the preparation of bis(indolyl)methanes

To a mixture of indole (197.5 mg, 1.69 mmol) and the appropriate aldehyde (0.85 mmol) in dry methanol (10 mL), $KHSO_4$ (115 mg, 0.85 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. Then, water (10 mL) was added to quench the reaction and precipitate the desired compound that was recrystallized from ethanol.

4.1.1.1. {[Bis(1H-indol-3-yl)](phenyl)}methane ***1a***. See Ref. 17b.

4.1.1.2. {[Bis(1H-indol-3-yl)](4-methoxyphenyl)}methane ***1b***. Yield: 0.269 g, 90%; mp 179–181 °C (from EtOH). ν_{max} (Nujol)/cm^{-1}: 3420, 3391, 1605, 1507, 1254, 1249, 1123, 1025 and 739. δ_H (400 MHz, DMSO-d_6): 3.69 (3H, s, OCH_3), 5.75 (1H, s, CH), 6.77–6.86 (6H, m, 4×CH ind and 2×CH–Ph), 7.01 (2H, t, *J* 7.80, ind), 7.24 (2H, d, *J* 8.41, Ph), 7.25 (2H, d, *J* 7.66, ind), 7.32 (2H, d, *J* 8.10, ind) and 10.76 (2H, s, 2×NH). δ_C (400 MHz, DMSO-d_6): 38.83 (CH), 54.92 (OCH_3), 111.42 (2×CH), 113.39 (2×CH), 118.12 (2×CH), 118.43 (2×C), 119.15 (2×CH), 120.84 (2×CH), 123.42 (2×CH), 126.62 (2×C), 129.19 (2×CH), 136.60 (2×C), 136.95 (C) and 157.31 (C). EIMS *m/z*: 352 (M^+, 100%), 245 (40), 235 (22) and 220 (8). Found: C, 81.54; H, 5.44; N, 7.70. $C_{24}H_{20}N_2O$ requires C, 81.82; H, 5.68; N, 7.95%.

4.1.1.3. {[Bis(1H-indol-3-yl)][(benzo-15-crown-5)-4′-yl]}methane ***1c***. Yield: 0.387 g, 89%; mp 170–172 °C (from EtOH). ν_{max} (Nujol)/cm^{-1}: 3346, 1511, 1352, 1270, 1135, 1103, 1054, 939 and 743. δ_H (400 MHz, DMSO-d_6): 3.58–3.57 (8H, m, 4×OCH_2), 3.67–3.69 (2H, m, 2×OCH_2), 3.71–3.74 (2H, m, 2×OCH_2), 3.90–3.92 (2H, m, 2×OCH_2), 3.96–3.98 (2H, m, 2×OCH_2), 5.72 (1H, s, CH), 6.79–6.82 (4H, m, 2×CH ind and 2×CH Ph), 6.84 (2H, t, *J* 7.92, ind), 6.95 (1H, s, Ph), 7.01 (2H, t, *J* 7.92, ind), 7.27 (2H, d, *J* 7.86, ind), 7.32 (2H, d, *J* 8.10, ind) and 10.77 (2H, s, 2×NH). δ_C (400 MHz, DMSO-d_6): 39.30 (CH), 68.46 (OCH_2), 68.54 (OCH_2), 68.90 (OCH_2), 68.95 (OCH_2), 69.84 (OCH_2), 69.85 (OCH_2), 70.38 (OCH_2), 70.39 (OCH_2), 111.41 (2×CH), 113.43 (CH), 114.51 (CH), 118.11 (2×CH), 118.32 (2×C), 119.15 (2×CH), 120.63 (CH), 120.81 (2×CH), 123.44 (2×CH), 126.63 (2×C), 136.56 (2×C), 137.87 (C), 146.72 (C) and 148.12 (C). EIMS *m/z*: 512 (M^+, 100%), 424 (7), 379 (15), 352 (17), 335 (7), 245 (46), 243 (29), 190 (10) and 117 (15). Found: C, 72.81; H, 6.12; N, 5.21. $C_{31}H_{32}N_2O_5$ requires C, 72.66; H, 6.25; N, 5.47%.

4.1.1.4. {[Bis(1H-indol-3-yl)](1-pirenyl)}methane ***1d***. Yield: 0.360 g, 95%; mp 292–294 °C (from EtOH). ν_{max} (Nujol)/cm^{-1}: 3412, 1581, 1340, 1176, 1119, 1086, 841, 735 and 715. δ_H (300 MHz, DMSO-d_6): 5.75 (1H, s, CH), 6.77 (2H, s, ind), 6.82 (2H, t, *J* 7.2, ind), 7.03 (2H, t, *J* 7.2, ind), 7.26 (2H, d, *J* 7.8, ind), 7.36 (2H, d, *J* 8.1, ind), 7.89 (1H, d, *J* 8.1, pyr), 8.03 (1H, t, *J* 7.5, pyr), 8.10–8.15 (4H, m, pyr), 8.24 (2H, t, *J* 7.8, pyr), 8.60 (1H, d, *J* 9.3, pyr) and 10.87 (2H, s, 2×NH). δ_C (300 MHz, DMSO-d_6): 36.2 (CH), 112.0 (2×CH), 118.4 (2×C), 118.7 (2×CH), 119.5 (2×CH), 121.4 (2×CH), 124.0 (CH), 124.6 (C), 124.8 (C), 124.9 (2×CH), 125.1 (CH), 125.3 (CH), 125.5 (CH), 126.5 (CH), 126.9 (CH), 127.0 (CH), 127.1 (2×C), 127.7 (CH), 127.9 (CH), 128.4 (C), 129.7 (C), 130.7 (C), 131.3 (C), 137.1 (2×C) and 139.2 (C). EIMS *m/z*: 446 (M^+, 66%), 328 (100), 243 (37) and 164 (25). Found: C, 88.55; H, 4.70; N, 6.55. $C_{33}H_{32}N_2$ requires C, 88.79; H, 4.93; N, 6.28%.

4.1.1.5. {[Bis(1H-indol-3-yl)](4-nitrophenyl)}methane ***1e***. Yield: 0.296 g, 95%; mp 175–177 °C (from EtOH). ν_{max} (Nujol)/cm^{-1}: 3452, 3424, 3383, 1593, 1507, 1422, 1336, 1090, 1070, 1017, 870, 812, 788 and 743. δ_H (400 MHz, DMSO-d_6): 6.01 (1H, s, CH), 6.84 (2H, t, *J* 5.89, ind), 6.89 (2H, s, ind), 7.04 (2H, t, *J* 6.10, ind), 7.27 (2H, d, *J* 6.15, ind), 7.35 (2H, d, *J* 6.32, ind), 7.60 (2H, d, *J* 6.81, Ph), 8.12 (2H, d, *J* 6.79, Ph) and 10.90 (2H, s, 2×NH). δ_C (400 MHz, DMSO-d_6): 39.5 (CH), 111.57 (2×CH), 116.65 (2×C), 118.41 (2×CH), 118.89 (2×CH), 121.09 (2×CH), 123.40 (2×CH), 123.84 (2×CH), 126.34 (2×C), 129.44 (2×CH), 136.57 (2×C), 145.74 (C) and 153.12 (C). EIMS *m/z*: 367 (M^+, 93%), 245 (100), 204 (47) and 117 (70). Found: C, 75.42; H, 4.51; N, 11.25. $C_{23}H_{17}N_3O_2$ requires C, 75.20; H, 4.63; N, 11.44%.

4.1.2. General procedure for the preparation of 3-{[3H-indol-3-ylidene](aryl)methyl}-1H-indoles

To a solution of adequate **1** (0.3 mmol) in acetonitrile (8 mL), a solution of DDQ (272.4 mg, 1.2 mmol) in the same solvent was slowly added. This reaction was allowed for 2 h giving a dark red precipitate, which was filtered, washed with CH_3CN and recrystallized from ethanol.

4.1.2.1. 3-{[3H-Indol-3-ylidene](4-methoxyphenyl)methyl}-1H-indole ***2a***. Yield: 0.119 g, 40%; mp >300 °C (from EtOH). ν_{max} (Nujol)/cm^{-1}: 3146, 2218, 1601, 1552, 1466, 1425, 1307, 1274, 1233, 1192, 1055, 1018, 888, 787 and 747. δ_H (300 MHz, DMSO-d_6): 4.11 (3H, s, OCH_3), 6.59–6.66 (2H, m, arom), 7.14–7.35 (6H, m, arom), 7.67–7.69 (4H, m, arom), 8.48–8.50 (2H, m, arom) and 13.70 (1H, s, NH). δ_C (300 MHz, DMSO-d_6): 56.06 (OCH_3), 114.17 (CH), 114.97 (CH), 120.90 (CH), 124.03 (CH), 125.61 (CH), 126.68 (C), 136.27 (C), 139.55 (C), 147.40 (C), 164.50 (C) and 168.42 (C). EIMS *m/z*: 350 (M^+, 100%), 305 (19) and 228 (25).

Found: C, 82.56; H, 4.89; N, 7.84. $C_{24}H_{18}N_2O$ requires C, 82.28; H, 5.14; N, 8.00%.

4.1.2.2. 3-{[3H-Indol-3-ylidene][(benzo-15-crown-5)-4′-yl]-methyl}-1H-indole **2b**. Yield: 0.269, 62%; mp >300 °C (from EtOH). ν_{max} (Nujol)/cm^{-1}: 3273, 2214, 1560, 1495, 1462, 1397, 1278, 1234, 1197, 1115, 1054, 796 and 727. δ_H (300 MHz, DMSO-d_6): 3.64–3.67 (10H, m, 5×OCH_2), 3.87–3.96 (4H, m, 2×OCH_2), 4.28–4.29 (2H, m, OCH_2), 6.89–6.99 (2H, m, arom), 7.16–7.36 (7H, m, arom), 7.66–7.67 (2H, m, arom), 8.50–8.51 (2H, m, arom) and 13.67 (1H, s, NH). δ_C (300 MHz, DMSO-d_6): 55.75 (C), 68.41 (2×CH_2), 68.82 (2×CH_2), 69.39 (CH_2), 69.52 (CH_2), 70.31 (2×CH_2), 113.02 (CH), 114.00 (CH), 118.49 (CH), 120.88 (CH), 123.69 (C), 125.25 (CH), 126.53 (CH), 128.94 (C), 130.28 (C), 139.35 (C), 146.18 (CH), 148.41 (C), 154.32 (C) and 168.20 (C). EIMS *m/z*: 510 (M^+, 10%), 228 (100) and 200 (92). Found: C, 72.69; H, 6.01; N, 5.77. $C_{31}H_{30}N_2O_5$ requires C, 72.94; H, 5.88; N, 5.49.

Acknowledgements

We gratefully acknowledge a grant from MEC-Spain CTQ2004-02201 and from Fundación Séneca (CARM) 02970/PI/05. R.M. also thanks MEC for a predoctoral grant.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.12.025.

References and notes

1. (a) De Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566; (b) Prodi, L.; Bolletta, F.; Montalti, M.; Zaccheroni, N. *Coord. Chem. Rev.* **2000**, *205*, 59–83; (c) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3–40; (d) De Silva, A. P.; Fox, D. B.; Huxley, A. J. M.; Moody, T. S. *Coord. Chem. Rev.* **2000**, *205*, 41–57.
2. (a) Linder, M. C.; Hazegh-Azam, M. *Am. J. Clin. Nutr.* **1996**, *63*, 797S–811S; (b) Uauy, R.; Olivares, M.; Gonzalez, M. *Am. J. Clin. Nutr.* **1998**, *67*, 952S–959S.
3. (a) Vulpe, C.; Levinson, B.; Whitney, S.; Packman, S.; Gitschier, J. *Nat. Genet.* **1993**, *3*, 7–13; (b) Bull, P. C.; Thomas, G. R.; Rommens, J. M.; Forbes, J. R.; Cox, D. W. *Nat. Genet.* **1993**, *5*, 327–337.
4. (a) Valentine, J. S.; Hart, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3617–3622; (b) Bruijn, L. I.; Miller, T. M.; Cleveland, D. W. *Annu. Rev. Neurosci.* **2004**, *27*, 723–749.
5. Barnharn, K. J.; Masters, C. L.; Bush, A. I. *Nat. Rev. Drug Discov.* **2004**, *3*, 205–214.
6. Brown, D. R.; Kozlowski, H. *J. Chem. Soc., Dalton Trans.* **2004**, 1907–1917.
7. (a) Ruiz, F. H.; Gonzalez, Y.; Bodini, M.; Opazo, C.; Inestrosa, N. C. *J. Neurochem.* **1999**, *73*, 1288–1299; (b) Maynard, C. J.; Bush, A. I.; Masters, C. L.; Cappai, R.; Li, Q.-X. *Int. J. Exp. Pathol.* **2005**, *86*, 147–159.
8. Hirose, J.; Fujiwara, H.; Magarifuchi, T.; Iguti, Y.; Iwamoto, H.; Kominami, S.; Hiromi, K. *Biochim. Biophys. Acta* **1996**, *1296*, 103–111.
9. (a) Sancenon, F.; Martinez-Mañez, R.; Soto, J. *Chem. Commun.* **2001**, 2262–2273; (b) Choi, M. J.; Kim, M. Y.; Chang, S. K. *Chem. Commun.* **2001**, 1664–1665; (c) Gunnlaugsson, T.; Leonard, J. P.; Murray, N. S. *Org. Lett.* **2004**, *6*, 1557–1560; (d) Cheng, Y.-F.; Zhao, D.-T.; Zhang, M.; Liu, Z.-Q.; Zhou, Y.-F.; Shu, T.-M.; Li, F.-Y.; Yi, T.; Huang, C.-H. *Tetrahedron Lett.* **2006**, *47*, 6413–6416; (e) Lee, S. J.; Lee, S. S.; Jeong, I. Y.; Lee, J. Y.; Jung, J. H. *Tetrahedron Lett.* **2007**, *48*, 393–396; (f) Liu, J.; Lu, Y. *Chem. Commun.* **2007**, 4872–4874.
10. (a) Klein, G.; Kaufmann, D.; Schürch, S.; Reymond, J.-L. *Chem. Commun.* **2001**, 561–562; (b) Zheng, Y.; Huo, Q.; Kele, P.; Andreopoulos, F. M.; Pham, S. M.; Leblanc, R. M. *Org. Lett.* **2001**, *3*, 3277–3280; (c) Zheng, Y.; Gattás-Asfura, K. M.; Konka, V.; Leblanc, R. M. *Chem. Commun.* **2002**, 2350–2351; (d) Zheng, Y.; Orbulescu, J.; Ji, X.; Andreopoulos, F. M.; Pham, S. M.; Leblanc, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 2680–2686; (e) Boiocchi, M.; Fabbrizzi, L.; Licchelli, M.; Sacchi, D.; Vazquez, M.; Zampa, C. *Chem. Commun.* **2003**, 1812–1813; (f) Roy, B. C.; Chandra, B.; Hromas, D.; Mallik, S. *Org. Lett.* **2003**, *5*, 11–14; (g) Kaur, S.; Kumar, S. *Tetrahedron Lett.* **2004**, *45*, 5081–5085; (h) Qi, X.; Jun, E. J.; Xu, L.; Kim, S.-J.; Hong, J. S. J.; Yoon, Y. J.; Yoon, J. *J. Org. Chem.* **2006**, *71*, 2881–2884.
11. (a) Rurack, K.; Kollmannsberger, M.; Resch-Genger, U.; Daub, J. *J. Am. Chem. Soc.* **2000**, *122*, 968–969; (b) Yang, J.-S.; Lin, C.-S.; Hwang, C.-Y. *Org. Lett.* **2001**, *3*, 889–892; (c) Wu, Q.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 14682–14683; (d) Martínez, R.; Espinosa, A.; Tárraga, A.; Molina, P. *Org. Lett.* **2005**, *7*, 5869–5872; (e) Yang, H.; Liu, Z.-Q.; Zhou, Z.-G.; Shi, E.-X.; Li, F.-Y.; Du, Y.-K.; Yi, T.; Huang, C.-H. *Tetrahedron Lett.* **2006**, *47*, 2911–2914.
12. (a) Kaur, S.; Kumar, S. *Chem. Commun.* **2002**, 2840–2841; (b) Xu, Z.; Xiao, Y.; Qian, X.; Cui, J.; Cui, D. *Org. Lett.* **2005**, *7*, 889–892; (c) Royzen, M.; Dai, Z.; Canary, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 1612–1613; (d) Weng, Z.-C.; Yang, R.; He, H.; Jiang, Y.-B. *Chem. Commun.* **2006**, 106–108; (e) Xie, J.; Ménand, M.; Maisonneuve, S.; Métivier, R. *J. Org. Chem.* **2007**, *72*, 5980–5985.
13. (a) Martínez, R.; Zapata, F.; Caballero, A.; Espinosa, A.; Tárraga, A.; Molina, P. *Org. Lett.* **2006**, *8*, 3235–3238; (b) Xiang, Y.; Tong, A.; Jiu, P.; Ju, Y. *Org. Lett.* **2006**, *8*, 2863–2866; (c) Jun, E. J.; Kim, J.-A.; Swamy, K. M. K.; Park, S.; Yoon, J. *Tetrahedron Lett.* **2006**, *47*, 1051–1054; (d) Liu, J.; Lu, Y. *J. Am. Chem. Soc.* **2007**, *129*, 9838–9839.
14. (a) Zeng, H. H.; Thompson, R. B.; Maliwal, B. P.; Fones, G. R.; Moffett, J. W.; Fierke, C. A. *Anal. Chem.* **2003**, *75*, 6807–6812; (b) Hu, J.; Lü, F.; Ding, L.; Zhang, S.; Fang, Y. *J. Photochem. Photobiol., A: Chem.* **2007**, *188*, 351–357; (c) Gouanvé, F.; Schuster, T.; Allard, E.; Méallet-Renault, R.; Larpent, C. *Adv. Funct. Mater.* **2007**, *17*, 2746–2756.
15. Rurack, K.; Resch-Genger, U.; Tettig, W. *J. Photochem. Photobiol., A: Chem.* **1998**, *118*, 143–149.
16. Recent papers in this area include: (a) Sessler, J. L.; Cho, W.-S.; Gross, D. E.; Shriver, J. A.; Lynch, V. M.; Marquez, M. *J. Org. Chem.* **2005**, *70*, 5982–5986; (b) Panda, P. K.; Lee, C.-H. *J. Org. Chem.* **2005**, *70*, 3148–3156; (c) Lee, C.-H.; Lee, J.-S.; Na, H.-K.; Yoon, D.-W.; Miyaji, H.; Cho, W.-S.; Sessler, J. L. *J. Org. Chem.* **2005**, *70*, 2067–2074; (d) Cafeo, G.; Kohnke, F. H.; White, A. J. P.; Grozzo, D.; Messina, A. *Chem.—Eur. J.* **2007**, *13*, 649–656; (e) Pfeffer, F. M.; Lim, K. F.; Sedgwick, K. J. *Org. Biomol. Chem.* **2007**, *5*, 1795–1799; (f) Plitt, P.; Gross, D. E.; Lynch, V. M.; Sessler, J. L. *Chem.—Eur. J.* **2007**, *13*, 1374–1381.
17. (a) Chang, K.-J.; Moon, D.; Lah, M.-S.; Jeong, K.-S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7926–7929; (b) He, X.; Hu, S.; Liu, K.; Guo, Y.; Xu, J.; Shao, S. *Org. Lett.* **2006**, *8*, 333–336; (c) Sessler, J.; Chi, D.; Lynch, V. *J. Am. Chem. Soc.* **2006**, *128*, 16518–16519.
18. He, C.-L.; Ren, F.-L.; Zhang, X.-B.; Han, Z.-H. *Talanta* **2006**, *70*, 364–369.
19. Nagarajan, R.; Perumal, P. T. *Chem. Lett.* **2004**, *33*, 288–289.
20. Förster, T.; Kasper, K. *Z. Elektrochem.* **1955**, *59*, 976–980.
21. The fluorescence quantum yields were measured with respect to anthracene as standard (Φ=0.27). Dawson, W. R.; Windsor, M. W. *J. Phys. Chem.* **1968**, *72*, 3251–3260.
22. Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+} were used as their perchlorate salts, while Cu^{2+}, Sm^{3+}, Eu^{3+}, Yb^{3+} and Lu^{3+} were used as their trifluoromethanesulfonate salts.
23. Specfit/32 Global Analysis System, 1999–2004, Spectrum Software Associates (SpecSoft@compuserve.com).

24. Shortreed, M.; Kopelman, R.; Kuhn, M.; Hoyland, B. *Anal. Chem.* **1996**, *68*, 1414–1418.
25. Debroy, P.; Banerjee, M.; Prasad, M.; Moulik, S. P.; Roy, S. *Org. Lett.* **2005**, *7*, 403–406.
26. (a) Fages, F.; Desvergne, J.-P.; Bouas-Laurent, H. *J. Am. Chem. Soc.* **1989**, *111*, 96–102; (b) Yuan, Z.; Taylar, N. J.; Mader, T. B.; Williams, I. D.; Kurts, S. K.; Cheng, L.-T. *J. Chem. Soc., Chem. Commun.* **1990**, 1489–1492; (c) Bodenant, B.; Fages, F.; Delville, M.-H. *J. Am. Chem. Soc.* **1998**, *120*, 7511–7519; (d) Maus, M.; Rettig, W.; Bonafoux, D.; Lapouyade, R. *J. Phys. Chem. A* **1999**, 3388–3401; (e) Goodall, W.; Williams, J. A. G. *Chem. Commun.* **2001**, 2514–2515; (f) Leroy-Lhex, S.; Parker, A.; Lapouyade, P.; Belin, C.; Ducasse, L.; Oberlé, J.; Fages, F. *Photochem. Photobiol. Sci.* **2004**, *3*, 949–959; (g) Kaletas, B. K.; Joshi, H. C.; Zwan, G.; Fanti, M.; Zerbetto, F.; Goubitz, K.; De Cola, L.; Köning, B.; Williams, R. M. *J. Phys. Chem. A* **2005**, *109*, 9443–9445.
27. Moreover, it has been reported the use of $CuBr_2$ as efficient catalyst for the preparation of bis(indolyl)methanes starting from indole and aldehydes. Li-Ping, M.; Zi-Chuan, M.; Zhan-Hui, Z. *Synth. Commun.* **2005**, *35*, 1997–2004.
28. (a) Grandini, P.; Mancin, F.; Tecilla, P.; Scrimin, P.; Tonellato, U. *Angew. Chem., Int. Ed.* **1999**, *38*, 3061–3064; (b) Xu, Z.; Qian, X.; Cui, J. *Org. Lett.* **2005**, *7*, 3029–3032; (c) Yang, L.; Chen, Q.; Li, Y.; Xiong, S.; Li, G.; Ma, J. S. *Eur. J. Inorg. Chem.* **2004**, 1478–1487; (d) Kaur, N.; Kumar, S. *J. Chem. Soc., Dalton Trans.* **2006**, 3766–3771.