Tetrahedron Letters 50 (2009) 4930–4933

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and characterization of novel indole-containing half-crowns as new emissive metal probes

Angelo Rocha [a], M. Manuel B. Marques [a,*], Carlos Lodeiro [a,b,*]

[a] *REQUIMTE-CQFB, Departamento de Química, Faculdade de Ciências e Tecnologia, Univeridade Nova de Lisboa, Quinta da Torre, 2829-516 Monte de Caparica, Portugal*
[b] *BIOSCOPE Research Group, Faculty of Science, Physical-Chemistry Department, Campus of Ourense, University of Vigo, E-32004 Ourense, Spain*

ARTICLE INFO

Article history:
Received 15 May 2009
Revised 9 June 2009
Accepted 12 June 2009
Available online 17 June 2009

Keywords:
Indole
Chemosensors
Silver(I)
Half-crown

ABSTRACT

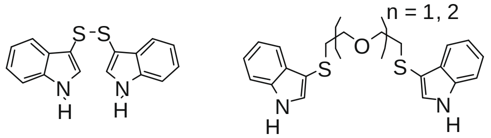
Two new indole derivatives have been synthesized by a one-pot procedure and their potential as fluorescence probes for metal ions was investigated. The sensor capability of **1** and **2** toward cations such as Ag^+, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, and Hg^{2-} was studied in dichloromethane solution by absorption, fluorescence emission, and ^{1}H NMR titrations. Both probes showed selectivity for Ag^+ and Hg^{2+} ions. The results suggest that these compounds may serve as promising models for future design of novel and more potent sensors.

The indole scaffold is an important and privileged structural motif found in a wide array of biologically active natural products, as well as in various indole-derived drugs possessing relevant biological activity. Indeed, synthesis of indole-containing compounds has attracted considerable attention from chemists searching for novel properties.[1] Despite the limited information on the metal–indole complexes, versatile metal–indole bonds in chemical systems have been reported.[2,3] Moreover, the indole ring–metal binding in biological systems has been recently identified.[4] Fluorescence spectroscopy is an extremely powerful and useful technique to visualize molecular recognition interactions, and when combined with the fluorescent property of the indole nucleus allows the exploration of novel indole derivatives as potential fluorescent chemosensors.

Our continued interest in the development of metal-ion fluorescence chemosensors,[5] led us to explore the potential utility of novel indole-containing half-crowns as emissive probes. Herein we report the synthesis, characterization, and photophysical studies of two novel indole derivatives **1** and **2** (Fig. 1) and the known ligand **L**[6] as potential fluorescence probes for metal ions.

Our research interest is focused on heavy and contaminant metals such as palladium(II), lead(II), mercury(II), zinc(II), cadmium(II), and silver(I).[7,8] The usual configuration of a chemosensor involves an organic emissive chromophore incorporating a binding site through a chemical spacer.[9] Taking this into account, although a variety of crown-ether integrating chromophores are known as chemosensors,[10] the corresponding acyclic ones are comparatively rare.[11]

Thus, the indolic sulfur–oxygen donor half-crown ethers **1** and **2** were prepared by a one-pot procedure as depicted in Scheme 1. The first step consisted of the treatment of **3** with thiourea and iodine in the ratio 1:2:1 under inert atmosphere, according to the reported procedure,[12] to afford the *S*-(3-indolyl)isothiuronium iodide **4**. Due to the easy oxidation of indolethiol **5** to the corresponding di(3-indolyl)disulfide **L**, the following steps were carried in situ, without isolation of iodide **4**. After alkaline hydrolysis of **4**, under reflux conditions, the dibromide **6** was subsequently added to afford compound **1** in 28% yield.[13] Similarly, addition of the dimesylate **7**[14] to the alkaline solution of **4** afforded compound **2** in 34% yield.[15] Despite all efforts, the formation of the di(3-indolyl)disulfide **L** could not be avoided, and after reaction the crude



L

1 n = 1

2 n = 2

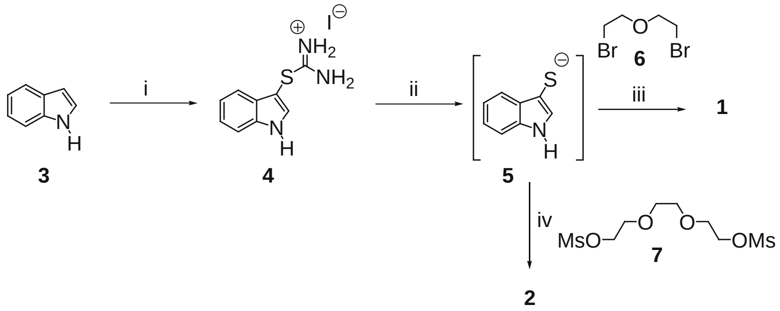
Figure 1. Structure of the prepared indole-containing half-crowns **1** and **2** and the disulfide **L**.[6]

---

[*] Corresponding authors. Tel.: +351 21 2948300x10983; fax: +351 21 2948550 (M.M.B.M.); tel.: +34 988 387072; fax: +34 988 387001 (C.L.).

E-mail addresses: mmbmarques@dq.fct.unl.pt (M.M.B. Marques), clodeiro@uvigo.es (C. Lodeiro).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.073



Scheme 1. Synthesis of the half-crowns **1** and **2**: Reagents and conditions: (i) thiourea, I_2, KI, MeOH/H_2O, rt; (ii) NaOH/H_2O, reflux, 10 min; (iii) **6**, rt, overnight; (iv) **7**, rt, overnight.

Table 1
UV–vis and fluorescence data of compounds **L**, **1**, and **2**

Compound	UV–vis		Fluorescence		
	λ_{exc} (nm)	$\varepsilon \times 10^4$ (mol^{-1} cm^{-1})	λ_{em} (nm)	ϕ_F	Stokes' shift (nm)
L	279	1.93	371	0.02	92
1	279	1.94	388	0.19	109
2	279	2.03	389	0.39	110

product was purified by column chromatography to afford pure compounds **1** and **2**. Compound **L** was prepared according to the known procedure.[16]

The photophysical characterization for compounds **L**, **1**, and **2** is summarized in Table 1. The fluorescence quantum yield increases with the half-crown chain length, thus representing a higher separation between the sulfur atoms. This effect is stronger for compound **2**.

The absorption spectra of **L**, **1**, and **2** in dichloromethane show a band centered at 279 nm assigned to the π–π^* transitions in the ligand (see Fig. 2). This band presents the characteristic shape of the indole group and is attributed to the two close low-lying $\pi\pi^*$ excited states ^1L_a and ^1L_b.[17]

The absorption spectra of **L** show a shoulder centered at 340 nm, and could indicate some interactions between the indole rings in the ground state. This shoulder disappears when the distance between both indole rings increases in compounds **1** and **2**.

The ligands exhibit a broad emission band centered at 371(**L**), 388(**1**), and 389(**2**) nm with a relative fluorescence quantum yield of $\Phi = 0.02$ (**L**), 0.19 (**1**), and 0.39 (**2**), when excited at 280 nm. The fluorescence quantum yield was determined using as reference solution naphthalene with $\Phi_f = 0.23$ in cyclohexane.[18]

In order to explore the effect of metal cations on the absorption and fluorescence emission spectra, several titrations with Ag^+, Cu^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, and Hg^{2+} were performed using absorption and fluorescence spectroscopies.[19] To conduct the analyses, the ligands were dissolved in dichloromethane and titrated with the analytes.

Selectivity toward Ag^+ and Hg^{2+} over the other metals studied was observed for **L**, where addition of 10 equiv of metal induced a 10-fold increase in the fluorescence emission band, but these spectra show an intense evolution with time. The emission spectrum remains stable only upon 48 h. However, addition of Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} in the same conditions did not produce any effect on the fluorescence band of **L**.

In order to understand the effect produced by the oxygen atoms, in the flexible chain between the indole units, introducing an extra stability in the complexes, the same metal titrations were performed with **1** and **2**. In general the absorption spectrum shows very small changes upon the metal interaction. A very small red-

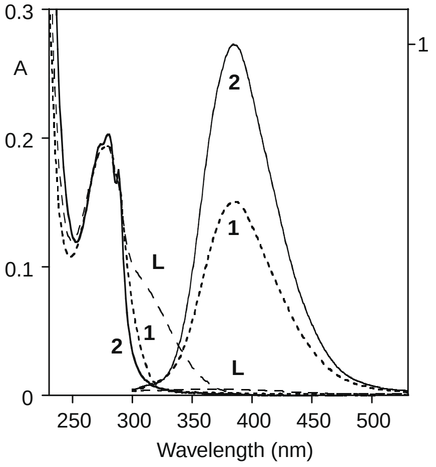


Figure 2. Absorption and emission spectra of **L**, **1**, and **2** in dichloromethane. (λ_{exc} = 280 nm; [**L**] = [**1**] = [**2**] = 1.0×10^{-5} M).

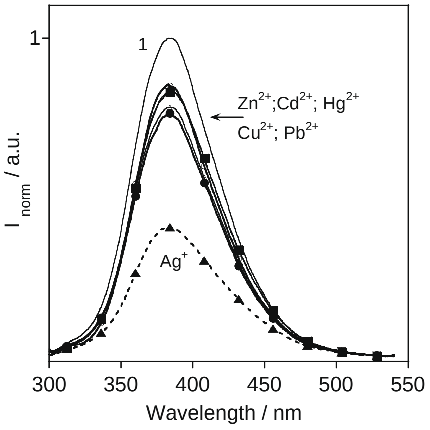


Figure 3. Fluorescence emission spectra of **1** in dichloromethane after the addition of 1 equiv of $AgBF_4$, $Zn(CF_3SO_2)_2$, $Cd(BF_4)_2$, $Hg(CF_3SO_2)_2$, $Cu(CF_3SO_2)_2$, and $Pb(ClO_4)_2$. (λ_{exc} = 280 nm; [**1**] = 1.0×10^{-5} M).

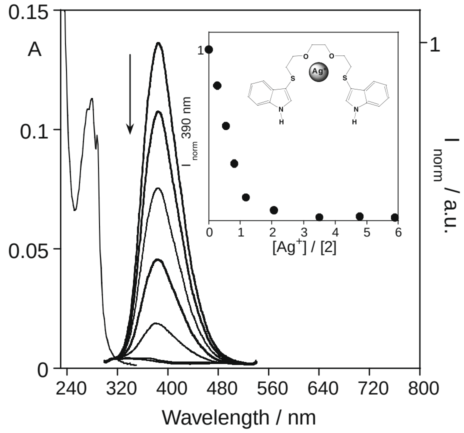


Figure 4. Fluorescence emission titration of **2** and absorption spectra in dichloromethane after the addition of increased amount of $AgBF_4$, (λ_{exc} = 280 nm; [**2**] = 1.0 × 10^{-5} M). In the inset is shown the maxima of emission at 390 nm.

shift in 3–5 nm was observed. More interesting was to study the fluorescence spectra of **1** and **2** in the presence of increasing amounts of the metals.

A quenching effect upon metal complexation was observed for **1** in the presence of all the metal ions studied, even for the d^{10} metals Ag^+, Zn^{2+}, Cd^{2+}, and Hg^{2+}, but the intensity of this CHEQ (Chelating Enhancement of the Quenching) effect was different in all of them.

The most effective quenching was upon Ag^+ complexation, after the addition of one equivalent the intensity of the emission was reduced in 65%, while a complete quenching of the emission was observed upon addition of the fifth equivalent. These results suggest a stronger complexation with Ag^+ when compared to the other metals, while after the addition of 20 equiv the intensity was reduced in 90% for Hg^{2+}, 30% for Pb^{2+}, and only 15% for Zn^{2+}, Cd^{2+}, and Cu^{2+}.

In Figure 3 are shown the fluorescence spectra of **1** in dichloromethane in the presence of 1 equiv of each metal ion.

In respect to compound **2**, a comparative study with **1** can be performed. In this compound the distance between both indole chromophores is longer, thus increasing the flexibility to chelate metal ions. This structural effect is observed upon metal complexation.

For the same quantity of metal added now the quenching observed is higher in all cases. After the addition of one equivalent of silver(I) the quenching reaches 90% becoming complete after the addition of the second metal ion.

In the case of the divalent metals, addition of 20 equiv to **1** in dichloromethane produces a 90% of quenching in the presence of mercury(II), 60% for lead(II), 50% for copper(II), and 40% for cadmium(II) and zinc(II), suggesting stronger interactions than ligand **1**. In Figure 4 is represented the fluorescence titration of **2** upon silver(I) interaction. In the inset is observed that with the addition of 1 equiv of Ag^+, the band at 390 nm reaches a plateau confirming the formation of a 1:1 complex.

Since ligand **2** showed to be the most selective for Ag^+ the complexation and interaction in solution with this metal were investigated by ^1H NMR. Thus, increasing amounts of $AgBF_4$ in CD_2Cl_2 were added to a 0.05 M solution of **2** in the same solvent. The ^1H NMR spectra of the resulting solutions were recorded at room temperature, 30 min after addition of Ag^+ (Fig. 5). The total amount of Ag^+ added was determined by ICP (24.71 ppm).

An increase in the silver ion concentration gradually downfield-shifted the proton resonance of H2′ (indolic proton), H3 as well as H1 from the half-crown, the latter being the most affected. This behavior suggests that Ag^+ is binding via the sulfur atoms as well as oxygen atoms.

The spectra resolution increases with the metal ion amount, suggesting that a more rigid conformation is forming in solution, in the presence of Ag^+. Moreover, these observations indicate that in solution, the complexed cation interacts not only with the half-crown moiety but also with the aromatic nuclei (H2′).

In conclusion, two new fluorescence indole-containing ligands **1** and **2**, with an S_2O and S_2O_2 donor set have been synthesized and their photophysical properties have been evaluated. Their capacity to act as a potential sensor for the soft metal ions Ag^+, Cu^{2+}, Zn^{2+},

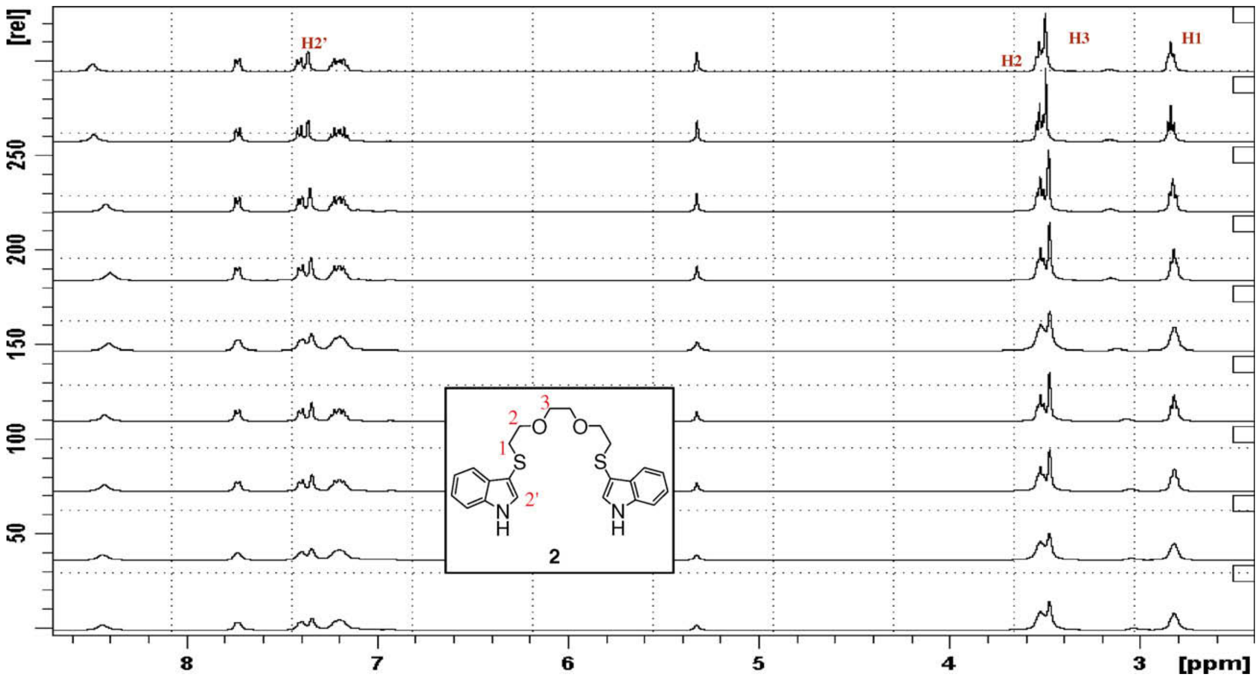


Figure 5. ^1H NMR spectra of ligand **2** in CD_2Cl_2 without Ag^+ and with increasing amounts of a solution of $AgBF_4$ in CD_2Cl_2 (400 MHz).

Cd^{2+}, Pb^{2+}, and Hg^{2+} was evaluated in dichloromethane solution. Among the cations studied, probes **1** and **2** have demonstrated a remarkable selectivity for Ag^{+} and a high affinity for Hg^{2+} at higher concentrations, and a stronger interaction with silver(I), depending on the mobility of the indole ring according to the crown chain length. The observed selectivity of the new probes is of interest due to their use as building blocks in the design of more complex chemosensors for this metal ion.

Acknowledgments

The authors are grateful to *REQUIMTE* Research Fund for financial support. C.L. thanks Xunta de Galicia, Spain, for the Isidro Parga Pondal Research Program and INOU-UVIGO K914/2009 Research Project.

References and notes

1. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
2. Li, Y.; Yang, C. M. *J. Am. Chem. Soc.* **2005**, *127*, 3527–3530; Motoyama, T.; Shimazaki, Y.; Yajima, T.; Nakabayashi, Y.; Naruta, Y.; Yamauchi, O. *J. Am. Chem. Soc.* **2004**, *126*, 7378–7385; Kaminskaia, N. V.; Ullmann, G. M.; Fulton, D. B.; Kostié, N. M. *Inorg. Chem.* **2000**, *39*, 5004–5013; Kaminskaia, N. V.; Johnson, T. W.; Kostié, N. M. *J. Am. Chem. Soc.* **1999**, *121*, 8663–8664.
3. For a review see: Shimazakia, Y.; Yajimab, T.; Takanic, M.; Yamauchib, O. *Coord. Chem. Rev.* **2009**, *253*, 479–492.
4. Xue, Y.; Davis, A. V.; Balakrishnan, G.; Stasser, J. P.; Staehlin, B. M.; Focia, P.; Spiro, T. G.; Penner-Hahn, J. E.; O'Halloran, T. V. *Nat. Chem. Biol.* **2008**, *4*, 107–109.
5. See for example: Lodeiro, C.; Pina, F. *Coord. Chem. Rev.* **2009**, *253*, 1353–1383.
6. Woodbridge, D. *J. Am. Chem. Soc.* **1950**, *72*, 4320–4322.
7. For example (a) Bazzicalupi, C.; Bencini, A.; Berni, E.; Bianchi, A.; Borsari, L.; Giorgi, C.; Valtancoli, B.; Lodeiro, C.; Lima, J. C.; Parola, A. J.; Pina, F. *Dalton Trans.* **2004**, 591–597; (b) Bazzicalupi, C.; Bencini, A.; Bianchi, A.; Danesi, A.; Giorgi, C.; Lodeiro, C.; Pina, F.; Santarelli, S.; Valtancoli, B. *Chem. Commun* **2005**, 2630–2632; (c) Tamayo, A.; Escriche, L.; Casabó, J.; Covelo, B.; Lodeiro, C. *Eur. J. Inorg. Chem.* **2006**, 2997–3004; (d) Tamayo, A.; Pedras, B.; Lodeiro, C.; Escriche, L.; Casabó, J.; Capelo, J. L.; Covelo, B.; Kivekas, R.; Sillampa, R. *Inorg. Chem.* **2007**, *46*, 7818–7826; (e) Batista, R. M. F.; Oliveira, E.; Costa, S. P.; Lodeiro, C.; Raposo, M. M. M. *Tetrahedron Lett.* **2008**, *49*, 6575–6578; (f) Pedras, B.; Fernandes, L.; Oliveira, E.; Rodríguez, L.; Raposo, M. M. M.; Capelo, J. L.; Lodeiro, C. *Inorg. Chem. Commun.* **2009**, *12*, 79–85.
8. (a) Park, C. S.; Lee, J. Y.; Kang, E.-J.; Lee, J.-E.; Lee, S. S. *Tetrahedron Lett.* **2009**, *50*, 671–675; (b) Schwarze, T.; Müller, H.; Dosche, C.; Klamroth, T.; Mickler, W.; Kelling, A.; Löhmannsröben, H.-G.; Saalfrank, P.; Holdt, H.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1671–1674; (c) Iyoshi, S.; Taki, M.; Yamamoto, Y. *Inorg. Chem.* **2008**, *47*, 3946–3948.
9. (a) Czarnik, A. W. *Acc. Chem. Res.* **1994**, *27*, 302–308; (b) Prasanna de Silva, A.; Gunaratne, H. W. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
10. See for example: Gokel, G. W.; Leevy, W. M.; Weber, M. E. *Chem. Rev.* **2004**, *104*, 2723–2750.
11. Morozumi, T.; Anada, T.; Nakamura, H. *J. Phys. Chem. B* **2001**, *105*, 2923–2931; Mello, J. V.; Finney, N. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1536–1538.
12. Levkoskaya, G. G.; Rudyakova, E. V.; Mirskova, A. N. *Russ. J. Org. Chem.* **2002**, *38*, 1641–1646.
13. *General procedure*: To a stirring solution of indole (503 mg, 4.3 mmol) and thiourea (650 mg, 8.6 mmol) in degassed methanol (9 mL), was slowly added a solution of iodine (1.1 g, 4.3 mmol)and KI (713 mg, 4.3 mmol) in degassed water (3 mL), at room temperature. After consumption of the indole, a degassed 20% aqueous solution of NaOH was added, and the resulting mixture was refluxed for 10 min. The dibromide **6** (0.9 mmol) was then added and the resulting mixture was stirred overnight at room temperature. The mixture was diluted with 10 mL of water and extracted with dichloromethane (2×, 10 mL). The organic layer was dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. The crude was purified by column chromatography (silica, ethyl ether/hexane, 9:1) to afford pure **1** (439 mg, 28%): IR (film) ν_{max}/cm^{-1} 3400; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.08 (2H, s, N*H*), 7.67 (2H, d, *J* = 7.7 Hz, Ar*H*), 7.31 (2H, d, *J* = 7.9 Hz, ArH), 7.12 (6H, m, Ar*H*), 3.42 (4H, t, *J* = 6.8 Hz, CH_2OCH_2), 2.75 (4H, t, *J* = 6.8 Hz, SCH_2); ^{13}C NMR ($CDCl_3$, 100.63 MHz): δ_C 136.2, 129.7, 129.4, 122.7, 120.5, 119.4, 111.4, 105.3, 69.9, 35.3. acc. mass: 368.101476, $C_{20}H_{20}N_2OS_2$ requires 368.101707.
14. Rabouin, D.; Perron, V.; N'Zemba, B.; Gaudreault, R.-C.; Berube, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 557–560.
15. *Compound* **2**: mp: 82–84 °C; IR (film) ν_{max}/cm^{-1} 3400; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.20 (2H, s, N*H*), 7.76 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.38–7.18 (8H, m, Ar*H*), 3.55 (4H, t, *J* = 6.9 Hz, SCH_2CH_2O), 3.50 (4H, s, OCH_2CH_2O), 2.84 (4H, t, *J* = 6.9 Hz, SCH_2). ^{13}C NMR ($CDCl_3$, 100.63 MHz): δ_C 136.2, 129.8, 129.3, 122.6, 120.4, 119.2, 111.5, 111.0, 104.9, 103.4, 70.3, 70.1, 35.3. acc. mass: 414.080804, $C_{22}H_{24}N_2O_2S_2$ requires 414.080697.
16. Shirani, H.; Janosik, T. *Synthesis* **2007**, *17*, 2690–2698.
17. (a) Serrano-Andrés, L.; Roos, B. O. *J. Am. Chem. Soc.* **1996**, *118*, 185; (b) Borin, A. C.; Serrano-Andrés, L. *Chem. Phys.* **2000**, *262*, 253.
18. Montalti, M.; Credi, A.; Prodi, L.; Gandolfi, M. T. *Handbook of Photochemistry*, 3rd ed.; CRC Press, Taylor & Francis Group: Boca Raton, New York, 2006.
19. Absorption spectra were recorded on a Perkin Elmer lambda 35 spectrophotometer, and fluorescence emission on a Perkin Elmer LS45. The linearity of the fluorescence emission versus concentration was checked in the concentration range used (10^{-4}–10^{-6} M). Corrections for the absorbed light and dilutions were performed when necessary. All spectrofluorimetric titrations were performed as follows: a stock solution of the ligand (ca. 1.00×10^{-3} M) was prepared by dissolving an appropriate amount of the ligand in a 50 mL volumetric flask and diluting to the mark with dichloromethane UVA-sol. The titration solutions ([**L = 1 = 2**] = 1.00×10^{-6} and 1.00×10^{-5} M) were prepared by appropriate dilution of the stock solution. Titrations were carried out by addition of microliter amounts of standard solutions of the ions dissolved in absolute ethanol or dichloromethane.