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The Synthesis of 1,4,7,10-Tetraazacyclododecanes with Acetylsalicylic Side Arm as Potential Cobalt(II) Fluorophores

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Abstract

New derivatives of 1,4,7,10-tetraazacyclododecanes have been synthesized. The coordination properties toward Co^{2+} of these ligands have been studied by means of spectroscopic methods. The stability constants of cobalt complexes with ligand **L-1** and **L-2** were determined. Unusual complexes with a 2:1 ($L:Co^{2+}$) stoichiometry have been found.

Introduction

The chemistry of crown ethers and their ability to form stable complexes with alkali metal ions is now well established [1–5]. This stability can be easily explained by the HSAB theory. Additionally, in contrast to complexes of open-chain ligands, their macrocyclic analogues are thermodynamically and kinetically more stable. This allows them to be used in biological, therapeutic and analytical applications. Replacing the polyether oxygen atoms for other atoms, for examples S, P or N, can modify the acceptor – donor properties of such ligands. The presence of sulfur atoms assures strong interaction with heavy metal ions, especially with mercury(I) and silver(I), whereas nitrogen atoms permit selective binding of divalent transition metal ions [6–9]. The last macrocycles can bind metal ions forming complexes with different molar ratios. Triazacyclononanes usually form 1:1 and 2:1 (ligand:metal ion) complexes [10, 11] but typical stoichiometry for tetrazacyclododecanes is 1:1 and 1:2 [12, 13]. The polyazamacrocycles can be easily modified by alkylation or acylation reaction [14, 15]. In this way different chromogenic or luminescent groups can be introduced [16, 17]. Luminescent chemosensing compounds present many advantages, since they show high sensitivity and versatility typical to photoluminescence spectroscopy. In this context, many efforts have been made to develop luminescent chemosensors for transition metal ions, so that chemical sensing of some of them may be achieved in biological systems where such cations are found. In this contribution, we describe new chemical systems able to act as luminescent ligands for Co(II) metal ions.

Experimental

General

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded at 500, 125, and 202.4 MHz on Varian instruments, respectively. Mass spectra were recorded on AMD-604 apparatus. Thin layer chromatography (TLC) analyses were performed on Alufolien covered with silica gel 60-F-254 (0.2 mm thickness) while Kieselgel 60 (70–230 mesh) was used for column chromatography.

All reagents were of the best grade commercially available and were distilled, crystallized or used without further purification, as appropriate.

Reagents: 1,4,7,10-tetraazadodecane (**1**) was purchased from Strem Co (France). Other reagents were of analytical grade. 1,4,7,-Tris(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (**2**) was synthesized according to literature procedure [18].

The purity of ligands was additionally determined by potentiometric measurements using pH-electrode (Radiometer PHG200). Potentiometric titrations were performed in water at 25 °C using an OP-205 Radelkis pH-meter linked to a personal computer *via* PCL-838 control card.

Absorption spectra were recorded using a Perkin Elmer Lambda 40P spectrophotometer. Fluorescence spectra were recorded on a Perkin Elmer LS-50B spectrofluorimeter with 7.5 nm band-width for excitation

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and emission. The excitation wavelength used was 300 nm. Spectroscopic titrations were performed manually using a 0.5 mL Hamilton syringe equipped with a gauge 30 tube and a micro-screw. Magnetic stirrers employing a counter-shaft placed inside the spectrophotometer were used continuously during measurements. The results were plotted and equilibrium constants were calculated if possible [19]. The program STOICHIO [20, 21] based on the nonlinear least squares Gauss–Newton–Marquardt algorithm was used to fit the parameters of the equilibrium models.

*1-N-(O-Acetylsalicyloyl)-4,7,10-tri(tert-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (**3**)*

A solution of acetylsalicylic acid chloride (0.99 g, 5 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise at room temperature to stirred solution of 1,4,7-tris-(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (2.36 g, 5 mmol) in dry CH_2Cl_2 (50 mL) in the presence of anhydrous Na_2CO_3 (1.06 g, 10 mmol). After 3 h of stirring, 60 mL of water was added and the organic layer separated. The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (acetate:hexane (1:2)) yielding **3** (1.58 g, 50% yield) as colorless amorphous solid.

^{1}H NMR: (δ, $CDCl_3$): 1.47 s, 18H; 1.51 s, 9H; 2.25 s, 3H; 3.48 br s, 4H; 3.72 br s, 4H; 3.74 br s, 8H; 7.17 d ($J = 8.24$ Hz), 1H; 7.28–7.38 m, 2H; 7.39–7.41 m, 1H.

^{13}C NMR: (δ, $CDCl_3$): 21.07 ($CH_3C{=}O$), 28.46, 28.62, 28.77 (CH_3C); 49.52, 49.85, 50.68, 51.65 (NCH_2CH_2N); 80.42, 80.66, 80.71 (CH_3CO); 123.39, 126.18, 127.51, 130.32, 146.98 (Ar); 155.81, 156.97, 157.36 (NC=O), 168.82 (ArC=O); 169.04 ($CH_3C{=}O$).

Mass spectrum (ESI) $(M + H)^+$ 635; $(M + Na)^+$ 657; HRMS [ESI, $(M + Na)^+$] 657.3470 calculated for $C_{32}H_{50}N_4O_9Na$, found 657.3491.

*1-N-(O-Acetylsalicyloyl)-1,4,7,10-tetraazacyclododecane (**L-1**)*

Trifluoroacetic acid (5 mL) was added to 1-*N*-(*O*-acetylsalicyloyl)-4,7,10-tri(*tert*-butyloxycarbonyl)-1,4,7,10-tetraazacyclododecane (**3**) (1.27 g, 2 mmol) at room temperature. After 2 h the excess of TFA was removed under reduced pressure, the resulting crude powder was dissolved in $CHCl_3$ (20 mL) and washed with 5% NaOH solution (5 mL). Water phase was concentrated under reduce pressure. The residue was placed on short silica gel column and eluted with chloroform:methanol (6:1) solvent system. The free ligand **L-1** was obtained as colorless amorphous solid. Yield 0.64 g; 96%.

^{1}H NMR: (δ, CD_3OD): 2.17 s, 3H; 2.83 br s, 1H; 2.96 br s, 4H; 3.07 br s, 2H; 3.23 br s, 1H; 3.46 br s, 1H; 3.54–3.60 br m 7H; 6.62–6.75 m, 2H; 7.06 dd ($J_1 = 1.46$ Hz, $J_2 = 8.23$ Hz), 1H; 7.31 dt ($J_1 = 1.46$ Hz, $J_2 = 8.80$ Hz), 1H.

^{13}C NMR: (δ, d-DMSO): 20.92, 21.20 ($CH_3C{=}O$), 44.97, 45.33, 46.56, 46.80, 47.12, 48.60, 49.15, 49.50 (NCH_2CH_2N); 116.43, 117.53, 117.94, 119.02, 124.65, 124.89, 128.12, 128.36, 131.14 (Ar); 156.84, 158.53, (NC=O); 174.14, 174.70 ($CH_3C{=}O$).

Mass spectrum (EI) $(M)^+$ 334; HRMS [EI, $(M)^+$] calculated 334.20049 for $C_{17}H_{26}N_4O_3$, found 334.20030.

*1-N-(O-Acetylsalicyloyl)-1,4,7,10-tetraazacyclododecane (**L-1**)*

Direct acylation: To a stirred solution 1,4,7,10-tetraazacyclododecane (1) (0.86 g, 5 mmol) in dry CH_2Cl_2 (100 mL) a solution of acetylsalicylic acid chloride (0.99 g, 5 mmol in 20 mL of CH_2Cl_2) was added dropwise at room temperature. The mixture was stirred overnight, and then 10% $NaHCO_3$ solution (20 mL) was added. The aqueous phase was extracted three times with 20 mL of $CHCl_3$ and the aqueous phase was evaporated under reduce pressure. The residue was treated with ethanol (20 mL) and the deposited inorganic salts were filtered off. The filtrate was concentrated under vacuum and the remaining residue was purified by column chromatography using $CHCl_3$:CH_3OH (6:1) as an eluent. Ligand **L-1** was obtained as colorless amorphous solid. Yield 0.46 g; 27%.

^{1}H NMR: (δ, CD_3OD): 2.18 s, 3H; 2.82 br s, 1H; 2.96 br s, 4H; 3.06 br s, 2H; 3.22 br s, 1H; 3.46 br s, 1H; 3.54–3.62 br m 7H; 6.62–6.76 m, 2H; 7.07 dd ($J_1 = 1.46$ Hz, $J_2 = 8.24$ Hz), 1H; 7.32 dt ($J_1 = 1.46$ Hz, $J_2 = 8.79$ Hz), 1H.

^{13}C NMR: (δ, d-DMSO): 20.93, 21.19 ($CH_3C{=}O$), 44.99, 45.34, 46.56, 46.79, 47.12, 48.61, 49.15, 49.49 (NCH_2CH_2N); 116.44, 117.53, 117.95, 119.03, 124.66, 124.88, 128.12, 128.35, 131.15 (Ar); 156.83, 158.57, (NC=O); 174.15, 174.70 ($CH_3C{=}O$).

Mass spectrum (EI) $(M)^+$ 334; HRMS [EI, $(M)^+$] calculated 334.20049 for $C_{17}H_{26}N_4O_3$, found 334.20021.

*1-N-(O-Acetylsalicyloyl-1,4,7,10-tetraazacyclododecane 4,10-bis(methanephosphonic acid diethyl ester (**L-2**)*

A mixture of paraformaldehyde (0.01 g, 3.3 mmol) and 1-*N*-(*O*-acetylsalicyloyl)-1,4,7,10-tetraazacyclododecane (**L-1**) (0.34 g, 1 mmol) in dry THF, was stirred at 40 °C for 0.5 h. Triethyl phosphite (0.7 mL, 4 mmol) was then added and the mixture was stirred for 2 days. The resulting clear oil was heated at 50 °C under vacuum for 4 h to remove volatile impurities. The residue was dissolved in ether (15 mL) and the solution was extracted with water (2 × 15 mL), 2% NaOH solution (2 × 15 mL), and water (2 × 15 mL). The ether layer was dried over Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by gradient chromatography ($CHCl_3$/MeOH). The fractions containing the desired product were combined, and the

solvents were removed under vacuum to give ligand **L-2** as colorless oil. Yield 0.38 g; 60%.

^{1}H NMR: (δ, $CDCl_3$): 1.31–1.33 m, 12H; 2.15 s, 3H; 2.85 br s, 1H; 2.92–2.99 br m, 10H; 3.54 br s, 2H; 3.57 br s, 2H; 3.70 br s, 2H; 3.71 br s 4H; 4.09–4.13 m, 8H; 6.85 t ($J = 7.32$ Hz), 1H; 6.97 d ($J = 8.30$ Hz), 1H; 7.21 dd ($J_1 = 1.46$ Hz, $J_2 = 7.81$ Hz), 1H; 7.29dt ($J_1 = 1.46$ Hz, $J_2 = 8.30$ Hz), 1H.

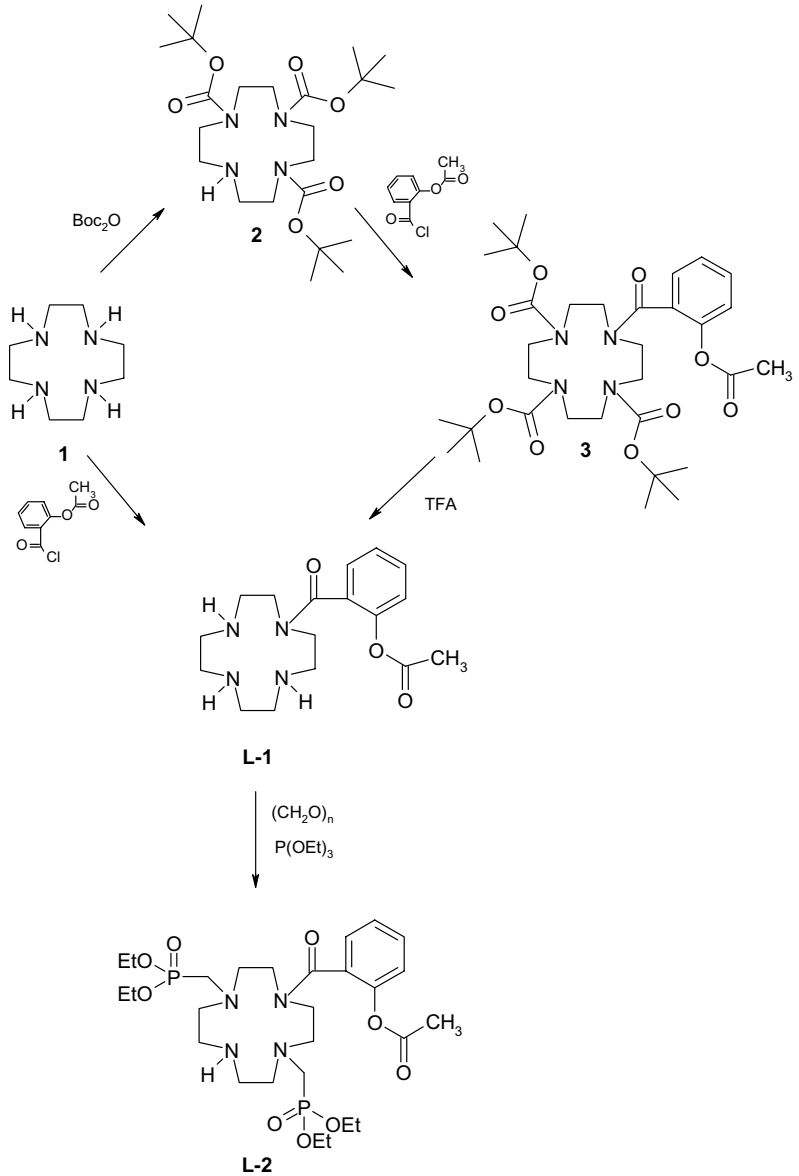
^{13}C NMR: (δ, $CDCl_3$): 16.61 d ($J = 5.38$ Hz), (CH_3CH_2OP), 22.18($CH_3C{=}O$); 48.60, 50.05, 55.32, 56.66 (NCH_2CH_2N); 57.77 (PCH_2N); 62.35 dd ($J_1 = 6.88$ Hz, $J_2 = 14.38$ Hz), ($POCH_2CH_3$); 117.18, 119.29, 122.50, 128.03, 130.99, 155.07 (Ar); 171.24 ($NC{=}O$); 176.03 ($CH_3C{=}O$). ^{31}P NMR ($CHCl_3$/H_3PO_4) δ 25.87, 25.90.

Mass spectrum (EI) $(M)^+$ 634, HRMS [ESI, $(M + Na)^+] = 657.2794$ calculated for $C_{32}H_{50}N_4O_9Na$, found 657.2790.

Results and discussion

The synthesis of *tetra-N*-substituted cyclen derivatives containing four identical coordinating pendant arms are high yielding and easy to run. Direct mono-*N*-acylation of cyclen usually provides a more complex mixture [22], even when using an excess of cyclen [23]. Reactions based on triply-protected cyclen prevent the peracylation [24, 25]. In our work we described both routes of synthesis of 1-*N*-(*O*-acetylsalicyloyl)-1,4,7,10-tetraazacyclododecane (Scheme 1).

The first one was based on direct acylation of 1,4,7,10-tetraazacyclododecane with *O*-acetylsalicylic acid chloride under high dilution conditions. The resulting mixture contains several products. Isolation of the main compound is complicated because of chromatographic similarity of the products. The yield of **L-1** is moderate (27%). The second two step synthesis



Scheme 1.

of **L-1** applies 1,4,7-tris(*tert*-butyloxycarbonyl)cyclen [5]. The reaction of *O*-acetylsalicylic acid chloride with tris-Boc-cyclen gave the fully protected product with 50% yield. Deprotection reaction was performed in TFA solution at room temperature.

Ligand **L-1** was allowed to react with paraformaldehyde and triethyl phosphite. This one pot reaction introduced methylenephosphonic ester groups to cyclen (**L-2**). Interestingly, only two methylenephosphonic acid ester groups can be introduced into this molecule, regardless how drastic conditions were applied.

The obtained ligands **L-1** and **L-2** show absorption bands of 200–450 nm with a maximum at 281 nm ($\log \varepsilon = 3.29$ and 3.41 for **L-1** and **L-2**, respectively). Ligand **L-1** has emission band at $\lambda = 403$ nm, characteristic for acetylsalicylic units. A direct consequence of the introduction of methylenephosphonic diethyl ester groups to ligand **L-1** is a quenching of the emission band.

Addition of Co^{2+} ions into acetonitrile solution of **L-1** and **L-2** causes strong changes in ultraviolet spectra. A typical series of UV–VIS spectra at various ligands:metal ratios are presented in Figure 1a. The absorbance in UV range increases and a new absorption bands at 274, 350, 460 nm for **L-1** and 274, 310 nm for **L-2** appear. Simultaneously, well pronounced isosbestic points at $\lambda = 300$ nm for **L-1** and at $\lambda = 286$ nm for **L-2** are formed. For ligand **L-1** the isosbestic point is found only in a restricted 1–0.45 (**L-1**:Co^{2+}) stoichiometry. Plot of absorbance *versus* Co^{2+}:**L-1** ratio show a strong increase of the absorption bands, which suggest the formation of an ionic complex $[Co(\mathbf{L\text{-}1})_2]^{2+}$ (Figure 1b). The absorbance–absorbance diagram for titration of **L-1** with cobalt(II) perchlorate in acetonitrile solution (Figure 1c) shows that two equilibriums exist for both ligands.

These equilibriums can be described as

$$Co^{2+} + L \overset{K_1}{\rightleftharpoons} CoL^{2+}$$

$$Co^{2+} + 2L \overset{\beta_2}{\rightleftharpoons} CoL_2^{2+}$$

$$K_1 = \frac{[CoL^{2+}]}{[Co^{2+}][L]}, \quad \beta_2 = \frac{[CoL_2^{2+}]}{[Co^{2+}][L]^2}.$$

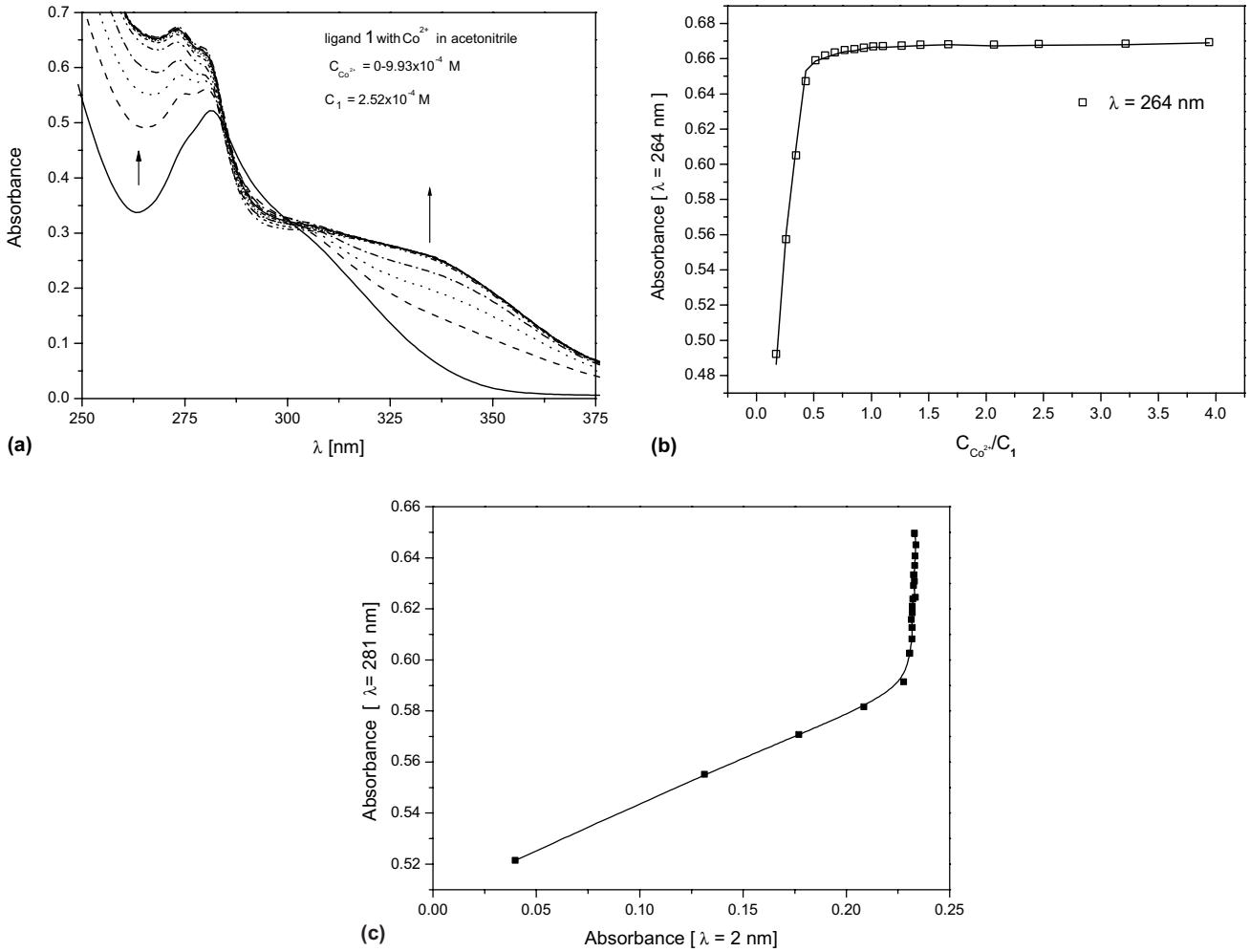


Figure 1. (a) Absorption spectra recorded in acetonitrile solution containing ligand **L-1** (2.52×10^{-4} mol dm^{-3}) and cobalt(II) perchlorate (0–9.93×10^{-4} mol dm^{-3}). (b) Dependence of absorbance at 264 nm for ligand **L-1** with cobalt(II) perchlorate. The experimental points (open squares) and fitted line (solid). (c) Absorbance diagram for measurement of ligand **L-1** with cobalt(II) perchlorate.

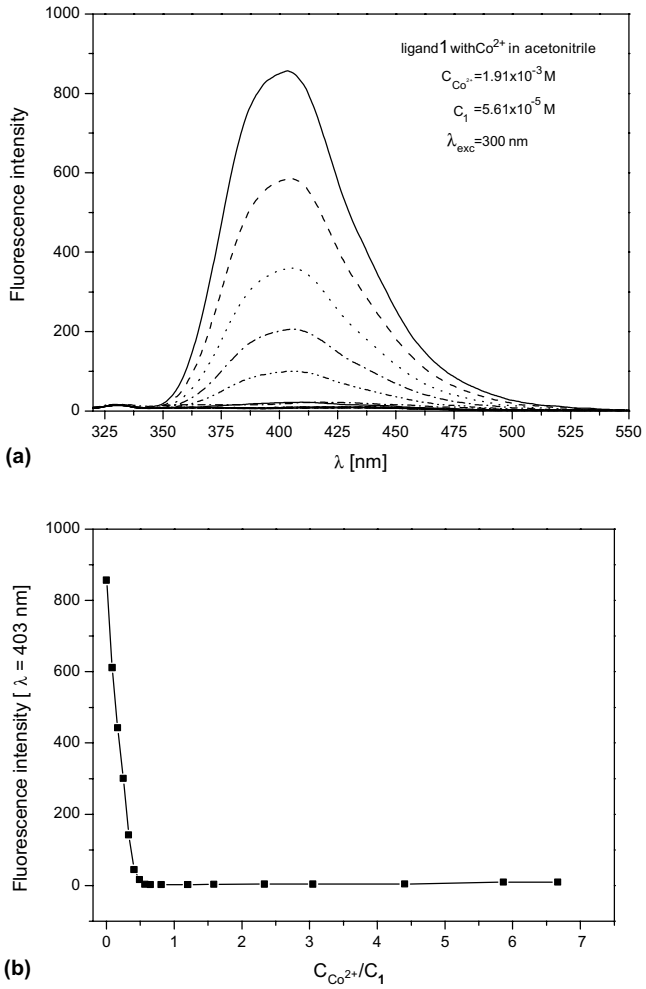


Figure 2. (a) Emission spectra recorded in acetonitrile solution containing ligand **L-1** (5.61×10^{-5} mol dm^{-3}) with cobalt(II) perchlorate (0–2.81×10^{-4} mol dm^{-4}). (b) Dependence of fluorescence intensity at 403 nm for ligand **L-1** with cobalt(II) perchlorate.

Although the absorbance diagram for titration of **L-1** with cobalt(II) perchlorate in acetonitrile solution (Figure 1c) shows that two equilibria exist, our fitting algorithm [19, 20] (Figure 1b and c) only allowed to determine the overall stability constant log $\beta_2 = 10.8 \pm 0.5$ and 9.2 ± 0.1 for $[Co(\mathbf{L\text{-}1})_2]^{2+}$ and $[Co(\mathbf{L\text{-}2})_2]^{2+}$, respectively. The similar models of equilibrium for the **L-1** and **L-2** have been found in methanol. Additionally, the formation of both complexes of ligand **L-1** has been studied by mass spectrometry. Two techniques have been applied; MALDI and ESI. MALDI technique allowed only for detection of 1:1 complex, but ESI spectrum has shown the peak ($m/z = 1002$) which can be assigned to complex $[Co(\mathbf{L\text{-}1})_2](ClO_4)_2{\cdot}4H_2O$.

The results of fluorometric titrations of **L-1** with Co^{2+} comply with spectroscopic measurements. The presence of Co^{2+} ions quenches the emission band at $\lambda = 403$ nm. Sharp changes of emission at molar ratio Co^{2+}:**L-1** *versus* intensity of emission band suggest the formation of the dominant form of $[Co(\mathbf{L\text{-}1})_2]^{2+}$ (Figure 2).

Conclusions

Synthesis of monosubstituted cyclen derivative **L-1** by two approaches (direct acylation and acylation of triprotected cyclen) was described. Trifunctional cyclen was obtained by further modification of **L-1** with paraformaldehyde and triethyl phosphite yielding **L-2**. Both **L-1** and **L-2** have light-harvesting moieties but only the monofunctional derivative exhibits weak fluorescence as introduction of chelating groups evidently quenches luminescence. UV–VIS spectroscopic studies suggest that the dominant form of cobalt(II) complexes with ligand **L-1** and **L-2** is $[CoL_2].^{2+}$ The stoichiometry of obtained complexes is unusual compared to those described so far for cyclen derivatives in the literature. Introduction of methanephosphonic acid diethyl ester group to cyclen slightly decreases the stability constants but does not change the overall equilibrium in acetonitrile and methanol solutions. Electrochemical measurements have confirmed that the unusual complex $[Co(\mathbf{L\text{-}1})_2]^{2+}$ is a dominant form under equilibrium. These results will be published elsewhere.

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