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Synthesis of an unsymmetrical *N*-functionalized triazacyclononane ligand and its Cu(II) complex

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ABSTRACT

The unsymmetrical 1,4-bis(2-aminophenyl)-7-(pyridin-2-ylmethyl)-1,4,7-triazacyclononane ligand (L3) has been prepared and characterized by NMR spectroscopy. The L3 ligand is based on the triazamacrocycle ring bearing one flexible 2-pyridylmethyl linked to the macrocycle group via the methyl group, and two rigid 2-aminophenyl pendant donor groups linked to the macrocycle *via* the aromatic carbon atoms. Reaction of this ligand with $Cu(ClO_4)_2{\cdot}6H_2O$ afforded the corresponding complex $[Cu(L3)](ClO_4)_2{\cdot}H_2O$ (**4**) which was structurally characterized both in solid state and in solution. The crystal structure of **4** consists of a discrete monomeric $[Cu(L3)]^{2+}$ in which the Cu(II) ion is six coordinated with three nitrogen atoms of the macrocycle ring, two of the aminophenyle and one of the pyridine appended functions. The triazacyclonane macrocycle ring is facially coordinated and the *N*-donor atoms of the three pendant groups (two aniline and one pyridine groups), are disposed in the same side of the basal macrocyclic ring, leading to a distorted and elongated CuN_4N_2 octahedron. UV–Vis spectroscopy of complex **4** in acetonitrile displays a d–d transition band at $\lambda = 673$ nm. The voltammetric studies show that the $[Cu(L3)]^{2+}$ cation can be reduced quasi-reversibly and oxidized irreversibly, both process being monoelectronic.

1. Introduction

More and more attentions are being attracted by the research on copper metal complexes due to their implications in many different domains, such as nuclear medicine for imaging diagnosis (PET) and radioimmunotherapy (RIT) [1,2], biochemistry for mimicking active sites of metalloenzymes [3–8], sensing for cation detection [9–12]. These various applications usually necessitate the design and tailoring of ligands which fit at best in the requirements. The polyazacycloalkane ligands such as tacn (1,4,7-triazacyclononane) are very much investigated in these different research fields owing to their ability to form very stable complexes with transition metals cations [13–15] and their possible easy transformation by *C*- or *N*-functionalization of the macrocyclic platform [16,17]. The small azamacrocycle tacn is known for coordinating transition metals as copper (II) in a facial manner, with the cation located above the plane formed by the three nitrogen atoms of the cycle. Additional pendant arms containing donor atoms on the triamine macrocycle complete the coordination sphere of the cation leading to the high stability of the complexes [13–15]. Configurational environment of the ligand around the transition metal ion depends strongly on the geometry and on these pendant arms. Therefore, such *N*-functionalized groups impact on the cation coordination sphere nature and geometry and, then on the complex properties. Among the already described $[CuN_6]$ tacn complexes, two complexes exhibiting five-membered chelate rings, caught our attention regarding the flexibility degree of the triazamacrocyclic coordinating arms. The first one is based on the macrocycle ligand bearing three flexible 2-pyridylmethyl which are linked to the N_3-macrocycle group *via* methylene groups (L1) [18,19]; the second one is based on the macrocycle ligand involving three rigid 2-aminophenyl pendant donor groups, linked to the macrocycle group *via* the aromatic carbon atoms (L2) [20] (Scheme 1).

Herein, we report the synthesis and characterization of the intermediary system based on unsymmetrical 1,4,7-triazacyclononane (L3) and of its Cu(II) complex $[Cu(L3)](ClO_4)_2{\cdot}H_2O$ (**4**), including its spectroscopic and electrochemical properties.

2. Experimental

2.1. Reagents and techniques

Solvents and reagents were obtained from commercial suppliers, and were used without further purification. Starting tacn was

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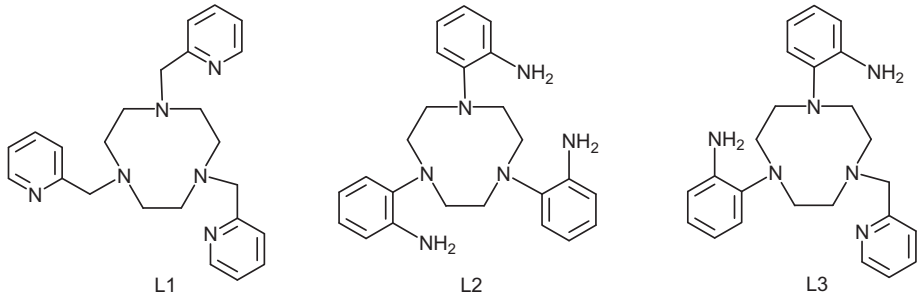

Scheme 1. Ligands discussed in this paper.

purchased from CheMaTech (Dijon, France). Elemental analyses were performed by the "Service Central d'Analyses du CNRS", Gif-sur-Yvette, France. Infrared spectra were recorded in the range 4000–200 cm^{-1} on a FT-IR BRUKER ATR VERTEX70 Spectrometer. Diffraction analyses were performed using an Oxford Diffraction Xcalibur -CCD diffractometer. NMR and MALDI mass spectra were carried out by the "Services communs" of the University of Brest. MALDI mass spectra were recorded with an Autoflex MALDI TOF III LRF200 CID spectrometer. NMR spectra were recorded on a Brucker Avance 400 (400 MHz) or a Bruker AMX-3 300 (300 MHz). UV–Vis–NIR spectroscopy was performed with a JASCO V-670 spectrophotometer with a classical cell holder. The electrochemical studies in acetonitrile were performed in a glovebox (Jacomex) (O_2 <1 ppm, H_2O <1 ppm) with a home-designed 3-electrodes cell (WE: vitreous carbon electrode, RE: Pt wire in a solution of CH_3CN/NBu_4PF_6 containing equimolar amounts of ferrocene and ferrocenium hexafluorophosphate, CE: Pt). Acetonitrile (CH_3CN) (99.9% BDH, VWR) was distilled over CaH_2 and stored after freeze-pumping in the glovebox under argon. NBu_4PF_6 was synthesized from NBu_4OH (Fluka) and HPF_6 (Aldrich). It was then purified, dried under vacuum for 48 h at 100 °C, then kept under N_2 in the glovebox. The potential of the cell was controlled by an AUTOLAB PGSTAT 302 (Ecochemie) potentiostat monitored by a computer. Ferrocene (Fc) was added at the end of each experiment to determine accurate redox potential values.

Cautions! Perchlorate salts of metal complexes are potentially explosive and should be handled with care in small quantities.

2.2. Synthetic procedures

2.2.1. Synthesis of 1,4-bis(2-aminophenyl)-7-(pyridin-2-ylmethyl)-1,4,7-triazacyclononane (**L3**)

*2.2.1.1. Preparation of 10-phenyl-1,4,7-triazabicyclo[5.2.1] decane (**1**).* 5 mmol of 1,4,7-triazacyclononane (645 mg) and benzaldehyde (508 μL, 5 mmol) were stirred at room temperature in distilled ethanol (80 mL) containing molecular sieve for 4 h. The solution was filtered and evaporated under reduced pressure to yield the aminal product as a white solid (980 mg, 4.5 mmol, 90%). NMR ($CDCl_3$) ^1H (300 MHz) 2.89–2.93 (m, 4H,CH_{2tacn}) 2.99–3.03 (m, 2H,CH_{2tacn}) 3.07–3.17 (m, 4H,CH_{2tacn}) 3.32–3.39 (m, 2H,CH_{2tacn}) 5.66 (s, 1H, H_{aminal}) 7.18 (t, 1H, H_{Phe}) 7.29 (t, 2H, H_{Phe}) 7.50 (2H, d, H_{Phe}); ^{13}C (75 MHz) 49.3 49.6 58.8 (CH_{2tacn}) 88.3 (C_{aminal}) 126.6, 126.7 128.2 (CH_{Phe}) 145.8 (C_{Phe}).

*2.2.1.2. Preparation of 1-(pyridin-2-ylmethyl)-1,4,7-triazacyclononane (**2**).* 10-phenyl-1,4,7-triazabicyclo[5.2.1] decane (1) (4.5 mmol, 980 mg) and 575 mg of 2-methylpyridine chloride (4.5 mmol) were stirred with potassium carbonate (3 g, excess) in distilled acetonitrile at room temperature for 4 days. Filtration and solvant elimination gave a brown oily product. After hydrolysis in HCl 1 M (15 mL) at room temperature for 3 h, extraction at pH1 with $CHCl_3$ (2 × 20 mL) allowed to eliminate traces of organic impurities. The aqueous solution was made basic (pH >12) with NaOH pellets and extracted with $CHCl_3$ (3 × 20 mL), dried over $MgSO_4$, filtered and the solvant evaporated to yield the compound (2) as a coloured oil (740 mg, 75%). NMR ($CDCl_3$, 300 MHz) ^1H 2.44–2.45 (m, 8H, CH_{2tacn}) 2.56–2.58 (m, 4H, CH_{2tacn}) 3.11 (bs, 2H, N*H*) 3.65 (s, 2H, CH_{2pyr}) 6.89 (m, 1H, CH_{pyr}) 7.17 (m, 1H, CH_{pyr}) 7.39 (m, 1H, CH_{pyr}) 8.28 (m, 1H, CH_{pyr}); ^{13}C ($CDCl_3$, 75 MHz) 45.9 46.3 52.4 (CH_{2tacn}) 61.6 (CH_{2pyr}) 121.5 122.5 135.9 148.5 (CH_{pyr}) 159.3 (C_{pyr}).

*2.2.1.3. Preparation of 1,4-bis(2-nitrophenyl)-7-(pyridin-2-ylmethyl)-1,4,7-triazacyclononane (**3**).* 1-fluoro-2-nitrobenzene (370 μL, 3.5 mmol) was added to 355 mg of 1-(pyridin-2-ylmethyl)-1,4,7-triazacyclononane (1.6 mmol) and an excess of potassium carbonate (1.10 g, 8.0 mmol (5 eq)) in distilled acetonitrile (20 mL). The reaction mixture was stirred at reflux under nitrogen atmosphere during 12 h. The hot solution was filtrated and the filtrate evaporated under reduced pressure. The residue was purified by silica gel chromatography (Hexane then Hexane/$CHCl_3$:1/1) to yield an orange oil (690 mg, 93%). NMR ($CDCl_3$, 300 MHz) ^1H 2.89 (m, 4H, CH_{2tacn}) 3.35 (m, 4H, CH_{2tacn}) 3.68 (bs, 4H, CH_{2tacn}) 3.77 (s, 2H, CH_{2pyr}) 6.81 (t, 2H, CH_{Phe}) 7.00 (d, 2H, CH_{Phe}) 7.08 (t, 1H, CH_{pyr}) 7.34 (m, 3H, CH_{Phe} + CH_{pyr}) 7.53 (t, 1H, CH_{pyr}) 7.59 (dd, 2H, CH_{Phe}) 8.44 (d, 1H, CH_{pyr}); ^{13}C ($CDCl_3$, 75 MHz) 53.8 54.5 55.1 (CH_{2tacn}) 64.2 (CH_{2pyr}) 118.6 119.4 (CH_{Phe}) 121.9 123.3 (CH_{pyr}) 126.1 132.8 (CH_{Phe}) 136.2 (CH_{pyr})141.1 143.7(*C*) 148.8 (CH_{pyr})159.1(*C*); MALDI-TOF: *m*/*z* 463.2 [M+1$^+$].

2.2.1.4. Preparation of 1,4-bis(2-aminophenyl)-7-(pyridin-2-ylmethyl)-1,4,7-triazacyclononane (L3). 1,4-bis(2-nitrophenyl)-7-(pyridin-2-ylmethyl)-1,4,7-triazacyclononane (325 mg, 0.80 mmol) in absolute ethanol (30 mL) was stirred at reflux under nitrogen atmosphere during 3 days with 10 mL (excess) of hydrazine monohydrate and activated carbon. After cooling, the solution was filtrated and the filtrate was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (20 mL) and $MgSO_4$ was added. After filtration, elimination of the solvent under reduced pressure yielded the product as a brown oil (205 mg, 73%). NMR ($CDCl_3$, 400 MHz) ^1H 2.99–3.02 (m, CH_{2tacn}, 4H) 3.29–3.31 (m, CH_{2tacn}, 4H) 3.35 (s, CH_{2tacn}, 4H) 3.94 (s, CH_{2pyr}, 2H) 6.65–6.72 (m, 4H, CH_{Phe}) 6.89 (t, 2H, CH_{Phe}) 7.07 (d, 2H, CH_{Phe}) 7.18 (t, 1H, CH_{pyr}) 7.46 (d, 1H, CH_{pyr}) 7.67 (t, 1H, CH_{pyr}) 8.56 (d, 1H, CH_{pyr}); ^{13}C ($CDCl_3$, 100 MHz) 55.8 56.0 56.7 (CH_{2tacn}) 64.9 (CH_{2pyr}) 115.4 118.2 (CH_{Phe}) 122.0 (CH_{pyr}) 123.3 (CH_{Phe}) 123.4 (CH_{pyr}) 124.4 (CH_{Phe}) 136.3 (CH_{pyr}) 140.9 142.7 (*C*) 149.1 (CH_{pyr}) 159.4 (*C*); MALDI-TOF: *m*/*z* 403.2 [M+1$^+$].

2.2.2. Synthesis of $[Cu(L3)](ClO_4)_2{\cdot}H_2O$ (**4**) complex

An aqueous solution (5 mL) of L3 (0.05 mmol, 20.13 mg) was added progressively, under continuous stirring, to an aqueous solution (10 mL) of $Cu(ClO_4)_2{\cdot}6H_2O$ (0.05 mmol, 18.53 mg). Slow