

Study of the cyclen derivative 2-[1,4,7,10-tetraazacyclododecan-1-yl]-ethanethiol and its complexation behaviour towards d-transition metal ions

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Abstract

The compound 2-[1,4,7,10-tetraazacyclododecan-1-yl]-ethanethiol (**L2**) has been synthesized and characterized by multinuclear NMR spectroscopy and mass spectrometry. Its thiol-protected precursor **L1** has also been isolated and characterized, including by X-ray structural analysis. The protonation constants of **L2** were determined by potentiometric methods at 25.0 °C and 0.10 mol dm⁻³ KNO₃ ionic strength. ¹³C NMR studies and 2D NMR spectra recorded at different pD values have been used to analyse its protonation scheme. Stability constants of **L2** with Cu²⁺, Zn²⁺ and Cd²⁺ were also determined by potentiometry, and the Zn(II) and Cu(II) complexes were studied in solution by NMR, UV–Vis, and EPR spectroscopies. The pM values (pH 7.4) calculated for the metal complexes of **L2** are higher than the corresponding values found for cyclen and cyclam, but the selectivity of **L2** for Cu²⁺ is low.

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1. Introduction

Copper offers an almost unique combination of radio-nuclides for imaging (^{60–62,64}Cu) and for targeted radio-nuclide therapy (^{64/67}Cu). The ⁶⁴Cu, due to its nuclear properties, is the most versatile of all copper radionuclides, being suitable both for positron emission tomography (PET) imaging (β^+ emission) and for targeted radiotherapy (β^- emission). Moreover, this duality offers the possibility of using PET to quantify *in vivo* the regional distribution of radioactivity, a crucial issue in the assessment of radiation dosimetry when planning targeted radionuclide therapy. Due to the well recognized preference of copper(II) for nitrogen and sulphur donor atoms, most of the studies

in the radiopharmaceutical field have involved open-chain nitrogen and/or sulphur chelators [1,2]. Concerning tetraazamacrocycles, the ones used for labelling peptides or antibodies with ^{64/67}Cu have mainly nitrogen and/or oxygen pendant arms [1,3]. To the best of our knowledge, the number of tetraazamacrocycles bearing thiol and/or thioether groups as pendant arms are scarce and some of them have been synthesized and coupled *in situ* to biologically active molecules, without being isolated and characterized [4,5].

As part of our ongoing research work on the synthesis and characterization of radiocomplexes with biological interest [6], we have synthesized and characterized a mono-*N*-substituted cyclen derivative with a 2-ethanethiol pendant arm, 2-[1,4,7,10-tetraazacyclododecan-1-yl]-ethanethiol (**L2**). This compound, although previously described as useful for site-specific labelling of proteins, has never been isolated in a pure form and/or characterized [4].

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Herein, we report on the synthesis and characterization of **L2**, as well as on its thiol-protected precursor **L1**. Protonation constants of **L2** and its stability constants with Cu^{2+} , Zn^{2+} and Cd^{2+} will also be reported. An analysis of the protonation scheme of **L2** is discussed, as well as the structural environment in solution of Cu(II) and Zn(II) in the complexes with **L2**.

2. Experimental

2.1. Reagents

Chemicals and solvents were of reagent grade and were used without further purification, unless stated otherwise. 1,4,7,10-tetraazacyclododecane (cyclen) was purchased from Strem (New-Buryport, MA, USA). Sodium hydride, triphenylmethane-thiol, tetrahydrofuran, dibromoethane, toluene, sodium hydroxide, methanol, dichloromethane, ammonium, hydrochloric acid, deuterated water and chloroform were obtained from Aldrich Chemical Co. Silica gel 60 (70–230 mesh, pH range = 6.5–7.5) was obtained from Merck.

2.2. Analytical methods

^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded in a Varian Unit Inova-300 spectrometer at a probe temperature of about 20°C. The spectra were performed in CDCl_3 (δ/ppm : ^1H : 7.24; ^{13}C : 77.00) or D_2O versus an external reference of 1,4-dioxane (δ/ppm : ^1H : 3.75; ^{13}C : 69.20). Positive-ion mass spectra were obtained in a Finnigan FT/MS 2001-DT FTICR mass spectrometer by laser desorption ionization. pH measurements were performed in a ORION SA 720. UV–Vis spectra were done in a Cary 500. EPR spectroscopic measurements of the copper complex were recorded with a Bruker ESP 380 spectrometer equipped with continuous-flow cryostats for liquid nitrogen, operating at X-band.

2.3. Synthesis of 2-[1,4,7,10-tetraazacyclododecan-1-yl]-ethanethiol (**L1**)

To a solution of cyclen (285 mg, 1.5 mmol) in hot toluene (50 cm^3) was slowly added bromoethyl tritylthiol [7] (210 mg; 0.5 mmol) dissolved in toluene (50 cm^3). The reaction mixture was refluxed overnight and then a solution of NaOH (20%) added. The organic phase was separated and the solvent evaporated under vacuo. The solid obtained was purified by silica-gel chromatography using as eluent a mixture of $\text{CHCl}_3/\text{MeOH}/\text{aq. NH}_3$ (gradient 100:0:0 \rightarrow 0:100:0 \rightarrow 0:80:20, $R_f = 0.2$ in 80:20 MeOH/aq. NH_3 solution) **L1** (100 mg, 43%); δ_{H} /(300 MHz, CDCl_3): 7.37 (6 H, d, aromatic protons), 7.26–7.14 (9 H, m, aromatic protons), 2.89–2.84 (4 H, m), 2.52–2.48 (8 H, m), 2.36–2.32 (8 H, m); δ_{C} (75.5 MHz, CDCl_3): 144.9 (Ph), 129.6 (Ph), 127.8 (Ph), 126.5 (Ph), 66.8 (SCPh_3), 53.5 ($\text{CH}_2\text{CH}_2\text{SCPh}_3$), 50.80 (C_{ring}), 46.9 (C_{ring}), 46.1 (C_{ring}), 44.9 (C_{ring}), 29.4 ($\text{CH}_2\text{CH}_2\text{SCPh}_3$).

2.4. Synthesis of 2-[1,4,7,10-tetraazacyclododecan-1-yl]-ethanethiol (**L2**)

Compound **L1** was refluxed in 20% HCl, for 2 h. After cooling to room temperature, the resulting solution was washed with dichloromethane, the aqueous extracts separated and vacuum dried yielding a white solid **L2** (75 mg, 80%). δ_{H} (300 MHz, D_2O , pD 1.05): 2.54 (2 H, t, C(1)H); 2.70 (2 H, t, C(2)H); 2.84 (4 H, t, C(3)H); 2.97 (4 H, br m, C(6)H); 3.07 (8 H, br m, C(4)H + C(5)H); δ_{C} (75.5 MHz, $\text{D}_2\text{O}/1,4\text{-dioxane}$, pD 1.05): 56.8 (C2); 50.3 (C3); 45.6 (C4); 44.4 (C6); 43.9 (C5); 22.0 (C1); m/z (LDI): calc. for $[\text{C}_{10}\text{H}_{25}\text{N}_4\text{S}]^+$: 233.179, $[\text{C}_{10}\text{H}_{24}\text{N}_4\text{S}^{23}\text{Na}]^+$: 255.161, $[\text{C}_{10}\text{H}_{25}\text{N}_4\text{S}^{32}\text{K}]^+$: 271.135; found: $[\text{M}+\text{H}]^+$: 233.191, $[\text{M}+\text{Na}]^+$: 255.156, $[\text{M}+\text{K}]^+$: 271.118.

2.5. X-ray crystal analyses

Crystal data for **L1**: $\text{C}_{29}\text{H}_{52}\text{N}_4\text{O}_{10}\text{S}_2$, $M_r = 680.87$, triclinic, space group $P\bar{1}$, $a = 8.1242(1)$, $b = 8.8600(1)$, $c = 27.0151(4)$ Å, $\alpha = 81.8670(10)$, $\beta = 82.1130(10)$, $\gamma = 63.9020(10)^\circ$, $U = 1722.57(4)$ Å³, $Z = 2$, $D_c = 1.313\text{ g cm}^{-3}$, μ (Mo $\text{K}\alpha$) = 1.260 mm^{-1} . Suitable colourless prismatic crystals ($0.40 \times 0.32 \times 0.06\text{ mm}$) were mounted in air on a goniometer head. X-ray diffraction experiments were performed with a Bruker AXS APEX CCD detector diffractometer using graphite monochromated Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073$ Å), at 150 K in the ϕ and ω scans mode. A semi empirical absorption correction was carried out using SADABS [8].

Data collection, cell refinement and data reduction were done with the SMART and SAINT programs [9]. The structures were solved by direct methods using SIR97 [10] and refined by fullmatrix least-squares methods using the program SHELXL97 [11] using the winGX software package [12]. Non-hydrogen atoms were refined with anisotropic thermal parameters. The H atoms of the CH and CH_2 were placed at calculated positions using a riding model, with distances C–H = 0.95 Å (aromatic) and C–H = 0.99 Å (CH_2) and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$ of the parent atom. The H atoms in the water, NH_2 and NH were located in difference Fourier maps and its coordinates and isotropic thermal parameters were refined.

The residual electronic density ranging from 0.393 to -0.392 e \AA^{-3} was within expected values. The final refinement of 472 parameters converged to final R and R_w indices $R_1 = 0.0408$ and $wR_2 = 0.0972$ for 7020 reflections with $I > 2\sigma(I)$. Molecular graphics were prepared using ORTEP 3 [13].

2.6. Potentiometric studies

2.6.1. Reagents and solutions

Metal ion solutions were prepared at about $2.5 \times 10^{-3}\text{ mol dm}^{-3}$ from the nitrate salts of the metals and were titrated using standard methods [14]. Deionized

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