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Synthesis and characterization of a new asymmetric dinucleating ligand and its dinuclear nickel(II) complex with $(\mu$–$\eta^2)_2$ phosphate ester bridge

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Abstract A new asymmetric phenol-based "end-off" dinucleating ligand HL was prepared using a modified methodology through a four-step synthesis. The ligand comprises two different coordination moieties, namely, a rigid 1,4-dimethyl-1,4,7-triazacyclononane unit and a more flexible *N*-(2-pyridyl)methyl-*N*-2-(2-pyridylethyl)amine unit. Its dinuclear Ni(II) complex containing two phosphate esters in a $\mu-\eta^2$ binding mode was synthesized and characterized by X-ray crystallography, in which each nickel atom is six-coordinate and adopts a slightly distorted octahedral coordination geometry.

Introduction

Bimetallic cores exist at the active sites of many metalloenzymes and play an essential role in biological systems [1, 2]. Urease is one such bimetallic hydrolase which hydrolyzes urea to ammonia and carbamate at its di-Ni(II) active site [3]. A previous study of the crystal structure of an urease from *K. Aerogenes* reveals that the two Ni(II) atoms are $\sim$3.5 Å apart and bridged by a bidentate carbamate side chain, having different coordination number and geometry for each nickel atom [3]. This structural asymmetry at the active site is consistent with the different roles played by two metal ions [4]. Interestingly, Ni(II)-substituted phosphotriesterase has higher specific activity than that of the native Zn(II) enzyme, while the Cu(II)-substituted enzyme has similar activity to the native one [5]. Although different coordination environments are found for the two metal centers in many dinuclear metalloenzymes, a large number of the enzyme mimics reported so far are based on symmetric dinucleating ligands [6–13]. These ligands generally result in the formation of dinuclear complexes with identical coordination geometries for the two metal centers. Less attention has been paid to the preparation of asymmetric dinuclear complexes, especially dinickel(II) complexes [14–16]. Synthesis and comparison of asymmetric and symmetric dinuclear enzyme models should provide deeper insight into the structure and mechanism of those enzymes and help to design more effective metalloenzyme models.

In our view, straightforward and flexible synthetic methodology for the preparation of asymmetric dinucleating ligands is highly desirable since these ligands force the two metal atoms in the resulting complex into well-defined and tunable but different chemical and/or coordination environments. This will ultimately result in the formation of more realistic enzyme mimics. In this article, we describe a modified methodology for the synthesis of a new asymmetric phenol-based 'end-off' dinucleating ligand, namely, 4-bromo-2-(1,4-dimethyl-1,4,7-triazacyclononane-7-ylmethyl)-6-{[*N*-(2-pyridyl)methyl-*N*-2-(2-pyridylethyl)amine]-methyl}-phenol (HL) and its dinuclear nickel(II) complex with a $(\mu$–$\eta^2)_2$ phosphate ester bridge.

Experimental

1,4-Dimethyl-1,4,7-triazacyclononane was prepared as described in the literature [17] The other reagents were of analytical grade from commercial sources and were used

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without any further purification. Elemental analysis was performed with a Vario EL-III instrument. The IR spectra were recorded on an Equinox 55 spectrophotometer in the 4,000–400 cm^{-1} region using powdered samples on a KBr plate. Electronic absorption spectra were determined on a CARY 300 Bio UV–Vis spectrophotometer. Mass spectra were measured on a Thermo Finnigan LCQ mass spectrometer.

Warning: Perchlorate salts are dangerous to handle, and only small quantities should be used. We did not encounter any difficulties during this work.

Synthesis of *N*-(2-pyridyl)methyl-*N*-2-(2-pyridylethyl) amine (**I**)

A solution of 2-(2-aminoethyl) pyridine (1.22 g, 10.0 mmol) in methanol (5 mL) was added to a stirred solution of 2-pyridinecarboxaldehyde (1.07 g, 10.0 mmol) in methanol (15 mL). The mixture was stirred at room temperature for 2 h. Sodium borohydride (0.756 g, 20.0 mmol) was then added in batches within 1 h. The reaction mixture was stirred overnight and then refluxed for 1 h. After cooling to room temperature, the solution was treated with hydrochloric acid (3 mL, 12 M) and vigorously stirred for 30 min. The mixture was adjusted to pH 8–9 with 5 M sodium hydroxide solution. Precipitated sodium borate was filtered off, and the solvent was distilled under reduced pressure. The residue was suspended in water (20 mL) and extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate. Evaporation of the solvent gave the product as a light yellow oil with 85% yield. ^{1}H-NMR ($CDCl_3$): $\delta = 8.52$, 2H; 7.60, 2H; 7.28, 1H; 7.16, 1H; 7.08, 2H; 3.95, 2H; 3.00–3.05, 4H; 2.25, 1H. MS (FAB, m/z): M + 1 = 214.

Synthesis of 5-bromo-2-hydroxy-3-(1,4-dimethyl-1,4,7-triazacyclononane-7-ylmethyl)-benzaldehyde **(II)**

A solution of paraformaldehyde (0.72 g, 24 mmol) in ethanol (5 mL) was added to a stirred solution of 1,4-dimethyl-1,4,7-triazacyclononane (3.14 g, 20 mmol) in ethanol (10 mL). The mixture was heated to 80 °C for 1 h and then 5-bromo-2-hydroxy-benzaldehyde (4.03 g, 20 mmol) in ethanol (40 mL) was added. The resulting solution was refluxed for 72 h under argon. Evaporation of the solvent gave an oily residue that was suspended in aqueous Na_2CO_3 (30 mL, 5%) and extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a yellow oil that was purified by column chromatography on silica gel (CH_2Cl/MeOH/Et_3N, 50/10/1, followed by MeOH/Et_3N, 10/1) to afford **II** (2.2 g, 30% yield) as a yellow oil. ^{1}H-NMR ($CDCl_3$): $\delta = 10.22$, 1H; 7.72, 1H; 7.41, 1H; 3.83, 2H; 2.83–2.94, 12H; 2.40, 6H. MS (FAB, m/z): M + 1 = 371.

Synthesis of 4-bromo-2-hydroxymethyl-6-(1,4-dimethyl-1,4,7-triazacyclononane-7-ylmethyl)-phenol (**III**)

Sodium borohydride (1.48 g, 39 mmol) was added in batches to a stirred solution of **II** (4.8 g, 13 mmol) in methanol (30 mL) within 1 h. The resulting solution was stirred overnight at room temperature and then refluxed for 1 h. After cooling to room temperature, the solution was treated with hydrochloric acid (12 M, 8 mL) and vigorously stirred for 30 min. The solution was adjusted to pH 8–9 with sodium hydroxide solution (5 M). Precipitated sodium borate was filtered off, and the solvent was distilled under reduced pressure. The residue was suspended in water (40 mL) and extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the product **III** as a light orange solid (4.5 g, 93% yield). ^{1}H-NMR ($CDCl_3$): $\delta = 7.06$, 1H; 7.02, 1H; 4.84, 2H; 3.96, 2H; 2.64-2.94, 12H; 2.42, 6H. MS (FAB, m/z): M + 1 = 373.

Synthesis of 4-bromo-2-chloromethyl-6-(1,4-dimethyl-1,4,7-triazacyclononane-7-ylmethyl)-phenol (**IV**)

Freshly distilled thionyl chloride (15 mL) was added dropwise to **III** (2.24 g, 6 mmol) at 0 °C. The solution was stirred at room temperature for 3 h. Thionyl chloride was then distilled out under reduced pressure at 30–40 °C, and the product **IV** was washed several times with hexane and dichloromethane (yield ca. 100%).

Synthesis of HL

The above product **IV** (6.0 mmol) was suspended in dried acetonitrile (40 mL). The flask was cooled to −40 °C in a liquid N_2–acetone cold trap and Et_3N (4.2 mL) was added dropwise with stirring. A solution of **I** (1.28 g, 6.0 mmol) and of Et_3N (2.5 mL) in dried acetonitrile (20 mL) was then added dropwise. The resulting solution was stirred for 24 h at room temperature and then for 48 h at 30–40 °C. After cooling in an ice-water bath, the resulting white precipitate was filtered off. Evaporation of the solvent produced an orange oil that was suspended in aqueous Na_2CO_3 (30 mL, 3%, pH ~9.0) and extracted with dichloromethane. The organic phase was dried over Na_2SO_4. Evaporation of the solvent gave the product as an orange oil that was purified by silica gel column chromatography (eluting with 10:1 (v/v) MeOH–Et_3N), gave pure HL as an orange oil. Yield: 1.4 g (42%). ^{1}H-NMR

(CD_2Cl_2): $\delta = 8.43$, 2H; 7.52, 2H; 7.22, 2H; 7.02–7.08, 4H; 3.78, 2H; 3.68, 4H; 2.78–2.96, 8H; 2.55–2.61, 8H; 2.29, 6H. IR (KBr, cm^{-1}): 3,438 (w), 2,934 (w), 2,802 (w), 1,590 (w), 1,456 (m), 1,439 (m), 1,370 (w), 1,215 (w), 1,119 (w), 755 (w). MS (FAB, m/z): M + 1 = 568.

Synthesis of $[Ni_2L(\mu\text{-BPP})_2]BPh_4$

A solution of nickel perchlorate (0.073 g, 0.2 mmol) and sodium biphenyl phosphate (NaBPP) (0.054 g, 0.2 mmol) in water (2 mL) was added to a solution of HL (0.057 g, 0.1 mmol) in ethanol (2 mL). The reaction mixture was then stirred for 1 h at 25 °C. A green precipitate was afforded after adding a solution of $NaBPh_4$ (0.068 g, 2 mmol) in ethanol (1 mL). The crude product was collected by filtration and then washed with water and ethanol. Green block-shaped crystals suitable for single crystal X-ray study were obtained by recrystallization from 1:2 (v/v) MeCN–EtOH solution (4 mL) with a yield of 52%. Elemental analysis for $C_{77}H_{72}BBrN_6Ni_2O_9P_2$: found (calcd. %): C, 62.19 (61.83); H, 5.23 (4.81); N, 5.45 (5.62). IR (KBr, cm^{-1}): 3,062 (w), 1,605 (m), 1,592 (m), 1,489 (s), 1,458 (m), 1,446 (m), 1,233 (s), 1,205 (s), 1,115 (s), 1,067 (s), 785 (m), 756 (m), 622 (m), 544 (m), 516 (m).

Crystal structure analysis

A single green crystal of the complex with dimensions 0.20 mm × 0.30 mm × 0.15 mm was attached to a glass fiber and mounted on a Rigaku R-AXIS SPIDER X-ray diffractometer with graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) at 293 K. The structure was solved by direct methods and refined on F^2 by full-matrix least squares technique with SHELXTL-97 [18]. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms of the ligands were located and included at their calculated positions. Crystal data: $C_{77}H_{72}BBrN_6Ni_2O_9P_2$, $M = 1501.53$, orthorhombic, space group $Pna2_1$, $a = 23.937$ (5), $b = 24.913$ (5), $c = 11.788$ (2) Å, $\alpha = \beta = \gamma = 90°$, $V = 7{,}030$ (2) $Å^3$, $D_c = 1.419$ g cm^{-3}, $\mu = 1.213$ mm^{-1}, Z = 4, MoKα radiation, $\lambda = 0.71{,}073$ Å, T = 293 K, Final R indices [I > 2sigma(I)]: $R_1 = 0.0405$, $wR_2 = 0.0898$, R indices (all data): $R_1 = 0.0635$, $wR_2 = 0.1028$, GOF = 1.046 for 12,363 unique reflections and 871 parameters. Selected bond distances and bond angles are given in Table 1.

Table 1 Selected bond distances (Å) and angles (°) for complex $[Ni_2L(\mu\text{-BPP})_2]BPh_4$

Ni(1)–O(1)	2.089(3)	Ni(2)–O(1)	2.151(2)
Ni(1)–N(1)	2.114(4)	Ni(2)–N(4)	2.102(4)
Ni(1)–N(2)	2.095(3)	Ni(2)–N(5)	2.093(4)
Ni(1)–N(3)	2.153(3)	Ni(2)–N(6)	2.149(3)
Ni(1)–O(2)	2.073(3)	Ni(2)–O(3)	2.029(3)
Ni(1)–O(6)	2.083(3)	Ni(2)–O(7)	2.044(3)
Ni(1)–Ni(2)	3.816		
O(2)–P(2)–O(3)	121.2(2)	O(6)–P(1)–O(7)	121.0(2)
O(4)–P(2)–O(5)	103.6(2)	O(8)–P(1)–O(9)	103.4(2)
Ni(1)–O(1)–Ni(2)	128.2(1)		

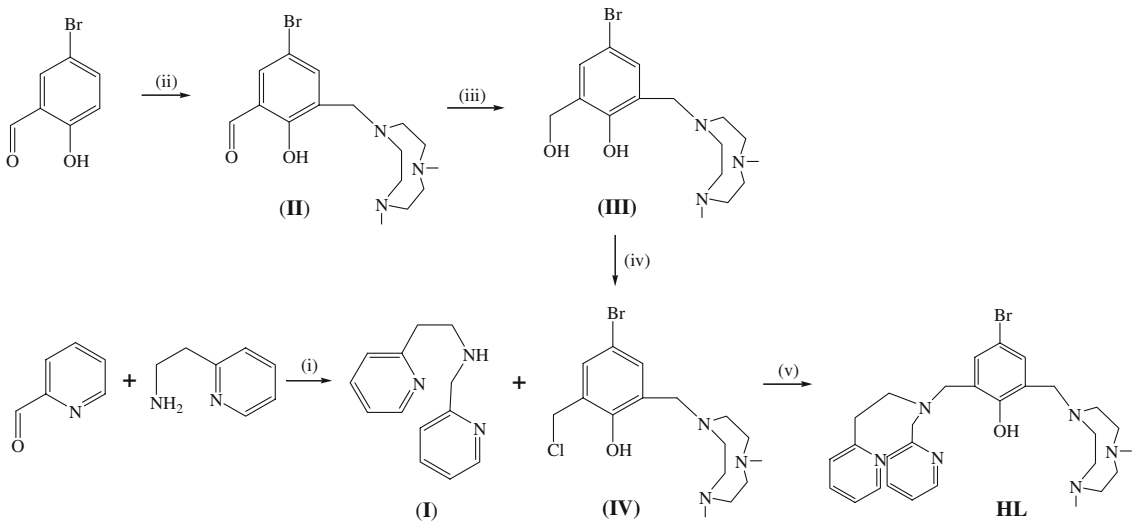
Results and discussion

The synthetic route to HL is illustrated in Scheme 1, which is modified on the basis of the reaction procedures reported previously [19, 20]. HL was obtained as an orange oil via four-step synthesis from 5-bromosalicyladehyde and two different synthetically easily accessible secondary amines (1,4-dimethyl-1,4,7-triazacyclononane and *N*-(2-pyridyl)-methyl-*N*-2-(2-pyridylethyl)amine). The first key step in the preparation was accomplished by an aromatic Mannich reaction, introducing a secondary amine group into position 3 of 5-bromosalicyladehyde. Next, $NaBH_4$ was used to reduce the aldehyde to a hydroxymethyl group, which was then converted into a chloromethyl group using $SOCl_2$. This allowed the subsequent alkylation with a second amine that was different from the first one. This four-step synthesis affords the desired ligand in gram quantities with an overall yield of ca. 35%. By this means, many similar asymmetric ligands that are chemically distinct on both sides of the phenolic ring moiety can be created. Previously, Gahan et al. [21] and Neves et al. [22] prepared analogous asymmetric ligands by a statistical synthesis from 2,6-bis(chloromethyl)-4-methylphenol.

Characterization of $[Ni_2L(\mu\text{-BPP})_2]BPh_4$

The IR spectrum of the complex $[Ni_2L(\mu\text{-BPP})_2]BPh_4$ displays characteristic sharp bands at 1,233, 1,205 and 1,115 cm^{-1}, assigned the symmetric and asymmetric vibrations of BPP bridges [23], which is confirmed by the X-ray crystal structure (see below). There are three bands in the electronic absorption spectrum of the complex in acetonitrile, with peak positions at 535, 710 and 859 nm, which are attributed to the d–d transitions of $3A_{2g} \rightarrow 3T_{1g}(p)$, $3A_{2g} \rightarrow 3T_{1g}$ and $3A_{2g} \rightarrow 3T_{2g}$ of Ni(II) ion in octahedral field [24], respectively.

The X-ray crystal structure of $[Ni_2L(\mu\text{-BPP})_2]BPh_4$ (Fig. 1) shows that the two nickel atoms are bridged by an endogenous cresolic oxygen atom from L and two exogenous phosphate ester groups from the anionic BPP ligand in syn–syn mode. Each nickel atom is six-coordinate and adopts a slightly distorted octahedral coordination geometry. Around atom Ni(1), the N_3O_3 donor set is comprised of a bridging cresolic-O, two bridging phosphodiester-O and



Scheme 1 Reagents and conditions: (i) $NaBH_4$ (2 equiv.) reflux, (ii) 1,4-dimethyl-1,4,7-triazacyclononane (1 equiv.), $(CH_2O)_n$ (1 equiv.), EtOH, 24 h, reflux, (iii) $NaBH_4$ (3 equiv.), 1 h, reflux, (iv) $SOCl_2$, 3 h and (v) Et_3N (5 equiv.), MeCN, 25 °C, 48 h

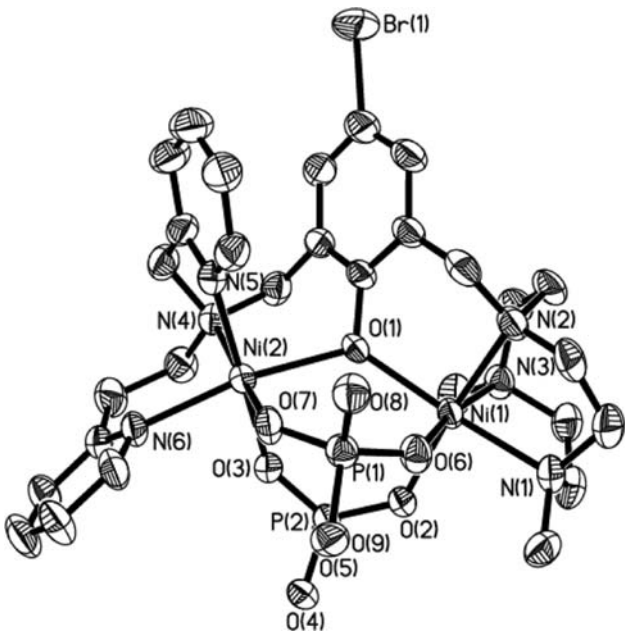


Fig. 1 Cationic structure of complex $[Ni_2L(\mu\text{-BPP})_2]BPh_4$. The four benzyl rings on BPPs and all hydrogen atoms are omitted for clarity. Thermal ellipsoids are at 30% probability

three tertiary amine-N atoms, while in other pendant, the Ni(2) atom is coordinated by a tertiary amine-N, two bridging phosphodiester-O and two pyridyl-N atoms. The average Ni(1)–N and Ni(2)–N distances are 2.121 and 2.115 Å, respectively, which are similar to those previously reported in other Ni(II) complexes with macrocyclic triamine [25] and multipyridine ligands [26–28]. The bond length of Ni(1)–O(1) (2.089 Å) is obviously shorter than that of Ni(2)–O(1) (2.151 Å), presumably because the coordination ability and geometrical rigidity of the macrocyclic pendant are stronger than those of the bipyridyl pendant. Furthermore, different coordination features can also be revealed by the different distances of the P–O bonds bounded to the two nickel atoms. The intra-ring O(2)–P(2)–O(3) and O(6)–P(1)–O(7) angles are expanded by ca. 10° from the ideal value of 109.5°, to 121.2(2)° and 121.0(2)°, respectively, whereas the other angles around the two phosphorus atoms only deviate slightly from tetrahedral. The distortion around the phosphoryl center appears to derive from the bridging bidentate coordination mode to the two nickel atoms. Similar expansion has been already found in other dimetallic complexes containing μ–η^2 phosphate esters [27, 28]. The distance between the two nickel atoms is 3.816 Å, longer than that in a previously reported di-Ni(II) complex with alkoxide and one BPP bridges [27], but slightly shorter than that of a di-Ni(II) complex that possesses two phosphate esters in a $(\mu$–$\eta^2)_2$ binding mode with no additional ligand between the two metals [28]. The appropriate intermetallic separation can facilitate the cooperative action for the phosphate bridging, reminiscent of substrate activation by the metal centers in dinuclear metallohydrolases [1].

In conclusion, we have developed a convenient and versatile procedure to synthesize a new asymmetric phenol-based "end-off" dinucleating ligand. In the dinickel(II) complex, the ligand forces the two metal ions into proximity with different chemical environments, as in related natural dinuclear metalloenzymes.

Supplementary data

CCDC reference number is 739403. See http://www.ccdc.cam.au.uk or email: deposite@ccdc.cam.au.uk for crystallographic file in CIF or other electronic format.

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