Received: 19 October 2011

(wileyonlinelibrary.com) DOI 10.1002/aoc.2839

Revised: 8 February 2012

Accepted: 19 February 2012

Published online in Wiley Online Library

Syntheses, structures of *N*-(substituted)-2-aza-[3]-ferrocenophanes and their application as redox sensor for Cu²⁺ ion

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Rigid *N*-(substituted)-2-aza-[3]-ferrocenophanes L1 and L2 were easily synthesized from 1,1 -dicarboxyaldehydeferrocene and the corresponding amines. Ligands L1 and L2 were characterized by ¹H NMR, ¹³C NMR and single-crystal X-ray crystallography. The coordination abilities of L1 and L2 with metal ions such as Cu²⁺, Mg²⁺, Ni²⁺, Zn²⁺, Pb²⁺ and Cd²⁺ were evaluated by cyclic voltammetry. The electrochemical shift ($\Delta E_{1/2}$) of 125 mV was observed in the presence of Cu²⁺ ion, while no significant shift of the Fc/Fc + couple was observed when Mg²⁺, Ni²⁺, Zn²⁺, Pb²⁺, Cd²⁺ metal ions were added to the solution of L1 in the mixture of MeOH and H₂O. Moreover, the extent of the anodic shift of redox potentials was approximately equal to that induced by Cu²⁺ alone when a mixture of Cu²⁺, Mg²⁺, Ni²⁺, Zn²⁺, Pb²⁺ and Cd²⁺ was added to a solution of L1. Ligand L1 was proved to selectively sense Cu²⁺ in the presence of large, excessive first-row transition and late-transition metal cations. The coordination model was proposed from the results of controlled experiments and quantum calculations. Copyright © 2012 John Wiley & Sons, Ltd. *Supporting information may be found in the online version of this article*.

Keywords: redox sensor; ferrocenophane; Cu²⁺

Introduction

Owing to potential applications in the analytical and environmental areas, recent attention has been focused on the molecular sensor, which is a rapidly growing research field of supramolecular science.^[1] The development of molecular sensors for metal ions, especially for cations with biological interest, has always been of particular interest.^[2] The Cu²⁺ ion is third in abundance (after Fe²⁺ and Zn²⁺) amongst the essential heavy metal ions in the human body and plays a pivotal role in a variety of fundamental physiological processes in organisms ranging from bacteria to mammals.^[3] On the other hand, Cu²⁺ can be toxic to biological systems. Alterations in its cellular homeostasis are connected to serious neurodegenerative diseases, including Menkes and Wilson diseases,^[4] familial amyotropic lateral sclerosis,^[5] Alzheimer's disease^[6] and prion diseases.^[7] Thus copper, on one hand, is important for life but, on the other hand, is highly toxic to organisms. For these reasons, the past few years have witnessed a number of reports on the design and synthesis of chemical sensors^[8] for the detection of copper ion. However, the low sensitivity and high order of interference by chemical closely related metal ions have necessitated the development of a new, highly selective and sensitive Cu^{2+} sensor.

Electrochemical sensors based on optical signal measurement represent advanced techniques in analytical chemistry because they can be miniaturized and manufactured to monitor our environmental samples quickly and economically, especially heavy metal ions *in situ*.^[9] The cyclopentadienyl (Cp) complex of ferrocene is easily modified and the electrochemical properties of the Fe(II)Cp₂ fragment can be tuned by selecting the substituents introduced to the Cp ligand.^[10] Ferrocene-containing

cryptands have attracted considerable attention in the last decades because of their potential applications in the field of redox sensors. Among these, ferrocenophane, with a rigid bridge containing nitrogen atom, showed remarkably selective cationsensing properties.^[11] However, compared to those macromolecules functionalized by ferrocene,^[12–15] the number of known examples of nitrogen-containing rigid macrocycles with bridged ferrocene units is limited, partly because of the lack of general preparation methods of the compounds and low yields.^[11,16–19]. Here we report a feasible method to synthesize compounds **L1** and **L2** (Scheme 1), and investigate their coordination behaviour with transition metal ions and alkaline earth metal ions, such as Cu²⁺, Mg²⁺, Ni²⁺, Zn²⁺, Pb²⁺ and Cd²⁺, by cyclic voltammetry. The coordination model of Cu²⁺ with **L1** was proposed with the aid of controlled experiments and quantum calculations.

Experimental

Silica gel was purchased from Qing Dao Hai Yang Chemical Industry Co. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DPX-400

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Scheme 1. Synthesis of Ligands L1 and L2

spectrometer. Mass spectra were obtained on a Waters Q-Tof MicroTM spectrometer. IR spectra were recorded on a Bruker VECTOR 22 spectrometer. Element analyses were obtained on a Carlo Erba 1160 element spectrometer. Melting points (uncorrected) were measured on an XT5 micro-melting point apparatus.

All reactions were carried out under nitrogen atmosphere. Solvents were dried and freshly distilled prior to use. All the chemicals were used as supplied, without further purification, except for 1,1 -dicarboxyaldehydeferrocene, which was prepared from ferrocene according to the literature, slightly modified.^[20]

Synthesis of L1 and L2

1,1 -Dicarboxyaldehydeferrocene (242 mg, 1.0 mmol) and 2picolylamine (109 mg, 1.01 mmol for L1; benzylamine, 108 mg, 1.01 mmol for L2) in 250 ml DCE (dichloroethane) were added simultaneously over 8 h to one four-necked 1-liter flask charged with a solution of NaBH(OAc)₃ (1.06 g, 5.0 mmol) in DCE (50 ml). The mixture was stirred under N₂ atmosphere overnight at room temperature. The reaction was monitored by thin-layer chromatography until 1,1 -dicarboxyaldehydeferrocene disappeared and quenched by saturated NaHCO₃ solution. The solvent was concentrated under vacuum to approximately 50 ml. The mixture was then extracted with CH_2Cl_2 (3 \times 20 ml). The organic extracts were combined, dried over Na₂SO₄ and evaporated to dryness. The oily residue was purified by column chromatography on silica gel under reduced pressure using hexane-acetic ether (3:1) as eluent to give the pure compounds L1 and L2 (128.2 mg for L1, 40.3% yield and 125.1 mg for L2, 39.5% yield) as a yellow solid.

- **L1** IR (KBr pellet): 3085, 3005, 2925, 2861, 2813, 1589, 1469, 1358, 1116, 1040, 756 cm⁻¹; ¹H NMR (CDCl₃) ppm: δ 4.10 (s, 4H, Cp&bond;*H*), 4.14 (s, 4H,Cp&bond;*H*), 2.96 (s, 4H, *CH*₂Cp), 4.02 (s, 2H, *CH*₂py), 7.20 (like td, *J*=7.3 Hz, 4.8 Hz, 1.5Hz, 1H, *Py*&bond;*H*5), 7.66 (like dd, *J*=7.9 Hz, 1.5Hz, 1H, *Py*&bond;*H*3), 7.74 (like td, *J*=7.9 Hz, 7.3 Hz, 0.9Hz, 1H, *Py*&bond;*H*4), 8.57 (like dd, *J*=4.8 Hz, 0.9Hz, 1H, *Py*&bond;*H*6). ¹³C NMR (CDCl₃) ppm: ¹³C NMR (CDCl₃) ppm: 160.8 (*Py*&bond; *C1*), 149.1 (*Py*&bond;*C5*), 136.4 (*Py*&bond;*C3*), 123.4 (*Py*&bond;*C*), 121.8 (*Py*&bond;*C4*), 83.6, 69.8, 69.1 (*Cp*&bond;*C*), 63.6 (*CH*₂Py), 52.8 (*CH*₂Cp). Anal. Found: C, 67.95%; H,5.70%; N, 8.80%. Calcd. for C₁₈H₁₈FeN₂: C, 67.66%; H, 5.59%; N, 8.62%. HRMS (ESI). Calcd for C₁₈H₁₈FeN₂ ([M + H]⁺): 319.0898. Found: 319.0951.
- **L2** IR(KBr): 3085, 3005, 2925, 2861, 2813, 1589, 1469, 1428, 1358, 1116, 1040, 756 cm⁻¹; ¹H NMR(CDCl₃) ppm: δ 4.08

(s, 4H, Cp&bond;*H*), 4.12 (s, 4H, Cp&bond;*H*), 2.90 (s, 4H, *CH*₂Cp), 3.87 (s, 2H, *CH*₂ph), 7.35 (dd, *J* = 7.3 Hz, 7.4 Hz, 2H, *phenyl-H3*), 7.44 (d, *J* = 7.4 Hz, 2H, *phenyl-H2*), 7.28 (t, *J* = 7.3 Hz, 1H, *phenyl-H4*). ¹³C NMR (CDCl₃): 139.5 (*phenyl-C1*), 129.2 (*phenyl-C2*), 128.7 (*phenyl-C3*), 126.6 (*phenyl-C4*), 84.2, 69.9, 68.5 (*Cp-C*), 61.6 (*CH*₂ph), 51.3 (*CH*₂Cp). Anal. Found: C, 72.11%; H, 6.12%; N, 4.50%. Calcd. for C₁₉H₁₉FeN: C, 71.94%; H, 6.04%; N, 4.42%. HRMS (ESI). Calcd for C₁₉H₁₉FeN ([M + H]⁺): 318.0946. Found: 318.0942.

Electrochemistry

Electrochemical experiments were carried out with a CHI 650A electrochemical analyzer connected to the data acquisition software used for the electrochemical measurements. Cyclic voltammetry experiments were performed in a glass cell enclosed in a Faraday cage, at room temperature under argon. The reference electrode was a 232 model saturated calomel electrode (SCE). The auxiliary electrode was a 7.5 cm platinum wire with a gold-plated connector. The working electrode was a glassy carbon electrode for L1 and platinum electrode for L2. The supporting electrolyte was CH₃OH and H₂O containing 0.1 M KNO₃ for L1 and CH₃OH containing 0.1 M tetrabutylammonium nitrate (ⁿBu₄NO₃) for L2. Between each CV scan the working electrode was electro-cleaned by multicycle scanning in the supporting electrolyte solution, polished on alumina 0.3 µm, cleaned with water-methanol and sonicated before use, according to standard procedures. Solutions of L1 (concentration: 1.0×10^{-3} mol dm $^{-3}$; KNO3: 0.1 mol dm $^{-3}$) and L2 (concentration: 1.0×10^{-3} mol dm⁻³, ⁿBu₄NNO₃: 0.1 mol dm⁻³) were prepared. All the transition metal ions and alkaline earth metal ions (Cu²⁺, Mg²⁺, Ni²⁺, Zn²⁺, Pb²⁺, Cd²⁺) were from their corresponding nitrate, and their concentration in 0.1 mol dm^{-3} KNO₃ for L1 and 0.1 mol dm^{-3} ⁿBu₄NNO₃ for L2 were confirmed exactly by titration experiment. All the CV experiments for the metal complexes were performed immediately after solution preparation. The scan rate was 50 mV s^{-1} .

Crystal Structure Determination

All the measurements were made on a RAXIS-IV imaging plate area detector with graphite monochromated Mo-K α radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods and expanded using Fourier techniques and refined by full-matrix least-squares methods. All calculations were performed using the ShelxI-97 crystallographic software package.^[21]

Yellow single crystals of **L1** and **L2** were developed from the mixture of dichloromethane and hexane. **L1**: $C_{18}H_{18}FeN_2$, $M_r = 318.19$, triclinic, space group. a = 6.4670(13) Å, b = 10.267(2)Å, c = 11.232(2) Å, $\alpha = 94.64(3)^\circ$, $\beta = 98.91(3)^\circ$, $\gamma = 93.80(3)^\circ$, V=732.0(3) Å³, Z=2, D=1.444 g cm⁻³, μ(MoKα) = 1.024 mm⁻¹, F(000) = 332. **L2**: C₁₉H₁₉FeN, M_r = 317.20, triclinic, space group. a = 6.1380(12) Å, b = 11.262(2) Å, c = 11.564(2) Å, α = 94.94(3)°, β = 101.86(3)°, γ = 104.38(3)°, V = 749.8(3) Å³, Z=2, D = 1.405 g cm⁻³, μ(MoKα) = 0.998 mm⁻¹, F(000) = 332.

Computational Details

The structures of ligand **L1** coordinated with different metal ions $([\mathbf{ML1}]^{2+} (\mathbf{M} = Mg, Ni, Pb, Cd, Zn, Cu))$ were fully optimized at the B3LYP/Genecp level of theory.^[22] The 6-31G (d, p) basis set was employed for C, H, O, N atom, while the LanL2DZ basis set with relativistic effective core potentials was used for the remaining metal atoms. The model systems chosen for the computational studies were $[(\eta^5-C_5H_4)Fe(\eta^5-C_5H_4)-(CH_2)_2N-R]$ [R = pyridine and phenyl]. All the calculations were performed using Gaussian 03 suite of programs.^[23]

Results and Discussion

Synthesis of L1 and L2

The ligands **L1** and **L2** were prepared by the condensation reaction of 1,1 -dicarbaldehydeferrocene with 2-picolylamine and benzylamine, respectively, in DCE under highly dilute conditions and sequent reduction by NaBH(OAc)₃. The reaction was monitored by thin-layer chromatography until no 1,1 - dicarbaldehydeferrocene was detected. The pure desired compounds were obtained in 40.3% yield for **L1** and 39.5% yield for **L2** as a light-yellow solid. **L1** and **L2** were characterized by NMR, IR, MS, HRMS (ESI) and X-crystal diffraction analysis. Both ligands were stable in the air and soluble in common solvents, such as DCM (dichloromethane), acetone and ethyl acetate, and less soluble in methanol and ethanol.

X-Ray Crystal Structure Analyses of L1 and L2

The molecular structures of **L1** and **L2** were determined by single-crystal X-ray diffraction. Suitable single crystals for X-ray diffraction analysis were obtained by slow evaporation from dichloromethane/hexane at room temperature. Perspective views of their molecular structures are shown in Figs 1 and 2, respectively.



Figure 1. Crystal structure of compound **L1**. Selected bond lengths (Å) for **L1**: N(1)–C(12) 1.468(4); N(1)–C(13) 1.471(4); N(1)–C(6) 1.475(4); C (11)–C(12) 1.499(5); C(13)–C(14) 1.525(5); C(5)–C(6) 1.510(5); selected bond angle (°) for **L1** C(12)–N(1)–C(13) 109.2(3); C(12)–N(1)–C(6) 112.0 (3); C(13)–N(1)–C(6) 109.4(3); N(1)–C(12)–C(11) 113.6(3); N(1)–C(13)–C(14) 112.6(3); N(2)–C(14)–C(15) 123.1(4); N(2)–C(14)–C(13) 114.9(4)



Figure 2. Crystal structure of compound **L2**. Selected bond lengths (Å) for **L2**: N(1)–C(12) 1.471(3); N(1)–C(13) 1.471(3); N(1)–C(6) 1.477(3); C(11)–C(12) 1.503(3); C(13)–C(14) 1.517; C(5)–C(6) 1.504(3); selected bond angle(°) for **L2**: C(5)–Fe(1)–C(2) 69.54(10); C(11)–Fe(1)–C(2) 154.39(10); C(1)–Fe(1)–C(2) 40.73(10); C(12)–N(1)–C(13) 109.95(18); C(12)–N(1)–C(6) 112.30(18); C(13)–N(1)–C(6) 110.04(18); N(1)–C(12)–C(11) 113.30(18); N(1)–C(13)–C(14) 113.19(19)

The cyclopentadienyl rings in both ligands were in the eclipsed conformation similar to the structure of the previously reported [3]ferrocenophanes.^[24-27] Two cyclopentadienyl rings (Cp) of ferrocene were not parallel and formed dihedral angels of 12.9 $^\circ$ and 12.1° for L1 and L2, respectively. Moreover, the two Cp rings in both L1 and L2 were arranged in nearly eclipsed form. The chelate cycle C5-C6-C11-C12-Fe1 in molecule L1 is nearly planar, with the largest distance deviation 0.7598 Å of N1 and C5, C6, C11, C12 and Fe1 atoms forming a chelate cycle with the largest distance deviation 0.7289 Å of N1 in L2. The distances of N1-C12, N1-C13, N1-C6 were 1.468(4), 1.471(4), 1.475(4) Å in L1 and 1.471(3), 1.471(3), 1.477(3) Å in L2, respectively. These are normal, as the C-N distances of neutral compounds. The bond angles are 109.2(3)-112.0(3) in L1 and the corresponding angles of C-N1-C in L2 are 109.95(18)-112.30(18), which is slightly larger than those of N-methylated N-hexyl-aza[3]ferrocenophanes (103 (1)-114(1)) [24b,24c].

Electrochemical Studies

Electrochemical experiments are necessary to test new redoxresponsive molecules. Therefore, cyclic voltammetry experiments of **L1** alone and in the presence of several cations were performed in a mixture of CH₃OH and H₂O. The ligand **L1** exhibited a reversible one-electron redox wave with a half potential ($\Delta E_{1/2}$) of +343 mV vs. Hg/HgCl₂ corresponding to the ferrocene–ferrocenium couple. Addition of 0.5 equiv. of Cu²⁺ resulted in two reversible one-electron redox waves, which were assigned as redox wave of parent ligand **L1** and complex of copper with ligand in the anodic region ($\Delta E_{1/2}$ +468 mV). The Fc/Fc⁺ couple of the parent ligand disappeared when 1.0 equiv. of Cu²⁺ was added (Fig. 3). Increasing amounts of Cu²⁺ up to 3.0 equiv. and prolonging the reaction time (3 days) did not cause an obvious shift, which implied that **L1** formed a stable mononuclear complex with Cu²⁺ (L:M = 1:1).

Upon addition of metal ions Mg^{2+} , Ni^{2+} , Zn^{2+} , Pb^{2+} , Cd^{2+} to the solution of **L1**, no significant shift of the redox potential of the Fc/Fc⁺ couple was observed (supporting information, Figs SI 1–5), which suggested that **L1** did not have any interaction with these metal ions. When a mixture of 1 equiv. Cu^{2+} , Mg^{2+} , Ni^{2+} , Zn^{2+} , Pb^{2+} and Cd^{2+} was added to the solution of **L1**, the



Figure 3. Cyclic voltammograms of **L1** and its complexes with different amounts of Cu^{2+} ions in 0.1 \mbox{M} KNO₃ solution. Scan rate 50 mV s⁻¹. Blue line, **L1** only; red line, 0.5 equiv. Cu^{2+} with **L1**; green line, 1.0 equiv Cu^{2+} ; violet line, 1.5 equiv. Cu^{2+} ; orange line, 2.0 equiv. Cu^{2+} ; black line, 3.0 equiv. Cu^{2+}

extent of the anodic shift of redox potentials were approximately equal to that induced by Cu^{2+} alone. These results indicated that ligand **L1** selectively sense Cu^{2+} ion and preferentially coordinated with Cu^{2+} without interference by chemically closely related metal ions. Therefore, **L1** could be a good candidate for a molecular sensor to detect copper electrochemically in the presence of large excesses of these first-row transition and posttransition metal cations. The results were unexpected, because the coordination behaviour of aza-ligand with Ni²⁺, Zn²⁺, Pb²⁺, Cd²⁺ is normally similar to that of Cu²⁺. We suspected that the Cu²⁺ may be located in the ferrocenophane cage and only coordinated with one nitrogen atom in the ferrocenophane chain (Fig. 4, Model 1). Perhaps the size of the cage and radius of Cu²⁺ ion match each other very well.

To compare with **L1** and test our hypothesis, ferrocenophane **L2** was synthesized by the same procedure. The electrochemical properties were studied by cycle voltammetry. No significant shift of the redox potential of the Fc/Fc⁺ couple was observed when Cu^{2+} ion was added. The results indicate that **L1** did not take the coordination Model 1 with Cu^{2+} ion, but Model 2, which means that Cu atom was coordinated by two nitrogen atoms in **L1**.

Calculation Binding Energies

Unfortunately, we failed to obtain a single crystal of Cu complex with **L1**. To clarify why ligand **L1** selectively sensed Cu ion in the presence of other chemically closely related metal ions, we applied computational studies. Quantum calculations based on



Figure 4. Proposed coordination model of ligand L1 with Cu²⁺

Table 1. Energy and relative excess energy (kcal mol^{-1}) of [**ML1**]²⁺ (**M** = Mg, Ni, Pb, Cd, Zn, Cu) at B3LYP/genecp level (unit: a.u.)

Species	Energy	Excess energy	Relative excess energy
Cu(NO ₃) ₂	-756.7656629		
[Cu L1] ²⁺	-1125.3490819	-368.583419	41.84
$Zn(NO_3)_2$	-626.2378383		
[Zn L1] ²⁺	-994.7843391	-368.5465008	18.76
$Cd(NO_3)_2$	-608.6898887		
[Cd L1] ²⁺	-977.2361029	-368.5462142	18.58
Pb(NO ₃) ₂	-564.12656315		
[Pb L1] ²⁺	-932.6703495	-368.54378635	5 17.06
Ni(NO ₃) ₂	-729.9404376		
[Ni L1] ²⁺	-1098.4740958	-368.5336582	10.73
$Mg(NO_3)_2$	-561.5600378		
[Mg L1] ²⁺	-930.0765333	-368.5164955	0.00



Figure 5. Relative excess energy profile of $[ML1]^{2+}$ (M = Mg, Ni, Pb, Cd, Zn, Cu) at B3LYP/genecp level

the stabilization constants have been performed at the B3LYP/6-31G (d, p)/LanL2DZ level of theory using the Gaussian 03 program. The calculation formula of binding energy is $E = E_{[M^{2+}+L1]} - (E_{M(NO_3)_2} - 2E_{(NO_3)^-})$. The calculated results are summarized in Table 1 and Fig. 5, which show that the largest binding energy was 41.84 kcal mol⁻¹ for Cu complex with L1, followed by Zn²⁺, Cd²⁺, Pb²⁺, Ni²⁺ and Mg²⁺ complexes. The results indicate that complex L1·Cu²⁺ was the most stable. Moreover, the distance between Cu and Fe is 4.123 Å (Fig. 6), longer than the sum of their radii. The distances of Zn–Fe (2.555 Å), Cd–Fe (20769 Å), Pd–Fe (3.117 Å), Ni–Fe (2.515 Å) and Mg–Fe (20618 Å) are shorter than the sum of their radii, which may lead these complexes to be unstable because of charge repulsion between the metal cations tested and the Fe atom.

Conclusion

We have developed an easy methodology to synthesize ligands **L1** and **L2**. Ligand **L1** was proved to be a stable and electrochemically selective sensor for Cu^{2+} in environments containing



Figure 6. Representation of the optimized geometries of the $[ML1]^{2+}$ (M = Mg, Ni, Pb, Cd, Zn, Cu) at B3LYP/genecp level (units in Å for bond lengths)

alkaline earth metals, transition and post-transition metal ions, such as Mg^{2+} , Ni^{2+} , Zn^{2+} , Pb^{2+} and Cd^{2+} ions, without interference. The coordination model of **L1** with Cu^{2+} was proposed from the results of controlled experiments and quantum calculations.

Acknowledgements

We are grateful to the NSF of China (20972139, 21102133) for financial support of this research. The authors also thank Prof. Dapeng Zou, Dr Weiguo Zhu and Mr Jianxun Kang from Zhengzhou University for NMR spectra analyses and valuable discussion.

The crystal structures of **L1** and **L2** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers are CCDC 845017 and CCDC 845016, respectively.

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