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Click-generated triazole based ferrocene-carbohydrate bioconjugates: A highly selective multisignalling probe for Cu(II) ions

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Abstract. Two Cu^{2+}-specific colorimetric sensors, based on ferrocene-carbohydrate bioconjugates, **2**, $C_{46}H_{56}O_{20}N_6Fe$ and **3**, $C_{28}H_{33}O_{10}N_3Fe$ were designed and synthesized in good yields. Both the compounds, **2** and **3**, behave as very selective and sensitive chromogenic and electrochemical chemosensor for Cu^{2+} ion in aqueous environment (CH_3CN/H_2O (2:8, *v*/*v*). The analytical detection limit (ADL) for receptor **2** was 7.5×10^{-7} M. The considerable changes in their absorption spectra of **2** and **3** are accompanied by the appearance of a new low energy (LE) peak at 630 nm (**2**: $\varepsilon = 1600$ M^{-1} cm^{-1} and **3**: 822 M^{-1} cm^{-1}). This is further accompanied by a strong colour change from yellow to dark green that allows the prospective for 'naked eye' detection of Cu^{2+} ion.

Keywords. Organometallic bioconjugates; Cu(II) cation sensor; chromogenic and electrochemical chemosensor.

1. Introduction

In recent years, there has been a growing need for constructing chemosensors for fast and economical monitoring of our environmental samples, especially for heavy metal ions.[1] Copper is one of the heavy metals which is an essential element not only for life in mammals but also for plants. It also plays an important role in carbohydrate and lipid metabolism.[2] It is the most significant metal ion in biological systems[3] and also a significant environmental pollutant.[4] Copper is implicated in inflammatory disorders[5] and Alzheimer's disease.[6] The Cu^{2+} proteins are involved in oxygen binding, electron transfer and the activation of small molecules.[7] As a result, a strong interest exists in the development of selective Cu^{2+} sensors for biological and environmental applications. A variety of Cu^{2+} probes exhibiting either fluorescence 'on–off' or 'off–on' signalling modes have been developed.[8] However, colorimetric Cu^{2+} sensors offering ratiometric response are rare.[9] Colorimetric probes are currently attracting area, since they can be tailored to allow 'naked eye' detection and ratiometric sensing[10] of the analyte.

The most attractive way of achieving sensor design is to functionalize a receptor capable of both selective substrate binding with a metal centre and reporting on the recognition event through a variety of physical responses. Therefore, the design of redox-active receptors in which a change in electrochemical behaviour can be used to monitor complexations of guest species is significant in molecular recognition.[11–20] Thus, from a synthetic standpoint, ferrocene is a very convenient building block for redox-active ligand as it can be easily functionalized and incorporated in many structures. These facts, along with its electrochemical and UV-vis spectroscopic properties, demonstrate that ferrocene is a particularly attractive functional antenna in area of sensor for transition metals, p-block anions and organic molecules. For example, water-soluble ferrocenyl sugars are useful for the development of ferrocene-containing drugs. Further this, also been observed that some ferrocenyl sugars possess anti-malarial activity.[21] Carbohydrate-based chemosensors are chiral entities with hydroxyl groups and oxygen atoms, that form quite suitable cation binding sites. Thus, in the design of chemosensors, the incorporation of sugar molecules is a good strategy for capturing cations.[22–24] In this article, we report the host–guest complexation properties of two triazole tethered ferrocenyl carbohydrate bioconjugates towards Cu^{2+} ion.

2. Experimental

2.1 *General procedures and instrumentation*

Perchlorate salts of Li^+, Na^+, K^+, Ag^+, Ca^{2+}, Mg^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Ni^{2+}, Pb^{2+}, and Hg^{2+},

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propargyl bromide, butyl-lithium, tetramethylethylenediamine (TMEDA) purchased from Aldrich were used directly without further purification. Ferrocene, sodium ascorbate, sodium azide, acetonitrile purchased were of analytical grade and used without further purification. DMF purchased from Aldrich and freshly distilled prior to use. Chromatography was carried out on 3 cm of silica gel in a 2.5 cm diameter column. Column chromatography was carried out using 100–200 mesh silica gel. All the solvents were dried by conventional methods and distilled under a N_2 atmosphere before use. Glycosyl azide[25] and compounds **1a**–**b** [$Fc(CH_2OCH_2C{\equiv}CH)_n$] (**1a**: n = 2, **1b**: n = 1, where Fc = ferrocene), were synthesized as per literature procedures.[26] The cyclic voltammetry (CV) and differential pulse voltammetry (DPV) were performed with a conventional three-electrode configuration consisting of glassy carbon as working electrode, platinum as an auxiliary electrode and Ag/Ag^+ as a reference electrode. The experiments were carried out with a 10^{-4} M solution of sample in CH_3CN or CH_3CN/H_2O (2/8) containing 0.1 M $[(n\text{-}C_4H_9)_4NClO_4]$ (TBAP) as supporting electrolyte. Deoxygenation of the solutions was achieved by bubbling nitrogen for at least 10 min, and the working electrode was cleaned after each run. The cyclic voltammograms were recorded at a scan rate of 0.1 V s^{-1}. The UV-vis spectra were carried out in CH_3CN or CH_3CN/H_2O (2/8) solutions at $c = 1 \times 10^{-4}$ M.

The ^1H and ^{13}C NMR spectra were recorded on Bruker 400 MHz FT-NMR spectrometers, using tetramethylsilane as the internal reference. Electrospray ionization mass spectrometry (ESI-MS) measurements were carried out on a Qtof Micro YA263 HRMS instrument. The absorption spectra were recorded with a JASCO V-650 UV-vis spectrophotometer at 298 K. The CV and DPV measurements were performed on a CH potentiostat model 660 B. *Caution*: Metal perchlorate salts are potentially explosive in certain conditions. All precautions should be taken while handling perchlorate salts.

2.2 *Synthesis of ferrocene-carbohydrate conjugates **2–3***

To a well-stirred solution of **1a** (0.5 g, 1.55 mmol) and glycosyl azide (3.31 g, 3.1 mmol) in 15 mL acetone/H_2O (2:1), an aqueous solution of $CuSO_4{\cdot}5H_2O$ (0.077 g, 0.31 mmol) was added. To this resultant mixture freshly prepared sodium ascorbate solution (0.122 g, 0.62 mmol) was added and stirred at room temperature for 12 h. 30 mL of ethyl acetate was added into the reaction mixture and the organic layer was washed several times with water and finally with brine (15 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography. Elution with EtOAc:hexane (8:2 v/v) yielded yellow **2** (1.42 g, 86%).

Compound **3** was prepared in good yield following the procedure adopted for **2** from alkyne, **1b** (0.5 g, 1.96 mmol), glycosyl azide (1.23 g, 1.96 mmol), aqueous $CuSO_4{\cdot}5H_2O$ (0.097 g, 0.392 mmol) and sodium ascorbate (0.149 g, 0.776 mmol). The crude product was purified by silica gel column chromatography and elution with EtOAc: hexane (7:2 v/v) to yield pure yellow, **3** (0.98 g, 80%).

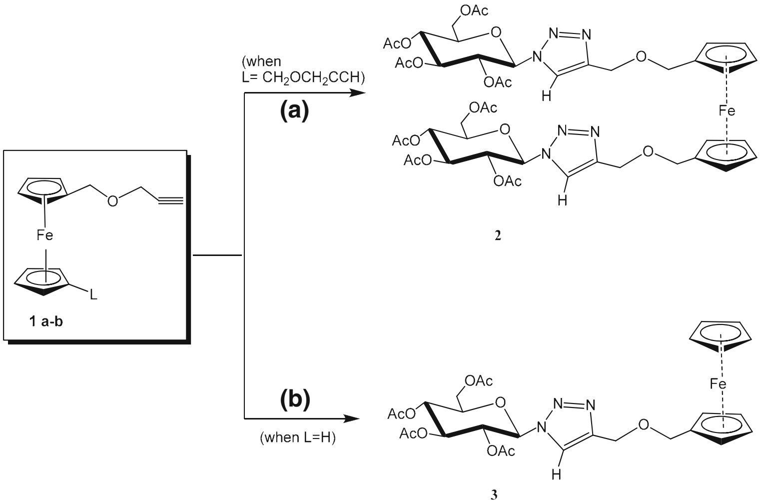
2: ^1H NMR ($CDCl_3$,400 MHz): $\delta = 7.71$ (s, 2H, $H_{triazole}$), 5.82 (d, 2H, H-1), 5.45 (s, 2H, H-5), 5.17 (s, 2H, H-2) 5.01 (s, 2H, H-3), 4.51 (s, 2H, H-4), 4.21 (dd, 4H, H6,H6′), 4.18 (s, 4H. OCH_2-triazole), 4.08 (t, 4H, H_{Fc}), 4.0 (t, 4H, H_{Fc}), 3.95 (s, 4H, OCH_2), 1.96–1.81(d, 12H, OAc); ^{13}C NMR ($CDCl_3$,100 MHz): $\delta =$ 170.5 (CO), 169.9 (CO), 169.4 (CO), 168.7 (CO), 146.0 ($C_{triazole}$), 121.0 ($C_{triazole}$), 85.6 (C-1), 75.0 (C-2), 72.6 (C-3), 71.7 (C-5), 70.3 (C-4), 68.8 (C_{Fc}), 68.4 (C_{Fc}), 67.6 (C_{Fc}), 62.9 (C-6), 61.5 (OCH_2), 53.6 (OCH_2), 27.7, 20.5, 20.2, 19.1 (CH_3CO); ESI MS, m/z (relative intensity): 1069 ($M^+ + 1$).

3: ^1H NMR ($CDCl_3$,400 MHz): $\delta = 7.68$ (s, 1H, $H_{triazole}$), 5.81(d, 1H, H-1), 5.30 (m, 1H, H-5), 5.23 (m, 1H, H-2), 5.01 (s, 1H, H-3), 4.53 (s, 1H, H-4), 4.26 (s, 2H, H6,H6′), 4.21(s, 2H, OCH_2-triazole), 4.06 (m, 4H, H_{Fc}), 4.0 (s, 5H, H_{Fc}), 3.99 (s, 2H, OCH_2), 2.08 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.94 (s, 3H, OAc), 1.80 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$,100 MHz): $\delta =$ 170.2 (CO), 169.7 (CO), 169.3 (CO), 168.9 (CO), 146.1 ($C_{triazole}$), 120.9 ($C_{triazole}$), 85.6 (C-1), 75.0 (C-2), 72.5 (C-3), 71.7 (C-4), 70.2 (C-5), 69.2 (C_{Fc}), 68.6 (C_{Fc}), 68.5 (C_{Fc}), 67.6 (C_{Fc}), 62.9 (C-6), 61.5 (OCH_2), 53.5 (OCH_2), 29.6, 27.7, 20.6, 19.0 (CH_3CO); ESI MS, m/z (relative intensity): 650 ($M^+ + 23$).

3. Results and discussion

3.1 *Synthesis*

Precursors **1a–b** were obtained following literature procedure.[26] As shown in scheme 1, they undergo the ‘click reaction’ with glycosyl azide to generate compounds **2** and **3** in 86% and 80% yields, respectively. Compounds **2** and **3** have been characterized by ^1H, ^{13}C NMR spectroscopy and ESI-MS spectrometry. Both the compounds **2** and **3** are moderately stable and



Scheme 1. Synthesis of mono and di-ferrocene-carbohydrate bioconjugates, **2** and **3**. (**a**) 2 equiv. glycosyl azide, 0.1 equiv. $CuSO_4.5H_2O$, 0.25 equiv. Na Ascorbate, Acetone/H_2O (2:1); (**b**) **1** equiv. glycosyl azide, 0.1 equiv. $CuSO_4.5H_2O$, 0.25 equiv. Na Ascorbate, Acetone/H_2O (2:1).

could be stored for several months. The complexation properties of the receptors **2** and **3** have been investigated by electrochemistry and UV-vis spectroscopic measurements.

3.2 *UV-vis absorption studies*

The UV-vis binding interaction studies of receptors **2** and **3** in CH_3CN (1×10^{-4} M) against cation of environmental relevance, such as of Li^+, Na^+, K^+, Ag^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, Ni^{2+}, Co^{+2}, Cd^{2+}, Hg^{2+} and Pb^{2+} as perchlorate salts, show selective response to Cu^{2+}. The change in the UV–vis absorbance spectra of receptors **2** and **3** in CH_3CN due to the step-wise addition of Cu^{2+} ion are shown in the figures 1 and 2, respectively. As shown in figures 1–2, a new and weak low-energy (LE) absorption band appeared at $\lambda = 630$ nm for both **2** ($\varepsilon = 1600$ M^{-1} cm^{-1}) and **3** ($\varepsilon = 822$ M^{-1} cm^{-1}) was developed. These facts are responsible for the change of colour from yellow to dark green. In addition, one well-defined isosbestic point at 408 nm and 415 nm was observed for **2** and **3**, respectively. The Cu^{2+} induced UV-vis response of **2** and **3** was almost unaffected in a background of environmentally relevant metallic cations.

The UV-vis spectral change suggests that the ferrocene moiety is oxidized upon complexation with

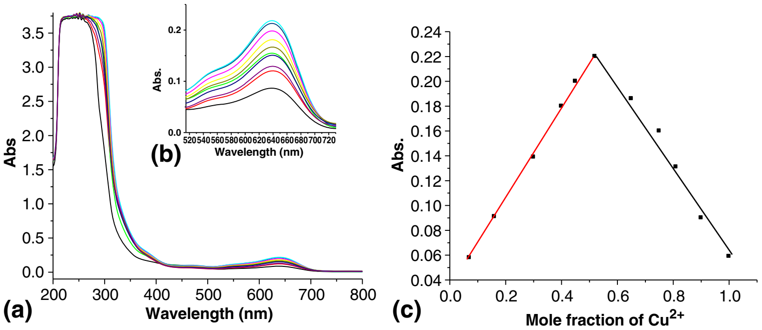


Figure 1. (**a**) Changes in the absorption spectra of **2** (10^{-4} M) in CH_3CN upon addition of increasing amounts of Cu^{2+} up to 1 equivalent. (**b**) Expanded form of part a. (**c**) Job's plot for **2** and Cu^{2+}, indicating the formation of 1:1 binding model. The total $[2] + [Cu^{2+}] = 1 \times 10^{-4}$ M.

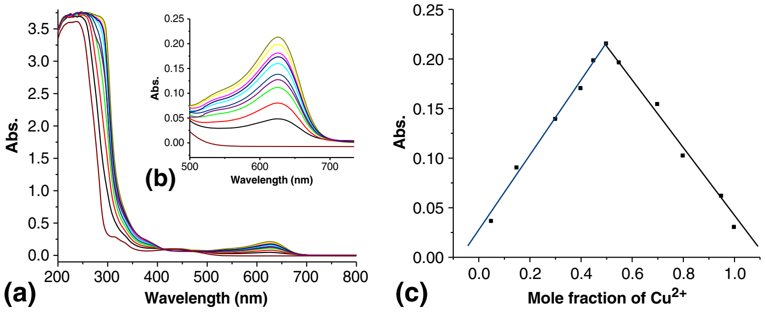


Figure 2. (**a**) Changes in the absorption spectra of **3** (10^{-4} M) in CH_3CN upon addition of increasing amounts of Cu^{2+} up to 1 equivalent. (**b**) Expanded form of part a. (**c**) Job's plot for and Cu^{2+}, indicating the formation of 1:1 binding model. The total [**3**] + [Cu^{2+}] = 1×10^{-4} M.

Cu^{2+} ion and the change of colour to deep green is characteristic of the ferrocenium ion formation.[27] On the basis of absorption intensity changes at 630 nm as a function of the amount of Cu^{2+} (inset figure 1b), it could be estimated that the stoichiometry of both **2** and **3** with Cu^{2+} is 1:1. This is further supported by the Job's plots (figures 1c for **2** and 2c for **3**) and ESI-MS experiments, where a peak at $m/z = 1131$ corresponds to [**2** + Cu^{2+} − H^+] and a small peak at $m/z = 1230$ for [**2** + $Cu.ClO_4$] was observed. Similarly, for **3** a peak at $m/z = 789$ was observed which corresponds to [**3** + $Cu.ClO_4$] (supporting information, figures S3 and S4).

3.3 *Electrochemical studies*

Chemical sensors bearing ferrocene nuclei as part of the sensing unit have been broadly studied. Earlier, the complexation of ferrocene with a variety of binding ligands have been studied by cyclic voltammetry that shows a positive shift of the Fe(II)/Fe(III) redox couple as a result of metal–ligand complxation.[28] The metal-recognition properties of receptors **2** and **3** were evaluated by cyclic (CV) and differential pulse voltammetry (DPV) analysis. The reversibility and relative oxidation potential of the redox process were

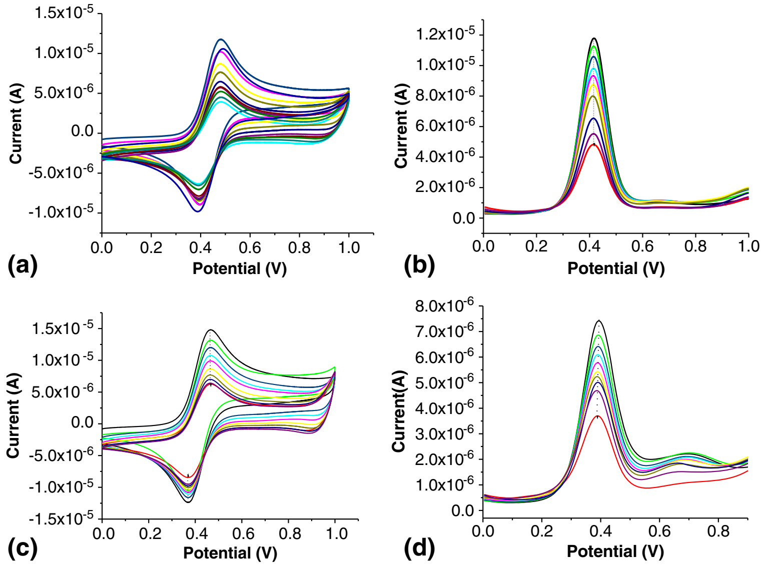


Figure 3. Evolution of the CV and DPV of **2** (**a** and **b**) and **3** (**c** and **d**) (10^{-4} M) in CH_3CN upon addition of increasing amounts of Cu^{2+} metal cation up to 1 equivalent using $[(n\text{-Bu})_4]ClO_4$ as supporting electrolyte. Arrow indicates the movement of the wave during the experiments.

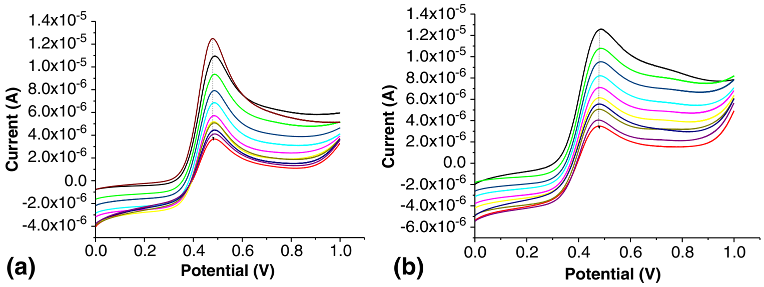


Figure 4. Evolution of LSV of **2** (**a**) and **3** (**b**) (10^{-4} M) in CH_3CN upon addition of with Cu^{2+} ion using $[(n\text{-}Bu)_4N]ClO_4$ as supporting electrolyte and scanned at 0.1 V s^{-1}.

determined by CV and DPV in CH_3CN solutions containing 0.1 M $[(n\text{-}Bu)_4N]ClO_4$ as supporting electrolyte. Both the compounds **2** and **3** display a reversible one-electron oxidation process at $E_{1/2}$ = 0.433 and 0.415 V, respectively due to the ferrocene/ferrocenium redox couple. No perturbation of the CV and DPV voltammograms of **2** and **3** were observed in the presence of several metal cations such as Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, Ag^+, Ni^{2+}, Co^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+} as their appropriate salts, even with large excess. However, as shown in figure 3a–d, the original peak gradually decreased upon step-wise addition of Cu^{2+} ion towards more cathodic current which indicate that free receptor is getting oxidized upon interaction with Cu^{2+} ion.

In addition, linear sweep voltammetry (LSV) studies carried out upon addition of Cu^{2+} to the CH_3CN solution of receptor **2**. As shown in the figure 4, a significant shift of the voltammetric wave towards more cathodic current was observed, indicating that this metal cation promotes the oxidation of the free receptor with its concomitant reduction to Cu^+. This is in agreement with the CV and DPV (figure 3a–d). Remarkably, the redox response towards Cu^{2+} is also preserved in the presence of an aqueous environment (CH_3CN/H_2O (2:8, v/v)).

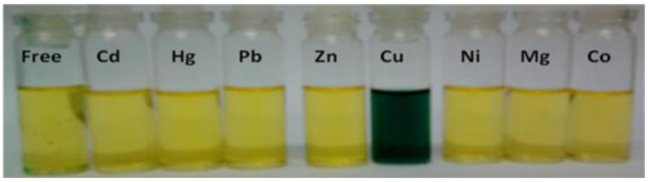


Figure 5. Visual features observed in CH_3CN solution of **2** (10^{-4} M) after addition of 10 equivalent of different metal cation tested.

3.4 *Visual detection of Cu^{2+} ion*

When an excess of different metal cations (Li^+, Na^+, K^+, Ag^+, Ca^{2+}, Mg^{2+}, Cr^{2+}, Zn^{2+}, Ni^{2+}, Fe^{2+}, Co^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+}) as their perchlorate salt were separately added to a solution of **2** and **3** in CH_3CN: H_2O (10^{-4} M), no significant colour change observed, except for Cu^{2+}. As shown in figure 5, Cu^{2+} shows a drastic colour change from yellow to dark green. The sensing potential of **3** toward Cu^{2+} in solution is very similar to **2**. This indicates that both **2** and **3** are highly selective colorimetric sensors for Cu^{2+} ion.

4. Conclusion

In this study, we have designed and synthesized two ferrocene-carbohydrate based organometallic bioconjugates, **2**, $C_{46}H_{56}O_{20}N_6Fe$ and **3**, $C_{28}H_{33}O_{10}N_3Fe$ in good yields. They behave as selective and sensitive electrochemical as well as chromogenic receptors for the determination Cu^{2+} ion. These receptors showed high selectivity towards Cu^{2+} ion not only through spectrochemical and electrochemical probe but also amenable to the facile colorimetric sensing of Cu^{2+} ion, thus allowing the potential for 'naked-eye' detection over some other cations.

Supplementary information

The ^1H, ^{13}C and ESI-MS data of **2** and **3**; electrochemical data for **2** and **3** upon titration with different metal ions; UV-Vis spectra upon titration with different metal ions; ESI-MS spectrum of [**2**.Cu^{2+}], [**3**.Cu^{2+}] are given as Supplementary information. Figures S1–S6 as supporting material are available on www.ias.as.in/chemsci.

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