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Metal-containing Trifurcate Chemosensing Ensemble for Phytate

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A trifurcated receptor system containing three Cu(II)-dipicolylamine ligands has been studied for the molecular sensing of phytate, *myo*-inositol hexakis(phosphate) sodium salt, through an indicator displacement approach. From the Cu(II) complex, a molecular sensing ensemble system was best constructed with eosin Y as indicator. The addition of phytate to the chemical ensemble system in an aqueous medium of physiological pH resulted in the restoration of fluorescence of eosin Y as it is displaced from the metal complex by the anion added. The ensemble system shows the maximum fluorescence change in the case of phytate, about 70% change in the cases of *myo*-inositol 1,4,5-tris(phosphate) and pyrophosphate ions, and negligible changes in the cases of monovalent anions (HPO_4^{2-}, $CH_3CO_2^-$, CO_3^{2-}, Cl^-, Br^-, ClO_4^-, N_3^-, NO_3^-) and inositol. A binding study by isothermal titration calorimetry suggests that the Cu(II) complex tends to recognize phytate preferably in a 2:1 binding mode with K_1 of $7.7 \times 10^8\,M^{-1}$, accompanied with a large favorable entropy change ($T\Delta S = 19.4$ kcal mol^{-1}) and an unfavorable enthalpy change ($\Delta H = 7.1$ kcal mol^{-1}) at 303 K. The present chemical ensemble system thus can be used for fluorescence sensing of phytate in the μM range.

Keywords: Phytate; Ensemble sensor; Cu(II) complex; Tripodal dipicolylamine

INTRODUCTION

Phytate, *myo*-inositol hexakis(phosphate) sodium salt, is an abundant plant ingredient, found in legumes, cereals, oil seeds, etc. It is an important constituent of the human diet, presenting in blood, urine, and intracellular fluids [1]. Because of its high phosphate content, phytate readily forms chelates of metal ions such as Zn^{2+}, Ca^{2+}, Mg^{2+}, Cu^{2+}, Co^{3+}, and Fe^{3+}, limiting the bioavailability of such minerals in animal [2,3]. Phytate is also an important source of environmental phosphorous pollution. Apart from causing such nutritional and environmental problems, phytate is being recognized to exert several therapeutic functions [4] such as antioxidant [5,6] and anticancer activities [7–10], lowering the risk of renal stone formation [11,12], and also being a cofactor of a human RNA deaminase [13,14].

The determination of phytate from various samples has been studied by a number of analytical methods, such as by refractive index HPLC analysis for phytate itself or its hydrolysis products (inositol and phosphate) [15–18], flow injection-capillary zone electrophoresis [19], and gas chromatography-mass spectrometry [20]. An amperometric phytate biosensor has also been developed, which is based on poly(carbamoylsufonate) hydrogel co-immobilization of phytase [21]. A fluorimetric determination has also been developed, which is based on the oxidation of 2,2′-dipyridyl ketone hydrazone by Cu^{2+} that is dissociated proportionally to the amount of phytate [22–25].

Molecular sensing of phytate based on artificial receptors has only appeared recently. Morey and coworkers reported a chemosensor system for phytate, which is based on a charge transfer complex between a trifurcate crown ether-phenolate receptor and picrate salt [26]. The ensemble system gives a colorimetric change upon treatment with phytate, enabling a naked-eye detection of phytate for the first time. The color change in this chemosensor results from acid–base interactions and thus the system also responds to basic anions such as F^-, acetate, $H_2PO_4^-$, and others. Although the chemosensing system needs to be improved in terms of guest selectivity,

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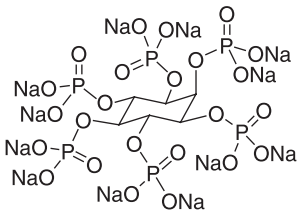
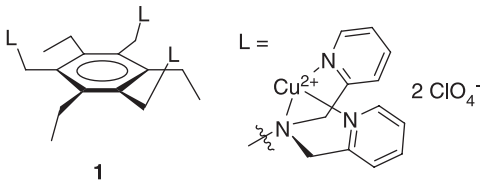
its operational simplicity is obviously an attractive aspect. We were interested in the chemical ensemble system, which composes of a receptor system and a dye competitive for the analyte, for its operational simplicity and versatility in the receptor design for specific analytes. Such a chemical ensemble system has been demonstrated to be useful in chemosensing of various analytes since the flourishing work of Anslyn and co-workers [27–29].



phytate

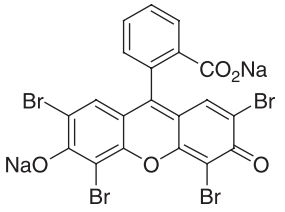


1

We were particularly interested in the chemical ensemble system based on metal-dipicolylamine coordination complexes, because coordination complexes can provide strong binding affinity toward phosphates even in aqueous media due to the strong metal coordination bonds. For the selective recognition of phytate among other related anions, a trifurcated system relevant to Morey's seems to be ideal for realizing multiple interactions toward the hexakis (phosphate) groups. We were interested in the tripodal benzene system [30–45], in which 1,3,5-trisubstituted ligands can provide "tripodal" binding interactions, because the three ligands readily exist in the "all-*syn*" conformation, so-called "ababab"-conformation [46,47]. Thus, with a structurally complementary receptor system, we may achieve the tripodal binding between the ligands and the phosphate groups. To this end, we chose the trifurcated Cu(II)-dipicolylamine complex **1** as the receptor system for phytate. Compounds containing two metal-dipicolylamine ligands are proven to be effective for anion sensing in aqueous media via the indicator-displacement approach [48–53]. However, their trifurcated analogues, which would obviously provide multiple interactions toward multivalent anions, have not been studied for chemosensing purposes. A trifurcate system containing three Cu(II)-cyclam subunits has been used for chemical ensemble sensing of citrate [54].

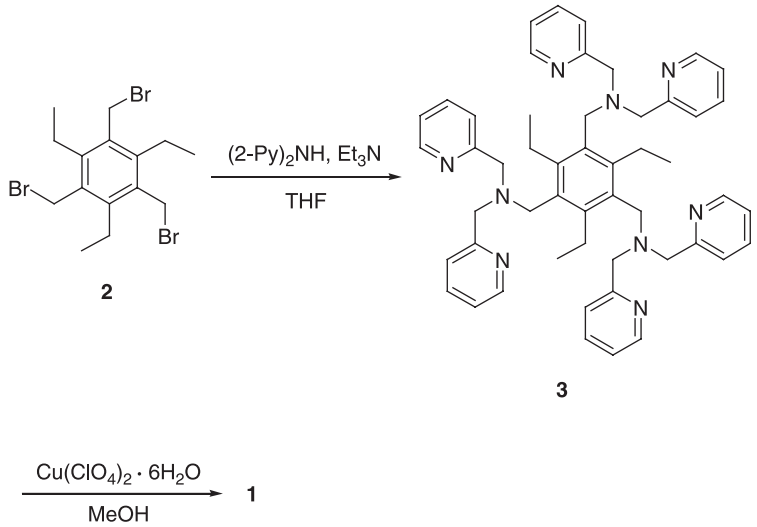
RESULTS AND DISCUSSION

The tris(picolylamine) **3** and its Cu(II) complex **1** are synthesized according to our experiences in related tripodal ligand systems [30–45] and literature procedures (Scheme 1). The corresponding Cu(I) complex is known in the literature [55].



EosinY

We screened several dyes such as eosin Y, fluorescein, and coumarine 343 to find a suitable



2 **3**

SCHEME 1 Synthesis of Cu(II) complex 1.

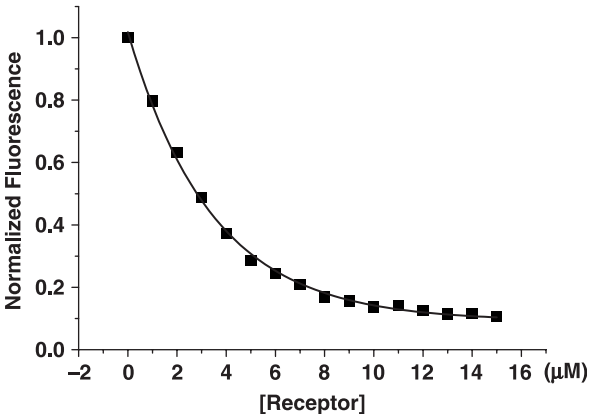


FIGURE 1 Fluorescence titration of eosin Y (3.0 μM) with Cu(II) complex **1** (0–15 μM) in water buffered at pH 7.0 (HEPES 10 mM), with $\lambda_{ex} = 517$ nm: the fluorescence peak heights at 536 nm depending on the concentration of Cu(II) complex **1** were plotted.

chemical ensemble system for Cu(II) complex **1**. The fluorescence titration of eosin Y (3.0 μM) with Cu(II) complex **1** (0 ~ 15 μM) in water buffered at pH 7.0 (HEPES buffer, 10 mM) resulted in significant quenching as shown in Fig. 1, whereas small or little quenching was observed in other cases. Interestingly, a Job plot for this complex formation process showed a maximum peak around $x = 0.7$ (where x = [eosin Y]/([eosin Y] + [Cu(II) complex **1**]), suggesting a 1:2 (**1**:eosin Y) binding stoichiometry, instead of a 1:1 binding mode (Fig. 2).

From this fluorescence titration experiments, an ensemble system of Cu(II) complex **1** and eosin Y was chosen for the chemical sensing study. We evaluated chemical sensing ability of the ensemble system toward phytate and other anions such as *myo*-inositol 1,4,5-tris(phosphate) (IP_3), pyrophosphate (PPi), acetate, chloride, bromide, perchlorate, azide, nitrate, sulfonate, hydrogen phosphate, and carbonate ions as their sodium salts. Thus, fluorescence titration toward each of the anions was carried out using an ensemble system containing 9.0 μM of Cu(II) complex **1** and 3.0 μM of eosin Y in

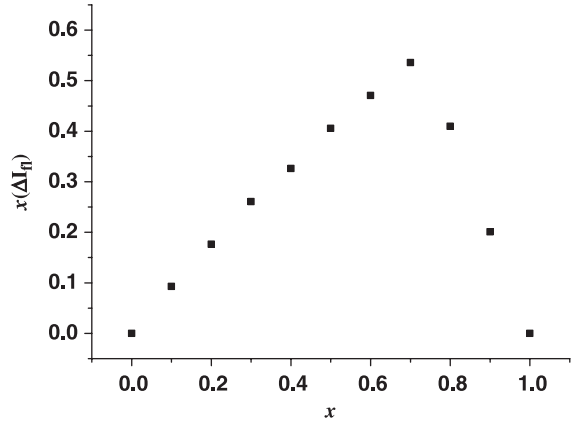


FIGURE 2 A job plot of $x\Delta I_{fl}$ versus x, where x = [eosin Y]/([eosin Y] + [Cu(II) complex **1**]).

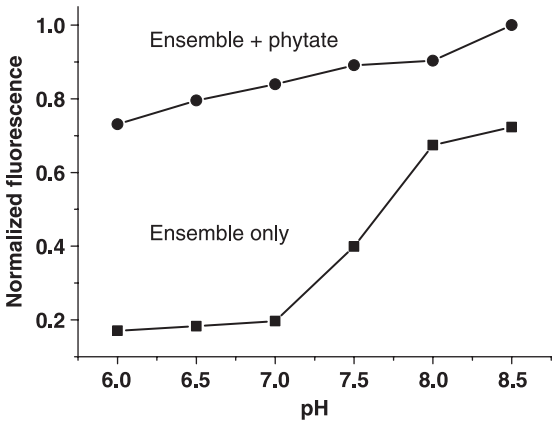


FIGURE 3 A plot of the fluorescence changes measured for the ensemble only (eosin Y, 3.0 μM and Cu(II) complex **1**, 9.0 μM) and for the ensemble with phytate (12.0 μM) in water buffered at various pHs. Compositions of the buffer solutions are as follows: pH 6.0 (MES 10 mM), pH 6.5 (MES 10 mM), pH 7.0 (HEPES 10 mM), pH 7.5 (HEPES 10 mM), pH 8.0 (HEPES 10 mM), pH 8.5 (CHES 10 mM).

an aqueous solution buffered at pH 7.0 (a HEPES buffer, 10 mM) at room temperature. The pH was selected based on separate fluorescence studies depending on pH for the sensor ensemble only and

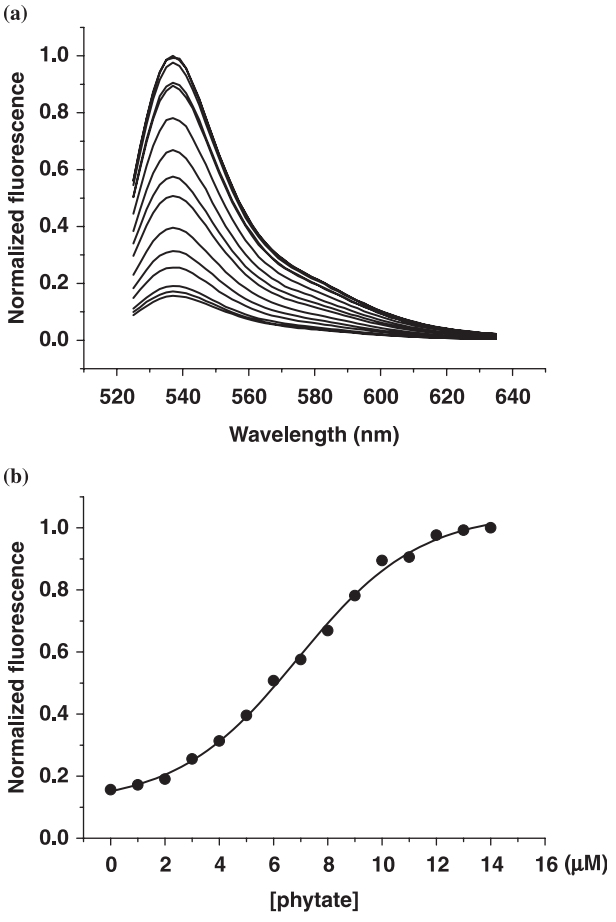


FIGURE 4 (a) Fluorescence titration of the chemical ensemble (Cu(II)-complex **1**, 9.0 μM and eosin Y, 3.0 μM) with phytate (0–15 μM) in water buffered at pH 7.0, $\lambda_{ex} = 517$ nm. (b) A plot of the fluorescence intensity (peak heights of the spectra in part (a) at 536 nm) versus the phytate concentration, μM.

the ensemble containing phytate, respectively (Fig. 3). Above pH 7.0, the difference in the fluorescence intensity between the two samples became small as the fluorescence of sensor ensemble increases suddenly.

The fluorescence titration data for the phytate ion is shown in Fig. 4. The addition of phytate in the μM range resulted in the restoration of fluorescence of eosin Y as it is replaced by the anion added. A plot of the fluorescence intensity versus anion concentration shows a sigmoid curve, suggesting a complex binding equilibrium, not a simple 1:1 binding mode.

The largest fluorescence increase was observed in the case of phytate ion, and most of the other anions resulted in a little change except for pyrophosphate and IP_3, for which anions significant fluorescence was observed. The fluorescence enhancement for each anion is collectively presented in Fig. 5, which indicates that the new chemical ensemble system responds to phytate in preference to monovalent anions, responds less to divalent pyrophosphate and trivalent IP_3 ions.

To get binding information further, we carried out isothermal titration calorimetry (ITC) for the phytate ion at 303 K. Thus, to a solution of Cu(II) complex **1** (0.05 mM, 1.5 mL) in the pH 7.0 buffer solution (HEPES, 10 mM) were added portions of phytate ion (0.5 mM, 7.0 μL × 30 times) and the corresponding binding isotherms were obtained (Fig. 6). A steep change in the binding isotherms occurs at the point where approximately 0.5 molar equivalents of phytate were added, which suggests that a 1:2 (phytate:**1**) binding mode is involved, rather than a 1:1 mode. A small increase in the binding isotherms was observed at the late stage of titration (after 0.7 equivalents of phytate were added), which suggests that an additional equilibrium accompanies at this stage. We ignored this minor change in the binding isotherms to calculate the thermodynamic parameters for the major binding processes involved. The resulting binding isotherms were fit well by a nonlinear least squares regression method under a condition of "two-sites" binding model, in other words, by assuming two different binding sites that are independent. The dominant binding process, which occurs with the binding stoichiometry of 0.57, provided a large binding affinity (K_1) of $7.7 \times 10^8\,M^{-1}$. This binding process is accompanied with a large favorable entropy change ($T\Delta S = 19.4$ kcal mol^{-1}) and an unfavorable enthalpy change ($\Delta H = 7.1$ kcal mol^{-1}). This is not unexpected result as solvent reorganization is an important factor in

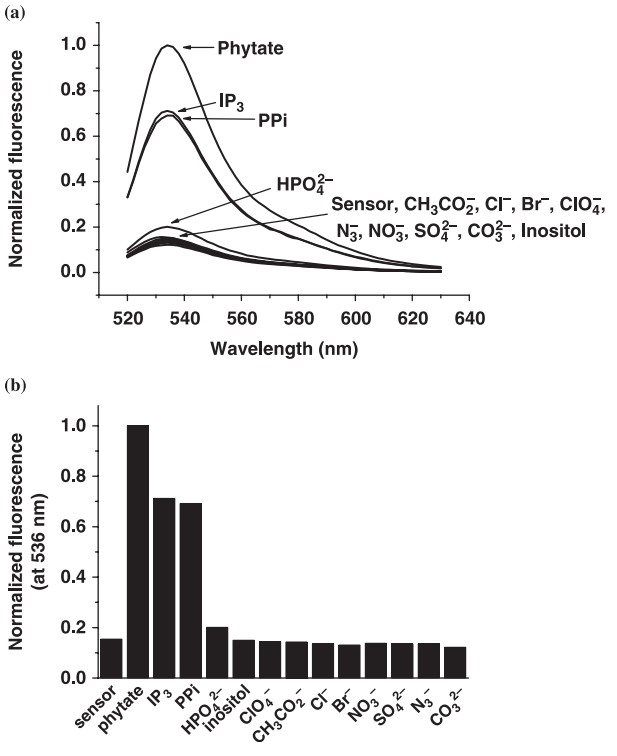


FIGURE 5 (a) Collective fluorescence data obtained from titrations of the ensemble (Cu(II) complex **1**, 9.0 μM and eosin Y, 3.0 μM) with various anions (12.0 μM) in water buffered at pH 7.0 (HEPES 10 mM), with $\lambda_{ex} = 517$. (b) Comparison of the relative fluorescence intensity of the ensemble system toward the anions, measured in part (a).

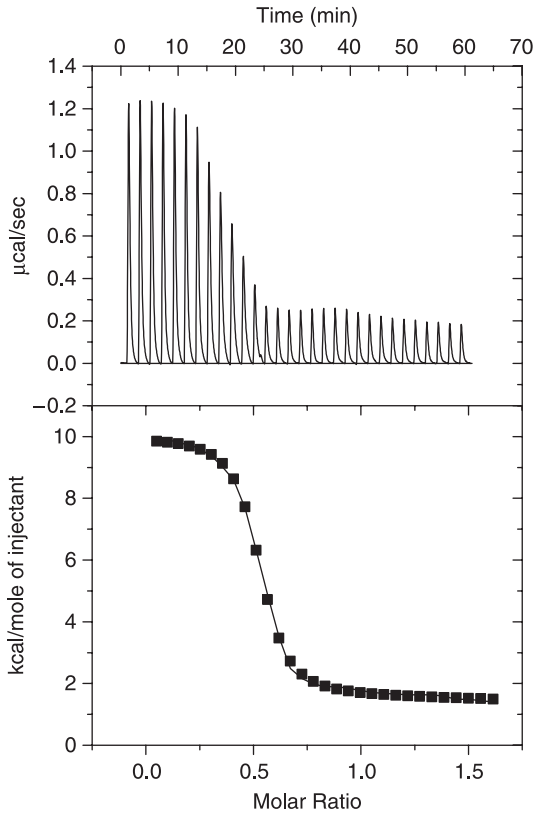


FIGURE 6 Binding isotherms and their integrated plot from the ITC titration of Cu (II) complex **1** with phytate at 303 K in water buffered at pH 7.0 (the lower integrated plot was obtained by ignoring the minor rises in the region from the molar ratio value of 0.7 to 1.5).

the molecular recognition process in aqueous media [56–59]. More interesting thing to us is that the present chemical ensemble system tends to recognize phytate preferably in a 2:1 (Cu(II) complex **1**:phytate) binding mode. This result suggests that the geometry of trifurcated metal-dipicolylamine complex does not match well with that of phytate to give a 1:1 complex. In any cases, the present study demonstrates that a trifurcated chemical ensemble system senses phytate in great preference to various monovalent anions and in some preference to a triphosphate ion, IP_3. A further structural fine tuning would warrant the realization of a 1:1 binding mode toward phytate for higher selectivity and sensitivity, which is under investigation.

CONCLUSION

We have studied a novel chemosensing ensemble system for phytate in aqueous medium of physiological pH. The ensemble system is composed of a trifurcate Cu(II)-dipicolylamine complex as receptor and commercially available eosin Y as the competing indicator. Upon treatment with anions, the ensemble system shows restoration of the indicator's fluorescence as it is replaced by the anion added; the maximum fluorescence change was observed in the case of phytate, about 70% changes in the cases of *myo*-inositol 1,4,5-trisphosphate and pyrophosphate, and negligible changes in the cases of monovalent anions (HPO_4^{2-}, $CH_3CO_2^-$, CO_3^{2-}, Cl^-, Br^-, ClO_4^-, N_3^-, NO_3^-) and inositol. Such a chemical ensemble approach to detect phytate seems to be promising for its operational simplicity and versatility in the receptor design. A structural fine tuning of the metal-ligand complex for higher selectivity and sensitivity is under investigation.

EXPERIMENTAL

Instruments and Material

Melting points were determined on a Barnstead International capillary melting point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 (300 MHz) instrument using tetramethylsilane as the internal standard. IR spectra were recorded on a Bruker Equinox 55 Fourier transform infrared spectrometer. Mass spectra were obtained with a Micro Mass M@LDI MALDI-TOF instrument. Fluorescence measurements were carried out with PTI fluorescence spectrophotometer. Silica gel 60 (230–400 mesh) was used for flash chromatography, and thin-layer chromatography was carried out on silica-coated glass sheets (Merck silica gel 60 F-254). All commercial reagents are of ACS reagent grade and used as supplied. All solvents were dried over 4 Å molecular sieves when necessary.

1,3,5-Tris[bis(pyridine-2-ylmethyl)aminomethyl]-2,4,6-triethylbenzene (3)

To an ice-chilled solution of dipicolylamine (2.7 g, 15.6 mmol) and triethylamine (4.13 g, 40.8 mmol) in THF (50 mL) was slowly added 1,3,5-triethyltris (bromomethyl)benzene **2** (2 g, 4.53 mmol) in THF (50 mL) at 0°C. After being stirred for 5 h at 0°C, the reaction solution was then allowed to warm to room temperature and was stirred for 4 days. The solvent was removed under reduced pressure and the residue was treated with aqueous KOH and extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was concentrated *in vacuo*, and the residue was solidified with ether. The solid was dissolved in warm toluene and filtered out to remove insoluble solids, and the filtrate was evaporated under reduced pressure, and again solidified using diethyl ether. This solid was recrystallized from CH_3CN to give yellow solid **3** (1.2 g, 33%). Mp 188–190°C (lit 185–190°C).; IR (KBr pellet, cm^{-1}) 1589, 2860, 2948, 3007; ^1H NMR 300 MHz ($CDCl_3$) δ 0.66 (t, 9 H, $J = 7.3$ Hz), 2.71–2.90 (q, 6H, $J = 7.2$ Hz), 3.65 (s, 6H), 3.70 (s, 12H), 7.02 (t, 6H, $J = 6.1$ Hz), 7.15 (d, 6H, $J = 7.7$ Hz), 7.41 (t, 6H, $J = 7.6$ Hz), 8.41 (d, 6H, $J = 4.7$ Hz); ^{13}C NMR 75 MHz ($CDCl_3$) δ 15.70, 22.19, 51.06, 60.23, 121.97, 123.55, 132.05, 136.37, 145.31, 148.69, 160.01.

1,3,5-Tris[bis(pyridine-2-ylmethyl)aminomethyl]-2,4,6-triethylbenzene Cu(II) Complex 1

To a solution of compound **3** (200 mg, 0.251 mmol) in MeOH (30 mL) was added $Cu(ClO_4)_2{\cdot}6H_2O$ (279 mg, 0.753 mmol) and the resulting solution was stirred at 40°C for 1 h. The solution was concentrated under reduced pressure and the obtained solid was suspended in CH_2Cl_2, filtered, and dried *in vacuo* to give **1** as a dark blue solid (290 mg, 83%). Mp 246°C (dec.).; IR (KBr pellet, cm^{-1}) 1611, 2969, 3081, 3463; MALDI-TOF calcd for $\mathbf{1}{\cdot}4ClO_4{\cdot}2H_2O$, 1420.073; found 1420.183. Anal. Calcd for $C_{51}H_{57}N_9{\cdot}3Cu{\cdot}6ClO_4{\cdot}2H_2O$: C, 37.82; H, 3.80; N, 7.78. found: C, 37.85; H, 3.88; N, 7.65.

Measurements

Isothermal Titration Calorimetry

The calorimetric analysis was performed on a MicroCal VP-ITC microcalorimeter. An aqueous buffer solution (1.5 mL, pH 7.0 HEPES 10 mM) of Cu(II) complex **1** (0.05 mM) was added to the calorimeter cell. To this solution was injected an aqueous buffer solution (pH 7.0 HEPES 10 mM) of

phytate (0.5 mM), with each injection of 7.0 μL portion and overall in 30 portions. The mixture was continuously stirred and was kept at the operating temperature of 303 K. The dilution effects were corrected, which were done by carrying out a separate titration experiment. The data was analyzed by a curve-fitting software implemented with the instrument.

Fluorimetric Titration

A stock solution (3.0 mL) containing 9.0 μM of Cu(II) complex **1** and 3.0 μM of eosin Y in the HEPES buffer (10 mM, pH 7.0) was prepared, and an initial fluorescence measurement was made. Aliquots of phytate from a standardized stock solution were titrated into the solution to give final concentration of 15 μM (1.0 μM increments) and the fluorescence spectra were recorded by exciting at 517 nm and collecting emission data from 525 nm to 635 nm.

Acknowledgements

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