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Zhaohua Dai[ab]; Nikhil Khosla[a]; James W. Canary[b]
[a] Department of Chemistry and Physical Sciences, Pace University, New York, USA [b] Department of Chemistry, New York University, New York, USA

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Visible colour displacement sensing system for manganese(II)

Zhaohua Dai[a,b]*, Nikhil Khosla[a] and James W. Canary[b]*

[a]*Department of Chemistry and Physical Sciences, Pace University, New York, USA;* [b]*Department of Chemistry, New York University, New York, USA*

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A visible colour displacement system has been developed for the colorimetric and ratiometric detection of Mn(II) ions. The supramolecular displacement system is composed of 2-(5-bromo-2-pyridylazo)-5-[*N*-propyl-*N*-(3-sulfopropyl)amino]phenol (5-Br-PAPS), which binds Zn^{2+} with a change in colour and binds Mn^{2+} without changing colour, ethylene glycol-bis (2-aminoethylether)-*N*, *N*, *N′*, *N′*-tetraacetic acid (EGTA) and Zn^{2+} at neutral pH. The sensing system exhibits the colour of 5-Br-PAPS itself since EGTA binds Zn^{2+} more strongly than 5-Br-PAPS does. However, upon presentation of Mn^{2+}, Zn^{2+} is displaced from EGTA to bind 5-Br-PAPS to produce a pronounced colour change from yellow to purple. The absorbance decreases at 449 nm and increases at 552 nm, both linearly to Mn^{2+} concentration at low micromolar levels. This should be very advantageous since no suitable colorimetric reagent is available for the direct declination of Mn^{2+} at physiological pH.

Keywords: manganese(II); colorimetric; sensor; displacement assay; ratiometric

Introduction

Manganese is a widespread element, essential for human health. However, overexposure to manganese, which may come from both natural and anthropogenic sources (*1*, *2*), can be harmful, especially to the nervous system. Chronic exposure to manganese has been associated with several mental disturbances and brain diseases, such as manganese madness, manganism and some Parkinsonism-like conditions (*2–4*). Neonatal dietary manganese exposure has been linked to attention deficit hyperactivity disorder (ADHD) (*5*). Studies of manganese(II) homeostasis are at an early stage (*6*). Manganese(II) plays a growing role as a contrast agent in magnetic resonance imaging (MRI) (*7*). Although neuroimaging with MRI and radiolabelling has been used in evaluating manganese exposure and its neurological consequences (*8*), there is an evolving interest in minimally invasive clinical imaging methods based on optical technologies (*9*), which bears other intrinsic advantages in compactness, low weight and robustness. Optical imaging gives clinical information arising from changes in the characteristics of light when it interacts with tissue, which can potentially play important roles in staging, diagnosis, disease localisation for therapeutic guidance, monitoring of therapeutic response and monitoring of metabolic and physiological functions. Test paper or stick-like devices can also be developed based on optical imaging materials and principles, enabling convenient application in estimating the amount of manganese in food, beverage, infant formula (*5*), water (*10*) and soil.

In recent years, the development of selective and sensitive optical imaging tools capable of reporting transition metal ions has attracted considerable attention, leading to significant progress in the design of probes for some metal ions. Among the extensively employed analytical sensing methods are the displacement assays (*11–14*), in which the analyte competes with a non-analyte for noncovalent binding to a receptor. This non-analyte can be either an indicator or a species that can form a complex with an indicator (*15*). Quantitative information about the analyte can be extracted if the different states of the indicator (or the receptor if the receptor itself is a chromophore/fluorophore) differ in their optical properties. Since the nature of the indicator as well as the indicator/receptor ratio can be varied in supramolecular systems depending on the sensing problem, displacement assays are very versatile (*12*). Recently, we devised a displacement sensor for the ratiometric determination of Cu(II) by fluorescence (*16*). The sensor employed two dyes and a reporter metal ion. Introduction of Cu(II) resulted in transference of the reporter ion from one chelating dye to another, accompanied by quench of one dye and enhancement of the fluorescence of the second dye.

Visible-light detection of Mn(II) presents a formidable challenge. Currently, Mn(II) can be detected by atomic absorption (*17*), ion chromatography (*18*) or capillary zone electrophoresis (*19*). Some colorimetric methods are available, but they involve catalytic reactions (*20*, *21*) or

*Corresponding authors. Email: james.canary@nyu.edu; zdai@pace.edu

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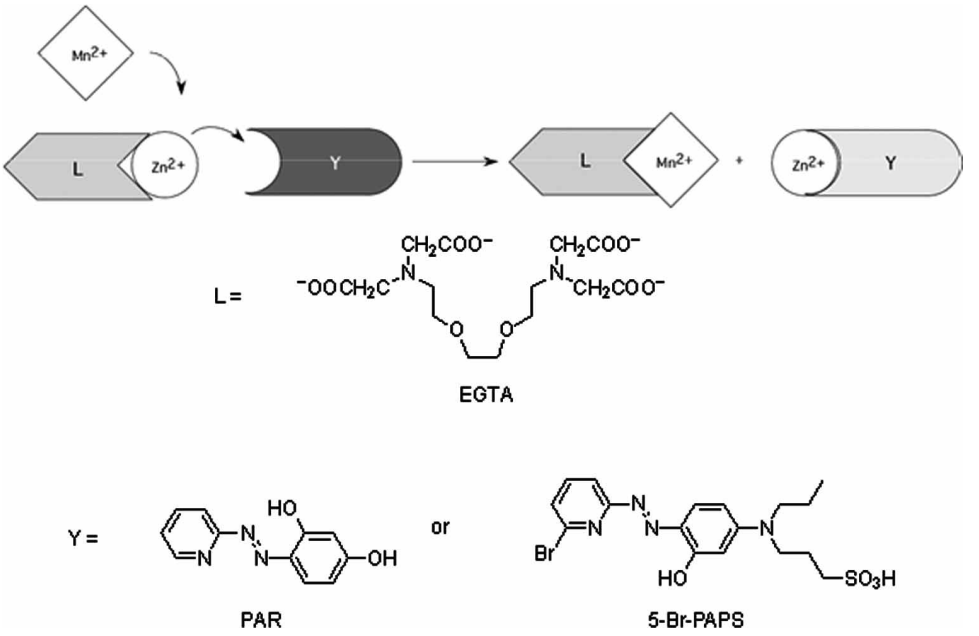

Scheme 1. Design of colorimetric sensory systems for Mn^{2+} and structures of selected chelators.

suffer from significant interference from other metals (*22*). Herein we describe a displacement system for the colorimetric and ratiometric determination of Mn(II) ions. This should be very advantageous since no simple colorimetric reagent is available for the direct detection of Mn(II) at physiological pH.

The principle of this displacement method can be given as follows (Scheme 1). Two chelate-forming agents and a reporter metal ion Zn^{2+} are employed. One chelator (L) is used as a masking agent and the other (Y) as a colorimetric reagent, both forming complexes with metal ions (*11*). To a reagent solution, which contains the colorimetric reagent Y and a stable stoichiometric colourless complex ZnL between the masking agent and the reporter metal ion, is added the analyte solution containing the metal ion Mn^{2+}. Under favourable conditions, Mn^{2+} replaces Zn^{2+} in the complex. The liberated Zn^{2+} reacts with Y to form a coloured complex ZnY, which can be quantified colorimetrically. To obtain a complete (>99%) displacement, the equilibrium constant of the displacement reaction must be greater than 100 (*11*, *16*).

Experimental

4-(2-Pyridylazo)resorcinol (PAR) was purchased from Acros (Geel, Belgium) and 2-(5-bromo-2-pyridylazo)-5-[*N*-propyl-*N*-(3-sulfopropyl)amino]phenol (5-Br-PAPS) was purchased from Fluka (Buchs, Switzerland). All the dyes were used without further treatment. Analytical grade $Zn(ClO_4)_2$, $MnCl_2$, KNO_3, *N*-2-hydroxyethylpiperazine-*N′*-2-ethanesulfonic acid (HEPES) and NaOH were obtained from commercial sources. Buffer solution was prepared using deionised water as solvent and pretreated with ion exchange resin Chelex 100. Electronic absorbance spectra were recorded on an Agilent 8453 Diode Array Spectrophotometer at 298 K.

Results and discussion

After screening a number of available ligands, the colorimetric reagent PAR (Scheme 1) and the masking reagent ethylene glycol-bis(2-aminoethylether)-*N*, *N*, *N′*, *N′*-tetraacetic acid (EGTA, Scheme 1) were chosen as a pair of chelators in sensory system **1**. These two chelators are available commercially at low cost. They are adequately soluble in water at physiological pH. Both chelators form complexes with Zn^{2+} and Mn^{2+}. EGTA and its complexes with Zn^{2+} or Mn^{2+} are colourless. The colour of PAR itself is light yellow, which remained light yellow and its spectrum does not change upon binding Mn^{2+} (*23*). The colour of the complex formed between PAR and Zn^{2+} is brownish yellow, which reverted back to light yellow upon addition of 0.5 equiv of EGTA. PAR associates with Zn^{2+} much more strongly than with Mn^{2+} ($\log \beta_{ZnPAR} = 11.2$ and $\log \beta_{MnPAR} = 8.5$) (*24*), while EGTA complexes with Mn^{2+} are more stable than those with Zn^{2+} ($\log \beta_{ZnEGTA} = 11.5$ and $\log \beta_{MnEGTA} = 12.2$). At the same time, although EGTA has only a slightly higher affinity to Zn^{2+} than PAR does, entropy favours Zn^{2+} to bind to EGTA rather than PAR, as Zn^{2+} forms 1:1 complex with EGTA, while it forms 1:2 complex with PAR. Therefore, a mixture of PAR, Zn^{2+}

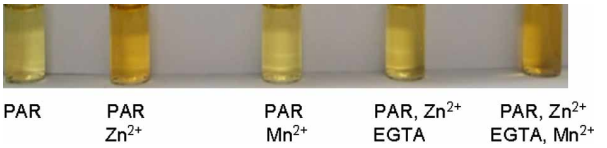

Figure 1. Colorimetric sensing of Mn^{2+} by PAR–Zn^{2+}–EGTA system in HEPES buffer (50 mM HEPES, 0.1 M KNO_3, pH 7.1): the concentration of PAR is 10 μM, other species 5 μM.

and EGTA appears to be light yellow, the colour of PAR itself. The introduction of Mn^{2+} resulted in displacement of Zn^{2+} from the EGTA binding pocket, allowing it to associate with PAR and to induce a change in colour. In this way, Mn^{2+} can be sensed colorimetrically, as shown in Figure 1. However, although excellent absorbance spectra could be produced by titration experiments, the colour change from light to brownish yellow was not visually dramatic. With a goal to produce an assay visible to the naked eye, a system with more distinct colour change was needed to be formulated.

The combination of the disodium salt of 5-Br-PAPS (Scheme 1), Zn^{2+} and EGTA resulted in displacement system **2**. Although 5-Br-PAPS is an analogue of PAR, it gives more dramatic colour change upon binding Zn^{2+} (*25*). Figure 2(A) shows substantial absorption spectral changes when titrated with Zn^{2+}. However, its absorption does not change upon exposure to Mn^{2+} (Figure 2(B)). As is shown in Figure 3(A), the 5-Br-PAPS–Zn^{2+}–EGTA system can be used as a colorimetric sensor for Mn^{2+}. This combination proved to be a much better alternative to the PAR-based displacement systems.

For system **2** in the absence of Mn^{2+}, Zn^{2+} is bound predominantly to EGTA. The 5-Br-PAS under such conditions is in its unbound form and shows an absorption maximum at 449 nm. Like PAR, 5-Br-PAPS associates with Zn^{2+} much more strongly than with Mn^{2+}, while EGTA complexes with Mn^{2+} are more stable than those with Zn^{2+}. At the same time, entropy favours Zn^{2+} to bind to EGTA rather than 5-Br-PAPS, as Zn^{2+} forms 1:1 complex with EGTA, while it forms 1:2 complex with 5-Br-PAPS. Addition of $MnCl_2$ results in displacement of Zn^{2+} from EGTA. As shown in Figure 4(A), the released Zn^{2+} is then consumed by 5-Br-PAPS, causing substantial change in electronic spectrum, with a linear decrease of absorption at 449 nm and the appearance of a new maximum at 552 nm (Figure 4(B)) due to the formation of $Zn(5\text{-Br-PAPS})_2$. The large red shift (103 nm) and absorbance of green light (552 nm) is the most sensitive to naked human eyes and gives rise to the dramatic visual change. There is a clear isosbestic point at 493 nm (Figure 4(A)), which makes this displacement assay ratiometric.

Finally, the sensing system of 5-Br-PAPS–Zn^{2+}–EGTA was loaded onto filter paper by soaking

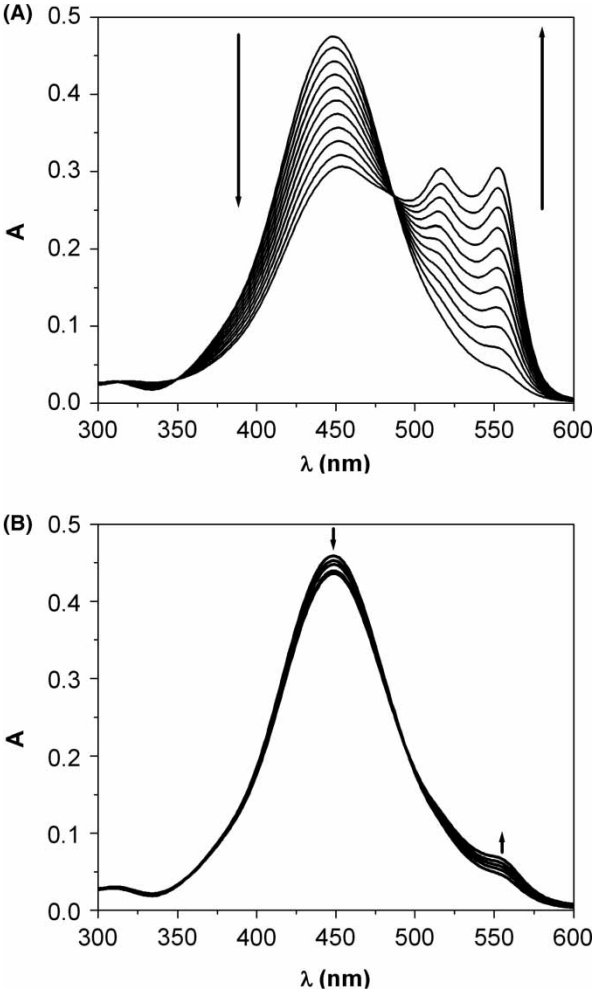

Figure 2. UV–vis spectral response of 5 μM 5-Br-PAPS to (A) Zn^{2+} and (B) Mn^{2+} in HEPES buffer (50 mM HEPES, 0.1 M KNO_3, pH 7.1).

Chelex-treated filter paper in 50 μM of dye solution in HEPES buffer. The filter paper was air dried before exposure to $MnCl_2$ solutions of different concentrations in HEPES buffer (pH 7.1), resulting in colour changes at different $MnCl_2$ levels (Figure 3(B)).

An apparent limitation to this approach is that the selectivity is dictated by the intrinsic affinity of the indicator to different analytes. However, this limitation can be overcome with structural modification of the indicator or can be compensated by using sensor array technology. If a sensor array of PAR, PAR–Zn–EGTA, 5-Br-PAPS and 5-Br-PAPS–Zn–EGTA is used, one would differentiate Mn^{2+} quite easily from other metal ions.

A potential application of this system might involve replacement of Zn–EDTA–PAR as the archetypical 'displacement' reagent (*26*) for the post-column detection of Mn^{2+} and other metal ions in ion chromatography in offering more sensitive and more selective responses.

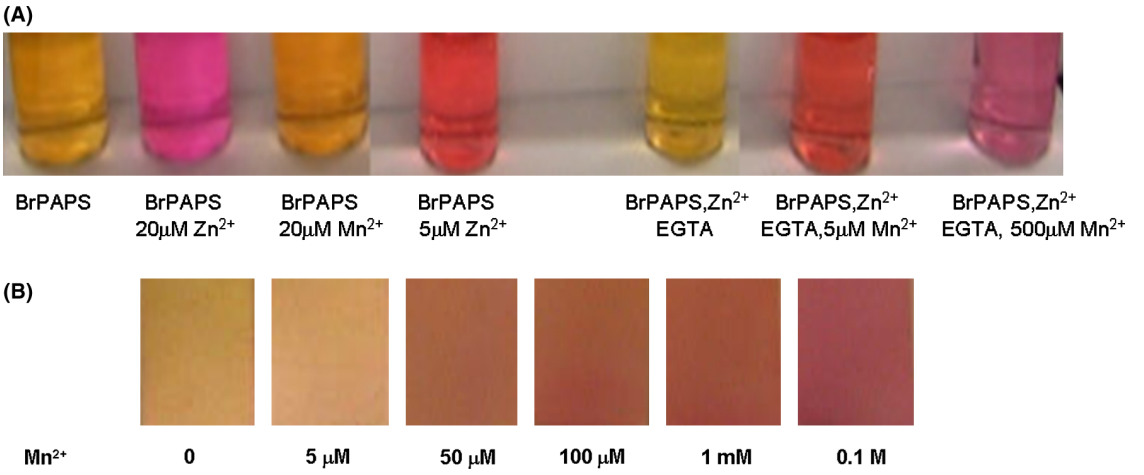

Figure 3. (A) Colorimetric sensing of Mn^{2+} by 5-Br-PAPS–Zn^{2+}–EGTA system in HEPES buffer (50 mM HEPES, 0.1 M KNO_3, pH 7.1): the concentration of 5-Br-PAPS is 10 μM, other species 5 μM unless specified. (B) Test paper sensing of Mn^{2+} by 5-Br-PAPS–Zn^{2+}–EGTA system in HEPES buffer (50 mM HEPES, 0.1 M KNO_3, pH 7.1): the concentration of 5-Br-PAPS is 50 μM, other species 25 μM unless specified.

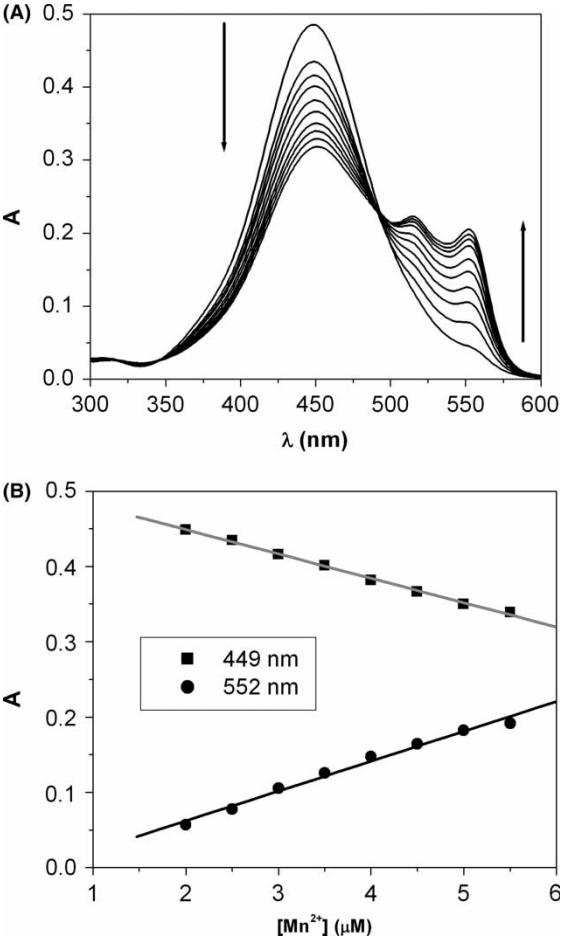

Figure 4. (A) UV–vis spectral response of 5-Br-PAPS–Zn^{2+}–EGTA system to Mn^{2+} in HEPES buffer (50 mM HEPES, 0.1 M KNO_3, pH 7.1). (B) Plot of absorbance at 449 and 552 nm against Mn^{2+} concentration.

Conclusion

In conclusion, we formulated a system that makes possible the colorimetric detection of Mn^{2+}. The system could be implemented in a simple paper test assay, giving a colour change for detection of micromolar concentrations. This approach may lead to the colorimetric imaging of Mn^{2+} in environmental and biomedical applications.

Acknowledgements

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