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A diamide–diamine based Cu^{2+} chromogenic sensor for highly selective visual and spectrophotometric detection

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Abstract—A diamide–diamine based sensor **3** possessing anthracene-9,10-dione as a chromogenic moiety has been synthesized and demonstrates a highly selective colour change from red to blue with Cu^{2+} for visual detection of Cu^{2+} (5–50 μM). Other metal ions, viz. Fe^{2+}, Cr^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Ag^{+}, Pb^{2+}, Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} cations do not lead to any change in colour and their presence does not interfere with the visual and quantitative analysis of Cu^{2+}. The selective deprotonation of an aryl amine NH by Cu^{2+} is responsible for a bathochromic shift and significant colour changes. Significantly, the stability of the **3**·Cu^{2+} complex between pH 7 and 12 allows Cu^{2+} estimation under neutral and basic conditions.

The development of new molecular systems for the colorimetric detection of anions,[1,2] cations[3,4] or neutral molecules[5] has attained prime significance due to their biological and environmental applications. Studies of the mechanisms responsible for these colour changes have resulted in further refinements of the procedures.

Amongst soft transition metal ions, Cu^{2+} is third in abundance (after Fe^{2+} and Zn^{2+}) in the human body and plays an important role in various biological processes.[6] Also, due to widespread use, Cu^{2+} is a significant metal pollutant and in excess causes Wilson's disease.[7] Certain microorganisms are affected by even submicromolar concentrations of Cu^{2+}. The monitoring/estimation of Cu^{2+} and removal of excess copper from the body is based on the availability of selective Cu^{2+} receptors. The design and synthesis of chemosensors for Cu^{2+} constitutes a very active area of research as a result of the demand for more sensitive and selective chemosensors for in vitro and in vivo purposes.[8,9]

In recent years, the anion induced polarization/deprotonation (in extreme cases) of OH in the case of appropriately substituted phenols[10] and NH in the case of appropriately substituted anilides and aryl ureas[11,12] have been used for developing chromogenic anion sensors. In the case of chromogenic sensors for metal ions[13] the deprotonation of phenolic chromophores has been commonly used for developing alkali and alkaline earth metal ion sensors. Recently, Qian et al. have shown that deprotonation of an amine NH conjugated to a 1,8-naphthalimide moiety leads to a bathochromic shift and provides aesthetic appeal for a colorimetric assay.[14]

1-Aminoanthracene-9,10-dione, a chromogenic moiety, has been successfully used for designing anion sensors[15] where NH deprotonation leads to colour changes. We envisaged that the presence of an appropriate metal interacting unit on the 1-aminoanthracene-9,10-dione unit would induce metal-mediated colour changes, enabling chromogenic metal ion sensors with bathochromic shifts.

Accordingly, we have designed and synthesized receptors **3** and **4** for transition metal ion estimation and have found that, as envisaged, the receptor **3** demonstrates a highly selective instantaneous colour change from red to blue with Cu^{2+} only, which is stable for more than 24 h and can be used for both qualitative and quantitative estimation of Cu^{2+} under neutral and basic conditions. The receptor **4** also demonstrates an instantaneous colour change with Cu^{2+} (though significantly less than **3**); however, other transition metal ions interfere in the estimation of Cu^{2+}.

2-Aminoethylaminoanthracene-9,10-dione (**1**)[16] on alkylation with ethyl bromoactate in DMF–K_2CO_3–TBA HSO_4 system provided diester **2**, 80%, mp 78 °C

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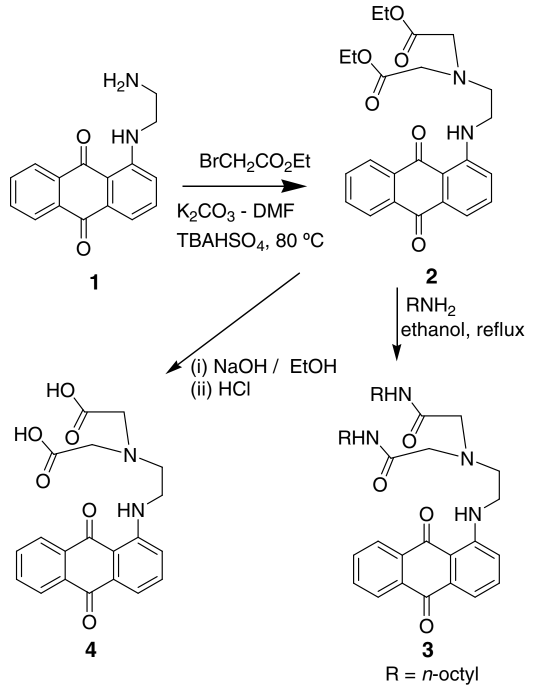

Scheme 1. Synthesis of chemosensors **3** and **4**.

(CH_3CN). On refluxing diester **2** with *n*-octylamine in ethanol, the respective diamide **3**[17] was obtained in 75% yield, mp 83 °C (CH_3CN–ether). Diester **2** on hydrolysis with ethanolic NaOH solution, followed by acidification, gave diacid **4**,[18] 60%, mp 185 °C (ethanol) (Scheme 1).

Chemosensing properties are, in general, highly dependent on the pH of the system. Therefore, the influence of pH on both the receptors and their complexes with Cu^{2+} was evaluated. The influence of pH on the absorbance of **3** was determined by UV–vis titration in CH_3OH–H_2O (3:1, v/v). The absorbance of **3** at 512 nm remained unaffected between pH 6 and 12. Significantly, when the pH of the solution was lowered from 6, small perturbations in the λ_{max} and absorbance were observed which point to the protonation of **3** in this pH range. Protonation of a tertiary amine is initiated at pH 9; then at pH 6.5 and 5.0, respectively, two amide oxygens are protonated and at pH < 4, protonation at the anthraquinone oxygen takes place. No visible change in colour or λ_{max} of **3** under acidic conditions shows that the aryl amine NH is not protonated. Its $\log\beta_{LH1} - \log\beta_{LH4}$ values are 7.98, 13.37, 16.93 and 19.18, respectively.

When 1 equiv of Cu^{2+} was added to a solution of **3** in methanol–water (1:1), the absorbance at λ_{max} 512 nm significantly decreased with the emergence of a new band at 620 nm due to the **3**·Cu^{2+} complex. On titration with NaOH, between pH 7 and 12, the absorbance at both 512 and 620 nm remained constant. However, on titration with acid, the intensity of the absorption band at 620 nm gradually decreased and that at 512 nm gradually increased. At a pH lower than 4, the absorbances again became constant. These results clearly show that **3** initiates complex formation with Cu^{2+} at pH 4 and that its formation is maximum at pH $\geqslant$ 7. Therefore, chemosensor **3** can be used for quantitative estimation of Cu^{2+} between pH 7 and 12. The appearance of a blue colour on addition of Cu^{2+} to a solution of **3** is quite evident at pH $\geqslant$ 5.

The spectral fitting of these data converges to the formation of MLH_{-1} and MLH_{-1} (OH^-) complexes with $\log\beta_{MLH-1}$ 5.8 ± 0.1 and $\log\beta_{MLH-1(OH-)}$ 0.3 ± 0.1. The visible colour changes with >100 nm bathochromic shift and these spectral fittings point to the increased electron density on the chromogenic moiety—anthracene-9,10-dione, and suggest deprotonation at the aryl amine NH.

Further, to increase the scope of **3** in Cu^{2+} analysis, the applicability of **3** for quantitative estimation of Cu^{2+} was evaluated. The affinity of **3** for a series of transition metal ions, alkali and alkaline earth metal ions has been investigated at pH 7.0 ± 0.1 (10 mM HEPES in CH_3OH–H_2O 3:1). A solution of **3** (50 μM), on gradual addition of Cu^{2+}, shows a gradual decrease in absorbance at λ_{max} 512 nm with concomitant appearance of a new absorption band at λ_{max} 620 nm, the colour turning from red to blue. In particular, the band at 620 nm reached its limiting value after the addition of 1 equiv of Cu^{2+} (Figs. 1 and 2), and adding more Cu^{2+} led to only nominal changes in the UV–vis spectra.

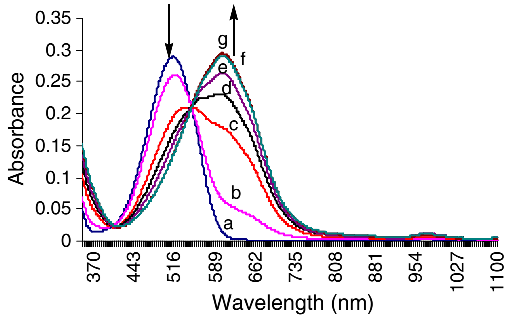

Figure 1. UV–vis spectra of **3** (50 μM) upon titration with $Cu(NO_3)_2$: (a) 0; (b) 10 μM; (c) 25 μM; (d) 40 μM; (e) 50 μM; (f) 75 μM and (g) 100 μM of Cu^{2+}.

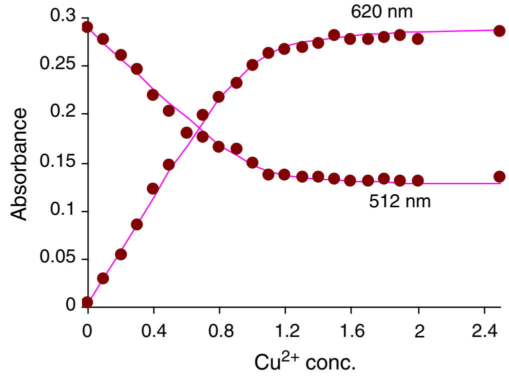

Figure 2. Plot of absorbance of **3** (50 μM) against Cu^{2+} concentration. The points refer to experimental values and solid lines to curve fitting.

The absorbance of solutions of **3** containing different concentrations (5–100 μM) of Cu^{2+} and 500 μM of Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} Fe^{2+}, Cr^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+} and Cd^{2+} both at λ_{max} 512 nm and of the **3**-Cu^{2+} complex at λ_{max} 620 nm remained unaffected by the presence of these metal ions. Significantly, in the case of **3**, both the decrease in absorbance at 512 nm and increase in absorbance at 620 nm can be used for the estimation of Cu^{2+} even in the presence of these metal ions.

The perceived colour and spectrophotometric changes with Cu^{2+} by receptor **3** would be useful not only for the rapid visual sensing, but also for the ratiometric method of detection of Cu^{2+}. Ratiometric probes have the important feature in that they permit signal rationing and thus, increase the dynamic range. The dependence of absorption ratios at A_{620}/A_{512} on metal ions shows that disturbance in the absorption spectrum of **3**-Cu^{2+} is insignificant due to the other metal ions, such as Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} Fe^{2+}, Cr^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Ag^+ and Pb^{2+} (Fig. 3a). Competitive experiments were conducted in the presence of Cu^{2+} at 50 μM mixed with Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} Fe^{2+}, Cr^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Ag^+, Pb^{2+}, etc. at 500 μM; no significant variation in the absorption ratios at A_{620}/A_{512} was found by comparison to those without the other metal ions besides Cu^{2+} (Fig. 3b).

The receptor **4** (100 μM at pH 7.0 ± 0.1; 10 mM HEPES in CH_3OH–H_2O 3:1) exhibits a λ_{max} at 492 nm, and on addition of 1 equiv of Cu^{2+}, a new absorption band at 615 nm appears which induces a colour change from red to blue. The addition of other metal ions, such as Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} and Cd^{2+}, produced nominal changes in the absorption spectrum; however, Ni^{2+}, Zn^{2+} and Co^{2+} showed interference in the absorption spectrum with a bathochromic shift, and change in colour from red to blue in the case of Co^{2+} only (after 12 h) (Fig. 4). Therefore, diacid **4** shows lower selectivity for Cu^{2+} than that observed for **3**. Similar interference of transition metal ions in diacid based Cu^{2+} receptor has been earlier reported by Gunnlaugsson et al.[4a]

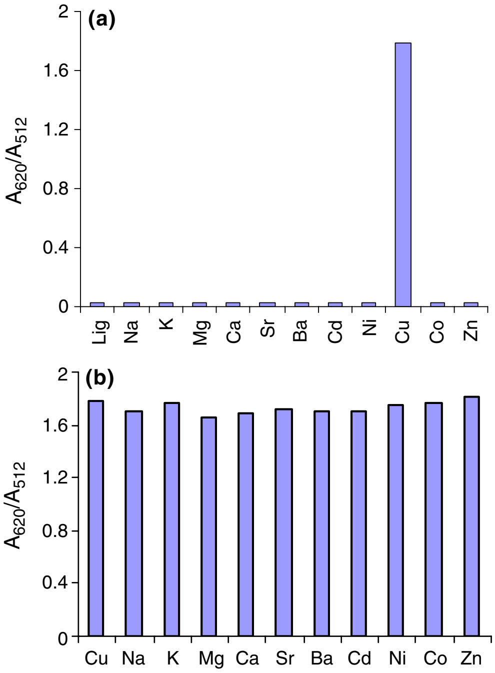

Figure 3. (a) Responses of receptor **3** (50 μM) to the selected metal ions (50 μM). (b) Spectrophotometric response of receptor **3** (50 μM) containing 50 μM Cu^{2+} to the selected metal ions (500 μM).

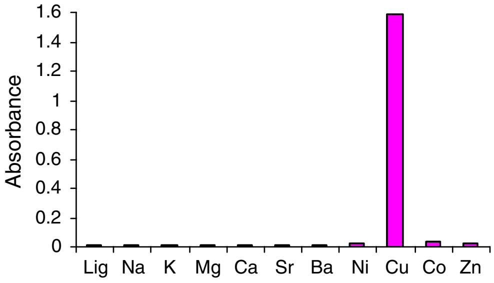

Figure 4. Responses of receptor **4** (100 μM) to metal ions (100 μM).

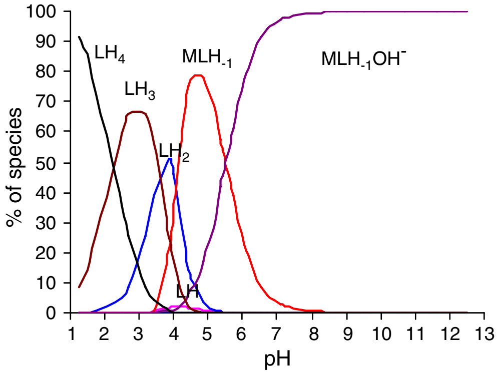

Figure 5. Species distribution diagram of **3** as a function of pH for a system containing 50 μM Cu^{2+} and 50 μM of **3**.

The spectral fitting of the spectra (Fig. 2) obtained by titration of **3** (50 μM) with Cu^{2+} at pH 7.0 ± 0.1 in CH_3OH–H_2O (3:1) shows the formation of ML ($\log \beta_{ML}$ 5.97 ± 0.1). A species distribution diagram of the combination of pH and UV–vis titration of a 1:1 complex of **3** and Cu^{2+} reflects that at pH $\geqslant$ 7.0, only $MLH_{-1}(OH^-)$ exists and remains stable even under strong basic conditions (Fig. 5). The stability of absorbance at pH $\geqslant$ 7.0 shows that **3** can be used in this pH range for the estimation of Cu^{2+}.

Thus, **3** can be used for the estimation of 5–50 μM Cu^{2+} in the pH range 7–12 but has the limitation of being insoluble in pure water. Efforts to make a water soluble receptor are in progress.

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17. *Diamide* **3**, dark red solid; 75%; mp 83 °C (CH_3CN–ether); FAB mass M^+ m/z 605 (M^++1); IR ν_{max} (KBr) 1624, 1649, 3273 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.82 (t, $J = 6.9$ Hz, 6H, $2 \times CH_3$), 1.08–1.25 (m, 20H, $10 \times CH_2$), 1.46 (q, $J = 6.9$ Hz, 4H, $2 \times CH_2$), 2.93 (t, $J = 5.1$ Hz, 2H, CH_2), 3.23 (t, $J = 6.9$ Hz, 4H, $2 \times CH_2$), 3.28 (s, 4H, $2 \times CH_2$), 3.48 (q, $J = 5.1$ Hz, 2H, CH_2), 7.06 (d, $J = 7.2$ Hz, 1H, ArH), 7.61–7.70 (m, 2H, ArH), 7.77–7.80 (m, 2H, ArH), 8.24–8.31 (m, 2H, ArH), 10.25 (br s, 1H, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 13.98 (+ve, CH_3), 22.50 (−ve, CH_2), 26.96 (−ve, CH_2), 29.13 (−ve, CH_2), 29.25 (−ve, CH_2), 29.59 (−ve, CH_2), 31.68 (−ve, CH_2), 39.06 (−ve, CH_2), 39.53 (−ve, CH_2), 53.22 (−ve, CH_2), 58.64 (−ve, CH_2), 112.99 (absent, ArC), 116.79 (+ve, ArCH), 118.13 (+ve, ArCH), 126.41 (+ve, ArCH), 127.19 (+ve, ArCH), 133.14 (+ve, ArCH), 133.63 (+ve, ArCH), 133.99 (absent, ArC), 134.59 (absent, ArC), 136.34 (+ve, ArCH), 151.33 (absent, ArC), 169.18 (absent, CO), 183.11 (absent, CO), 186.04 (absent, CO). Found: C, 71.42; H, 8.65; N, 9.28. $C_{36}H_{52}N_4O_4$ requires C, 71.49; H, 8.67; N, 9.26.
18. *Diacid* **4**, dark red solid; 60%; mp 185 °C (ethanol); FAB mass M^+ m/z 383 (M^++1); IR ν_{max} (KBr) 1632, 1676, 1728, 3284 cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.42 (br s, 2H, CH_2), 3.75 (br s, 2H, CH_2), 4.10 (br s, 4H, $2 \times CH_2$), 7.32 (d, $J = 8.4$ Hz, 1H, ArH), 7.48 (d, $J = 7.2$ Hz, 1H, ArH), 7.63 (t, $J = 8.4$ Hz, 1H, ArH), 7.79–7.90 (m, 2H, ArH), 8.11–8.27 (m, 2H, ArH), 9.71 (br s, 1H, NH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$–DMSO-d_6): δ 38.19 (−ve, CH_2), 53.50 (−ve, CH_2), 54.52 (−ve, CH_2), 112.68 (absent, ArC), 115.24 (+ve, ArCH), 118.22 (+ve, ArCH), 126.06 (+ve, ArCH), 126.25 (+ve, ArCH), 132.19 (absent, ArC), 133.17 (+ve, ArCH), 133.94 (absent, ArC), 134.14 (+ve, ArCH), 135.28 (+ve, ArCH), 150.60 (absent, ArC), 168.83 (absent, CO), 182.61 (absent, CO), 183.83 (absent, CO). Found: C, 62.80; H, 4.73; N, 7.35. $C_{20}H_{18}N_2O_6$ requires C, 62.82; H, 4.74; N, 7.33.