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Colourimetric and fluorescent detection of oxalate in water by a new macrocycle-based dinuclear nickel complex: a remarkable red shift of the fluorescence band†

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A new macrocycle-based dinuclear nickel chemosensor selectively binds oxalate anions both in solution and the solid state, displaying a remarkable red shift of the fluorescence band with a visible colour change in water at physiological pH in the presence of an external dye.

The selective recognition and sensing of anions is an important research area in supramolecular chemistry because of the fundamental roles played by anions in chemical, biological, medicinal, and environmental applications.[1] In particular, the optical sensing *via* the fluorescence technique is a rapid and cost-effective way to detect an anion at a micromolar level in solution.[2] Therefore, a significant effort has been made towards the design of chromogenic and fluorogenic receptors that can selectively recognize anions and act as sensors.[3] In this regard, the oxalate anion is of great interest due to its vital roles in chemistry as well as in biochemistry.[4] It is naturally present in several foods and serves as a nutrient in the human body; however, an excess consumption of oxalate may result in a number of pathological conditions including renal failure, cardiomyopathy disorder, and the development of kidney stones.[5] Oxalate is also produced in the human body as a result of cellular metabolism.[5c] Since there is no enzyme in the human body to degrade oxalate, it is excreted by the kidney into the urine.[5b] Therefore, the quantitative information of oxalate is widely used in identifying several diseases including *hyperoxaluria*, *vulvodynia*, and kidney stones.[6a] It is known that the normal level of urinary oxalate excretion is 110 to 460 μmol in 24 hours.[6b] The oxalate content is clinically determined in urine using several techniques including high performance liquid chromatography, gas chromatography, ion chromatography and enzyme assays which are quite expensive instruments and often require time-consuming sample preparation.[7]

In recent years, a number of synthetic receptors which are primarily based on H-bond donors, have been developed for the selective binding of anions;[8] however, there are only a few known receptors that effectively bind oxalate in aqueous phase.[9] Therefore, the chemistry of simple and efficient sensors for the selective sensing of oxalate, particularly at physiological pH in water, remains a major challenge for researchers. On the other hand, dinuclear metallic complexes are generally soluble in water, and are known to bind anions through Lewis-acid–base interactions.[10] In particular, macrocycle-based receptors as dinuclear copper,[11] cobalt,[12] zinc[13] and ruthenium[9c] complexes have been shown to bind various anions, but their applications as dinuclear nickel complexes in anion binding have not been explored yet. Herein, we report a novel macrocycle-based dinuclear nickel complex that selectively binds oxalate anions in a 1 : 2 (host–guest) binding mode both in solution and the solid state, displaying a remarkable red shift of the fluorescence band with a visible colour change in water at physiological pH in the presence of an external dye.

Macrocycle **1** was synthesized according to a procedure reported earlier.[11d] The nickel complex was prepared from the reaction of **1** with two equivalents of $Ni(NO_3)_2$ in a H_2O–CH_3OH (5 : 1, v/v) mixture (Scheme 1). Green crystals as $[Ni_2(\mathbf{1})(H_2O)_6](NO_3)_4$ (**L**) suitable for X-ray diffraction‡ were grown from the nickel complex dissolved in H_2O–CH_3OH (5 : 1, v/v) under slow evaporation at room temperature. As shown in Fig. 1A, the macrocycle contains two Ni^{II} ions at both N_3 terminals in $[Ni_2(\mathbf{1})(H_2O)_6]^{4+}$, where each Ni^{II} is coordinated in an octahedral environment with three nitrogens at one face and three water molecules at the other face of the octahedron (*fac* conformation), with a Ni···Ni distance of 9.397 Å. The charge (4+) of the complex is balanced by four nitrates located outside the coordination sphere, indicating the poor affinity of Ni^{II}

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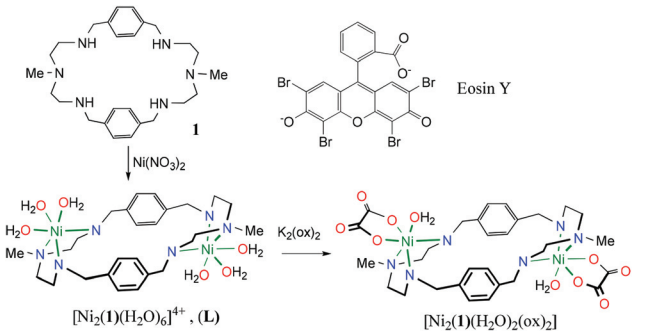

Scheme 1 Synthetic pathway to L and oxalate complex from **1**, and the chemical structure of the indicator (eosin Y) used.

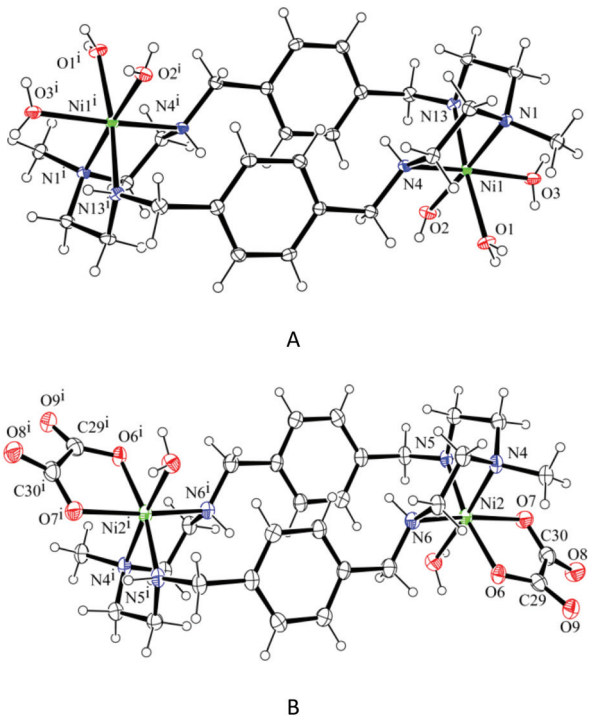

Fig. 1 ORTEP plots of the chemosensor L, $[Ni_2(\mathbf{1})(H_2O)_6]^{4+}$ (A) and the oxalate complex, $[Ni_2(\mathbf{1})(H_2O)_6(ox)_2]$ (B). External non-bonded nitrates in A and water molecules in B are not shown for clarity.

centres for nitrates. The cationic unit $[Ni_2(\mathbf{1})(H_2O)_6]^{4+}$ possesses an inversion center where the aromatic units are parallel to each other, exhibiting π···π interactions (Ar···Ar = 3.403 Å). Notably, three water molecules in each subunit are directed outside the cavity that could possibly be replaced by competitive anions. To test this hypothesis, two equivalents of potassium oxalate were added to the solution of **L** in H_2O–CH_3OH (5 : 1, v/v), resulting in the formation of oxalate bound complex $[Ni_2(\mathbf{1})(H_2O)_2(ox)_2]$. The structure of the oxalate complex as shown in Fig. 1B is surprisingly similar to that of **L**. Two coordinating water molecules at each N_3 unit in **L** are exchanged by one oxalate, demonstrating a clear tendency of $[Ni_2(\mathbf{1})(H_2O)_6]^{4+}$ to complex oxalate without the compensation of its geometrical transformation. On the basis of a closer look

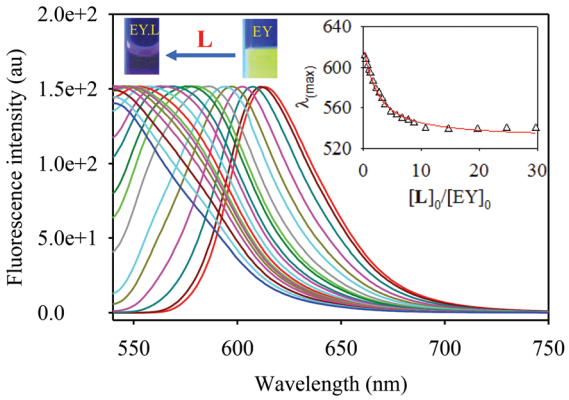

Fig. 2 The change of emission λ_{max} (blue shift) of EY upon the gradual addition of L in water buffered with 20 mM HEPES at pH 7.4. $[EY]_o$ = 2×10^{-6} M, $[L]_o$ = 2×10^{-4} M. Excitation = 516 nm. The inset shows the plot of λ_{max} against the concentrations of L.

at the two structures, it is likely that the minimum steric strain is required for oxalate to displace the bound water molecules lying at the *trans*-position of two coordinating secondary amines (N4 and N17) in **L**.

In order to evaluate the interaction of **L** for oxalate, an indicator displacement assay (IDA) was performed using an Eosin Y (EY) fluorescent dye. First, we examined the interaction of **L** with EY in water. As shown in Fig. 2, upon the incremental addition of **L** to a solution of EY buffered at pH 7.4 (20 mM HEPES), the fluorescence band (λ_{max}) at 613 nm gradually shifted to a lower wavelength (blue shift), resulting in a saturation at 539 nm of the band with about 15 equivalents of **L** (inset in Fig. 2). It is noteworthy that this tendency of the blue shift of the fluorescence band is in contrast with that observed for related dinuclear Cu^{II} complexes by others[9a,b,11c] and us[11e] showing the quenching of fluorescence. The change in the λ_{max} against the concentration of **L** gave the best fit of a 1 : 2 (**L**–EY) binding model,[14] yielding the binding constant, log K = 4.42. Such a shift instead of a quenching of the fluorescence band could be due to the fact that the dye interacts with a Ni^{II} ion from outside rather than inside forming a 1 : 2 adduct, as observed in the crystal structure.

The sensing ability of the receptor–dye complex (**L**·EY) for oxalate was then investigated by fluorescent titrations using a mixture of the **L** and EY dye (**L**–dye = 2 : 1, mol/mol) in water at pH 7.4 (0.02 M HEPES). After the addition of potassium oxalate (2×10^{-4} M, pH 7.4) to **L**·EY, the fluorescence band shifted to the higher wavelength, indicating the displacement of EY from the receptor–dye complex to the solution (Fig. 3). The addition of about 3 equivalents of the anion provided a full revival of the fluorescence band at λ = 613 nm due to the free EY. Interestingly, the addition of oxalate in the range of 5–50 μM (0 to 0.25–2.50 equiv.) to **L**·EY gave the characteristic emission wavelength of **L**·EY, displaying the complementary colour of the solution (Fig. 4). This detection limit is much lower than the normal range of oxalate content (110 to 460 μM) in urine;[6b] thereby this receptor could be used as a probe for the direct measurement of the oxalate concentration

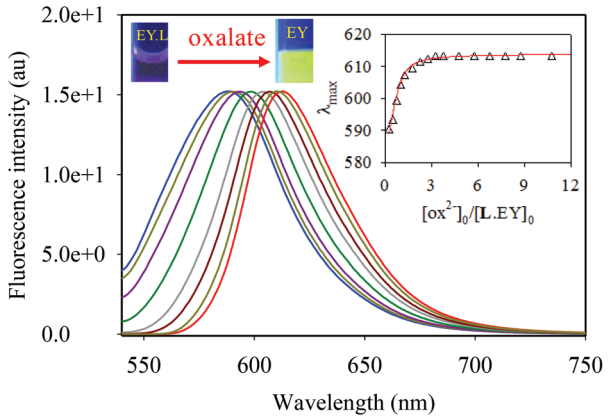

Fig. 3 The change of emission λ_{max} (red shift) of [L·EY] (L–EY = 2 : 1) upon the addition of $K_2C_2O_4$ in water buffered with 20 mM HEPES at pH 7.4. $[L]_o = 2 \times 10^{-6}$ M, $[K_2C_2O_4]_o = 2 \times 10^{-4}$ M. Excitation = 516 nm. The inset shows the plot of λ_{max} against the concentration of $K_2C_2O_4$.

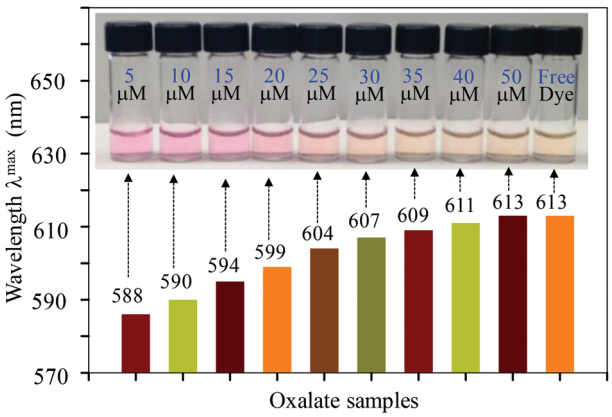

Fig. 4 Progressive colour change with the increasing amount of oxalate (in ppm) and the corresponding λ_{max} of the fluorescence band during the titration of [L·EY] (L–EY = 2 : 1) with $K_2C_2O_4$ as shown in Fig. 3.

in practical applications. The change of the fluorescence band as a function of the concentration of oxalate gave the best fit of a 1 : 2 binding model,[14] which was further confirmed by Job's plot (Fig. S5 in ESI†) and is in agreement with the solid state structure of the oxalate complex. The calculated binding constant for oxalate was 6.68 (in log *K*) as compared to the reported value for that with a dinuclear copper complex (log *K* = 5.11).[9a] In contrast, the addition of other anions including F^-, Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, SO_4^{2-} and PO_4^{3-} to the receptor–dye complex did not result in any significant change of the fluorescence band (Fig. 5), indicating that the interactions of the receptor–dye complex with these anions are not strong enough to displace the dye from the complex.

The new sensor was further studied for the colourimetric detection of the oxalate anion. Fig. 5 shows the results of colourimetric experiments on **L**·EY (2×10^{-5} M, **L**–EY = 1 : 2) after the addition of various anions (20 equivalents) in water (20 mM HEPES at pH 7.4) under visible (A), and UV lights at

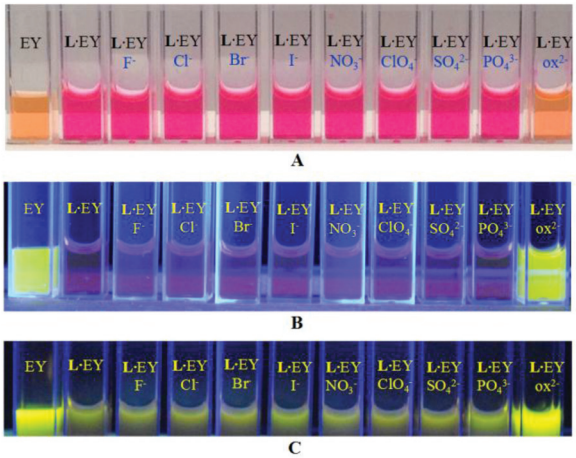

Fig. 5 Colourimetric detection of oxalate against various anions (F^-, Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, SO_4^{2-} and PO_4^{3-}) with the solution of L·EY ($[L]_o = 2 \times 10^{-5}$ M, L–EY = 1 : 2) in water buffered with 20 mM HEPES at pH 7.4. A: visible light; B: UV light at 365 nm; C: UV light at 254 nm. 10 equiv. of the anion were added to each solution.

365 nm (B) and 254 nm (C). Upon the addition of oxalate to the **L**·EY solution, the deep magenta colour of the **L**·EY complex turned into pale orange, which is the original colour of EY (Fig. 5A). This observation suggests the decomplexation of the dye, which was further confirmed by UV studies (Fig. S8 and S9 in ESI†). However, other anions did not affect the colour of the **L**·EY solution. The colour change event for oxalate is also visually detectable (pale purple to green yellow) when viewed at 365 nm (Fig. 5B). Therefore, the sensor is very useful for detecting oxalate simply by a colour change at a very low concentration in water at physiological pH. It is noteworthy that the fluorescence of the complex EY·**L** (as well as the mixture of EY·**L** + other anions) was visually detectable when viewed at 254 nm (Fig. 5C), an observation that is consistent with the titration results of EY with **L** (Fig. 2), showing a blue shift instead of a quenching of the fluorescence band.

Conclusions

In summary, we have presented a new type of macrocycle-based dinuclear nickel complex that selectively binds an oxalate over a wide range of anions in water at physiological pH. An indicator displacement approach has been successfully applied to identify the oxalate anion under very dilute conditions, providing the remarkable red shift of the fluorescence band upon oxalate binding. Further, oxalate can be detected from the sharp colour change under both visible and UV light in water at physiological pH. Structural characterization of both free and oxalate complexes demonstrates that the dinuclear metal complex provides an ideal geometrical environment where no rearrangement of the structure is necessary to bind oxalate. This new approach provides an insight into the design of selective sensors for other anions that are biologically and chemically important.

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Notes and references

‡ Crystal data for $[Ni_2(\mathbf{1})(H_2O)_6]^{4+}\cdot 4NO_3^-$, M = 984.28, monoclinic, a = 9.233(3) Å, b = 16.580(5) Å, c = 14.170(4) Å, β = 91.545(7)°, V = 2168.4(11) Å^3, T = 100(2) K, space group $P2_1/n$, Z = 2, μ(MoKα) = 0.958 mm^{-1}, R_{int} = 0.0543, R_1 = 0.0413 ($I > 2\sigma(I)$). Crystal data for $[Ni_2(\mathbf{1})(H_2O)_2(ox)_2]\cdot 4.85(H_2O)$, M = 891.36, triclinic, a = 8.9574(10) Å, b = 15.128(2) Å, c = 15.402(2) Å, α = 94.199(9)°, β = 103.866(9)°, γ = 106.950(10)°, V = 1915.1(4) Å^3, T = 90.0(5) K, space group $P\bar{1}$, Z = 2, μ(CuKα) = 1.923 mm^{-1}, R_{int} = 0.0699. R_1 = 0.0471 ($I > 2\sigma(I)$). CCDC 970398–970399.

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