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Human Vision Inspired Adaptive Platform for One-on-Multiple Recognition

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The fluorescence of a coordinative molecule DCM displaying intramolecular charge transfer (ICT) effect is regulated by several metal ions. These DCM-metal compelxes were adopted to recognize different chemicals, including recognition of triethylenetetramine, thiol-containing amino acids, and H_2S upon binding DCM with Zn^{2+}, Ag^{+}, and Pb^{2+}, respectively. This is in analogy to the general mode of human trichromatic color vision.

Nature has long been a grandmaster in teaching chemists to make complicated functionality out of the simplest building blocks. One impressive lesson is the trichromatic color vision of human's eyes, where one simple pigment of retinal is used to recognize different colors of light (Scheme 1a) [1]. Generally, the excited states of retinal is tuned when it binds to different proteins, including Red, Green, Blue opsins, which enable the recognition of R, G, B colors on one platform [2, 3]. Such a one-on-multiple strategy is commonly utilized by animals. There are numerous evolving opsins and several analogues of retinal, which helped animals to adapt to certain living environments using limited molecules [4-6].

Inspired by these natural masteries, we believe that the chemical recognition activity can also be designed in a similar way, namely, to achieve diversified recognition on the platform formed by the same molecule. The key point is to design a reporting unit that can non-covalently bind to different recognizing units. However, so far, people haven't master such an elegant strategy to recognize desired components in artificial world, and considerable efforts was put on to design specific detectors for each target [7-13]. Such a 'one-on-one' method will cost too much energy and resources, which is in clear contrast with the smart behavior of retinal in receiving the full spectrum of light.

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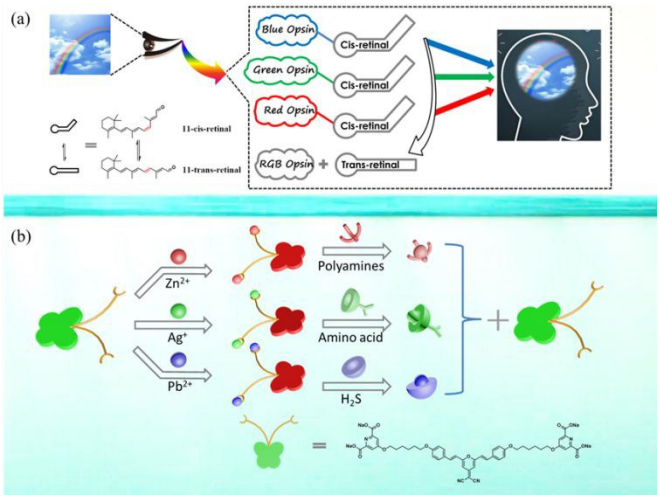
Herein, we report a 'one-on-multiple' strategy, which resembles the typical mode of human vision generation (Scheme 1b). Starting with the single fluorescent molecule **DCM**, we differentiated three categories of small molecules, including polyamine, thiol-containing amino acid, and the H_2S. The **DCM** is designed to have a dicyanomethylene-4H-pyran-based reporting unit, which is expect to display emission color change in different environments owing to the presence of conjugated donor –acceptor groups. Two coordinating arms were covalently attached to the reporting unit. Upon coordinating to metal ions, the DCM-Metal complex displayed an emission different from the native DCM as a result of the existence of intramolecular charge transfer (ICT) states. Excitingly, each DCM-Metal system exhibited a specific recognition ability toward a specific chemical, which were accompanied by reversed fluorescent transitions. As a result, starting from the same DCM molecule, we can respectively recognize three categories of chemicals mediated by the coordination of three metal ions. This one-on-multiple strategy is in analogue to the human vision generation. We envision that such a bio-inspired strategy will open up a new horizon for the development of chemical recognition.



Scheme 1. Illustration of (a) human vision formation and (b) our strategies for the construction of sensing platform.

DCM is a coordinative amphiphile synthesized in our lab (Scheme S1). This molecule has a butterfly-like topology in which two coordinating antennae are attached to a fluorescent core (Scheme 1). According to previous research, phenyl substituted dicyanomethylene-4H-pyran displays distinct optical behaviors in different environments due to the interconversion between local excited (LE) states and intramolecular charge transfer (ICT) states [14, 15]. Here, the attachment of coordinating arms does not impact its ICT process. As evidence, both the absorption and emission of DCM solution can be easily regulated by varying the solvent compositions in water-ethanol mixtures. DCM displayed green emission in its good solvent of 1-1(volume ratio) water-ethanol mixture, while red fluorescence was observed in solvents either rich in water or rich in ethanol (Figure S1a). The characteristic red shifts of both absorption maxima(from 560 nm to 630 nm) and emission peaks (arise of new peak at 499 nm), together with the large Stokes-shift indicated the occurrence of ICT complexes in water or ethanol rich solvents (Figure S1b&S1c) [15].

Next, the interaction of DCM with different metal ions was explored based on the coordinative ability of the dicarboxylate pyridine head groups. Figure 1a shows the fluorescent color change of the DCM in 1-1 water-ethanol mixed solvents upon addition of equivalent (two for Ag^+, Figure S2) metal ions. Notably, the emission color of **DCM** exhibited dramatic changes after addition of Ca^{2+}, Zn^{2+}, Pb^{2+} and Ag^+. FT-IR measurements confirms that these metal ions have coordinated to the dicarboxylate pyridine head (Figure S3). Spectra examination reveals (Figure 1b and 1c) new absorption maxima near 500 nm and new emission peaks at around 650 nm, verifying the occurrence of ICT states under these conditions.

The coordination triggered red emission is drastically different from the green emission of DCM itself. Since metal ions can bind to different molecules respectively, these **DCM**-metal complexes can be further used as individual species for specific recognition purpose. In principle, any material that can rob metal ions from **DCM** will induce a reversed fluorescence

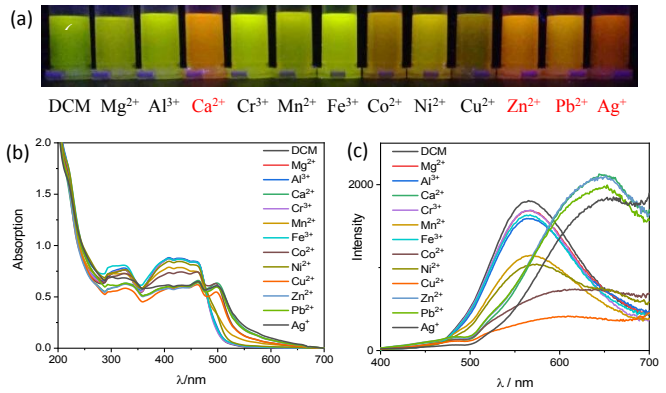


Figure 1. (a) Fluorescent pictures of **DCM-M^{n+}** systems in 1-1(volume ratio) water-ethanol mixed solvents under 365nm UV lamp. [DCM] = [M^{n+}] = [Ag^+]/2 = 50 μM. (b) Absorption spectrums and (c) Emission spectrums of DCM-M^{n+} systems in 1-1 water-ethanol mixed solvents.

change in the corresponding **DCM**-metal system. This provided us the fundaments to construct multiple recognition platform based on one single fluorescent molecule **DCM**. Though most small molecules failed to destruct **DCM-Ca^{2+}** system, we succeeded in other three systems.

Triethylenetetramine (TETA) is an orphan drug that has been commonly used in the treatment of Wilson's disease for decades [16]. Recent studies also revealed its potential uses in cancer chemotherapy and other diseases [17-19]. However, clinical applications and pharmacologic studies of TETA are greatly hindered by the lack of versatile analytical methods, as current protocols for TETA detection are majorly based on chromatography or labelling reagents [20, 21]. Here, we achieved direct fluorescent detection of TETA using **DCM-Zn^{2+}** system. Upon addition of 0.5 mM TETA to 50 μM **DCM-Zn^{2+}** solution, a red-to-green fluorescent transition can be observed (Figure 2a). Using fluorescent titration method, we can achieve quantitative detection of TETA in the concentration range of 50~500 μM (Figure 2b), which covers the commonly used concentrations in preclinical studies [22]. Notably, its analogues including ethylenediamine (EDA) and diethylenetriamine (DETA) only show limited influence on the DCM-Zn^{2+} system. Under equivalent concentration, the co-existence of EDA or DETA is negligible and doesn't significantly affect the detection of TETA (Figure 2b&S4). Besides, other competing species such as S^{2-} and CO_3^{2-} or the presence of other metal ions, show ignorable influences (Figure 2c and Figure S5). This desirable selectivity of **DCM-Zn^{2+}** towards TETA can be related to the octahedral coordination configuration usually adopted by Zn^{2+}, which favors the formation of planar chelating structures with multi-dental ligands.

Recognition of specific amino acid has always been an interesting topic in fluorescent sensing area. Among them, most efforts were dedicated to the selective detection of thiol-containing ones, such as cysteine (Cys) and glutathione (GSH), [23-25] due to their crucial role in many physiological aspects [26, 27].

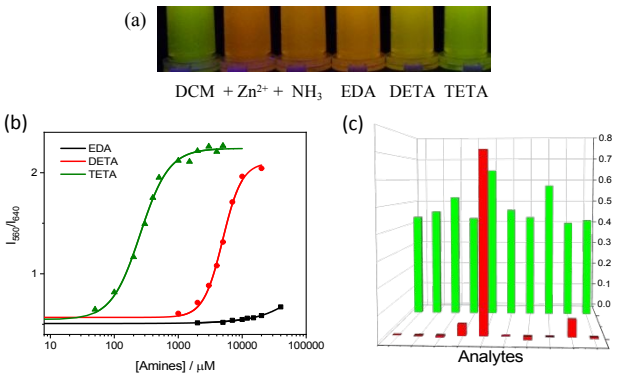


Figure 2. (a) Fluorescent pictures of **DCM-Zn^{2+}** systems with polyamines in 1-1(volume ratio) water-ethanol mixed solvents under 365nm UV lamp. [DCM] = [Zn^{2+}] = 50 μM, [NH_3] =2 [EDA] = 3 [DETA] = 4 [TETA] = 5 mM. (b) Ratiometric titration of **DCM-Zn^{2+}** upon the addition of polyamines. The ratios of I_{560}/ I_{640} were plotted as a function of polyamine concentrations. (c) Ratiometric response of **DCM-Zn^{2+}** towards TETA without (Red bar) or with (Green bar) additional competing species. From left to right: None, NH_3, EDA,

DETA, TETA, Et_3N, C_6NH_2, H_2NNH_2, S^{2-}, CO_3^{2-}. [DCM] = [Zn^{2+}] = 50 μM, [Analytes] = 500 μM.

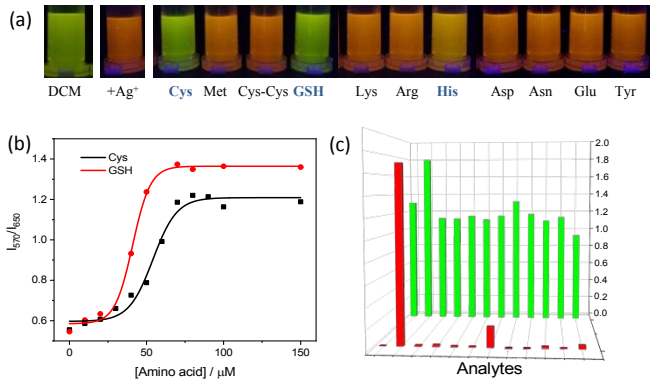


Figure 3. (a) Fluorescent pictures of **DCM-Ag$^+$** systems with polar amino acids in 1-1(volume ratio) water-ethanol mixed solvents under 365nm UV lamp. (b) Ratiometric titration of **DCM-Ag$^+$** upon the addition of Cys and GSH. The ratios of I_{570}/ I_{650} were plotted as a function of amino acid concentrations. (c) Ratiometric response of **DCM-Ag$^+$** towards thiol-containing amino acid Cys without (Red bar) or with (Green bar) various competitiors. From left to right: None, Cys, Cys-Cys, Met, Lys, Arg, His, Asp, Asn, Glu, Tyr, BSA (Bovine serum albumin). [DCM] = [Ag^+]/2 = 50 μM, [Amino acids] = 100 μM if not mentioned.

Here, we achieved discrimination of Cys and GSH from other amino acids based on the high affinity of Ag^+ to thiol groups. On the addition of 1 equivalent Cys or GSH, the red fluorescence of **DCM-Ag$^+$** system turned green immediately. As indicated by the ratiometric signal, quantitative detection of Cys and GSH is viable between the concentration range of 30-70 μM with a detection limit of 20 μM (Figure 3b). Other types of amino acids bearing coordinating groups, such as carboxyl group, hydroxyl group, amino group and guanidine group, show limited interferences (Figure 3c) and do not significantly affect the detection of Cys and GSH (Figure S6). Basically, the selectivity of Ag^+ to thiol containing amino acids can be explained by HSAB theory, where thiol group is soft base, and Ag^+ is a soft acid [28].

Hydrogen sulfide (H_2S) has been regarded as a toxic gas for a long time [29]. However, recent studies revealed that H_2S also play some important roles in biological systems [30], therefore the detection of solution H_2S level in biosystem has attracted intensive interests [31-34]. Herein, **DCM-Pb^{2+}** system were proved to be optimizing for the selective detection of H_2S. Upon addition of 150 μM H_2S to the solution, the red bright fluorescence of **DCM-Pb^{2+}** system turned dark green (Figure 4a), accompanied by the darkening of solution color (Figure 4b). In the fluorescent titration curve, there was a sharp increase of ratiometric signal when the concentration of H_2S exceeded 30 μM (Figure 4c), and quantitative detection is viable between the concentration range of 40-100 μM. This detection ability is comparable to some previously reported H_2S fluorescent sensors [33, 34]. Significantly, the existence of other coordinative species, such as I^-, CO_3^{2-}, SO_4^{2-}, HPO_4^{2-}, GSH, do not significantly affect the detection of H_2S using **DCM-Pb^{2+}**

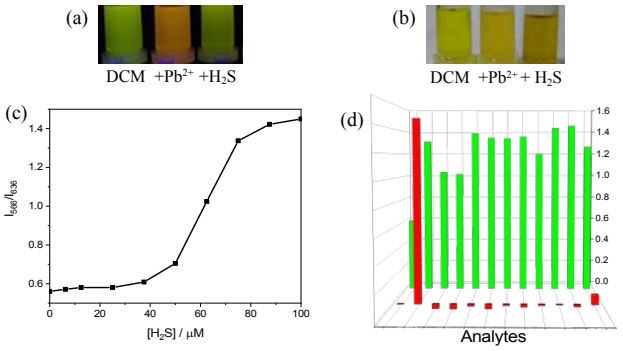


Figure 4. (a) Fluorescent pictures of **DCM-Pb^{2+}** systems in the presence of H_2S in 1-1 water-ethanol mixed solvents under 365nm UV lamp. (b) Optical pictures of **DCM-Pb^{2+}** systems in the presence of H_2S. [DCM] = [Pb^{2+}] = 50 μM, [H_2S] = 150 μM. (c) Ratiometric titration of DCM-Pb^{2+} upon the addition of H_2S. The ratios of I_{566}/ I_{636} were plotted as a function of H_2S concentrations. (d) Ratiometric response of **DCM-Pb^{2+}** towards H_2S against other competitors (Red bar) and the response of **DCM-Pb^{2+}** in the presence of competitors towards H_2S (Green bar). From left to right: None, S^{2-}, F^-, Cl^-, Br^-, I^-, CO_3^{2-}, $C_2O_4^{2-}$, SO_4^{2-}, PO_4^{3-}, CH_3COO^-

complex (Figure 4d&S7), indicating the specificity of the **DCM-Pb^{2+}** system toward H_2S.

In summary, we demonstrated a facile strategy to develop one-on-multiple molecular recognition platform based on the combination of one fluorescent amphiphile **DCM** and metal ions. Upon coordinating with metal ions, **DCM** exhibited a huge red-shift of fluorescent color in comparison to itself. This regulation was reversible when metal ions were extracted from DCM-metal complexes. Because each metal ion may have specific binding affinity to different chemicals resulting to recover of the **DCM** emission, the **DCM-metal** system is able to recognize different chemicals. We verified that it is possible to discriminate TETA, Cys and GSH, and H_2S using **DCM-Zn^{2+}**, **DCM-Ag$^+$**, and **DCM-Pb^{2+}**, respectively. This is very similar to the way that human's eyes recognize red, green, and blue colors with the same retinal molecule when it binds to Red, Green, and Blue opsins. Such a bio-inspired strategy will open up a new horizon in the design of adaptive platform for versatile chemical recognition.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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One-on-multiple recognition resembling human vision generation is built through the conjunction of ICT-bearing amphiphile with different metal ions.