Coordination Chemistry Reviews xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

# Recent progress in the development of organic dye based near-infrared fluorescence probes for metal ions

Di Wu [a], Liyan Chen [a], Woolin Lee [a], Gyeongju Ko [a], Jun Yin [b,*], Juyoung Yoon [a,*]

[a] Department of Chemistry and Nano Science, Ewha Womans University, Seoul 120-750, Republic of Korea
[b] Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China

## ARTICLE INFO

*Article history:*
Received 24 April 2017
Received in revised form 15 June 2017
Accepted 15 June 2017
Available online xxxx

*Keywords:*
Fluorescence probes
Near-infrared (NIR)
Metal ions
Boron dipyrromethene difluoride (bodipy)
Si–rhodamine
Cyanine
Squaraine
Bioimaging

## ABSTRACT

Metal ions play important roles in various industrial and biochemical processes. Some metal ions are essential for the survival of humans, animals and plants. However, some metal ions are toxic and hence cause serious health and environmental problems. Because of these features, the detection of metal ions is of great importance. In this review, we summarize various NIR fluorescence probes for metal ions that have been developed in recent years. Additionally, this review includes some personal perspective and insight into how and where this field is progressing and key challenges to be overcome in the future.


**Contents**

1. Introduction . . . . . 00
2. NIR fluorescence probes for alkali metal ions ($Na^+$, $K^+$) . . . . . 00
3. NIR fluorescence probes for alkaline earth metal ions ($Ca^{2+}$) . . . . . 00
4. NIR fluorescence probes for $Al^{3+}$, $Pb^{2+}$ . . . . . 00
5. NIR fluorescence probes for transition metal ions . . . . . 00
   5.1. NIR fluorescence probes for chromium ($Cr^{3+}$) . . . . . 00
   5.2. NIR fluorescence probes for iron ($Fe^{3+}$) . . . . . 00
   5.3. NIR fluorescence probes for copper ($Cu^+$/$Cu^{2+}$) . . . . . 00
      5.3.1. NIR fluorescence probes for $Cu^+$ . . . . . 00
      5.3.2. Coordination interaction based NIR fluorescence probes for $Cu^{2+}$ . . . . . 00
      5.3.3. Chemical reaction based NIR fluorescence probes for $Cu^{2+}$ . . . . . 00
   5.4. NIR fluorescence probes for zinc ($Zn^{2+}$) . . . . . 00
   5.5. NIR fluorescence probes for palladium ($Pd^0$/$Pd^{2+}$) . . . . . 00
   5.6. NIR fluorescence probes for silver ($Ag^+$) . . . . . 00

*Abbreviations:* ICT, intramolecular charge transfer; PET, photoinduced electron transfer; FRET, Förster resonance energy transfer; ESIPT, excited-state intramolecular proton transfer; CHEF, chelation induced enhanced fluorescence; NIR, near-infrared; AD, Alzheimer's disease; LOD, limit of detection; TAC, 2-triazacryptand [2,2,3]-1-(2-methoxyethoxy)benzene; TCF, 2-dicyanomethylene-3-cyano-4,5,5-trimethyl-2,5-dihydrofuran; Bodipy, boron dipyrromethene difluoride; BAPTA, 1,2-bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid; GFP, green fluorescence protein; ARBD, Al-related bone disease; DPA, di-2-picolylamine; TBET, through-bond energy transfer; BETA, bis(2-((2-(ethylthio)ethyl)-thio)ethyl)amine; TPA, tris[(2-pyridyl)methyl]amine; PPi, pyrophosphate anion; DCM, dicyanomethylene-4H-pyran; TPEA, N,N,N′-tri(pyridin-2-ylmethyl)ethane-1,2-diamine; D–A, donor–acceptor; FUCL, frequency upconversion luminescence; BSA, bovine serum albumin; ACQ, aggregation-caused quenching; EDTA, ethylenediaminetetraacetic acid; THF, tetrahydrofuran; EET, excitation energy transfer; CB8, Cucurbit[8]uril.

* Corresponding authors.
*E-mail addresses:* yinj@mail.ccnu.edu.cn (J. Yin), jyoon@ewha.ac.kr (J. Yoon).

http://dx.doi.org/10.1016/j.ccr.2017.06.011
0010-8545/

Please cite this article in press as: D. Wu et al., Recent progress in the development of organic dye based near-infrared fluorescence probes for metal ions, Coord. Chem. Rev. (2017), http://dx.doi.org/10.1016/j.ccr.2017.06.011

5.7. NIR fluorescence probes for cadmium ($Cd^{2+}$) . . . . . 00
5.8. NIR fluorescence probes for mercury ($Hg^{2+}$) . . . . . 00
5.8.1. Coordination interaction based NIR fluorescence probes for $Hg^{2+}$ . . . . . 00
5.8.2. Chemical reaction based NIR fluorescence probes for $Hg^{2+}$ . . . . . 00
6. Conclusions and outlooks . . . . . 00
Acknowledgement . . . . . 00
References . . . . . 00

## 1. Introduction

Metal ions play a vital role in our daily life. For example, metal ions such as potassium ($K^+$), calcium ($Ca^{2+}$), copper ($Cu^+$ and $Cu^{2+}$) and zinc ($Zn^{2+}$) are important in various biological processes [1–10]. Moreover, palladium ($Pd^0$ and $Pd^{2+}$) is commonly used as a transition metal catalyst for organic chemical reactions [11,12]. However, mercury ($Hg^{2+}$) has high permeability through human skin, and it causes respiratory and gastrointestinal problems as well as serious damage to the central nervous system [13–15].

Methods to detect metal ions are of great importance. Probes based on fluorescence signaling have been investigated extensively and widely used for the detection of analytes including metal ions because of the advantages associated with low cost, high sensitivity and in particular the ability to be utilized for temporal and spatial sampling and in vivo imaging applications [16–30]. Common photophysical mechanisms, which promote fluorescence changes such as intramolecular charge transfer (ICT), photoinduced electron transfer (PET), Förster resonance energy transfer (FRET), excited-state intramolecular proton transfer (ESIPT) and chelation induced enhanced fluorescence (CHEF), have been used advantageously in the design of these probes. A large number of fluorescence probes have been designed based on these conventional approaches, including those that contain ligand linked fluorophores and that operate via reactions promoted by biologically important metal ions. However, most of the probes devised to date require light absorption and emission in the ultraviolet–visible (UV/Vis) range. As a result, they can't be utilized for sensing and imaging target metal ions in live animals, because of light absorption and autofluorescence of biomolecules normally occurring in the UV/Vis region. In contrast, near-infrared (NIR) fluorescence probes that operate in the wavelength range of 650–900 nm can be applied to vivo bioimaging owing to the absorption and autofluorescence in this spectral range being low. Consequently, NIR fluorescence probes have minimal background interference, improved tissue depth penetration and high image sensitivities. Furthermore, it is particularly important that NIR dyes cause minimum photo-damage to biological specimens, organisms and tissues as a result of the fact that NIR light has low energy [31–34].

Although a few reviews have been compiled describing NIR fluorophores and fluorescence probes for metal ions, to the best of our knowledge no reviews that focus on the topic of NIR fluorescence probes for metal ions have been published [35–45]. Because of this, we prepared this review, which summarizes recent progress made from 2010 to the present in the development of near-infrared fluorescence for metal ions. This review utilizes a format that follows different metal ion types and then each section is further subcategorized by different binding sites or reaction types.

## 2. NIR fluorescence probes for alkali metal ions ($Na^+$, $K^+$)

Alkali metal ions include lithium ($Li^+$), sodium ($Na^+$), potassium ($K^+$), rubidium ($Rb^+$), cesium ($Cs^+$) and francium ($Fr^+$) ions. Francium, which is highly radioactive and most likely toxic, plays no known biological role [1,2]. Cesium is not an essential element for human beings, but its role in biochemistry and physiology has been well established [46,47]. Its radioactive counterparts can cause many health problems such as cardiovascular disease, gastrointestinal distress, hyperirritability and spasms [48,49]. The biological function of rubidium is ambiguous. Rubidium chloride, which has been reported to have antidepressive activity, can cause some health issues due to its preferential accumulation property [50]. The other alkali metal ions play important roles in physiological and pathological processes. Lithium salts are widely used in medical and clinical applications for the treatment of bipolar disorders and manic-depressive psychosis. It is worth noting that the plasma concentration of $Li^+$ should be tightly controlled in the 0.6–1.2 mM range, since too low levels of this metal ion have no effect while an overdose of lithium ion can cause serious detrimental effects, possibly leading to death [51–53]. Sodium and potassium are two of the most important cations in living organisms because they play essential roles in many biological processes [54,55]. Furthermore, imbalances of sodium and potassium are closely related to many diseases such as Alzheimer's disease (AD), anorexia, heart disease and diabetes. [56,57]. The large number of fluorescence probes for these alkali metal ions developed to date are mainly based on crown ethers. However, the NIR fluorescence probes for alkali metal ions are rare and in great demand.

In mammals, sodium ions mainly reside in the extracellular compartment (greater than 100 mM) and much less amounts of $Na^+$ exist inside cells (5–30 mM). In contrast, the concentration of $K^+$ inside cells (~150 mM) is much higher than that in the extracellular compartment (~5 mM). To understand the functions of $Na^+$ and $K^+$ in the biologic processes, a number of fluorescence probes have been developed. However, the number of NIR fluorescence probes for these two species are limited.

Li et al. developed a method to simultaneously quantify $Na^+$ and $K^+$ in single cells using the new fluorescence probe **1** along with the technology of microchip electrophoresis [58]. Probe **1** was designed to contain four nitrogen atoms and to have a cavity size that leads to selective binding of $Na^+$ or $K^+$ (Scheme 1) [59]. The probe displays very weak fluorescence at 675 nm ($\lambda_{ex}$ = 630 nm) in Tris–HCl (20 mM, pH 7.4). Upon binding $Na^+$ and $K^+$, remarkable fluorescence enhancements at 675 nm (8 and 6.8-fold) occur in association with a fluorescence quantum yield increase from 0.012 to 0.11 and 0.10, respectively. The binding stoichiometries of **1** with $Na^+$ and $K^+$ are 1:1 and the binding affinities ($K_d$) are 18.62 mM and 19.50 mM, respectively. The limits of detection (LODs) of **1** for $Na^+$ and $K^+$ were calculated to be 2.5 μM and 2.7 μM, respectively. Using microchip electrophoresis, the probe was applied to simultaneously quantify $Na^+$ and $K^+$ in single cells. The results reveal that the $Na^+/K^+$ ratio (average: 0.6) in the tumor cells is higher than that (average: 0.16) in normal cells.

Indeed, **1** cannot discriminate between $Na^+$ and $K^+$ without the help of microchip electrophoresis, but no NIR fluorescence probe with high selectivity for $Na^+$ has been reported thus far. As mentioned above, $Na^+$ plays very important roles in physiological and pathological processes, developing NIR fluorescence probes with high selectivity and sensitivity for $Na^+$ is of great importance. The 2-triazacryptand [2,2,3]-1-(2-methoxyethoxy)benzene (TAC) group displays a very high selectivity for detecting $K^+$ over other physiologically relevant metal ions and to date it is the best $K^+$-