Chem Soc Rev

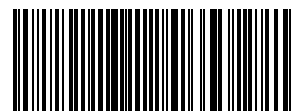**TUTORIAL REVIEW**
Jong Seung Kim, Juyoung Yoon *et al.*
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chemosensors: application of
spirolactam ring-opening to sensing
ions

CRITICAL REVIEW
Vladimir Ya. Lee and Akira Sekiguchi
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A new trend in rhodamine-based chemosensors: application of spirolactam ring-opening to sensing ions

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This *tutorial review* focuses on the recent development of rhodamine derivatives, in which the spirolactam (non-fluorescent) to ring-opened amide (fluorescent) process was utilized.

Introduction

Fluorescent sensors for ions and neutral analytes have consistently demonstrated their potential in a variety of fields, such as biological probes,[1] environmental sensors,[1] molecular devices,[2] nerve gas sensor,[3] *etc*. As a fluorophore and chromophore probe, the rhodamine fluorochrome has attracted considerable interest from chemists on account of its excellent photophysical properties.[4] Rhodamine derivatives are non-fluorescent and colorless, whereas ring-opening of the corresponding spirolactam gives rise to strong fluorescence emission and a pink color (Scheme 1).[5] In general, a rhodamine derivative displays a red color change and strong fluorescence in acidic solution by activating a carbonyl group in a spirolactone or spirolactam moiety as shown in Scheme 1. In a similar way, an appropriate ligand on spirolactam ring can induce color change as well as fluorescent change upon the addition of metal ions even though this process is somewhat dependent on the solvent system.

Noelting and Dziewonsky first reported the preparation of the rhodamine in 1905.[6] In the middle of the 20th century, analytical research groups (1945–1988) reported the colorimetric determination of various metals (*e.g.* antimony, zinc, silver, osmium) in biological materials using rhodamine.[7–10]

However, it was only 1997 when the rhodamine-B derivative and its ring-opening reaction received a great deal of attention from organic chemists. Czarnik *et al.* reported pioneering work utilizing this unique process. In their study, rhodamine-B hydrazide (1) was used as a fluorescent chemodosimeter for Cu^{2+}.[11] As shown in Scheme 2, Czarnik's rhodamine-B hydrazide can recognize Cu^{2+} selectively, and Cu^{2+}-promoted hydrolysis can provide fluorescent rhodamine-B as a product. They demonstrated that this system can detect 10 nM Cu^{2+} within 2 min at pH 7.

Since Czarnik's work, many exciting papers on the utilization of this unique ring-opening process have been published. This review focuses on the recent development of rhodamine derivatives over the past 3–4 years, when the spirolactam (non-fluorescent) to ring-opened amide (fluorescent) process was

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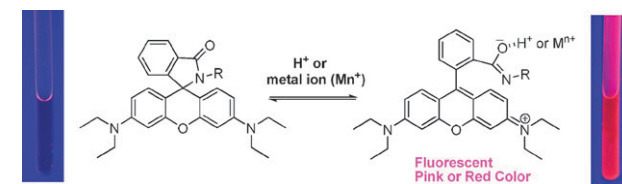[b] *Department of Chemistry, Korea University, Seoul, 136-701, Korea. E-mail: jongskim@korea.ac.kr; Fax: +82 (0)2 3290-3121; Tel: +82 (0)2 3290 3143*
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Scheme 1 Spirolactam ring-opening process of rhodamine derivative.

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Juyoung Yoon received his PhD (1994) from The Ohio State University. After completing postdoctoral research at UCLA and at the Scripps Research Institute, he joined the faculty at Silla University in 1998. In 2002, he moved to Ewha Womans University, where he is currently an Associate Professor of the Division of Nano Sciences and the Department of Chemistry. His research interests include investigations of fluorescent chemosensors, molecular recognition and organo EL materials.
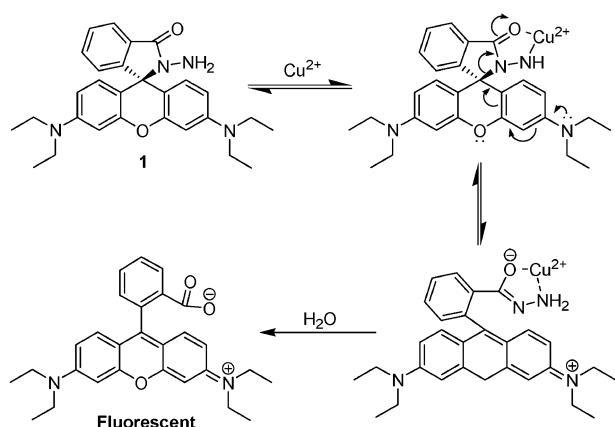
Scheme 2 Cu^{2+}-assisted hydrolysis of Czarnik's rhodamine-B hydrazide (**1**).

utilized. Beyond the conventional findings from rhodamine compounds, this review describes new types of rhodamine derivatives for use in biological applications as well as silica mesoporous-hybrid materials that were developed by our research laboratories and others groups for the selective detection of specific ions.

Lead-ion sensor utilizing spirolactam ring-opening process

Since the report of Czarnik's rhodamine-B hydrazine, Yoon *et al.* reported another rhodamine-B derivative as a fluorescent chemosensor for Pb^{2+}.[12] A single crystal of compound **2** was characterized using X-ray crystallography (Fig. 1), which clearly represented the unique spirolactam-ring formation. This is the first example of the X-ray structure of the rhodamine-B derivative bearing the lactam moiety. Among the various metal ions, compound **2** showed significant fluorescent enhancement *only* with Pb^{2+} in acetonitrile, even though there was relatively small fluorescent enhancement with Cu^{2+} and Zn^{2+}. Yoon *et al.* used three different methods to verify the complexation and its mechanism, ESI mass spectroscopy, IR and ^{13}C NMR spectroscopy. The spiro carbon in compound **2** appeared at δ 64.7 ppm in CD$_3$CN:CDCl$_3$ (9:1, v/v). This peak disappeared upon the addition of Pb^{2+} or Zn^{2+}. From these results, a reversible ring-opening mechanism was proposed, as shown in Scheme 3.[12]
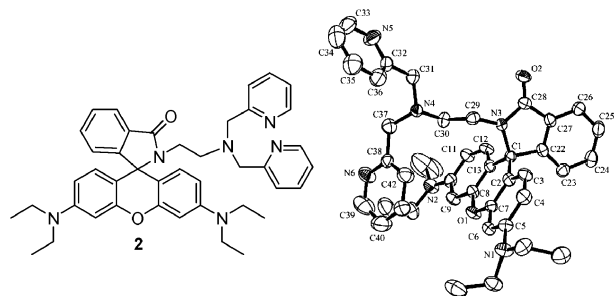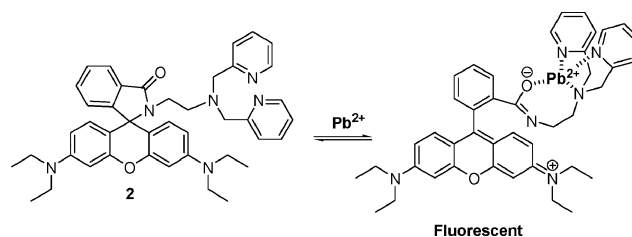

Fig. 1 Yoon's rhodamine-B derivative (**2**) and its X-ray crystal structure.

**Scheme 3** Proposed binding mode of **2** with Pb^{2+}.

Mercury-ion sensors utilizing spirolactam ring-opening processes or oxadiazole formation

Tae *et al.* developed a quite intelligent system using a rhodamine-6G derivative, which works as a highly selective and sensitive chemodosimeter for Hg^{2+} in aqueous solution (Scheme 4).[13] The system, which utilizes an irreversible Hg^{2+}-promoted oxadiazole-forming reaction of rhodamine derivative **3**, is monitored by the changes in colorimetric and fluorescence intensity that respond instantaneously at room temperature in a 1:1 stoichiometric manner to the amount of Hg^{2+} present. The selectivity of this system for Hg^{2+} over other metal ions is remarkably high, and its sensitivity is <2 ppb in aqueous solutions.[13]

Shin *et al.* further applied this system to a biological study.[14] They demonstrated that this system can be used as a real-time method for monitoring the concentration of mercury ions in living cells, particularly vertebrate organisms.

Zheng *et al.* utilized a rhodamine-B thiohydrazide as a fluorescent chemosensor for Hg^{2+}.[15] This sensor **4** (Fig. 2) exhibits reversible dual chromo- and fluorogenic changes for Hg^{2+} in aqueous solution at pH 3.4 in a highly selective and sensitive manner. This result was attributed to the coordination of Hg^{2+} at the N and S binding sites in **4** (1:2 stoichiometry) to open its spirolactam ring.

Kim *et al.* synthesized and reported new rhodamine-based tren (triethylenetetramine) and diethylenetriamine (**5** and **6**) with tosyl groups (Fig. 2), in which the Hg^{2+} was entrapped by the tren or the diethylenetriamine.[16] The addition of Hg^{2+} ions to the CH$_3$CN solutions of molecules **5** or **6** produced both a visual color change and enhanced fluorescence intensity (Fig. 3). In order to gain further insight into the role of the
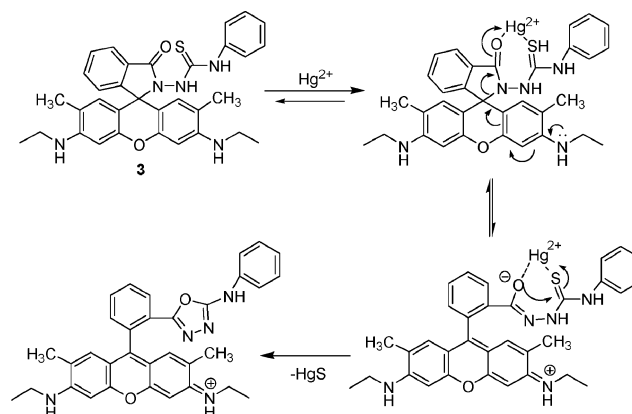
Scheme 4 The reaction scheme of Tae's chemodosimeter **3** with Hg^{2+}.
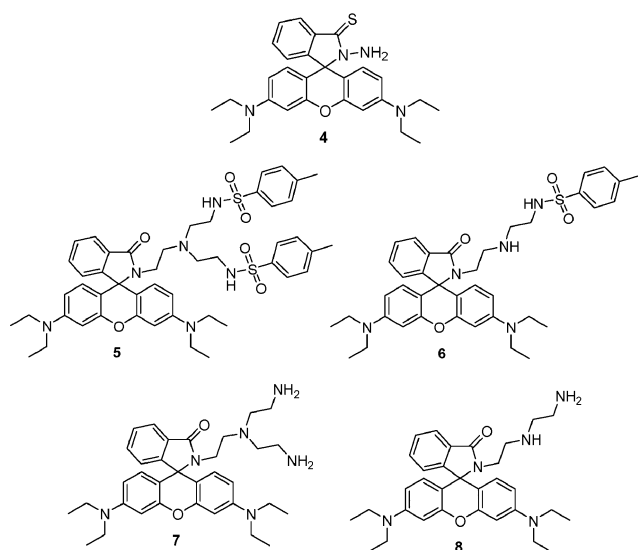
Fig. 2 Structures of rhodamine-B derivatives 4–8.

tosyl group in molecules 5 and 6, molecules 7 and 8 were used independently for spectral tests.[16] Unlike molecules 5 and 6, neither molecule 7 nor 8 showed distinct absorption or fluorescence spectral changes upon the addition of Hg^{2+} ions. This suggests that the tosyl groups linked to tren/diethylenetriamine accelerates the ring-opening of spirolactam in molecules 5 and 6 to play an important role as a Hg^{2+} sensor. In addition, the increased fluorescence intensity of complex 5–Hg^{2+} is 6 times greater than that of complex 6–Hg^{2+}.[16] It should be noted that compared with molecule 6, tosylated ethyleneamine from the tren in molecule 5 can also bind Hg^{2+} ions, inducing ring-opening of the spirolactam of molecule 5 more effectively. In terms of practical applicability, Hg^{2+} detection were carried out in a 10% aqueous solution $(CH_3CN–H_2O)$.[16]
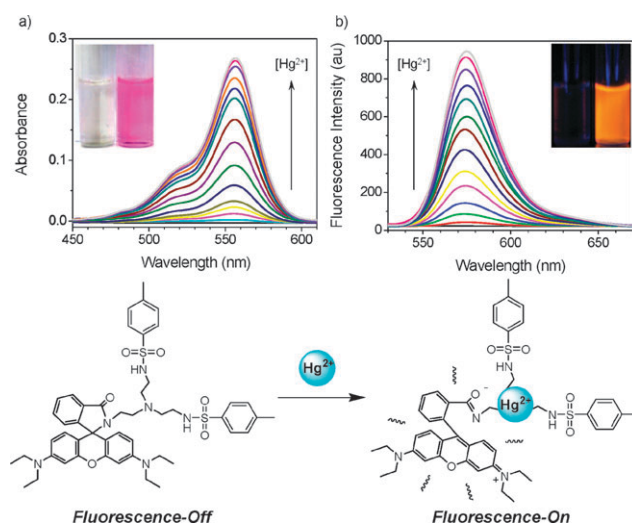

Fig. 3 Kim's rhodamine-B derivative. (a) Absorption spectra of 5 (10 μM) and (b) fluorescence spectra of 5 (1 μM), with the addition of various concentrations of $Hg(ClO_4)_2$ (a: 0–100 μM; b: 0–10 μM) in CH_3CN with an excitation at 520 nm. Also, a proposed complexation mode between 5 and Hg^{2+}.
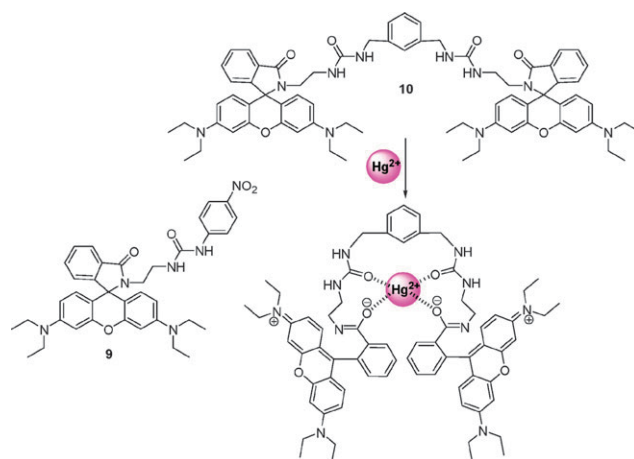

Fig. 4 Structures of rhodamine-B urea derivatives (9 and 10) and a proposed binding mode of 10 with Hg^{2+}.

Yoon et al. reported rhodamine derivatives (9 and 10) with urea groups (Fig. 4).[17] In particular, the dimeric system 10 showed a highly selective fluorescent enhancement and colorimetric changes upon the addition of Hg^{2+} in acetonitrile, which used the spirolactam (non-fluorescent) for the ring-opened amide (fluorescent) process. The association constant of molecule 10 with Hg^{2+} was calculated to be 3.2×10^5 M^{-1}.

Duan et al. reported a simple and easy-to-prepare rhodamine-based Hg^{2+} probe (11) containing a carbohydrazone unit (Scheme 5) and fully characterized its X-ray structure with Hg^{2+} (12).[18] This first X-ray crystal structure (12) with a metal ion clearly showed the ring-opened structure of the rhodamine derivative with Hg^{2+}. This probe 11 showed Hg^{2+}-selective fluorescence enhancement and detection limits as low as 2 ppb in a DMF aqueous solution.
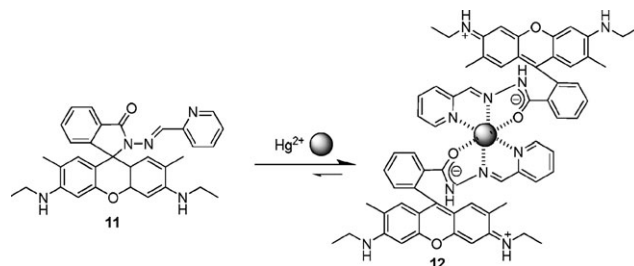

Scheme 5 Proposed binding mode of 11 with Hg^{2+}.

On the other hand, Huang et al. recently reported a multi-signaling optical–electrochemical sensor 13 for Hg^{2+} based on a rhodamine dye bearing both a ferrocenyl group and an 8-hydroxyquinoline moiety (Scheme 6).[19] Upon the addition of Hg^{2+} in ethanol–HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) buffer (1 : 1, v/v, pH 7.2), sensor 13 displayed a selective fluorescence enhancement, colorimetric change (colorless to pink) and a clear evolution of oxidation peak ($E_{1/2}$) versus decamethylferrocene (from 0.40 to 0.15 V). Using the confocal-laser scanning microscopy experiments, it was also demonstrated that 13 can be used as a fluorescent probe for monitoring Hg^{2+} in living cells.[19]
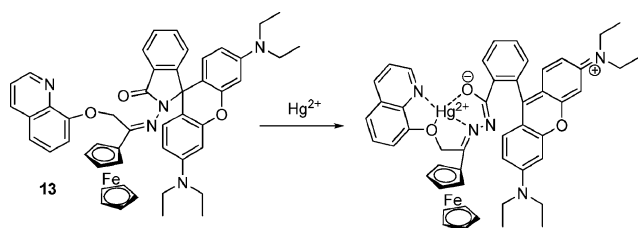
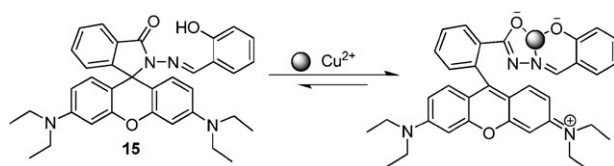**Scheme 6** Proposed binding mode of **13** with Hg^{2+}.

Ma and Shi[20] and Xu et al.[21] independently reported a rhodamine-B thiolactone **14** as a highly selective and sensitive sensor for Hg^{2+} in 20 mM phosphate buffer (pH 7) and 10 mM acetate buffer (pH 4) respectively (Scheme 7). Under these conditions, **14** displayed a selective fluorescence enhancement as well as colorimetric change only with Hg^{2+} among the various metal ions examined. Even though Xu et al. reported this ring-opening process was reversible under their experimental conditions,[21] Ma and Shi reported[20] that the introduction of KI into the system can reverse the color reaction only in the presence of less than 0.5 equiv. of Hg^{2+}. Based on the ESI mass spectroscopic data, Ma and Shi further proposed Scheme 7; complex A is relatively stable in the solution, however, complex B can be further degraded to rhodamine-B.[20]
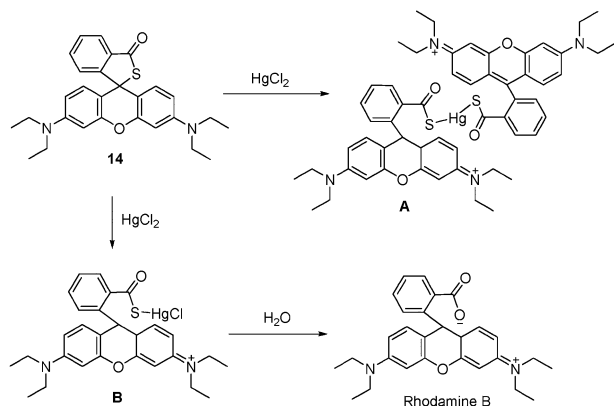
Scheme 7 Proposed reaction mechanism of **14** with $HgCl_2$.

Copper-ion sensors utilizing spirolactam ring-opening processes

A rhodamine hydrazone derivative that can be readily synthesized from Czarnik's rhodamine hydrazide was reported by Tong et al. as a highly selective sensor for Cu^{2+}. They reported the first rhodamine hydrazone derivative **15** as a selective fluorescent sensor for Cu^{2+} at pH 7.0 (10 mM tris-HCl buffer : CH_3CN = 1 : 1, v/v) (Scheme 8).[22]

Scheme 8 Proposed binding mode of **15** with Cu^{2+}.
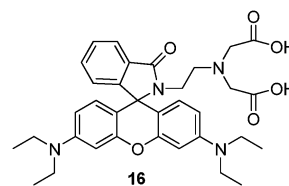

Fig. 5 Structure of rhodamine diacetic acid derivative **16**.

Shiraishi et al. recently reported a rhodamine diacetic acid derivative **16** (Fig. 5), which shows strong green fluorescence in CH_3CN with Cu^{2+} while showing very weak orange fluorescence with other metal ions.[23]

Czarnik's rhodamine hydrazide **1** was recently reexamined by Chang et al.[24] They reported that compound **1** can be turned into a Cu^{2+}-selective fluorescent sensor in different solvent systems, such as a 20% aqueous methanol solution at pH 5. The off–on type of signalling was attributed to the selective Hg^{2+}-induced hydrolysis of the spirolactam ring of the hydrazine group, as has been reported by Czarnik et al.[11] for the Cu^{2+}-signaling process of the same compound.

Ferric-ion sensors utilizing spirolactam ring-opening processes

Fe^{3+}-selective two-rhodamine molecules linked through a diethylenetriamine spacer were recently synthesized by Tong et al. as shown in Scheme 9.[25] This fluorescent probe **17** exhibited high selectivity for Fe^{3+} over other metal ions in both ethanol and water (pH 7.15, tris-HCl buffer). The selectivity for Fe^{3+} was even better in a buffer solution than in ethanol.
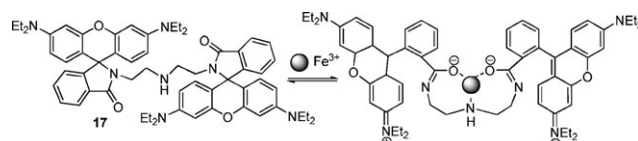
Scheme 9 Proposed binding mode of **17** with Fe^{3+}.

Tae and Bae utilized the fact that siderophores contain hydroxamates as binding sites for Fe^{3+}.[26] They introduced the hydroxamate unit into the rhodamine amide's equilibrium between spirolactam and the ring-opened amide. The addition of Fe^{3+} into a solution of this rhodamine hydroxamate derivative **18** (Fig. 6) induces a red–purple color and rapidly induces a strong fluorescence in MeOH–CH_3CN (1 : 1, v/v).

Based on the equilibrium between the spirolactam (non-fluorescence) to the ring-opened amide (fluorescence), Huang et al. demonstrated a rhodamine hydrazone derivative **19** (Fig. 6) to be a turn-on fluorescent sensor for Fe^{3+} over other
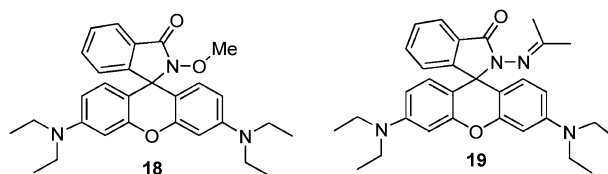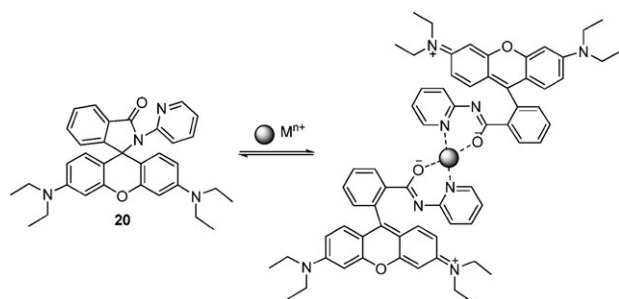

Fig. 6 Structures of rhodamine-B derivatives **18** and **19**.

Scheme 10 Proposed binding mode of **20** with metal ions.

Fig. 8 Cu^{2+}-induced FRET OFF → ON along with visual colour changes upon irradiation at 420 nm.

metal ions. Furthermore, the derivative **19** was used to sense Fe^{3+} within living cells.[27]

A new rhodamine-based fluorescent chemosensor (**20**) was synthesized by Shiraishi *et al.* through the one-step facile condensation of rhodamine-B and 2-aminopyridine (Scheme 10). In the absence of metal cations, molecule **20** was colourless and non-fluorescent, whereas the addition of metal cations (Fe^{3+}, Hg^{2+}, Pb^{2+} and Fe^{2+}) led to an obvious color change to pink and the appearance of an orange fluorescence.[28] Based on Job's plot analysis, a 2:1 binding mode was proposed, as shown in Scheme 10.

FRET in addition to ring-opening process

FRET (fluorescence resonance energy transfer) is defined as an excited-state energy interaction between two fluorophores in which the excited donor energy is transferred non-radiatively to an acceptor unit.[29] There are few reports on these FRET-based ion chemosensors. As shown in Fig. 7, Kim *et al.* designed and synthesized a series of rhodamine–dansyl (energy acceptor–energy donor) fluorophores (**21–23**) incorporated into a tren spacer, which implements the FRET system in Cu^{2+} ion recognition.[30]

Upon irradiation at 420 nm, a strong emission at ∼507 nm was observed, which was attributed to the fluorescence emitted from the dansyl energy-donor unit. When Cu^{2+} ions were added, molecule **21** showed an emission band at approximately ∼580 nm, which is the region of an energy acceptor. The binding of a Cu^{2+} ion induces opening of the spirolactam ring in molecule **21**, inducing a shift of the absorption spectrum of rhodamine. Subsequently, increased overlap between the emission of the energy donor (dansyl) and the absorption of the energy acceptor (rhodamine) greatly enhances the
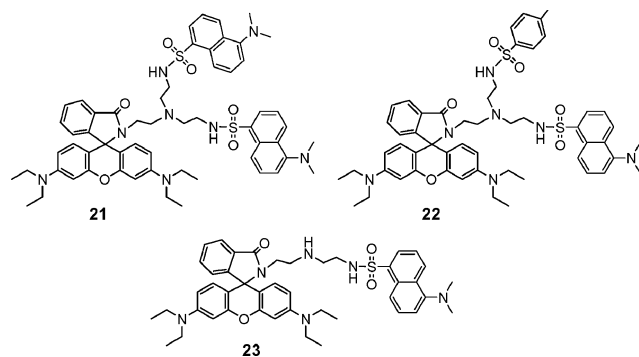
intramolecular FRET, producing an emission from the energy acceptor unit in molecule **21** (Fig. 8). In addition, density functional theory (DFT) calculations provide further structural evidence for the switching-ON of the FRET upon the addition of Cu^{2+}. We previously reported rhodamine–dansyl fluorophores showing metal-ion-induced FRET 'OFF → ON' behavior.[30]

Vicens *et al.* reported a novel calix[4]arene–rhodamine-based chemosensor **24** of which the fluorescence changes were observed in the case of complexation with only two different metal cations (Hg^{2+} and Al^{3+}) (Fig. 9).[31]

The addition of Hg^{2+} to a CH_3CN solution of molecule **24** resulted in significantly enhanced fluorescence at λ_{em} = 575 nm *via* FRET-ON from the pyrenyl excimer to the ring-opened rhodamine moiety with excitation at 343 nm, as indicated in Fig. 10. As a reference, compound **25** showed a
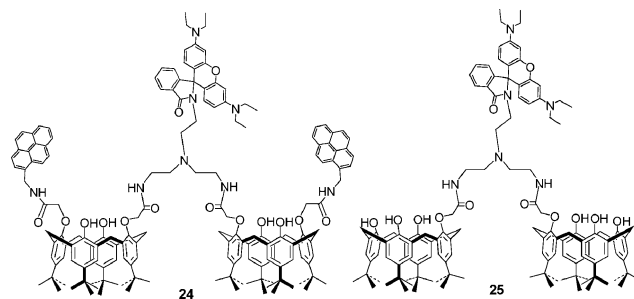

Fig. 9 Structures of calix[4]arene–rhodamine-B derivatives **24** and **25**.
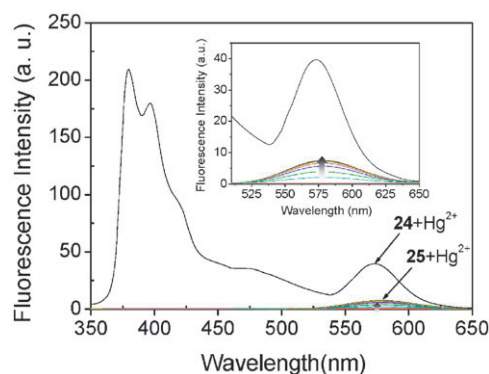
Fig. 10 Fluorescence spectra of **24** (0.001 mM in CH_3CN) with 0.02 mM of $Hg(ClO_4)_2$ and **25** (0.001 mM in CH_3CN) upon gradual addition of $Hg(ClO_4)_2$ (0, 0.001, 0.01, 0.02, 0.03, 0.04, 0.05 and 0.1 mM). Excitation at 343 nm.
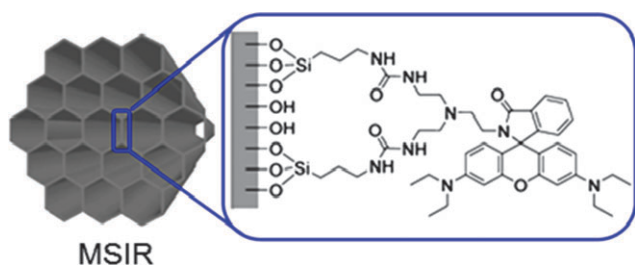

Fig. 7 Structures of Kim's rhodamine-B derivatives **21**, **22** and **23**.

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Fig. 11 Mesoporous silica-immobilized rhodamine.

small change in rhodamine emission (λ_{em} = 575 nm) due to the absence of the two pyrenyl groups (energy donor). On the other hand, complexation of Al^{3+} resulted in an obviously different fluorescence change. The addition of Al^{3+} induced strong emission of the pyrenyl excimer but weak rhodamine emission, suggesting that Al^{3+} prefers the formation of a pyrenyl excimer but not the ring-opening of the spirolactam of the rhodamine. This can be rationalized by two different binding structures of molecule **24**: tren-spirolactam and tren-diamide units. As shown in Scheme 11, in the presence of Hg^{2+}, the metal ion interacts with the tren-spirolactam unit and induces ring-opening of the rhodamine to produce FRET-ON. On the other hand, Al^{3+} prefers to coordinate with the tren-diamide unit, leading to enhanced pyrenyl excimer emission. However, this process does not open the spirolactam unit of the rhodamine moiety, which means that energy transfer cannot take place.

Mesoporous silica-immobilized rhodamine

The use of organic–inorganic hybrid materials has attracted considerable interest the research of new methodologies for ion recognition and sensing. Receptor-immobilized inorganic materials, such as SiO_2, Al_2O_3 and TiO_2, have some important advantages[32] as solid chemosensors in heterogeneous solid–liquid phases. The attachment of the rhodamine as a signal unit to SiO_2 can be used in a chemosensory kit. Kim *et al.* reported a novel mesoporous silica-immobilized rhodamine (**MSIR**) anchored by a tren (Fig. 11).[33]

From the fluorescent spectroscopic experiments, the **MSIR** shows a high selectivity and sensitivity for Hg^{2+} ions over other metal cations.[33] The interaction between Hg^{2+} ions and rhodamine on the surface of the **MSIR** induces a highly conjugated rhodamine system through the formation of an opened-spirolactam to give a strong fluorescence emission and a pink color. In addition, the **MSIR** can be easily recovered by treatment with a TBA^+OH^- solution. **MSIR**-coated glass plate had also been developed for Hg^{2+} detection in the environmental field, and has shown excellent function in terms of both the visual and fluorescence changes with Hg^{2+} ions (Fig. 12).

Sensing oxidative species and glutathione

Czarnik's rhodamine-B hydrazide **1** was further utilized by other groups. Sasamoto and Rieth reported that the colourless rhodamine-B hydrazide **1** reacts with nitrite in an acidic pH to produce absorption at 561 nm (Scheme 12).[34] Molecule **1** also
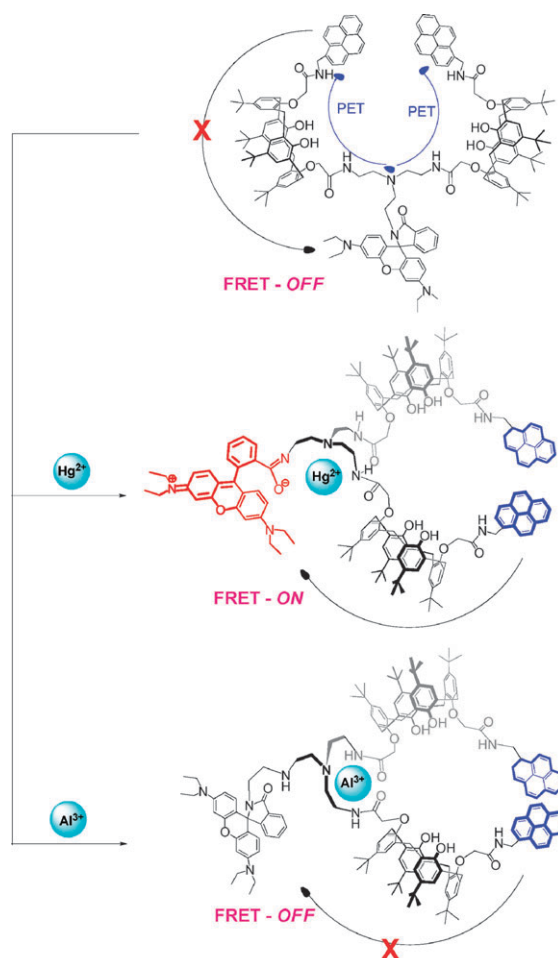
Scheme 11 Proposed different complexation behaviors of **24** with Hg^{2+} and Al^{3+}.

demonstrated a fluorescence at 581 nm when incubated with an NO donor at neutral pH. Moreover, the reaction was enhanced using an NO scavenger, carboxy-PTIO [2-(4-carboxy-phenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide].

Chen and Zou recently used Czarnik's rhodamine-B hydrazide **1** as a fluorogenic indicator to determine the hydrogen peroxide and glucose concentrations.[35] They reported that rhodamine-B hydrazide **1** can be oxidized by hydrogen
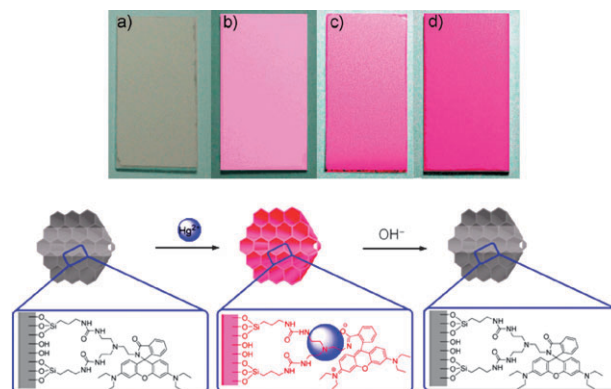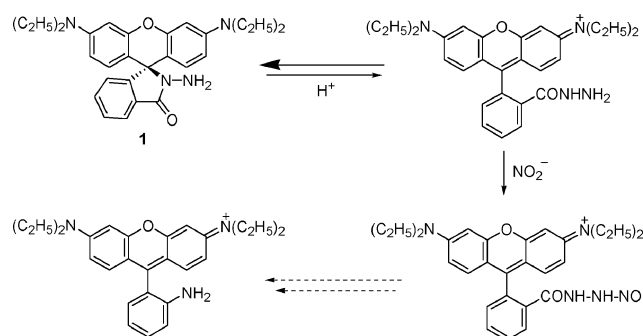

Fig. 12 **MSIR**-coated glass substrate (a) without Hg^{2+}, (b) 1.0×10^{-5}, (c) 1.0×10^{-4} and (d) 1.0×10^{-3} M.

Scheme 12 A proposed mechanism for the reaction of **1** with NO_2^-.

peroxide to generate highly rhodamine-B-like fluorescence, and the reaction can be catalyzed by iron(III)–tetrasulfona-tophthalocyanine (FeTSPc). Nagano *et al.* reported a new tetramethylrhodamine derivative **26** as a selective fluorescent probe for hypochlorous acid (HOCl) among the various reactive oxygen species (ROS) such as hydroxy radical, peroxynitrite, nitric oxide, superoxide, singlet oxygen and hydrogen peroxide.[36] In 0.1 M phosphate buffer (pH 7.4, containing 0.1% DMF), **26** displayed a selective fluorescence enhancement with HOCl as shown in Scheme 13. They also confirmed that **26** can detect HOCl being generated inside phagosomes in real time.[36]
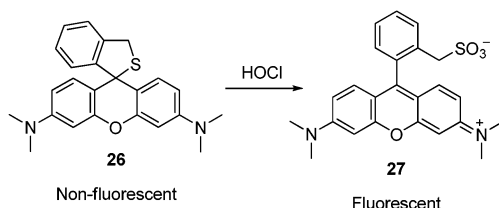

Scheme 13 Proposed reaction mechanism of **26** with hypochlorous acid (HOCl).

On the other hand, Ma *et al.* recently reported a chemodosimeter **28** as a highly selective and sensitive fluorescent probe for the hypochlorite anion (OCl$^-$) (Scheme 14).[37] Among the various metal ions and anions, **28** displayed a selective fluorescence enhancement with OCl$^-$ at pH 12 (30 mM $Na_2B_4O_7$/NaOH buffer). As shown in Scheme 14, the OCl$^-$ anion selectively oxidizes the hydrazo group and forms the analogue of dibenzoyl diimide, which in turn hydrolyzes and releases the fluorophore.
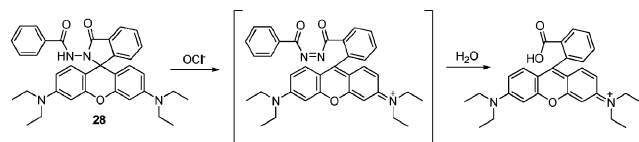
Scheme 14 The possible ring-opening reaction of **28** that is induced by the oxidative action of OCl$^-$.

Chmielewski and Pires synthesized a new rhodamine derivative (**29**) bearing a disulfide unit, which becomes fluorescent upon reduction by cellular thiols such as glutathione (GSH) *in vitro* and *in cyto*.[38] As shown in Scheme 15, the reduction of
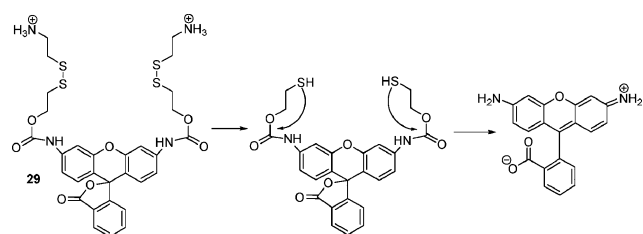
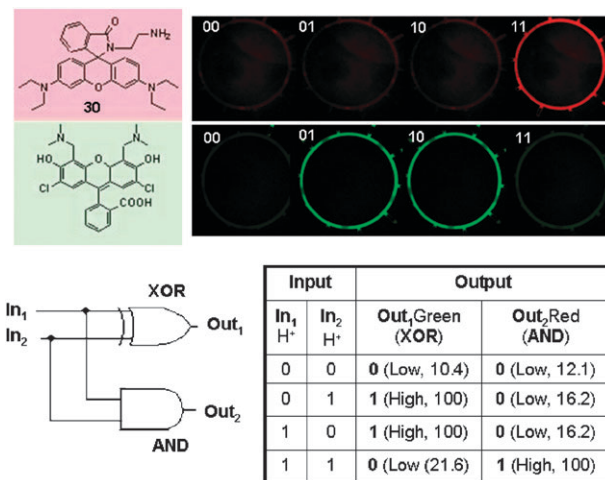**Scheme 15** Mechanism of unmasking for **29**.

Fig. 13 A "half-adder" molecular logic gate composed of an "XOR" gate (green) and an "AND" gate (**30**, red): fluorescence images of red (**30**) in the presence of two H$^+$ inputs, fluorescence images of green (XOR gate) in the presence of two H$^+$ inputs, a half-adder circuit, and a truth table of XOR and AND logic gates.

disulfide bonds by intracellular GSH would reveal nucleophilic sulfhydryl groups that would cause the break down of the neighboring carbamate bonds, thereby unmasking the rhodamine-110. Importantly, **29** was demonstrated to respond to changing levels of GSH in cells.

Application of ring-opening process to molecular logic gate

Since the pioneering work by de Silva *et al.*,[39] remarkable progress has been made in the development of molecular logic gates.[1m] Yoon *et al.* recently demonstrated the first example of molecular logic gate on a microfluidic device.[40] In particular, a combinatorial circuit, such as a half-adder, was demonstrated using a rhodamine-B derivative (**30**) and fluorescein derivative (Fig. 13). For example, rhodamine-B derivative **30** was used to construct a XOR gate, in which rhodamine-B showed strong fluorescence in acidic regions only, which was attributed to the spirolactam ring-opening process.[40]

Concluding remarks

Rhodamine derivatives certainly have their merits in long excitation and emission wavelengths, relatively high quantum efficiency, favorable solubility in water, *etc.* Most importantly, the distinct color and fluorescent changes due to the spirolactone or spirolactam ring-opening makes these derivatives more

valuable for sensing ions through fluorescence or naked-eye detection.

This examination provides an insight into how the structural modulation of the rhodamines can be utilized for metal-ion as well as oxidative-species sensing within the fluorescence and color changes. In addition, silica-based rhodamine immobilization techniques or molecular logic gates for further application were introduced. In some cases, solvent-dependent ring-opening process, response time towards ions and relationship between ligand rigidity and ring-opening process are still in question. However, it is also believed that the relatively easy manipulation of rhodamine derivatives and ligand engineering will interest many organic chemists, analytical chemists and biochemists in the future.

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