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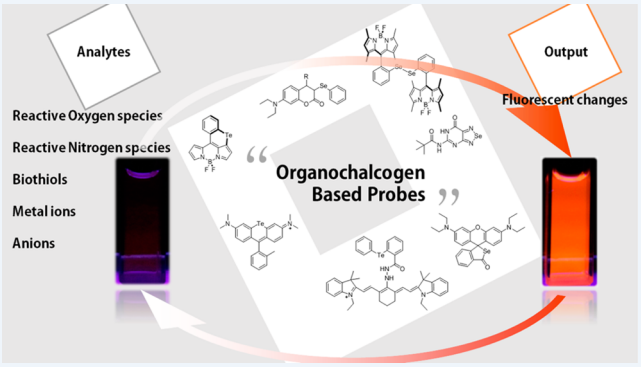
Selenium- and Tellurium-Containing Fluorescent Molecular Probes for the Detection of Biologically Important Analytes

Sudesh T. Manjare,[†,‡] Youngsam Kim,[‡] and David G. Churchill*[,‡]

[†]Center for Catalytic Hydrocarbon Functionalization, Institute for Basic Science (IBS), 373-1 Guseong-dong, Yuseong-gu, Daejeon, 305-701, Republic of Korea

[‡]Molecular Logic Gate Laboratory, Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), 373-1 Guseong-dong, Yuseong-gu, Daejeon, 305-701, Republic of Korea

CONSPECTUS: As scientists in recent decades have discovered, selenium is an important trace element in life. The element is now known to play an important role in biology as an enzymatic antioxidant. In this case, it sits at the active site and converts biological hydrogen peroxides to water. Mimicking this reaction, chemists have synthesized several organoselenium compounds that undergo redox transformations. As such, these types of compounds are important in the future of both medicinal and materials chemistry. One main challenge for organochalcogen chemists has been to synthesize molecular probes that are soluble in water where a selenium or tellurium center can best modify electronics of the molecule based on a chemical oxidation or reduction event.



In this Account, we discuss chemists' recent efforts to create chalcogen-based chemosensors through synthetic means and current photophysical understanding. Our work has focused on small chromophoric or fluorophoric molecules, in which we incorporate discrete organochalcogen atoms (e.g., R-Se-R, R-Te-R) in predesigned sites. These synthetic molecules, involving rational synthetic pathways, allow us to chemoselectively oxidize compounds and to study the level of analyte selectivity by way of their optical responses. All the reports we discussed here deal with *well-defined and small synthetic* molecular systems.

With a large number of reports published over the last few years, many have notably originated from the laboratory of K. Han (P. R. China). This growing body of research has given chemists new ideas for the previously untenable reversible reactive oxygen species detection. While reversibility of the probe is technically important from the stand-point of the chalcogen center, facile regenerability of the probe using a secondary analyte to recover the initial probe is a very promising avenue. This is because (bio)chalcogen chemistry is extremely rich and bioinspired and continues to yield important developments across many scientific fields. Organochalcogen (R-E-R) chemistry in such chemical recognition and supramolecular pursuits is a fundamental tool to allow chemists to explore stable organic-based probe modalities of interest to develop better spectroscopic tools for (neuro)biological applications.

Chalcogen donor sites also provide sites where metals can coordinate, and facile oxidation may extend to the sulfone analogues ($R\text{-}EO_2\text{-}R$) or beyond. Consequently, chemists can then make use of reliable reversible chemical probing platforms based on the chemical redox properties valence state switching principally from 2 to 4 (and back to 2) of selenium and tellurium atoms. The main organic molecular skeletons have involved chemical frames including boron-dipyrromethene (BODIPY) systems, extended cyanine groups, naphthalimide, rhodamine, and fluorescein cores, and isoselenazolone, pyrene, coumarin, benzoselenadiazole, and selenoguanine systems. Our group has tested many such molecular probe systems in cellular milieu and under a series of conditions and competitive environments. We have found that the most important analytes have been reactive oxygen species (ROS) such as superoxide and hypochlorite. Reactive nitrogen species (RNS) such as peroxynitrite are also potential targets. In addition, we have also considered Fenton chemistry systems. Our research and that of others shows that the action of ROS is often reversible with H_2S or biothiols such as glutathione (GSH).

We have also found that a second class of analytes are the thiols (RSH), in particular, biothiols. Here, the target group might involve an R-Se-Se-R group. The study of analytes also extends to metal ions, for example, Hg^{2+}, and anions such as fluoride (F^-), and we have developed NIR-based systems as well. These work through various photomechanisms, including photoinduced electron transfer (PET), twisted internal charge transfer (TICT), and internal charge transfer (ICT). The growing understanding of this class of probe suggests that there is much room for creative thinking regarding modular designs or unexpected organic chemical synthesis designs, interplay between analytes, new analyte selectivity, biological targeting, and chemical switching, which can also serve to further the neurological probing and molecular logic gating frontiers.

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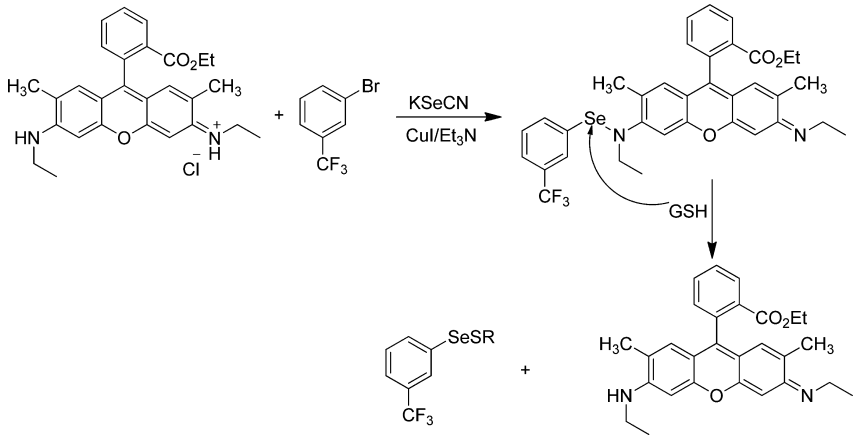
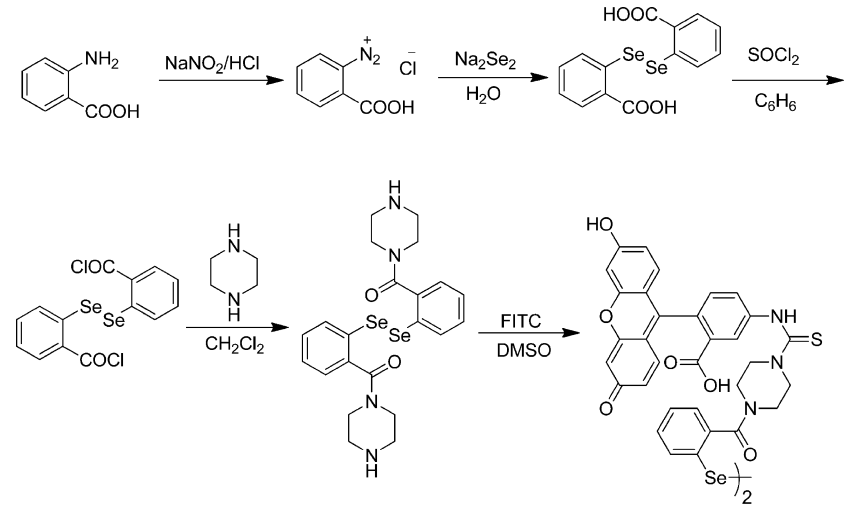
INTRODUCTION

In recent decades, selenium biology was discovered, and selenium is now known in its multifarious forms as a trace element in life. In particular, it is known to play an important enzymatic antioxidant role; at the active site of certain enzymes, selenium acts to convert biological hydrogen peroxide species to water.[1,2] To date, various organoselenium compounds have been synthesized and used for mimicking redox transformations. Thus, organoselenium compounds continue to be of growing importance in medicinal as well as materials chemistry fields.[3−7] Recent advances in enzymology, medicine, and bioorganic chemistry have profiled heterocyclic selenium-containing compounds that possess vital biological activity, including antibacterial, antifungal, anti-inflammatory, and antitumor properties. Enzymatic antioxidative properties such as those found in glutathione peroxidase are crucial systems to fully understand for their therapeutic value.[8−13] However, from a different angle, in recent years, sulfur-,[14,15] selenium-,[16] and tellurium-based[16] compounds have emerged as potential sensors for the detection of reactive oxygen species (ROS), reactive nitrogen species (RNS), and biothiols. A great number of novel heterocycles bearing single or multiple oxygen, sulfur, selenium, or tellurium sites have been investigated over the years;[1] some have also included nitrogen and other heteroatoms. Many of these heterocyclic systems have been pursued as pharmacophores bearing biological activity.[17−19] One important challenge for organochalcogen chemists has been to synthesize

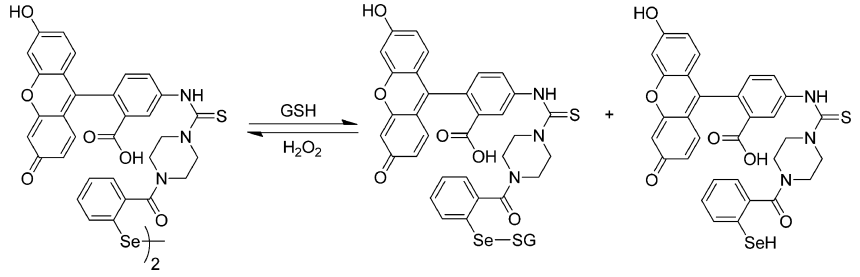
Scheme 1



Scheme 2



Scheme 3



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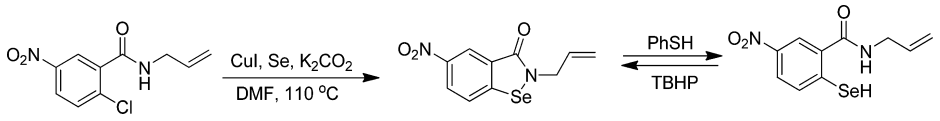
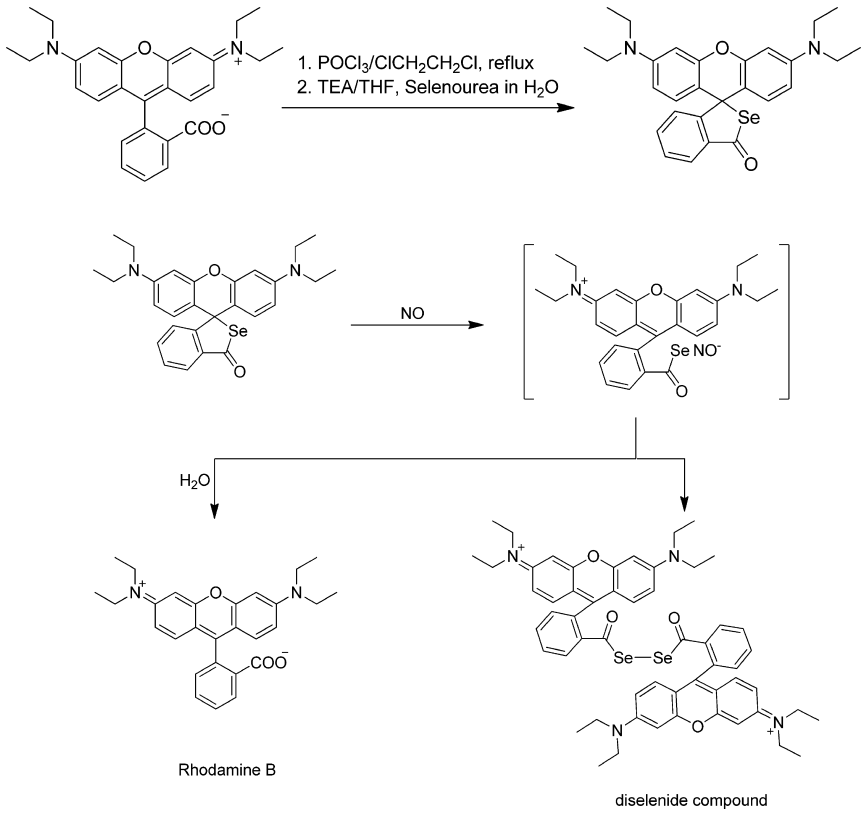
Scheme 4



Scheme 5



novel and water-soluble molecular probes in which a selenium or tellurium center is placed at a point to best modify electronics based on a chemical oxidation or reduction event. Moreover, it is also important to understand property trends of probes such as the tendency for them to hydrogen-bond with water and other biomolecules and expected photophysical changes in aqueous solution for further utilization and study in *vitro or vivo*.[20−22]

Essential to molecular enzymes in living organisms are the so-called 20 naturally occurring canonical amino acids and related species: alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophane, tyrosine, valine, as well as biothiols (glutathione (GSH), homocysteine (Hcy), and *N*-acetyl-L-cysteine; cysteine is also classified as a biothiol).[23] Biothiols, featuring an -SH group, play a particularly crucial role in many essential biological processes such as detoxification, gene regulation, metabolism, protein synthesis, and signal transduction.[24−27] The thiol-containing amino acid cysteine is involved in establishing the ubiquitous disulfide bonds [-S-S-], an essential factor for the formation of protein structure and a requisite for normal health. However, these thiols, when their relative concentration is considered, are also implicated in several diseases. An unbalanced level of these thiols may be involved in the etiology of hypoglycemic brain damage and neurotoxicity. Also, their deficiency is believed to be a cause of other diseases and disorders including edema, unexplained fat loss, hair depigmentation, lethargy, leukocyte loss, liver damage, muscle weakness, psoriasis, skin lesions, and slow growth.[28] Selective detection of amino acids, especially biothiols, is currently a focus of intense research, which involves various fluorophore classes and chemodosimeter-type platforms. There are several probes reported for the detection of these species, which are presented in this Account. However, reviews to-date, dealing with more recently published work involving the development of selenium- and tellurium-containing probes for the sensitive and selective detection of biothiols, have been lacking.

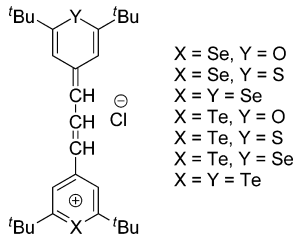


Figure 1.

Reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), hypochlorite (OCl^-), superoxide ($O_2^{\bullet-}$), and hydroxyl radical ($^{\bullet}OH$), and reactive nitrogen species (RNS), such as nitric oxide ($^{\bullet}NO$) and peroxynitrite ($ONOO^-$), play a very important role in health and disease; diseases and disorders frequently

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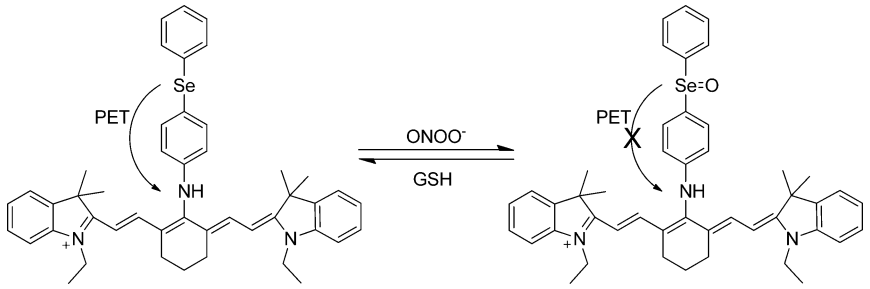
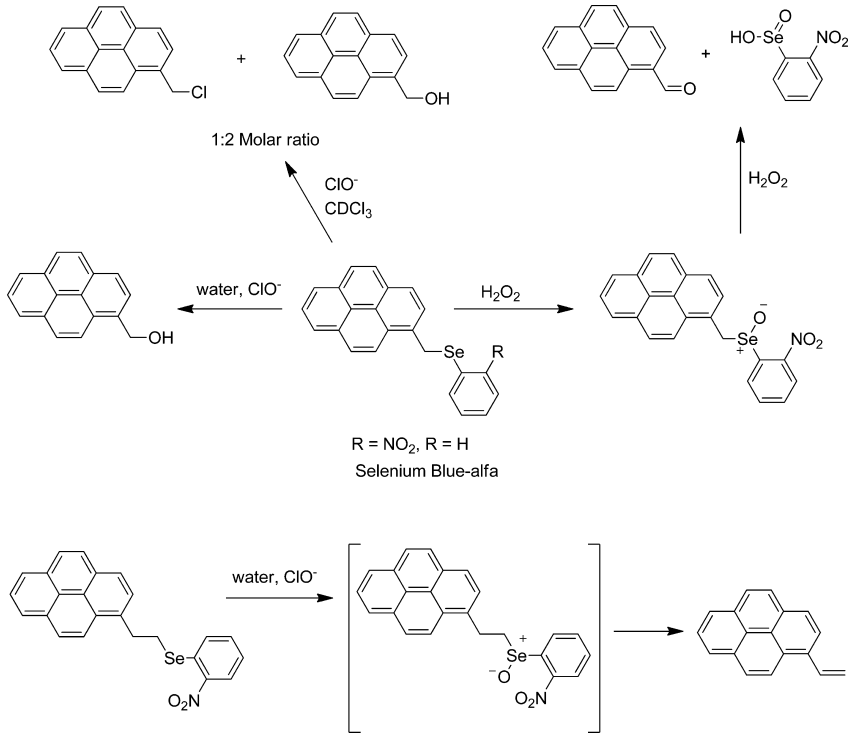
Scheme 6



Scheme 7

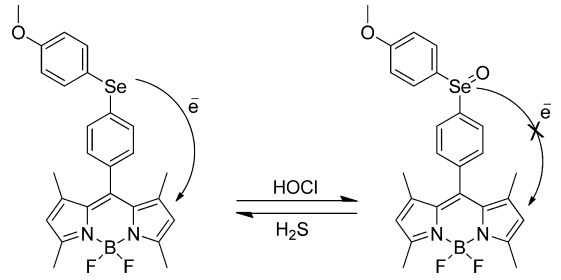


considered include cancer, diabetes, and neurodegenerative disease disorders such as Parkinson's disease and Alzheimer's disease.[29−35] However, excess production of these species (so-called "oxidative stress") can also lead to diseases such as atherosclerosis, cardiovascular disease, lung injury, and rheumatoid arthritis. Thus, to understand the role of these very small and transient species in living systems, it is very important to monitor their concentration accurately, especially in aqueous solutions. Many articles report the use of various molecular probes, which often are also summarized in related and recent reviews. In recent years, months, and even weeks, selenium- and tellurium-containing probes are the point of attraction for the detection of ROS and RNS due to the efficient chemical redox properties of selenium and tellurium. However, as with the biothiol literature, there is no contemporary review to our knowledge reporting the recent developments of Se- and Te-containing probes for the sensitive and selective detection of ROS and RNS, most likely because of the velocity of this research.

■ THIOL SENSING PROBES

Tang et al. developed the first selenium-containing rhodamine-based probe for the detection of thiols in living cells.[36] The target molecule was synthesized through the reaction of rhodamine 6G

Scheme 8



utilizing *meta*-trifluoromethylbromobenzene and potassium selenocyanide in the presence of copper iodide with triethylamine as base. The probe was found to be selective for thiols over other "biorelevant" analytes through nucleophilic substitution of the sulfhydryl group (Scheme 1). This reaction gives fluorescence signaling at $\lambda_{em,max}$ = 550 nm (λ_{ex} = 525 nm); the probe was also able to detect intracellular thiols in cell types including both HL-7702 and HepG2 cells. The probe showed good sensitivity (detection limit = 1.4 nM) and selectivity. It was more effective than two other previously reported probes, which were studied for imaging in thiol or GSH.

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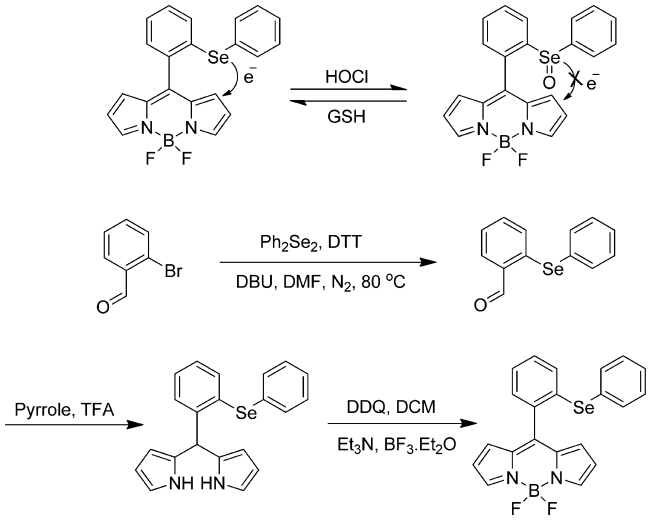
Scheme 9



A diselenide-containing fluorescein-based probe was developed by Han and co-workers (Schemes 2 and 3).[37] This probe skeleton was found to be selective and sensitive for thiols and was reversible with hydrogen peroxide. The reaction of the probe with thiols involved the cleavage of the diselenide bond to give a selenenyl sulfide group and a selenol compound; strong fluorescence was emitted by the fluorescein-containing selenol at $\lambda_{em,max}$ = 514 nm (λ_{ex} = 488 nm). The selenenyl sulfide and selenol generated from this reaction can be converted back to the original diselenide unit upon treatment with hydrogen peroxide, thus establishing reversible activity for thiols and ROS. The limit of detection for GSH was determined to be 2.25 × 10^{-7} M.

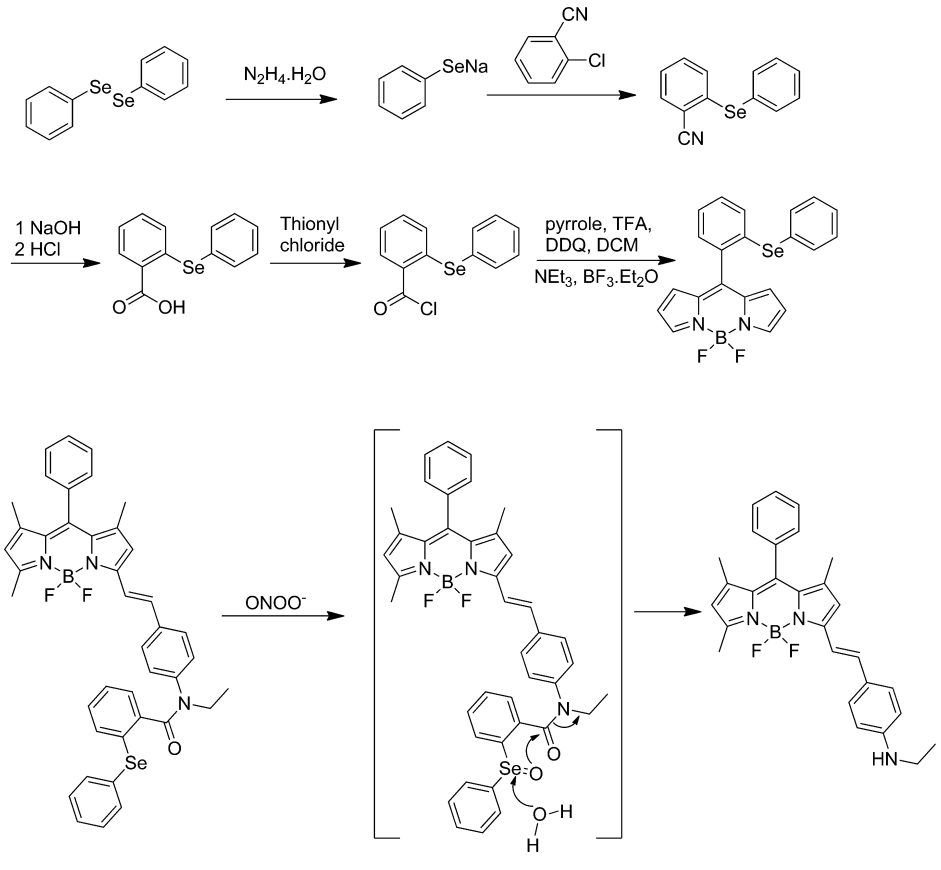
Kumar and co-workers have synthesized chalcogen-based colorimetric probes for the detection of thiols.[38] Isoselenazolone-based probes were synthesized from their corresponding 2-chlorobenzamides through the use of Cu-catalyzed selenation (Scheme 4). The probes have high specificity for thiophenols, cysteine, and glutathione and exhibit rapid colorimetric responses involving a change from colorless to bright yellow.

Next, various ebselen derivatives were exploited to study the activity of glutathione peroxidase (GPx)-like chemistry. This is a key understood role of selenoenzymes in protecting an organism from oxidant damage. Herein, the introduced selenium-containing sensors for the detection of thiols are designed to mimic GPx-like activity. Derivatives bearing close analogy to ebselen that contain a diselenide bond and selenide−nitrogen bond were observed to have activity with thiol groups. As followed catalytic cycles of ebselen, each probe undergoes a cleavage process to obtain optical signals.

■ ROS AND RNS SENSING PROBES

Further contributions involving the same selenium-containing probe have been made by Ma and co-workers for selective and sensitive detection of nitric oxide through reaction with the selenide group (Scheme 5).[39] The rhodamine B selenolactone (probe) itself shows very weak fluorescence due to its spirocyclic structure. The probe showed a conversion to a fluorescence "turn-on" event that involved high fluorescence selectivity for nitric oxide over many other related species, as assayed by the opening of the spirocyclic rhodamine B selenolactone structure.

Scheme 10



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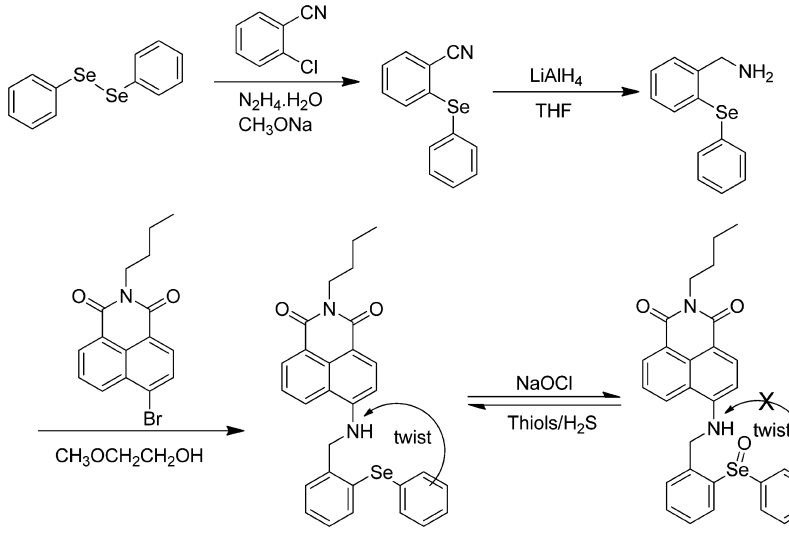
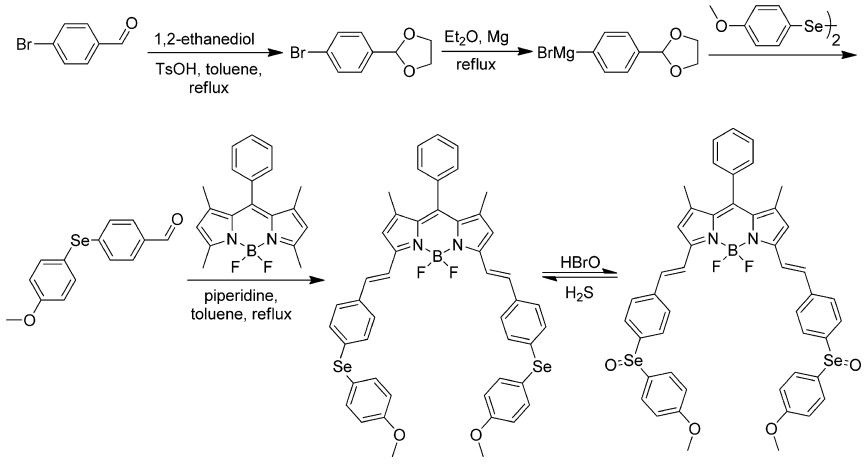
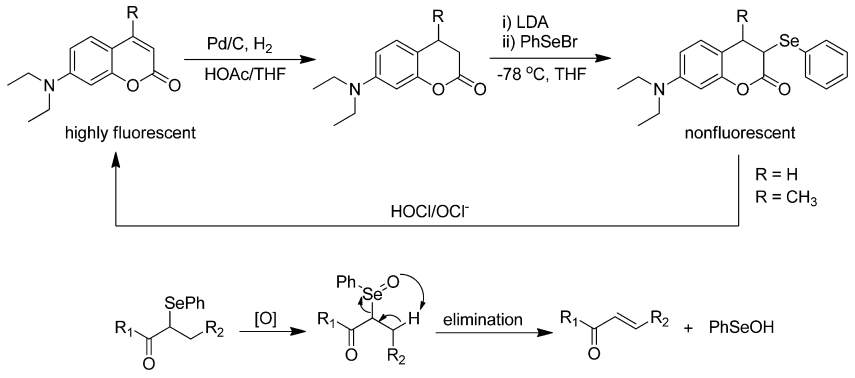
Scheme 11



Scheme 12



Scheme 13



The emission fluorescent peak was observed at $\lambda_{em,max}$ = 580 nm (λ_{ex} = 520 nm). The detection limit was determined to be 38 nM. The utility of this probe for nitric oxide was also demonstrated in Hela cells. In 1990, Detty et al. reported that the cationic selena- and tellurapyrylium dyes (Figure 1) gave yellow-green fluorescence in the mitochondria presumably due to the photooxidized versions of the dyes ($\lambda_{em,max}$ = 560 nm and λ_{ex} = 480 nm, aqueous solution).[40]

Han and co-workers developed and reported a selenium-containing near-IR fluorescent probe; this allowed for a demonstration of continuous monitoring of peroxynitrite in living cells and operates reversibly (Scheme 6).[41] The modular probe involves a cyanine dye as a NIR fluorescent dye bearing a high extinction coefficient enabling signal transduction and 4-(phenylselenyl)aniline as a modulator that allows for specific responses to $ONOO^-$ over H_2O_2, OCl^-, $O_2^{\bullet-}$, $^{\bullet}OH$, $^{\bullet}NO$, methyl linoleate

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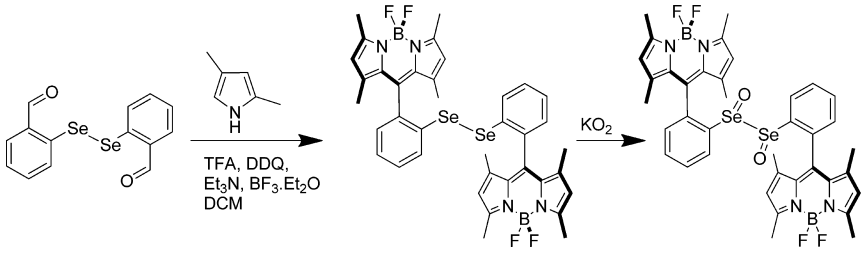
Scheme 14



hydroperoxide (MeLOOH), *tert*-butyl hydroperoxide (^{t}BuOOH), and cumene hydroperoxide (CuOOH).

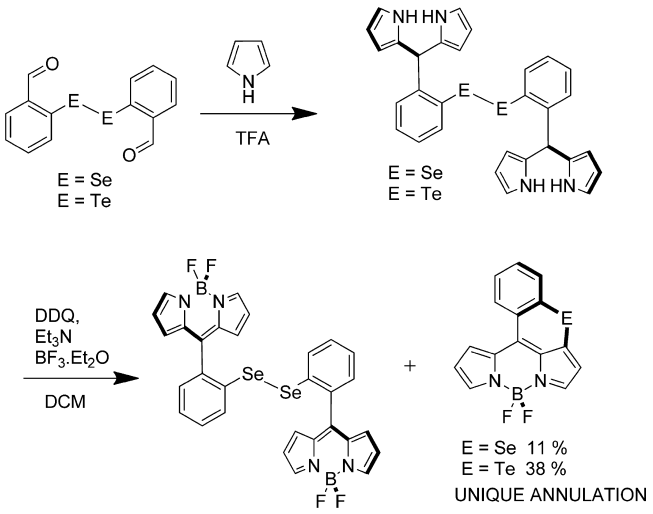
As a separate parameter, "near-IR" compatibility is a very important consideration in *in vivo* sensing. The probe showed good selectivity for $ONOO^-$ at 800 nm (λ_{ex} = 758 nm), and it was reversible with glutathione (GSH) without any observed changes in fluorescence intensity in the cuvette titration. Also, the probe was utilized in living cells for the detection of peroxynitrite.

A nonfluorescent selenium-containing pyrene-based probe was synthesized by Huang and co-workers (Scheme 7).[42] This simple selenide-containing probe emits blue or bluish-green, depending on the ROS analyte used. The rapid oxidation of the nonfluorescent pyrenyl-based compound by hypochlorite (OCl^-) gives blue fluorescence with concomitant formation of pyrenyl-CH_2Cl and pyrenyl-CH_2OH. The formation of these two compounds reveals two closely spaced bands in the emission spectra (380 and 392 nm). However, upon treatment with excess H_2O_2, the reaction of this probe leads to the formation of pyrenyl-CHO, which yields bluish-green fluorescence ($\lambda_{em,max}$ = 470 nm, λ_{ex} = 337 nm).

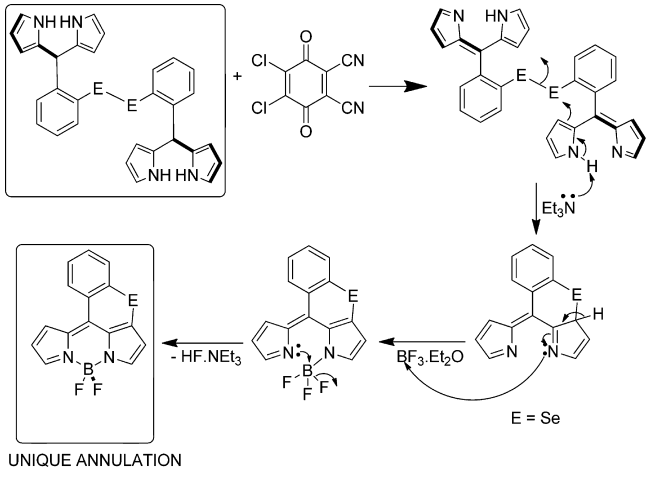
Han and co-workers have reported a novel selenium-containing boron-dipyrromethene (BODIPY)-based probe, in which the BODIPY dye possesses a high extinction coefficient, photostability, and fluorescence quantum yield (Φ_F) as the signal transducer, and 4-methoxylphenylselenyl benzene as the modulator (Scheme 8).[43] The probe detects hypochlorite with a "turn on" fluorescence response; it is selective, sensitive, and importantly reversible with H_2S in solution and in living cell matrixes (λ_{ex} = 460 nm, $\lambda_{em,max}$ = 510 nm). The faint fluorescence exhibited by this BODIPY-based probe is due to a photoinduced electron-transfer (PET) photomechanism from the 4-methoxylphenylselenyl benzene donor to the BODIPY acceptor according to the excited state dynamics. Cell membrane permeability of the probe was shown from confocal microscopy imaging data; RAW264.7 cell lines were used as the medium. A preceding and very closely related organosulfide reported by Churchill et al. involved multi-input detection of reactive oxygen species in which the sulfurs are oxidized to sulfide and sulfone groups in a stepwise fashion.[15]

Next, Liu and Wu developed a similar selenium-containing BODIPY-based probe.[44] Here, the unsubstituted fluorophore was prepared from the reaction of 2-(phenylselenyl)benzaldehyde with conventional BODIPY synthesis involving the use of excess pyrrole in the presence of trifluoroacetic acid; this affords the corresponding dipyrromethene, and further treatment of this dipyrromethene with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, triethylamine, and BF_3 yields the corresponding BODIPY species (Scheme 9). The probe exhibits a rapid selective and sensitive detection of hypochlorite with "turn-on" green fluorescence ($\lambda_{em,max}$ = 526 nm, λ_{ex} = 510 nm). The limit of detection was found to be 7.98 nM. The fluorescence "turn on" process of

Scheme 15



Scheme 16



the probe can be rationalized on the basis of a PET mechanism, in which the organoselenoxide is produced; importantly, this fluorescence signal is reversible with GSH to give the original reduced probe. Confocal fluorescence microscopy imaging in living cells (RAW264.7 cell types) for the detection of hypochlorite suggests the cell permeability and underscores potential medicinal utility of these probes.

In the meantime, more of a focus on the development of a new selenium-containing probe resulted in the synthesis of a BODIPY-based probe by Han et al. (Scheme 10).[45] The selenium-based probe was selective and sensitive for the detection of peroxynitrite through oxidation at the organoselenium center. The spirocyclization reaction at selenium gives the free

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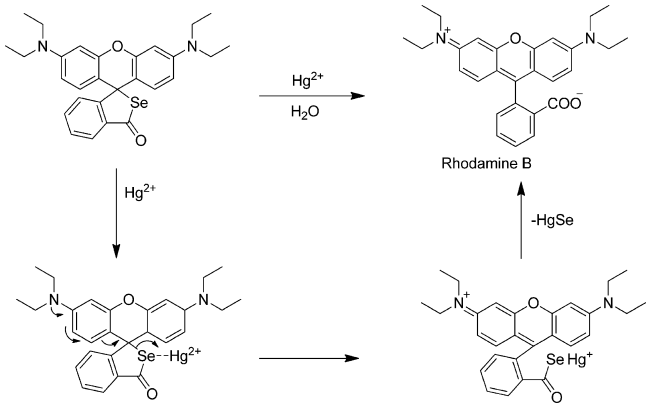
Scheme 17



3-ethylamino-styryl-BODIPY, which emits blue fluorescence through an intramolecular charge-transfer/internal charge transfer (ICT) mechanism.

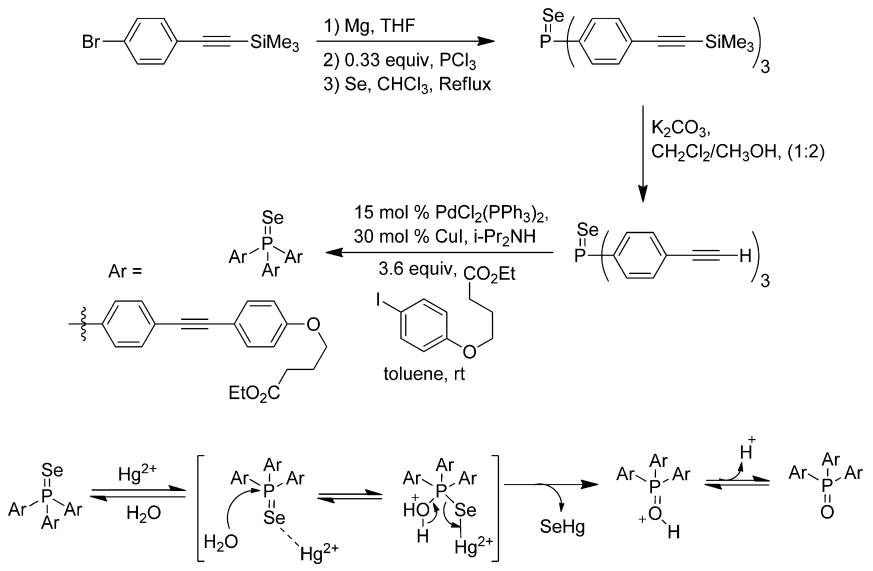
A 1,8-naphthalimide-based selenium-containing probe was synthesized from the reaction of the corresponding bromo-derivative of 1,8-naphthalimide and (2-(phenylselenyl)phenyl)-methanamine (Scheme 11).[46] The probe showed selective and sensitive detection of hypochlorite via a so-called "twist internal charge-transfer" (TICT) photomechanism.[47] The selenium center of the probe, upon reaction with hypochlorite, again becomes oxidized to form the organoselenoxide, which can inhibit the previously allowed internal motion of the molecule and shows a strong fluorescence signal at $\lambda_{em,max}$ = 523 nm (λ_{ex} = 450 nm). The detection limit was determined to be 5.86 × 10^{-7} M. The active site of this oxidized selenium was found to be reduced by thiols or H_2S to help reinstate the properties of the original probe, thus indicating the reversibility of the probe. Medicinal applicability of the probe was shown in experiments that helped to visualize hypochlorite concentration and involved experiments on living mice.

Next, Han et al. developed a near-infrared (NIR) ratiometric and reversible fluorescence probe from the reaction of 4-(4-methoxyphenylselenyl)benzaldehyde and the tetramethyl-substituted BODIPY skeleton (Scheme 12).[48] The probe was capable of selective and sensitive detection of hypobromous acid, HOBr (analogous to hypochlorous acid, HOCl). HOBr was detected over HOCl and other ROS species (H_2O_2, OCl^-, $O_2^{\bullet-}$, $^{\bullet}OH$, $^{t}BuOOH$) by a fluorescence "turn on" detection event at $\lambda_{em,max}$ = 635 nm (λ_{ex} = 610 nm), and the reaction was reversible with H_2S to allow for the recovery of the original reduced selenium probe. The limit of detection was found to be 0.97 μM. This signifies a participation in the reversible redox cycle by the probe through the means of organoselenium redox behavior. The medicinal applicability of the probe was shown by monitoring an intracellular HBrO/H_2S redox cycle in RAW264.7 cells.

Jiang and co-workers developed a novel coumarin-based selenium-containing probe platform for the detection of hypochlorite (HOCl).[49] The probe type was synthesized from coumarin and phenyl selenium bromide serving as starting materials; it was found to be highly selective and sensitive for the detection of hypochlorite based on the selenoxide elimination reaction (Scheme 13). The limit of detection was determined to be as low as 10 nM. The reaction of probes with hypochlorite eliminates selenoxide to give the corresponding coumarin, responsible for the fluorescence signal response observed at $\lambda_{em,max}$ = 480 nm (R = H) and 468 nm (R = CH_3) (λ_{ex} = 405 nm). The utility of the probe for detection of hypochlorite was also shown in living cells, which also helped determine the permeability of the probe in the cells.

Churchill and co-workers developed a novel diselenide-containing bis(BODIPY)-based probe for the selective and sensitive detection of superoxide.[50] The bis(BODIPY)-based probe was obtained from bis(*o*-formyl-phenyl)diselenide via a conventional Lindsey based BODIPY synthesis method (Scheme 14). The probe was found to be selective and sensitive for superoxide over other ROS species (H_2O_2, OCl^-, $O_2^{\bullet-}$, $^{\bullet}OH$, or $^{t}BuOOH$) via a fluorescence "turn-on" response at $\lambda_{em,max}$ = 514 nm (λ_{ex} = 504 nm). The detection limit was calculated to be 12.9 μM. The treatment of the probe with superoxide allows for the formation of the fluorescent selenoxide−BODIPY derivative; probing was reversible through the use of biothiols, as it is well-known that the thiols act to reduce the oxidized diselenium probe to its original nonoxidized form. The fluorescence "turn on" event of the probe, after reaction with superoxide, is due to the monooxidation of both selenium centers. This oxidation of both seleniums was confirmed

Scheme 18



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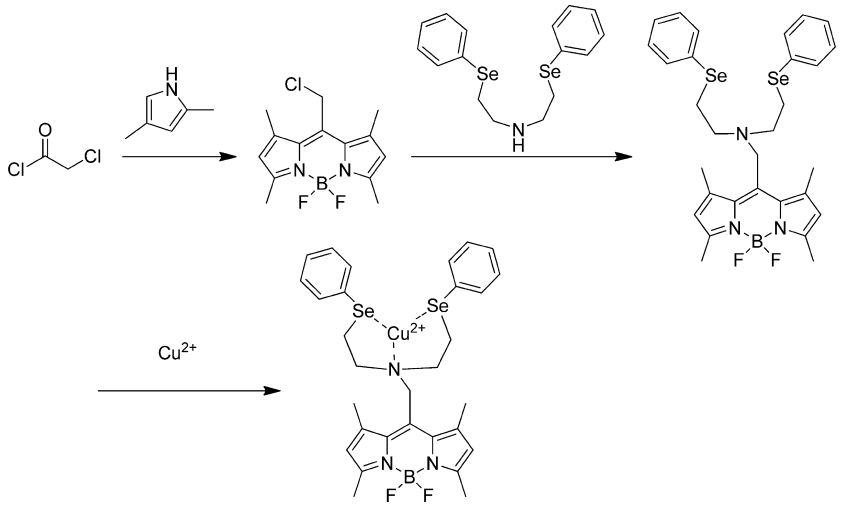
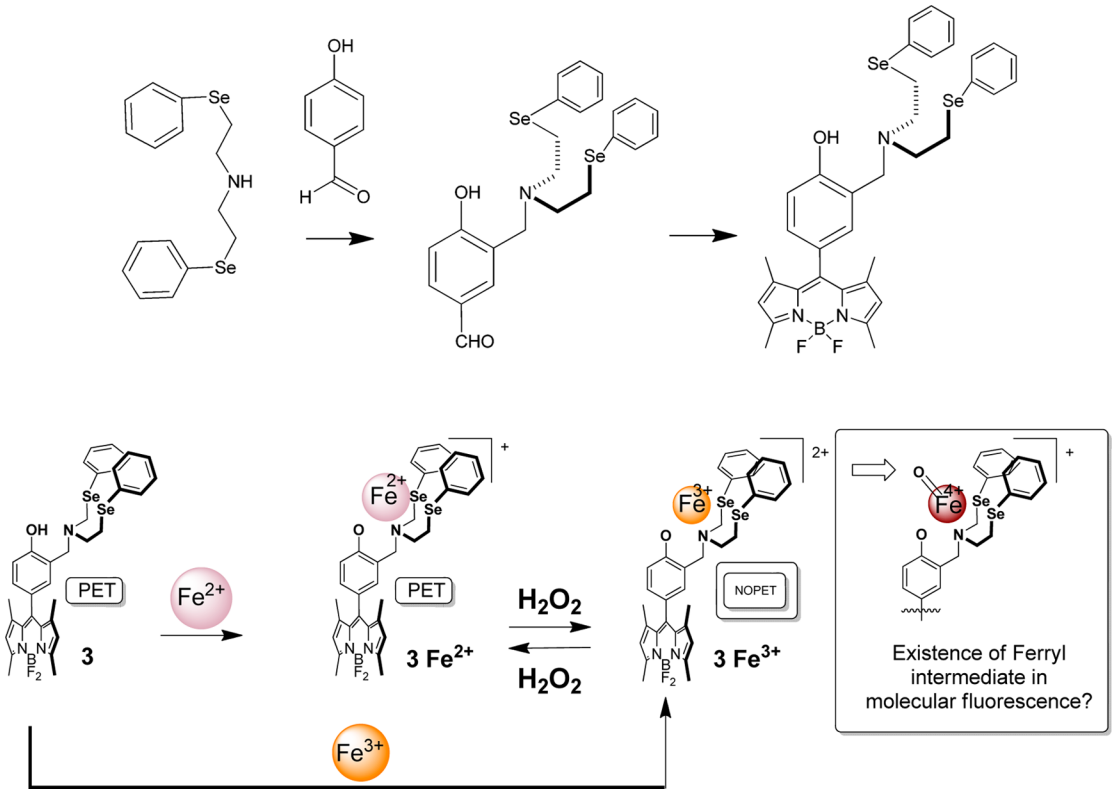
Scheme 19



Scheme 20



by ^{77}Se NMR spectroscopy; the probe, after chemical oxidation, gave only one ^{77}Se NMR signal (1008 ppm). The possible medicinal utility of the probe was demonstrated through the detection of superoxide in living breast cancer cells (MCF-7/ADR cancer cells), which also confirms the permeability of the probe in cells.

Churchill and co-workers synthesized a novel annulated BODIPY selenide/telluride probe for the selective and sensitive detection of hypochlorite in water.[51] The annulated BODIPY selenide probe was obtained as a secondary product in the process of bis(BODIPY)diselenide probe synthesis (Scheme 15). However, the analogous annulated BODIPY telluride was synthesized from bis(*o*-formyl-phenyl)ditelluride as a single product via a common BODIPY synthesis method; its mechanism of formation was supported by the isolation and characterization of some intermediates (Scheme 16). Both types (Se and Te) of probes were found to be selective for hypochlorite; in particular, the organotelluride version of the annulated BODIPY shows highly sensitive and extremely rapid detection of hypochlorite in water through its fluorescence "turn-on" response at $\lambda_{em,max}$ = 597 nm (λ_{ex} = 572 nm). The probe was found to have a 3.7 μM detection limit and exhibits a 62-fold fluorescence intensity increase. Also, the annulated BODIPY telluride probe shows reversibility with biothiols for up to 10 chemically induced redox cycles.

Selenium has various oxidation states and an ability for vital antioxidant behavior in biology systems. Selenium was proposed

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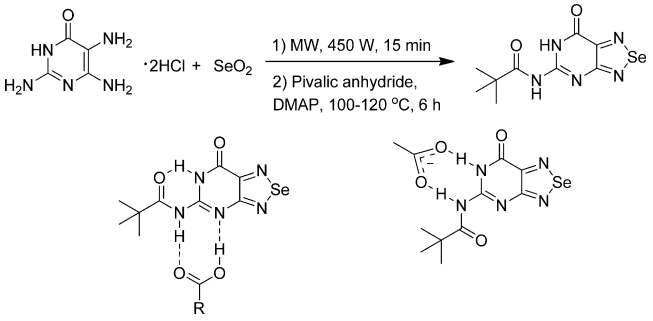
Scheme 21



as the most oxidizible part and electron-rich group in the molecule, which can also contribute electron density transfer from selenium to the fluorophore or chromophore core in ROS/RNS sensing probes. This quenches the fluorescence of the fluorophore or chromophore. After selenium oxidation by ROS/RNS, selenium electron-richness is lost, resulting in generation of a "turn-on" fluorescence response by recovery of the fluorophore or chromophore itself, or by blocking of the electron transfer. Though the rules are still being written regarding which ROS/RNS will be selective to which rationally-designed molecule, organoselenium centers could be used selectively through tuning of geometrical and electronic aspects.

METAL SENSING PROBES

In 2010, Ma and Yoon and their co-workers reported a novel simultaneous selenium-based fluorescent type of chemodosimeter originating from rhodamine B. It was used to monitor mercury/methylmercury species *in vitro* and *in vivo*.[52,53] The probe was synthesized from the reaction of rhodamine B and selenourea (Scheme 17). The probe selectively detects Hg^{2+} and Ag^{+} ion, compared with other metal ions, with a detection limit of 23 nM for Hg^{2+} and 52 nM for Ag^{+}. It does so with a strong fluorescence signal (λ_{ex} = 520 and λ_{em} = 580 nm). The plausible mechanism for the detection of mercury is through the opening of the spirocyclic ring of rhodamine, allowing for the formation of rhodamine B followed by the deselenation with mercury to form the selenium version of cinnabar (HgSe).

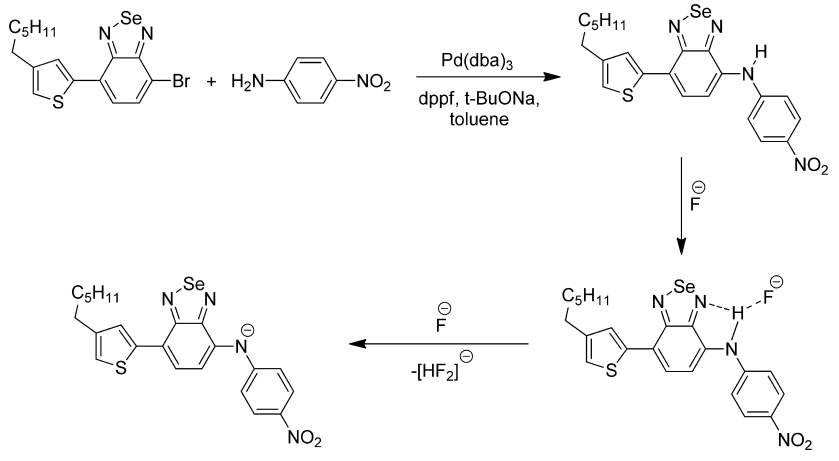
Leray and co-workers synthesized a phosphane selenide probe system. This was found to enable selective "turn-on" fluorescence detection for Hg^{2+} (Scheme 18).[54] The phosphane selenide probe reacts selectively with mercury in the presence of water to summarily form mercury selenide and also the reporting phosphane oxide as a product, giving a "turn-on" fluorescence response at 406 nm (λ_{ex} = 326 nm) in which a value of 0.9 nM was determined for the detection limit.

Wu et al. designed and synthesized a BODIPY-based fluorescent probe involving a [N,Se,Se] chelating group via the reaction of bis[2-(phenylselenyl)ethyl]amine and 8-chloromethyl-BODIPY for metal ion detection (Scheme 19).[55] The [N,Se,Se] moiety of the probe acted as a highly selective and sensitive site for the binding and detection of Cu^{2+} in solution with a fluorescence "turn-on" signal observed at $\lambda_{em,max}$ = 516 nm (λ_{ex} = 500 nm). The detection limit and emission intensity enhancement of the probe was determined to be 0.87 μM and 18-fold, respectively. The binding ratio of the Cu^{2+}-probe complex was determined to be 1:1 from Job plot analysis. The methyl thiazolyl tetrazolium (MTT) assay suggested that the probe imparts low cytotoxicity. Confocal microscopy imaging revealed the cell permeability of the probe and the effective detection of Cu^{2+} in RAW264.7 living cells.

In the process of investigating probes for metal ion sensing, Churchill and co-workers developed a novel soluble [O,N,Se,Se] BODIPY-based iron ion-chelating probe. This could be configured for fluorescence probing of the ferric Fenton reaction.[56] The probe was synthesized from a selenium-containing phenyl-4-amino-based donor group via Mannich conditions followed by conversion of the aldehyde group to the corresponding BODIPY system (Scheme 20). The probe is highly selective and sensitive for the detection of Fe^{3+} through a 15-fold "turn-on" fluorescence response with a 96.3 μM detection limit; the addition of hydrogen peroxide acts to "turn-off" the fluorescence in solution. Also, the probe with Fe^{2+} and hydrogen peroxide shows a fluorescence "turn-on" capacity. Here, hydrogen peroxide plays an important role for this redox reaction, which can allow for reduction of Fe^{3+} to Fe^{2+}, as well as oxidation of Fe^{2+} to Fe^{3+}. Thus, this probe can be used to discriminate between Fe^{2+} and Fe^{3+} via Fenton chemistry, and the optical responses were also interpreted as a 2:1 multiplexing molecular logic gate in which Fe^{3+}, Fe^{2+}, and hydrogen peroxide serve as chemical inputs. DFT calculational results suggested that high-valent [Fe^{IV}] ferryl complexation may be favored under aqueous conditions and responsible for the observed contributions to PET quenching.

Many atoms (nitrogen, oxygen, sulfur, etc.) have been used to bind metal ions in ligand frames. There have been efforts in the chemosensing field as well to design molecules bearing

Scheme 22



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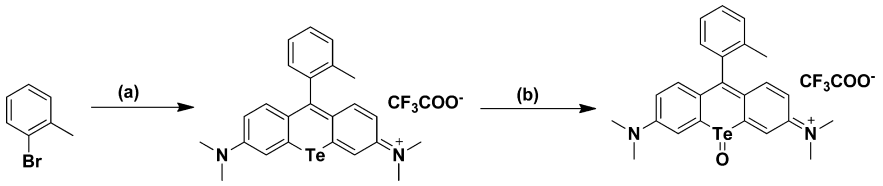
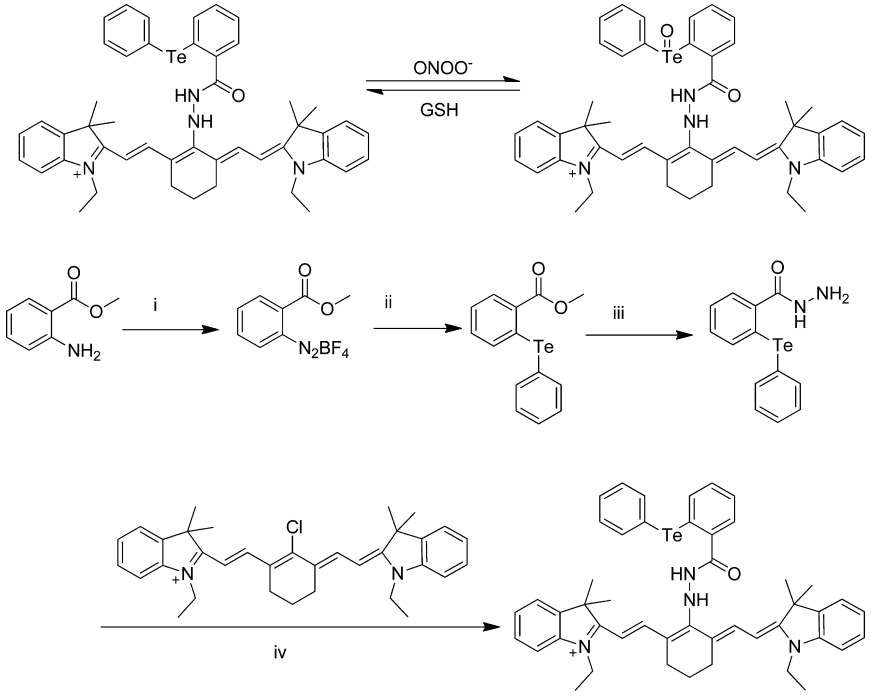
Scheme 23[a]



[a]Reagents and conditions: (a) (i) s-BuLi/THF, −78 °C, (ii) Te-xanthone/THF, −78 °C to rt, (iii) 2 N HCl, rt, yield 68%; (b) H_2O_2/MeOH, rt, yield 20%.

Scheme 24[a]



[a]Reagents and conditions: (i) $BF_3{\cdot}Et_2O$, isoamyl nitrite, anhydrous CH_2Cl_2, −15 °C, 1 h; (ii) diphenyl ditelluride Zn, dimethylcarbonate, 85 °C, 12 h; (iii) 85% hydrazine hydrate, ethanol, reflux 24 h; (iv) chloro-fluorophore, anhydrous acetonitrile, 50 °C, 12 h.

customized receptor sites for the selective detection of metal ions. Selenium works in a similar way as oxygen and sulfur for chelating iron and mercury, but it is "softer" yet less metallic than tellurium. Similar to the previous thiols and ROS/RNS sensors, electron-rich selenium causes the fluorescence to be quenched by allowing its electron density to be transferred to the fluorophore or chromophore core. The chelation of selenium to metal ions leads to a prohibition of electron transfer resulting in the recovery of a "turn-on" response. An alternative strategy, as introduced here to detect metal ions, is to use the strong potential binding between selenium and a soft metal ion. The selenium−metal adduct can also detach completely from the molecule giving a "turn-on" fluorescence to help recover a fluorophore or chromophore parent molecule.

■ ANION SENSING PROBES

The selenium-based sensor 5-pivaloylamino-1,2,5-selenodiazolo-[3,4-*d*]pyrimidin-7-(6*H*)-one (2-pivaloyamino-6-selenoguanine) was synthesized by Goswami et al.[57] The probe was synthesized from the reaction involving 2,5,6-triamino-3*H*-pyrimidin-4-one dihydrochloride and selenium dioxide where microwave energy was utilized as the energy source. The absorption intensity of the probe decreased at 356 nm and increased at 304 and 396 nm, while allowing for the ducking of both carboxylic acids and carboxylate moieties due to the available binding modes of the probe that facilitate carboxylic acid moiety interactions (Scheme 21). The probe showed good selectivity for carboxylate anions over carboxylic acids and other anions, and offered a fluorescence signal at 459 nm (λ_{ex} = 356 nm).

Next, Wang and co-workers synthesized a benzoselenadiazole-based fluorescent probe, which was found to be selective for near-IR detection of the fluoride ion (Scheme 22).[58] The probe probes fluoride ion with high selectivity and sensitivity through optical and "off−on" ratiometric fluorescence methods. It does so over other competitive analytes.

In these probing modalities, a selenium contributes not only heavy-atom characteristics but also semimetal character to the benzochalcogenodiazole. These heavy organic compounds, herein involving selenium, lead to a red-shifting and lowered photoexcitation transition energy. As insinuated in the preceding articles, organoselenium could be substituted in almost any position that exists currently for sulfur and oxygen; it is a feature to be greatly exploited due to its intermediate properties that allow for bathochromic shifts and good photostability.

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TELLURIUM-BASED PROBES

Nagano et al. synthesized the tellurium-based Te-rhodamine probe that was able to be implemented for the reversible near-IR detection of ROS species.[59] The Te-rhodamine probe was synthesized through the replacement of the oxygen atom at the 10-position of the xanthene moiety (typical for rhodamines) with tellurium (Scheme 23).[36] The probe was sensitive for the detection of ROS, giving a "turn-on" fluorescence response at 690 nm (λ_{ex} = 660 nm); it showed reversibility with GSH through the redox properties open to the organotellurium center. Also, this reactivity and probe cell-permeability were confirmed in living cells.

Han and co-workers reported a tellurium-based near-IR fluorescent probe for monitoring the redox cycles between peroxynitrite and glutathione (GSH) *in vivo*.[60] The probe was synthesized in four steps (Scheme 24). The probe was found to be selective and sensitive for peroxynitrite through a fluorescence "turn-on" event at 820 nm (λ_{ex} = 793 nm). The detection limit was found to be 9.17×10^{-7} M. Confirmation was made in solution and in living cells. The system was importantly reversible upon the reaction with GSH and cysteine. The probe was also used for the detection of mitochondrial peroxynitrite in macrophase RAW264.7 cells and in living mouse models, which also suggested the permeability of the probe in cells.

CONCLUSION AND OUTLOOK

Potential antioxidant and antitumor properties of organochalcogen (Se, Te) centers have become a promising and active field for research. Even though the antioxidant mechanisms, chemomechanisms, photomechanisms, and the chemical and photophysical properties are still not fully elucidated, various researchers are sure to pay attention to applications of organochalcogen compounds. In this Account, probing and sensing efforts and tactics from recent reports in the literature have been reported. We have focused on small chromophoric molecules bearing rational and discrete organochalcogen atom (Se, Te) incorporation in predesigned sites for completing an optical system; the chemical redox properties of selenium and tellurium atoms can then be exploited and the concept of "reversibility" can be conveniently explored. Mainly, organochalcogen atoms provide oxidizable, GPx-like, metal-binding, and heavy-atom properties to give fluorescent "turn-on" optical responses and red-shifting. The main molecular skeletons have involved the chemical frames of BODIPY, cyanine, and rhodamine. While the analytes of central importance have involved reactive oxygen species (ROS) and thiols (RSH), the study of analytes such as metal ions and anions have also been included. Building organochalcogen atom (Se, Te) sites into molecular sensors is an interesting recent research field. Especially, tellurium is promising for researchers because it is still largely unclaimed in the fluorescence chemosensing field. It is sometimes challenging to develop novel sensors involving organotellurium sites due to stability issues. This is especially true with ditelluride sites. Also, there are potential toxicological issues with tellurides that need to be better profiled.

There have been occasional issues raised by reviewers about the practicality of the "reversibility" aspect of the probes that requires clarification. Technically, the probes that are claimed to be reversible are not strictly so in a global sense. They are the best attempts so far to be such, but despite this encouraging dimension in chemosensing, cautionary steps need to be taken: while the probe clearly reverts, the exact analyte that was used in the chemical oxidation is not strictly regenerated or at least is not regenerated in the same concentration as the initial concentration when the "reverse" reaction is effected to chemically reduce the probe. Instead, in most examples, an oxygen atom (or atoms) is stripped off of a tetravalent organochalcogen center by a thiol (lighter chalcogen), which then undergoes sacrificial chemical oxidation to reinstate the starting probe. (This chemical oxidation of the sacrificial thiol is analogous to the initial chemical oxidation of the probe.) For proper biological function, a probe might be envisaged to (i) enter one biological compartment and (ii) become chemically oxidized. Then, perhaps due to a change in physical properties or other factors, the probe could (iii) migrate to a secondary compartment where it (iv) encounters heightened concentrations of a thiol or other reductant and then returns to a reduced state. Notably, if both analytes are present in the same space at exactly the same time, they could *react with each other*. This annihilation would preempt probing efforts, except, for example, in cases where one analyte is found in great excess. Lastly, to date, while the biological assaying may currently be seen as being heavily handled, we feel that future cellular biological research will find great reliance on probes of this class. The probes could be multimodel or conjugated with, for example, Gd(III) MRI contrast agents. The ability for smooth chemosensing "reversibility" with these types of bioinspired synthetic probes will surely come of age.

Hopefully, this Account encourages chemists working on organochalcogen-based atoms and chromophoric or fluorophoric molecular sensors to explore synthetic avenues, especially unpopular ones, to achieve a solid understanding of the capability that organochalcogen systems have in producing novel and finalized sensors.

AUTHOR INFORMATION

Corresponding Author

*Email address: dchurchill@kaist.ac.kr.

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Notes

The authors declare no competing financial interest.

Biographies

Sudesh T. Manjare has recently started as an Assistant Professor at the Department of Chemistry, University of Mumbai (Maharashtra, India). He studied as a postdoctoral fellow under Professor David G. Churchill at KAIST, South Korea, as an IBS-sponsored postdoctoral fellow. He pursued his Ph.D. with Professor H. B. Singh from the Department of Chemistry, IIT Bombay, India.

Youngsam Kim is presently studying Ph.D. coursework at KAIST. He has obtained a bachelor's degree in Chemistry from Kyung Hee University. While an undergraduate, he worked in the "Organic catalyst and Synthesis Laboratory" as a research student.

David G. Churchill obtained a B.S. degree in Chemistry at the University at Buffalo (NY, USA) while performing X-ray crystallographic studies in the laboratory of his father, M. R. Churchill. He then studied intensively under Professor Gerard (Ged) Parkin at Columbia University (NY). As a graduate student, he earned Departmental distinctions for both teaching (Miller award) and research (Pegram award). After his Ph.D., he served as a postdoctoral fellow for Professor Kenneth

N. Raymond in the Department of Chemistry at UC Berkeley (CA). Churchill moved to East Asia in 2004. He becomes the first American to build a tenure track academic career in the Republic of (South) Korea. He has given over 70 invited seminars worldwide and has been distinguished as an important international scholar for Korea. His current research deals with various aspects of molecular neurodegeneration. He became an associate professor in 2009.

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