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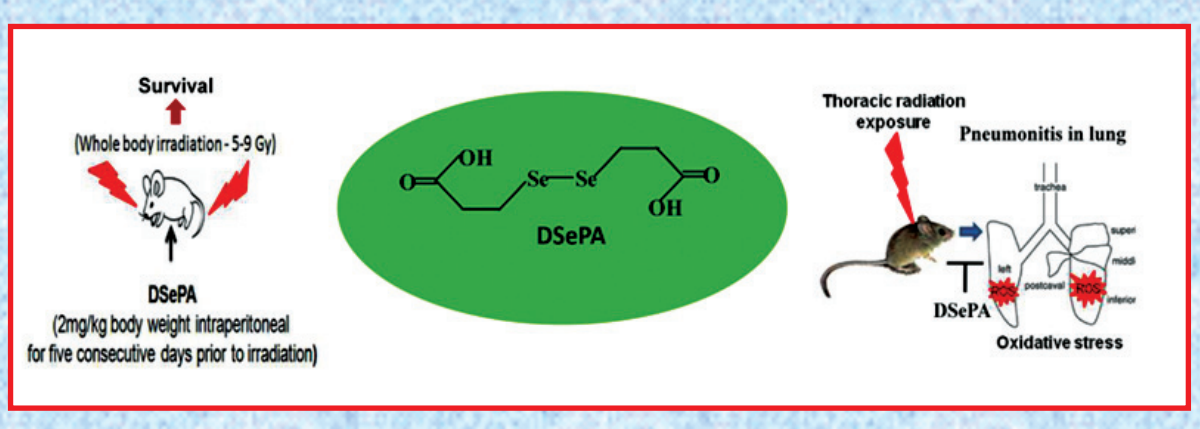

Special Issue on Selenium

SOCIETY FOR MATERIALS CHEMISTRY

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Society for Materials Chemistry was mooted in 2007 with following aims and objectives:

(a) to help the advancement, dissemination and application of the knowledge in the field of materials chemistry,

(b) to promote active interaction among all material scientists, bodies, institutions and industries interested in achieving the advancement, dissemination and application of the knowledge of materials chemistry,

(c) to disseminate information in the field of materials chemistry by publication of bulletins, reports, newsletters, journals.

(d) to provide a common platform to young researchers and active scientists by arranging seminars, lectures, workshops, conferences on current research topics in the area of materials chemistry,

(e) to provide financial and other assistance to needy deserving researchers for participation to present their work in symposia, conference, etc.

(f) to provide an incentive by way of cash awards to researchers for best thesis, best paper published in journal/national/international conferences for the advancement of materials chemistry,

(g) to undertake and execute all other acts as mentioned in the constitution of SMC

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Contact address
Society for Materials Chemistry
C/o Chemistry Division
Bhabha Atomic Research Centre, Trombay, Mumbai, 400 085, India
Tel: +91-22-25592001, E-mail: socmatchem@gmail.com

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Guest Editor

Dr. K. Indira Priyadarsini
Head, Chemistry Division
Bhabha Atomic Research Centre
Trombay, Mumbai-400 085

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C/o. Chemistry Division
Bhabha Atomic Research Centre, Trombay, Mumbai, 400 085
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Front cover shows radioprotective activities of diselenodipropionic acid (DSePA) in preclinical models.

Guest Editorial

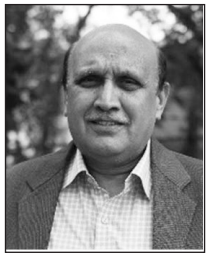
Dr. K. Indira Priyadarsini

Selenium, a rare element on earth, was initially considered to be a poison, but has now become an essential element for humans and animals. Its deficiency is now linked to increased infection risks and correlated with the onset of many disorders such as neuro-degeneration, altered immune response, cardiovascular diseases and cancer. There have been significant advances in the design and synthesis of organoselenium compounds exhibiting potential biological activities. To mark 200 years of discovery of selenium by the Swedish Chemist *Jöns Jacob Berzelius*, SMC in collaboration with Chemistry Division, BARC has organised a special conference on selenium in November 2017.

This special issue of SMC bulletin on selenium includes four articles. The first article by Prof Kaim compares co-ordination chemistry of selenium with that of sulphur, second article by Dr Jain highlights new synthetic methods for preparing new organoselenium compounds. The third article by Prof Churchill from S. Korea describes selenium/chalcogen based fluorescence sensors to detect oxidative stress and the last article discusses the possible application of selenium in cancer radiotherapy. This special bulletin thus provides a glimpse of a wide range of topics of research on selenium. I take this opportunity to thank all the authors for their contribution.

I hope the readers of SMC bulletin will find this special issue interesting.

From the desks of the President and Secretary



Dr. V.K. Jain
President

Dr. P. A. Hassan
Secretary

Dear Fellow Members and Readers,

Greetings from the Executive Council of SMC.

The tradition of SMC in disseminating scientific advancements in frontier areas of science and technology has reached another milestone. It is with great pleasure, we introduce this special issue of SMC Bulletin. To commemorate the bicentenary year of discovery of selenium by a Swedish chemist Jöns Jacob Berzelius, SMC has taken keen interest in co-organising a mega international event entitled "Symposium on Selenium Chemistry & Biology (SSCB-2017)" during 9 - 11 November, 2017 at DAE Convention Centre, Anushaktinagar, Mumbai.

Selenium finds its place in a wide range of commercial products including semiconductor devices and plays a crucial role in human health and nutrition. It is an essential micronutrient for humans, though excess of selenium can be toxic. The SSCB-2017 gave an opportunity to interact with several renowned scientists working in the area of selenium chemistry from across the world. This was the genesis to collect a few articles from the delegates of SSCB-2017 and release a compendium of important scientific advancements in selenium research.

The present issue of the bulletin discusses various aspects of selenium research ranging from coordination chemistry of selenium and its comparison with sulfur, synthesis of organoselenium compounds, selenium based fluorescence sensors to detect oxidative stress and application of selenium in cancer radiotherapy. We are extremely thankful to the Guest Editor, Dr. K. I. Priyadarsini, who was the convenor of SSCB-2017, for her keen interest and enthusiasm in coordinating with all authors. We thank all contributing authors for their painstaking effort in drafting the manuscripts and submitting the same on time. We are sure that this collection will be an asset to all our readers.

We thank all our members and readers for their constant endeavour to support the growth of the Society.

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Selenium vs Sulfur Coordination Effects in Metal Compounds with Neutral Ligands

Wolfgang Kaim
Institut für Anorganische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70550 Stuttgart, Germany
E-mail: kaim@iac.uni-stuttgart.de

Abstract

Following a brief presentation of the essential atomic differences between Se and S and their prototypical compounds, a number of transition metal complexes with neutral organoselenium ligands will be discussed in relation to corresponding sulfur analogues. The ligands include π accepting 2,1,3-benzochalcogenadiazoles and chalcogeno ethers with added redox-active chelate functions such as α-diimines or *o*-iminosemiquinones. The relatively small differences observed between S and Se analogues stand in contrast to the more pronounced variety noted for anionic species, pointing to π back donation contributions due to a non-negligible π acceptor capacity of the chalcogens in the neutral systems.

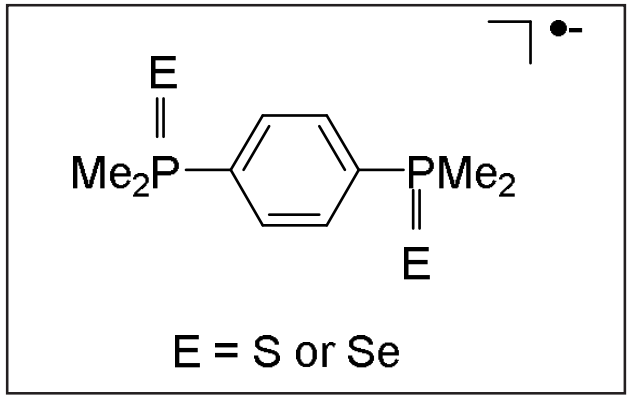
1. Introduction

The attention paid to selenium in the life sciences [1] and in electronics research [2] is remarkable, considering the low relative abundance of this element in the earth's crust (Se/S ≈ 10^{-5}) [3] and the apparent similarity with its lighter homologue, sulfur. The similarity between organic S and Se analogues regarding neutral ligands in coordination compounds will be elaborated in this article, however, a comparison here in the beginning will point out that there are significant differences which should become manifest under certain conditions. Among these are

- the non-trivial difference in atomic mass (78.97 g/mol vs. 32.06 g/mol, i.e. a factor of about 2.5 higher for Se),
- the increased size of Se vs. S (by about 0.1 Å in typical radii) [3] which leads to longer and less "stable" bonds, while it also
- allows for higher coordination numbers at the bigger chalcogen atom,
- the spin-orbit coupling constant for the heavier Se is much higher at 1700 cm^{-1} than that of sulfur (380 cm^{-1}) [4] being relevant for excited state phenomena,
- the ^{77}Se nucleus with 7.6% natural abundance has much more favorable magnetic properties (I = ½, large isotropic hyperfine constant of 1144.34 mT) [5] than all available sulfur isotopes,
- electron transfer parameters such as ionization energy, oxidation potential, electronegativity are all lower for Se, and
- the acidity of E-H is typically about 3 pK units higher for E = Se [6].

In purely aqueous environment the selenium system is distinguished by several accessible intermediate oxidation states (-II, 0, +IV, +VI) whereas sulfur is thermodynamically restricted to terminal (-II) and (+VI) states [7].

The heavier Se vs. S causes a higher moment of inertia $I = m\,r^2$ for rotational movement which can cause special linewidth effects in EPR spectroscopy with its typical time scale of micro- to nanoseconds. For instance, symmetrical phosphane containing radicals $[Me_2(E)P\text{-}C_6H_4\text{-}P(E)Me_2]^{\bullet-}$ (1) exhibit unusual line broadening effects in solution only for the selenium species (E = Se) due to insufficiently averaged A and g anisotropy, caused by slowed down rotation of the molecule with the heavier homologue [8].

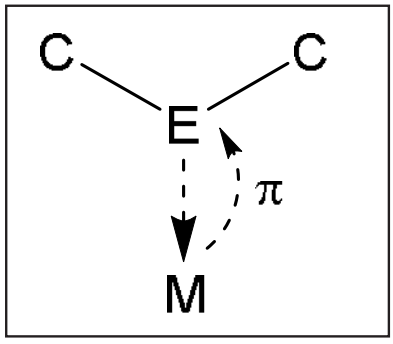


(1)

2. Neutral Se vs S ligands

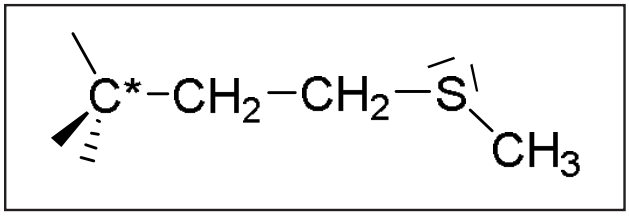
Whereas the biochemically significant difference between RSH and RSeH analogues has received wide attention due to the antioxidative and other function of natural (mostly cysteine based) and artificial selenols,[6] there has been less attention given to the seemingly conventional diorganochalcogeno ethers R-E-R', probably because of their neutrality and low Lewis basicity.

As ligands in a coordination compound the chalcogeno ethers R-E-R′ should be different (i) due to enhanced "softness" of the heavier homologue and (ii) because of the potential for π back donation (2) from lower valent metals into low-lying unoccupied orbitals of the ligand [9].



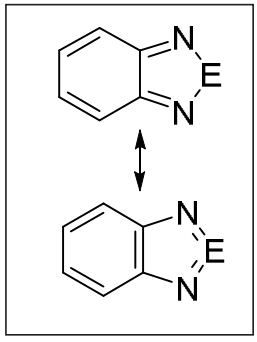
(2)

That interaction shows parallels to the situation in organophosphane or –arsane complexes [10] which, however, exhibit less geometrical freedom and stronger electronic effects. Earlier discussions of this potential for π back bonding to π acidic thioethers and selenoethers have been inconclusive [9], raising doubt on any significance of such a mechanism. Nevertheless, it should be noted that the thioether methionine (3) is the only non-π-donor essential amino acid residue, thus stabilizing low-valent states such as Cu^{I} and Fe^{II} [7,11].



(3)

The potential for metal binding is also present in 2,1,3-benzochalcogenadiazoles (4) which are well established as electron acceptors in polymers for optoelectronics [12].



(4)

However, even with low-valent "soft" metal species such as $W(CO)_5$ or $[Re(CO)_3(bpy)]^+$ (bpy: 2,2′-bipyridine) the nitrogen lone pairs are superior in coordinating (5), as evidenced by experiment and theory [13].

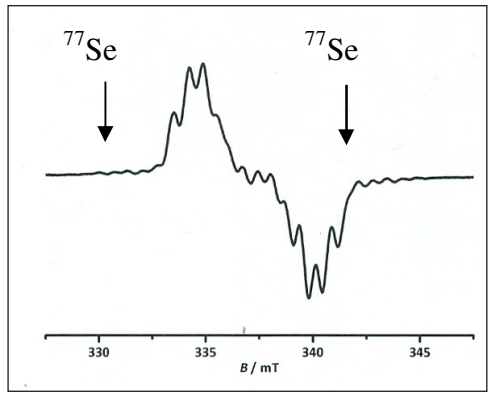
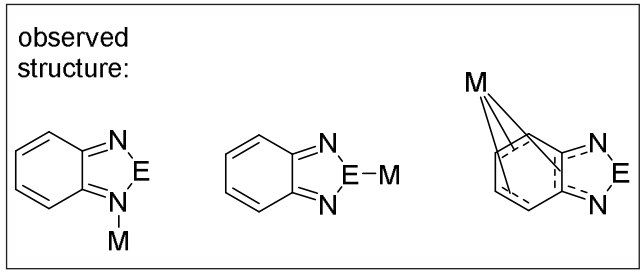


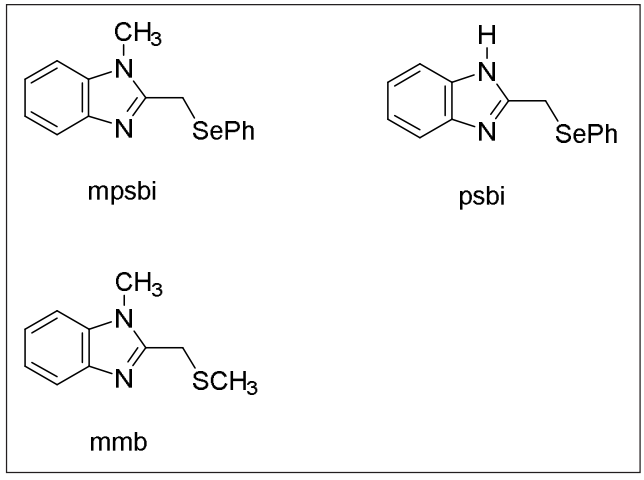
Fig.1: *EPR Spectrum of electrogenerated* $[Re(CO)_3(bpy)(bsd)]^{\bullet}$ *in 0.1 M* CH_2Cl_2/NBu_4PF_6 *(bsd: 2,1,3-benzoselenadiazole).*



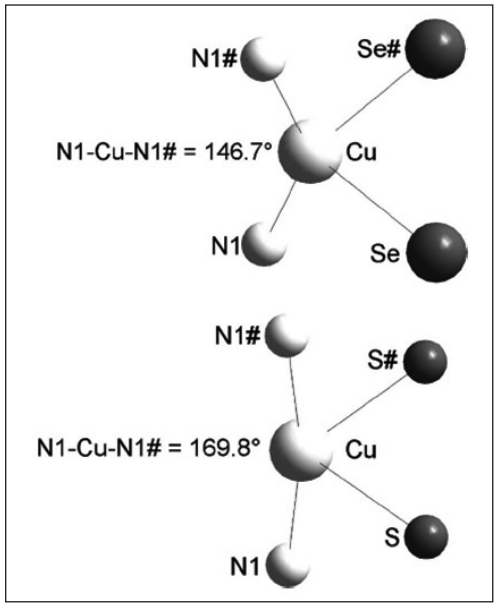
(5)

The dominant imine functions vs. the less basic chalcogens can be made responsible for this preference (4). Nonetheless, addition of an electron produces a radical complex species with notable ^{77}Se hyperfine coupling (I = ½) in the EPR spectrum (Figure 1) [13]. An additional common feature of such compounds is the inter- or even intramolecular[14b] non-covalent attraction Se---X, e.g. Hal [14].

Attempts to model the His/Met coordination in copper proteins [12] by simple imidazole/thioether chelates (6) have been carried out, with additional variation by S/Se substitution.



(6)



(7)

The structural results reveal qualitatively similar coordination albeit with notable differences. As a most conspicuous result for complexes $[CuL_2]^+$, the remarkably strict 2N+2S coordination with sawhorse structure (7, lower structure) is attenuated in a 2N+2Se analogue in the direction of a tetrahedral arrangement (7, upper structure) [15-17].

The N_2S_2 donor combination typical for type 1 Cu centers in blue copper proteins[7] has been mimicked with various model ligands.[11] A recent example combines the familiar α-diimine chelate function with two chalcogenoether groups (Figure 2).[18] Both kinds of donors are π accepting, and the whole arrangement then involves a tetradentate chelate ligand L[4]. Compounds of Copper(I) and Copper(II) were obtained and structurally and electrochemically characterized.

Sulfur and selenium analogues showed strong similarities: The Cu^I forms $[CuL^4]^+$ are best described as distorted tetrahedral whereas the copper(II) species exhibit a square pyramidal structure (Figure 2).[18] Apparently, the slight structural and electronic differences between sulfur and selenium analogues cancel out and lead to very comparable systems. It should be noted, however, that multidentate chelate ligands with their reduced degrees of freedom do not allow much structural variation.

In a less biochemically motivated approach one copper(II) center was made to coordinate two "non-innocent" [19] iminosemiquinone radical species with the added option of chalcogenoether coordination in a hemilabile [20] sense. Studies of such three-spin copper(II) compounds $[Cu^{II}(Q^{\bullet-})_2]$ have shown a remarkable sensitivity of intramolecular spin-spin interaction and of the resulting magnetism in corresponding materials [21]. In contrast, organometallic half-sandwich compounds of ruthenium and osmium (Figure 3) have been shown to undergo an intramolecular reversible one-electron oxidative addition/reductive elimination reaction. Analysis of cyclic voltammograms yielded hysteresis-type square schemes with sulfur and selenium analogues exhibiting only slight differences in terms of redox potentials and kinetics [22].

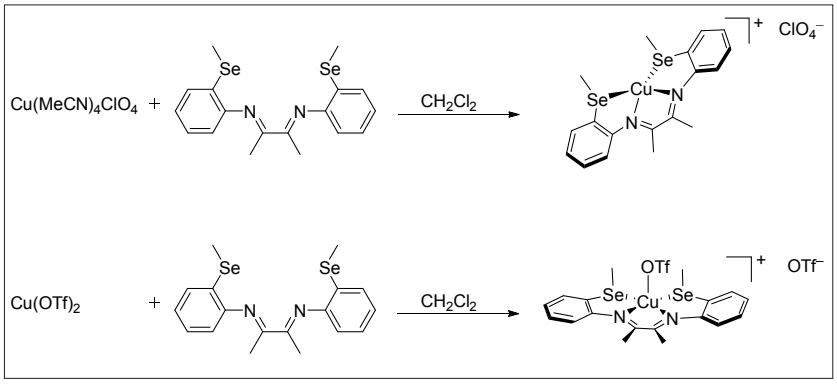


Fig. 2: *Copper(I) and copper(II) complexes of tetradentate α-diimine/selenoether hybrid ligands.*

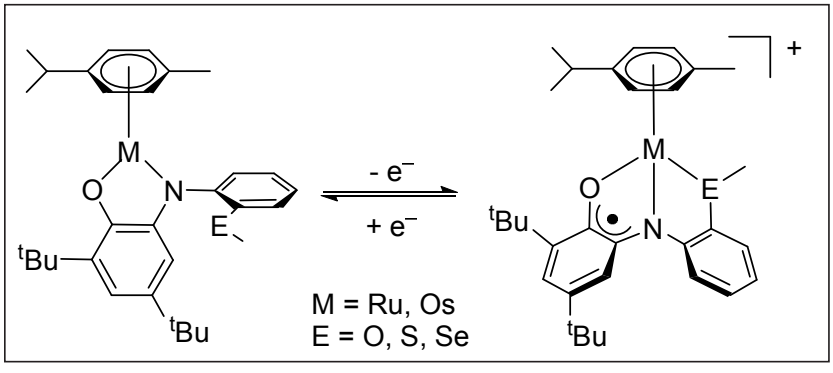


Fig. 3: *Reversible intramolecular 1e⁻ oxidative addition.*

3. Conclusions

The use of thio- and corresponding selenoethers as coordinating entities in complex ligands yields generally very similar results, in spite of the atomic differences delineated in the Introduction. The diminished difference in comparison to thiolate vs selenolate examples such as aminochalcogenolate chelate compounds[23] is tentatively attributed to the compensation of diminished coordinative bonding (longer E-M distances for E = Se) by enhanced π back

donation from the metal to lower lying unoccupied orbitals in the Se containing acceptors. It remains a challenge to provide further experimental and theoretical evidence for the latter kind of interaction.

Acknowledgement

This project was supported by the Land Baden-Württemberg. Support from the Deutsche Forschungsgemeinschaft, the COST program, and from the Fonds der Chemischen Industrie is gratefully acknowledged. I also thank the dedicated coworkers mentioned in those references which pertain to our own work. Special thanks are due to Mrs. Angela Winkelmann for her contributions to preparing this article and to Drs. Jan Fiedler and Stanislav Záliš (J. Heyrovsky Institute, Prague) for continued cooperation.

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Wolfgang Kaim *has obtained a PhD degree in physical main group organoelement chemistry in Frankfurt/Germany. After a postdoctoral year with F. A. Cotton in Texas and his return to Frankfurt he took up a chair in coordination chemistry at the University of Stuttgart in 1987. His main interest lies in the electron transfer behaviour of redox-active molecules. In 2014 he received the Alfred Stock medal for "outstanding scientific investigations in inorganic chemistry".*

Synthetic Methods in Organoselenium Chemistry

Vimal K. Jain
UM-DAE Centre for Excellence in Basic Sciences
Health Centre, University of Mumbai, Kalina Campus
Vidyanagari, Santacruze (E), Mumbai-400 098
E-mail: jainvk@cbs.ac.in

Abstract

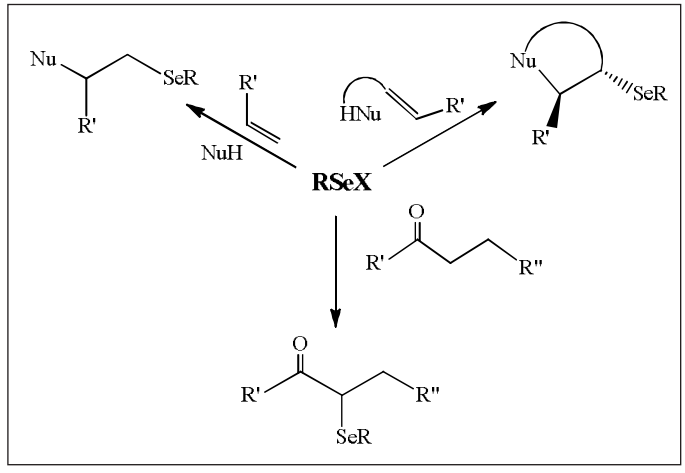
Selenium is an essential micronutrient; its deficiency is implicated in several diseases. It constitutes an active site in several important selenoproteins such as glutathione peroxidase and is responsible for important physiological functions such as antioxidant action, redox regulation, immune function, etc. Having recognized the role of selenium in biological functions several efforts have been made to develop synthetic mimics. Oragnoselenium compounds are now extensively used in synthetic organic chemistry and their utility in materials science is rapidly growing. This article aims to give a brief overview of synthetic methods which are practiced in organoselenium chemistry.

1. Introduction

Selenium is the first member of the chalcogen family (Group 16 of the periodic table) which shows some metallic character. It was discovered by a Swedish Chemist Jöns Jacob Berzelius in 1817 and named after the Greek goddess 'Selene' meaning moon.

Organoselenium compounds have been known for a long time, diethylselenium and ethyl selenol were the first derivatives reported by Löwing and Wöhler and Siemens in 1836 and 1847, respectively. Selenium was long considered as a poison until Schwarz and Foltz in 1957 recognized it as an essential micronutrient. The role of selenium in mammals was reported some fifteen years later with the discovery of selenocysteine (21st amino acid) at the active site of glutathione peroxidase (GPx)-an important family of antioxidant enzyme. Selenium intake varies worldwide and depends on the concentration as well as on the nature of chemical species present in the source. There is very narrow window between dietary deficiency (< 40 µg/day) and toxic levels (>400 µg/ day) in human and the recommended optimum levels being 50-70 µg/day. Recent developments in the chemistry of organoselenium compounds stems from their applications in organic synthesis, biochemistry, and inorganic materials, ligands in coordination chemistry and metal selenolate / selenide complexes [1].

Selenium can be introduced as an electrophile, a nucleophile or as aradical under mild reaction conditions [2]. Selenenyl halides (RSeX) are the most common electrophile used in organic synthesis (Scheme 1). There are several inorganic (M_2Se_2 (M = Li or Na), NaSeH, KSeCN, Na_2Se, $Se(SiMe_3)_2$) and organic (RSeLi, RSeMgX, RSe^-) selenium nucleophiles. Selenolates (RSe^-) are highly nucleophilic and are readily oxidized by various oxidants.



Scheme-1

Several oxidation states, both integral and fractional (e.g., ½, ¼, etc.) are possible for selenium, -2 (selenide), 0 (element), +4 (selenite) and +6 (selenate) being the most common oxidation states. Redox process in various oxidation states is quite facile (Eq.1).

$$Se^{6+} \underset{-2e^-}{\overset{+2e^-}{\rightleftharpoons}} Se^{4+} \underset{-2e^-}{\overset{+2e^-}{\rightleftharpoons}} Se^{2+} \underset{-2e^-}{\overset{+2e^-}{\rightleftharpoons}} Se^{0} \underset{-2e^-}{\overset{+2e^-}{\rightleftharpoons}} Se^{2-} \quad (1)$$

This article intends to cover, in brief, general synthetic approaches for the preparation of different families of organoselenium compounds.

2. Diorganodiselenides

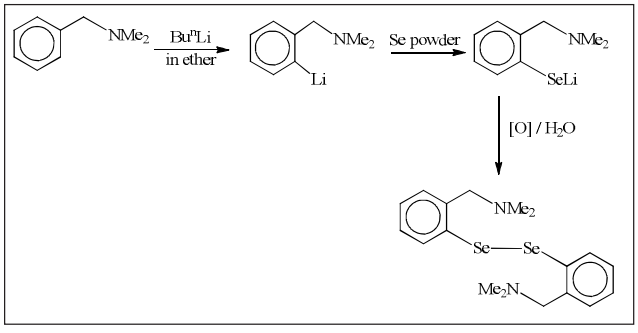
Diorganodiselenides (R_2Se_2) are an important family of organoselenium compounds which are used extensively

in synthetic chemistry. These compounds are prepared in several ways. The most commonly employed method involves the reaction between M_2Se_2 (M = Li or Na) with an appropriate alkyl or aryl halide followed by areal oxidation (Eq-2) [3, 4].Alternatively, sodium hydrogen selenide (NaSeH), prepared either by reduction of selenium by $NaBH_4$ [5] or by treatment of NaOEt with H_2Se in ethanol [6], can be used in these reactions. These reactions are usually accompanied by the formation of diorganoselenides (R_2Se) in variable amounts, and hence purification of diselenide is always recommended.

$$M_2Se_2 + 2\,RX \xrightarrow[-2\,MX]{} R_2Se_2 \xleftarrow[-NaX]{[O]} 2\,NaSeH + 2\,RX \quad (2)$$

(M = Li or Na)

Heteroatom-directed aromatic lithiation method has been successfully employed for the preparation of a variety of aromatic diselenides [7]. In this method an alkyl lithium (usually Bu^nLi) is employed to deprotonate the *ortho* proton of substituted aromatic compound and the resulting lithiated product is treated with selenium powder which after hydrolysis and areal oxidation affords the corresponding diselenide (Eq-3). A variety of aromatic compounds, such as N-substituted benzylamines, 2-phenoxazolines, aromatic Schiff bases, ferrocenes, 3-substituted thiophenes, etc., have been used for the preparation of dieselenides.



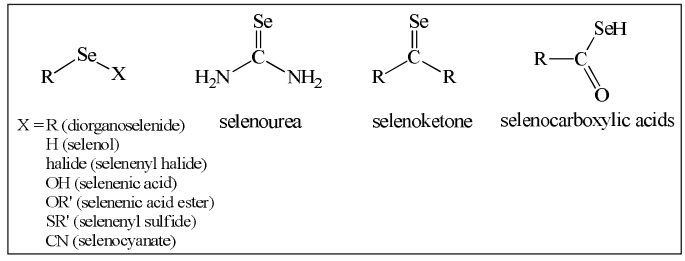
(3)

Scheme 3

Diselenidesare yellow to orange-red, shelf-stable molecules and in general show skewed structures both in the solid state and in solution.Their relative stability makes them convenient precursors for the synthesis of several other classes of organoselenium compounds. They can readily be reduced to selenol and nucleophilicselenolate ions (RSe^-) by reductive cleavage of Se-Se bond. Oxidation is equally facile yielding selenenic (RSeOH), seleninic (RSe(O)OH) and selenonic ($RSe(O)_2OH$) acids. Reactions with halogens afford yet another important electrophilic species (e.g., RSeX or $RSeX_3$). They are used as catalyst in a number of organic reactions [8] as well as selenium precursors in materials science for the synthesis of metal selenide nanoparticles [9].

3. Organoselenium compounds in divalent state

Selenium forms numerous compounds in divalent state which can be clubbed in different classes (Scheme 2). General synthetic routes for some of these compounds are briefly described here.



Scheme 2

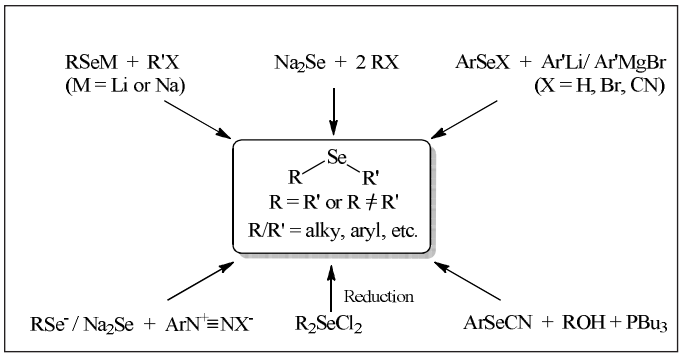
3.1 Diorganoselenides

Diorganoselenides or seleno ethers (R_2Se) are the oldest synthetic organoselenium compounds isolated as early as 1836 by Löwig who reported the preparation of diethylselenide. A myriad of symmetrical (R_2Se) and unsymmetrical (RSeR′) diorganoselenides have been isolated and characterized by various techniques [10, 11]. These compounds are extensively used as ligands in coordination and organometallic chemistry [12] and as a nucleophile in organic reactions.

Several synthetic approaches have been developed for the preparation of diorganoselenides (Scheme 3). The reaction between sodium selenide (Na_2Se) and an organic halide in an appropriatesolvent is commonly used for the preparation of a variety of symmetrical and functionalized selenides [10, 11, 13]. Another most commonly employed route involves a reaction of selenolate ion with an organic halide. The method is very convenient for the preparation of unsymmetrical selenides. Other approaches, like (i) addition of electrophilic (RSeX; X = Cl or Br) and nucleophilic (RSeH) selenium compounds to alkynes, alkenes and carbonyl compounds for the preparation of functionalized selenides, and (ii) ring opening of epoxides, aziridines with selenols, etc. have also been used.

3.2 Selenols

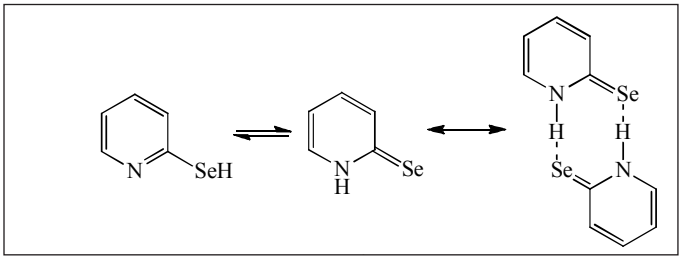
Selenols (RSeH) are heavieranalogues of alcohols and thiols and are stronger acids than the corresponding thiols. They are readily oxidized by areal oxidation to the corresponding diorganodiselenides and therefore generated *in situ* for a chemical reaction. However, with bulky organic groups such as supermesityl (2,4,6-$Bu^t_3C_6H_2$),



Scheme 3

$C(SiMe_3)_3$ and $Si(SiMe_3)_3$, selenols are fairly stable. They are generated by protonolysis of the corresponding alkali metal chalcogenolates [14].Selenols are, in general, obtained either by the reaction of Grignard reagent or organolithium with elemental selenium followed by acid hydrolysis or by reduction of diselenide with a reducing agent such as sodium borohydride, hypophosphorus acid (H_3PO_2), etc. (Eq. 4) Selenols are readily deprotonated in alkaline solution to the corresponding selenolate ions. Selenols containing N-heterocyclic ring, e.g. 2-pyridyl/ 2-pyrimidyl selenols, tautomarize to the corresponding selone form (Scheme 4), the latter may oligomerize through hydrogen bonding in to dimers.

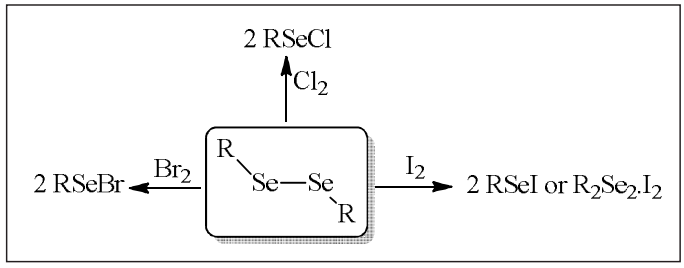
$$RSe^- \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} RSeH \underset{reduction}{\overset{oxidation}{\rightleftharpoons}} RSeSeR \qquad (4)$$



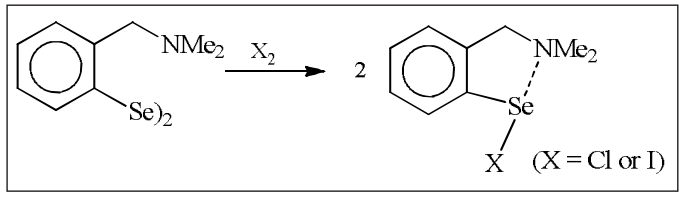
Scheme 4

3.3 Selenenyl halides

Selenenyl halides (RSeX) are readily prepared by the reactions of diorganodiselenides with halogens or halogenating agents such as sulfuryl chloride (Scheme 5). Use of excess halogen or halogenating reagents results into trihalides, $RSeX_3$. Selenenyl halides (RSeX; X =Cl or Br) are discrete molecules whereas the corresponding iodo compounds show considerable structural diversity. Depending on the nature of organic group on selenium, the iodo compounds may exist as RSeI with covalent Se-I bond or as charge transfer complexes. Majority of iodo derivatives are charge transfer complexes but the compounds containing bulky organic groups or substituted aryl groups with the substituents containing hetero-atoms (Scheme 6) on pendant arms usually exist in the former category. Selenenyl halides are powerful electrophiles, PhSeX being the most common electrophile used for selenenylation of olefins and carbonyl compounds.



Scheme 5



Scheme 6

3.4 Selenenic acids

Selenenic acids (RSeOH) are highly reactive intermediates and are formed during oxidation of selenols and diorganodiselenides. These compounds are unstable and disproportionate to the corresponding diselenides and seleninic acids or anhydrides (Eq. 5). These compounds containing nitro, carbonyl or amine substituted aryl group or bulky aryl group have been reported in solution. Hydrolysis of selenenyl halides yield selenenic acids.

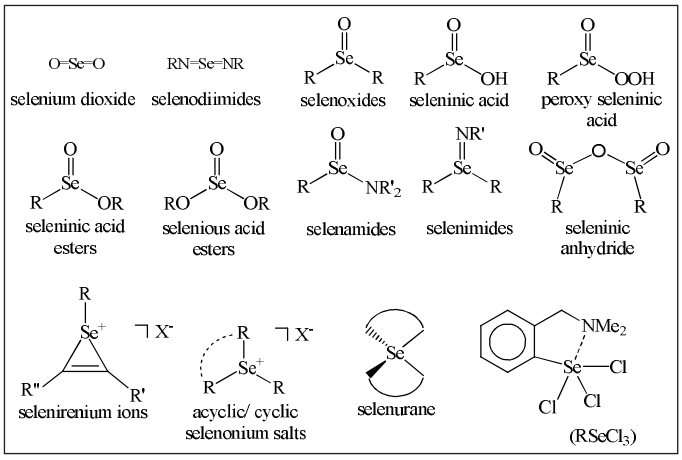
$$3\ RSeH \xrightarrow{3O} 3\ RSeOH \rightarrow [RSe{-}SeR / RSe{-}O{-}SeR] \rightleftharpoons RSeSeR + RSe(O)OH + H_2O \qquad (5)$$

3.5 Selenenylsulfides

Selenenylsulfides (RSeSR') are important intermediates during the catalytic cycle of glutathione peroxidase (GPx). They are formed by the reactions of diorganodiselenides with thiols. The method is conveniently employed for the preparation of selenenylsulfideglycopeptides [15] and selenenylsulfide bearing lipids [16].

4. Organoselenium compounds in tetravalent state

Selenium forms numerous compounds in tetravalent state with the coordination number varying between two and five (Scheme 7). The most common derivatives are diorganoselenoxides and seleninic acids.



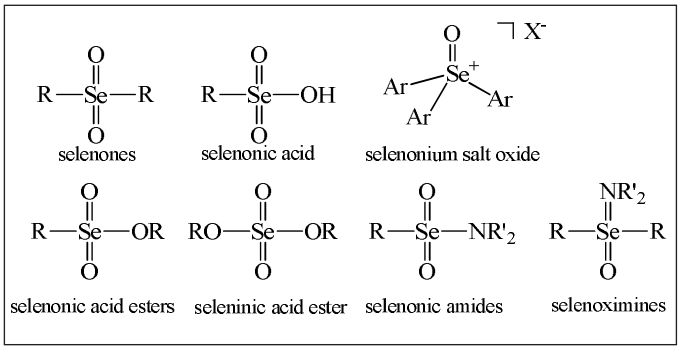
Scheme 7

4.1 Diorganoselenoxides

Diorganoselenoxides (R_2SeO) are prepared conveniently by oxidation of diorganoselenides. Several oxidizing agents, such as hydrogen peroxide, peroxy acids, sodium hypochlorite (NaOCl), etc. have been used for oxidation of selenides. Selenoxides can also be prepared by hydrolysis of diorganoseleniumdichlorides. Rearrangement in selenoxides containing hydroxyl or carboxylic acid substituents at the terminal position of the alkyl group can take place during oxidation leading to the formation of cyclized organoselenium compounds. Selenoxides containing β–hydrogens yield alkenes via *syn* elimination. Selenoxides find numerous applications as oxygen transfer agents in organic/ organometallic synthesis and as oxygen donor ligands in coordination chemistry.

4.2 Seleninic acids

Seleninic acids (RSe(O)OH) are colourless and odourless solids. They are isolated by oxidation of diorganodiselenides by 30% hydrogen peroxides, concentrated HNO_3 or chlorine in aqueous medium. Other oxidizing agents have also been used. Seleninic acids are optically active compounds, but due to rapid racemization it is difficult to isolate them in optically pure form.



Scheme 8

5. Organoselenium compounds in hexavalent state

There are several classes of organoselenium compounds in hexavalent state (Scheme 8). These compounds are much less stable than the analogues sulfur derivatives and are strong oxidizing agents.

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Dr.Vimal K. Jain *is Director of UM-DAE Center for Excellence in Basic Sciences, an aided institution of Department of Atomic Energy. His research interests include: organometallic and metalloorganic chemistry of platinum group metals and main group elements, design and synthesis of molecular precursors for inorganic materials, multinuclear NMR spectroscopy and high purity materials. He is author/ co-author of ~350 research papers including more than a dozen review articles published in international peer reviewed Journals. He has supervised the thesis work of 26 Ph.D. and 7 masters' degree students. He has received several awards including "HomiBhabha Science and Technology Award (1996)" of Department of Atomic Energy and was elected Fellow of the National Academy of Sciences, India and a Fellow of Royal Society of Chemistry (U.K.). He has co-edited (with Dr. K. I. Priyadarsini) a multi-author book 'Organoselenium Compounds in Biology and Medicine' published by the Royal Society of Chemistry, UK.*

Chalcogenide centers as fluorescence chemosensors for important analytes (ROS/RNS and Biothiols) for intended aging and neurodegenerative disease research

Tesla Yudhistira[1,3], Woohyun Lee[1], Jaehyuck Choi[1], Minkyung Jang[1], Mahesh B. Halle[1], Prasad Sonawane Malhari[1], Donghyeon Kim[1], and David G. Churchill[*1,2]

[1] *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.*

[2] *Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), 373−1 Guseong−dong, Yuseong−gu, Daejeon, 305−701, Republic of Korea.*

[3] *Lembaga Pengelola Dana Pendidikan (LPDP), Indonesia Endowment Fund for Education, Kementrian Keuangan Republik Indonesia, Gedung Ali Wardhana Lt. 2 Kementerian Keuangan Jl. Lap. Banteng Timur No. 1 Jakarta 10710, DKI Jakarta, Negara Kesatuan Republik Indonesia.*

**- E-mail: dchurchill@kaist.ac.kr*

Abstract

Organochalcogen centers are now known to play important and essential roles in aspects of medicinal and materials chemistry. In this chapter, we discuss a chalcogenide-based approach to chemosensing in which we focus on small fluorophore molecules embedded with organochalcogen atoms (R-S-R, R-Se-R, and R-Te-R; R Ar-S-Ar, Ar-Se-Ar, and Ar-Te-Ar) at specific sites next to a fluorophore. In this brief Bulletin article, we overview the approach and leave the reader to explore other recent review sources for more specifics. This organochalcogenide chemical configuration allows us to study the chemoselectivity of the chalcogen compounds through oxidation reactions and/or cleavage reactions of the chalcogen containing groups and with analytes by observed experimental optical responses through a "turn-on" fluorescence mechanism that involve photoinduced electron transfer (PET), ratiometric, Förster resonance energy transfer (FRET), and aggregation-induced emission (AIE). These chalcogen-embedded fluorophores have showed great promise during the last decade in the detection of important biological analytes such as reactive oxygen/nitrogen species (ROS/RNS) and biothiols (Cysteine, Homocysteine, and Glutathione). All of these biological species are very important in maintaining the homeostatic condition in biological and physiological systems, within the human body and throughout biology. An overproduction and/or deficiency of them can lead to severe diseases such as cancer and neurodegenerative diseases (e.g Alzheimer's disease). In this chapter, we discuss recent efforts by our research team and others to synthesize chalcogen-based chemosensors; we show various but not all possible examples.

1. Introduction

Chalcogenides are "ore forming" found in the main group (p-block). The elements consist of column VIA (group 16) in the periodic table and are namely oxygen, sulfur, selenium, tellurium, polonium, and livermorium. Compounds of the more commonly encountered S, Se, and Te, show similarity in terms of electronic configuration resulting in similar trends in chemical behavior sometimes relating to redox chemistry. Nowadays, chalcogenides are attracting a lot of interest from researchers around the world who explore e.g., organoselenium molecules as candidates for many applications such as thermal solar energy research, imaging materials, or as sensors prepared for the use in detecting many important analytes in the human body, biology and the environment.

Sulfur is present in the human body in the form of thiols and sulfides in small biomolecules such as cysteine (Cys), homocysteine (Hcy), and glutathione (GSH). These are known as the common, natural and small biothiols (amino acids). Biothiols which contain sulfhydryl groups have important roles in biological systems as endogenous species. GSH for example, is the most abundant intracellular biothiol which has a role as a vital antioxidant; it exists in equilibrium between its oxidized disulfide form, and reduced thiol form [1]. The level of GSH concentration are closely related to oxidative stress; this state could lead as a causative facts or indication of various diseases and symptoms such as in neurological diseases of dementia, as well as cancer and diabetes.

Interestingly, selenium was considered poisonous until Schwarz and Foltz identified it as a trace element in biology. In particular, selenium exists as a micronutrient in bacteria, mammals, and birds. It is sold in pharmacies in the form of a mineral supplement [2]. Then, in 1973

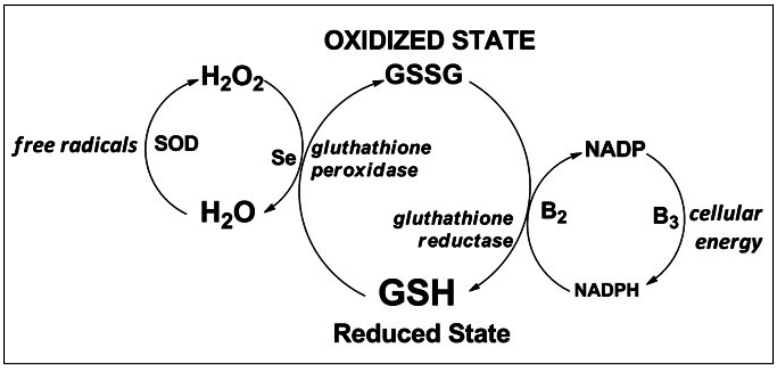

Fig. 1: *Enzymatic antioxidant involves glutathione peroxidase as a selenium-dependent enzyme.*

selenium was found in two bacterial enzymes, formate dehydrogenase and glycine reductase. At the same time, researchers also found that selenium possesses a major role in the active site of the antioxidant enzyme glutathione peroxidase (GPx) (Figure 1). Since then, many researchers have discovered that chalcogens, especially selenium, has an important role in biological systems as an enzymatic antioxidant in systems including anti-inflammatory, antitumor, antifungal, and antibacterial properties.

Organochalcogenides heterocycles and related molecules are an important class of organic compounds; they have been extensively used as tools in pharmaceuticals, functional materials, and synthetic intermediates in the drug discovery process. They are well-known to display diverse biological activities *in vivo* and *in vitro*, such as antibacterial, antidiabetic, antiarrhythmic, antitumor, and studied in the context of neurodegenerative diseases (e.g. Parkinson's disease and Alzheimer's disease).

Ongoing research related to phenylchalcogenide-related molecular probes for bioimaging continues on the basis of a broad spectrum of important pharmaceutically-active compounds and natural products, organochalcogenide derivatives have gained tremendous attention in the synthetic and medicinal chemistry research communities. The development of new, short, efficient, and environmentally benign synthetic methodologies for the incorporation of these chalcogenides into organic frameworks (especially chromophore and fluorophore frameworks) is a very important and challenging process.

Our group has synthesized a series of molecular probe bearing chalcogenide (sulfur, selenium, and tellurium) [3-6]. These chalcogenides probes have an ability to detect the presence and concentration of important analytes such as reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) such as hydrogen peroxide (H_2O_2), hypochlorite (^-OCl), superoxide ($O_2^{\cdot -}$), hydroxyl radical ($^{\cdot}OH$), nitric oxide (NO), and peroxynitrite ($ONOO^-$) and biothiols.

The ROS and RNS are suspected to play important roles in the molecular causation of the various neurodegenerative diseases. This chapter will discuss about chalcogen-based chemosensors which focus on small molecules classified as fluorophores. These fluorophores contain organochalcogen center (R-S, R-Se, and R-Te) and are studied in their ability to undergo oxidation with specific ROS analytes. The small synthetic molecular systems possess various photo-mechanisms which can be involved in detecting the analyte.

2. How fluorescence arises from Se-containing organic compounds

Fluorescence is a process that produces an emission of light from electronic excited molecules that can absorb light. Molecules that have an ability to produce emissions are called fluorophores; this ability can be easily visualized by the electron-state diagram called a Jablonski diagram (Figure 2). A Laser or incandescent lamp is used as a source of photon for the process of the energy of excitation; then they are excited to a higher vibrational energy level in the first excited state (S_1) before rapidly relaxing to the lowest energy level and shows emission. Besides that, a promoted electron can undergo a spin conversion into a "forbidden" triplet state (T_1) instead of the lowest singlet excited state, a process known as intersystem crossing. Emission from the triplet state occurs with lower energy relative to fluorescence; hence, emitted photons have longer wavelengths. However, since the selenium embedded in fluorophore can be mainly used for fluorescence studies; phosphorescence will not be discussed in this chapter.

3. Major fluorescence technique for detecting analyte

To date, a lot of techniques have been employed to modulate the fluorescence of the fluorophore to detect important analytes such as photoinduced electron transfer, ratiometric, Förster resonance energy transfer (FRET), and aggregation-induced emission (AIE) (Figure 3). Among other techniques, photoinduced electron transfer (PET) is the most common pathway exploited to modulate the fluorescence of the molecule.

PET is the process of electron transfer from LUMO of the quencher to HOMO of the fluorophore; thus, the fluorescence of the fluorophore diminished. There are two types of PET that depend on the oxidation potential between

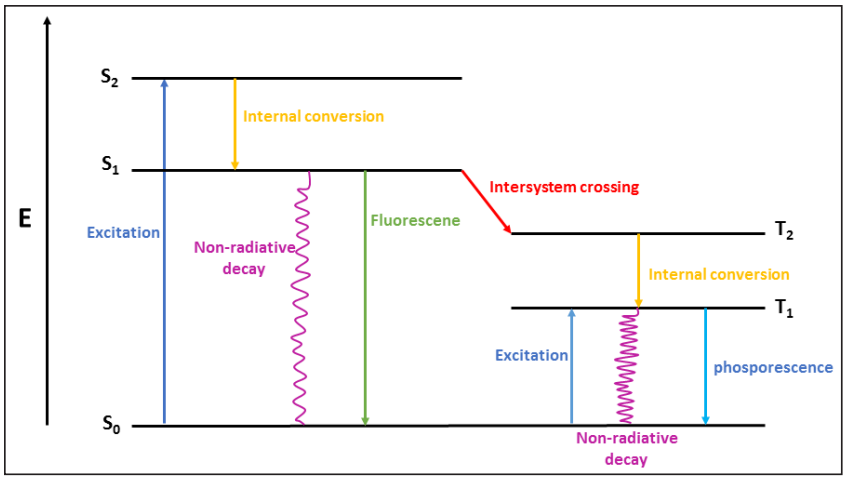

Fig. 2: Simplified Perrin-Jablonski Diagram showing the various possible pathways.

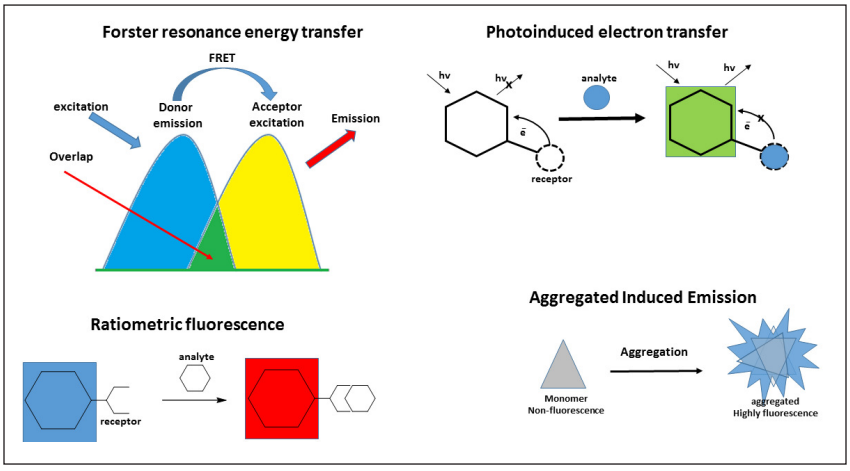

Fig. 3: Simplified fluorescence technique for detecting analyte.

fluorophore and quencher. Reductive PET (acceptor-PET) and Oxidative PeT (donor-PET). The PET system could offer sensitivity and reliable responses towards specific analyte; however, this system could be hindered by the background noises of the sample media and environmental effects. In an organochalcogen-containing molecule, that substituent or site within the small molecule probe that will be reduced first will be the electron-rich chalcogen.

Therefore, to overcome these obstacles, a ratiometric approach to data interpretation involving considering the relative intensity between two wavelengths are chosen. This method relies on the fluorescence spectrum shift upon the reaction with the analyte. There are two types of fluorescence shifts; hypsochromic shift (to higher wavelength – high energy) and bathochromic shift (to lower wavelength – low energy). Ratiometric sensing is important since offers high sensitivity, eliminates the environmental effect, and involving instrument efficiency.

The fluorescence resonance energy transfer (FRET) strategy relies on the interaction between two excited states of fluorophores through electronic dipole-dipole coupling. The donor fluorophore is transferring the electron to the other acceptor fluorophore without actual emission of a photon. Thus, the emission spectrum between the fluorophore donor and acceptor should overlap. This system is related to the distance between the fluorophore donor and acceptor. FRET is very sensitive to the distance between the interacting fluorophores. To optimize the system, the distance between the fluorophore donor and acceptor should be around 1 to 10 nm [7].

Aggregation-induced emission (AIE) is a photophysical phenomenon that occurs within the fluorophore in which the solved monomers are not fluorescent in solution but are highly emissive when situated in the aggregated state (for example, J- and H-aggregation). This phenomenon was discovered by Tang et al. in 2001 based on the propeller shaped silole derivatives which allowed for "turn-on" fluorescence in condensated state [8]. Many researchers have tried to study the mechanism of the AIE including conformational planarization, J-aggregation, excited state intramolecular proton transfer (ESIPT), and twisted intramolecular charge transfer (TICT).

Then, in 2015 Tang et al. hypothesized that within aggregated or solid state, the molecules interlock themselves that restrict the intramolecular rotation and vibration and allows for relaxation through radiative pathways. In addition, the molecules should avoid a dense face-to-face packing that favors the strong π–π stacking interaction and subsequently, these radiationless relaxation effects lead to aggregation caused quenching (ACQ) [9].

4. Reactive Oxygen/Nitrogen Species

Reactive oxygen species / reactive nitrogen species (ROS/RNS) are oxygen or nitrogen containing species that exist in biology and our body in a range of low concentrations and are produced in the body as a defense mechanism against various pathogens and they play important roles in signaling and homeostatic control. Thus, an excess amount of ROS/RNS in the body may cause several human diseases such as inflammatory diseases (e.g., arthritis), hepatic ischemia reperfusion, atherosclerosis, neuron degeneration and death (e.g., Alzheimer's disease), lung injury, and cardiovascular diseases. Several

functional groups such as p-methoxyphenol, oxime, dibenzylhydrazine hydroquinone, and chalcogen (S, Se, and Te) containing systems display good response andhigh oxidation properties that can be used to detect ROS/RNS via the reactive sites borne on the probe. These reactive moieties are embedded to fluorophores so to modulate the fluorescence intensity in accordance with the ROS/RNS concentration. Among the rest of the functional groups, oxidation of selenide and telluride offers a rapid response as well as chemical reversibility upon the addition of biothiol; thus, it is very reliable as a probe which can provide real time detection of ROS/RNS.

4.1 Detection of reactive oxygen/nitrogen species (ROS/RNS)

In recent years, our research group has published several papers related to chalcogenide containing (S, Se, and Te) functionalities in rationally designed synthetic fluorophores for the detection of ROS/RNS (Figure 4). The system used phenylselenide to help modulate the fluorescence of the fluorophore through PET mechanism and underwent very fast reaction towards ROS/RNS due to the facile oxidation of the oxygen rich selenide to the selenoxide. In 2014, our group synthesized a diselenide based probe with BODIPY as a fluorophore backbone (Compound 1, Figure 4). The probe can detect superoxide in living breast cancer cell model systems and has reversible properties toward biothiols. Then, in the same year, our laboratory discovered the first example of BODIPY organoselenide and organotelluride annulation (Compound 2, Figure 4) [10]. The X-ray structure of the annulated BODIPY was obtained. Further studies showed that the annulated BODIPY telluride was highly sensitive and selective for hypochlorite and can be used in living neuronal cells [11]. In early 2016, we reported a novel diselenide-based dipyrazolopyridine probe through the use of a domestic microwave oven without the need of solvent (Compound 3, Figure 5). The probe showed selectivity towards hypochlorite with a 180-fold emission increase. Further study in confocal microscopy in living breast cells demonstrated the detection of hypochlorite in real-time [5]. Then, in the Summer of 2016 our laboratory successfully reported a functionalized BODIPY with phenylselenide at the 6-position and chlorine atom at 3-position. The presence of chlorine diminished the background fluorescence of the BODIPY and the probe showed selectivity towards hypochlorite which undergoes reaction within 1 second [12]. Intrigued by this property, we synthesized the derivative of Compound 4 and added mesitylene at the meso-position of the BODIPY (Compound 5, Figure 4). As expected, the probe was selective toward hypochlorite; however, when we performed a cell imaging study, the probe (Compound 5, Figure 5) underwent aggregation-induced emission (AIE) within the lipid droplets in living cells. Therefore, besides its selectivity towards hypochlorite as demonstrated *in vitro*, the probe can

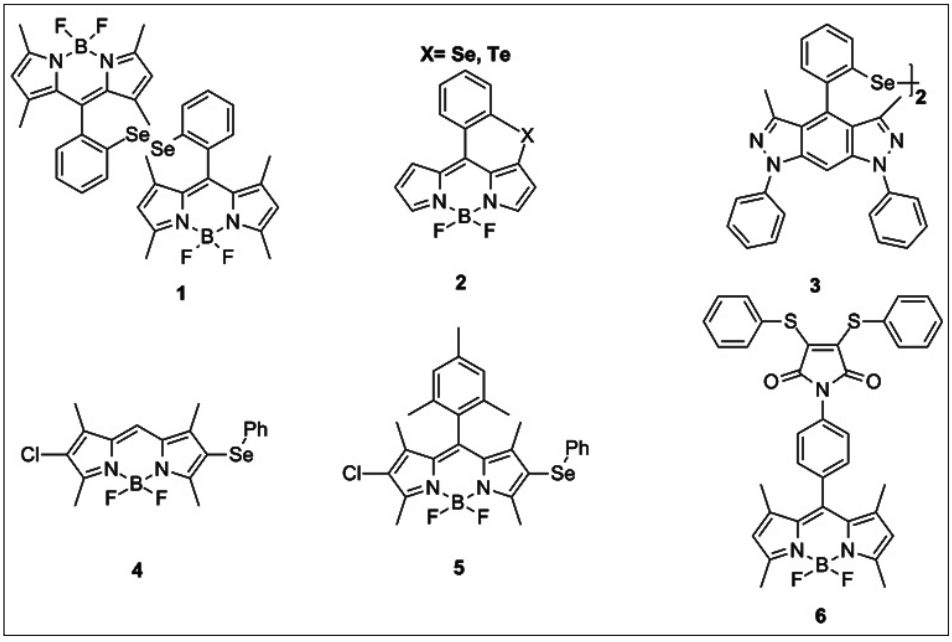

Fig. 4: *Novel fluorescence sensors from the Churchill group at KAIST for the reversible detection of ROS and RNS.*

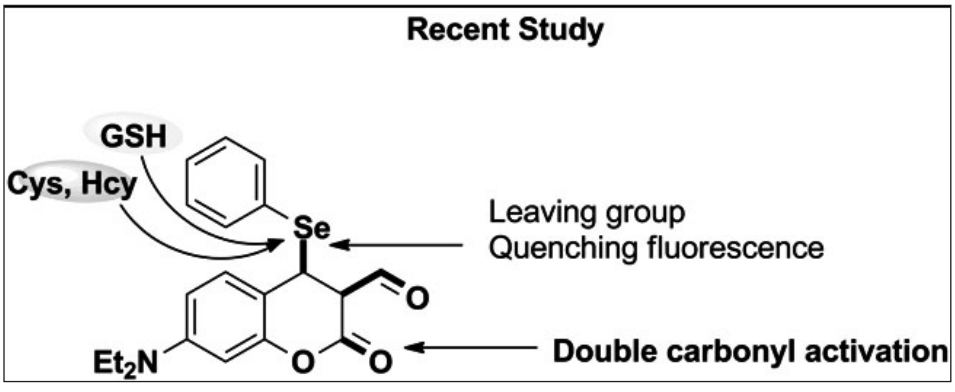

Fig. 5: *Strategy for fluorescent of thiol detection.*

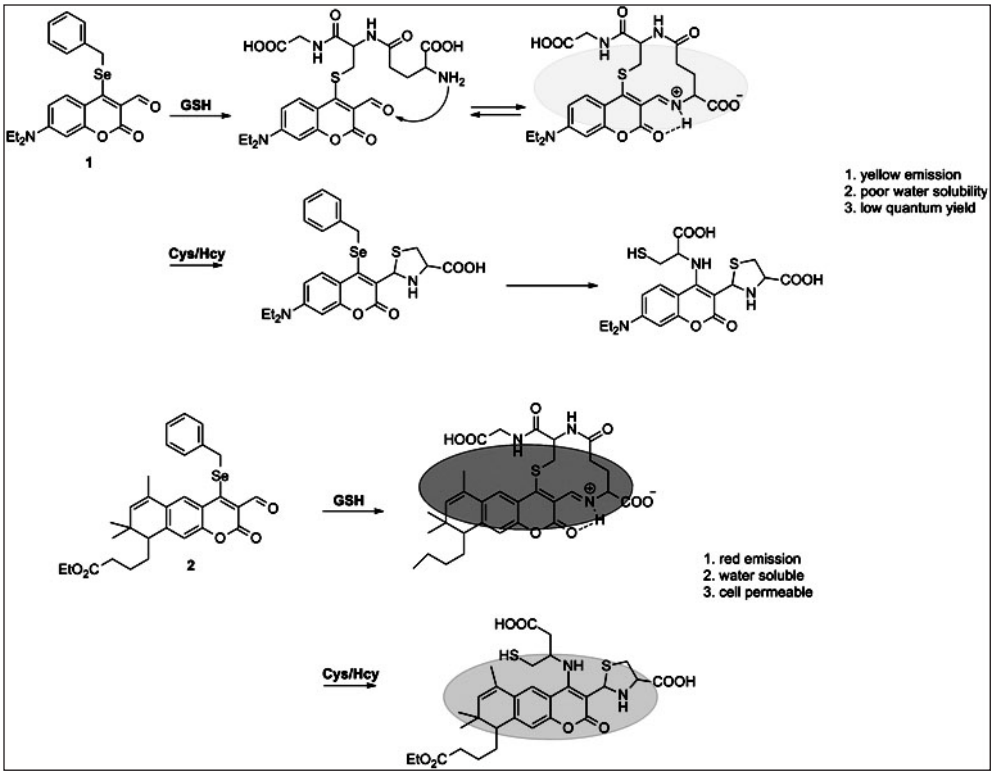

Fig. 6: *Compound 1 and 2 from the Churchill laboratory for selective detection of GSH.*

also be used as a lipid droplet trackers in the living cells [6]. Next, in 2017 our laboratory reported a novel probe for the detection of peroxynitrite ($ONOO^-$) (Compound 6, Figure 4). The probe showed low fluorescence due to the PET effect, however after the addition of $ONOO^-$ we observed an increase in emission intensity up to 18-fold was observed, due to oxidation of sulfide to sulfone (observed in HR-MS). The probe is not-toxic to the cells and can be used to detect exogeneous and endogeneous $ONOO^-$ in HeLa and Raw 264.7 macrophage cells [13].

5. Detection of biothiols (Glutathione, Cysteine, and Homocysteine)

Biothiols containing sulfhydryl groups such as cysteine (Cys), homocysteine (Hcy), and glutathione (GSH) have important roles to play in biological systems as endogenous species. GSH is a vital antioxidant and the most abundant intracellular biothiol; it exists in equilibrium between its oxidized disulfide form and reduced thiol form. An increase in the concentration of GSH could relate to oxidative stress; this state correlated to, various diseases and symptoms such as the neurological diseases of Alzheimer's disease (dementia) and Parkinson's disease, as well as cancer, AIDS, sickle cell anemia, and the presence of liver damage. Due to the important role of the biothiols, many researchers around the globe developed a probe which can discriminate between biothiols and amino acids. Recently, nucleophilic substitution reactions enacted by strong nucleophilic sulfhydryl groups has allowed for the discrimination of GSH over Cys and Hcy through intramolecular displacement and intramolecular cyclization. Considering the current state-of-the-art and relevant/reliable current methods, we developed a probe which has two potential reactive sites, the aldehyde and phenyl selenide for selective detection of GSH (Figure 5).

In this work, we incorporated a phenylselenide group at the 4-position of the coumarin formation. This group has an ability to quench fluorescence of the coumarin via a photoinduced electron transfer (PET) mechanism and also behave as a leaving-group. The aldehyde group plays a dual role: it enhances the electrophilicity of the 4-position as a Michael acceptor and enables for the formation of a cyclization reaction with the sulfhydryl and primary amine groups of the biothiols [14]. The probe (Compound 1) showed yellow fluorescence after reaction with GSH and blue fluorescence after reaction with Cys/Hcy. Our hypothesis is that the 4-position of Compound 1 (Figure 5), which is doubly-activated by two carbonyl groups, undergoes faster substitution with a strong nucleophilic sulfhydryl group such as that for GSH. Compound 1 shows very rapid analyte detection with a detection time of 150 microseconds for GSH due to the presence of a doubly-activated α, β-unsaturated system. Confocal microscopy imaging of living cell systems indicate the probe detects GSH in Hep3B cells rapidly and specifically. Furthermore, cell viability testing showed low cytotoxicity of the probe and its potential for biological uses. However, the Compound 1 still have several limitations such as fluorescence emission wavelength which is not red-shifted (~550 nm) after cyclization, Compound 1 is poorly water soluble, and a low quantum yield. All of these factors restrict the use of Compound 1 for further in vivo applications.

With this in mind, in 2017, we developed a more reliable probe for in vivo applications based on the structure of Compound 1. To make an improvement to the new probe (Compound 2) we had to modify several parts of

Compound 1. First, we tried to block the rotational freedom of the alkylamino group by preparing the N-heterocyclic derivative. This derivatization fixed the amino group and afforded the desired red shift in absorption/emission by eliciting a planar intramolecular charge transfer (PICT) mechanism. Next, additional π-conjugation was added; the effected rigidity within the newly introduced heterocyclic ring enhanced a more bathochromic shift in the absorption and emission wavelengths, the new double bond increases optical attributes for chemosensing. To improve water solubility of the new probe (Compound 2), an ethyl butanoate group was incorporated at the amino position which may, in turn, further assist cell permeability. The result suggested that the new probe (Compound 2) possesses a strong fluorescence enhancement with GSH (red fluorescence), selectively over all amino acid interfering groups including Cys/Hcy (green fluorescence). The maximum intensities were found at 635 nm (near NIR region).

The new probe (Compound 2) showed selective detection of GSH and Cys/Hcy in the red and green channels, respectively, in live A549 cells. Furthermore, the selective detection of Cys through the green channel with human fibroblast cells was confirmed by confocal microscopy imaging experiments. In vivo optical fluorescence imaging in mice was employed; the results suggested that the new probe (Compound 2) could detect GSH in the living animals (mouse). In conclusion, the new probe (Compound 2) can be implemented in future biomedical research for the selective detection of GSH for diagnostic applications [1].

6. Summary

The development of organochalchogen (S, Se, Te) based probes is a promising and active are of research for the detection of ROS and biothiols. The incorporation of S, Se, and Te atoms within or external to the chromophores skeleton provides a selective site for oxidation and a fluorescent "turn-on" optical response, reversible, as well as red-shifting to detect certain important analytes such as ROS/RNS and biothiols. Hopefully, this chapter could shows optimistic glimpses of the application of organochalcogen-based fluorophore molecular sensors. In the next 5 years, advances toward achieving a solid understanding of the capability in selective and reversible detection with organochalcogen flourescent systems. This can be pursued through the rational design and mechanistic study of novel sensing platforms for understanding neurochemistry of disease in neurodegenerative diseases.

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	**Tesla Yudhistira** *is eagerly studying for his PhD in the Department of Chemistry at the Korea Advanced Institute of Science and Technology (KAIST) under the supervision of Prof. David G Churchill. He has obtained a bachelor's degree in Chemistry from the University of Indonesia. While pursuing science as an undergraduate, he worked in the bioelectrochemistry laboratory as a student Researcher.*
	**Woo Hyun Lee** *received his bachelor's degree in Chemistry from KAIST (2016). Presently, he is studying Ph.D. coursework at KAIST.*
	**Jae Hyuck Choi** *received his bachelor's degree in the Department of Chemistry from Kyungpook National University (2016). Presently, he is currently studying Ph.D. coursework at KAIST.*
	**Min Kyung Jang** *is presently studying Ph.D. coursework at KAIST. She recently received her bachelor's degree from Kyungpook National University in the Department of Chemistry.*
	**Dr. Mahesh B. Halle** *obtained his PhD. From IIT Bombay, India under the supervision of Prof. Rodney Fernandes in 2016. After that, he went to South Korea where he currently serves as a postdoc in the Molecular Logic Gate Laboratory under the supervision of Prof. David G. Churchill. His research topic related to the synthesis of organochalcogenides compound for the probing of biological problems.*
	**Prasad Malhari Sonawane** *received his M. Sc. from the University of Pune, India and is pursuing PhD at KAIST since 2017.*
	**Dong-Hyeon Kim** *received his B.S. degree in chemistry and biological science from UNIST in february 2018. He is currently taking a M.S. degree at the department of chemistry, KAIST.*
	**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 a full professor in 2017.*

Selenium in Radioprotection: Current Status and Future Direction

A. Kunwar[1,3] and K. I. Priyadarsini[2,3]
[1]Radiation & Photochemistry Division, [2]Chemistry Division
Bhabha Atomic Research Centre, [3]Homi Bhabha National Institute, Mumbai - 400085, India
E-Mail: kamit@barc.gov.in; kindira@barc.gov.in

Abstract

Radiotherapy is one of the important modalities of cancer treatment. Although this has been effective to kill tumor cells, unwanted exposure of normal cells to radiation would result in many side effects, sometimes leading to irreversible effects. In order to minimise these unwanted effects, radioprotectors are employed. Since most important clinically used radioprotectors are sulfur based compounds, selenium, has also been explored to develop as radioprotectors. Selenium belonging to the same chalcogen group has other advantages of being a micronutrient and a constituent of antioxidant enzymes in humans. Most of the research in this direction was focused on inorganic selenium including several clinical studies where selenium supplementation has yielded beneficial outcomes in patients undergoing cancer radiotherapy. With the understanding that organic selenium is less toxic than inorganic selenium, researchers are also focusing on development of organoselenium compounds for radioprotection. A few details on the current status of research in this subject are summarized here.

1. Radiation exposure and radioprotector

One of the important programmes of Atomic Energy in health care has been to use high energy radiation for cancer diagnosis and therapy. During radiotherapy along with tumor cells, it is likely that some normal cells are also exposed to radiation and undergo unwanted damage. Such effects can also be expected during accidental exposure as in nuclear accidents and nuclear terrorism. While interacting with radiation, living cells can undergo chemical and biological changes mainly through radiolysis of cellular water to produce oxidising free radicals.[1,2] Depending on the type of radiation and its linear energy transfer (LET), the chemical events occur from femtoseconds to milliseconds, while the biological alterations start later, over seconds to hours [1,2]. Sometimes, delayed and chronic effects are observed, after many months of exposure. The radiation dose absorbed is expressed in the units of Gray (Gy), which is equal to one joule of energy deposition in one kilogram (1 J/kg) of the material [3]. Additionally, different organs show varied manifestation of radiation injury. For example, organs like brain, muscle, thyroid and liver are radio-resistant, whereas others like lymphoid organs, reproductive organs, haematopoetic stem cells and intestinal crypts are radiosensitive [1,2].

A radioprotector is a chemical substance, or a mixture of compounds, capable of minimizing the damaging effects of ionizing radiation to normal tissue [4]. Development of radioprotectors has been an area of active research from the beginning of the nuclear era. Most of the initial research was mainly focussed on radiotherapy as it was realised that normal tissue protection is as important as the destruction of cancer cells [5]. Ideally, a radioprotector should be able to protect against the deleterious effect of every type of radiation, both during therapeutic and diagnostic procedures (planned exposure), and also during unintentional radiation exposure (unplanned exposure) [5,6]. Radioprotection by small molecules can happen in three ways: (i) as prophylactic agents administered before radiation exposure; (ii) as mitigators given immediately after exposure, and (iii) as therapeutic agents supplemented much after the induction of radiation damage [4,6,7].

Extensive research on several natural and synthetic small molecules has led to identification of sulfhydryl compounds as promising radioprotectors. After screening thousands of sulphur compounds, only one compound amifostine, also called as WR-2721, was approved for usage in clinic to protect normal tissues in patients undergoing head and neck radiotherapy [8]. It is a pro-drug having an active thiol group attached to a phosphate moiety to reduce toxicity [8,9]. In spite of its usage in treatment, its considerable toxicity at radioprotective doses and its limited utility under post-irradiation, warrants search for more effective and non-toxic alternate drugs [8,9].

2. Selenium as radioprotector

Having understood that sulphur compounds act as good radioprotectors, it was anticipated that selenium which shares same group as sulphur, could be a better radioprotector [4,6,10]. Selenium is a stronger nucleophile than sulfur and is a well established micronutrient. Its role in cellular defense against oxidative stress through incorporation in to antioxidant selenoenzymes like

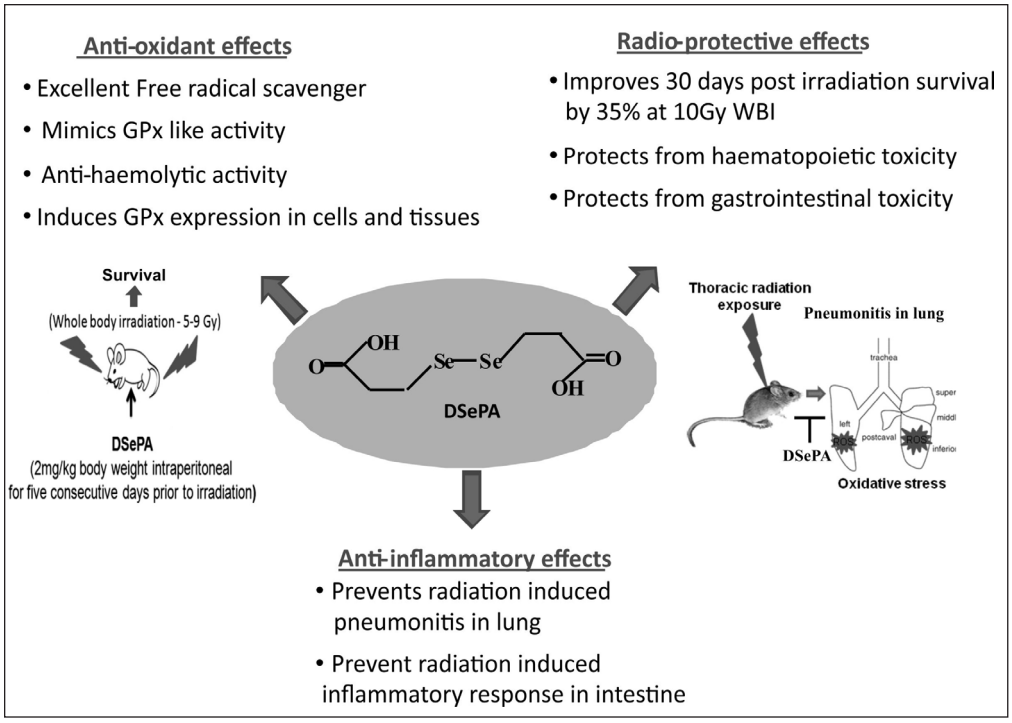

Fig. 1: Radioprotective activities of DSePA, an in house synthesized compound in preclinical models.

glutathione peroxidase (GPx), thioredoxin reductase (TrxR) and selenoprotein P (SelP) was also known [11]. All these factors led to an extensive evaluation of selenium in different chemical forms (inorganic and organic selenium) to act as a radioprotector over the last two decades. Inorganic selenium has also been tested in the clinic for reducing the radiotherapy side effects, while majority of studies on organic selenium is still in pre-clinical stage.

The most commonly used inorganic selenium forms are sodium selenite and sodium selenate. The first report on the radioprotective effect of selenium dates back to1960 by Hollo and Zlatarov to prevent the death caused by thallium or X ray radiation in a rat model [12]. Subsequently Weiss and co-workers at Armed Forces Radiobiology Institute, USA, performed a series of experiments in a mouse model, aimed to evaluate selenium alone or in combination with WR-2721, to decrease the toxicity and increase the effectiveness of WR-2721 [13,14]. A synergistic effect on post-irradiation survival was observed when sodium selenite was injected 24 hr before WR-2721 administration. Recognising the radioprotective potential of sodium selenite, researchers have also explored it for reducing the radiotherapy side effects or the organ specific toxicities incurred during whole body irradiation (WBI). For example, selenium pre-treatment prevented the radiation-induced retardation of the sternum in new born foeti. Systemic or topical administration of sodium selenite significantly delayed the radiation-induced mucositis in the mice model during clinically relevant fractionated irradiation protocols [15]. Similarly supplementation up to 200 µg sodium selenite/day provided a safe, effective and practical way to mitigate radiation injury to kidneys [16].

In general it is believed that selenium in organic form exhibits lesser toxicity than in inorganic form. Over the years, organoselenium compounds from both natural as well as synthetic origin have been evaluated for radioprotection. The naturally occurring organoselenium compounds are mainly selenoaminoacids like selenomethionine, selenocysteine and methylselenocystine. Selenomethionine has been evaluated as a dietary supplement to reduce radiation abnormalities. Selenomethionine enriched diet started after whole body exposure (1.4 Gy) increased average lifespan and decreased leukaemia and other malignancies at later times. Other studies confirmed that selenomethionine although non-toxic, yielded mixed results for radioprotector application.

With regard to synthetic organoselenium compounds for radioprotection, the initial thrust was to synthesize the analogous sulfhydril compounds. But most of the synthetic sulphur analogues did not show any radioprotection, instead were found to be more toxic than their sulphur counterparts. The first successful synthetic organic selenium compound was selenourea, reported by Badiello et al, who showed good radioprotection when examined for the blood changes, mortality, and general clinical condition of irradiated animals [17]. Subsequently a number of other organoselenium compounds like selenocystine, colloidal selenium, selenourea, selenoxanthene, selenoxanthone and selenochromone were examined for radioprotection in rats. From the clinical point of view, the animals treated with all these compounds showed less pronounced disorders such as leucopoenia than the irradiated control animals.

Other organoselenium compounds tested for radioprotection are five-membered selenoheterocycles like 2-amino-selenazoles, 4-aryl-l,2,3-selenadiazoles, 2-dialkylamino-l,3,4-selenadiazolines, 2-benzylidene-l,3,4-selenadiazolines, and 2-arylidene-l,3-diselenols [18].

These compounds were synthesized by replacing sulphur with selenium in the respective five-member unsaturated sulphur containing heterocyclic ring compounds. Toxicity studies revealed that introduction of a selenium atom into the ring in place of the sulphur atom led to the appearance of toxicity. Further, results on radioprotective properties showed that these compounds lacked such properties at the doses used with the exception of few 2-amino-selenazoles derivatives.

In recent times, synthetic organoselenium compounds mimicking GPx like activity have gained a lot of attention as multifunctional therapeutic agents. Ebselen is one such efficient GPx mimicking compound that has been evaluated for radioprotection in mice [19]. On a similar hypothesis, a number of organoselenium compounds like selenoethers, diselenides and cyclic selenolanes have been synthesized in house and screened for radioprotection in model systems. After screening several aliphatic selenium compounds, the most effective diselenide, 3'3'- diselenodipropionic acid (DSePA) was found to be a promising radioprotector (Fig. 1) [20-24]. DSePA is non-toxic and an effective free radical scavenger, GPx mimicking antioxidant. Its maximum tolerable dose (MTD) in mice was estimated as ~ 88 mg/kg body weight (i.p.). DSePA administration (2 mg/kg i.p.) not only improved the survival of mice against WBI but also protected radiosensitive organs from radiation damage. Late lung tissue responses like pneumonitis and fibrosis are the most serious dose-limiting side effects of thoracic radiotherapy for several kinds of malignancies affecting organs in the thorax area [24]. Administration of DSePA during the post irradiation period was capable of delaying the thoracic radiation (18 Gy)-induced pneumonitis response in mice. Encouraged by all these results, DSePA is being developed as oral supplemented lung radioprotector for thoracic radiotherapy.

3. Clinical studies with selenium in radiotherapy

The preclinical studies have encouraged researchers to undertake clinical trials in human subjects to know whether selenium administration can reduce the radiotherapy-associated side effects. During the treatment of cancerous tissues with radiation, normal tissues are also exposed, leading to unwanted side effects such as mucositis, xerostomia, fibrosis, pneumonitis, lymphedema, diarrhea and many others. These side effects subsequently become not only the reason for the less aggressive treatment of cancer, but also affect the quality of life and sometimes even add to the mortality in patients during the treatment phase. The ultimate goal of radiation therapy is thus to attain maximal tumor killing with minimal normal tissue damage and to achieve this several radioprotective compounds including selenium are being evaluated in the clinic. So far eighteen clinical studies are reported in the literature citing selenium and radiotherapy together [25]. These studies have been conducted across the world including American, European, and Asian countries. Of these, seven are interventional studies demonstrating the therapeutic benefit of selenium administration in reducing the radiation-associated toxicities. The other eleven are observation studies investigating the effect of radiotherapy on the patient's selenium levels. The clinical studies performed so far suggested that selenium supplementation neither reduced the effectiveness of radiotherapy nor caused any toxicity at the administered doses. Additionally, selenium supplementation showed a positive effect on the general health condition of the patients and their quality of life.

4. Conclusions

Selenium, a micronutrient and an active constituent of important redox regulating enzymes, has been explored for radioprotection. Sodium selenite, the inorganic and highly active selenium species has showed promising radioprotection both by itself and also in combination with other radioprotectors. Clinical trials have confirmed that it can be used as a supplement at low doses (<200 µg/day) to reduce the radiotherapy-associated side effects. However, whether selenium supplementation is necessary for radiotherapy patients needs to be corroborated with the basal selenium levels in the population. The selenium status subsequent to radiotherapy is an important factor to be considered.

New organoselenium compounds are being developed exhibiting important pharmacological properties. Among these, GPx mimetics, and water soluble selenium compounds have shown encouraging results with regard to radioprotection. However till date no synthetic organoselenium compound has been examined for clinical trial. New synthetic models are necessary for the design and development of novel organoselenium based radioprotectors.

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Dr. Amit Kunwar *received his M. Sc degree in Biotechnology from Tamil Nadu Agricultural University in 2003 and joined Radiation & Photochemistry Division, BARC in 2005 after graduating from BARC Training School (48th Batch, Bioscience discipline). After his Ph.D. from the Homi Bhabha National Institute in 2010, he carried out his postdoctoral research at Meakins Christie Laboratories, McGill University, Montreal, Canada, 2012-2014. His current research interests focus on the evaluation of synthetic as well as natural molecules for radioprotective and anticancer activities and understanding their mechanisms of action. He is the recipient of "Outstanding Doctoral Thesis Award" from Homi Bhabha National Institute, "Young Scientist Award" from DAE and "Richard and Edith Strauss Postdoctoral Fellowship in Respiratory Medicine" from Strauss Foundation, McGill University, Canada*

Dr K. Indira Priyadarsini *is Head, Chemistry Division, Bhabha Atomic Research Centre, Department of Atomic Energy and Government of India and also a senior professor of Homi Bhabha National Institute. Her research interests are on development of antioxidants, radioprotectors and cancer therapeutics, with expertise in the multidisciplinary research areas of radiation-chemistry, free radicals, nanomedicine and radiation biology. Dr Priyadarsini is an elected Fellow of National Academy of Sciences, India and Royal Society of Chemistry, UK. She is a recipient of Homi Bhabha Science and Technology award and Indian Nuclear Society's Outstanding Service award*

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