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Chalcogen bonding interactions between reducible sulfur and selenium compounds and models of zinc finger proteins

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ABSTRACT

Reducible sulfur and selenium (r-S/Se) compounds, defined as sulfur and selenium compounds not in the lowest −2 oxidation state (e.g., −1 to +6), release Zn^{2+} from zinc-sulfur proteins such as zinc fingers (ZFs) and metallothionein. A series of density functional theory calculations was performed on donor–acceptor complexes between r-S/Se compounds and models of the Cys_2His_2, Cys_3His and Cys_4 ZF sites. These S···S/Se chalcogen bonding interactions consist of the donation of electron density from a S lone pair on the ZF model to a S/Se–X antibonding molecular orbital of the r-S/Se compound. The strength of the interaction was shown to be dependent upon the Lewis basicity of the ZF model ($Cys_4 > Cys_3His > Cys_2His_2$) and the Lewis acidity of the r-S/Se compound as measured by the energy of the S/Se–X antibonding orbital. Interactions with the softer r-Se compounds were stronger than the r-S compounds, consistent with the greater reactivity of the former with ZF proteins.

1. Introduction

Redox signaling by zinc-sulfur proteins is involved in many cellular processes including replication, repair, transcription, translation, cell proliferation, apoptosis, metabolism, and signaling [1–8]. Zn^{2+} plays a structural role by tetrahedrally coordinating to 2–4 Cys residues in conjunction with His to ensure the correct folding of a zinc finger (ZF) motif required for interaction with DNA, RNA, proteins, or other molecules [1,2,9,10]. ZFs can be divided into three classes based on the number and type of residues involved in Zn^{2+} coordination: (1) CCHH, where Zn^{2+} is coordinated to 2 Cys and 2 His, (2) CCCH, 3 Cys and 1 His, and (3) CCCC, 4 Cys (Fig. 1) [2,3]. Zn^{2+} itself is redox inactive, but oxidation of the Cys thiolates releases Zn^{2+}, causing the ZF to lose its secondary structure and its ability to bind DNA or RNA [1,11–14]. Similarly, the zinc storage protein metallothionein (MT), which reversibly binds 7 Zn^{2+} in CCCC coordination, regulates cellular Zn^{2+} levels and triggers signaling pathways through Cys redox processes [1,4,15]. Proliferation of viruses and tumor cells could be inhibited by electrophilic compounds that release Zn^{2+} from conserved ZF motifs essential for replication (e.g., the nucleocapsid protein NCp7 (CCCH) of human immunodeficiency-1 virus (HIV-1) [16–18] and the E6 oncoprotein (CCCC) of the human papillomavirus (HPV) [19]) as a potential treatment mechanism [20–28].

Reducible sulfur and selenium (r-S/Se) compounds, defined as sulfur and selenium compounds not in the lowest −2 oxidation state (e.g., −1 to +6; 1, 2 and 5–16 in Fig. 2), release Zn^{2+} from various ZF proteins [29–39]. For example, the disulfides cystamine 1a and disulfiram 2 (oxidation state = −1) were able to release Zn^{2+} from NCp7, but the analogous thiols cysteamine 3 and dithiocarb 4 (oxidation state = −2) could not, even after prolonged incubation [40]. Dithiobenzamides (5, DIBAs) react with ZFs [29] and quickly cyclize in aqueous solution to benzisothiazolones (6, BITAs) which unfold NCp7 through Zn^{2+} release [41,42]. BITAs are more active than the parent DIBAs and have been hypothesized to be the major contributor to anti-viral activity [30]. DIBA compounds that release Zn^{2+} rapidly were found to be highly toxic, possibly through reactions with other cellular thiols [42]. The less reactive BITAs were much less toxic and considered more promising as anti-viral chemotherapy agents [42]. Aldrithiol-2 (7a, AT-2), but not diphenyl disulfide 7b, releases Zn^{2+} irreversibly from NCp7 under cellular conditions [19,25,43–46] and has been studied to inactivate HIV-1 infectivity for vaccine development [47,48].

Ebselen 6d and other r-Se compounds, well-known for their antioxidant activity, also release Zn^{2+} from zinc-sulfur proteins and have potential as antiviral and anticancer agents [32,34–38]. r-Se compounds also react faster than r-S: selenocystamine 1b releases Zn^{2+} from MT faster than 1a [34]. Zn^{2+} release by selenite may explain how it suppresses tumor cell growth and activates apoptosis [35]. Selenocystine 8b, along with benzeneselenenyl chloride 9, 6d, 2-nitrophenylselenocyanate 12, and 13, inactivate the CCCC-type ZF DNA-repair proteins formamidopyrimidine-DNA glycosidase (Fpg) and xeroderma pigmentosum group A protein (XPA) to inhibit DNA binding [37]. Benzeneselenenic acid 13 (oxidation state 0) and benzeneseleninic acid 14 (oxidation state +2) release Zn^{2+} from MT even in the presence of a 200 to 500-fold excess of glutathione [34], but selenomethionine (oxidation state −2) was inactive [37]. 6d

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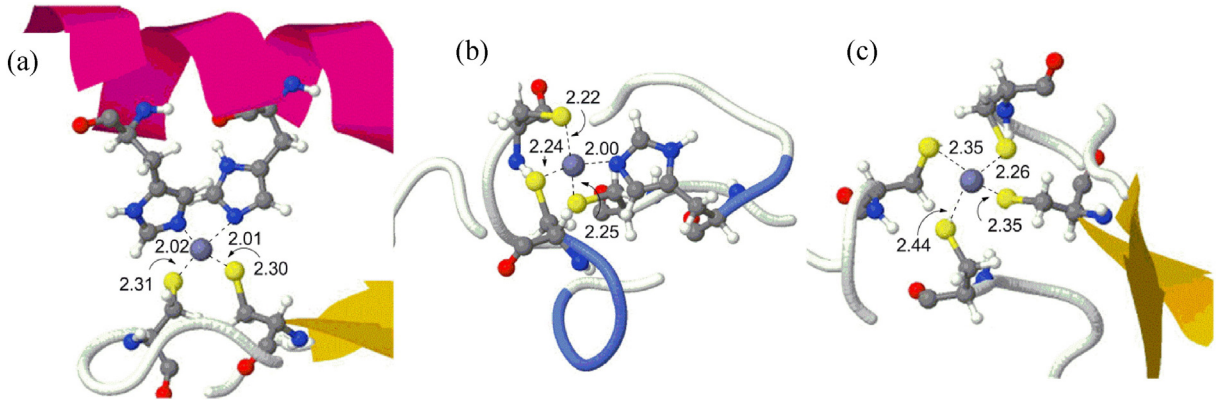

Fig. 1. NMR solution structure of each class of zinc-finger proteins: (a) CCHH: transcription factor Sp1 DNA binding domain (PDB 1VA1 [83]; (b) CCCH: NCp7 (PDB 1ESK); (c) CCCC: DNA-binding domain of human repair factor XPA (PDB 1XPA [84]). Bond distances in Å.

inhibits the binding of DNA to transcriptions factors TFIIIA and Sp1 (CCHH) [34,35]. 1,4-phenylenebis(methylene)selenocyanate 15 (p-XSC), a chemopreventive agent in many preclinical animal studies, inhibited DNA binding to transcription factors Sp1 and Sp2 (CCHH) [49–51] and was proposed to target the CCCC-type DNA binding domain of the androgen receptor in prostate E6 cancer cells [19]. In contrast, the sulfur analog of 15 had no effect on DNA binding to transcription factors [52].

The proposed mechanism for the release of Zn^{2+} involves the initial attack of the electrophilic r-S/Se compound on a ZF Cys sulfur. (Scheme 1) [39]. The r-S/Se compound (represented by RE–X (E = S or Se) in Scheme 1) transfers an RE^+ group to the Cys with loss of X^- to oxidize the thiolate to a disulfide or selenenylsulfide (e.g. 1a: $RE^+ = H_2NCH_2CH_2S^+$, $X^- = H_2NCH_2CH_2S^-$; 9: $RE^+ = PhSe^+$, $X^- = Cl^-$). A chalcogen bonded donor–acceptor intermediate analogous to the ion-dipole complex proposed for the related thiol-disulfide exchange mechanism [53] may be formed along the pathway for initial electrophilic attack, especially in the case of the weaker electrophiles that are of greater interest as potential drugs. Sulfen—/selenenation of Cys weakens its ability to coordinate to Zn^{2+} leading to its replacement in the coordination sphere by solvent. From this sulfen/selenenated intermediate, the ZF either undergoes (a) internal attack of a remaining Cys to form an intramolecular disulfide linkage (ZF_{ox}) with release of thiolate or selenolate (RE^-) or (b) persulfen—/selenenation of the remaining Cys ($Zn(S\text{-}ER)_n$) by additional equivalents of r-S/Se compounds. The former appears to be preferred in CCHH-type proteins and the latter in CCCC ZFs and MT. When DIBAs and BITAs react with NCp7 (CCCH), Loo et al. found apoproteins with intra- (Cys–Cys) and intermolecular (Cys–DIBA) disulfide bonds [41]. Oxidation of Cys thiolate ligand by any of these paths will destabilize the coordination of Zn^{2+} to the protein resulting in release of the ion and unfolding of ZF. Selenolates RSe^- released by disulfide formation to ZF_{ox} can be oxidized by reactive oxygen species (ROS) to form R-SeOH, which can then react with other ZFs to catalyze Zn^{2+} release [54]. The r-S compounds do not show the same catalytic potential due to the relative stabilities of selenenic and sulfenic acid [34,54].

Understanding how r-S/Se compounds can react with ZF proteins can guide the development of new chemopreventive, chemotherapeutic, and anti-viral agents. Density functional theory (DFT) has been used previously to explore the oxidation of ZF models by reactive oxygen species [55–58]. In this study, we expand upon earlier DFT studies on the interaction of r-Se compounds with CCHH ZF models [39,59] to

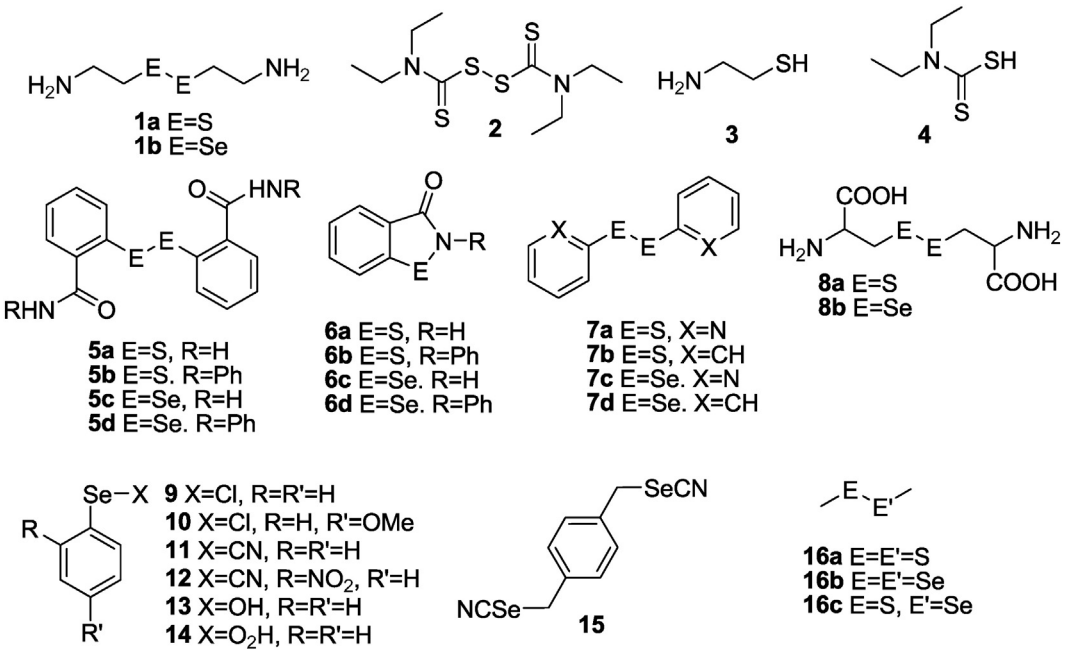

Fig. 2. Examples of reducible sulfur and selenium compounds.