

Mechanistic details of the dehydrative carbon-heteroatom bond construction *via* the benzoisochalcogenazolone-catalyzed acylative oxidation–reduction–condensation strategy

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Dedicated to the 70th Birthday of Prof. Lanny L. Liebeskind

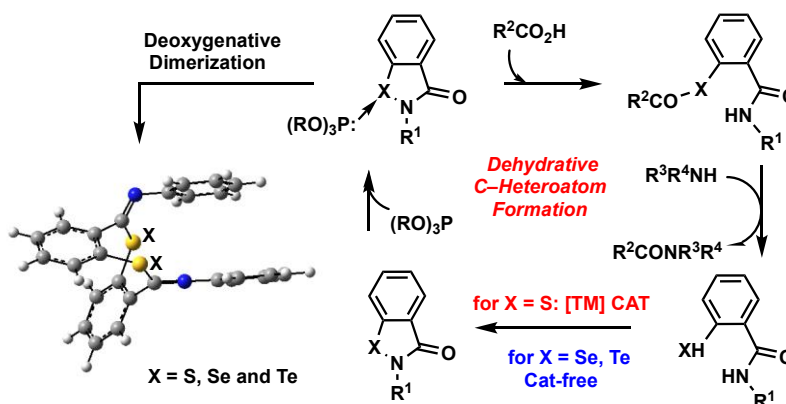
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Abstract

DFT has been used to study the mechanism, nature, and thermodynamics of each of the elementary steps of the redox dehydrative carbon-heteroatom bond formation via a benzoisochalcogenazolone-catalyzed oxidation–reduction–condensation strategy. It is shown that this reaction, in the absence of the carboxylic acid, proceeds via a deoxygenative dimerization pathway: the formation of new benzoisoselezolone and benzoistellurazolone deoxygenation dimers are predicted. In the presence of a carboxylic acid, this reaction leads to productive S-, Se-, and Te-ester formation. These calculations confirm regeneration of the oxidants to be an energy-demanding step of the overall reaction.



Keywords: DFT Studies, oxidation–reduction–condensation, dehydrogenative regeneration, organochalcogens, dehydrative C-C coupling.

Introduction

Dehydrative C-C, C-N, and C-O bond formation is a fundamental approach in organic synthesis (see Scheme 1).



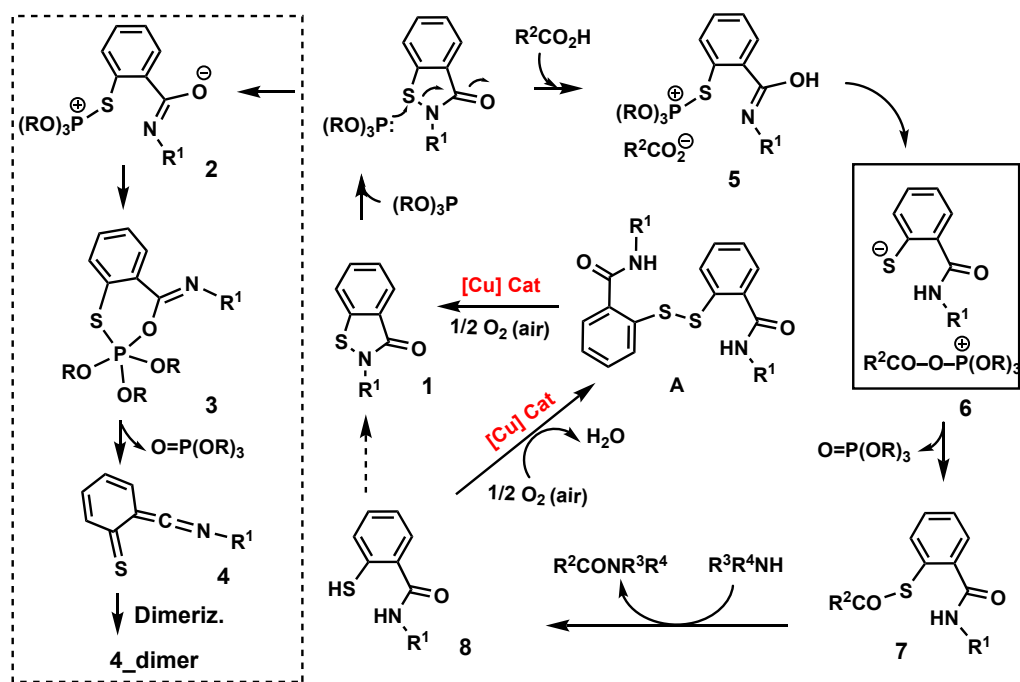
Scheme 1. Dehydrative C–heteroatom bond construction.

Overall dehydration can be achieved through a redox approach where a stoichiometric reducing agent removes an “O” atom and an organic oxidant accepts two hydrogen atoms.¹⁻⁵ In the literature, a variety of oxidants have been explored, however, the reductant has been largely restricted to triorganophosphines, phosphinites, and triaryl phosphites.¹⁻⁵ The generality and mild reaction conditions of oxidation–reduction–condensation have stimulated interest in the development of a catalytic and environmentally friendly version of this reaction.⁶⁻¹² Recently, Liebeskind and coworkers^{13,14} described an aerobic and environmentally friendly catalytic oxidation–reduction–condensation reaction for efficient acylative C–heteroatom bond formations that is based upon the use of benzoisothiazolones (BITs), **1**, as organocatalytic oxidants (coupled to O₂ in air as the terminal oxidant), triethyl phosphite as the reductant, and a complex of earth-abundant copper as a co-catalyst (Scheme 2). Notably, the process is distinct from the existing methodologies in the following ways: (a) the BITs used in Liebeskind’s reaction represent a specific heterocyclic subset of sulfenamides whose S–N bond reactivity can be easily tuned through simple modification of the aromatic ring as well as the *N*-substituent (see below), and (b) it is atom-economical and environmentally benign.

Control experiments enabled Liebeskind and coworkers to propose a mechanism for this reaction, which starts with the attack of triethyl phosphite at the S-atom of the S–N bond of the BIT, **1**. In the absence of the carboxylic acid, the reaction is proposed to proceed via: (a) formation of a zwitterionic complex **2**, (b) bond rotation and formation of a neutral five-coordinate phosphorus intermediate **3**, and (c) elimination of (EtO)₃PO from intermediate **3** to form the highly reactive intermediate **4**, which dimerizes (overall, a deoxygenative dimerization of the BIT). In contrast, the presence of a carboxylic acid diverts the undesired deoxygenation-dimerization pathway toward productive thioester formation if the amidic oxygen atom of the benzoisothiazolone is protonated prior to attack by the phosphite that generates **5**. Then, the reaction would proceed via amide tautomerization and exchange at phosphorus to generate the ion pair **6** that reacts to deliver the anticipated thioester **7** and triethyl phosphate. Furthermore, it was established that: (a) compared to the *N*-aryl substituted BITs, *N*-alkyl substituted BITs in general react slowly in a direct redox reaction with triethyl phosphite, regardless of the solvent used, and (b) the *N*-aryl substituted BITs are uniformly very reactive to deoxygenation-dimerization by triethyl phosphite in DMF. Slower deoxygenation reactions of the same set of *N*-aryl BITs were observed in EtOAc, while very slow reactions were observed in toluene.

Extensive control experiments by Liebeskind and coworkers¹⁴ suggest that the slow step in this catalytic redox dehydration reaction is the regeneration of the benzoisothiazolone **1** from the 2-mercaptobenzamide, **8**. To facilitate of this process, a Cu cocatalyst was used.^{13,14} However, the presence of competitive side reactions and the slow rate of aerobic regeneration of the benzoisothiazolone from the 2-mercaptobenzamide compromised the viability of the overall process. Thus, a better understanding of the mechanism, nature of the participating intermediates, as well as thermodynamic parameters of each

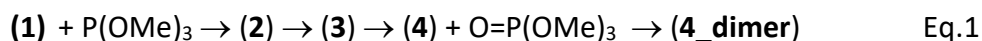
proposed elementary reaction steps are critical for improvement of efficiency of this reaction. Bearing this in mind, we launched computational studies on the nature and thermodynamics of each of the proposed steps of the reaction given in Scheme 2. To extend the scope of this reaction, we used not only benzoisothiazolones (**1**) in our calculations, but also benzoisoselenazolone (**1_Se**, also known as ebselen) and benzoisotellurazolone (**1_Te**, also called ebtellur). For the sake of simplicity, we modeled triethyl phosphite using trimethyl phosphite.



Scheme 2. Previously^{13,14} proposed mechanism of the dehydrative C–heteroatom bond construction via the oxidation–reduction–condensation strategy utilizing benzoisothiazolone, **1**, as an organocatalytic oxidant (coupled to O₂ in air), trialkyl phosphite as the reductant, and a Cu-complex as a co-catalyst.

Results and Discussion

We start our discussion of the reaction in the absence of carboxylic acid leading to deoxygenative dimerization (see Scheme 2)



In general, the BIT–[P(OMe)₃] interaction in **2** could have either zwitterionic or neutral character. The presented calculations favor the neutral BIT–[P(OMe)₃] interaction, see complex (**2'**) (see Figure 1). In complex (**2'**) the calculated BIT–[P(OMe)₃] interaction energy is $\Delta H = -4.6/\Delta G = 3.4$ kcal/mol, and S–P distance is 3.457 Å. Regardless the nature of the BIT–[P(OMe)₃] interaction in **2**, it rearranges to complex (**3**) prior the elimination of O=P(OMe)₃. We found that the (**2'**) → (**3**) rearrangement is endergonic by 12.1 kcal/mol. In (**3**), the calculated P–O¹ and P–S distances are 1.659 and 2.226 Å, respectively. In contrast, transformation of (**3**) into (**4**) + O=P(OMe)₃ is exergonic by 16.7 kcal/mol, which makes the reactions involved in Eq. 1 only slightly (by 1.3 kcal/mol) exergonic. As demonstrated by Liebeskind and coworkers,¹⁴ complex **4** is highly reactive and

undergoes a fast dimerization. Consistent with this experimental finding, calculations show that dimerization of **4** (to give **4_dimer**, see Figure 1) is 37.0 kcal/mol exergonic. Thus, the elementary reactions involved in the deoxygenative dimerization upon the reaction of oxidant BIT, (**1**), with reductant P(OMe)₃ is the dimer **4-dimer**. The overall process is highly exergonic, but may require a few kcal/mol activation barrier.

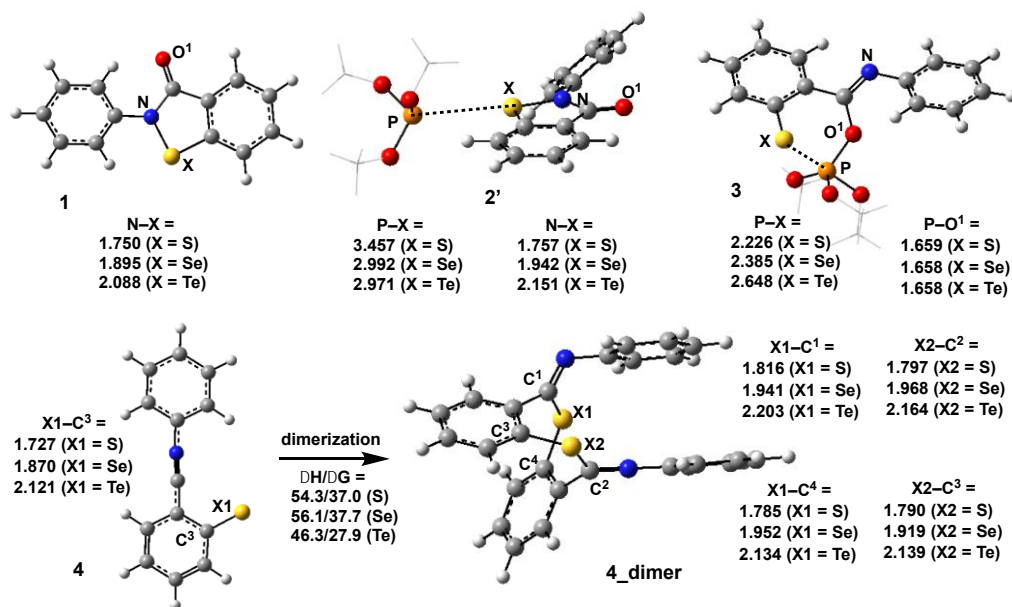
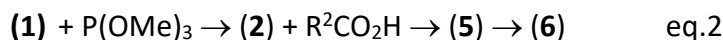


Figure 1. The calculated structures (with their essential geometric parameters, distances are given in Å) of important intermediates of the reaction of organochalcogens, trimethyl phosphite in the absence of carboxylic acids (see Eq. 1). The calculated energies of the reactions of **4** → **4_dimer**, **4_{Se}** → **Se_4_dimer**, **4_{Te}** → **Te_4_dimer** are given in kcal/mol.

We have found that reactions involved in Eq. 1 with the benzoisoselenazolone and benzoisotellurazolone oxidants: (a) are as facile as the those with BIT, and (b) lead to the formation of the **Se_4_dimer** and **Te_4_dimer** dimers, respectively. We propose that dimeric species **Se_4_dimer** and **Te_4_dimer** can be isolated and synthesized by utilizing the same synthetic approach as that used to prepare species **4_dimer** by Liebeskind and coworkers.¹⁴

As mentioned above, the presence of the carboxylic acid diverts the undesired deoxygenation pathway (i.e. eq.1) toward productive thioester formation (see Scheme 2). Calculations show that the initial steps of the thioester formation are facile processes. Indeed, the process shown in eq. 2



is 8.6 kcal/mol exothermic at the ΔH level, but only by 2.2 kcal/mol endergonic at the ΔG level. In other words, overall, eq. 2 is almost thermoneutral. However, one should mention that each elementary reaction of Eq. 2 is a very complex process and involves multiple charge and atom transfer events which could be influenced by the reaction conditions, including, but not limited to, the nature of *N*-substituent (i.e., R¹) and the solvent.

From intermediate (**6**) the reaction is proposed to proceed via elimination of OP(OMe)₃ and *S*-acyl, (**7**), (see Figure 2) formation, i.e., (**6**) → (**7**) + OP(OMe)₃. This process is calculated to be thermodynamically favorable by 29.0 kcal/mol. Overall, the reaction, (**1**) + P(OMe)₃ + R²CO₂H → (**7**) + OP(OMe)₃, leading to the *S*-acyl

formation is energetically highly favorable (by 26.8 kcal/mol). This finding enables us to conclude that in the presence of the carboxylic acid, but with no coupling partners, the reaction of **(1)** with reductant $\text{P}(\text{OMe})_3$ will directly lead to the S-acyl product, which can be the resting stage of the overall reaction.

If we now add the coupling partners (for example, amine), then the S-acyl intermediate **(7)** will rapidly react and lead to the product with the C-Heteroatom bond and 2-mercaptobenzamide, **(8)** (see Figure 2). Our calculations show that (see Figure 2), the reaction $(7) + \text{HNMe}_2 \rightarrow \text{Me}(\text{O})\text{C-NMe}_2 + (8)$ is exergonic by *ca* 11 kcal/mol.

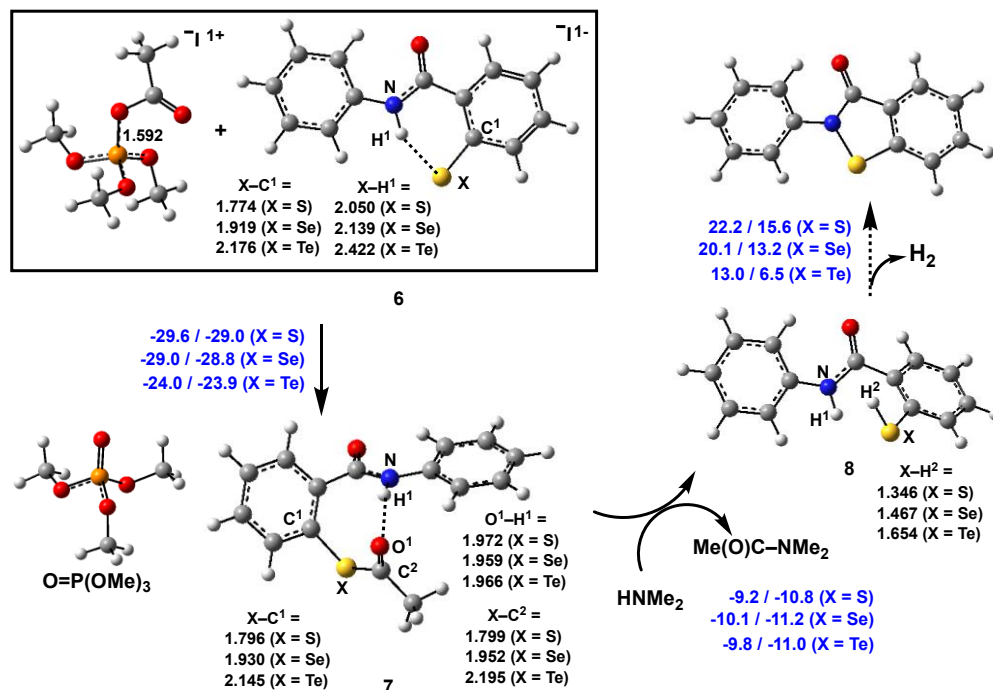


Figure 2. The calculated structures (with their essential geometric parameters, distances are given in Å) of important intermediates of the reaction of organochalcogens, trimethyl phosphite in the presence of carboxylic acids and coupling partner (HNMe_2) (see Eq. 2). The calculated relative energies of each elementary reactions are given in kcal/mol, in blue.

Regeneration of oxidant **(1)** requires removal of two hydrogen atoms from the 2-mercaptobenzamide, **(8)**. This process may proceed either via the use of a catalyst or directly via the dehydrogenation pathways. Calculations show that dehydrogenative regeneration of oxidant **(1)** is highly endergonic and may possess a large energy barrier: in other words, the use of catalyst to facilitate regeneration of oxidant **(1)** seems unavoidable. Consistent with this notion, as mentioned above, Liebeskind and coworkers^{13,14} have previously suggested the regeneration of the benzoisothiazolone **(1)** from the 2-mercaptobenzamide, **(8)**, as the slow step in the catalytic redox dehydration reaction, and have developed a Cu cocatalyst to facilitate the process.

The presented computations show that formation of the acyl intermediate from **1_{Se}** and **1_{Te}** is energetically as facile as that for the reaction **(1)**. In addition, the dehydrogenative regeneration of **1_{Se}** and **1_{Te}** from the corresponding intermediates **8_{Se}** and **8_{Te}** is less energy-demanding than that for **(1)**, especially for **1_{Te}**. Indeed, as seen in Figure 2, dehydrogenative regeneration of **1_{Se}** and **1_{Te}** from the corresponding 2-hydroseleenebenzamide (**8_{Se}**) and 2-hydrotellurobenzamide (**8_{Te}**) intermediates requires only 13.2 and 6.5 kcal/mol free energy, respectively. Furthermore, the dehydrogenative regeneration of the **1_{Se}**, and **1_{Te}** may

possess relatively small energy barriers. These hypotheses are in line with (a) Nature's use of selenocysteine-containing enzymes, such as glutathione oxidase and peroxidase, rather than their S-analogs, in direct oxidations with O₂ and hydroperoxides,^{25,26} and (b) previous results by Musaev and coworkers²⁷⁻³⁰ in their study of the peroxyxynitrite → nitrate isomerization by the **1** (ebsulfur), **1_Se** (ebselen) and **1_Te** (ebtellur) showing that (i) the O-O oxidative addition barrier to these organochalcogens reduces in the order **1** > **1_Se** > **1_Te**, (ii) the nature of the N-substituent critical impacts the O-O bond value of the oxidative addition barrier. Thus, the above presented results suggest that the redox dehydrative C-heteroatom bond formation by reaction of **1_Se** and **1_Te** as oxidants, trimethyl phosphite as a reductant, carboxylic acids, and couplings partners via the oxidation–reduction–condensation strategy may proceed via a different mechanism compared to **1**. This conclusion is consistent with recent experiments by Liebeskind and coworkers^{31,32} who have shown that the redox dehydrative formation of amides, peptides and O-esters under simple aerobic, transition metal-free conditions, can be achieved by use of ortho-functionalized diselenides as catalytic oxidants linked to O₂ in air. We are expecting that the above presented computational findings will guide the making of redox dehydrative C-heteroatom bond formation, via the oxidation–reduction–condensation, even more atom-economical and environmentally friendly.

Conclusions

We used density functional theory to study mechanism, as well as the nature and thermodynamics of each elementary steps of the redox dehydrative Carbon-Heteroatom bond formation via the oxidation–reduction–condensation strategy. Here we used organochalcogens (such as benzoisothiazolones (**1**), benzoisoselenazolone (**1_Se**), and benzoisotellurazolone (**1_Te**) as oxidants, trimethyl phosphite as a reductant, and carboxylic acids. We found that:

1. This reaction, consistent with previous experiments,^{13,14} in the absence of the carboxylic acid, proceeds via a deoxygenative dimerization pathway with a few kcal/mol energy barrier, and leads to the deoxygenative dimerization product. On the basis of these findings we predicted the formation of new benzoisoselenazolone and benzoisotellurazolone deoxygenation dimers. The calculated dimerization free energies of the monomers **4**, **4_Se** and **4_Te** are 37.0, 37.7 and 27.9 kcal/mol, respectively.
2. The presence of the carboxylic acid diverts the undesired deoxygenation pathway toward productive ester formation. These processes, i.e., oxidant + P(OMe)₃ → ester + OP(OMe)₃, are thermodynamically favorable by 26.8, 24.0, and 17.5 kcal/mol for oxidants **1**, **1_Se** and **1_Te**, respectively, and may require only small free energy barriers. Calculations, consistent with previous experiments by Liebeskind,^{13,14} have identified the regeneration of the organochalcogen oxidants from the corresponding ester intermediates as a slow step of the overall reaction. Furthermore, the energy required for this final step of the reaction reduces via **1** (15.6 kcal/mol) > **1_Se** (13.2 kcal/mol) > **1_Te** (6.5 kcal/mol). Consistent with previous experiments,^{13,14,27,28} it seems that regeneration of oxidant **1** from S-ester would require catalyst, while this process with **1_Se**, and **1_Te** oxidants may not need a transition metal cocatalyst.

Experimental Section

Computational Procedure.

Geometry optimizations and frequency calculations of all reported structures were performed with the Gaussian-16 suite of programs¹⁵ at the B3LYP-D3(BJ)/BS1 level of theory with the corresponding Hay-Wadt effective core potential for Te,^{16,17} and Grimme's empirical dispersion-correction (D3)^{18,19} with Becke-Johnson (BJ)¹⁸ damping for B3LYP.^{20,21,22,23} Here, BS1 is a basis set including LanL2dz for Te and 6-31G(d,p) for all other atoms. Frequency analysis was used to characterize each calculated structure. Bulk solvent effects were incorporated for all calculations (including geometry optimizations) using the self-consistent reaction field polarizable continuum model (IEF-PCM).²⁴ As a solvent we chose water. The reported thermodynamic data were computed at 298.15 K and 1 atm pressure. Below, while we present the calculated relative energies as $\Delta H/\Delta G$ (in kcal/mol), we discuss only the Gibbs free energies. Calculated Cartesian coordinates of all systems are provided in the Supporting Information (SI).

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Supplementary Material

Cartesian coordinates of all reported structures are available in the supplementary material associated with this paper.

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