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Oxidation of thiols promoted by PhSeZnCl

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ABSTRACT

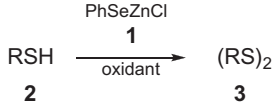
The ability of PhSeZnCl **1** to catalyze the oxidation of thiols to disulfides has been evaluated and correlated to a catalytic GPx-like activity. The first evidence that vinyl phenylselenides can promote the oxidation of thiols reducing hydrogen peroxide through the formation of a selenoxide intermediate is also reported.

Selenium containing compounds have been recently investigated as efficient and promising catalysts in electrophilic reactions, coordination chemistry and oxygen transfer processes.[1]

Selenium is a biologically relevant element involved in some redox regulating enzymes such as the glutathione peroxidase (GPx) and thioredoxin reductase (TRx).[2] Small size organoselenium derivatives can be used to develop GPx mimetic molecules.[3] Even if various oxidation states of selenium have been observed within proteins, at physiological pH the selenol moiety, that represents the catalytic site of GPx, is fully dissociated conferring to the selenium atom strong nucleophilicity toward peroxide substrates.[4] Selenolates are usually very unstable and reactive species but, a –SeH group participates to the catalytic triad of the enzyme being stabilized by hydrogen bonds to tryptophan and glutamine residues.[4]

We recently reported the synthesis of PhSeZnCl[5] (**1**) as the first example of air-stable selenolate, easily available through oxidative zinc insertion starting from the commercially available PhSeCl. In 'on water' conditions,[6] it is an excellent nucleophilic reagent, and it has been used for several synthetic purposes such as nucleophilic substitution at sp^3 and sp^2 carbon,[5,7] ring-opening reaction of epoxides,[5] and aziridines[8] as well as Michael-type addition reactions.[9] Considering that the oxidation state of selenium in **1** is the same as in the catalytic site of the enzyme, we investigated the reactivity of PhSeZnCl toward thiols in the presence of air or peroxides as stoichiometric oxidants (Scheme 1) comparing its GPx-like activity with that of other selenium containing compounds.

From a synthetic point of view the oxidation of thiols to disulfides has important applications in the preparation of biomolecules as well as ligands and it has recently received considerable attention by several research groups.[10–13] This reaction plays an important role in redox signaling and in structural and functional regulations of proteins. A preliminary evaluation has been carried out starting from a series of thiols **2a–g** and using stoichiometric or catalytic amount of PhSeZnCl at room temperature in D_2O or THF under aerobic conditions. The results, summarized in Table 1, clearly indicate that the reaction strongly depends on the nature of the substrate. Cysteine (**2a**) and homocysteine (**2b**) resulted to be completely unreactive under the above mentioned conditions and after 48 h the starting material can be quantitatively recovered. On the contrary glutathione (GSH) **2c** slowly reacted with a stoichiometric amount of PhSeZnCl and was completely converted into **3c** in 30 h (using a 10% of **1**, after 168 h the conversion was lower than 10%). We also verified that in the absence of **1**, GSH is not subjected to spontaneous oxidation when exposed to air (Fig. 1). Better results were obtained starting from dithiotreitol (DTT) **2d**, a non physiological thiol. In this case, even using a



Scheme 1. Oxidation of thiols promoted by **1**.

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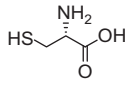
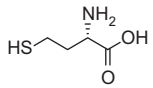
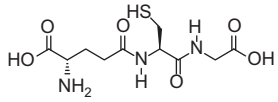
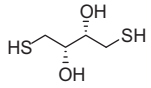
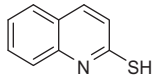
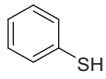
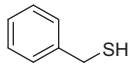
Table 1
Oxidation of thiols **2a–g** in presence of PhSeZnCl[a]

	Thiol **2**	%1	Solvent	Time (h)	Yield %
a		100	D_2O	48	–
b		100	D_2O	48	–
c		10 100	D_2O D_2O	168 30	<10 100
d		10 100	D_2O D_2O	120 48	100 100
e		100	THF	48	22[b]
f		100	THF	48	36[b,c]
g		10 100	THF THF	120 48	60[b] 82[b]

[a] Conditions: Reaction carried out under aerobic conditions thiol concentration 0,04 M, stirring speed 800 rpm, 23 °C.
[b] The yield is referred to the isolated product after chromatographic purification.
[c] $(PhSe)_2$ and PhSZnCl were obtained as side products.

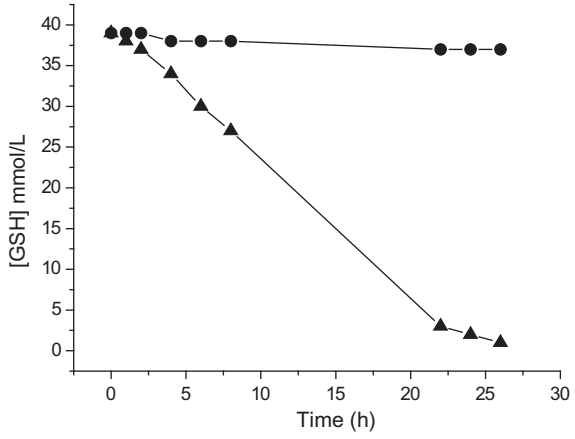


Figure 1. Oxidation of GSH under aerobic conditions without catalysts (●), in the presence of a stoichiometric amount of PhSeZnCl (▲).

catalytic amount (10%) of PhSeZnCl, disulfide **3d** was quantitatively obtained in 120 h.

The oxidation of the thiols **2a–d** was performed at room temperature in D_2O and monitored directly by ^1H NMR. The yields reported in Table 1 are referred to the conversion observed from the NMR spectra and, in all the cases, were confirmed after the workup.

Starting from non water soluble thiols **2e–g** the reactions were carried out in THF and the corresponding disulfides **3e–g** were purified by flash chromatography on silica gel column. The yields were moderate for the aromatic compounds **2e** and **2f** and good in the case of the benzyl derivative **2g** for which catalytic conditions afforded 60% of **3g** in 120 h.

The oxidation of GSH has been further investigated in the presence of hydrogen peroxide and TBHP as terminal oxidants. As shown in Figure 2, the reactions promoted by peroxides are faster

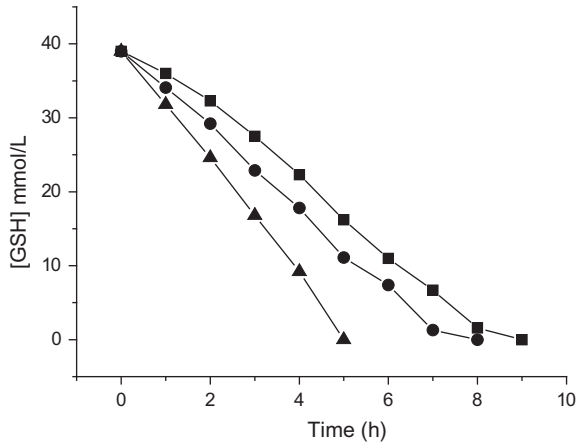
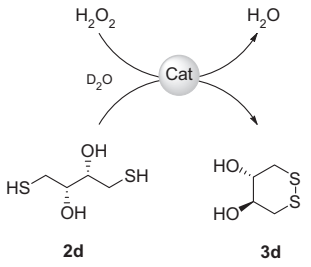


Figure 2. Oxidation of GSH in the presence of: TBHP (●), H_2O_2 (■) H_2O_2 and **1** (10%) (▲).

than those effected under aerobic conditions and the oxidation rate, in the case of hydrogen peroxide, is accelerated by the presence of a catalytic amount of PhSeZnCl, suggesting a GPx-like mechanism. The GSH/GSSG ratio has been measured by the integration of the corresponding proton NMR signals.

In order to better evaluate this GPx-like activity, the oxidation of **2d** was performed in D_2O and followed by ^1H NMR spectroscopy modifying the procedure previously reported by Iwaoka and coworkers.[14] Resonances at $\delta = 2.58$ and 3.64 ppm relative to **2d** (DTT_{red}) decreased with respect to the increasing intensity of the signals centered at $\delta = 2.85$, 3.04 e 3.55 ppm relative to **3d** (DTT_{ox}). Figure 3 shows the comparison between the results obtained using L-selenocystine, PhSeZnCl, and diphenyl diselenide, as catalysts (10%), respectively. The time required to convert DTT_{red} into DTT_{ox}



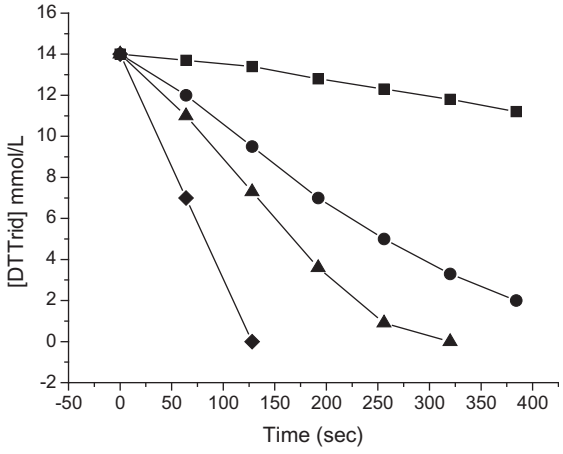
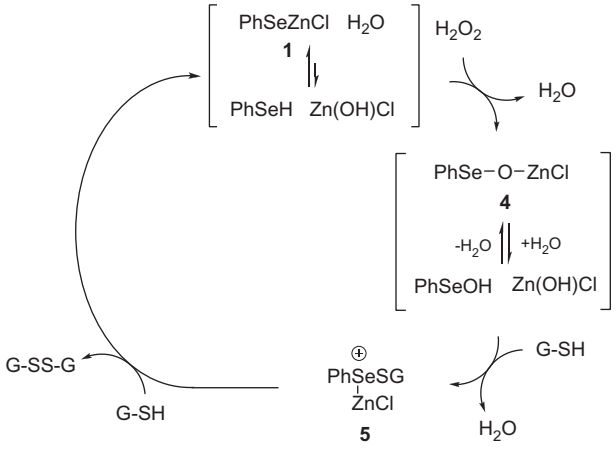


Figure 3. Comparison of the catalytic activity for the oxidation of DTT: without catalysts (■), $(PhSe)_2$ [$1{,}4*10^{-3}$N] (●), PhSeZnCl [$1{,}4*10^{-3}$N] (▲), $(L\text{-Sec})_2$ [$1{,}4*10^{-3}$N] (♦).



Scheme 2. Proposed mechanism for GPx-like activity of **1**.

by 50% (T50) can be conveniently used to compare GPx-like activities of different organoselenium compounds.

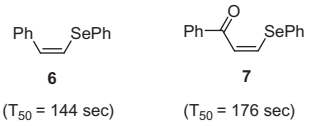
It is interesting to observe that **1** showed T50 (128 s) higher than the one of the dimer of the natural amino acid $(L\text{-Sec})_2$ (64 s) but shorter than that of $(PhSe)_2$ (192 s).

This latter evidence suggests that PhSeZnCl does not simply act as a precursor of the selenenic acid intermediate, which is the case of diphenyl diselenide. Reasonably, a zinc containing Lewis acid may play an active role in the catalytic cycle as proposed in Scheme 2. Similar experiments have been carried out using benzylthiol **2g** as oxidation probe in *d*-chloroform.[15] While $(L\text{-Sec})_2$ and $(PhSe)_2$ gave results similar to that obtained in the experiment with **2d** in D_2O, a very low catalytic activity was observed for PhSeZnCl that was ascribed to its quite complete insolubility in *d*-chloroform.

The mechanism proposed in Scheme 2 is in agreement with the evidence that a stoichiometric amount of zinc chloride increased the catalytic activity of diphenyl diselenide in the oxidation of GSH with hydrogen peroxide, [T50 $(PhSe)_2$ = 3,75 h, T50 $(PhSe)_2 + ZnCl_2$ 3,0 h, T50 PhSeZnCl 2,8 h] (for this latter result see Fig. 2). These experiments were carried out pre-treating the catalytic mixture with the H_2O_2 for 30 min before the thiol addition.

During the screening of several organoselenium compounds, a surprising and unexpected GPx-like activity has been observed for some vinyl selenides that can be easily prepared starting from **1**.[9] Two selected examples (**6** and **7**) are reported in Scheme 3. Also in these cases the GPx-like activity has been evaluated comparing the corresponding T50 for the oxidation of DTT in D_2O at 23 °C in the presence of 1 equiv of H_2O_2 and 10% of catalyst [$1{,}4*10^{-3}$N]. ^{77}Se-NMR investigations demonstrate that, in the case of these compounds the intermediate is a selenoxide.

Further investigations are now ongoing in order to define the correlation between structure and catalytic activity of vinyl



Scheme 3. Vinyl selenides **6**, **7** and the corresponding T_{50} = time required to convert DTT_{rid} into DTT_{ox} by 50%.

selenides. Biological assays will be performed to demonstrate the effective correlation between the proposed catalytic mechanism and an actual GPx-like activity at the cellular levels.

Acknowledgments

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