Tetrahedron xxx (2018) 1–9

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Key steps and intermediates in the catalytic mechanism for the reduction of peroxides by the antioxidant ebselen

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ARTICLE INFO

Article history:
Received 4 March 2018
Received in revised form
5 May 2018
Accepted 8 May 2018
Available online xxx

Dedicated to the memory of Professor Sir Derek H. R. Barton, an extraordinary scientist, mentor and gentleman.

Keywords:
Organoselenium chemistry
Glutathione peroxide mimetics
Ebselen
Peroxides
Redox balance

ABSTRACT

Hydrogen peroxide and lipid hydroperoxides are formed during aerobic metabolism and contribute to oxidative stress, a major factor in many diseases and degenerative conditions. Although the selenoenzyme glutathione peroxidase (GPx) affords antioxidant protection in vivo by catalytically reducing harmful peroxides with glutathione, certain conditions benefit from the administration of small-molecule GPx mimetics for additional protection. To date, ebselen has been the most widely studied such compound, but its catalytic mechanism is complex and highly variable with conditions. Progress in elucidating the mechanistic details of its antioxidant activity is described in this review.

1. Introduction

Peroxides and other reactive oxygen species (ROS) are byproducts of normal aerobic metabolism and contribute to the maintenance of redox balance in living organisms. However, the excessive production of ROS leads to oxidative stress that has been implicated as a contributing factor in many diseases and degenerative conditions.[1] The selenoenzyme family of glutathione peroxidases (GPx)[2] suppress oxidative stress by catalytically reducing peroxides with glutathione (GSH), which serves as a stoichiometric reductant in this process, as shown in Scheme 1. In some disease states, however, GPx is overwhelmed by excessive peroxide formation and small-molecule mimics of the selenoenzyme are therefore of interest for restoring redox homeostasis. Extensive investigations of diverse classes of organoselenium compounds have been reported in this context,[3] but the drug ebselen (**1**) has been the most widely studied to date.

Ebselen was first reported in 1924 by Lesser and Weiss[4] and several other methods for its preparation were subsequently described.[5] An interesting historical account of its development as a drug was recently provided by Parnham and Sies.[6] The function of ebselen as a biological antioxidant[7] has been investigated in the treatment of ischemic reperfusion of heart attack and stroke patients,[8] in mitigation of neurodegeneration,[9] as a lithium surrogate in bipolar disease,[10] for the restoration of hearing loss,[11] and as an antibacterial,[12] antimycotic[12c,d] and antiviral[13] agent. Its anticancer activity[14] and effect on diabetes[15] have also been scrutinized. Unfortunately, ebselen possesses only moderate catalytic activity and is highly insoluble in aqueous media, resulting in problematic intravenous administration. This is of particular importance in cases where rapid delivery is required, as in the suppression of reperfusion injury to heart attack and stroke patients. On the other hand, the ease of synthesis of ebselen[5] and its demonstrated lack of toxicity in several clinical trials[16] have contributed to its popularity as a drug candidate.

Ebselen is known to interact with a variety of enzymes and other biomolecules in the context of the above medicinal properties. It is also known to catalyze the reduction of other ROS such as peroxynitrites. Numerous analogues and congeners of ebselen have been reported for structure-activity studies. These aspects are beyond the scope of the present review and are described elsewhere.[3,7] Herein is presented a review of the mechanisms that have been

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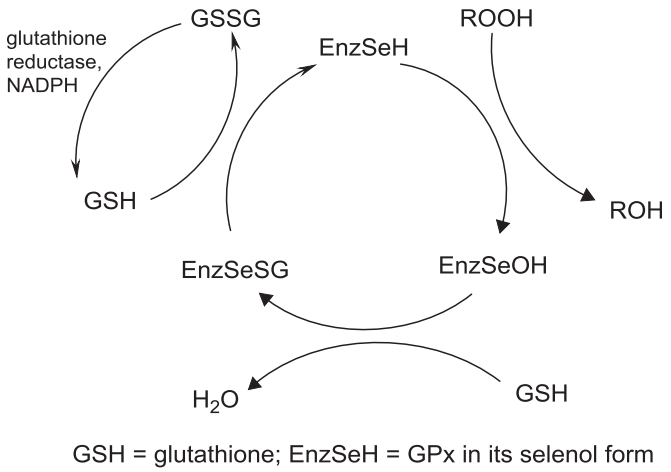
https://doi.org/10.1016/j.tet.2018.05.027
0040-4020/



Scheme 1. Catalytic cycle of glutathione peroxidase.

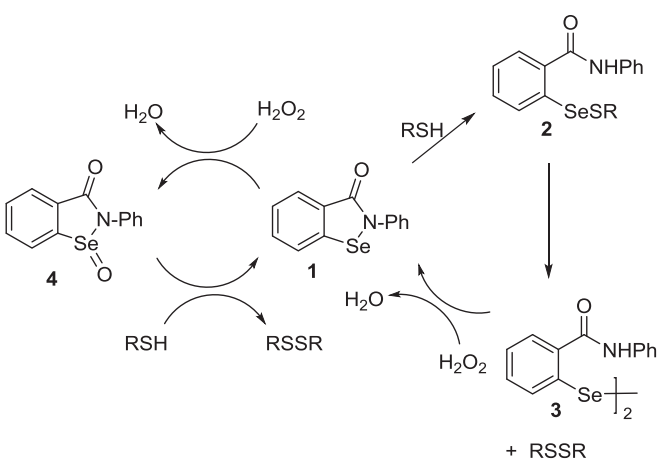
proposed to account for the catalytic reduction and detoxification of peroxides and hydroperoxides by glutathione and other thiols in the presence of ebselen.

2. An overview of ebselen catalytic cycles

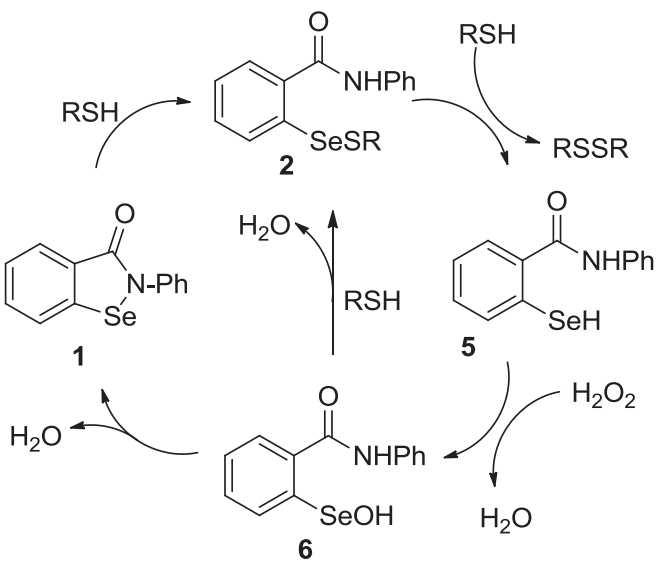
The mechanism for the catalytic activity of ebselen (**1**) has been the source of considerable debate and occasionally divergent opinions. This is likely due to the different conditions, types of assays and reactants (thiols, peroxides) that were employed by various groups. The results of several early investigations were summarized in reviews by Sies in 1993[17] and by Schewe in 1995.[18] After preliminary work by groups including Sies et al.,[19] Wendel et al.[20] and Fischer and Dereu,[21] an early catalytic cycle for the GPx-like behaviour of ebselen emerged and is shown in Scheme 2.[17] In this scenario, a high thiol concentration results in thiolysis of **1** to afford the selenenyl sulfide **2**, followed by disproportionation (metathesis)[22a] to diselenide **3** and the corresponding disulfide, then by oxidation of the diselenide with the peroxide to regenerate the original catalyst **1**. On the other hand, at high peroxide concentration, it was proposed that ebselen forms the corresponding cyclic seleninamide **4**[22b] that is subsequently reduced back to **1** by the thiol.

A revised mechanism followed from the work of Maiorino et al.,[23] Haenen et al.,[24] Engman et al.[25] and others. In particular, the Engman group demonstrated that the catalytic cycle resembles that of GPx, wherein formation of **2** with GSH or dithiothreitol is followed by further reaction with the thiol to produce the corresponding selenol **5** and disulfide, then oxidation by the peroxide to generate the selenenic acid **6** and finally regeneration of **2** by thiolysis of **6** or by dehydration-cyclization to afford **1** (Scheme 3). The possible formation of the corresponding diselenide from the reaction of selenol **5** with selenenyl sulfide **2** was also indicated.[25b] Trapping experiments with iodoacetate[23] and with 1-chloro-2,4-dinitrobenzene[25a] confirmed the formation of the postulated selenol intermediate under the conditions employed. Kinetic experiments by Engman et al.[25b] indicated that the selenol **5** underwent the fastest oxidation with hydrogen peroxide when compared with ebselen **1**, selenenyl sulfide **2** (prepared from GSH) and diselenide **3**, with the following rate constants: k (**5**) = 2.8 $mM^{-1}min^{-1}$; k (**1**) = 0.29 $mM^{-1}min^{-1}$; k (**2**) $\leq$0.01 $mM^{-1}min^{-1}$ and k (**3**) = 0.32 $mM^{-1}min^{-1}$. The relatively poor activity of the selenenyl sulfide **2** toward oxidation was also evident from this work.[26] Computational studies by Pearson and Boyd[27] provided activation energies of 36.8, 32.5, and 38.4 kcal/mol for the oxidation of ebselen (**1**), the corresponding selenol **5**, and the diselenide **3**, respectively, with hydrogen peroxide.[27a] These results are consistent with the kinetic measurements previously reported by Engman et al.[25b] and indicate that the selenol intermediate is a particularly effective reductant for the peroxide substrate.

More recently, extensive mechanistic studies by Mugesh et al.[28–30] suggested an alternative mechanism (Scheme 4),[28] wherein **1** first reacts with the sacrificial thiol (RSH) to form the corresponding selenenyl sulfide **2**. However, instead of thiol attack at the sulfur atom of **2** to produce the selenol and disulfide, as in Scheme 3, disproportionation of **2** to the diselenide **3** and the disulfide dominates. Oxidation of the diselenide with hydrogen peroxide (or presumably with a hydroperoxide) generates the selenenic acid **6** or seleninic acid **7**. Intermediate **6** can then either cyclize with loss of water to regenerate the original catalyst **1** or react with the thiol to afford the selenenyl sulfide **2**, while the seleninic acid **7** is similarly reduced by the thiol to **6**. Alternatively, it is known that seleninic acids and diselenides comproportionate to afford selenenic acids, as in Scheme 5.[31] Thus, a similar reaction between **7** and **3** would also be expected to produce the selenenic acid **6**.



Scheme 2. Early catalytic cycles for ebselen.



Scheme 3. The GPx-like mechanism.

Please cite this article in press as: Sands KN, Back TG, Key steps and intermediates in the catalytic mechanism for the reduction of peroxides by the antioxidant ebselen, Tetrahedron (2018), https://doi.org/10.1016/j.tet.2018.05.027