Diferrocenyl diselenides: excellent thiol peroxidase-like antioxidants

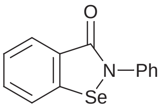
G. Mugesh,[a] Arunashree Panda,[a] Harkesh B. Singh,*[a] Narayan S. Punekar[b] and Ray J. Butcher[c]

[a] *Department of Chemistry, Indian Institute of Technology, Powai, Bombay 400 076, India. E-mail: chhbsia@chem.iitb.ernet.in*
[b] *Biotechnology Centre, Indian Institute of Technology, Powai, Bombay 400 076, India*
[c] *Department of Chemistry, Howard University, Washington DC, 20059, USA*

Synthesis, structure and thiol peroxidase-like antioxidant activity of several diaryl diselenides having intramolecularly coordinating amino groups are described; the diselenides having both tertiary amino groups and redox-active ferrocenyl units show excellent peroxidase activity.

Glutathione peroxidase (GPX) is a well known selenoenzyme which functions as an antioxidant.[1] This selenoprotein catalyses the reduction of harmful peroxides by glutathione and protects the cell membrane from oxidative damage. Recently, much attention has been devoted to the synthesis of simple organoselenium compounds that mimic the action of GPX. After the discovery of Ebselen **1**,[2] several other mimetics have been reported which include the Ebselen homologue,[3] benzoselenazolinones,[4] selenenamide **2**[5a] and related derivatives,[5b] diaryl diselenides,[6] various tellurides and ditellurides,[7] and the enzyme selenosubtilisin.[8]

Recently, diaryl diselenides **3–5** with basic amino groups have attracted much attention as GPX mimics because the Se···N intramolecular non-bonded interactions, (i) activate the Se–Se bond towards the oxidative cleavage and, (ii) stabilize the resulting selenenic acid intermediate against further oxidation.[6] In continuation of our work on intramolecularly coordinated organochalcogens,[9] we report here the synthesis, structure and thiol peroxidase activity of a series of closely related novel diselenides **7–12**.



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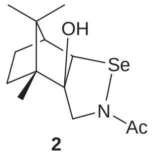

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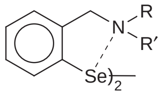
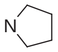
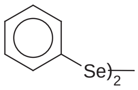


3 R = R′ = Me

4 NRR′ =



5 R = Me, R′ = c-C$_6$H$_{11}$



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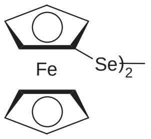

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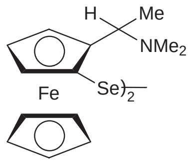
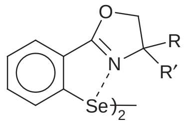
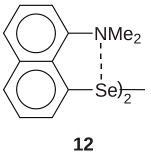


8 (*R,S;R,S*) (+)
9 (*S,R;S,R*) (–)



10 R = R′ = Me
11 *R*(–), R = Et, R′ = H



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Diselenides **3**,[9a] **7**,[10] **8**,[11] and **9**[11] used in the present study were prepared by the methods indicated. Novel diselenides **10–12** were prepared by the ortholithiation method.† The structures of **8**, **10**, **11** and **12** were determined by X-ray diffraction.‡ The catalytic activity was studied according to the method reported by Tomoda and coworkers[6b] using benzenethiol (PhSH) as a glutathione alternative. The initial rates (v_0) for the reduction of H_2O_2 (3.75 mM) by thiol (1 mM) in the presence of various catalysts (0.01 mM) [eqn. (1)] were determined in methanol medium by monitoring the UV absorption at 305 nm due to the formation of diphenyl disulfide (PhSSPh).

$$H_2O_2 + 2PhSH \xrightarrow{\text{Catalyst}} 2H_2O + PhSSPh \qquad (1)$$

Diselenide **6** showed a slight enhancement in the rate (v_0 = 0.55 ± 0.18 μmol dm^{-3} min^{-1}) as compared with the uncatalyzed rate (v_0 = 0.15 ± 0.04 μmol dm^{-3} min^{-1}). Ferrocene was inactive, however, *N,N*-dimethyl(ferrocenylethyl)amine, a ferrocene compound containing a basic amino group showed a much better activity (v_0 = 3.16 ± 0.52 μmol dm^{-3} min^{-1}). The rate (v_0 = 3.83 ± 0.32 μmol dm^{-3} min^{-1}) observed for **6** together with *N,N*-dimethyl(ferrocenylethyl)amine was equal to the sum of the rates observed for the individual cases (v_0 = 3.71 ± 0.70 μmol dm^{-3} min^{-1}). There was a significant improvement in the activity when the phenyl groups in **6** were replaced by redox active ferrocenyl groups, **7** (v_0 = 3.39 ± 0.37 μmol dm^{-3} min^{-1}). The activity of **7** could not be enhanced by the addition of *N,N*-dimethyl(ferrocenylethyl)amine as the rate of the mixed case (v_0 = 5.78 ± 0.79 μmol dm^{-3} min^{-1}) was almost equal to the sum of their rates in the individual cases (v_0 = 6.55 ± 0.45 μmol dm^{-3} min^{-1}). The initial rate in the presence of crystalline Wilson's catalyst (**3**), which has been previously used as liquid or HCl salt,[6a] was 28.38 ± 3.88 μmol dm^{-3} min^{-1}. Surprisingly, under similar conditions, the initial rates for the redox-active diselenides **8** and **9** were 574.01 ± 23.98 and 466.49 ± 28.26 μmol dm^{-3} min^{-1}, respectively. Diselenides **10**, **11** and **12** did not show any noticeable activity under identical conditions.

Almost 18 fold enhancement in the initial reduction rate of **8** and **9** compared with the Wilson's catalyst and *ca.* 900 fold enhancement compared with PhSeSePh under identical experimental conditions was observed. Although compounds **3**, **8** and **9** have similar amino groups, the large increase in the activities of **8** and **9** as compared with **3** indicates that the presence of redox-active group is crucial for high peroxidase activity of **8** and **9**. On the other hand, while compound **7** is much more reactive than **6**, the observation that **7**, whose redox potential§ is as low as those of **8** and **9**, is much less reactive than **8** or **9** clearly suggests that the nearby nitrogen moiety should be equally responsible for activity enhancement of **8** and **9**. In other words, these two functionalities (tertiary amino and redox-active) individually show moderate effects on the activity, however, when present together (**8** and **9**), the effect is synergistic.

The Se···N interaction of an intermediate strength (2.856 and 2.863 Å) in **3** shows moderate effect on the activity whereas, the most active compounds **8** and **9** do not have any such interactions in the solid state as the Se···N bond lengths (3.697 and 4.296 Å for **8**; 3.98 and 4.12 Å for **9**[11b]) are greater than the sum of their van der Waals radii (3.54 Å). However, the activity of **8** and **9** cannot be regarded as evidence for unimportance of nearby nitrogen since the nitrogen atoms present in the compounds may come closer to the selenium in solution. The inactivity of **10**, **11** and **12** [in which the Se···N interactions are quite strong; **10** (2.705, 2.891 Å), **11** (2.778, 2.794 Å) and **12** (2.628, 2.652 Å)], may be ascribed not only to steric effect, but also to the nature of the nitrogen lone pairs which are either imine lone pair (**10**, **11**) or a lone pair in π-conjugation (**12**), suggesting that they are not basic enough to incorporate in the redox cycle.

In conclusion, we observe that the diselenides which have quite strong Se···N intramolecular interactions do not show any noticeable activity whereas the diselenides which have in-built coordinating basic amino group but do not have Se···N interaction show excellent activity. Secondly, the diselenides in which the selenium atom is directly bonded to a redox active group (ferrocenyl) show a dramatic increase in the peroxidase activity thus supports the supposition made by Back and Dyck.[5a]

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Notes and References

† Compound **10**: yield: 60%, mp 158–160 °C. Compound **11**: yield: 40%, mp 120–122 °C. Compound **12**: yield: 60%, mp 136 °C (decomp.). Satisfactory elemental analyses were obtained for all new compounds.

‡ *Crystallographic data*: **8**: $C_{28}H_{36}Fe_2N_2O_2Se_2$, M = 670.21, orthorhombic space group $P2_12_12_1$, a = 10.7903(11), b = 15.1341(12), c = 17.7815(14) Å, V = 2903.7(4) Å^3, Z = 4, D_c = 1.533 Mg m^{-3}, $R(R_w)$ = 0.0511(0.0870), T = 293(2) K, μ = 3.524 mm^{-1}, observed reflections = 4597. **10**: $C_{22}H_{24}N_2O_2Se_2$, M = 506.36, rhombohedral, space group $R\bar{3}$ a = 33.198(4), c = 10.564(2) Å, V = 10083(2) Å^3, Z = 18, D_c = 1.501 Mg m^{-3}, $R(R_w)$ = 0.0500(0.0837), T = 293(2) K, μ = 3.319 mm^{-1}, observed reflections = 4884. **11**: $C_{22}H_{24}N_2O_2Se_2$, M = 506.35, orthorhombic, space group $P2_12_12_1$, a = 8.778(3), b = 12.643(3), c = 20.268(4) Å, V = 2249.2(11) Å^3, Z = 4, D_c = 1.495 Mg m^{-3}, $R(R_w)$ = 0.0456(0.0869), T = 293(2), μ = 3.306 mm^{-1}, observed reflections = 2167. **12**: $C_{24}H_{24}N_2Se_2$, M = 498.37, orthorhombic, space group $P2_12_12_1$, a = 7.6738(10), b = 11.0274(11), c = 26.127(3) Å, V = 2210.9(4) Å^3, Z = 4, D_c = 1.497 Mg m^{-3}, $R(R_w)$ = 0.0564(0.1015), T = 293(2) K, μ = 3.356 mm^{-1}, observed reflections = 2839. CCDC 182/1016.

§ Supporting electrolyte 0.1 M Et_4NClO_4 in MeCN, SCE reference electrode, scan rate 50 mV s^{-1}. Compounds **7**–**9** undergo two quasi-reversible one-electron oxidations at relatively low potentials (**7**: 0.60, 0.79 V; **8**: 0.44, 1.02 V; **9**: 0.45, 1.08 V) whereas the other diselenides undergo irreversible oxidations at higher potentials (**3**: 1.02 V; **6**: 1.82 V; **10**: 0.97 V; **11**: 1.04 V; **12**: 0.95 V); ferrocene: 0.45 V.

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