Formation of a spirodiazaselenurane and its corresponding azaselenonium derivatives from the oxidation of 2,2′-selenobis(benzamide). Structure, properties and glutathione peroxidase activity†

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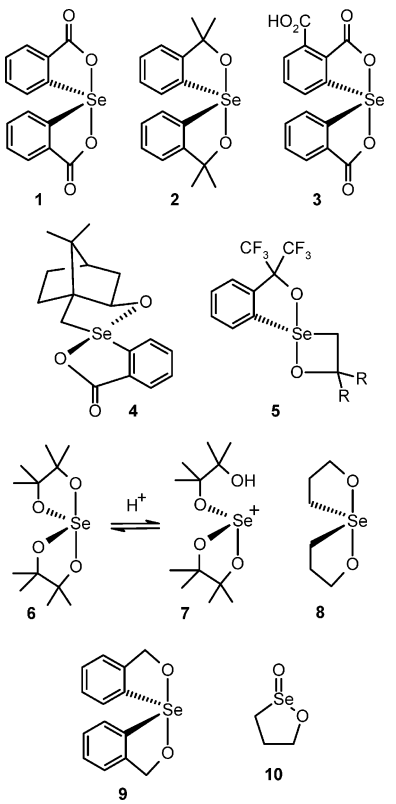
The oxidation of 2,2′-selenobis(benzamide) with *N*-chlorosuccinimide or hydrogen peroxide afforded the corresponding stable azaselenonium chloride and hydroxide, respectively. Both structures were characterized by spectroscopic and X-ray crystallographic methods. Each contains a covalent N–Se bond, as well as a noncovalent interaction between the selenium atom and the carbonyl oxygen atom of the other amide moiety. The treatment of the azaselenonium chloride with an excess of potassium hydride in DMSO-d_6 afforded the corresponding spirodiazaselenurane species, which proved hydrolytically unstable, but was characterized by NMR spectroscopy. The azaselenonium chloride displayed significant glutathione peroxidase-like catalytic activity in an assay with benzyl thiol and either hydrogen peroxide or *tert*-butyl hydroperoxide.

Introduction

Although the spirodioxyselenurane **1** was first reported in 1914 by Lesser and Weiss,[1] this class of selenium compounds[2] attracted relatively little attention until recently. The X-ray crystal structure of **1**[3] revealed that the selenium atom resides at the center of a distorted trigonal bipyramid, in which two oxygen substituents occupy apical positions, while two carbon atoms and the selenium lone pair define the equatorial plane. Such structures are chiral,[4] prompting several investigations into their stereochemistry. Thus, spirodioxyselenurane **2**, where the carbonyl groups of **1** are replaced by geminal dimethyl substituents, was shown to possess high configurational stability, even when heated to 200 °C.[5] Both **1**[6] and **2**[7] have been resolved by HPLC, using chiral stationary phases, and their absolute configurations have been established.[6,8] The carboxy derivative **3** has been partially resolved by classical means,[9] while several camphor-derived spirodioxyselenuranes, such as **4**, were prepared as pure diastereomers.[10] The syntheses and reactions of several oxaselenetanes of general structure **5**, have also been reported.[11] Several spirotetraoxyselenuranes (*e.g.* **6**) were prepared and observed to undergo acid-catalyzed equilibration with the corresponding selenonium species **7**.[12] Other spirodiacyloxyselenuranes[13] and trifluoromethyl-substituted spirodioxyselenuranes[14] are also known.

Very recently, we reported the first synthesis of the unsubstituted, aliphatic parent structure **8**[15] and its homologues, and demonstrated that they act as efficient mimetics[16] of the selenoenzyme glutathione peroxidase (GPx).[17] The latter catalyzes the reduction of harmful peroxides that are formed during aerobic metabolism and contribute to oxidative stress. GPx functions in conjunction with the stoichiometric reductant glutathione, which is oxidized to the corresponding disulfide during this process. The corresponding tellurium analog displayed significantly higher catalytic activity than **8** in a model assay,[18] while aromatic derivatives such as **1**[18] and **9**[18,19] showed generally diminished activity[18] compared to **8**. Related GPx mimetics that contain covalent Se–O bonds include cyclic seleninates such as **10** and its benzo derivative.[18–20]



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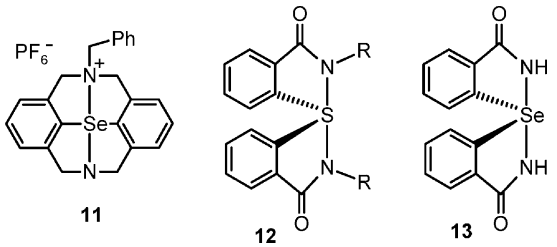
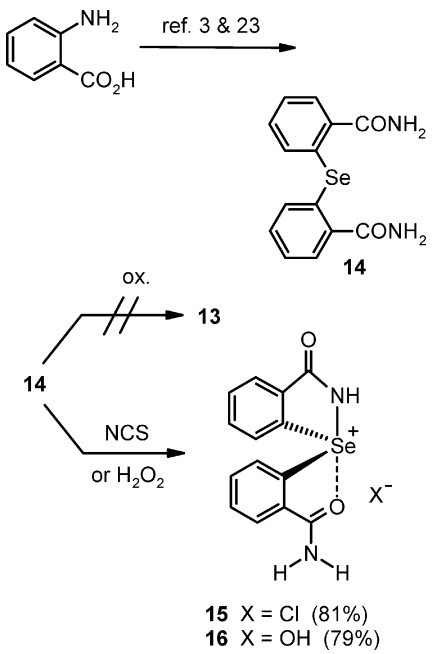
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of **15**, **16** and **21**. Catalytic activity of **15**. X-Ray crystallographic data for **15** and **16**. See DOI: 10.1039/b710685h

Diazaselenurane **11**[21] was recently synthesized, while spirodiazasulfuranes **12**, where R = alkyl or acyl, have been the subjects of several investigations.[22] Although they are hydrolytically labile,[22a] several such compounds have been isolated and characterized by X-ray crystallography.[22a,e] However, to our knowledge, spirodiazaselenuranes have not yet been reported. In view of the interesting structural, stereochemical and biological properties of spirodioxyselenuranes, we endeavoured to prepare the spirodiaza derivative **13**, corresponding to the oxygen analog **1**.



Results and discussion

The route envisaged for the attempted preparation of **13** involved oxidation of 2,2′-selenobis(benzamide) (**14**) to its selenoxide or haloselenonium derivatives, followed by spontaneous or base-promoted cyclization. The required selenide **14** was prepared from anthranilic acid by a variation of literature procedures (Scheme 1).[3,23] Oxidation of **14** was then investigated under a variety of conditions, but did not afford the corresponding diazaselenurane **13**. Instead, when the oxidation was performed with NCS in methanol–dichloromethane solution, we obtained a new product **15** in 81% yield (Scheme 1). Its ^{1}H and ^{13}C NMR spectra (see ESI†) clearly indicated the nonequivalence of the two aromatic rings. Moreover, three separate amide N–H signals were apparent, including one that produced a NOE with the corresponding aromatic proton ortho to the amide substituent. These observations were consistent with the unsymmetrical structure **15**, in which hindered rotation of the primary amide group renders the corresponding protons nonequivalent. Similarly, when the oxidation of selenide **14** was repeated with hydrogen peroxide instead of NCS, it afforded the crystalline product **16** in comparable yield (Scheme 1). The latter displayed nonequivalent aromatic rings in its ^{1}H and ^{13}C NMR spectra (see ESI†), as in the case of **15**. Although the preparations, hydrolyses and X-ray crystallographic structures of several azasulfonium salts have been investigated,[22c–f] their corresponding selenium analogs such as **15** and **16** have not yet been reported.



Scheme 1

Products **15** and **16** afforded suitable crystals for X-ray diffraction, which confirmed their respective structures unequivocally.‡ The ORTEP diagrams for **15** and **16** are shown in Fig. 1 and 3,

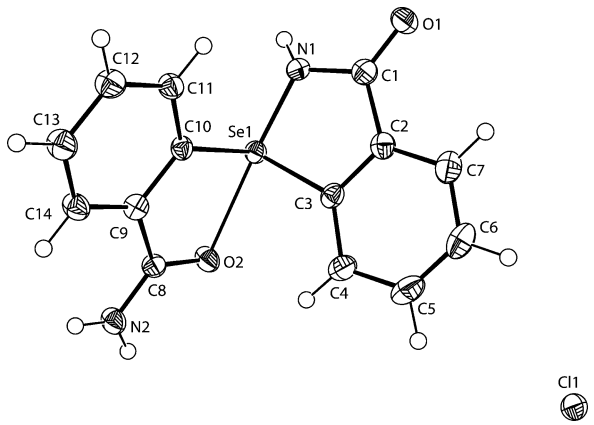


Fig. 1 ORTEP diagram of **15**, plotted with 50% probability thermal ellipsoids; H-atoms have been assigned arbitrary radii.

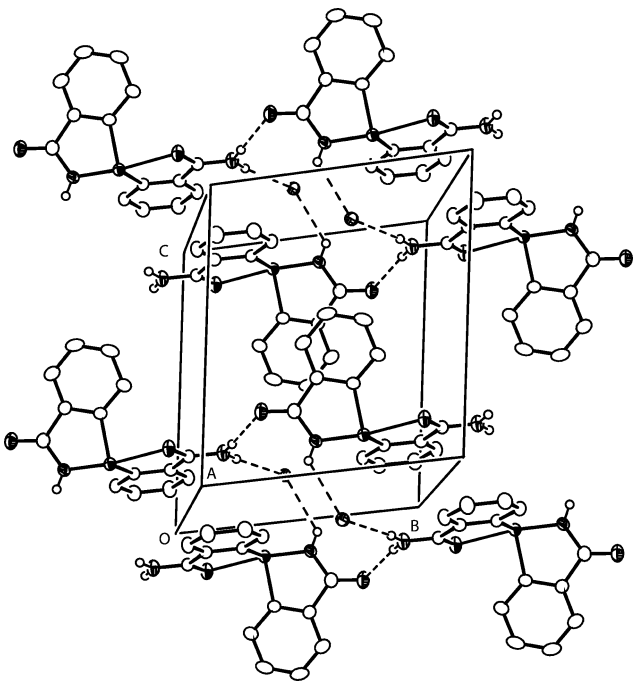


Fig. 2 Unit cell packing of **15** showing H-bonding; H-atoms not involved in H-bonds and disordered water of hydration have been ignored.

‡ CCDC reference numbers 653872 and 653873. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b710685h

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while their corresponding unit cells are displayed in Fig. 2 and 4, respectively. Additional crystallographic data for **15** and **16** are provided in the ESI.† In the case of **15**, the electronegative oxygen (O2) and nitrogen (N1) atoms occupy the apical positions of a distorted trigonal bipyramid, in which the N1(axial)–Se1–O2(axial) bond angle of 169.00(9)° is roughly linear. The equatorial plane is occupied by C3 and C10 (as well as by the selenium lone pair), and the C3–Se1–C10 bond angle is 101.42(11)°, while the N1(axial)–Se1–C3(equatorial) angle is 84.93(11)°. The Se1–O2 bond distance of 2.311(2) Å is significantly longer than the typical covalent value of 1.76 Å.[24] This indicates a weak interaction between Se1 and O2, rather than a covalent bond. On the other hand, the Se1–N1 bond length of 1.852(3) Å is consistent with a covalent Se–N single bond, which is typically 1.87 Å.[24] The torsion angles N2–C8–C9–C10, O2–C8–C9–C10, N1–C1–C2–C3 and O1–C1–C2–C3 are −177.9(3), 2.3(4), 5.2(4) and −174.8(3)°, respectively, indicating that each amide moiety is essentially coplanar with its corresponding aromatic ring. On the other hand, the aromatic rings are nearly orthogonal, as evidenced by the C3–Se1–C10 bond angle of 101.42(11)°. The unit cell of **15**, as shown in Fig. 2, indicates a network of intermolecular hydrogen bonds between NH_2 and O=C groups, as well as chloride bridges between NH and NH_2 hydrogens on adjacent molecules.

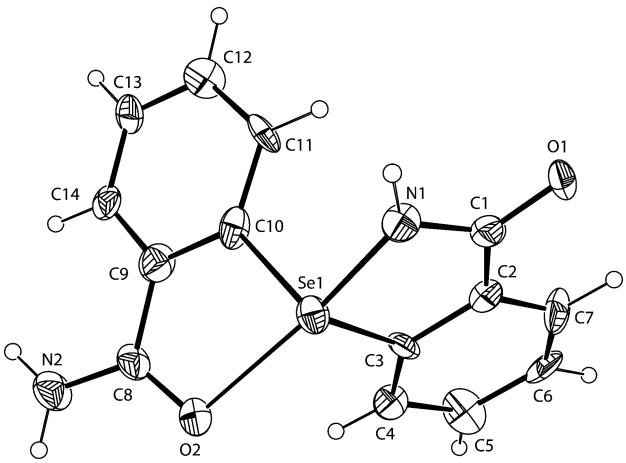


Fig. 3 ORTEP diagram of the cation of **16** plotted with 30% probability thermal ellipsoids; H-atoms have been assigned arbitrary radii.

The X-ray crystal structure of product **16** (Fig. 3) was similar to that of **15**, except that hydroxide replaced the chloride counterion. Again, the Se1–O2 bond length of 2.492(14) Å indicates a weaker interaction than a covalent bond. The unit cell shown in Fig. 4 indicates the presence of intermolecular H-bonding between NH_2 and O=C groups, as well as between both types of nitrogen and oxygen atoms of **16** and adjacent water molecules.

When azaselenonium salt **15** was treated with 30% aqueous acetic acid for 5 h at 70 °C, it underwent hydrolysis to **1**, rather than to the corresponding hydroxyselenurane **17**, or selenoxide **18** (Scheme 2). This is in contrast to the sulfur series, where the hydrolysis of **12** (R = *i*-Pr) afforded the corresponding bis[2-(*N*-isopropylcarbamoyl)phenyl] sulfoxide.[22a] While we cannot rule out **17** or **18** as intermediates in the hydrolysis of **15**, an alternative route involves imine/iminium species such as **19** and **20** (Scheme 2).

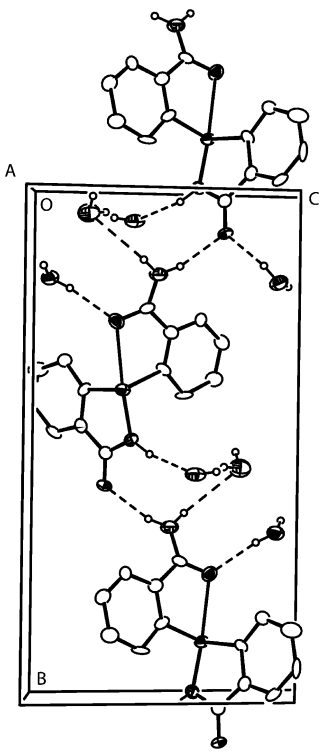
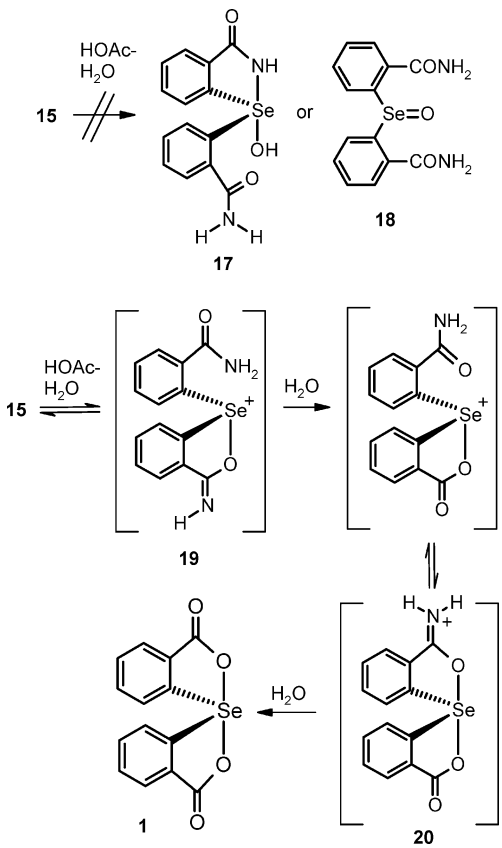
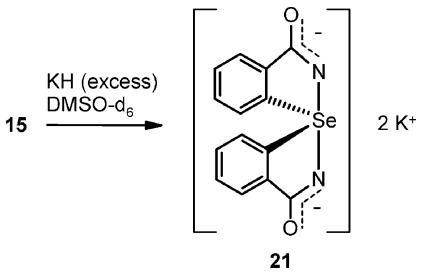


Fig. 4 Unit cell packing of **16** showing H-bonded chains of the cations extended along the *b*-axis; H-atoms not involved in H-bonds have been ignored.



Scheme 2

The azaselenonium chloride **15** was treated with an excess of potassium hydride in anhydrous DMSO-d_6 in an effort to effect ring-closure to the spirodiazaselenurane **21** (Scheme 3). The ^{1}H NMR spectrum of the product revealed only two doublets and two triplets, while the ^{13}C NMR spectrum collapsed from fourteen to seven signals (see ESI†). This indicates equivalent aromatic rings and is consistent with the structure **21**.



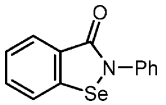
Scheme 3

The GPx-like activity of **15** was also investigated using the assay system that we had previously developed for this purpose.[20] Thus, benzyl thiol was added to a solution of 10 mol% of **15** in dichloromethane–methanol in the presence of an excess of *tert*-butyl hydroperoxide or hydrogen peroxide. The reaction was monitored by HPLC and the time required for the oxidation of 50% of the thiol to dibenzyl disulfide ($t_{1/2}$) was measured. The results (entries 5 and 6) are shown in Table 1, along with the previously determined $t_{1/2}$ values for **1**[18] (entries 1 and 2) and **8**[15] (entries 3 and 4) that are included for comparison. The $t_{1/2}$ is also given (entries 7 and 8) for ebselen (**22**),[15] a compound that has undergone considerable scrutiny as a GPx mimetic,[25] and is currently in clinical trials for the treatment of cardiovascular conditions related to oxidative stress. Under these conditions, a control reaction without any catalyst shows a $t_{1/2}$ of >300 h. The results indicate that **15** is a considerably superior catalyst to **1** and is significantly more active than ebselen (**22**) with both *tert*-butyl hydroperoxide and hydrogen peroxide. However, it is inferior in this regard to the aliphatic spirodioxyselenurane **8**. The catalytic mechanism of **15** is presumably analogous to that of **8**,[15] involving addition of the thiol to the selenium atom of **15**, followed by

Table 1 GPx-like activity of azaselenonium chloride **15** and related compounds[a]

Entry	Catalyst	$t_{1/2}$/h	Oxidant
1	**1**	113	*t*-BuOOH
2		35	H_2O_2
3	**8**	1.9	*t*-BuOOH
4		0.2	H_2O_2
5	**15**	18	*t*-BuOOH
6		2.7	H_2O_2
7	**22**	62	*t*-BuOOH
8		20	H_2O_2

[a] Reactions were performed with BnSH (0.031 M), the catalyst (0.0031 M), and either *tert*-butyl hydroperoxide (0.038 M) or H_2O_2 (0.040 M) in CH_2Cl_2–MeOH (95 : 5) at 18 °C, except for entries 5 and 6, where the solvent was CH_2Cl_2–MeOH (4 : 1).



Ebselen (**22**)

reductive elimination to afford selenide **14** and dibenzyl disulfide, and reoxidation of **14** to the catalytic azaselenonium species.

Conclusions

The oxidation of 2,2′-selenobis(benzamide) **14** with NCS or hydrogen peroxide afforded the novel unsymmetrical azaselenonium species **15** and **16**, respectively, rather than the corresponding spirodiazaselenurane **13**. The structures of the two products were confirmed by X-ray crystallography, which revealed that in each case the selenium atom is covalently bonded to the nitrogen atoms of one amido group and weakly coordinated to the carbonyl oxygen atom of the other. The NMR spectra of these compounds indicated similar unsymmetrical structures in solution. Ring-closure to the symmetrical dipotassium salt **21** was achieved by treatment with an excess of potassium hydride in DMSO-d_6 solution. While related sulfur-based structures containing secondary rather than primary amide groups have been reported,[22] the spirodiazaselenurane **21** and azaselenonium compounds **15** and **16**, are unprecedented in the selenium series. Finally, it was determined that **15** functions as an effective GPx mimetic, with superior catalytic activity to that of ebselen.

Experimental

IR Spectra were recorded on a Nicolet Nexus 470 FTIR ESP spectrometer. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker UG 300, Bruker DMX 300, or a Bruker AMX 300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz). Coupling constants *J* are given in Hz and chemical shifts are referenced to the solvent. ^{77}Se NMR spectra were acquired at 57 MHz on a Bruker AMX 300 spectrometer with diphenyl diselenide in $CDCl_3$ (δ 461.0 ppm) or selenium dioxide in D_2O (δ 1302.6 ppm) as the standard, relative to dimethyl selenide (δ 0.0 ppm). Mass spectra were obtained by electrospray ionization on a Bruker Esquire 3000 spectrometer. Elemental analyses were performed by Ms. Roxanna Smith at the University of Calgary. HPLC measurements were performed on a Waters 600 HPLC, equipped with a Novapak C_{18} 3.9 × 150 mm column and using a Waters 486 Tunable Absorbance Detector (λ 254 nm). Glassware for the kinetic experiments was rinsed with acetone and was flame-dried prior to use. Benzyl thiol was distilled prior to use and the concentrations of *tert*-butyl hydroperoxide and hydrogen peroxide were determined by iodometric analysis.

Oxidation of selenide 14 with NCS

Selenide **14**[23] (178 mg, 0.558 mmol) was dissolved in 30 mL of methanol–dichloromethane (1 : 1) and cooled in an ice-bath. NCS (150 mg, 1.12 mmol) was added in 5 mL of methanol–dichloromethane (1 : 1). The mixture was stirred at room temperature for 5 h, concentrated and the crude product was recrystallized from glacial acetic acid to give 160 mg (81%) of **15** with mp 286–287 °C (Found: C, 46.79; H, 3.03; N, 7.61. Calc. for $C_{14}H_{11}ClN_2O_2Se{\cdot}0.5H_2O$: C, 46.36; H, 3.34; N, 7.73%); ν_{max}/cm^{-1}

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(KBr) 3268, 1665, 1595, 1550, 1298, 743; δ_H (DMSO-d_6) 10.67 (1 H, br s, N–H, exchanged with D_2O), 9.77 (1 H, br s, N–H, exchanged with D_2O), 9.33 (1 H, br s, N–H, exchanged with D_2O), 8.42 (1 H, d, *J* 6.9), 8.00–7.78 (7 H, m); irradiation of the signal at δ 9.77 enhanced the signals at δ 9.33 and 8.42 by 16 and 21%, respectively, while irradiation of the signal at δ 8.42 enhanced the signal at δ 9.77 by 7%; δ_C (DMSO-d_6) 171.1 (C=O), 171.0 (C=O), 140.5, 140.0, 136.0, 135.9, 133.8, 133.4, 130.4, 130.1, 129.8, 129.2, 127.8, 126.2; δ_{Se} (DMSO-d_6) δ 653.8; *m/z* (ESI) 319 $(M - Cl)^+$.

Oxidation of selenide 14 with hydrogen peroxide

Selenide **14**[23] (208 mg, 0.652 mmol) was dissolved in 15 mL of acetone and treated with 29% hydrogen peroxide (0.67 mL, 6.7 mmol). After three days at room temperature, white crystals precipitated and were filtered to afford 173 mg (79%) of **16** with mp 263–266 °C (Found: C, 49.98; H, 3.39; N, 8.01. Calc for $C_{14}H_{12}O_3N_2Se$: C, 50.16; H, 3.61; N, 8.36%); ν_{max}/cm^{-1} (KBr) 3217, 1700, 1676, 1616, 1596, 1560, 1409, 1295, 745; δ_H (DMSO-d_6) 8.90 (1 H, br s, N–H, exchanged with D_2O), 8.47 (1 H, br s, N–H, exchanged with D_2O), 8.15 (1 H, dd, *J* 7.2, 1.5), 7.95 (1 H, d, *J* 7.2), 7.81 (1 H. d, *J* 7.2), 7.74–7.52 (5 H, m); δ_C (DMSO-d_6) 179.3 (C=O), 168.7 (C=O), 142.2, 139.0, 134.1, 133.6, 131.9, 131.7, 131.5, 130.8, 128.5, 127.4, 126.2, 124.7; δ_{Se} (DMSO-d_6) 701.7; *m/z* (ESI) 319 $(M - OH)^+$.

Preparation of the dipotassium salt of spirodiazaselenurane 21

Azaselenonium chloride **15** (7.8 mg, 0.022 mmol) was dissolved in 0.5 mL of dry DMSO-d_6 in a 5 mm NMR tube. Potassium hydride (6.3 mg, 0.16 mmol) was added to the mixture under an argon atmosphere. The reaction mixture turned yellow immediately. When kept under argon at room temperature, the solution of **21** survived unchanged for at least 12 h. δ_H (DMSO-d_6) 8.23 (2 H, d, *J* 7.2), 7.73 (2 H, d, *J* 7.2), 7.31 (2 H, t, *J* 7.2), 7.16 (2 H, t, *J* 7.2); δ_C (DMSO-d_6) 168.9 (C=O), 147.4, 137.8, 130.4, 129.5, 126.5, 124.3; δ_{Se} (DMSO-d_6) 723.1; *m/z* (ESI) 395 $(M + H)^+$, 317 $(M - 2K + H)^-$.

Acknowledgements

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