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Selenium Heterocycles

Octaselenocyclododecane**

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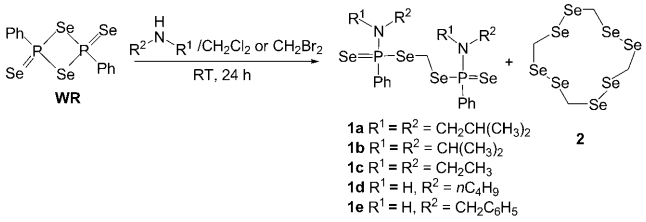
Following the discovery of selenoenzymes, selenium-containing compounds have been studied extensively because of their interesting reactivity profile[1] and potential pharmaceutical significance.[2] For example, there has been considerable interest in organoselenium compounds as reagents or intermediates in synthetic chemistry,[3] as heavy-atom versions of oligonucleotides and proteins for crystallographic study,[4–6] as human metabolites,[7] as cancer-preventative agents,[6–9] and as substrates for biomimetic studies.[10–12]

We have been engaged in studying the insertion of selenium into a range of molecules using the P-Se heterocycle Woollins reagent (**WR** in Scheme 1).[13] We[14] and others[15]



Scheme 1. Reaction of Woollins reagent with primary and secondary alkylamines in CH_2Cl_2 or CH_2Br_2.

have prepared some organic and phosphorus-containing examples of larger rings with diselenide linkages but we are not aware of simple systems like the new ring described below. Here we note that reaction of **WR** with secondary amines in the presence of CH_2Cl_2 or CH_2Br_2 proceeds to give, predictably, bis(*N*,*N*-dialkyl-*P*-phenyl)phosphonamidodiselenoates (**1**, Scheme 1). More excitingly, we also obtained the new heterocycle 1,2,4,5,7,8,10,11-octaselenacyclododecane (**2**) from this very simple reaction. **1a–e** were characterized spectroscopically and in the case of **1a** by X-ray crystallography (Figure 1). Interestingly, in the structure of **1a** the Se(2) atom resides atop the face of the central Se_2C unit with an Se(2)···Se(1A) distance of 3.880(2) Å.

The very poor solubility of **2** precluded characterization by solution-state NMR spectroscopy. However, the X-ray

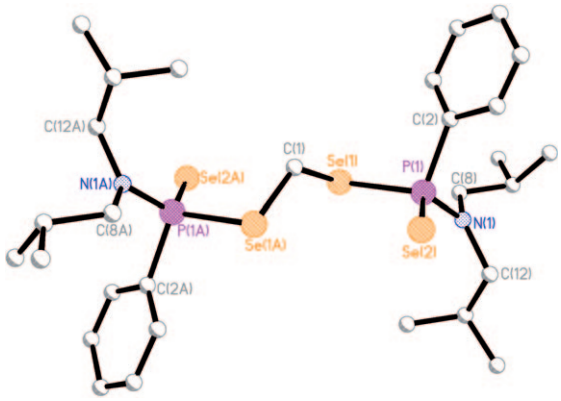


Figure 1. X-ray structure for compound **1a**; H atoms omitted for clarity. C(1) is disordered, and only one location is displayed. Selected bond lengths [Å] and angles [°]: P(1)–Se(1) 2.273(3), P(1)–Se(2) 2.058(3), C(1)–Se(1) 1.836(17); C(1)-Se(1)-P(1) 100.6(6), Se(1)-C(1)-Se(1) 123.8(10), Se(1)-P(1)-Se(2) 112.91(12).

structure reveals the 12-membered ring (Figure 2). The centrosymmetric molecule has a crown-like structure though transannular Se···Se distances [Se(1)···Se(1A) 5.401(1), Se(2)···Se(2A) 7.646(1), and Se(5)–Se(5A) 6.512(1) Å] vary considerably. As might be expected there are some intramolecular contacts [Se(1)···Se(4) 3.959(1), Se(2)···Se(4) 3.225, Se(1)···Se(4A) 3.793(1), Se(1)···Se(5 A) 3.117(1) Å] which are within the van der Waals radii. The 12-membered rings pack through Se···Se contacts along the crystallographic *a* axis [Se(5)···Se(2D) 3.566(1), Se(5)···SeE(1D) 3.543(1) Å] (Figure 3). The Raman spectrum of **2** has an intense band at 282 cm^{-1} which we assign to ν_{SeSe}.

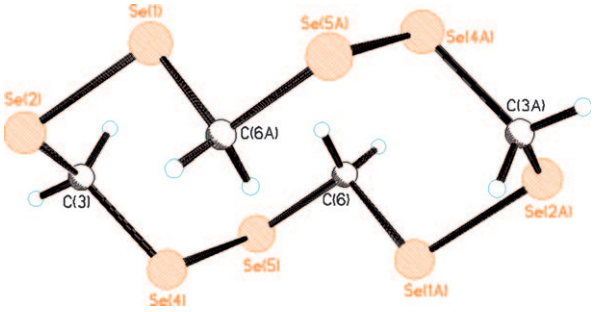


Figure 2. X-ray structure of 1,2,4,5,7,8,10,11-octaselenacyclododecane (**2**). Selected bond lengths [Å] and angles [°]: Se(1)–Se(2) 2.3162(9), Se(4)–Se(5) 2.3094(8), Se(2)–C(3) 1.931(5), Se(1)–C(6) 1.945(5), Se(5)–C(6) 1.940(5), Se(4)–C(3) 1.954(5); C(6)-Se(1)-Se(2) 102.04(16), C(3)-Se(2)-Se(1) 100.06(17), Se(2)-C(3)-Se(4) 112.2(3), C(3)-Se(4)-Se(5) 100.79(17), C(6)-Se(5)-Se(4) 99.80(16), Se(5)-C(6)-Se(1) 106.7(2).

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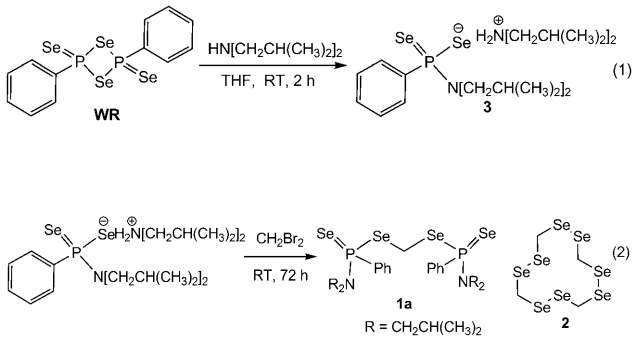
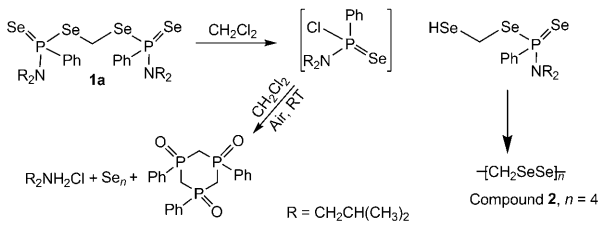
Figure 3. Intramolecular interactions in **2** showing the packing along the crystallographic *a* axis.

The formation of **2** raises some mechanistic questions and we have investigated the reaction pathway. Attempts to follow the reaction directly by ^{31}P NMR spectroscopy were hampered by the heterogeneous nature of the reaction. We did not observe any intermediates in these studies.

However, some insight could be obtained from other studies. Treatment of **WR** with diisobutylamine [Eq. (1)] gave the simple cleavage product as salt **3** in a similar fashion to the reaction of **WR** with alkoxides.[16] Treatment of **3** with dibromomethane [Eq. (2)] gave **1a** and **2** (13 and 21 % yield after work-up) indicating that **3** is probably formed in the early stage of the reaction in Scheme 1. We considered that further aminolysis of **1a**–**1e** might release $[CH_2Se_2]^{2-}$ which would couple to give **2** but the only phosphorus-containing product that we observed from treatment of **1a** with isobutylamine was **3.**



Interestingly, stirring **1a** in THF leaves it unchanged whereas in CH_2Cl_2 **2** is obtained in almost quantitative yield along with two new PSe-containing species (see Supporting Information). It does appear that **1a**–**e** are intermediates in the formation of **2** and that a polar solvent is required for the formation of **2** from **1a**. This leads us to suggest the mechanism shown in Scheme 2.



Scheme 2. Possible mechanism for the formation of **2**.

Having obtained **2** as described above, we investigated the direct synthesis. Reaction of **WR** with dichloromethane does not yield **2**, however, stirring sodium selenide with dichloromethane for 72 h at room temperature gives polymeric material along with a trace of **2**.

We studied **2** by solid-state NMR spectroscopy. The ^{1}H magic angle spinning (MAS) NMR spectrum of **2** is shown in Figure 4. Two main resonances are observed at chemical shifts of $\delta = 5.9$ and 4.6 ppm. A slight "shoulder" is also observed at

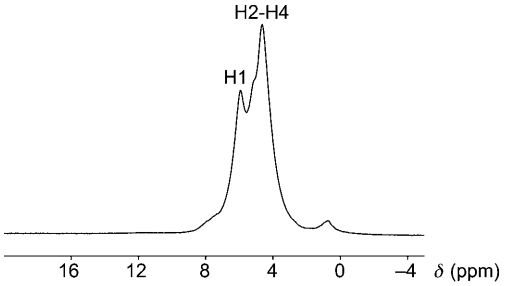


Figure 4. ^{1}H MAS NMR spectrum (14.1 T) of **2** recorded at a MAS rate of 60 kHz.

$\delta = 5.1$ ppm, indicating the presence of an unresolved resonance. A weaker intensity resonance is also observed at $\delta =$ 0.7 ppm. However, this peak is attributed to an impurity or residual solvent, as it was found to exhibit much faster longitudinal relaxation. The resonance at $\delta = 5.9$ ppm can be assigned to the H1 protons, which periodic DFT calculations on the full crystal structure predict to be shifted downfield by approximately $\delta = 2$ ppm relative to the rest of the CH_2 protons (full details of DFT calculations are given in the Supporting Information). The broader, more intense resonance at $\delta = 4.6$ ppm can be assigned to the remaining protons in the structure which have calculated chemical shifts within a range of $\delta = 0.5$ ppm.

The ^{13}C cross-polarized (CP) MAS NMR spectrum is shown in Figure 5. Two main resonances are observed at chemical shifts of $\delta = 28.4$ and 31.2 ppm, with weaker resonances at $\delta = 47.6$ ppm and between $\delta = 17$ and 24 ppm attributed to residual solvent in the sample. The observation of two resonances is consistent with the crystal structure, which contains two crystallographically distinct carbon sites. Periodic DFT calculations predict a $\Delta\delta = 4.6$ ppm difference

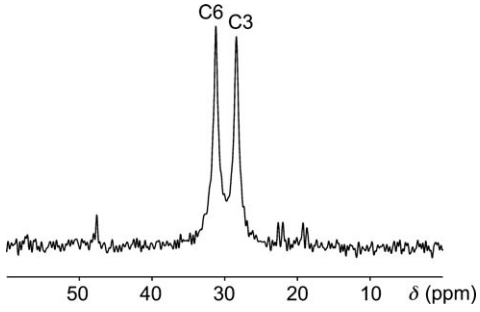


Figure 5. ^{13}C CP MAS NMR spectrum (14.1 T) of **2** recorded at a MAS rate of 12.5 kHz.

in chemical shift between the two sites, which is in relatively good agreement with the observed difference of $\Delta\delta = 2.8$ ppm. On the basis of the calculated NMR parameters, the resonance at $\delta = 28.4$ ppm can be assigned to C3 and the resonance at $\delta = 31.2$ ppm is assigned to C6.

The ^{77}Se CP MAS NMR spectrum recorded at a MAS rate of 12.5 kHz is shown in Figure 6a. In addition to the isotropic resonances, a number of spinning sidebands are observed,

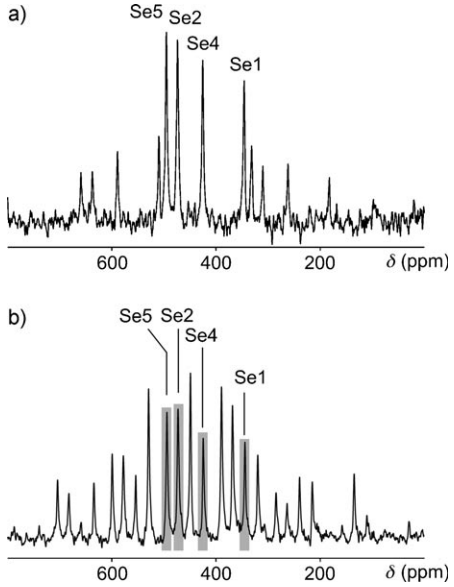


Figure 6. ^{77}Se CP MAS NMR spectra (9.4 T) of **2** recorded at MAS rates of a) 12.5 kHz and b) 8 kHz. Isotropic resonances in (b) are highlighted for clarity.

arising from the large chemical shielding anisotropy (CSA). Spinning sidebands are separated from each other by the MAS frequency and can therefore be identified by comparison with a second spectrum recorded at 8 kHz MAS, shown in Figure 6b. Here, the positions of the spinning sidebands are altered while the positions of the isotropic resonances remain unchanged. A slight difference in chemical shift of the isotropic resonances (up to $\Delta\delta = 2$ ppm) was observed between the two MAS rates; this is attributed to the temperature change induced by increased frictional heating of the sample at the higher rate (estimated to be approximately 10 K). Isotropic resonances observed at $\delta = 495.2$, 473.8, 425.4, and 345.8 ppm are assigned to Se5, Se2, Se4, and Se1, respectively, on the basis of periodic DFT calculations. CSAs were measured by lineshape analysis of the spinning sideband pattern. The magnitudes of these interactions were found to be in the range $\delta = 280$–360 ppm, which is consistent with the large CSAs typically observed for selenium nuclei and also in approximate agreement with calculated CSAs of between $\delta = 327$ and 422 ppm.

A common reaction in selenium chemistry is a simple selenium elimination reaction; e.g. RSeSeR on heating gives RSeR. We have investigated the thermal stability of **2** and surprisingly did not observe elimination of selenium.

In conclusion, we have demonstrated a straightforward synthesis of a new 12-membered C_4Se_8 heterocycle which contains four diselenide groups. The observations here suggest the possibility of a range of simple C-Se rings and polymers that have yet to be uncovered.

Experimental Section

General procedure for formation of **1a**–**e** and **2**: A mixture of dialkylamine (4.0 mmol) and Woollins reagent (1.07 g, 2.0 mmol) in dry dichloromethane (50 mL) or dibromomethane (10 mL) was stirred at room temperature for 24 h. The brown suspension disappeared and a grayish yellow suspension was formed. After filtration to remove unreacted solid, the filtrate was reduced to dryness in vacuum and the residue was extracted with dichloromethane and purified by silica gel column chromatography (eluent 1:1 hexane/dichloromethane) to give a mixture of **1a**–**e** and **2**. Compound **2**, poorly soluble crystals, could be harvested from dichloromethane solution of these mixtures three days later. After removing the compound **2**, the filtrate was dried to give pure **1a**–**e**. Characterizing data for **1a**–**e** are given in the Supporting Information.

Pale yellow crystals of **2** were obtained in 13–18% yields [18% (125 mg) from mixture with **1a**, 15% (105 mg) from **1b**, 13% (90 mg) from **1c**, 16% (110 mg) from **1d**, and 13% (92 mg) from **1e**]. M.p. 122–123°. The crystals were found to be insoluble in normal organic solvents. Selected IR (KBr): $\tilde{\nu} = 2925$(s), 2853(m), 1458(m), 1088(w), 694 cm^{-1}(w). Raman (capillary): $\tilde{\nu} = 2985$(w), 2918 (m), 1362(vw), 1350(vw), 610(w), 576(w), 557(w), 282 cm^{-1}(s). MS [EI$^+$, m/z]: 518 [$M-CH_2Se_2$]$^+$, 424 [$M-CH_2SeSeCH_2$]$^+$, 346 [$M-CH_2SeSeCH_2Se$]$^+$, 254 [$M-CH_2SeSeCH_2SeSeCH_2$]$^+$, 172 [$CH_2SeSeCH_2SeSeCH_2Se$]$^+$, 94 [$CH_2SeSeCH_2SeSeCH_2SeSe$]$^+$.

Solid-state NMR experiments were performed using Bruker Avance III spectrometers at B_0 of 14.1 T (^{1}H and ^{13}C) and 9.4 T (^{77}Se), corresponding to ^{1}H and ^{13}C Larmor frequencies of 600.2, 150.9, and 76.3 MHz, respectively. Experiments were carried out using Bruker 1.3 mm, 2.5 mm, and 4 mm probes for ^{1}H, ^{13}C, and ^{77}Se MAS NMR experiments, respectively, with MAS rates of 60 kHz (^{1}H), 12.5 kHz (^{13}C and ^{77}Se), and 8 kHz (^{77}Se). For ^{13}C and ^{77}Se, MAS NMR spectra were obtained using cross-polarization from ^{1}H, with contact pulse durations of 1 and 15 ms, respectively, and two-pulse phase modulation (TPPM) decoupling during acquisition. ^{1}H and ^{13}C MAS NMR spectra are referenced to TMS (^{1}H, ^{13}C) and $(CH_3)_2Se$ (^{77}Se).

X-ray crystal data for compounds **1a** and **2** were collected using the St Andrews Robotic diffractometer[17] (Saturn724 CCD) at 125 K with graphite monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). CCDC 794662 (**1a**) and 794663 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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