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Selenation/Thionation of α-Amino Acids: Formation and X-ray Structures of Diselenopiperazine and Dithiopiperazine and Related Compounds

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N-Phenylglycine reacts with an equivalent of 2,4-bis-(phenyl)-1,3-diselenadiphosphetane 2,4-diselenide (Woollins' reagent, WR) to generate as the major product 1,4-diphenylpiperazine-2,5-diselenone and as the minor product 1,4-diphenyl-5-selenoxopiperazin-2-one. Whereas, reacting *N*-phenylglycine with an equivalent of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent, LR) affords 1,4-diphenylpiperazine-2,5-dithione and *N*-phenyl-2-(phenylamino)ethanethioamide. 2-Phenylglycine treated with an equivalent of Woollins' reagent under identical reaction conditions leads to only the formation of 2,5-diphenylpyrazine. Six X-ray structures are reported. DFT-B3LYP calculations suggest that the planar conformation is around 2 kcal/mol less stable than the puckered conformation for the bis-seleno derivative.

Introduction

2,5-Dioxopiperazines are an important class of biological active natural peptide derivatives.[1,2] Their derivatives have been used widely in the inhibition of the cell growth cycles of mammals,[3] the inhibition of glutathione-S-transferase,[4] the inhibition of the activated factor of thrombocytes,[5] and as inhibitors of various enzymes including topoisomerases and collagenase-1.[6,7] The effect of introduction of a sulfur or selenium atom into these molecules has not been tested. Furthermore, to the best of our knowledge, the synthesis of the sulfur or selenium counterparts of 2,5-dioxopiperazines from α-amino acids has not been reported.

2,4-Bis(4-methoxylphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide, Lawesson's reagent (LR), is best known as a versatile and effective thionation reagent[8] because of its applications on the conversion of a wide variety of carbonyl into thiocarbonyl compounds and the synthesis of phosphorus- and sulfur-containing heterocycles[9] and many other reactions.[10] 2,4-Bis(phenyl)-1,3-diselenadiphosphetane 2,4-diselenide [{PhP(Se)(μ-Se)}$_2$] (Woollins' reagent, WR, the selenium counterpart of Lawesson's reagent) is becoming an efficient selenation reagent in synthetic chemistry[11] due to its relatively pleasant chemical properties and ready preparation.[12] Herein, we report the synthesis of new sulfur and selenium counterparts of 2,5-dioxopiperazines and the related compounds by the intermolecular cyclocondensation reaction of α-amino acids with Lawesson's reagent or Woollins' Reagent. Six related single-crystal X-ray structures are also provided. The X-ray structures reveal that the central piperazine ring can adopt planar or puckered conformations and DFT calculations have been performed to estimate the barriers between these two conformerations.

Results and Discussion

The synthesis of diketopiperazine-2,5-dione has previously been accomplished by intermolecular cyclization of α-halocarboxamide in a mixture of dichloromethane and 50% aqueous sodium hydroxide in the presence of strong basic ion exchange resin in good yields.[13] However, we had no success in attempts to synthesize diketopiperazine-2,5-dithiones or diketopiperazine-2,5-diselenones from α-halothiocarboxamide or α-haloselenocarboxamide.

Fortunately, treating *N*-phenylglycine with equimolar quantities of Woollins' reagent in refluxing toluene gave rise to, upon work up in air, the coupling adduct 1,4-diphenylpiperazine-2,5-diselenone (**1**) in 31% yield and a tiny amount of product 1,4-diphenyl-5-selenoxopiperazin-2-one (**2**) (Scheme 1). The result can be explained through the following two step reactions: the selenation of C=O by Woollins' reagent generates the corresponding C=Se intermediate; and subsequent cyclization of two unstable α-amino selena-acid by loss of two molecules of H_2O gives rise to the major product 1,4-diphenylpiperazine-2,5-diselenone (**1**) or subsequent cyclization of one unstable molecule of α-amino selena-acid with one moleculae of the starting *N*-phenylglycine by loss of two molecules of H_2O gives rise to the minor product 1,4-diphenyl-5-selenoxopiperazin-2-one (**2**).

Reacting *N*-phenylglycine with one molar equivalent of Lawesson's reagent under identical reaction conditions led

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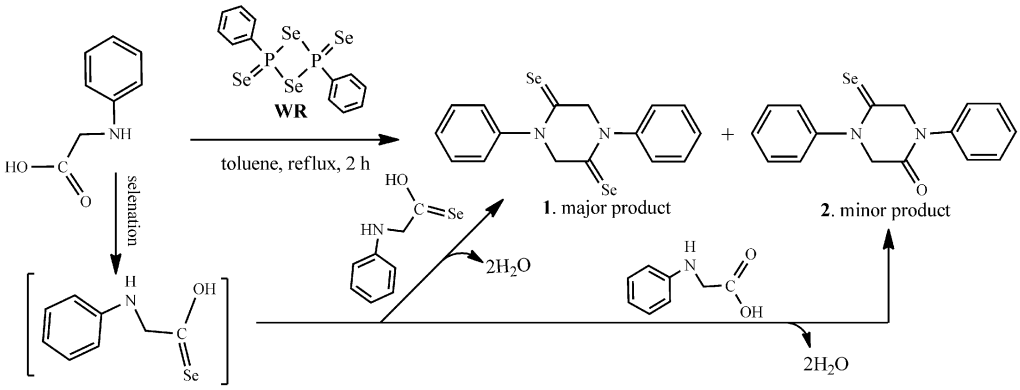
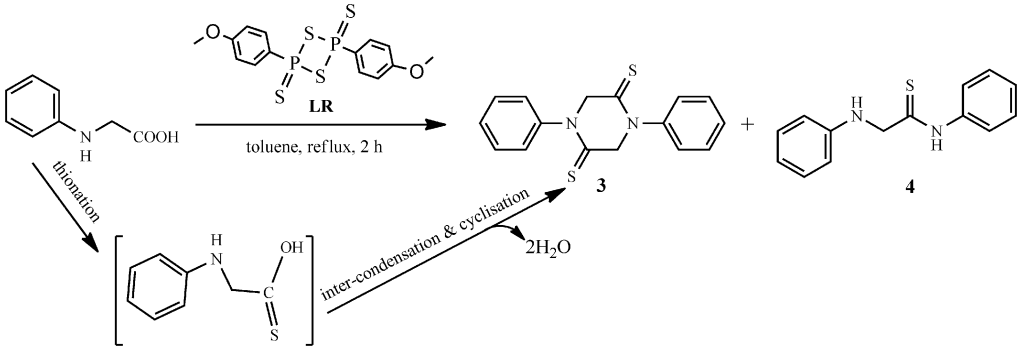


Scheme 1. Synthesis of **1** and **2** via the selenation and condensation of *N*-phenylglycine.



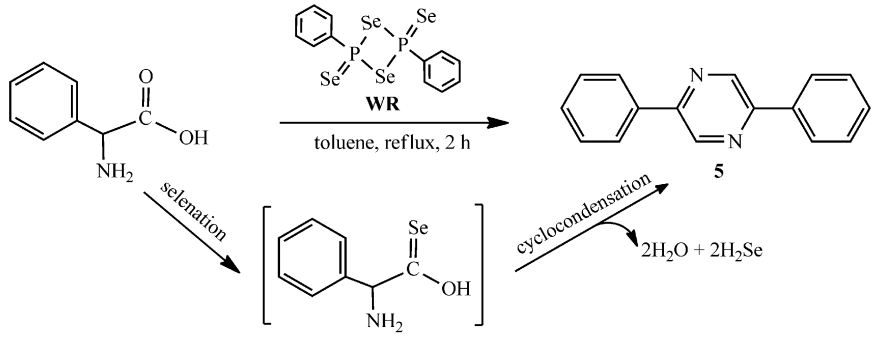
Scheme 2. Synthesis of **3** and **4** via the thionation and condensation of *N*-phenylglycine.

to two products, 1,4-diphenylpiperazine-2,5-dithione (**3**) in 17% yield and *N*-phenyl-2-(phenylamino)ethanethioamide (**4**) in 25% yield (Scheme 2). The production of 1,4-diphenylpiperazine-2,5-dithione (**3**) would follow a similar mechanism to the above selenium counterparts. However, the mechanism for the formation of *N*-phenyl-2-(phenylamino)ethanethioamide (**4**) is unclear.

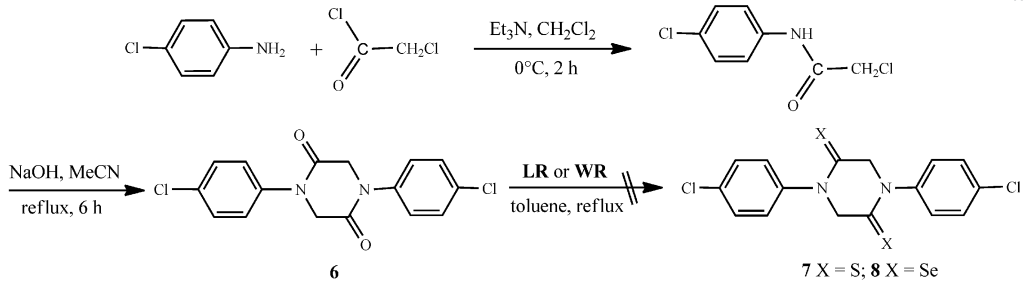
Treating 2-phenylglycine, with one molar equivalent of Woollins' reagent in refluxing toluene generated only 2,5-diphenylpyrazine (**5**) in 31% yield rather than 2,5-diselenopiperazine (Scheme 3) suggesting that the formation of **5** follows the same initial pathway as in the formation of **1**; but in the second step, not only two molecules of water but also two molecules of hydrogen selenide are eliminated.

For comparison, 1,4-bis(4-chlorophenyl)piperazine-2,5-dione (**6**) was prepared according to a modified procedure[14] from the reaction of 2-chloro-*N*-(4-chlorophenyl)-acetamide[15] and sodium hydroxide in the presence of sodium oxide in 45% yield (Scheme 4). However, attempts to convert (**6**) into the corresponding dithione (**7**) or diselenone (**8**) by thionation/selenation using Lawesson's reagent/Woollins' reagent were unsuccessful, suggesting high stability of the secondary amide.

Compounds **1**, **3** and **4** are stable in air for several months at room temperature without appreciable decomposition. All compounds are soluble in common chlorinated solvents. The microanalyses of **1**, **3** and **4** were satisfactory, and all compounds showed the anticipated $[M]^+$ or [M +



Scheme 3. Synthesis of **5** from the selenation of 2-phenylglycine.



Scheme 4. Attempt to synthesize **7** or **8** from the thiation/selenation of 1,4-bis(4-chlorophenyl)piperazine-2,5-dione (**6**).

H]$^+$ peak in their mass spectra. The chemical shift for C=Se double bond (δ_{Se} = 668.2 ppm) in **1** is significantly higher than that in primary aryl-substituted selenoamides (average value is ca. 631 ppm)[16] and considerably higher than that in methyl dimethyldiselenocarbamate (δ_{Se} = 602 ppm),[17] however, it is drastically shifted to high-field, compared to that in the similar six-membered systems such as 1-thia-3,3,5,5-tetramethyl-4-cyclohexanselenone (δ_{Se} = 2131 ppm) and selenofenchone (δ_{Se} = 1613 ppm).[18] The ^{13}C chemical shift for C=Se (δ_C = 197 ppm) in **1** is considerably lower than that in the similar five- or six-membered cyclic compounds containing C=Se double bonds (δC = 287–294 ppm)[19] and is marginally lower, compared to that in selenoamides (δ_C = 202–218 ppm).[19,20]

Recrystallization from chloromethane/hexane solution gave crystals of **1**–**3** suitable for X-ray diffraction studies (Figures 1, 2, and 3 and Table 1). **1** and **3** are the first structurally characterized 2,5-piperazinediselenone and 2,5-piperazinedithione; in both compounds the structural unit contains a crystallographic center of symmetry at the center of the six-membered N_2C_4 ring, and the eight heavy atoms N–C(X)–C–N–C(X)–C (X = Se or S) are essentially coplanar. Surprisingly, the structure of **2**, in contrast to the structures of **1** and **3**, is appreciably puckered into a boat conformation. Similar boat conformations have also been found for the parent 2,5-piperazinedione system in the gas phase[21a] and, for 1,4-bis(2-methylphenyl)-2,5-piperazinedione (**9b**), in the solid.[21b] In order to probe for the intrinsic structural preferences of the seleno derivatives, density functional theory (DFT) calculations were performed at the B3LYP level for the dione 1,4-bis(2-methylphenyl)-2,5-piperazinedione (**9a** in Scheme 5), the diselenone **1** and the mixed Se/O derivative **2**. In all cases, the planar forms in C_{2h} or C_s symmetry are transition states connecting two degenerate minima in boat conformation. The planar form is computed to be less stable than the puckered one by 1.1, 1.6 and 2.0 kcal/mol for **9a**, **2**, and **1**, respectively. This energetic difference is thus indicated to increase with the Se content, but to remain small enough in all cases to be overriden by intermolecular interactions in the solid.

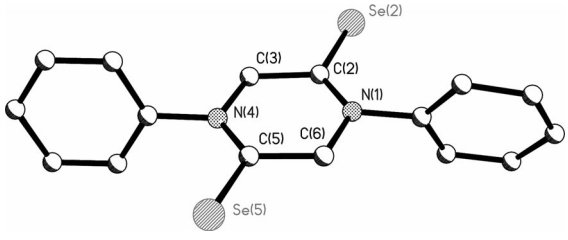


Figure 1. Single crystal X-ray structure of **1** (hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°] (esd values in parentheses): Se(2)–C(2) 1.822(7), Se(5)–C(5) 1.815(7), N(1)–C(2) 1.317(9), N(1)–C(6) 1.469(10), N(4)–C(3) 1.478(9), N(4)–C(5) 1.322(8); C(2)–N(1)–C(6) 124.6(7), C(3)–N(4)–C(5) 123.3(6), Se(2)–C(2)–N(1) 125.8(6), Se(2)–C(2)–C(3) 116.7(5), N(1)–C(2)–C(3) 117.4(7), N(4)–C(3)–C(2) 118.1(6), Se(5)–C(5)–N(4) 125.6(6), Se(5)–C(5)–C(6) 116.5(6), N(4)–C(5)–C(6) 117.9(6), N(1)–C(6)–C(5) 117.9(6).

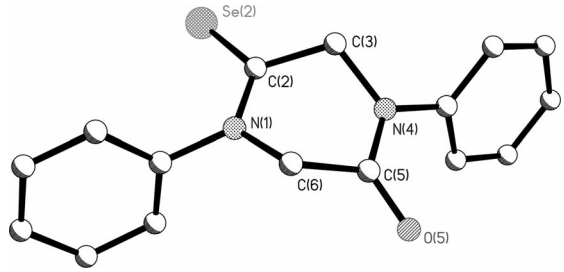


Figure 2. Single crystal X-ray structure of **2** (hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°] (esd values in parentheses): Se(2)–C(2) 1.818(4), O(5)–C(5) 1.225(5), N(1)–C(2) 1.330(5), N(1)–C(6) 1.481(5), N(4)–C(3) 1.476(5), N(4)–C(5) 1.357(6); C(2)–N(1)–C(6) 119.2(4), C(3)–N(4)–C(5) 118.4(3), Se(2)–C(2)–N(1) 126.4(3), Se(2)–C(2)–C(3) 120.3(3), N(1)–C(2)–C(3) 113.2(3), N(4)–C(3)–C(2) 111.0(4), O(5)–C(5)–N(4) 125.4(2), O(5)–C(5)–C(6) 122.1(4), N(4)–C(5)–C(6) 112.7(3), N(1)–C(6)–C(5) 111.2(3).

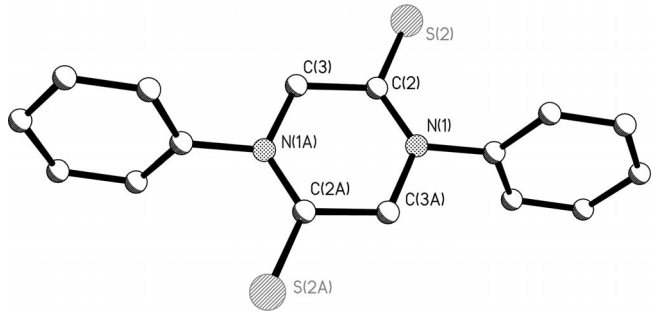
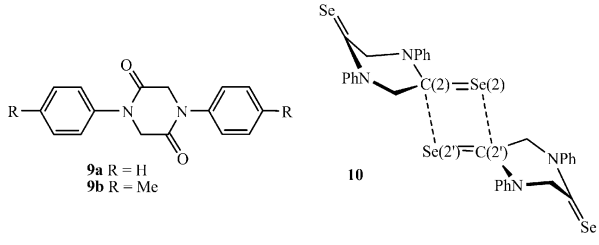


Figure 3. Single crystal X-ray structure of **3** (hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°] (esd values in parentheses): S(2)–C(2) 1.663(3), N(1)–C(2) 1.328(3), N(1)–C(3A) 1.474(3), C(2)–C(3) 1.499(5); C(2)–N(1)–C(3A) 124.8(3), S(2)–C(2)–N(1) 125.6(3), S(2)–C(2)–C(3) 116.89(18), N(1)–C(2)–C(3) 117.5(3), N(1A)–C(3)–C(2) 117.7(2).

Table 1. Details of the X-ray data collections and refinements for **1**, **2** and **3**.

	1	**2**	**3**
Formula	$C_{16}H_{14}N_2Se_2$	$C_{16}H_{14}N_2OSe$	$C_{16}H_{14}N_2S_2$
M	392.22	329.26	298.42
Crystal size /mm; crystal system	$0.3\times0.15\times0.03$; triclinic	$0.09\times0.09\times0.03$; triclinic	$0.09\times0.09\times0.06$; monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a /Å	7.053(4)	4.9903(9)	5.5306(15)
b /Å	9.998(5)	11.6672(16)	21.964(5)
c /Å	11.277(6)	12.945(2)	6.2566(17)
α	107.697(14)	70.153(14)	90
β	92.283(4)	82.324(16)	111.047(6)
γ	103.980(14)	78.543(17)	90
U /A^3	729.6(7)	693.01(19)	709.3(3)
Z	2	2	2
d /gcm^{-3}	1.785	1.578	1.379
Reflections collected	7507	7201	4127
Independent reflections	2517	2379	1421
R_{int}	0.055	0.051	0.049
R1; *wR2* [$I>2\sigma(I)$]	0.0608; 0.1140	0.0443; 0.0883	0.0603; 0.1115



Scheme 5. Targets for DFT computations.

To probe for such intermolecular interactions, a simple dimer of **1** was optimised imposing *Ci* symmetry and fixing the nonbonded C(2)···Se(2′) and C(2′)···Se(2) distances to the value observed in the solid (3.717 Å), see structure **10** in Scheme 5. A significant driving force for this dimerisation is predicted, ΔE = –21.6 kcal/mol, two thirds of which are due to dispersion. The piperazine moieties optimise to the same boat conformation as in monomeric **1**. Interestingly, enforcing a planar conformation in this dimer (by fixing the necessary dihedral angles in the C_4N_2 ring to zero and optimising all other parameters) costs only 1.0 kcal/mol per monomer, i.e. half the amount as in pristine **1**. Additional interactions in the fully periodic crystal may further reduce this value, ultimately producing the observed planar strusture.

The molecular structure of **4** (Figure 4 and Table 2) reveals an intramolecular hydrogen bonding interaction between the sulfur atom in C=S double bond and the H atom of the amine nitrogen leading to a polymeric structure. Within the hydrogen bonded pairs the S(1)···H(3N) distance of 2.704 Å with N(3)–H(3N)···S(1) angle of 170° is considerably bigger than that in primary selenoamides [H···Se 2.527(7) and 2.535(8) Å; N–H···Se 164(3) and 165(4)°].[20] The C=S distance 1.673(9) Å is slightly shorter that in *N*-thioamide thiosemicarbazone derivatives [1.692(2) and 1.694(2) Å],[21] while the shortness of the C(1)–N(1) length 1.336(11) Å, compared to other N(1)–C(9) [1.427(11) Å], N(3)–C(2) [1.439(11) Å] and N(3)–C(3) [1.403(11) Å] single bonds, suggests some multiple bond character. The geometry in C(1) adopts a highly distorted tetrahedral with angles of S(1)–C(1)–N(1) [129.0(7) Å] and S(1)–C(1)–C(2) [118.0(6) Å].

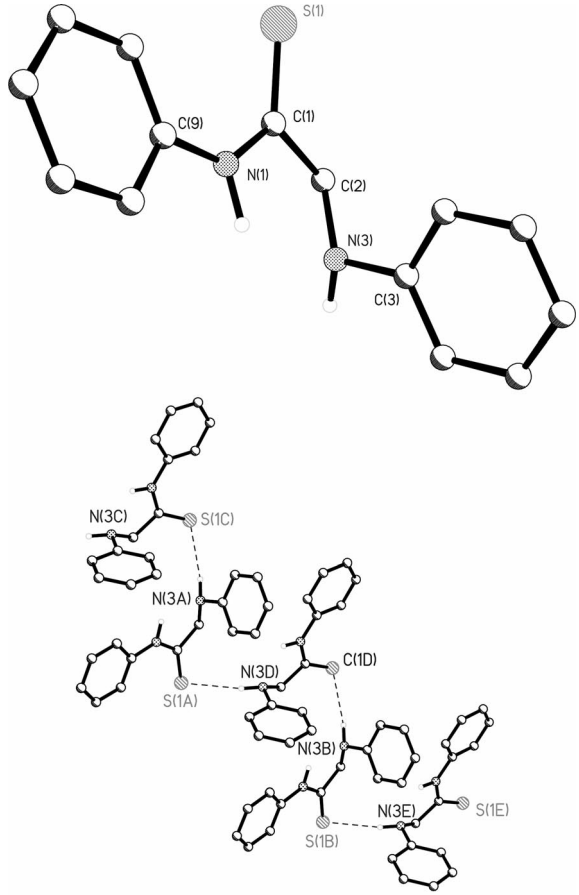


Figure 4. Top: Single crystal X-ray structure of **4** (hydrogen atoms on carbon atoms omitted for clarity). Bottom: hydrogen bonding interaction leading to chains of polymer. Selected bond lengths [Å] and angles [°] (esd values in parentheses): S(1)–C(1) 1.673(9), N(1)–C(1) 1.336(11), N(1)–C(9) 1.427(11), N(3)–C(2) 1.439(11), N(3)–C(3) 1.403(11), C(1)–C(2) 1.531(12); C(1)–N(1)–C(9) 133.1(7), S(1)–C(1)–N(1) 129.0(7), N(1)–C(1)–C(2) 113.0(7), C(2)–N(3)–C(3) 119.1(6), S(1)–C(1)–C(2) 118.0(6), N(3)–C(2)–C(1) 113.2(7).

Table 2. Details of the X-ray data collections and refinements for **4**, **5** and **6**.

	4	**5**	**6**
Formula	$C_{14}H_{14}N_2S$	$C_{16}H_{12}N_2$	$C_{16}H_{12}Cl_2N_2O_2$
M	242.34	232.28	335.19
Crystal size /mm; crystal system	0.15 × 0.09 × 0.03; monoclinic	0.09 × 0.09 × 0.09; monoclinic	0.21 × 0.12 × 0.12; orthorhombic
Space group	$P2_1/n$	$P2_1/c$	*Cmca*
a /Å	11.118(5)	13.391(7)	6.754(8)
b /Å	11.604(5)	5.727(3)	15.116(17)
c /Å	9.640(4)	7.530(4)	14.086(15)
α	90	90	90
β	95.828(11)	93.652(15)	90
γ	90	90	90
U /A^3	1237.3(9)	576.3(5)	1438(3)
Z	4	2	4
d /gcm^{-3}	1.301	1.339	1.548
Reflections collected	6942	3460	2092
Independent reflections	2158	1000	672
R_{int}	0.0136	0.065	0.046
R1; *wR2* [$I > 2\sigma(I)$]	0.1745; 0.2468	0.0851; 0.1795	0.0760; 0.1633

The crystal structure of **5** (Figure 5 and Table 2) reveals a similar conformational motif to **1** and **3**, though the C–N bond lengths within the C_4N_2 ring are significantly shorter in **5**. The structure is built around a central six-membered ring with two phenyl ring wings. The six-membered C_4N_2 ring is essentially planar, the dihedral angle between the central plane and two phenyl rings is 21°. The N(1)–C(2) and N(1A)–C(2A) distances are identical since they are symmetry related [1.339(3) Å]. The shortness of the C–N [N(1)–C(3A) 1.337(4) Å] and C–C [C(2)–C(3) 1.396(4) Å] suggests delocalisation in the six-membered C_4N_2 ring.

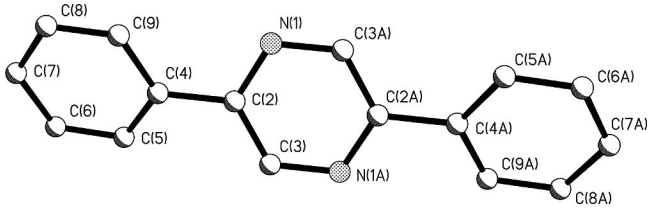


Figure 5. Single crystal X-ray structure of **5** (hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°] (esd values in parentheses): N(1)–C(2) 1.339(3), N(1)–C(3A) 1.337(4), C(2)–C(3) 1.396(4); C(2)–N(1)–C(3A) 117.7(2), N(1)–C(2)–C(3) 119.7(2), N(1A)–C(3)–C(2) 122.6(2).

Compound **6** was first synthesized here. Previously, four similar derivatives of *N*-substituted phenyl-2,5-piperazinedione, 1,4-bis(4-methoxyphenyl)-2,5-piperazinedione, 1,4-bis(2-methylphenyl)-2,5-piperazinedione, 1,4-bis(1-naphthyl)-2,5-piperazinedione, and 1,4-bis(2-methoxyphenyl)-2,5-piperazinedione have been synthesized by the cyclocondensation reaction of two molecules of the corresponding *N*-substituted chloroacetamides in acetone solution under sodium carbonate basic condition with potassium iodide used as a catalyst.[21b,23–25] Compound **6** is soluble in DMSO rather than in common chlorinated solvents. Its microanalysis was satisfactory, and showed the anticipated $[M + H]^+$ peak in its mass spectrum. The crystal structure of **6** (Figure 6 and Table 2) consists of discrete $C_{16}H_{12}Cl_2N_2O_2$ unit. The structure reveals a crystallographically imposed symmetry centre at the centre of the piperazinedione ring and the central six-membered ring C_4N_2 is essentially planar with two wing phenyl rings being also essentially coplanar with a N(1)–N(1A) axial. With the sterically hindered effect of the *p*-Cl atom attached to the phenyl ring causes the whole molecule being not coplanar. The dihedral angle between the entre ring and each of the two phenyl rings is 90.0°, significantly broader than that (74.7°) in 1,4-bis(2-

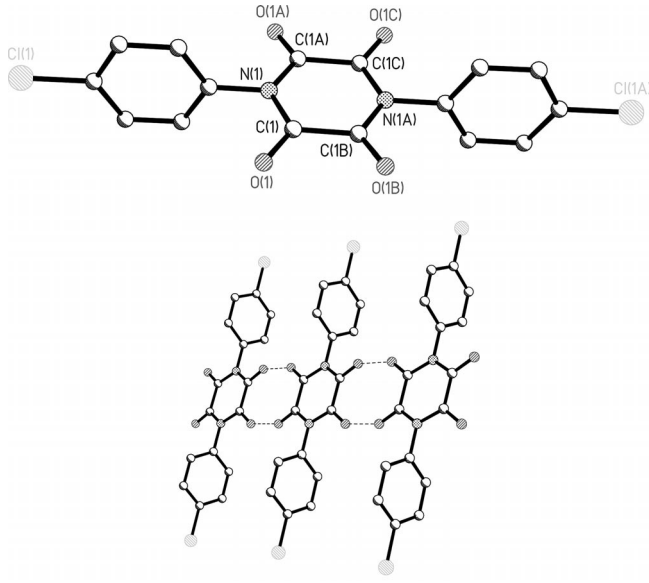


Figure 6. Single crystal X-ray structure of **6** (hydrogen atoms omitted for clarity). Upper diagram, single molecular structure with oxygen atoms are at 50% occupancy; lower diagram, interaction forming polymeric structure with oxygen atoms are at 50% occupancy. Selected bond lengths [Å] and angles [°] (esd values in parentheses): O(1)–C(1) 1.233(7), N(1)–C(1) 1.404(4), N(1)–C(1A) 1.404(4), C(1), C(1B) 1.528(5); C(1)–N(1)–C(1A) 126.0(3), O(1)–C(1)–N(1) 122.9(4), O(1)–C(1)–C(1B) 120.0(4), N(1)–C(1)–C(1B) 117.0(3).

methoxyphenyl)-2,5-piperazinedione.[25] All bond lengths and angles are within normal ranges. In addition, the distance of C=O double bonds [1.233(7) Å] in **6** are comparable with those [1.223–1.228 Å] in related compounds.[21b,22–25]

Conclusions

We have developed new methods to synthesize 1,4-diphenylpiperazine-2,5-dithione and 1,4-diphenylpiperazine-2,5-diselenone via the thionation or selenation of α-amino acids. The structures of all new compounds have been elucidated by using ^{1}H, ^{31}P, ^{77}Se NMR spectroscopy and microanalysis in conjunction with single-crystal X-ray crystallography. The diselenone shows an unusual planar structure of the piperazine moiety in the crystal, which, according to DFT computations, is probably due to intermolecular interactions in the solid.

Experimental Section

General: Unless otherwise stated, all reactions were carried out under on oxygen free nitrogen atmosphere using pre-dried solvents and standard Schlenk techniques, subsequent chromatographic and work up procedures were performed in air. ^{1}H (270 MHz), ^{13}C (67.9 MHz), $^{31}P\{^{1}H\}$ (109 MHz) and $^{77}Se\text{-}\{^{1}H\}$ (51.4 MHz referenced to external Me_2Se) NMR spectra were recorded at 25 °C (unless stated otherwise) on a JEOL GSX 270. IR spectra were recorded as KBr pellets in the range of 4000–250 cm^{-1} on a Perkin–Elmer 2000 FTIR/Raman spectrometer. Microanalysis was performed by the University of St-Andrews microanalysis service. Mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea and the University of St Andrews Mass Spectrometry Service. X-ray crystal data for compounds **1**–**6** were collected using the St Andrews Robotic diffractometer (Saturn724 CCD) at 125 K with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å).[26–28] Intensity data were collected using ω steps accumulating area detector images spanning at least a hemisphere of reciprocal space. All data were corrected for Lorentz polarization effects. Absorption effects were corrected on the basis of multiple equivalent reflections or by semi-empirical methods. Structures were solved by direct methods and refined by full-matrix least-squares against F^2 by using the program SHELXTL.[29,30] Hydrogen atoms were assigned riding isotropic displacement parameters and constrained to idealized geometries.

CCDC-782915 (for **1**), -782196 (for **2**), -78197 (for **3**), -78198 (for **4**), -78199 (for **5**) and -782920 (for **6**) 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.

Synthesis of Compounds 1 and 2: A toluene solution of *N*-phenylglycine (0.31 g, 2.0 mmol) and Woollins' reagent (0.54 g, 1.0 mmol) was refluxed for 7 h. The red suspension disappeared and pale brown solution was formed along with small amount of elemental selenium. Upon cooling to room temperature and removing solvent the residue was purified by silica gel column (eluented by 1:4 ethyl acetate/dichloromethane) to give the major product, 1,4-diphenylpiperazine-2,5-diselenone (**1**) and a tiny amount of 1,4-diphenyl-5-selenoxopiperazin-2-one (**2**) that was found during crystallization from dichloromethane solution to hexane under aerobic condition. No full characterisation is given due to lack of substance.

1,4-Diphenylpiperazine-2,5-diselenone (1): Pale yellow solid (0.12 g), 31% yield. IR (KBr, selected data): $\tilde{\nu}$ = 3045 (w), 2920 (w), 2849 (w), 1686 (m), 1595 (m), 1531 (vs), 1490 (m), 1316 (m), 1258 (m), 1105 (s), 1027 (m), 754 (m), 692 (s), 553 (m) cm^{-1}. ^{1}H NMR (CD_2Cl_2): δ = 7.53–6.64 (m, 10 H, Ar-H), 3.08 (s, 4 H, CH_2) ppm. ^{13}C NMR (CD_2Cl_2): δ = 197.4 (C=Se), 145.8 (Ar-C), 130.0 (Ar-C), 129.4 (Ar-C), 125.9 (Ar-C), 58.4 (C-N) ppm. ^{77}Se NMR (CD_2Cl_2): δ = 68.2 ppm. Mass spectrum (EI^+, *m*/*z*), 394 $[M]^+$. $C_{16}H_{14}N_2Se_2$ (392.22): calcd. C 49.00, H 3.60, N 7.14; found C 48.94, H 3.86, N 7.47.

Synthesis of Compounds 3 and 4: A mixture of *N*-phenylglycine (0.31 g, 2.0 mmol) and Lawesson's reagent (0.41 g, 1.0 mmol) in 30 mL of dry toluene was refluxed for 7 h. The white suspension disappeared and pale grey solution was formed. Upon cooling to room temperature and removing solvent the residue was purified by silica gel column (eluented by dichloromethane) to afford **3** and **4**.

1,4-Diphenylpiperazine-2,5-dithione (3): Yellow solid (0.05 g), 17% yield. IR (KBr, selected data): $\tilde{\nu}$ = 3062 (w), 2922 (w), 1706 (m), 1595 (m), 1515 (vs), 1452 (m), 1410 (m), 1319 (s), 1268 (s), 1144 (vs), 1072 (m), 760 (m), 718 (m), 692 (s), 628 (s) cm^{-1}. ^{1}H NMR (CD_2Cl_2): δ = 7.52 (m, 4 H, Ar-H), 7.44 (m, 2 H, Ar-H), 7.39 (m, 4 H, Ar-H), 5.02 (s, 4 H, CH_2) ppm. ^{13}C NMR (CD_2Cl_2): δ = 191.5 (C=S), 143.3 (Ar-C), 129.8 (Ar-C), 128.9 (Ar-C), 126.2 (Ar-C), 65.6 (C-N) ppm. Mass spectrum (CI^+, *m*/*z*), 299 $[M + H]^+$. $C_{16}H_{14}N_2S_2$ (298.43): calcd. C 64.39, H 4.73, N 9.39; found C 64.21, H 4.56, N 9.47.

***N*-Phenyl-2-(phenylamino)ethanethioamide (4):** Grey solid (0.06 g), 25% yield. IR (KBr, selected data): $\tilde{\nu}$ = 1565 (m), 1525 (s), 1452 (m), 1415 (m), 1320 (m), 1268 (m), 1144 (s), 1082 (m), 760 (m), 720 (m), 620 (m) cm^{-1}. ^{1}H NMR (CD_2Cl_2): δ = 10.32 (s, 1 H, N-H), 7.76–7.19 (m, 10 H, Ar-H), 6.84 [t, *J*(H,H) = 7.4 Hz, 1 H, N-H], 5.01 [d, *J*(H,H) = 7.4 Hz, 2 H, CH_2] ppm. ^{13}C NMR (CD_2Cl_2): δ = 191.5 (C=S), 147.0 (Ar-C), 143.3 (Ar-C), 129.9 (Ar-C), 129.7 (Ar-C), 128.6 (Ar-C), 126.8 (Ar-C), 126.2 (Ar-C), 123.2 (Ar-C), 65.7 (C-N) ppm. Mass spectrum (CI^+, *m*/*z*), 243 $[M + H]^+$. $C_{14}H_{14}N_2S$ (242.34): calcd. C 69.39, H 5.82, N 11.56; found C 69.70, H 5.66, N 11.47.

2,5-Diphenylpyrazine (5): A suspension of 2-phenylglycine (0.302 g, 2.9 mmol) and Woollins' reagent (0.54 g, 1.0 mmol) in 20 mL of toluene was refluxed for 7 h. Upon cooling to room temperature and removing solvent the residue was purified by silica gel column (eluented by 1:4 ethyl acetate/dichloromethane) to afford **5**. A white solid (0.073 g) in 31% yield. IR (KBr, selected data): $\tilde{\nu}$ = 1565 (m), 1505 (s), 1352 (m), 1319 (s), 1268 (m), 1172 (m), 769 (m), 620 (m) cm^{-1}. ^{1}H NMR (CD_2Cl_2): δ = 9.10 (s, 2 H, Pyr-H), 8.08–7.14 (m, 10 H, Ar-H) ppm. ^{13}C NMR (CD_2Cl_2): δ = 150.6 (Pyr-C), 148.3 (Pyr-C), 141.2 (Ar-C), 129.1 (Ar-C), 128.6 (Ar-C), 126.8 (Ar-C) ppm. Mass spectrum (CI^+, *m*/*z*), 233 $[M + H]^+$. $C_{16}H_{12}N_2$ (232.28): calcd. C 82.73, H 5.21, N 12.06; found C 82.09, H 6.16, N 12.07.

1,4-Bis(4-chlorophenyl)piperazine-2,5-dione (6): A mixture of 2-chloro-*N*-(4-chlorophenyl)acetamide (0.41 g, 2.0 mmol) and sodium hydroxide (0.18 g, 4.5 mmol) in 30 mL of dry acetonitrile was refluxed for 6 h. A white resulting suspension was formed. Upon cooling to room temperature and removing the solvent the residue was extracted by the mixture of water/ethyl acetate (30/30 mL). The organic layer was washed three times with water (30 mL × 3) and was dried with $MgSO_4$ overnight. The organic residue was purified by silica gel column (eluented by dichloromethane) to give **6**. A

white solid (0.15 g) in 45% yield. IR (KBr, selected data): $\tilde{\nu}$ = 1666 (s), 1488 (s), 1451 (m), 1321 (m), 1260 (m), 1144 (m), 1087 (m), 812 (s), 522 (m), 418 (m) cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 7.51 [d, J(H,H) = 8.8 Hz, 4 H, Ar-H], 7.46 [d, J(H,H) = 8.8 Hz, 4 H, Ar-H], 4.52 (s, 4 H, CH_2) ppm. ^{13}C NMR ([D_6]DMSO): δ = 164.6 (C=O), 139.4 (Ar-C), 131.4 (Ar-C), 129.4 (Ar-C), 127.5 (Ar-C), 53.0 (CH_2) ppm. Mass spectrum (CI^+, m/z), 335 $[M + H]^+$, 337 $[M + H]^+$. $C_{16}H_{12}Cl_2N_2O_2$ (335.18): calcd. C 57.33, H 3.61, N 8.36; found C 57.25, H 3.76, N 8.47.

Computational Details: Geometries were fully optimised in the gas phase at the B3LYP level[31] using Curtis and Binning's 962(d) basis on Se,[32] standard 6-311+G(d) basis on the $C_4N_2H_4$ core, and 6-31G(d) on the Ph rings. The nature of the stationary points was verified by calculation of the harmonic frequencies, which were also used to calculate zero-point corrections. Dispersion energies were evaluated through the empirical Scheme proposed by Grimme et al. (denoted B3LYP-D3),[33] employing the B3LYP optimised geometries. Energies are reported at the B3LYP-D3+ZPE(B3LYP) level, except for the constrained dimers, where no zero-point energies have been computed (energies are reported at the B3LYP-D3 level). The computations were performed using the Gaussian 03 suite of programs.[34]

Supporting Information (see footnote on the first page of this article): For additional tabular and graphical material on parent and phenyl diketopiperazine derivatives.

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