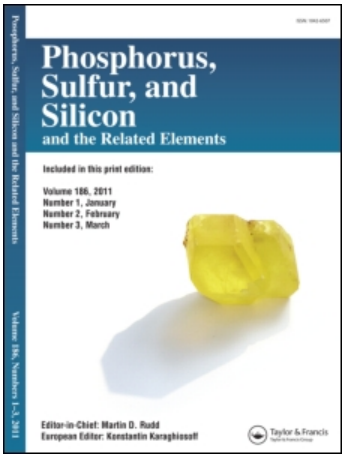

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DIRECT OBSERVATION OF INTRAMOLECULAR INTERACTION BETWEEN A DIVALENT SELENIUM AND A *TERTIARY* AMINE BY MEANS OF SINGLE CRYSTAL X-RAY ANALYSIS AND NMR SPECTROSCOPY

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Abstract Intramolecular interaction between a divalent selenium and a *tertiary* amino moiety has been observed in the solid state for 2,2'-diselenobis(N-cyclohexyl-N-methylbenzyl amine) (1). A similar interaction between an electrophilic selenium and a *tertiary* amine has also been observed in solution for the corresponding selenenyl bromide (6).

INTRODUCTION

The importance of selenium has been recognized in the biological processes involving glutathione peroxidase which catalyzes the reduction of superoxide and hydroperoxide that are detrimental to organisms.[1] At the active site of the enzyme the selenium moiety, which plays an essential role on the enzyme activity, is repeatedly subjected to a catalytic cycle involving the oxidation with hydroperoxide and the reduction with glutathione. Recently some organoselenium compounds have been reported to have similar activities to those of glutathione peroxidase, although their activities were much lower than those of the enzyme.[2] The most successful one, which exhibited about 0.001 activity of the enzyme, was 2,2'-diselenobis[(pyrrolidin-1-ylmethyl)benzene] bis(hydrochloride):[3] It was suggested that the *tertiary* amine at the *ortho*-position of the selenium served as a key ligand to the electrophilic selenium which was produced by oxidative cleavage of the Se-Se bond by hydroperoxide. We report here experimental evidence for novel intramolecular interaction between a divalent selenium and a *tertiary* amine by using 2,2'-diselenobis(N-cyclohexyl-N-methylbenzylamine) (1) and the corresponding selenenyl bromide(6) as model compounds.

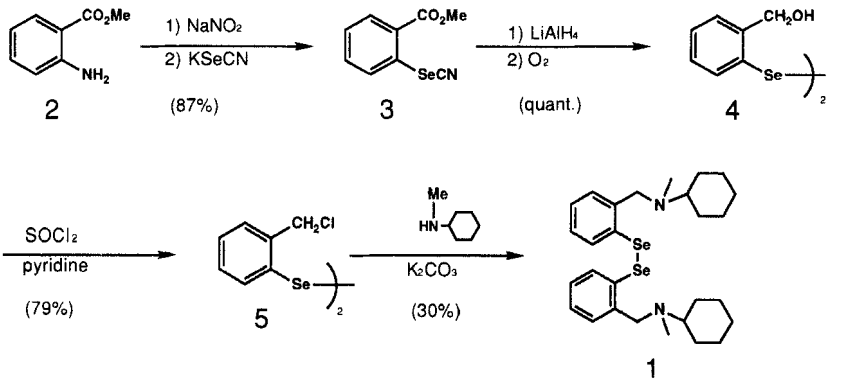
RESULTS AND DISCUSSION

The design of the model compounds required some consideration because it is

usually difficult to detect the intramolecular interaction between the selenium and the *tertiary* amine (Se···N) by means of spectroscopic methods. We thought that *ortho*-selenobenzylamino derivatives possessing two different alkyl groups on the nitrogen would exhibit discrete NMR signals of two benzylic protons, when the *tertiary* amine interacts with the selenium, due to slow inversion at the nitrogen atom within the NMR time scale. The model compound **1** possessing methyl and cyclohexyl groups on the benzylamino nitrogen provided single crystals suitable for X-ray analysis.

Synthesis of **1** starts with methyl anthranilate(**2**) as shown in scheme 1. X-ray analysis was performed for a single crystal of **1**, which was obtained by recrystallization from acetonitrile.

Molecular structure of **1** in the solid state is shown in figure 1 and selected bonding parameters are listed in Table 1. Atomic distances of Se1···N9 and Se21··· N29 are 2.78 and 2.96 Å respectively, both of which are significantly shorter than the sum of the corresponding van der Waals radii. Bond angles for Se21—Se1···N9 (172 °) and Se1—Se21···N29 (165°) indicate approximately linear alignment of the four atoms (N9···Se1—Se21···N29). The above structural parameters as well as bond angles around N9 and N29 clearly show that the intramolecular interaction between the selenium and the *tertiary* amine do exist for **1** in the solid state and that the interaction is caused by the coordination of the non-bonding orbital of the nitrogen to the divalent selenium. The results of the X-ray analysis of **1** are in good agreement with the previous suggestion that nucleophiles approach selenium in the selenide plane along the σ^* orbital on the back side of one of the selenide bonds.[4] Conformation of the five-membered rings, Se1—C2—C7—C8—N9 and Se21—C22—C27—C28—N29, is the envelope form in which the nitrogen is placed out of the plane containing the other four atoms. The distortion of the ring may be attenuated by the shortening of the atomic distance between the selenium and the nitrogen, in other words by the increase of the intramolecular Se···N interaction. ^{1}H-NMR spectrum of **1** in



Scheme 1

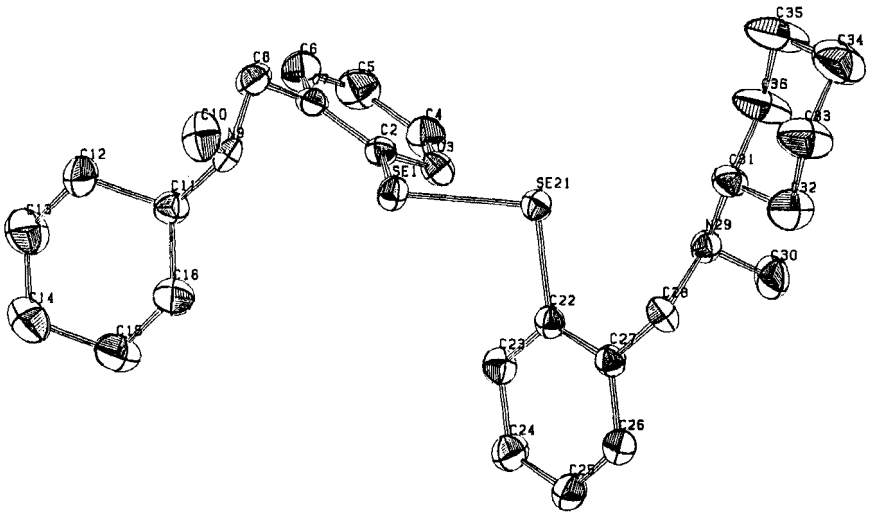
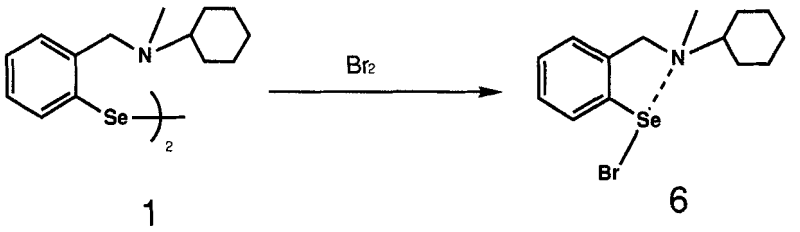


Figure 1. Molecular structure of 1.

Table 1. Selected bonding parameters of 1.

atomic distances (Å)			
Se1—Se21	2.362(1)		
Se1—C2	1.94(1)	Se21—C22	1.94(1)
Se1···N9	2.78(1)	Se21···N29	2.96(1)
C8—N9	1.47(2)	C28—N29	1.47(2)
N9—C10	1.50(1)	N29—C30	1.47(1)
N9—C11	1.48(1)	N29—C31	1.49(1)
bond angles (deg)			
Se21—Se1—C2	101.8(2)	Se1—Se21—C22	100.6(2)
Se21—Se1···N9	172(1)	Se1—Se21···N29	165(1)
C2—Se1···N9	75(1)	C22—Se21···N29	73(1)
Se1···N9—C8	87(1)	Se21···N29—C28	82(1)
Se1···N9—C10	104(1)	Se21···N29—C30	125(1)
Se1···N9—C11	121(1)	Se21···N29—C31	105(1)
C8—N9—C10	112(1)	C28—N29—C30	111(1)
C8—N9—C11	114(1)	C28—N29—C31	111(1)
C10—N9—C11	115(1)	C30—N29—C31	117(1)
dihedral angles (deg)			
C2—Se1—Se21—C22	102(1)		
Se21—Se1—C2—C7	151(1)	Se1—Se21—C22—C27	143(1)
Se1—C2—C7—C8	3(1)	Se21—C22—C27—C28	1(1)
C2—C7—C8—N9	52(1)	C22—C27—C28—N29	57(1)



1 6

Scheme 2

chloroform-d_1 at room temperature, however, did not suggest any evidence for the intramolecular Se···N interaction. The signal due to benzylic protons was singlet (δ 3.72), which was not splitted into AB quartet even at -100℃ at 90MHz. The results imply that the intramolecular Se···N interaction is not dominant for 1 in solution presumably because of poor electrophilicity of the divalent selenium.

We therefore decided to oxidize 1 by equimolar bromine and synthesized selenenyl bromide 6 (scheme2). ^{1}H-NMR signals due to benzylic protons of 6 appeared as AB quartet (δ 4.15, 3.83, J=13.6Hz), which strongly suggested the existence of the intramolecular Se···N interaction. About 150ppm downfield shift of ^{77}Se-NMR for 6 (1019.4ppm) relative to benzeneselenenyl bromide (869.0ppm)[5] also indicated the strong Se···N interaction.[6] To determine the magnitude of the observed interaction, we carried out variable temperature ^{1}H-NMR experiment on 6. The signals due to the benzylic protons coalesced above 80℃ at 90MHz, but 6 decomposed upon prolonged heating resulting in significant complication of the NMR spectrum. It was therefore suggested that a strong chemical bonding might be formed between the selenium and the nitrogen.

In conclusion intramolecular interaction between a divalent selenium and a *tertiary* amine is observed for 1 in the solid state, but it is not observed in solution. The observed stabilizing interaction may arise from the orbital interaction between the non-bonding orbital of the nitrogen and the σ^* orbital of the selenium moiety. At the same time, the interaction between low-lying nitrogen lone pair and the highest occupied molecular orbital localized at the Se-Se bond may facilitates the oxidative cleavage of the Se-Se bond of 1. In the case of selenenyl bromide 6, strong Se···N interaction was really observed in solution. Considering the previous work on the biological activity of some organoselenium compounds,[3] the interaction observed here may possibly be closely related to the enzyme activity of glutathione peroxidase. Application of the intramolecular Se···N interaction to enzyme-like catalytic reaction is now in progress and will be reported in due course.

EXPERIMENTAL

90MHz ^{1}H-NMR was measured on a Varian EM390 instrument and ^{13}C-NMR and ^{77}Se-NMR were measured on a JEOL FX90Q instrument. All NMR samples were dissolved in chloroform-d_1 containing tetramethylsilane as internal standard for ^{1}H and ^{13}C-NMR. For ^{77}Se-NMR dimethylselenide was used as external standard.

Synthesis of methyl 2-selenocyanatobenzoate(3).

2 (37.8g, 0.25mol) was suspended in 6N HCl (150ml) at 0℃ and 3M $NaNO_2$ (100ml) was added to the mixture dropwise so that the reaction temperature was kept below zero. After stirring for 1 h, saturated aqCH_3COONa (ca.120ml) was added dropwise until the pH of the reaction solution was reached 6. Then the mixture was poured into aqueous solution of KSeCN (0.25mol) all at once. Precipitates were collected and washed with water. After recrystallization from methanol, pure **1** was obtained as yellow crystals (51.2g, 87%). ^{1}H-NMR(δ) 8.05 (1H, m), 7.47 (3H, m), 3.96 (3H, s); ^{13}C-NMR(ppm) 167.6 (C=O), 134.1, 131.0, 130.6, 129.3, 127.2, 125.7, 105.1 (CN), 52.9 (OMe); ^{77}Se-NMR(ppm) 398.0.

Synthesis of 2,2'-diselenobis(benzyl alcohol)(4).

$LiAlH_4$ (3.57g, 0.094mol) was suspended in ether under nitrogen atmosphere and ethereal solution of **3** (15.0g, 0.063mol) was slowly added to the mixture. After refluxed for 2 h, the reaction mixture was cooled. Then an excess amount of 2N HCl was added, and the mixture was stirred under air overnight. Ethereal layer was separated, washed with water, and dried over Na_2SO_4. Crude **4**, obtained after evaporation, was used for the next reaction without further purification.

Synthesis of 2,2'-diselenobis(benzyl chloride)(5).

4 (7.44g, 0.020mol) and pyridine (0.060mol) were dissolved in dichloromethane (100ml). Thionyl chloride (0.048mol) was then slowly added to the solution at 0℃ under nitrogen atmosphere. The mixture was stirred for 4 h at room temperature, and an excess amount of 2N HCl was added. After the usual extraction with dichloromethane, the crude product, obtained after evaporation of the solvent, was purified by column chromatography (3:1 hexane-CH_2Cl_2 as eluent) and **5** was obtained as yellow crystals (6.48g, 79%). ^{1}H-NMR(δ) 7.65 (2H, m), 7.22 (6H, m), 4.60 (4H, s); ^{13}C-NMR(ppm) 138.3, 134.7, 131.6, 129.4, 129.1, 128.5, 46.1; ^{77}Se-NMR(ppm) 442.2.

Synthesis of 2,2'-diselenobis(N-cyclohexyl-N-methylbenzylamine)(1).

5 (1.64g, 4mmol), N-methylcyclohexylamine (1.13g, 10mmol), and K_2CO_3 (40mmol) were dissolved in aqueous acetone and the mixture was stirred for 2 days at room temperature. Crude product, obtained from the reaction mixture by extraction with dichloromethane, was then recrystallized from acetonitrile. **1** was obtained as fine yellow crystals (666mg, 30%). ^{1}H-NMR(δ) 7.76 (2H, m), 7.10 (6H, m), 3.72 (4H, s), 2.61 (2H, m), 2.17 (6H, s), 2.0-1.2 (20H, m); ^{13}C-NMR(ppm) 140.0, 133.8, 131.2, 128.3, 127.7, 125.4, 62.2 (N-CH=), 60.2 (N-CH_2-), 34.8 (N-CH_3), 28.1, 26.3, 26.0; ^{77}Se-NMR(ppm) 429.8.

Synthesis of 2-(N-cyclohexyl-N-methylaminomethyl)benzeneselenenyl bromide(6).

1 was dissolved in dichloromethane under nitrogen atmosphere and equimolar bromine was slowly added to the solution. After removal of the solvent **6** was quantitatively obtained as red-yellow crystals. ^{1}H-NMR(δ) 8.16 (1H, m), 7.20 (3H, m), 4.15 (1H, d, J=13.6Hz), 3.83 (1H, d, J=13.6Hz), 3.16 (1H, m), 2.58 (3H, s), 2.0-1.3 (10H, m); ^{13}C-NMR(ppm) 135.0, 134.2, 130.4, 128.4, 125.9, 125.1, 66.7 (N-CH=), 62.6 (N-CH_2-), 38.0 (N-CH_3), 30.6, 25.9, 25.2, 24.8; ^{77}Se-NMR(ppm) 1019.4.

X-ray analysis of 1.

A Rigaku automated 4-circle diffractometer was employed with the MoK_α radiation monochromatized by graphite. The crystal data obtained is as follows. $C_{28}H_{40}N_2Se_2$,

M=562.56, triclinic, a=12.455(11), b=12.749(2), c=9.943(2) Å, α =107.73(1)°, β =112.15(3)°, γ =75.78(3)°, U=1377.4(13) Å^3, space group $P\bar{1}$, Z=2, D_c=13.6g/cm^3. After the absorption correction[7] was performed by using the data of psi scan, the structure was solved by the heavy atom method and was refined by the full-matrix least-squares method neglecting hydrogen atoms.[8] R-value was reduced to 0.064 for 3647 independent reflections.

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