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Nature of the Intramolecular Se$\cdots$N Nonbonded Interaction of 2-Selenobenzylamine Derivatives. An Experimental Evaluation by ^{1}H, ^{77}Se, and ^{15}N NMR Spectroscopy

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Abstract: ^{1}H NMR analysis of seven 2-selenobenzylamine derivatives (ArSeX, **1**−**7**) has revealed the existence of attractive nonbonded interaction between the divalent selenium and an unsymmetric amino nitrogen, whose strength significantly depends on the relative electrophilic reactivity of the selenium moiety. In the intermediate cases (**5**, X = CN; **6**, X = SPh), the dissociation energy of the Se$\cdots$N nonbonded interaction was evaluated as 12.4 and 10.8 kcal/mol, respectively, by variable-temperature ^{1}H NMR spectral simulations. The corresponding values were roughly estimated as $>$18.8 kcal/mol for the strong cases (**2**, X = Br; **3**, X = Cl; **4**, X = OAc) and $<$7.7 kcal/mol for the weak cases (**1**, X = SeAr; **7**, X = Me). In order to elucidate physicochemical properties of the interaction, ^{15}N-labeled compounds were synthesized. Downfield shifts of ^{15}N NMR ($\Delta\delta_N$) and increment of $J_{Se\cdots N}$ (coupling constant between ^{77}Se and ^{15}N) were observed with increasing Se$\cdots$N interaction. In the case of strong Se$\cdots$N interaction, saturation of coupling constants was observed. These experimental observations as well as large NBO deletion energies (3-21G* and LANL1DZ) between the selenium and the nitrogen for model compounds (**9**−**13**) strongly suggested that the observed Se$\cdots$N interaction is mainly caused by the orbital interaction between the nitrogen lone pair (n_N) and the antibonding orbital of the Se−X bond (σ^*_{Se-X}).

Introduction

Selenium in organic compounds usually exists in a divalent state with two covalently bonded substituents and two lone pairs of valence electrons. In the solid state and in solution, however, it has been frequently discovered that the divalent selenium further interacts with (a) nearby heteroatom(s) (O, N, Se, etc.) forming a pseudo-high-valent selenium species.[1−7] This phenomenon has been interpreted by assuming the nonbonded interaction between the divalent selenium and a heteroatom. The nonbonded interaction, which is derived from the hypervalent nature of the selenium, is expected to be responsible for the specific redox reactivity of organoselenium compounds[8] as well as the high bioactivity of selenium,[9] because such an interaction may occur at an early stage along the reaction coordinate. Herein we wish to present the first quantitative evaluation of one of these interactions, *i.e.*, the nonbonded interaction between a divalent selenium and a tertiary amino nitrogen (Se$\cdots$N interaction), and its theoretical interpretation.

A pseudo-high-valent state has also been found in other divalent chalcogen compounds and has been frequently discussed in the literature.[10] The theory that the hypervalent property of divalent chalcogens increases in the order O $<$ S $<$ Se $<$ Te is now widely accepted, although the dissociation energy and the essential force of the nonbonded interaction are still uncertain. In order to answer these physicochemical questions, it is necessary to study a series of divalent chalcogen compounds systematically. Divalent selenium compounds have advantages for this purpose: (1) they are usually more stable than organotellurium compounds, (2) they sometimes exhibit such a strong nonbonded interaction in solution that the dynamic process can be investigated by ^{1}H NMR spectroscopy, and (3) they contain an NMR-active isotope (^{77}Se, $I = 1/2$) that should allow invaluable NMR analysis of the interaction.

In the solid state, pseudo-high-valent behavior of a divalent selenium has been reported in numerous crystals.[2] Ramasubbu and Parthasarathy first analyzed it statistically and found that there are two types of nonbonded interactions involving a divalent selenium (Figure 1).[3] Type A selenium weakly donates

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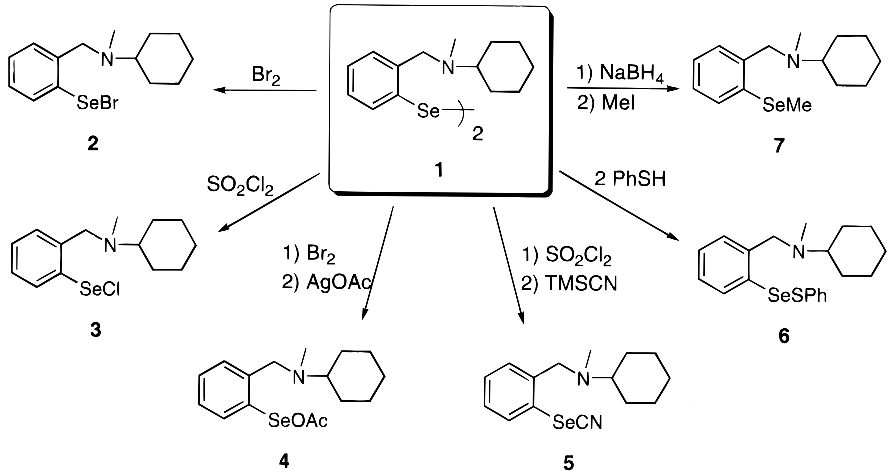
Scheme 1



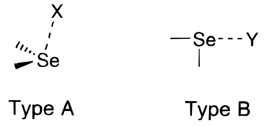


Figure 1. Nonbonded interaction involving a divalent selenium.

the selenium lone pair to atom X (X = Pt, Hg, etc.), which is located just above the divalent selenium plane. This type is observed in the C−H···Se hydrogen bond recently reported by us.[11] On the contrary, type B selenium partially accepts lone pair electrons of atom Y (Y = O, N, Cl, etc.), which is located at the backside of one of the covalent bonds. These variable structural features can be reasonably attributed to the orbital interaction (*i.e.*, the charge transfer interaction) between the selenium and electrophile X or nucleophile Y.

More advanced analyses were independently made by two research groups as to an Se···O interaction that belongs to type B. Goldstein *et al.* showed an electrostatic character of Se···O interaction in selenazofurins.[4] On the other hand, Barton *et al.* analyzed the Se···O interaction of selenoiminoquinones and suggested a three-center four-electron interaction on the basis of X-ray structure and Bader electron density analysis.[5] These results clearly suggested that there is a wide spectrum from ionic to covalent character in the nonbonded interaction involving a divalent selenium. Thus, the interaction has been thoroughly studied in some particular cases, but it has never been systematically analyzed in a series of organoselenium compounds and no quantitative experimental data have been available as to the dissociation energy of the interaction.

We have recently found Se···N nonbonded interaction of diselenide **1** in the solid state[6] and have shown the possibility that the interaction may play important roles in the catalytic cycle of glutathione peroxidase, a selenium-containing antioxidant enzyme,[12] and that it can be applied to novel synthetic reactions.[13] More recently, we have for the first time succeeded in the X-ray structural determination of areneselenenyl chloride strongly stabilized by Se···N nonbonded interaction,[7] in which the predominant force is the $n-\sigma^*$-type orbital interaction between the nitrogen and the selenenyl chloride moiety. In this paper, Se···N nonbonded interaction of a series of 2-selenobenzylamine derivatives (**1**−**7**) is analyzed quantitatively by using various methods. They include variable temperature (VT) ^{1}H NMR of two benzylic protons, dynamic ^{1}H NMR analysis of **5** and **6**, ^{77}Se and ^{15}N NMR chemical shifts analysis, measurement of $J_{\mathrm{Se}\cdots\mathrm{N}}$ coupling constants, and *ab initio* molecular orbital (MO) calculations and natural bond orbital (NBO) analysis. On the basis of the results from these analyses, the mechanism of the Se···N nonbonded interaction is discussed.

Results and Discussion

1. Synthesis. Six 2-selenobenzylamine derivatives (**2**−**7**) were synthesized from diselenide **1**[6] according to the previously known methods (Scheme 1).[14] All compounds were obtained in almost quantitative yields except for **7**. Similarly, corresponding ^{15}N-labeled compounds were easily synthesized from ^{15}N-labeled **1**, which was synthesized from aniline-^{15}N according to Scheme 2. Selenenyl bromide **2**,[6] selenenyl chloride **3**, and selenenyl acetate **4**[12] were relatively stable in solution as compared with the corresponding benzeneselenenyl derivatives and did not rapidly decompose in $CDCl_3$ in the presence of a small amount of water and oxygen. This may be due to significant stabilization by strong Se···N nonbonded interaction as described below. Selenocyanate **5**, selenenyl sulfide **6**,[12] and methyl selenide **7** were indefinitely stable and could be characterized by elemental analysis.

2. ^{1}H NMR of Benzylic Protons. Compounds **1**−**7** have an unsymmetrical tertiary amino nitrogen at the position separated by four bonds from a divalent selenium. Therefore, it is expected that two benzylic protons become magnetically nonequivalent when the unsymmetric nitrogen inversion or the rotation around the C−N bond is sufficiently slow within an NMR time scale due to the intramolecular Se···N interaction, which allows the formation of a five-membered ring.

^{1}H NMR chemical shifts of benzylic protons for **1**−**7** are listed in Table 1. According to the NMR spectral properties, **1**−**7** can be classified into three groups. The first group, which contains **2**−**4**, shows a strong Se···N interaction. The benzylic protons of these compounds resonate as an AB quartet at room temperature. At higher temperatures the NMR signals significantly broaden, resulting in irreversible decomposition. The second group, which contains **5** and **6**, possesses an intermediate Se···N interaction, showing a dynamic mutual exchange process between two benzylic protons. The benzylic protons of **5** and **6** resonate as a singlet at room temperature. These signals broaden and split into an AB quartet upon cooling. Detailed

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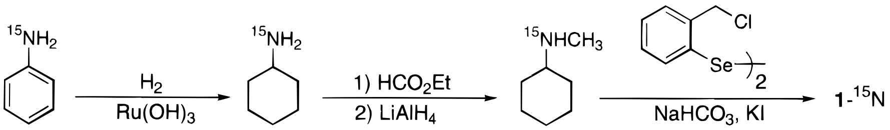
Scheme 2



Scheme 3

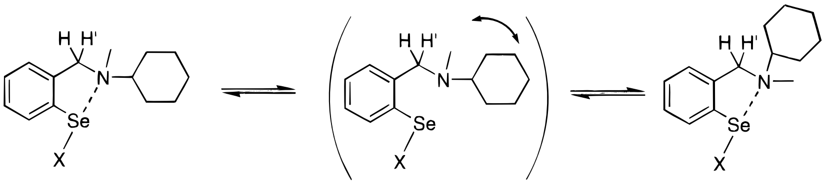


Table 1. 90 MHz ^{1}H NMR of Benzylic Protons for **1**−**7**

compd (ArSeX)	$\delta_H{}^a$/ppm	($^2J_{HH}$/Hz)	$T_c{}^b$/K
2: X = Br	4.15, 3.83	(13.6)	>320
3: X = Cl	4.16, 3.92	(13.9)	>320
4: X = OAc	4.05, 3.83	(13.1)	>320
5: X = CN	3.68		241
	3.75, 3.54^c	(13.8)	
6: X = SPh	3.73		217
	3.82, 3.62^d	(13.0)	
1: X = SeAr	3.72		<183
7: X = Me	3.67		<183

^{a} Chemical shifts measured in $CDCl_3$ at room temperature. ^{b} Coalescence temperature in $CDCl_3$ for **2**−**4** and in CD_2Cl_2 for **1** and **5**−**7**. ^{c} Measured in CD_2Cl_2 at 215 K. ^{d} Measured in CD_2Cl_2 at 196 K.

analysis of the dynamic processes is described in the following two sections. The third group, which contains **1** and **7**, has a weak (or no) Se···N interaction. The singlet ^{1}H NMR signals of the benzylic protons for these compounds broaden at low temperature but do not split even at −90 °C at 500 MHz. Since the weak Se···N nonbonded interaction has been found in the solid state of **1**,[6] a similar interaction may exist in **1** in solution. However, it is not clear at present whether weak Se···N interaction exists in **7** or not according to the NMR line broadening of benzylic protons, though in fact a weak interaction may exist in **7** on the basis of *ab initio* MO calculation as described later.

The above classification indicates that the strength of the Se···N interaction correlates with relative electrophilicity of the selenium moiety (the Se−X bond). In general, selenenyl bromides, selenenyl chlorides, and selenenyl acetates smoothly add to simple olefins to produce *trans*-1,2-adducts,[15] whereas selenocyanates and selenosulfonates can add only to activated olefins or simple olefins in the presence of a Lewis acid.[16] Diselenides and methyl selenides are totally unreactive toward olefins under the usual reaction conditions. The observed correlation between the strength of the Se···N interaction and the electrophilic reactivity of the selenium moiety strongly suggests that the Se···N interaction may represent the initial stage or near-transition-state of the electrophilic reaction of a divalent selenium with a nitrogen lone pair, suggesting that it should mainly arise from orbital interaction between the nitrogen lone pair (n_N) and the low-lying antibonding orbital (σ^*_{Se-X}) of the selenium moiety.

3. VT ^{1}H NMR Analysis. The dynamic process of the mutual exchange between two benzylic protons (Scheme 3) was observed only for **5** and **6**. The barrier of this process should be related to both the strength of Se···N interaction and the barrier of nitrogen inversion or C−N rotation because the magnetic nonequivalence arises from the chirality of the unsymmetrical tertiary amine. The benzylic protons of *N*-cyclohexyl-*N*-methylbenzylamine (**8**),[17] which does not have a selenium substituent at the 2-position of the phenyl ring, resonate as sharp singlet even at −90 °C at 500 MHz, indicating that the nitrogen is magnetically achiral if the Se···N interaction is absent for **1**−**7**.

Figure 2 compares 90 MHz ^{1}H NMR spectra of **5** at various temperatures (left) with the simulated ones (right).[18] Similar spectral changes were observed for **6**.[19] Coalescence temperatures (T_c) were 241 and 217 K for **5** and **6**, respectively, indicating a higher activation barrier of the mutual exchange (Scheme 3) for **5** than that for **6**. According to the Eyring plots (Figure 3), the activation enthalpy ($\Delta H^‡$) and the activation entropy ($\Delta S^‡$) for **5** were determined as 19.1 ± 1.6 kcal/mol and +28.9 ± 6.7 eu, and those for **6** were 17.5 ± 1.1 kcal/mol and +30.8 ± 5.0 eu, respectively. The $\Delta H^‡$ values showed that the mutual exchange of two benzylic protons was 1.6 kcal/mol more difficult for **5** than **6**. The observed large positive $\Delta S^‡$ values were very consistent with the assumption that the Se···N interaction dissociated during the mutual exchange process.

4. Se···N Dissociation Energy. The mutual exchange of two benzylic protons requires several individual steps. They should include (1) the dissociation of Se···N nonbonded interaction accompanied by internal rotation around the Ar−C and Ar−Se bonds, (2) the rotation around the C−N bond, (3) the inversion of the unsymmetrical tertiary amine, and (4) the association of the selenium with the nitrogen to regenerate the Se···N interaction. A possible mechanism is shown in Figure 4 with a hypothetical reaction coordinate.

The activation enthalpy ($\Delta H^‡_{exp}$) determined by the VT NMR method was approximately equal to the highest barrier of the reaction coordinate. Since the rotational barrier E_1 and the nitrogen inversion barrier E_3 may be small (∼1.5 and 3.8 kcal/mol, respectively, according to MO calculations[20]), the $\Delta H^‡_{exp}$ can be estimated as the sum of Se···N dissociation energy (DE) and the C−N rotational barrier (E_2), which may be equal to the

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(19) Data are indicated in the supporting information.

(20) The detailed method of the E_1, E_2, E_3 estimation is described in the Experimental Section.

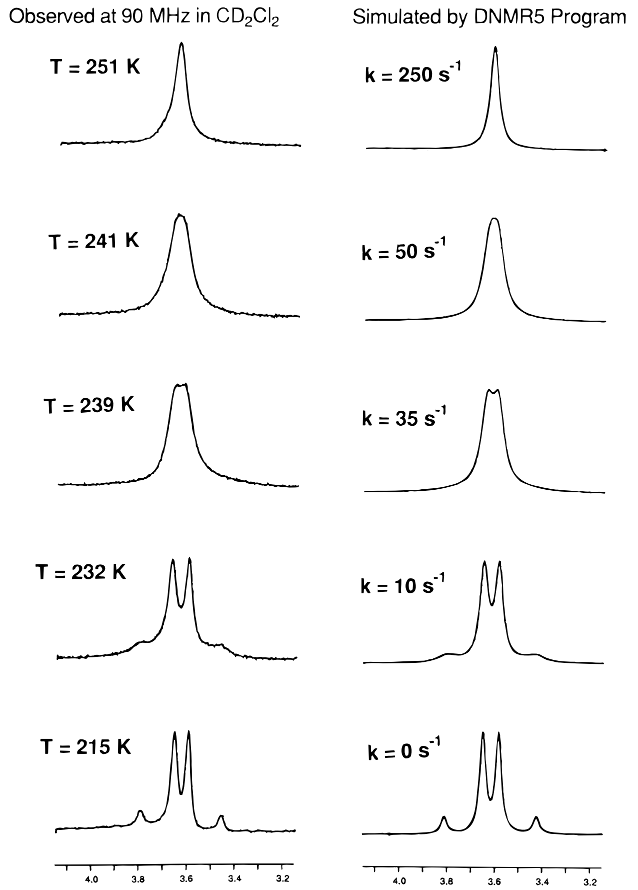

Figure 2. Variable-temperature ^{1}H NMR spectra of benzylic protons for **5** (left) and the simulated ones (right).

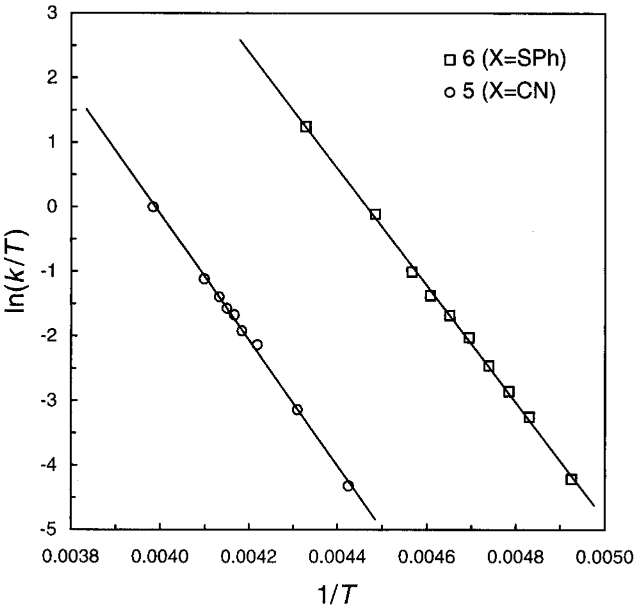

Figure 3. Eyring plots of the mutual exchange process of two benzylic protons for **5** (circles) and **6** (squares).

corresponding barrier of **8**. However, E_2 could not be experimentally determined by VT ^{1}H NMR analysis of **8** ($\Delta G^\ddagger \ll 8.9$ kcal/mol).[21] We therefore estimated it by *ab initio* MO calculations.[20] The calculated barrier was 6.7 kcal/mol, which is not unreasonable as compared with the experimental barrier for *N*-isopropyl-*N*-methylbenzylamine ($\Delta G^\ddagger = 6.2$ kcal/mol).[22] By subtracting this value from the $\Delta H^\ddagger_{\text{exp}}$ for the mutual exchange process of two benzylic protons, the DE of Se···N interaction can be determined as 12.4 ± 1.6 kcal/mol for **5** and 10.8 ± 1.1 kcal/mol for **6**. According to ^{1}H NMR analysis for **1**−**7** (Table 1), it is obvious that the dissociation energy for **2**−**4** is larger than that for **5** and that those for **1** and **7** are smaller than that for **6**. By assuming that the $\Delta S^\ddagger$ value is equal to +30 eu for these compounds and that the chemical shift difference of two benzylic protons and their coupling constant are 18 and 13.5 Hz, respectively, the DE can be roughly estimated as >18.8 kcal/mol for **2**−**4** and <7.7 kcal/mol for **1** and **7** based on the well-known correlation between $\Delta G^\ddagger$ and T_c,[23] which is higher than 320 K for **2**−**4** and lower than 183 K for **1** and **7**.

5. ^{77}Se NMR Chemical Shift. In order to elucidate the mechanism of the formation of Se···N nonbonded interaction, we subsequently analyzed ^{77}Se and ^{15}N NMR of the ^{15}N-labeled compounds. The observed ^{77}Se NMR chemical shifts (δ_{Se}), ^{15}N NMR chemical shifts (δ_{N}), and $J_{\text{Se}\cdots\text{N}}$ coupling constants of ^{15}N-labeled **1**−**7** are listed in Table 2. It is known that the ^{77}Se NMR chemical shift is susceptible to the electronic structure around the selenium and has a wide range from −100 ppm to +1100 ppm in a divalent state with respect to dimethyl selenide.[24] The observed ^{77}Se NMR chemical shifts of **1**−**7** almost cover this range.

The comparison of ^{77}Se NMR chemical shifts of **1**−**7** with those of the corresponding 2-methyl benzeneselenenyl derivatives will be useful for elucidating the Se···N interaction. Unfortunately, however, there was only one piece of data available in the literature: 2-methylphenyl methyl selenide shows a ^{77}Se NMR absorption at 161.6 ppm,[25] which is shifted upfield by 19 ppm with respect to methyl selenide **7**, suggesting a small downfield shift due to the Se···N interaction. On the other hand, when the ^{77}Se NMR chemical shifts of **1**−**3** and **5**−**7** are compared with those of unsubstituted benzeneselenenyl derivatives in the literature,[24] similar downfield shifts are observed for **2** (−142 ppm), **3** (−9 ppm), **5** (−41 ppm), and **6** (−46 ppm). The opposite upfield shifts are observed for **1** (+32 ppm) and **7** (+21 ppm). Since an *o*-methyl substituent results in a large upfield shift of ^{77}Se NMR (+40 ppm for methyl selenide), it is strongly suggested that the intramolecular Se···N nonbonded interaction results in an apparent downfield shift of ^{77}Se NMR. Similar phenomena have previously been reported by Baiwir *et al.* in an intramolecular Se···O interaction.[26] However, the values of downfield shifts do not seem to correlate with the strength of Se···N and Se···O interaction.

6. ^{15}N-Induced Isotope Shifts in ^{77}Se NMR. We subsequently examined isotope shifts in ^{77}Se NMR due to the substitution of the natural abundant ^{14}N with the ^{15}N isotope. The observed isotope shifts (listed in Table 2) scatter from −1.2 ppm to +0.2 ppm. Because of the lack of data about this kind of isotope shifts in the literature, a detailed analysis cannot be made at this moment. However, it is suggested that the strong

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(21) Two benzylic protons of **8** resonated as a sharp singlet even at −90 °C due to rapid nitrogen inversion or C−N rotation. The activation barrier was estimated as ≪8.9 kcal/mol according to the well-known correlations[23] by assuming that the chemical shift difference of two benzylic protons and their coupling constant were 18 and 13.5 Hz, respectively.

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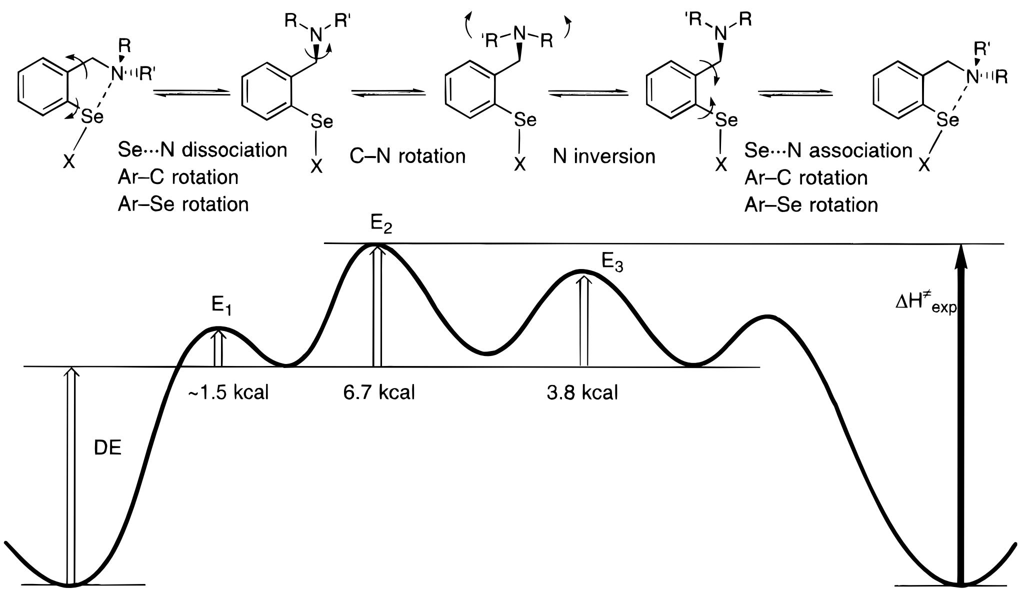

Figure 4. Plausible mechanism of the mutual exchange of two benzylic protons with a hypothetical reaction coordinate.

Table 2. ^{77}Se and ^{15}N NMR Chemical Shifts and $J_{\mathrm{Se}\cdots\mathrm{N}}$ Coupling Constants of ^{15}N-Labeled **1**−**7**

compd (ArSeX)	^{77}Se NMR^{a} δ_{Se}/ppm	^{15} NMR δ_{N}/ppm	coupling constant^{c} $J_{\mathrm{Se}\cdots\mathrm{N}}$/Hz
2: X = Br	1011.2 (−1.2)	−298.2	47.0
3: X = Cl	1051.3 (−1.0)	−300.3	48.6
4: X = OAc	1158.1 (−1.0)	−311.2	59.3
5: X = CN	362.2 (+0.2)	−326.1	51.9
6: X = SPh	571.5 (0.0)	−323.1	53.1
1: X = SeAr	431.9 (0.0)	−327.7	32.4
7: X = Me	181.0 (−0.2)	−332.2	13.0

[a] ^{77}Se NMR chemical shifts in $CDCl_3$ with dimethyl selenide as an external standard. The values in parentheses are isotope shifts in ^{77}Se NMR due to the substitution of ^{14}N with ^{15}N. A negative value means a downfield shift. [b] ^{15}N NMR chemical shifts with nitromethane (δ +5.0) as an external standard. [c] Coupling constants measured from expanded ^{77}Se NMR spectra.

Se•••N interaction results in a slight downfield ^{15}N-induced isotope shift in ^{77}Se NMR.

7. ^{15}N NMR Chemical Shifts. The chemical shift of an amino nitrogen (δ_{N}) is significantly influenced by the electron delocalization of the nitrogen lone pair.[27] Therefore, it should be a good measure for the strength of the Se•••N interaction for **1**−**7** if a covalent interaction is an essential force. Observed δ_{N} of **1**−**7** (Table 2) is shifted downfield by 30 ppm as the strength of the Se•••N interaction increases except for **5**, showing that the lone pair of the nitrogen efficiently delocalizes with increasing Se•••N interaction. However, the δ_{N} of **5** is slightly shifted upfield with respect to **6**. According to the results from VT ^{1}H NMR analysis, it is anticipated that the δ_{N} of **5** should be shifted downfield with respect to **6**. This reversal can be reasonably understood by assuming that the Se•••N interaction of **5** has a less covalent character than **6**, but it has a more ionic character due to the larger electron-withdrawing ability of the cyano group. Thus, the Se•••N interaction of **5** becomes slightly stronger than that of **6**.

8. $J_{\mathrm{Se}\cdots\mathrm{N}}$ Coupling Constants. Another useful measure for the covalent strength of the Se•••N interaction is a direct coupling constant between ^{77}Se and ^{15}N ($J_{\mathrm{Se}\cdots\mathrm{N}}$). The NMR coupling constant can be theoretically divided into three terms;[28] a spin−dipolar term, a spin−orbital term, and a Fermi-contact term. Among these, the Fermi-contact term is usually a major component of a coupling constant because the spin state of the one nucleus transmits to the other nucleus via electrons, among which s-electrons are most important due to the possibility of the direct contact (Fermi contact) at the nuclear position. Pople and Santry[29] showed that this term is proportional to the square of the s-bond character between two atoms. Therefore, $J_{\mathrm{Se}\cdots\mathrm{N}}$ should approximately depend on the s-bond order of the Se•••N interaction if the spin−dipolar and spin−orbital terms are negligible.

The observed coupling constants (Table 2) are significantly increased with the increase in the strength of the Se•••N interaction as expected, though those for **2** and **3** are saturated. This saturation may be due to the participation of a spin−dipolar or a spin−orbital term that will be relatively large in the case that the Se•••N interaction possesses a higher bond order. Again, the reverse order of the magnitude of $J_{\mathrm{Se}\cdots\mathrm{N}}$ is observed for **5** and **6**. This may be also due to the relatively small covalent character of the Se•••N nonbonded interaction of **5** with respect to **6** as suggested by the discussion in the previous section (the downfield shifts of ^{15}N NMR).

9. MO Calculations. According to the above NMR analyses, two statements seem reasonable: (1) the strength of the Se•••N interaction increases with the increase in the electrophilic reactivity of the selenium moiety, and (2) the Se•••N interaction mostly arises from the orbital interaction between the selenium and the nitrogen. In order to ascertain these, *ab initio* MO calculations and their NBO analysis[30] were performed on **9**−**13**. According to our previous MO calculations on **9** at various basis set levels,[7] it has been found that the minimum limit of a basis set to treat such pseudo-high-valent selenium species is 3-21G*[31] or LANL1DZ.[32] We therefore employed these basis sets for the MO calculations of **10**−**13**.

The fully optimized geometries at the HF/3-21G* and HF/

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(31) A standard 3-21G basis set with d polarization functions for heavier atoms.[39]

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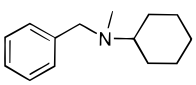

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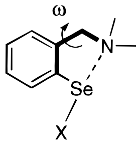

9 X = Cl
10 X = OH
11 X = CN
12 X = SMe
13 X = Me

LANL1DZ levels are listed in Table 3 along with X-ray structural parameters of the related compounds (**14**[7] and **1**[6]). The global energy minima of **9**−**13** have the conformation with an Se···N van der Waals contact like X-ray structures of **14** and **1**. The obtained Se···N interatomic distance increases in the order **9** (X = Cl) < **10** (X = OH) < **11** (X = CN) < **12** (SMe) < **13** (Me), which is completely in accordance with the experimental results from ^{1}H NMR of **1**−**7** without the reversal of the order. The fact that the averaged Se···N distance (2.87 Å) of **1** determined by X-ray analysis is larger than that of **12** and smaller than that of **13** is also consistent, suggesting the accuracy of these calculations. It should be noted that methyl selenide **13** also has weak Se···N interaction in its global energy minimum conformation. The results from two levels of calculations are slightly different from each other, but they are internally consistent within one basis set level. It is clear that a strong Se···N interaction causes shortening of the Se···N interatomic distance, increase in the linearity of the N···Se−X alignment, and decrease in *ω*. The N−C−C(Ar) bond angle narrows by 3−4°.

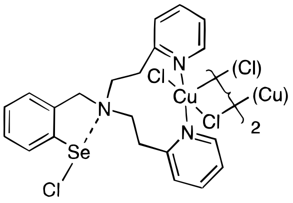

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Table 3. Molecular Structures of **9**−**13** Obtained by *ab Initio* MO Calculations at HF/3-21G* and HF/LANL1DZ Levels along with Structural Parameters of **14** and **1** Determined by X-ray Analysis

compd (ArSeX)	basis set[a]	*r*(Se−X)/ Å	*r*(Se···N)/ Å	∠N···Se−X/ deg	*ω*[b]/ deg
14: X = Cl[c]		2.432	2.191	178.4	26
9: X = Cl[d]	3-21G*	2.290	2.331	174.6	35.6
	LANL1DZ	2.448	2.359	174.4	32.9
10: X = OH	3-21G*	1.826	2.513	170.4	35.1
	LANL1DZ	1.863	2.653	170.0	37.5
11: X = CN	3-21G*	1.881	2.631	170.6	42.9
	LANL1DZ	1.889	2.826	168.2	47.2
12: X = SMe	3-21G*	2.202	2.752	172.0	47.8
	LANL1DZ	2.358	2.845	169.0	48.1
1: X = SeAr[e]		2.362	2.78	172	52
			2.96	165	57
13: X = Me	2-21G*	1.968	2.924	168.2	53.4
	LANL1DZ	1.986	3.185	162.4	61.0

[a] 3-21G* is a standard 3-21G basis set with d polarization functions for Se, S, and Cl.[39] LANL1DZ is a Los Alamos ECP+DZ basis set for Se, S, and Cl and Dunning/Huzinaga valence double-ζ basis set for other atoms. [b] A dihedral angle of an Ar−C bond. [c] X-ray structure from ref 7. [d] Data from ref 7. [e] X-ray structure from ref 6.

Table 4. Results of NBO Deletion Analysis on **9**−**13**

compd (ArSeX)	basis set[a]	ΔE_{del}/ kcal·mol^{-1}	Δq(σ*)[c]/ electron	d*q*(n)[d]/ electron
9: X = Cl[e]	3-21G*	47.0	+0.133	−0.143
	LANL1DZ	47.4	+0.116	−0.141
10: X = OH	3-21G*	22.9	+0.006	−0.069
	LANL1DZ	12.9	+0.046	−0.038
11: X = CN	3-21G*	15.8	+0.045	−0.050
	LANL1DZ	6.9	+0.022	−0.018
12: X = SMe	3-21G*	11.7	+0.035	−0.038
	LANL1DZ	7.1	+0.031	−0.025
13: X = Me	3-21G*	6.3	+0.018	−0.020
	LANL1DZ	2.1	+0.006	−0.006

[a] 3-21G* is a standard 3-21G basis set with d polarization functions for Se, S, and Cl.[39] LANL1DZ is a Los Alamos ECP+DZ basis set for Se, S, and Cl and Dunning/Huzinaga valence double-ζ basis set for other atoms. [b] NBO deletion energy between the divalent selenium moiety and the amino nitrogen atom. [c] Charge increase of the σ* orbital of an Se−X bond due to the orbital interaction between the selenium moiety and the nitrogen. [d] Charge decrease of the n_N orbital of an amino nitrogen due to the orbital interaction between the selenium moiety and the nitrogen. [e] Data from ref 7.

10. NBO Analysis.[30] The results of NBO analysis on **9**−**13** are listed in Table 4. NBO deletion energy (ΔE_{del}) in the table means the orbital interaction energy between the divalent selenium moiety and the tertiary amino nitrogen. The values $\Delta q(\sigma^*)$ and $\Delta q(\mathrm{n})$ are the charge increase of the σ* orbital of an Se−X bond due to the Se···N interaction formation and the corresponding charge decrease of the nitrogen lone pair for **9**−**13**, respectively.

The ΔE_{del} value obtained at a LANL1DZ basis set level increases in the order **13** (X = Me) < **11** (X = CN) ≈ **12** (X = SMe) < **10** (X = OH) < **9** (X = Cl). The order is the same as the order of the Se···N orbital interaction strength suggested by the ^{15}N NMR downfield shifts ($\Delta\delta_{\mathrm{N}}$) and the $J_{\mathrm{Se\cdots N}}$ coupling constants for **1**−**7**. It is quite reasonable that the ΔE_{del} for **12** (X = SMe) is larger than that for **11** (XCN) in spite of the larger Se···N interatomic distance for **12**. This fact clearly suggests that the δ_{N} and $J_{\mathrm{Se\cdots N}}$ are good indices for the extent of the Se···N orbital interaction though $J_{\mathrm{Se\cdots N}}$ values for **2** and **3** seem to be saturated. At the 3-21G* basis set level, however, the ΔE_{del} increases in the order, **13** < **12** < **11** < **10** < **9**, which is the same with the order of the total Se···N interaction energy. The discrepancy between the results from two different basis set levels may be due to the incorporated relativistic effects or the lack of d orbitals for Se in LANL1DZ. In order to elucidate this point, higher level calculations, such as MP2, which includes electron correlation effects, using a more accurate basis set will be required.

The obtained ΔE_{del} values for **11** (15.8 kcal at 3-21G* and 6.9 kcal at LANL1DZ) and **12** (11.7 kcal at 3-21G* and 7.1 kcal at LANL1DZ) are comparable with the experimentally determined Δ*E*′s (12.4 kcal for **5** and 10.8 kcal for **6**). This suggests that the greater part of the Se···N nonbonded interaction should arise from the orbital interaction between the divalent selenium moiety (the Se−X bond) and the nitrogen atom (Figure 5). The significantly large changes of the orbital occupancies are only observed for $\sigma^*_{\mathrm{Se-X}}$ and $\mathrm{n_N}$ natural orbitals ($\Delta q(\sigma^*)$ and $\Delta q(\mathrm{n})$) with marginal changes for the bonding orbital of the Se−X bond ($\sigma_{\mathrm{Se-X}}$) and the Rydberg orbitals on Se. These results clearly shows that the orbital interaction between the divalent selenium moiety and the tertiary amino nitrogen is predominant for the Se···N nonbonded interaction as well as that the main origin of the interaction is the electron delocalization from the nitrogen lone pair to the low-lying σ* orbital of an Se−X bond.

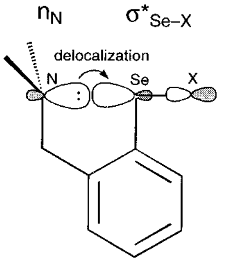

Figure 5. Electron delocalization from the nitrogen lone pair (n_N) to the antibonding orbital of an Se−X bond (σ^*).

Conclusions

The strength of the Se···N nonbonded interaction was quantitatively evaluated for **5** (12.4 ± 1.6 kcal/mol) and **6** (10.8 ± 1.1 kcal/mol) and was roughly estimated for **2**−**4** (>18.8 kcal/mol) and **1** and **7** (<7.7 kcal/mol) on the basis of dynamic ^{1}H NMR study of diastereotopic benzylic protons and the calculated C−N rotational barrier of **8**. A strong correlation between the electrophilic reactivity of the selenium moiety and the strength of Se···N interaction was clear. The estimated dissociation energy for **2**−**4** was unexpectedly large as compared with the bond dissociation energy of the Se−Se covalent bond in diphenyl diselenide (64.9 ± 1.2 kcal/mol)[33] and that of the Se−Br bond in benzeneselenenyl bromide (61.7 kcal/mol).[34] ^{77}Se NMR analysis of ^{15}N-labeled **1**−**7** showed that a small downfield isotope shift, due to the substitution of the natural abundant ^{14}N with the ^{15}N isotope, arises from the strong Se···N interaction. A large downfield shift of ^{15}N NMR and a significant enhancement of $J_{Se\cdots N}$ coupling constants were also observed with an increase in the Se···N interaction, though $J_{Se\cdots N}$ seems to be saturated for **2** and **3**. These experimental observations are reasonably understood by assuming a predominant n−σ^* orbital interaction between the nitrogen and the Se−X bond, because δ_N and $J_{Se\cdots N}$ should make good measures for a covalent character of the Se···N interaction. In selenocyanate **5**, however, electrostatic interaction between the selenium and the nitrogen may also participate to the interaction formation due to the strong electron-withdrawing ability of a cyano group.

Molecular structures of **9**−**13** obtained by *ab initio* MO calculations at HF/3-21G* and HF/LANL1DZ levels are very consistent with the experimental results, though they are slightly discrepant within the two basis sets. NBO deletion analysis clearly indicated that the orbital interaction between a divalent selenium moiety and a nitrogen atom largely contributes to the Se···N interaction formation as well as that the main component of the interaction is the mixing of a low-lying σ^*_{Se-X} into a nitrogen lone pair (n_N). The electron delocalization from n_N to σ^*_{Se-X} may cause kinetic activation, or weakening, of the Se−X bond whereas it provides overall thermodynamic stabilization for the X−Se···N system. These conclusions are in accordance with our previous conclusion that the electronic structure of the Cl−Se···N nonbonded interaction of **14** is most likely compared to the S_N2 transition-state at a divalent selenium.[7]

Experimental Section

General Procedures. Commercially available organic and inorganic reagents were used without further purification. Tetrahydrofuran (THF) was dried over sodium wire and was distilled under nitrogen. Dichloromethane (CH_2Cl_2) was dried over calcium hydride and was distilled under nitrogen before use. Methanol (MeOH) was distilled under nitrogen. Other organic solvents were used without purification. ^{1}H, ^{13}C, ^{77}Se, and ^{15}N NMR spectra were measured on a JEOL α-500 spectrometer in $CDCl_3$ containing tetramethylsilane as an internal standard for ^{1}H and ^{13}C NMR. For ^{77}Se or ^{15}N NMR, dimethyl selenide (δ 0 ppm) or nitromethane (δ 5 ppm) in $CDCl_3$ was used as an external standard, respectively. ^{15}N-induced isotope shifts in ^{77}Se NMR were measured at 297 K in $CDCl_3$. The solutions were prepared separately for a natural abundant sample and the ^{15}N-labeled one. $J_{Se\cdots N}$ coupling constants of ^{77}Se NMR absorptions were measured from the expanded ^{1}H-decoupled ^{77}Se NMR spectra of ^{15}N-labeled **1**−**7**. Variable-temperature ^{1}H NMR spectra were recorded on a JEOL FX90Q spectrometer in $CHCl_3$ for **1**−**7** at room or higher temperature and in CD_2Cl_2 for **1** and **5**−**7** at low temperature. The low-resolution mass spectrum was measured on a Shimadzu QP1000 spectrometer operating at 70 eV by using the direct insertion method. Diselenide **1** was synthesized by the literature method[6] and was characterized by ^{1}H, ^{13}C, and ^{77}Se NMR spectra and elemental analysis: ^{77}Se NMR δ 431.9 (429.8 ppm in the literature[6]). **2**, **4**, and **6** were synthesized from **1** according to the literature methods[6,12] and were fully characterized by ^{1}H, ^{13}C, and ^{77}Se NMR (see the supporting information) as well as by elemental analysis for **6** (see below).

2-[(*N*-Cyclohexyl-*N*-methylamino)methyl]benzeneselenenyl Bromide (2). **2** was quantitatively synthesized from **1** by the reaction with an equimolar amount of bromide in CH_2Cl_2 according to the literature method.[6] ^{1}H, ^{13}C, and ^{77}Se NMR spectra of **2** are shown in the supporting information. ^{77}Se NMR: δ 1010.0 (1019.4 ppm in the literature[6]).

2-[(*N*-Cyclohexyl-*N*-methylamino)methyl]benzeneselenenyl Chloride (3). **1** (28.1 mg, 0.05 mmol) was dissolved in dry THF (2 mL) under nitrogen atmosphere, and SO_2Cl_2 (4.0 mL, 0.05 mmol) was added to the solution. After 1 h the reaction mixture was concentrated under reduced pressure. **3** was quantitatively obtained as a yellow-white powder. Spectral data for **3**: ^{1}H NMR δ 1.3 (m, 5H), 1.9 (m, 5H), 2.61 (s, 3H), 3.08 (m, 1H), 3.92 (d, 1H, J = 13.9 Hz), 4.16 (d, 1H, J = 13.9 Hz), 7.1−7.3 (m, 3H), 8.1−8.2 (m, 1H); ^{13}C NMR δ 25.3, 25.4, 25.6, 26.3, 30.9, 38.6, 63.1, 67.2, 125.3, 126.3, 129.0, 129.1, 134.7, 136.8; ^{77}Se NMR δ 1050.3. ^{1}H, ^{13}C, and ^{77}Se NMR spectra of **3** are shown in the supporting information.

2-[(*N*-Cyclohexyl-*N*-methylamino)methyl]benzeneselenenyl Acetate (4). **4** was quantitatively obtained from **2** by the treatment with an equimolar amount of silver acetate in CH_2Cl_2 according to the literature method.[12] ^{1}H, ^{13}C, and ^{77}Se NMR spectra of **4** are shown in the supporting information. ^{77}Se NMR: δ 1157.1 (1158.3 ppm in the literature[12]).

2-[(*N*-Cyclohexyl-*N*-methylamino)methyl]phenylselenenyl Cyanate (5). **3**, quantitatively prepared from **1** (218 mg, 0.5 mmol) by the above method, was dissolved in dry THF, and cyanotrimethylsilane (135 mL, 1.0 mmol) was added to the solution. After 10 min the reaction mixture was concentrated under reduced pressure. **5** was quantitatively obtained as a pale yellow oil from the residue by column chromatography on silica gel (CH_2Cl_2 as eluent). Spectral data for **5**: ^{1}H NMR δ 1.2−1.4 (m, 5H), 1.8−1.9 (m, 5H), 2.11 (s, 3H), 2.56 (m, 1H), 3.68 (s, 2H), 7.2−7.3 (m, 3H), 7.8−7.9 (m, 1H); ^{13}C NMR δ 25.4, 25.6, 27.3, 33.8, 58.7, 61.6, 108.9, 126.9, 127.0, 128.3, 128.4, 130.5, 137.6; ^{77}Se NMR δ 362.4; mass spectrum *m/e* 308 (M^+), 265 (base). Anal. Calcd for $C_{15}H_{20}N_2Se$: C, 58.63; H, 6.56; N, 9.12. Found: C, 58.40; H, 6.36; N, 8.99.

2-[(*N*-Cyclohexyl-*N*-methylamino)methyl]benzeneselenenyl Phenyl Sulfide (6). **6** was synthesized from **1** by the reaction with 2 molar equiv of benzenethiol in CH_2Cl_2 according to the literature method.[12] ^{1}H, ^{13}C, and ^{77}Se NMR spectra of **6** are shown in the supporting information. ^{77}Se NMR: δ 571.5 (571.9 ppm in the literature[12]). Anal. Calcd for $C_{20}H_{25}NSSe$; C, 61.52; H, 6.45; N, 3.59. Found: C, 61.29; H, 6.36; N, 3.72.

2-[(*N*-Cyclohexyl-*N*-methylamino)methyl]phenyl Methyl Selenide (7). **1** (169 mg, 0.3 mmol) was suspended in MeOH (10 mL) under nitrogen atmosphere, and sodium borohydride (22 mg, 0.6 mmol) was added to the solution. After 10 min, methyl iodide (0.19 mL, 3 mmol) was added, and the mixture was stirred for 2 h. It was then added to $NaHCO_3$ solution and was extracted by ether. The crude product was purified by column chromatography on silica gel (CH_2Cl_2−MeOH as eluent). **7** was obtained as a colorless oil (0.122 g, 69%). Spectral

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data for **7**: ^{1}H NMR δ 1.3 (m, 5H), 1.8 (m, 5H), 2.11 (s, 3H), 2.23 (s, 3H), 2.58 (m, 1H), 3.67 (s, 2H), 7.1−7.3 (m, 4H); ^{13}C NMR δ 6.2, 25.9, 26.2, 28.0, 35.2, 59.3, 62.0, 124.6, 127.2, 128.3, 129.0, 134.5, 139.8; ^{77}Se NMR δ 180.8; mass spectrum *m/e* 297 (M^+), 202 (base). Anal. Calcd for $C_{15}H_{23}NSe$; C, 60.80; H, 7.82; N, 4.83. Found: C, 60.54; H, 7.64; N, 5.00.

^{15}N-Labeled 1−7. ^{15}N-labeled **1** was synthesized as follows. Aniline-^{15}N (>99 atom % ^{15}N, ISOTEC Inc.) was hydrogenated over ruthenium(III) hydroxide.[35] The obtained cyclohexylamine-^{15}N was formylated by ethyl formate[36] and then reduced by lithium aluminum hydride to give cyclohexylmethylamine-^{15}N.[37] The obtained secondary amine was coupled with 2,2′-diselenobis(benzyl chloride)[6] in the presence of $NaHCO_3$ and excess potassium iodide to give **1**-^{15}N. ^{15}N-labeled **2−7** were obtained from **1**-^{15}N according to the methods described above.

***N*-Cyclohexyl-*N*-methylbenzylamine (8).** **8** was synthesized in 44% yield by the condensation between benzyl bromide and cyclohexylmethylamine in the presence of excess triethylamine. Spectral data for **8** were identical with the literature.[17]

Spectral Simulation. Variable-temperature ^{1}H NMR spectra for **5** and **6** were simulated by using the DNMR5 program.[18] The chemical shifts, coupling constant, and line width were read from the spectrum measured at low temperature (215 K for **6** and 196 K for **7**). Then the rate constant (*k*) at each temperature was determined so that the simulated spectrum became almost identical with the experimental one.

Calculation Methods. Gaussian 92[38] and Spartan 3.0[39] were used as source programs for *ab initio* MO calculations and NBO deletion analysis.[30] The N inversion barrier (E_3) and the C−N rotational barrier (E_2) of **8** were calculated at the HF/3-21G level. The most favorable path from the global energy minimum conformation of **8** (Ph is antiperiplanar to *c*-Hex) to its enantiomer was found to be the C−N rotation to the rotational isomer (Ph is antiperiplanar to the nitrogen lone pair) followed by the nitrogen inversion. All the transition states were fully characterized by frequency calculations, and their energies were corrected by the zero point energy. The values obtained were 6.7 kcal/mol for E_2 and 3.8 kcal/mol for E_3. The rotational barrier E_1 was estimated by semiempirical PM3 calculations on **9−13** changing the dihedral angle of the Ar−C bond (ω) from 0° to 120°. The geometry was fully optimized in each calculation with the constraint ω. The heat of formation was maximized at 90° and then minimized at 100°. The energy difference between these two dihedral angles was ∼1.5 kcal/mol for **9−13**. It was found that the conformation changes drastically when the ω increases from 100° to 120°.

Geometries of **9−13** were fully optimized at the Hartree−Fock level using a 3-21G* basis set (3-21G with d polarization functions for Se, S, and Cl)[39] and a LANL1DZ basis set (Los Alamos ECP+DZ basis set[32] for Se, S, and Cl and Dunning/Huzinaga valence double-ζ basis set for N, O, C, and H). NBO analysis, which is included in Gaussian 92, was then performed on the optimized conformations using the same basis set. The electron delocalization energy (ΔE_{del}) between Se−X and N was calculated by using the NBO deletion method.[30]

Acknowledgment. We thank the Ministry of Education, Science and Culture of Japan for financial support (Nos. 07854043, 06854029, 06640681, and 04854043).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1−7** and a comparison of 90 MHz ^{1}H NMR spectra of benzylic protons for **6** at various temperatures with simulated ones (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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