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Synthesis and Structural Characterization of 1-Mesityl-1,3-dihydro-imidazole-2-selone and Bis(1-mesitylimidazol-2-yl)diselenide: Experimental Evidence That the Selone Is More Stable Than the Selenol Tautomer

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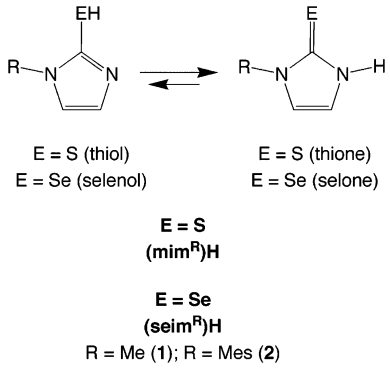
Abstract: 1-Mesityl-1,3-dihydro-imidazole-2-selone, (seim^{Mes})H, may be obtained from 1-mesitylimidazole via (i) deprotonation with Bu^{n}Li, (ii) treatment with elemental selenium, and (iii) addition of HCl(aq). Structural characterization of (seim^{Mes})H by X-ray diffraction demonstrates that the compound exists as the selone rather than selenol tautomer, a result that is in accord with DFT calculations. Solutions of (seim^{Mes})H are oxidized by air to give bis(1-mesitylimidazol-2-yl)diselenide, (seim^{Mes})$_2$. A corresponding investigation of (seim^{Me})H demonstrates that, in contrast to a previous report, the selenium analogue of methimazole exists in the selone form with a structure analogous to that of methimazole. ^{1}H and ^{77}Se NMR studies demonstrate that the (seim^R) groups of the selone (seim^R)H and diselenide (seim^R)$_2$ undergo facile exchange on the NMR time scale.

Introduction

1-R-2-Mercaptoimidazoles and their 1-R-imidazole-2-thione tautomers, represented by the general description (mim^R)H, comprise a well-known class of compounds that have been investigated most extensively (Scheme 1).[1] In large part, the interest in these compounds derives from the early discovery that the parent derivative, i.e., 1-methyl-2-mercaptoimidazole/1-methylimidazole-2-thione (also known as methimazole), is an antithyroid drug that operates via inhibiting thyroid hormone synthesis.[2] Furthermore, 2-mercaptoimidazole/imidazole-2-thione derivatives have other biological properties, as illustrated by the recent demonstration that they are a new class of potent CCR2 antagonists.[1c] By comparison to the extensive chemistry of 1-R-2-mercaptoimidazole and 1-R-imidazole-2-thione compounds, however, that of their selenium counterparts is virtually nonexistent. Specifically, the only 1-R-2-hydroselenoimidazole/1-R-imidazole-2-selone system reported in the literature is that for the methimazole analogue, (seim^{Me})H (**1**),[3,4] which has also been investigated with respect to its antithyroid activity.[4,5] However, the molecular structure of the selenium analogue of methimazole has not been determined by X-ray diffraction, and reports concerning the relative stability of the selone[6] and selenol tautomers are contradictory.[3−5] In this paper, we report the

Scheme 1



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10.1021/ja063168e CCC: $33.50

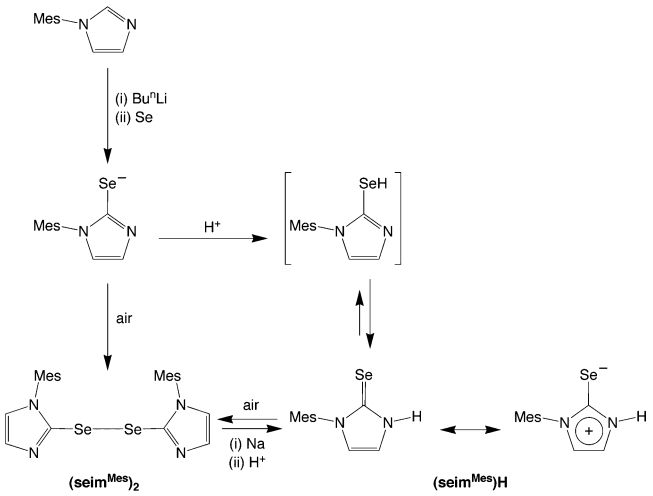
synthesis of the mesityl counterpart (seim^{Mes})H (**2**), provide the first structural characterization of 1-R-imidazole-2-selone derivatives, and discuss their stability with respect to the selenol tautomers.

Results and Discussion

As an extension of our studies concerned with tris(2-mercapto-1-R-imidazolyl)hydroborato ligands [Tm^R], which feature an [S_3] donor array,[7] we sought 1-R-imidazole-2-selones with bulky substituents to prepare the corresponding class of ligands that present a [Se_3] donor array to a metal center. However, only one 1-R-imidazole-2-selone derivative has been previously described in the literature, namely the selenium analogue of methimazole, (seim^{Me})H. The literature pertaining to (seim^{Me})H is, however, contradictory. For example, the first report of (seim^{Me})H, by Guziec and Guziec (GG) in 1994, stated that the complex existed as an orange selone tautomer,[3] but subsequent investigations by Roy, Nethaji, and Mugesh (RNM) concluded that the final orange product isolated by GG is *not* (seim^{Me})H, but is actually the oxidized dimer, (seim^{Me})$_2$.[4,5,8] Roy and Mugesh (RM) further stated that all attempts to isolate the selone were unsuccessful, but noted that (seim^{Me})H could be obtained as the selenol tautomer by reducing (seim^{Me})$_2$ with $NaBH_4$.[4] On the basis of these observations, RM concluded that the selenol tautomer of (seim^{Me})H is more stable than the selone form, in marked contrast to the methimazole system, for which the thione tautomer is more stable than the thiol.[9] In view of the apparent complexity and controversy associated with the selenium analogue of methimazole, and our desire to incorporate bulky substituents, we deemed it worthwhile to prepare and structurally characterize other 1-R-2-hydroselenoimidazole/1-R-imidazole-2-selone systems.

1. Synthesis and Structural Characterization of 1-Mesitylimidazole-2-selone. We selected the mesityl derivative 1-mesityl-1,3-dihydro-imidazole-2-selone (hereafter abbreviated 1-mesitylimidazole-2-selone) as our initial target since (i) we have previously prepared a variety of [Tm^{Mes}] derivatives that would provide a useful comparison[7a] and (ii) the required

Scheme 2



1-mesitylimidazole[10] is readily available. However, in view of the above discussion with respect to oxidation of (seim^{Me})H to (seim^{Me})$_2$, we considered that an important precaution would be to perform the workup procedure under anaerobic conditions. Significantly, using this approach, 1-mesitylimidazole-2-selone (seim^{Mes})H was obtained in three steps from 1-mesitylimidazole via (i) deprotonation with Bu^{n}Li, (ii) treatment with elemental selenium, and (iii) addition of HCl(aq), as illustrated in Scheme 2.

The molecular structure of (seim^{Mes})H has been determined by X-ray diffraction, as illustrated in Figure 1. Importantly, the hydrogen atom attached to nitrogen was located and refined, thereby providing excellent evidence that it corresponds to the selone[6] rather than the selenol tautomer. Further support for this description of the bonding in (seim^{Mes})H is provided by consideration of the C−Se bond length. Specifically, the C−Se bond length of 1.845(2) Å in (seim^{Mes})H is in the middle of the range observed for related selenourea and other derivatives (1.83−1.88 Å) that are not subject to tautomerization, namely the 1,3-dialkyl and benzo derivatives illustrated in Figure 2.[11−14] It is important to note, however, that these bond lengths do not correspond to a pure C═Se double bond and are intermediate between the values predicted by the respective sum of the single and double bond covalent radii of carbon and selenium: d(C−Se) = 1.94 Å and d(C═Se) = 1.74 Å.[15] As such, the structural data are consistent with the notion that an important resonance contributor is the zwitterionic form with a C−Se single covalent bond (Scheme 2).[16] This proposal is supported by examination of the occupied π-symmetry molecular orbitals of the imidazoleselone moiety, as illustrated in Figure 3. Specifically, the

(6) Unless otherwise specified, the term "selone" is used generally in this paper as an abbreviated form of "imidazoleselone" to refer to the terminal [CSe] group. The term is not intended to distinguish between C═Se and zwitterionic C$^+$—Se$^-$ resonance structures, but is rather intended to make a distinction with a selenol tautomer.

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(8) For example, ref 5 states: "In contrast to MMI (methimazole), the selenium analogue exists in a diselenide form".

(9) For example, ref 4 states: "...aqueous workup afforded the selenol as yellow solid, which was found to be stable under inert atmosphere...", "Although compound 2 can exist in both selenol and selone forms in solution, the ^{77}Se NMR spectrum recorded immediately after the workup of the reaction showed a signal at 4 ppm, which can be ascribed to the selenol (2b) tautomer", and "Experimental and theoretical studies show that the selenium analogue of methimazole (MSeI) exists predominantly in its selenol form, whereas the sulfur compound exists in its thione form...".

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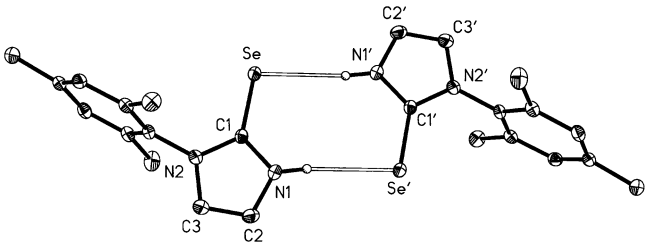

Figure 1. Molecular structure of (seim^{Mes})H. Selected bond lengths (Å): Se−C(1) 1.845(2), Se···N(1′) 3.384(2).

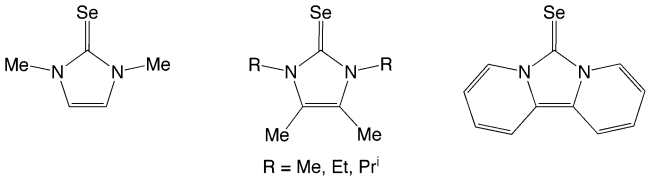

Figure 2. Examples of 1,3-disubstituted imidazole-2-selone derivatives.

molecular orbitals indicate that there is relatively little π-overlap between the selenium atom and the adjacent carbon atom of the aromatic ring.[17]

(seim^{Mes})H is the first monosubstituted imidazole-2-selone derivative to be structurally characterized by X-ray diffraction,[18] and a noteworthy aspect, which distinguishes it from the aforementioned 1,3-dialkyl and benzo derivatives, is that it exists as an N−H···Se hydrogen-bonded dimer in the solid state. In this regard, the structure is closely related to those of several (mim^R)H sulfur counterparts (*vide supra*) which exist in the thione form[7e,19c,20] and therefore provides additional supporting evidence that (seim^{Mes})H exists as the selone tautomer. Furthermore, the intermolecular N···Se separation is 3.384(2) Å and is comparable to the N···S separations in (mim^R)H derivatives (3.27−3.35 Å);[19c] as such, the N−H···Se hydrogen-bonding interaction must be considered significant.[21] Undoubtedly, the zwitterionic resonance structure with the negative charge on selenium contributes to a favorable hydrogen-bonding interaction.

(seim^{Mes})H has also been characterized by NMR spectroscopy, as illustrated by the ^{1}H NMR spectrum of Figure 4. In this regard, ^{77}Se NMR chemical shift and $^1J_{Se-C}$ coupling constant data have been previously used to identify the nature of a C−Se bond[22] and also provide compelling evidence pertaining to the

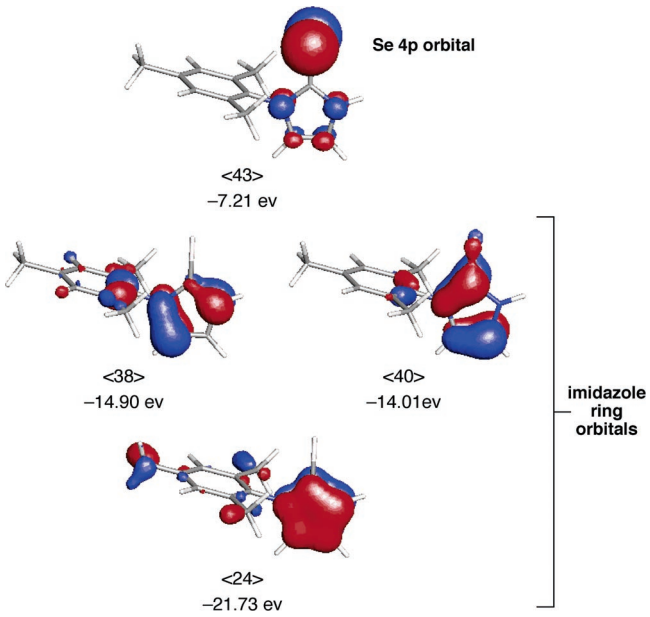

Figure 3. Occupied π-symmetry molecular orbitals of the imidazole-2-selone moiety comprising the three bonding orbitals of the imidazole ring and a selenium 4p orbital. Note that there is little π-overlap between the selenium 4p orbital and the adjacent carbon atom.

identity of (seim^{Mes})H. Specifically, the ^{77}Se NMR chemical shifts of compounds with C═Se groups span a very large range of ca. 2500 to −500 ppm,[22] with the selone moiety in simple selenoaldehyde and selenoketone derivatives being characterized by large downfield chemical shifts, e.g., 2398 ppm for (2,4,6-Bu$^t_3$C$_6$H$_2$)C(H)Se and 2131 ppm for Bu$^t_2$CSe, while selenoureas are characterized by chemical shifts in the range 150−245 ppm.[22,23] This large variation has been rationalized by π-donation from the nitrogen increasing the electron density at selenium, thereby causing an upfield shift for selenoureas relative to R$_2$CSe.[22] The ^{77}Se NMR chemical shift of the selone tautomer of (seim^{Mes})H is likewise characterized by a relatively upfield ^{77}Se NMR chemical shift of 28 ppm, a value that is comparable to the chemical shifts for a series of 1,3-dialkylimidazole-2-selone derivatives (19−34 ppm).[12,24]

$^1J_{Se-C}$ coupling constants also provide information concerned with the nature of the C−Se bond because its magnitude depends strongly on the hybridization state of the carbon and selenium and are typically in the range 203−292 Hz for C═Se groups[22,23,25] and much lower for sp^2-hybridized compounds with C−Se single bonds; for example, $^1J_{Se-C}$ for the diselenide (seim^{Me})$_2$ is 163 Hz (Table 1), while $^1J_{Se-C}$ for the vinyl selenol CH$_2$═CHSeH is 93 Hz.[26] On this basis, a $^1J_{Se-C}$ value of 231 Hz for (seim^{Mes})H is most consistent with the selone form.

2. Relative Thermodynamic Stabilities of the Selone and Selenol Tautomers of (seim^{Mes})H. The X-ray diffraction and

(16) Although C═Se and zwitterionic C$^+$—Se$^-$ are resonance structures, ref 4 implies that species with C═Se and C$^+$—Se$^-$ structures may have an independent existence. However, examination of Table 1 and the Supporting Information of ref 4 indicates that compounds 2a (C═Se) and 2c (C$^+$—Se$^-$) have identical calculated C−Se bond lengths, ^{77}Se NMR chemical shifts, and energies. Thus, the two forms do not have an independent existence.

(17) In support of the zwitterionic character, the NBO charges on C and Se of the selone moiety of (seim^{Mes})H are 0.15 and −0.24, respectively. For comparison, the corresponding charges for (seim^{Mes})$_2$ are 0.11 and 0.19, respectively.

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(24) For further comparison, a series of oxazolidine-2-selone derivatives are characterized by ^{77}Se NMR chemical shifts in the range 117−156 ppm. See ref 21.

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Table 1. NMR Spectroscopic Chemical Shift (ppm) and Coupling Constant (Hz) Data for $(seim^{Me})H$ and $(seim^{Me})_2$ in $CDCl_3$

	$(seim^{Me})H$			$(seim^{Me})_2$	
	selone this work	selone GG	"selenol" RM	this work	RM
^{1}H	3.67[a]	3.69	3.69	3.66	3.52
	6.81[a]	6.86	6.89	7.05	7.00
	6.85[a]	6.90	6.95	7.15	7.09
	12.19[a]	−[b]	8.75		
^{77}Se	−5	−[b]	−5	400	397
^{13}C	35.7	36.06, 36.13[c]	36.1	35.1	35.2
	116.2	116.9	118.6	124.6	124.7
	120.4	120.8	121.2	130.9	131.3
	150.2	150.7	148.8	132.9	133.0
	$^{1}J_{Se-C} = 222$	$^{1}J_{Se-C} = 220$	−[b]	$^{1}J_{Se-C} = 163$	−[b]

[a] The ^{1}H NMR chemical shifts for $(seim^{Me})H$, and especially that for the NH group, are concentration dependent. [b] Value not listed. [c] Two chemical shifts are listed for the methyl group.

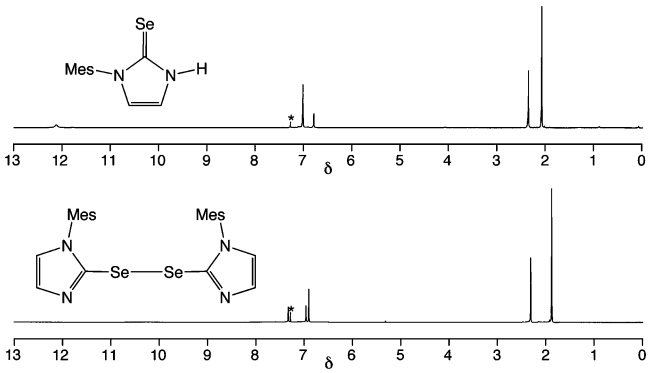


Figure 4. Comparison of the ^{1}H NMR spectra (400 MHz) of the selone tautomer of $(seim^{Mes})H$ with the diselenide $(seim^{Mes})_2$ in $CDCl_3$ (* = $CHCl_3$).

NMR spectroscopic studies described above provide compelling evidence that $(seim^{Mes})H$, as isolated, exists as a selone tautomer. While this observation is in accord with studies on 1-R-2-mercaptoimidazole/1-R-imidazole-2-thione systems for which the thione is more stable,[7e,19,20,27] it does not prove that the selone is more stable than the selenol tautomer since it is possible that there could exist a sufficiently large barrier to prevent the conversion. However, evidence that the selone is the more stable tautomer is provided by density functional theory (DFT) calculations. The fully geometry optimized (B3LYP) structures of the selone and selenol tautomers of $(seim^{Mes})H$ are illustrated in Figure 5. In agreement with the experimental structure of the selone derivative, the mesityl and imidazole groups are orthogonal and the calculated C═Se bond length (1.859 Å) compares favorably with the experimental value [1.845(2) Å].

With respect to the selenol tautomer of $(seim^{Mes})H$, the energy is expected to be a function of the position of the selenol hydrogen atom as defined by the H−Se−C−N_{unsub} torsion angle.[4] In this regard, the energies of several idealized conformations, including that of the fully geometry optimized structure, are summarized in Table 2, thereby indicating that the favored location of the selenol hydrogen is in the imidazole plane and directed towards the unsubstituted nitrogen. This conformation is the same as the favored conformation of the thiol tautomer of $(mim^{Me})H$,[4] but is different from the selenol tautomer of $(seim^{Me})H$, for which the favored conformation has a H−Se−C−N angle of 107°, such that the Se−H bond is almost orthogonal to the imidazole plane,[4] although the differences in energy are relatively modest. The most important result from the DFT calculations, however, is that the selone tautomer of $(seim^{Mes})H$ is considerably more stable than the selenol tautomer by 10.7 kcal mol^{-1}, a result that is in accord with the ability to isolate the selone tautomer.

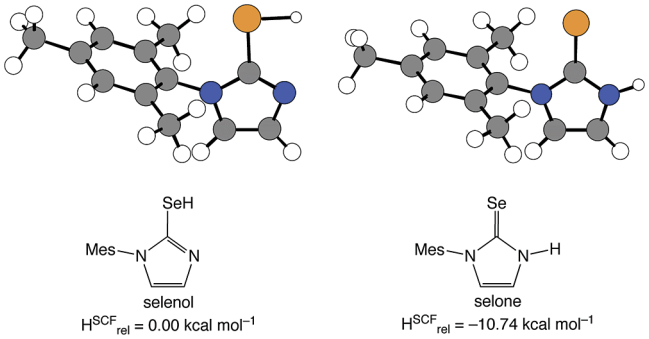


Figure 5. DFT (B3LYP) geometry optimized structures of the selenol and selone tautomers of $(seim^{Mes})H$.

Table 2. Relative Energy of the Selenol Tautomer of $(seim^{Mes})H$ as a Function of the H−Se−C−N_{unsub} Dihedral Angle

H–Se–C–N_{unsub}/°	relative energy/kcal mol^{-1}
0.00	0.002
0.27[a]	0.000
45.00	1.124
90.00	1.577
135.00	0.863
180.00	0.539

[a] Value for fully geometry optimized structure.

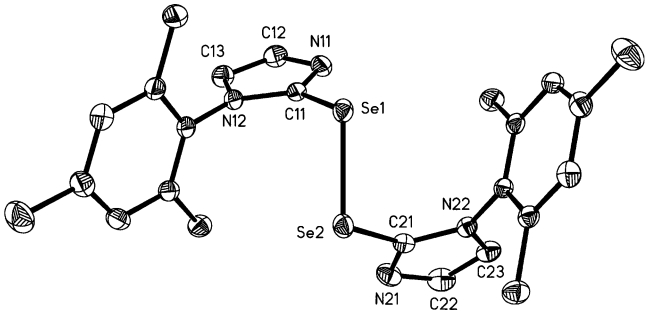


Figure 6. Molecular structure of $(seim^{Mes})_2$. Selected bond lengths (Å): Se(1)−C(11) 1.896(3), Se(2)−C(21) 1.901(3), Se(1)−Se(2) 2.3298(4).

3. Synthesis and Structural Characterization of the Diselenide, $(seim^{Mes})_2$. The successful isolation and structural verification of $(seim^{Mes})H$ indicates that the method of GG may be used to prepare imidazole-2-selone compounds if appropriate precautions are taken. In this regard, the diselenide $(seim^{Mes})_2$ is obtained if the reaction vessel is exposed directly to air after treatment with $Bu^{n}Li$ and Se (Scheme 2). Furthermore, the diselenide is also obtained over a period of days by exposing a solution of $(seim^{Mes})H$ in chloroform to air (Scheme 2). The formation of $(seim^{Mes})_2$ is reversible, and the Se−Se bond may be cleaved by Na to regenerate the selone $(seim^{Mes})H$ upon workup (Scheme 2).

The molecular structure of $(seim^{Mes})_2$ has been determined by X-ray diffraction, as illustrated in Figure 6, and the Se−Se bond length [2.3298(4) Å] compares favorably with that of $(seim^{Me})_2$ [2.36 Å].[5] As expected, the C−Se bond lengths [1.896(3) and 1.901(3) Å] are longer than the corresponding

(27) Laurence, C.; El Ghomari, M. J.; Le Questel, J.-Y.; Berthelot, M.; Mokhlisse, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1545−1551.

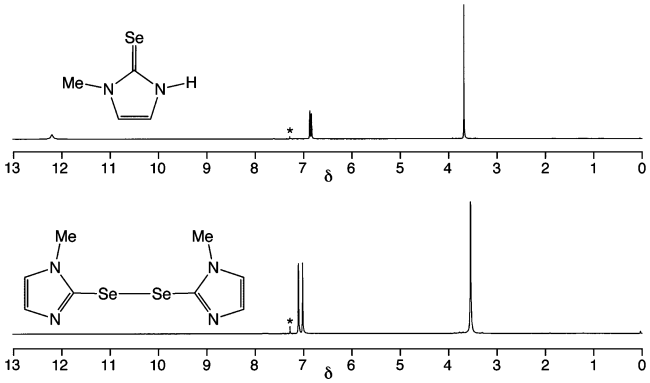


Figure 7. Comparison of the ^{1}H NMR spectra (300 MHz) of the selone tautomer of (seim^{Me})H and the diselenide (seim^{Me})$_2$ in $CDCl_3$ (* = $CHCl_3$).

value in (seim^{Mes})H [1.845(2) Å], but the difference is much smaller than that predicted on the basis of the single and double bond covalent radii of carbon and selenium (0.2 Å).[15] As noted above, this observation is in accord with the notion that the C═Se bond in (seim^{Mes})H is zwitterionic, C$^+$—Se$^-$, and possesses considerable single bond character. The diselenide (seim^{Mes})$_2$ has also been characterized by ^{77}Se NMR spectroscopy, and the chemical shift of (seim^{Mes})$_2$ (415 ppm, $CDCl_3$) is comparable to that of (seim^{Me})$_2$ (397 ppm, $CDCl_3$),[4] but very distinct from that of the selone (seim^{Mes})H (17 ppm, $CDCl_3$).

4. The Nature of the Selenium Analogue of Methimazole. As noted above, there are discrepancies in the literature pertaining to the synthesis and nature of the selenium analogue of methimazole (seim^{Me})H.[3−5] In this regard, GG were the first to report that (seim^{Me})H could be synthesized by treatment of 1-methylimidazole with Bu^{n}Li, followed by treatment with elemental selenium and acidification (cf. Scheme 2); GG also stated that (seim^{Me})H exists as the selone tautomer, evidence for which was provided by the magnitude of the $^1J_{Se-C}$ coupling constant (220 Hz).[3] RM and RNM, however, suggested that the final compound synthesized by GG was actually the diselenide (seim^{Me})$_2$ on the basis that they repeated GG's synthesis and structurally characterized the product obtained by X-ray diffraction.[4,5,8] RM stated that all attempts to isolate the selone were unsuccessful.[4] RM also described that the diselenide (seim^{Me})$_2$ could be reduced to (seim^{Me})H by $NaBH_4$, but that the product obtained is the *selenol* rather than selone tautomer;[28] RM subsequently concluded that the selenium analogue of methimazole is quite distinct from methimazole since the latter exists in the thione form whereas the former exists as the selenol.[4,9]

In view of the above discrepancies, we considered it worthwhile to reevaluate the reports of GG, RNM, and RM in order to place them in context with our studies on the mesityl derivative (seim^{Mes})H. Therefore, on the basis of our experience with the synthesis of (seim^{Mes})H, we repeated the synthesis of (seim^{Me})H as reported by GG,[3] but with the additional precaution of excluding air during the workup procedure. The product isolated possesses a ^{1}H NMR spectrum (Figure 7) which is very similar to that reported by GG (Table 1); the only significant difference is the presence of an additional signal at ca. 12.2 ppm assignable to NH,[29] which was not reported by GG,

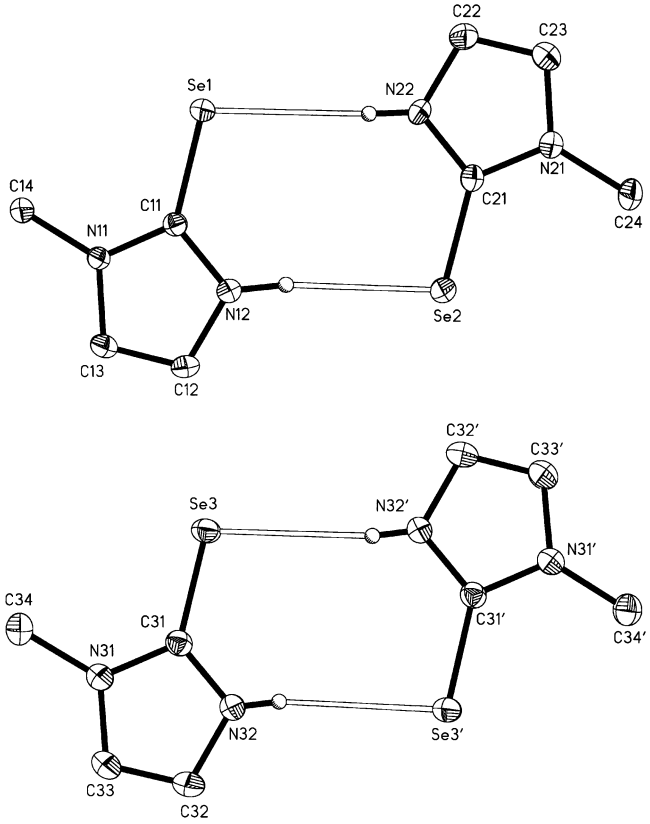


Figure 8. Molecular structure of (seim^{Me})H. Selected bond lengths (Å): C(11)−Se(1) 1.849(3), C(21)−Se(2) 1.849(3), C(31)−Se(3) 1.849(3), Se(1)···N(22) 3.414(3), Se(2)···N(12) 3.390(3), Se(3)···N(32′) 3.394(3).

possibly because it was either outside the spectral window or broadened into the baseline. The spectral features of (seim^{Me})H are also very similar to those of the selone tautomer of the mesityl counterpart (seim^{Mes})H, with the NH group being characterized by a broad signal at 11.9 ppm. In addition to the ^{1}H NMR spectroscopic data, the ^{13}C NMR spectroscopic data of the two samples of (seim^{Me})H are also similar;[30] in particular, the ^{13}C signal of the C═Se group exhibits a $^1J_{Se-C}$ coupling constant of 222 Hz, comparable to the value of 220 Hz reported by GG. While the $^1J_{Se-C}$ coupling constant is consistent with a selone tautomer, further evidence is provided by X-ray diffraction studies (Figure 8). Specifically, the hydrogen atom attached to nitrogen was located and refined, thereby identifying the compound as the selone rather than the selenol tautomer. Furthermore, the average C═Se bond length (1.849 Å) of the crystallographically independent molecules is virtually identical to that of the mesityl counterpart [1.845(2) Å] and marginally shorter than the C−Se single bond lengths in (seim^{Me})$_2$ [1.88 Å][5] and (seim^{Mes})$_2$ [1.896(3) and 1.901(3) Å]; thus, the selone tautomer of (seim^{Me})H possesses considerable zwitterionic, C$^+$—Se$^-$, character. Also of note, the structure of (seim^{Me})H consists of pairs of hydrogen-bonded dimers analogous to that of the sulfur counterpart, methimazole, which exists in the thione form.[19] It is, therefore, evident that the product isolated by the method of GG under anaerobic conditions is the selone tautomer of (seim^{Me})H. One additional aspect of the selone tautomer of (seim^{Me})H which deserves mention is that crystals of the pure

(28) Specifically, ref 4 states, "...the corresponding selenol (2b) can be conveniently obtained by reducing the diselenide by $NaBH_4$ or glutathione (GSH)".

(29) The chemical shift of the NH group is concentration dependent.

(30) A notable difference is that GG reports two very closely separated chemical shifts for the methyl group (see Table 1); it is possible that this is an artifact.

material are colorless and not orange as reported by GG; we consider it likely that the orange appearance described by GG is a result of contamination by small quantities of the orange diselenide $(seim^{Me})_2$ which results from exposure to air (*vide infra*).

RM's characterization of $(seim^{Me})H$ as a selenol derivative employed ^{77}Se NMR spectroscopy, including calculations of ^{77}Se NMR chemical shifts.[4,31] However, it has recently been reported that the chemical shift of terminal selenium anions and selenols cannot be calculated reliably due to the influence of solvation effects,[31a] and so such correlations must be viewed with a degree of caution.

While $(seim^{Me})H$ may be readily isolated as its selone tautomer by employing a synthetic method that uses anaerobic conditions, the diselenide $(seim^{Me})_2$ is obtained if the workup procedure is performed in air (see Experimental Section). The diselenide $(seim^{Me})_2$ can also be obtained by exposing a solution of the selone $(seim^{Me})H$ to air overnight. The identification of the diselenide is based on comparison of (i) the ^1H, ^{13}C, and ^{77}Se NMR spectroscopic data (Table 1) and (ii) the unit cell[32] with that reported by RM. Although RM concluded that the final compound obtained by GG was the diselenide $(seim^{Me})_2$, rather than the selone $(seim^{Me})H$, a consideration of the data listed in Table 1 indicates that such a conclusion is not valid because the spectroscopic properties of $(seim^{Me})_2$ and $(seim^{Me})H$ are very distinct.

RM also reported that $NaBH_4$ reduction of the diselenide $(seim^{Me})_2$ gives the selenol tautomer of $(seim^{Me})H$.[28] We have repeated this synthesis and have obtained a product that has a ^1H NMR spectrum which is very similar to that described by RM for their "selenol". However, this ^1H NMR spectrum is indistinguishable from that of the selone (Table 1). The logical conclusion, therefore, is that RM obtained the selone rather than the selenol tautomer. As such, RM's statement that the selenium analogue of methimazole exists primarily as a selenol is not substantiated by the results reported here. In fact, calculations by RM on $(seim^{Me})H$ actually disagree with their assertion that the selenol is the more stable tautomer. Specifically, the calculations indicate that the selone form of $(seim^{Me})H$ is 13.4 kcal mol^{-1} more stable than the selenol tautomer.[4] The body of evidence, and in particular our structural verification by X-ray diffraction, indicates that the selenium analogue of methimazole can be synthesized by the method of GG and that the thermodynamically more stable structure is the selone rather than the selenol tautomer. Thus, whereas the selenium analogue of methimazole has been proposed to exist in a form different to that of methimazole,[4] it is evident that it actually possesses the same type of structure.

5. Chemical Exchange between Selone and Diselenide Compounds. An interesting aspect of the selone $(seim^R)H$ and diselenide $(seim^R)_2$ compounds (R = Me, Mes) is that the $(seim^R)$ groups undergo facile exchange between the two molecules in chloroform solution. For example, while the ^1H NMR spectra of $(seim^R)H$ and $(seim^R)_2$ in $CDCl_3$ are distinct (Figures 4 and 7), solutions composed of a mixture of $(seim^R)H$ and $(seim^R)_2$ show only a single set of resonances that appear at the weighted average of the signals of pure $(seim^R)H$ and $(seim^R)_2$. This observation provides clear evidence that the exchange of $(seim^R)$ groups is rapid on the NMR time scale. In this regard, the small differences in chemical shifts for $(seim^{Me})H$ listed in Table 1 may be a consequence of variable quantities of the diselenide $(seim^{Me})_2$ impurity. More significant than rapid exchange on the ^1H NMR time scale, however, is the fact that exchange is also rapid on the ^{77}Se NMR time scale. For example, the ^{77}Se NMR spectrum of a 1.3:1 molar mixture of $(seim^{Me})H$ and $(seim^{Me})_2$ consists of a broad signal at a weighted average of the chemical shifts of $(seim^{Me})H$ (−5 ppm) and $(seim^{Me})_2$ (400 ppm), as illustrated in Figure 9. In view of the large frequency difference between the signals for the individual compounds (23,135 Hz on a spectrometer operating at 57.2 MHz), the rate of exchange is *very* fast, with a value of ~25,000 s^{-1}.[33]

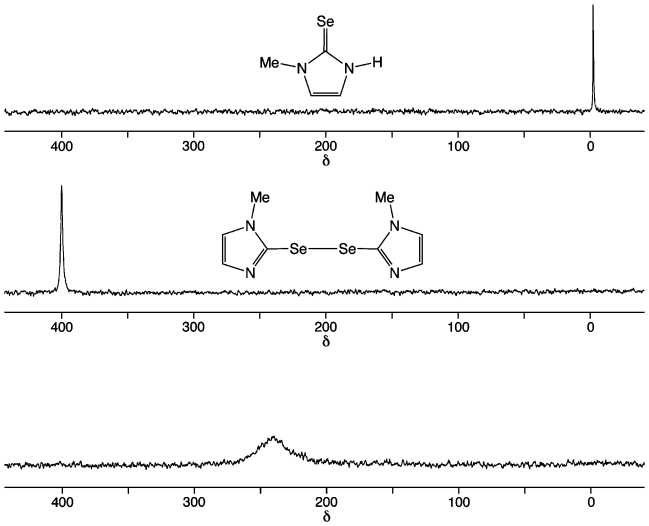


Figure 9. ^{77}Se NMR spectra of $(seim^{Me})H$ (top), $(seim^{Me})_2$ (middle), and a 1.3:1 mixture (bottom), corresponding to an exchange rate of ~25,000 s^{-1}.

In addition to NMR spectroscopy, further evidence for exchange is provided by the observation that $(seim^{Mes})H$ and $(seim^{Me})_2$ react to give a mixture that may be shown by mass spectrometry to comprise, *inter alia*, $(seim^{Me})(seim^{Mes})$, $(seim^{Mes})_2$, and $(seim^{Me})_2$.

Selenol/diselenide exchange reactions between RSeH and $(RSe)_2$ have been previously investigated, e.g., R = CH_2CH_2OH[33] and $CH_2CH_2NH_3^+$,[34,35] with the conclusion that the deprotonated selenolate, RSe^-, is the species responsible for effecting the exchange.[36−38] On this basis, a reasonable mechanism for the $(seim^{R*})H/(seim^R)_2$ exchange process (where R* is a label to describe the exchange) involves (i) proton transfer from $(seim^{R*})H$ to one of the nitrogen atoms of $(seim^R)_2$ to generate $[(seim^{R*})]^-$ and $[(seim^R)\{(seim^R)H\}]^+$, followed by (ii) nucleophilic attack by $[(seim^{R*})]^-$ on $[(seim^R)\{(seim^R)H\}]^+$ to

(31) For other recent calculations of ^{77}Se NMR chemical shifts, see: (a) Bayse, C. A. *J. Chem. Theor. Comput.* **2005**, *1*, 1119−1127. (b) Bayse, C. A. *Inorg. Chem.* **2004**, *43*, 1208−1210. (c) Keal, T. W.; Tozer, D. J. *Mol. Phys.* **2005**, *103*, 1007−1011.

(32) Monoclinic, a = 12.629(6) Å, b = 7.581(5) Å, c = 11.423(6) Å, α = 90°, β = 97.54(2)°, γ = 90°, V = 1084(1) $Å^3$, T = 243 K.

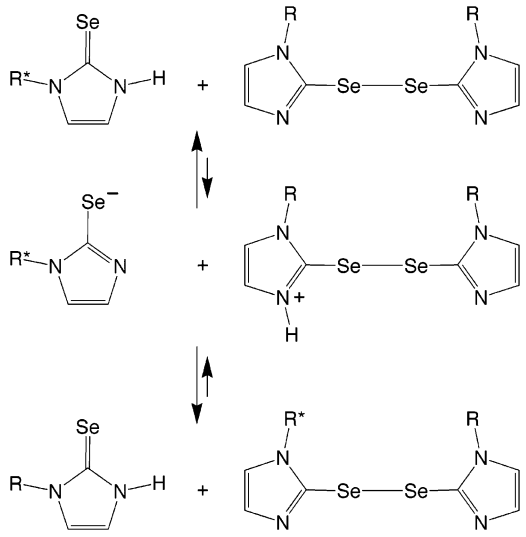
(33) For other examples of exchange on the ^{77}Se NMR time scale, see: Tan, K.-S.; Arnold, A. P.; Rabenstein, D. L. *Can. J. Chem.* **1988**, *66*, 54−60.

(34) Pleasants, J. C.; Guo, W.; Rabenstein, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 6553−6558.

(35) For another study which suggests that selenol/diselenide exchange is rapid on the NMR time scale, see: Reich, H. J.; Jasperse, C. P. *J. Am. Chem. Soc.* **1987**, *109*, 5549−5551.

(36) Analogous exchange reactions between R*SeSeH and RSeSeR are also known. See, for example: Ishii, A.; Mori, Y.; Uchiumi, R. *Heteroat. Chem.* **2005**, *16*, 525−528.

Scheme 3



liberate (seim^{R})H and form (seim^{R*})(seim^{R}),[39] as illustrated in Scheme 3.

Conclusions

In summary, 1-mesitylimidazole-2-selone (seim^{Mes})H may be obtained from 1-mesitylimidazole via (i) deprotonation with Bu^{n}-Li, (ii) treatment with elemental selenium, and (iii) addition of HCl(aq). Structural characterization of (seim^{Mes})H by X-ray diffraction demonstrates that the compound exists as the selone rather than the selenol tautomer, a result that is confirmed by DFT calculations. A reexamination of the selenium analogue of methimazole demonstrates that, in contrast to recent reports, the compound exists in the selone form with a structure that is analogous to methimazole.

Experimental Section

General Considerations. All manipulations were performed using Schlenk techniques under a nitrogen atmosphere unless otherwise specified. Solvents were purified and degassed by standard procedures. ^{1}H and ^{13}C NMR spectra were measured on Bruker 300 DRX, Bruker 400 DRX, and Bruker Avance 500 DMX spectrometers. ^{1}H and ^{13}C chemical shifts are reported in ppm relative to $SiMe_4$ ($\delta = 0$) and were referenced internally with respect to the protio solvent impurity (δ 7.26 for $CHCl_3$, 2.50 for Me_2SO). ^{77}Se chemical shifts are reported in ppm relative to neat Me_2Se ($\delta = 0$) and were referenced using a solution of Ph_2Se_2 in C_6D_6 ($\delta = 460$) as external standard.[40] Coupling constants are given in hertz. Infrared spectra were recorded on Nicolet Avatar 370 DTGS spectrometer and are reported in cm^{-1}. Mass spectra were obtained on a Micromass Quadrupole-Time-of-Flight mass spectrometer using fast atom bombardment (FAB). 1-Mesitylimidazole was obtained by a method analogous to the literature procedure.[10]

Synthesis of (seim^{Mes})H. A solution of 1-mesitylimidazole (0.5 g, 2.7 mmol) in tetrahydrofuran (THF; 30 mL) was cooled to −78 °C and treated with Bu^{n}Li (1.7 mL of a 1.6 M solution in hexane, 2.7 mmol). The solution was stirred at −78 °C for 30 min, allowed to warm to room temperature, and stirred for 1 h. The solution was cooled to −78 °C, and powdered selenium (0.43 g, 5.4 mmol) was added. The mixture was stirred at room temperature overnight and neutralized using HCl (5%), maintaining a N_2 atmosphere. The mixture was filtered, and water (50 mL) and $CHCl_3$ (50 mL) were added to the filtrate. The organic layer was separated, washed with brine (50 mL), and dried with Na_2SO_4. The solution was separated from the Na_2SO_4, and the solvent was removed *in vacuo* to give (seim^{Mes})H as a pale yellow solid (0.35 g, 49%). IR data (KBr pellet, cm^{-1}): 3118 (w), 3053 (s), 2982 (s), 2880 (s), 2700 (w), 1561 (m), 1487 (m), 1459 (s), 1439 (m), 1406 (w), 1373 (w), 1318 (s), 1294 (vs), 1277 (m), 1249 (s), 1128 (w), 1100 (s), 1076 (vs), 1030 (w), 974 (w), 911 (m), 870 (w), 837 (w), 796 (m), 715 (s), 680 (s), 584 (w). Mass spectrum: $m/z = 267.3$ $\{M + 1\}^+$. Anal. Calcd for $C_{12}H_{14}N_2Se \cdot 0.1(CHCl_3)$: C, 52.4; H, 5.1; N, 10.1%. Found: C, 52.4; H, 4.7; N, 10.0%. ^{1}H NMR ($CDCl_3$): δ 2.06 [s, 6H of *o*-Me], 2.34 [s, 3H of *p*-Me], 6.78 [d, $^{2}J_{HH} = 2$ Hz, 1H of imidazole ring], 6.99 [s, 2H of aryl ring], 7.04 [d, $^{2}J_{HH} = 2$ Hz, 1H of imidazole ring], 11.91 [br, N−H]. ^{1}H NMR (Me_2SO-d_6): δ 1.92 [s, 6H of *o*-Me], 2.28 [s, 3H of *p*-Me], 6.99 [s, 2H of aryl ring], 7.15 [d, $J_{H-H} = 2$ Hz, 1H of imidazole ring], 7.24 [d, $J_{H-H} = 2$ Hz, 1H of imidazole ring], 12.8 [br, N−H]. ^{13}C{^{1}H} NMR ($CDCl_3$): δ 18.2 [*o*-Me], 21.3 [*p*-Me], 117.7 [C−H of imidazole ring], 120.6 [C−H of imidazole ring], 129.4 [C−H of mesityl], 133.7 [*ipso* C of mesityl], 135.7 [*C*−Me of mesityl], 139.6 [*C*−Me of mesityl], 152.5 [C═Se of imidazole ring]. ^{13}C{^{1}H} NMR (Me_2SO-d_6): δ 17.7 [*o*-Me of mesityl], 20.6 [*p*-Me of mesityl], 118.1 [C−H of imidazole ring], 120.9 [C−H of imidazole ring], 128.6 [C−H of mesityl], 134.2 [*ipso* C of mesityl], 135.1 [*C*−Me of mesityl], 138.0 [*C*−Me of mesityl], 152.4 [C═Se of imidazole ring, $J_{Se-C} = 231$ Hz]. ^{77}Se{^{1}H} NMR ($CDCl_3$): δ 17 ppm. ^{77}Se{^{1}H} NMR (Me_2SO-d_6): δ 29 ppm.

Synthesis of (seim^{Mes})$_2$. Procedure a: A solution of 1-mesitylimidazole (1 g, 5.4 mmol) in THF (50 mL) was cooled to −78 °C and treated with Bu^{n}Li (3.4 mL of a 1.6 M solution in hexane, 5.4 mmol). The solution was stirred at −78 °C for 30 min, allowed to warm to room temperature, and stirred for 1 h. Powdered selenium (0.85 g, 10.8 mmol) was added to the solution and the mixture stirred at room temperature overnight. The mixture was filtered, treated with distilled water (15 mL), and exposed to air, with occasional shaking, for approximately 2 h. The THF was removed from the solution *in vacuo*, and the remaining aqueous solution was extracted with $CHCl_3$ (2 × 20 mL). The organic layer was washed with water and dried with Na_2SO_4. The $CHCl_3$ was removed *in vacuo* to give (seim^{Mes})$_2$ as an orange powder (0.73 g, 51%), which may be crystallized from $CHCl_3$. IR data (KBr pellet, cm^{-1}): 3132 (m), 3104 (m), 2954 (w), 2916 (m), 2848 (w), 1606 (w), 1492 (s), 1483 (s), 1439 (w), 1413 (s), 1376 (w), 1309 (w), 1290 (m), 1264 (w), 1109 (m), 1087 (w), 1034 (vw), 979 (w), 909 (w), 865 (s), 759 (s), 735 (w), 682 (w), 586 (w). Mass spectrum: $m/z = 531.4$ $\{M + 1\}^+$. Anal. Calcd for $C_{24}H_{26}N_4Se_2$: C, 54.6; H, 5.0; N, 10.6%. Found: C, 54.4; H, 5.0; N, 10.6%. ^{1}H NMR ($CDCl_3$): δ 1.87 [s, 12H of *o*-Me], 2.30 [s, 6H of *p*-Me], 6.89 [s, 4H of aryl ring], 6.96 [br, 2H of imidazole ring], 7.35 [br, 2H of imidazole ring]. ^{1}H NMR (Me_2SO-d_6): δ 1.76 [s, 12H of *o*-Me], 2.26 [s, 6H of *p*-Me], 6.94 [s, 4H of aryl ring], 7.25 [br, 2H of imidazole ring], 7.34 [br, 2H of imidazole ring]. ^{13}C{^{1}H} NMR ($CDCl_3$): δ 17.4 [*o*-Me of mesityl], 20.6 [*p*-Me of mesityl], 123.5 [C−H of imidazole ring], 128.5 [C−H of mesityl], 131.4 [C−H of imidazole ring], 132.2 [C−Se of imidazole ring], 133.3 [*ipso* C of mesityl], 135.1 [C−Me of mesityl ring], 138.4 [C−Me of mesityl ring]. ^{77}Se{^{1}H} NMR ($CDCl_3$): δ 415 ppm. ^{77}Se-{^{1}H} NMR (Me_2SO-d_6): δ 407 ppm.

Procedure b: A solution of (seim^{Mes})H (10 mg, 0.038 mmol) in $CDCl_3$ (0.7 mL) was exposed to air and monitored by ^{1}H NMR

(37) For thiol/disulfide exchange, see: (a) Singh, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 1190−1197. (b) Singh, R.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 6931−6933. (c) Guo, W.; Pleasants, J.; Rabenstein, D. L. *J. Org. Chem.* **1990**, *55*, 373−376. (d) Fernandes, P. A.; Ramos, M. J. *Chem. Eur. J.* **2004**, *10*, 257−266. (e) Lees, W. J.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 642−647. (f) Theriault, Y.: Cheesman, B. V.; Arnold, A. P.; Rabenstein, D. L. *Can. J. Chem.* **1984**, *62*, 1312−1319. (g) Theriault, Y.; Rabenstein, D. L. *Can. J. Chem.* **1985**, *63*, 2225−2231. (h) Rabenstein, D. L.; Theriault, Y. *Can. J. Chem.* **1984**, *62*, 1672−1680. (i) Keire, D. A.; Guo, W.; Rabenstein, D. L. *Magn. Reson. Chem.* **1992**, *30*, 746−753. (j) Rabenstein, D. L.; Theriault, Y. *Can. J. Chem.* **1985**, *63*, 33−39.

(38) For thiol/diselenide exchange, see: Engman, L.; Stern, D. *J. Org. Chem.* **1994**, *59*, 5179−5183.

(39) Calculations suggest that the mechanism of nucleophilic displacement at a diselenide proceeds by a two-step process involving addition, giving a three-coordinate T-shaped intermediate, followed by elimination. See: (a) Bachrach, S. M.; Demoin, D. W.; Luk, M.; Miller, J. V., Jr. *J. Phys. Chem. A* **2004**, *108*, 4040−4046. (b) Bachrach, S. M.; Hayes, J. M.; Dao, T.; Mynar, J. L. *Theor. Chem. Acc.* **2002**, *107*, 266−271.

(40) Lardon, M. *J. Am. Chem. Soc.* **1970**, *92*, 5063−5066.

spectroscopy, thereby demonstrating the clean conversion to $(seim^{Mes})_2$ over a period of 2 days.

Cleavage of the Diselenide $(seim^{Mes})_2$. A stirred solution of $(seim^{Mes})_2$ (50 mg, 0.095 mmol) in THF (4 mL) was treated with small pieces of Na (ca. 50 mg) over the course of approximately 1 h, over which period the bright orange solution became brown. The mixture was filtered, and the filtrate was quenched with distilled water (0.5 mL). The volatile components were removed *in vacuo* to give the selone tautomer of $(seim^{Mes})H$ as a light brown solid which was identified by ^1H NMR spectroscopy.

Synthesis of $(seim^{Me})H$. A solution of 1-methylimidazole (2.9 mL, 3.0 g, 36.5 mmol) in THF (150 mL) was cooled to −78 °C and treated with Bu^nLi (23 mL of a 1.6 M solution in hexanes, 36.5 mmol). The solution was stirred at −78 °C for 30 min and then allowed to warm to room temperature and stirred for an additional hour. Powdered selenium (5.8 g, 73 mmol) was added to the solution, and the mixture was stirred at room temperature under N_2 overnight. After this period, the mixture was neutralized using 5% HCl, maintaining a N_2 atmosphere. The mixture was filtered, and the filtrate was treated with brine (50 mL) and $CHCl_3$ (50 mL). The organic layer was isolated and dried with Na_2SO_4, and the solvent was removed *in vacuo*, giving $(seim^{Me})H$ as a light brown solid (3.1 g, 53%). $(seim^{Me})H$ is obtained as colorless crystals from CH_2Cl_2. ^1H NMR ($CDCl_3$): δ 3.67 [s, 3H of CH_3], 6.81 [d, $J_{H-H} = 2$ Hz, A part of AB quartet, imidazole], 6.85 [d, $J_{H-H} = 2$ Hz, B part of AB quartet, imidazole], 12.19 [br, N−H]. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 35.7 [CH_3], 116.2 [C−H of imidazole ring], 120.4 [C−H of imidazole ring], 150.2 [C═Se, $^1J_{Se-C} = 222$ Hz]. ^{77}Se NMR ($CDCl_3$): δ −5 ppm.

Synthesis of $(seim^{Me})_2$. Procedure a: A solution of 1-methylimidazole (2.9 mL, 3.0 g, 36.5 mmol) in THF (150 mL) was cooled to −78 °C and treated with Bu^nLi (23 mL of a 1.6 M solution in hexanes, 36.5 mmol). The solution was stirred at −78 °C for 30 min and then allowed to warm to room temperature and stirred for an additional hour. Powdered selenium (5.80 g, 73 mmol) was added to the solution, and the mixture was stirred at room temperature under N_2 overnight. The mixture was filtered in air, and orange crystals of $(seim^{Me})_2$ deposited over a period of ca. 1 h. The solid was isolated by filtration and dissolved in $CHCl_3$ (30 mL). The chloroform solution was washed with water (2 × 50 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo* to give $(seim^{Me})_2$ as a bright orange powder (350 mg). The THF filtrate from the reaction was treated with water (50 mL), the THF was removed *in vacuo*, and the resulting aqueous mixture was extracted with $CHCl_3$ (2 × 50 mL). The organic layer was washed with distilled water (2 × 50 mL) and dried with Na_2SO_4. The solvent was removed *in vacuo* to give $(seim^{Me})_2$ as a bright orange powder (1.06 g). Total yield of $(seim^{Me})_2$: 1.41 g, 24%. ^1H NMR ($CDCl_3$): δ 3.66 [s, 3H of CH_3], 7.05 [d, $J_{H-H} = 1.3$ Hz, 1H of imidazole], 7.15 [d, $J_{H-H} = 1.3$ Hz, 1H of imidazole]. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 35.1 [CH_3], 124.6 [C−H of imidazole], 130.9 [C−H of imidazole], 132.9 [C−Se, $^1J_{Se-C} = 163$ Hz]. $^{77}Se\{^1H\}$ NMR ($CDCl_3$): δ 400 ppm.

Procedure b: A solution of $(seim^{Me})H$ (80 mg) in $CHCl_3$ (2 mL) was stirred in a flask open to air overnight. The pale yellow-brown solution became orange after ca. 1 h and deposited an orange solid upon overnight evaporation of the solvent, which was shown to be pure $(seim^{Me})_2$ by ^1H NMR spectroscopy.

Reduction of the Diselenide $(seim^{Me})_2$ with $NaBH_4$. The reduction of $(seim^{Me})_2$ with $NaBH_4$ was performed according to the literature procedure.[4] A suspension of $(seim^{Me})_2$ (150 mg, 0.47 mmol) in water (10 mL) was treated with $NaBH_4$ (54 mg, 1.4 mmol), resulting in a color change from bright orange to colorless after stirring for 5 h. The solution was extracted with CH_2Cl_2 (10 mL), and the solvent was removed from the organic layer *in vacuo*, to give a white solid. Recrystallization of the product from CH_2Cl_2 gave $(seim^{Me})H$ as colorless crystals (96 mg, 64%), and the product was identified as the selone tautomer by ^1H NMR spectroscopy.

Exchange between $(seim^{Mes})H$ and $(seim^{Me})_2$. A mixture of $(seim^{Mes})H$ (10 mg, 0.04 mmol) and $(seim^{Me})_2$ (12 mg, 0.04 mmol) was dissolved in $CDCl_3$ (0.7 mL) and observed by ^1H NMR spectroscopy to give an exchange-averaged spectrum. The sample was examined by mass spectrometry, which demonstrated that the mixture comprised, *inter alia*, $(seim^{Me})(seim^{Mes})$, $m/z = 427.4$ $\{M + 1\}^+$; $(seim^{Mes})_2$, $m/z = 531.5$ $\{M + 1\}^+$; and $(seim^{Me})_2$, $m/z = 323.3$ $\{M + 1\}^+$.

Table 3. Crystal, Intensity Collection, and Refinement Data

	$(seim^{Mes})H$	$(seim^{Mes})_2$	$(seim^{Me})H$
lattice	monoclinic	monoclinic	monoclinic
formula	$C_{12}H_{14}N_2Se$	$C_{24}H_{26}N_4Se_2$	$C_4H_6N_2Se$
formula weight	265.21	528.41	161.07
space group	$P2_1/c$	$P2_1/n$	$P2_1/c$
a/Å	7.6278(5)	9.6415(7)	6.6820(5)
b/Å	21.183(1)	15.614(1)	15.083(1)
c/Å	7.4022(5)	16.096(1)	17.919(1)
α/°	90	90	90
β/°	90.193(1)	102.776(1)	96.524(1)
γ/°	90	90	90
V/Å^3	1196.0(1)	2363.1(3)	1794.3(2)
Z	4	4	12
temperature/K	243	243	243
radiation, λ/Å	0.71073	0.71073	0.71073
ρ(calcd)/g cm^{-3}	1.473	1.485	1.789
μ(Mo Kα)/mm^{-1}	3.109	3.147	6.152
θ_{max}/°	28.2	28.3	28.3
no. of data	2736	5332	4225
no. of parameters	137	272	226
R_1	0.0334	0.0310	0.0319
wR_2	0.0975	0.0778	0.0738
GOF	1.022	1.088	1.096

X-ray Structure Determinations. X-ray diffraction data were collected on a Bruker P4 diffractometer equipped with a SMART CCD detector; crystal data and data collection and refinement parameters are summarized in Table 3. The structures were solved using direct methods and standard difference map techniques, and were refined by full-matrix least-squares procedures on F^2 with SHELXTL (version 5.10).[41]

Computational Details. All calculations were carried out in the gas phase using DFT as implemented in the Jaguar 6.0 suite of *ab initio* quantum chemistry programs.[42] Geometry optimizations were performed with the B3LYP density functional[43] and the 6-31G** (C, H, N) and LAV3P (Se) basis sets. The energies of the optimized structures were reevaluated by additional single-point calculations on each optimized geometry using the cc-pVTZ(-f) correlation-consistent triple-ζ basis set that includes a double set of polarization functions. Molecular orbital analyses were performed with the aid of Jimp 2,[44] which employs Fenske−Hall calculations[45] and visualization using MOPLOT.[46]

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Supporting Information Available: Cartesian coordinates for geometry optimized structures; crystallographic data in CIF format for $(seim^{Mes})H$, $(seim^{Mes})_2$, and $(seim^{Me})H$. This material is available free of charge via the Internet at http://pubs.acs.org.

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