$t_{1/2}$ is 27 times that of wild type.

Arg 45 and Arg 78 are isolated charges on the surface of α-lytic protease and do not appear to participate in stabilizing intramolecular interactions. Both residues are highly solvent accessible and tolerate numerous amino acid substitutions with little effect on enzyme stability in aqueous buffer. In contrast, the stability of α-lytic protease in DMF is significantly increased by seven surface substitutions, six of which are large, hydrophobic side chains. Similarly, replacement of a surface lysine by tyrosine improved the stability of an engineered subtilisin BPN′ in DMF.[7] It is commonly assumed that there is relatively little change in the solvent environment of a surface residue upon folding and, therefore, that surface amino acids contribute little to stability. However, the folded, biologically active state preferred in water may no longer be preferred in an organic solvent. Replacement of a charged side chain with a hydrophobic one enhances the compatibility between the surface of the folded protein and the solvent environment and may remove a potential driving force for formation of alternate (inactive) structures. The observed stabilization of the Glu 45 variant cannot, of course, be fully explained by this argument; proteins are complex, and interactions other than those with solvent can be introduced or perturbed by the surface mutations. Since protein surfaces are relatively tolerant of amino acid substitutions, the replacement of charged surface residues with hydrophobic ones may be a generally useful strategy for engineering enzymes that are stable in polar nonaqueous solvents.

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New Hypervalent σ-Selenanes with a Transannular Se–N Bond from *N*-Methyl-5*H*,7*H*-dibenzo[*b*,*g*][1,5]selenazocine

Hisashi Fujihara,*,[†] Hisatomo Mima,[†] Megumi Ikemori,[‡] and Naomichi Furukawa*,[†]

Department of Chemistry, University of Tsukuba
Tsukuba, Ibaraki 305, Japan
Tsukuba Research Laboratories, Eisai Co., Ltd.
5-1-3 Tokodai, Tsukuba, Ibaraki 300-26, Japan

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A number of hypervalent organosulfur compounds, sulfuranes, have been reported.[1] In contrast, much less is known about the chemistry of selenanes.[2] Recently, we reported the isolation of a new σ-bonded selenaza dication salt of *N*-methyl-5*H*,7*H*-dibenzo[*b*,*g*][1,5]selenazocine (**1**).[3] We have now found that either the reaction of **1** with *tert*-butyl hypochlorite (*t*-BuOCl) or the reaction of the selenoxide **2** of **1** with $SOCl_2$ gave the corresponding chloroselenane **3** containing a transannular Se–N bond, which was further converted into the methyl- or phenyl-substituted ammonioselenane upon treatment with $(CH_3)_2CuLi$ or $(C_6H_5)_2CuLi$. This is the first example of an isolable σ-ammonioselenane with a chlorine ligand or a methyl or phenyl group at the apical position, although analogous sulfur compounds of **3** have been reported.[4]

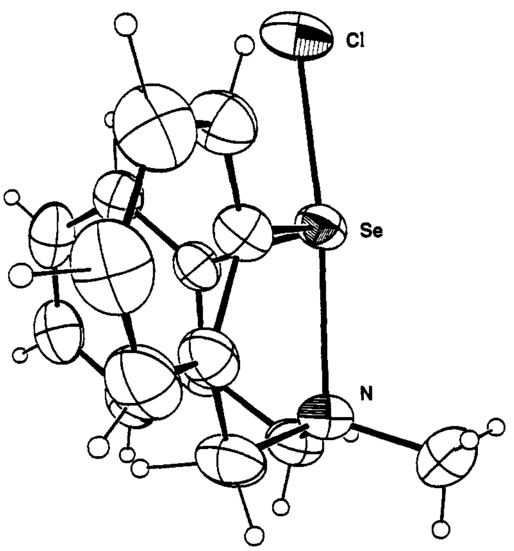
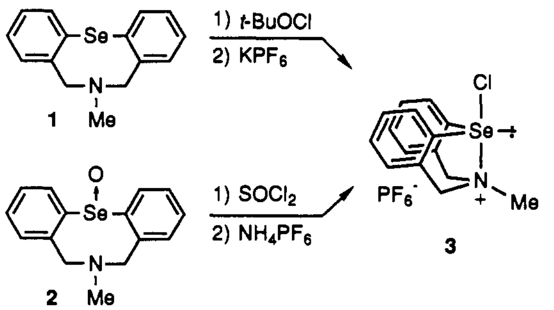


Figure 1. The crystal structure of **3**. The PF_6^- anion has been omitted for clarity.

Scheme I



Chloro-substituted σ-ammonioselenane **3** was isolated from the reaction of selenide **1** with *t*-BuOCl (Scheme I).[5] *t*-BuOCl is widely used as an oxidant for the conversion of selenides into selenoxides;[6] e.g., treatment of **1** first with *t*-BuOCl followed by alkaline hydrolysis with saturated sodium hydrogen carbonate solution gave exclusively the selenoxide **2** in 83% yield, contrasting with the oxidation of **1** using *m*-chloroperbenzoic acid, which gave a mixture of **2** and the *N*-oxide.[3] Although a chloroselenonium salt and/or hypervalent species have been proposed as intermediates in the reaction of diaryl selenides with *t*-BuOCl,[6] there is no example of isolation of its selenane.

Analogously, treatment of selenoxide **2** with $SOCl_2$ in anhydrous CH_2Cl_2 at room temperature followed by addition of NH_4PF_6

[†] University of Tsukuba.

[‡] Eisai Co., Ltd.

(1) For a review: Hayes, R. A.; Martin, J. C. Sulfurane Chemistry. In *Organic Sulfur Chemistry, Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; Chapter 8.

(2) *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1986; Vol. 1, Chapters 3 and 14. The term selenane has been used for tetracoordinate selenium(IV) compounds.

(3) Fujihara, H.; Mima, H.; Erata, T.; Furukawa, N. *J. Chem. Soc., Chem. Commun.* **1991**, 98–99.

(4) Akiba, K.; Takee, K.; Ohkata, K.; Iwasaki, F. *J. Am. Chem. Soc.* **1983**, *105*, 6965–6966.

(5) (a) To a solution of 1^3 (300 mg, 1.04 mmol) in anhydrous MeOH (5 mL) was added *t*-BuOCl (0.12 mL, 1.07 mmol) under an Ar atmosphere at −78 °C, and after 30 min the solution was allowed to reach 0 °C, followed by addition of KPF_6 and anhydrous CH_2Cl_2 (40 mL). Then the whole mixture was stirred at 0 °C for 21 h. Filtration under dry conditions and recrystallization from anhydrous CH_3CN-Et_2O gave a colorless crystal of **3** (65%). **3**: mp 178–180 °C dec. Anal. Calcd for $C_{15}H_{15}NClSePF_6$: C, 38.44; H, 3.23; N, 2.99. Found: C, 38.79; H, 3.19; N, 3.08. (b) In the above reaction with *t*-BuOCl, a trace amount (<10%) of *Se*-methoxy derivative **4** was produced after evaporation of the filtrate. **4**: mp 208.5–210.5 °C dec; ^1H NMR (CD_3CN) δ 2.85 (s, 3 H, NCH_3), 3.94 (s, 3 H, OCH_3), 4.31 (s, 4 H, CH_2), 7.36–7.53 (m, 2 H, Ar H), 7.53–7.72 (m, 4 H, Ar H), 7.92–8.14 (m, 2 H, Ar H); ^{13}C NMR (CD_3CN) δ 42.7, 56.6, 59.7, 128.7, 128.8, 130.8, 131.6, 133.6, 138.9; ^{77}Se NMR (CD_3CN) δ 828 (s); ^{31}P NMR (CD_3CN) δ −145.5 (sept, J_{PF} = 707 Hz). Anal. Calcd for $C_{16}H_{18}NOSePF_6$: C, 41.39; H, 3.91; N, 3.02. Found: C, 41.31; H, 3.75; N, 3.04.

(6) Detty, M. R. *J. Org. Chem.* **1980**, *45*, 274–279. Kobayashi, M.; Ohkubo, H.; Shimizu, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 503–506.

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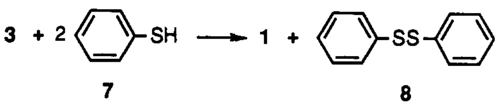
Scheme II

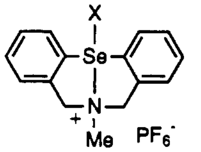


afforded selenane **3** in 85% yield (Scheme I).

The structure of **3** in solution was characterized by multinuclear NMR (^1H, ^{13}C, ^{77}Se, and ^{31}P) spectroscopy. With regard to the conformational properties of heterocyclic analogues of dibenzocyclooctane, for eight-membered rings typically two different conformers, the boat-chair (BC) and the twist-boat (TB) and/or the boat-boat (BB) forms, can exist.[7] The conformers can be assigned by the ^1H NMR spectral data for benzylic protons of the eight-membered ring.[7] The ^1H NMR (500 MHz) spectrum of **3** in CD_3CN shows peaks at δ 3.12 (s, 3 H, CH_3), 4.59, 4.63 (AB q, J = 15.7 Hz, 4 H, CH_2), 7.49–7.54 (m, 2 H, Ar H), 7.68–7.75 (m, 4 H, Ar H), and 8.35–8.40 (m, 2 H, Ar H), which show downfield shifts relative to those of **1** and **2**,[3] while the ^{13}C NMR (125 MHz, CD_3CN) spectrum shows absorptions at δ 45.1, 62.4, 128.7, 130.7, 131.6, 132.6, 134.7, and 139.4. The ^{77}Se NMR spectrum of **3** in CH_3CN shows a singlet peak at δ 813.4 (relative to Me_2Se).[8] The ^{31}P NMR spectrum of the PF_6^- anion of **3** in CH_3CN shows a phosphorus absorption at δ −143.2 (sept, J_{PF} = 707 Hz; relative to H_3PO_4), in the region of ionic PF_6^-. This spectroscopic evidence indicates that **3** is a single conformer, i.e., TB or BB form in solution. The selenane **3** exists solely as a single conformer from −40 to +70 °C as evidenced from the variable-temperature ^1H NMR spectral data, though the selenazocine **1** shows the existence of two conformers.[3]

The crystal structure of **3** was determined by X-ray diffraction analysis (Figure 1).[9] The Se–N distance is 2.191 Å, which is significantly shorter than the sum of the van der Waals radii (3.50 Å), indicating transannular bond formation between Se and N. The Se–Cl bond length (2.296 Å) is close to that of diphenylselenium dichloride (2.30 Å).[10] The Cl–Se–N bond angle of 174.3° is approximately collinear, and the C_{eq}–Se–C_{eq} bond angle is 101.7°. Thus, the configuration about the selenium atom is slightly distorted trigonal bipyramidal with two apical Se–N and Se–Cl bonds, two equatorial Se–C bonds, and the lone-pair electrons considered to occupy the third equatorial position. These structural features are consistent with a σ-selenane structure.

Treatment of the *Se*-chloro derivative **3** with lithium dimethylcuprate, $(CH_3)_2CuLi$, or lithium diphenylcuprate, $(C_6H_5)_2CuLi$[11] (1.2 equiv), in anhydrous tetrahydrofuran at −78 °C resulted in the formation of the *Se*-methyl- or *Se*-phenylammonioselenane (**5** or **6**), which was recrystallized from $CH_3CN–Et_2O$.[12,13] The selenanes of *Se*-methyl **5**, *Se*-phenyl **6**, and *Se*-methoxy **4**[5b] also show one type of absorption in the ^1H, ^{13}C, and ^{77}Se NMR spectra. The ^1H NMR spectra of **4**–**6** in CD_3CN did not show any temperature dependence between −40 and +70 °C. These results indicate that the conformations of **4**–**6** are fixed as the TB or BB form by a transannular bond between the selenio and amino groups, although normally the BC conformer has been shown to be more stable and rigid than TB and/or BB conformers.[7]



4 X = OMe
5 X = Me
6 X = Ph

Interestingly, the new σ-selenane **3** behaves as an oxidizing agent, as follow (Scheme II). Treatment of benzenethiol (**7**) (2 equiv) with **3** (1 equiv) in the presence of triethylamine (2 equiv) in CH_3CN under an Ar atmosphere at room temperature for 1 h gave diphenyl disulfide (**8**) as the oxidation product in 88% yield and the selenazocine **1** as the reduction product in 83% yield.

The selenanes **3**–**6** are a new type of hypervalent selenium compounds, since generally σ-selenanes bear two electronegative groups such as oxygen atoms or halogen atoms at the apical positions.[2]

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Supplementary Material Available: Detailed information of the X-ray crystal structure of **3** and tables of positional parameters, bond distances and angles, and torsional angles (7 pages). Ordering information is given on any current masthead page.

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(8) The ^{77}Se NMR spectrum of **1** in CH_3CN shows a broad peak due to the existence of conformers.[3]

(9) Crystal data for **3**: $C_{15}H_{15}NClSePF_6$, orthorhombic, space group *Pbca*, a = 15.525 (5) Å, b = 16.970 (5) Å, c = 13.217 (3) Å, $\alpha = \beta = \gamma = 90°$, V = 3482.015 Å^3, Z = 8, D_{calcd} = 1.788 g/cm^3, Cu Kα radiation (λ = 1.5418 Å), $F(000)$ = 1856, CAD4 diffractometer, 2296 reflections ($2° < \theta < 60°$), 3069 observed with $I > 3\sigma(I)$. The structure was solved by direct methods and refined anisotropically by full-matrix least squares using the SDP program package. The final R value was 0.050.

(10) Baenziger, N. C.; Buckles, R. E.; Maner, R. J.; Simpson, T. D. *J. Am. Chem. Soc.* **1969**, *91*, 5749–5755 and references cited therein.

(11) Whitesides, G. M.; Fischer, W. F., Jr.; Filippo, J. S., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871–4882.

(12) **5**: mp 225–228 °C dec; ^1H NMR (CD_3CN) δ 2.55 (s, 3 H, CH_3), 2.95 (s, 3 H, CH_3), 4.04 (s, 4 H, CH_2), 7.38–7.40 (m, 2 H, Ar H), 7.53–7.61 (m, 4 H, Ar H), 7.69–7.71 (m, 2 H, Ar H); ^{13}C NMR (CD_3CN) δ 18.9, 40.5, 57.4, 126.8, 129.2, 130.4, 131.2, 133.3, 140.5; ^{77}Se NMR (CH_3CN) δ 452.5 (s); ^{31}P NMR (CH_3CN) δ −145.5 (sept, J_{PF} = 707 Hz). Anal. Calcd for $C_{16}H_{18}NSePF_6$: C, 42.87; H, 4.05; N, 3.12. Found: C, 43.09; H, 4.02; N, 3.12. **6**: mp 263–266 °C dec; ^1H NMR (CD_3CN) δ 2.56 (s, 3 H, CH_3), 4.05, 4.19 (AB q, J = 15.7 Hz, 4 H, CH_2), 7.33–7.61 (m, 8 H, Ar H), 7.78–7.89 (m, 5 H, Ar H); ^{13}C NMR (CD_3CN) δ 40.2, 56.8, 127.0, 130.2, 131.0, 131.6, 133.5, 133.6, 134.3, 135.4, 135.6, 141.1; ^{77}Se NMR (CH_3CN) δ 554.5 (s); ^{31}P NMR (CH_3CN) δ −149.0 (sept, J_{PF} = 707 Hz). Anal. Calcd for $C_{21}H_{20}NSePF_6$: C, 49.42; H, 3.95; N, 2.74. Found: C, 49.37; H, 3.85; N, 2.72.

(13) The *N,N*-dimethylammonium salt of **1** shows the following ^1H NMR spectral data, which is similar to that of its sulfur analogue:[7b] mp 222.5–224 °C; ^1H NMR (CD_3CN) δ 2.61, 3.54 (s, CH_3; BC form), 2.97 (s, CH_3; TB form), 4.52, 5.63 (AB q, J = 13.5 Hz, CH_2; BC), 4.08, 4.67 (AB q, J = 13.5 Hz, CH_2; TB), 7.33–7.97 (m, Ar H); ^{13}C NMR (CD_3CN) δ 52.5, 64.7, 129.1, 129.5, 130.6, 130.7, 132.6, 137.3. Anal. Calcd for $C_{16}H_{18}NSePF_6$: C, 42.87; H, 4.05; N, 3.12. Found: C, 42.70; H, 3.90; N, 3.09.

Reversible Screw Sense Inversion of the 3_{10}-Helix in a Dehydropeptide

Osvaldo Pieroni,[*,†,‡] Adriano Fissi,[†] Claudio Pratesi,[∥]
Pier Andrea Temussi,[⊥] and Francesco Ciardelli[‡,§]

CNR, Institute of Biophysics
26 Via S. Lorenzo, 56100 Pisa, Italy
Department of Chemistry and Industrial Chemistry
University of Pisa, Pisa, Italy
CNR, Center for the Study of Stereoordered and
Optically Active Macromolecules, Pisa, Italy
Scuola Normale Superiore/ENI, Pisa, Italy
and Department of Chemistry
University of Naples, 80134 Naples, Italy

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Dehydro amino acid residues, that is, amino acid residues containing a C=C double bond in the α,β-position, are characterized by very peculiar geometric features, so their presence in a peptide sequence produces remarkable conformational consequences.[1]

[†] CNR, Institute of Biophysics.

[‡] University of Pisa.

[§] CNR, Center for the Study of Stereoordered and Optically Active Macromolecules.

[∥] Scuola Normale Superiore/ENI.

[⊥] University of Naples.

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