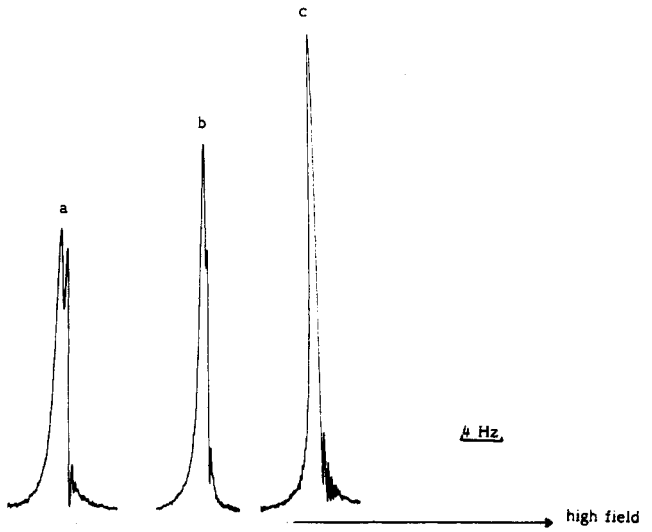


Figure 1. NMR spectra of TTF 1, SMe peak: (a) 0.6 g of 1 dissolved in boiling commercial $CDCl_3$ with 10 drops of C_5D_5N added, spectra recorded before any precipitation; (b) remaining filtrate after removal of the precipitate formed upon ice bath cooling (2 cis-rich solution), observed only if the spectra is immediately recorded; (c) peak observed for the precipitate in a CCl_4 solution (1 trans isomer).

cipitation of the trans isomer.

The thiomethyl group in 1 exhibits a particularly well-resolved singlet at 2.25 ppm in either CCl_4, C_6D_6, C_5D_5N, or basic alumina $CDCl_3$ purified. However, two signals were observed when these solvents were slightly acidified by gaseous HCl or when commercially available $CDCl_3$ was used without further purification.

These results can be explained by an isomerization of the trans TTF 1 catalyzed by H^+.

$$\text{TTF 1 (trans)} \overset{H^+}{\rightleftharpoons} [\text{TTF}]H^+ \overset{-H^+}{\rightleftharpoons} \text{TTF 2 (cis)}$$

In agreement with such equilibria two signals were observed when TTF 1 (trans) was first dissolved in commercial $CDCl_3$ (rapid isomerization) and then pyridine added, while only one signal was present when the TTF 1 (trans) was dissolved into a previously prepared mixture of $CDCl_3$ and pyridine. However, after a few minutes the second signal appeared, showing that the rate of isomerization was slowed by addition of pyridine but not eliminated.

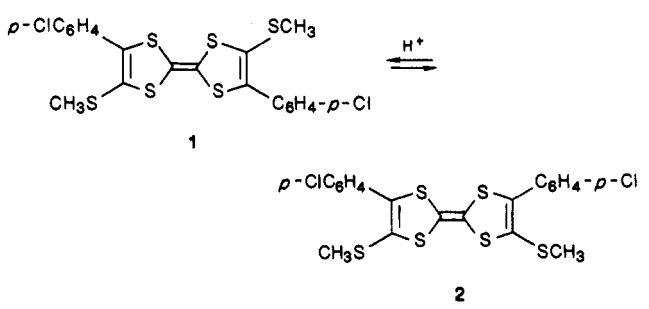
The second methyl peak does not arise from the protonated intermediate because when the isomerization was achieved, the relative intensity of the two methyl peaks was independent of the acidity of the medium. For instance, the two methyl peaks observed in a weakly acidic $CDCl_3$ solution of TTF 1 were not modified by further addition of pyridine, even after 1 h.

Another noteworthy feature of the TTF solutions is the selective precipitation of the trans isomer from saturated solutions. It was not possible to isolate the cis isomer even when pyridine was added *after* isomerization of the trans isomer (Figure 1a); cooling the solution afforded a precipitate of pure solid trans isomer 1 (Figure 1c) and a solution in which the cis isomer was the major compound (Figure 1b). However, the cis–trans equilibrium was too rapidly established to permit isolation of the cis TTF 2. After concentration of the solution, the trans isomer 1 was quantitatively recovered and identified on the basis of identical melting points as well as IR and NMR spectra.

Experimental Section

TTF 1 was selected because the thiomethyl group exhibits a well-resolved ^1H NMR signal. It was prepared according to the published procedure, and its physical data were as expected.[1] ^1H NMR spectra were recorded at 80 MHz on a Brüker WP 80 spectrometer. An expanded scale was used (2 Hz/cm^{-1}), and Me_4Si was the internal standard. The thiomethyl group signal is shifted upfield by about 5×10^{-3} ppm (Figure 1). Each experiment was repeated at least three times in order to avoid artifacts.

Scheme I



To show that isomerization was linked to the acidity of the medium, two final solutions were prepared in two different ways:

(a) A 0.5-g portion of 1 was first dissolved in 0.5 mL of commercially available $CDCl_3$ followed by addition of 10 drops of C_5H_5N; two methyl peaks were observed.

(b) A 0.5-g portion of 1 was dissolved in a previously prepared mixture of 0.5 mL of commercial $CDCl_3$ and 10 drops of C_5H_5N.

A single methyl peak was observed when the spectrum was immediately recorded, but two peaks appeared after a few minutes and equilibrium was reached after 40 min (identical spectra for a and b solutions).

The configuration of TTF 1 in the solid state was determined by an X-ray single-crystal structure determination. A reddish needle-shaped crystal ($0.40 \times 0.12 \times 0.04$ mm) was mounted on a Nonius CAD4 automatic diffractometer (graphite-monochromated Mo Kα radiation, θ–2θ scan technique). Data: monoclinic; space group $P2_1/n$; a = 8.994 (4), b = 25.343 (7), c = 4.821 (3) Å; β = 98.70 (5)°; V = 1086 Å^3; Z = 2, d_{calcd} = 1.583 g·cm^{-3}.

A total of 2780 independant reflections were collected up to θ = 28° of which 961 with $I > 3\sigma(I)$ were considered observed and included in the refinement. The structure was solved by direct methods and difference Fourier synthesis. Full-matrix least-squares refinement with anisotropic temperature factors for all non-hydrogen atoms (with the hydrogen atoms included in fixed calculated positions) converged to R = 0.064 and R_w = 0.070. The asymmetric unit consists of a half molecule located on a center of symmetry. Accordingly, the thiomethyl groups are trans to each other as verified by the full-structure determination.

A Novel Synthesis of Selenium-Containing Heterocyclic Compounds. Carbonylation of Ortho-Substituted Anilines with Carbon Monoxide in the Presence of Selenium

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Received September 10, 1986

During the course of our study on selenium-assisted carbonylation with carbon monoxide,[1] we have found that

(1) (a) Sonoda, N.; Yasuhara, T.; Kondo, K.; Ikeda, T.; Tsutsumi, S. *J. Am. Chem. Soc.* **1971**, *93*, 6344. (b) Intramolecular aminolysis of selenol carbamate intermediates gives cyclic ureas in good yields: Yoshida, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1986**, *27*, 3077. (c) Kondo, K.; Takarada, M.; Murai, S.; Sonoda, N. *Synthesis* **1979**, 597.

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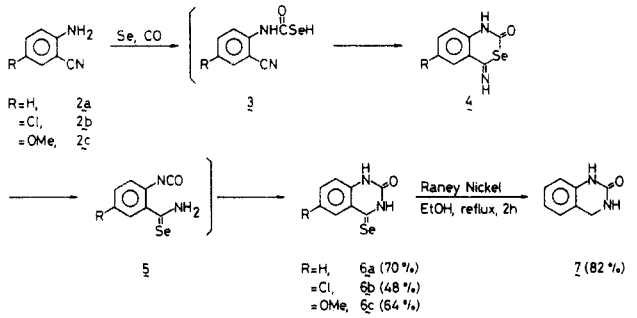
Scheme I



the selenol carbamate **1** is readily formed by the reaction of amine, carbon monoxide, and selenium (eq 1).

$$R_2NH + CO + Se \xrightarrow{\text{base}} R_2NC(=O)Se^- H^+ \cdot \text{base} \quad (1)$$

1

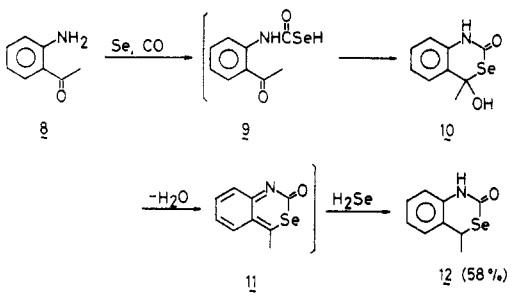
The selenol carbamate group ($NCOSe^-$) has not only an electrophilic site at the carbonyl carbon[1a,b] but also a nucleophilic site at selenium.[1c] Therefore, it can be expected that a nucleophilic reaction of the selenol carbamate may proceed intramolecularly to give a new class of selenium-containing heterocycles when anilines that carry a substituent having an electrophilic center at the ortho position are employed in this reaction system.

We report here that the reactions of *o*-cyanoaniline (**2**) and *o*-aminoacetophenone (**8**) with carbon monoxide and selenium give new selenium-containing heterocycles, i.e., selenoxoquinazolinone (**6**) and benzoselenazinone (**12**), respectively. Although the sulfur analogues[2] of quinazolinedione[8] and benzoxazinone[9] have already been synthesized for pharmacological interest, synthetic methods to prepare the corresponding selenium-containing compounds **6** and **12** have not been reported.

o-Aminobenzonitrile (**2a**) was treated with excess amounts of selenium and carbon monoxide (30 kg/cm^2) in the presence of *N*-methylpyrrolidine (NMP) at 100 °C to give 4-selenoxo-3,4-dihydroquinazolin-2(1*H*)-one (**6a**) in 75% yield. 2-Cyano-4-chloroaniline (**2b**) and 2-cyano-4-methoxyaniline (**2c**) also reacted in the same manner to yield selenoxoquinazolinone derivatives **6b** (48%) and **6c** (64%), respectively.

A plausible reaction mechanism[10] is shown in Scheme I. This reaction may involve the initial formation of selenol carbamate **3** by the reaction of the aromatic amino group with selenium and carbon monoxide. Intramolecular addition of the SeH moiety of **3** to the cyano group might occur to form cyclic intermediate **4**, followed by a ring-opening, ring-closure sequence to yield **6a–c**.

Scheme II



These products, **6a–c**, showed spectral data (^{13}C NMR, ^1H NMR, IR, MS) reasonable for the assigned structures.[11] The structure of **6a** was also confirmed by reduction with Raney nickel (activity W-5), leading to **7** in 82% yield (Scheme I).

o-Aminoacetophenone (**8**) also reacted with carbon monoxide and selenium under similar reaction conditions to afford 4-methyl-3,4-dihydro-3,1-benzoselenazin-2-(1*H*)-one[12] (**12**) in 58% yield. This reaction may also proceed via selenol carbamate intermediate **9**. Subsequent cyclization giving rise to **10**, followed by reduction[13] via **11**, may afford **12** (Scheme II).

All products tend to retain water during a usual workup. In order to obtain an anhydrous sample, careful workup under dry conditions is recommended. The selenium-containing products are relatively stable in air, at least for a few days, and can be stored for several months at ambient temperature under nitrogen in a flask wrapped with aluminum foil.

Experimental Section

Apparatus. Melting points were determined under N_2 on a Yanagimoto hot-stage microscope apparatus HP-S2 and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-PS-100 and a JEOL FX-60s with Me_4Si as an internal standard. Infrared spectra were obtained on a Shimadzu IR-400. Mass spectra were recorded on a Hitachi Model RMU-6E. Elemental analyses were performed on a Yanagimoto CHN-Corder MT-2.

Materials. THF was freshly distilled from sodium/benzophenone prior to use. *N*-Methylpyrrolidine was distilled from CaH_2. Pentane was distilled from sodium. Metallic selenium (99.9%) and carbon monoxide were purchased from Nakarai Chemicals Ltd. and Seitetsu Chemical Co., respectively. 2-Cyano-4-methoxyaniline (**2c**) was prepared by a procedure reported previously.[14] All other starting materials were obtained from commercial sources and purified by distillation or recrystallization.

Isolation and purification of the reaction products **6a–c** and **12** were carried out by recrystallization from appropriate solvents given below. Attempted purification by column chromatography has resulted in the decomposition of the products.

(2) Synthetic methods are classified as follows. For thioquinazolinone derivatives: (a) direct displacement of oxygen by sulfur using P_4S_{10};[5] (b) cyclization of *o*-aminothiobenzamide with $ClCO_2Et$;[3] (c) reaction of aromatic *o*-amino nitrile with carbon disulfide[4] or carbonyl sulfide.[5] For benzothiazinone derivatives: (a) reaction of anthranilic acid derivatives with 2,4-bis(alkoxycarbonylcyanomethylene)-1,3-dithioetane;[6] (b) hydrolysis of benzothiazinethione.[7]

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(4) Hernanadez, M. A.; Chung, F.-L.; Earl, R. A.; Townsent, L. *J. Org. Chem.* **1981**, *46*, 3941.

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(10) This mechanism of the ring-closure reaction is similar to that proposed for the reaction of *o*-amino nitrile with carbon disulfide by E. C. Taylor.[5]

(11) The signals for $^{13}C{=}Se$ carbons of the selenocarbonyl compounds (e.g., selenoamide or selenoketone) appear far downfield (approximately δ 200 relative to Me_4Si as internal standard), so their assignments pose few problems: (a) Cullen, E. R.; Buziec, F. G., Jr.; Murphy, C. J.; Wong, T. C.; Andersen, K. K. *J. Chem. Soc., Perkin Trans. 2* **1982**, 473. (b) Rae, I. D. *Aust. J. Chem.* **1979**, *32*, 567.

(12) In contrast, *o*-hydroxyacetophenone reacted with selenium and carbon monoxide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford only 4-hydroxycoumarin, and a selenium-containing heterocyclic compound was not obtained: Ogawa, A.; Kondo, K.; Murai, S.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1982**, 1283.

(13) The reducing agent, H_2Se, was presumably formed by the reaction of selenium, carbon monoxide, and water under similar reaction conditions: Sonoda, N.; Kondo, K.; Nagano, K.; Kambe, N.; Morimoto, F. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 308.

(14) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1972**, *25*, 2621.

4-Selenoxo-3,4-dihydroquinazolin-2(1*H*)-one. *o*-Aminobenzonitrile (**2a**; 296 mg, 2.5 mmol), selenium (592 mg, 7.5 mmol), *N*-methylpyrrolidine (0.79 mL, 7.5 mmol), and THF (10 mL) were placed in a 50-mL stainless steel autoclave. The reaction mixture was stirred under carbon monoxide pressure (30 kg/cm^2) at 100 °C for 20 h. After the evacuation of excess carbon monoxide at room temperature, the deposited selenium was filtered off, and the solvent was evaporated in vacuo. The residual solid was recrystallized from THF/pentane to yield 422 mg of **6a** (73%). The sample seemed to contain a small amount of water: pale yellow plates, mp 233–234 °C dec, ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 195.82, 146.97, 137.09, 135.79, 133.32, 123.72, 123.32, 116.04; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 13.48 (br s, 1 H, NH), 11.79 (br s, 1 H, NH), 8.37 (d, J = 8.9 Hz, 1 H, aromatic), 7.75 (t, J = 8.9 Hz, 1 H, aromatic), 7.21 (t, J = 7.7 Hz, 1 H, aromatic), 7.13 (d, J = 7.7 Hz, 1 H, aromatic), 3.27 (s, H_2O); IR (KBr) 3350–2760, 1710, 765, 753 cm^{-1}; MS m/e 226 (M^+). Anal. Calcd for $C_8H_6N_2OSe \cdot {}^1/_4H_2O$: C, 41.85; H, 2.85; N, 12.20. Found: C, 41.69; H, 2.99; N, 12.09. ^{1}H NMR and IR spectra and elemental analysis showed that **6a** contained $^1/_4$ H_2O as a hydrate or 1.95 wt % H_2O as moisture.

In order to obtain an anhydrous sample of **6a**, the sample was dissolved in THF (50 mL) and dried over Na_2SO_4 under nitrogen atmosphere. The solvent was evaporated in vacuo to obtain anhydrous **6a** in 70% (396 mg) yield: pale yellow powder, mp 233–234 °C dec. Anal. Calcd for $C_8H_6N_2OSe$: C, 42.67; H, 2.68; N, 12.44. Found: C, 42.27; H, 2.56; N, 12.30.

6-Chloro-4-selenoxo-3,4-dihydroquinazolin-2(1*H*)-one (6b). 4-Chloro-6-cyanoaniline (**2b**; 381 mg, 2.5 mmol) was reacted under the same conditions, and similar workup as described for the preparation of **6a** gave 334 mg (50%) of **6b**: pale yellow plates; mp 289–290 °C dec; ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 194.45, 146.72, 135.94, 135.14, 131.71, 127.59, 124.34, 118.38; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 13.40 (br, 2 H, NH), 8.37 (d, J = 2.9 Hz, 1 H, aromatic), 7.89 (dd, J = 9.6, 2.9 Hz, 1 H, aromatic), 7.21 (d, J = 9.6 Hz, 1 H, aromatic), 4.28 (s, H_2O); IR (KBr) 3240–2900, 1705, 1000, 809 cm^{-1}; MS m/e 262 (M^+). Anal. Calcd for $C_8H_5N_2ClOSe \cdot {}^1/_4H_2O$: C, 36.39; H, 2.10; N, 10.60. Found: C, 36.44; H, 2.27; N, 10.24.

In a similar manner as described above was obtained anhydrous **6b** in 48% (271 mg) yield: pale yellow powder, mp 289–290 °C dec. Anal. Calcd for $C_8H_5N_2ClOSe$: C, 37.02; H, 1.94; N, 10.79. Found: C, 37.00; H, 2.27; N, 10.42.

6-Methoxy-4-selenoxo-3,4-dihydroquinazolin-2(1*H*)-one (6c). 2-Cyano-4-methoxyaniline (**2c**; 370 mg, 2.5 mmol) was reacted under the same conditions. A similar workup as described for the preparation of anhydrous **6a** under dry conditions gave 409 mg (64%) of anhydrous **6c**: pale yellow powder, mp 273.5–274.5 °C dec; ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 194.58, 155.36, 146.81, 131.47, 125.13, 123.70, 117.63, 113.71, 55.49; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 12.86 (br, 2 H, NH), 7.93 (d, J = 2.8 Hz, 1 H, aromatic), 7.52 (dd, J = 9.2, 2.8 Hz, 1 H, aromatic), 7.21 (d, J = 9.2 Hz, 1 H, aromatic), 3.87 (s, 3 H, OCH_3); IR (KBr) 3400–3020, 1703, 818, 865 cm^{-1}; MS m/e 256 (M^+). Anal. Calcd for $C_9H_8N_2O_2Se$: C, 42.37; H, 3.16; N, 10.97. Found: C, 42.10; H, 3.30; N, 10.55.

4-Methyl-3,4-dihydro-3,1-benzoselenazin-2(1*H*)-one (12). Reaction of *o*-aminoacetophenone (**8**; 337 mg, 2.5 mmol) with selenium (592 mg, 7.5 mmol) in the presence of *N*-methylpyrrolidine (0.79 mL, 7.5 mmol) in THF (10 mL) under carbon monoxide pressure (30 kg/cm^2) at 100° C for 20 h, followed by a similar workup, gave 352 mg (60%) of **12**: yellow needles, mp 135–136 °C dec; ^{13}C NMR (Me_2SO-d_6/Me_4Si) δ 166.07, 140.21, 137.49, 129.04, 127.09, 124.75, 119.42, 36.26, 25.21; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 10.70 (br s, 1 H, NH), 6.95–7.61 (m, 4 H, aromatic), 4.55 (q, J = 7.6 Hz, 1 H, CH), 1.75 (d, J = 7.6 Hz, 3 H, CH_3), 3.28 (s, H_2O); IR (KBr) 3280–3150, 1614, 822, 757 cm^{-1}; MS m/e 227 (M^+). Anal. Calcd for $C_9H_9NOSe \cdot {}^1/_2H_2O$: C, 45.97; H, 4.28; N, 5.95. Found: C, 46.22; H, 4.31; N, 6.24.

In a similar manner as described above, anhydrous **12** was obtained in 58% (342 mg) yield: yellow powder, mp 135–136 °C. Anal. Calcd for C_9H_9NOSe: C, 47.80; H, 4.01; N, 6.19. Found: C, 47.90; H, 4.10; N, 6.24.

Reductive Deselenation of 6a with Raney Nickel. In a 100-mL round-bottomed flask fitted with a reflux condenser were placed anhydrous **6a** (130 mg, 0.58 mmol), 2 g of Raney nickel (activity W-5), and ethyl alcohol (30 mL). The mixture was refluxed for 2 h with stirring. After cooling to room temperature, the reaction mixture was filtered, and the solvent was evaporated in vacuo. The residual solid was purified by recrystallization from THF/hexane to give 71 mg (82%) of 3,4-dihydroquinazolin-2-(1*H*)one (**7**): white needles, mp 241–242 °C;[15] ^{1}H NMR (Me_2SO-d_6) δ 9.08 (br s, 1 H, NH), 7.50–6.80 (m, 5 H, aromatic and NH), 4.40 (s, 2 H, CH_2); IR (KBr) 3240, 1720, 1264, 740 cm^{-1}; MS m/e 148 (M^+). Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.92. Found: C, 64.60; H, 5.20; N, 18.95.

Acknowledgment. This work was supported in part by a Grant in Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

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Inhibition of Choline Acetate Hydrolysis in the Presence of a Macrocyclic Polyphenolate[1]

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While there is an increasing number of reports on synthetic enzyme analogs,[2] little attention has been paid so far to the use of host compounds as inhibitors. Rate retardation by complexation of substrates in suitable macromolecular cavities is of interest not only for biological systems but also for potential synthetic applications, e.g., with multifunctional compounds or with parallel reactions that could be made more selective by addition of suitable blocking reagents. It must be noted, however, that inhibition of reactions, which should not be confused with the more common inhibition of catalysts such as enzymes, places much more stringent requirements than catalysis. Whereas even small catalytic effects can be easily recognized, a corresponding rate retardation requires a complex formation which is strong enough to compete with the reaction outside a cavity, or, in other words, a competition between ground-state and—usually much larger—transition-state energy effects. This is likely to be the reason why saturation kinetics for rate retardations with organic substrates to our knowledge have been barely reported.

Recently we have demonstrated[3] that the electrostatic interaction between four negative charges of a macrocyclic polyphenolate H and trimethylammonium derivatives can lead to almost micromolar dissociation constants K in water which partially exceed corresponding constants in biological systems. The present paper describes how the delocalized negative charge in the cyclic cavity not only

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