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Optically Active Seleninic Acid: Isolation, Absolute Configuration, Stability, and Chiral Crystallization

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Each optical isomer of methaneseleninic acid (**1a**) was isolated as chiral crystals by recrystallization from methanol/toluene. The absolute configuration of one of the enantiomers was determined by X-ray crystallographic analysis, and the relationship between the absolute configuration and the circular dichroism spectra of **1a** was clarified. The optically active seleninic acid (*R*)-**1a** was stable toward racemization in the solid state, although it racemized very rapidly in solution. Each enantiomer of **1a** was obtained in bulk by chiral crystallization in the presence of a seed crystal or chiral solvents. The absolute configuration of optically active methanesulfinic acid (**4**) was also assigned by comparing its circular dichroism spectra with those of **1a**.

Tricoordinated chalcogen compounds have pyramidal structures around the chalcogen atoms.[1,2] Therefore, chiral centers exist on the chalcogen atoms of these compounds. Recently, many chiral tricoordinated selenium and tellurium compounds, such as oxides, onium salts, ylides, and imides, have been isolated and their properties have been clarified.[1] However, optically active chalcogenic acids, which are also tricoordinated chalcogen compounds, have not been reported so far. Chiral chalcogenic acids are difficult to isolate because they racemize rapidly. Recently, we succeeded in the optical resolution of areneseleninic acids with bulky substituents on a chiral column.[3,4] However, the optically active areneseleninic acids racemized in solution and the concentration of the eluates under reduced pressure led to complete racemization. Thus, no optically active seleninic acids have been isolated as stable solids so far. It is known that some racemic substances can be obtained as chiral crystals (conglomerates), and that the racemates can be optically resolved by preferential crystallization.[5] On the other hand, chiral crystallization is a well-known method for isolating optically active compounds in bulk that readily racemize in solution.[6] If seleninic acids crystallized in a chiral space group, the isolation of enantiomers would be realized and optically active seleninic acids could be obtained in bulk by chiral crystallization.

Therefore, we examined the chiral crystallization of various seleninic acids and found that methaneseleninic acid can be obtained as chiral crystals. We describe herein the isolation of an optically pure seleninic acid as a stable solid, the absolute configuration, and the methods for preparing the optically active seleninic acid in bulk.[7]

Results and Discussion

Recrystallization of Seleninic Acids. Seleninic acids **1a–e** (Chart 1) having various substituents, which were prepared from the corresponding diselenides by oxidation with hydrogen peroxide or ozone and subsequent hydrolysis, were recrystallized from several solvents, such as methanol, ethanol, chloroform, acetone, acetonitrile, toluene, and their mixtures. Circular dichroism spectra were measured in the solid state to check whether an obtained crystal is chiral or not, because seleninic acids racemize rapidly in solution. Each single crystal obtained was pulverized with KBr and the mixture was pressed into a disk for measurement. In the case of **1a**, one of the single crystals obtained by recrystallization from methanol/toluene showed a positive Cotton effect at around 250 nm, and another one showed a negative Cotton effect in the same region (Fig. 1), meaning that the crystals are chiral. However, the crystals of **1a** that were recrystallized from methanol or the other solvents did not show any Cotton effects, indicating that the crystals are racemic. In the cases of **1b–e**, no crystal that showed the Cotton effect was obtained, although a number of recrystallization attempts were made.

Absolute Configuration and Crystal Structure of Optically Active Methaneseleninic Acid (1a). The X-ray crystal-

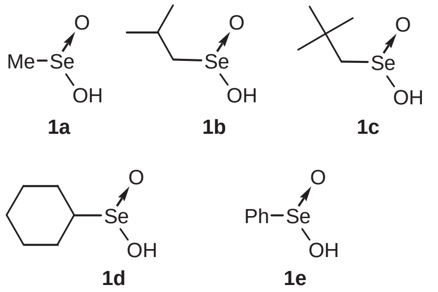

Chart 1.

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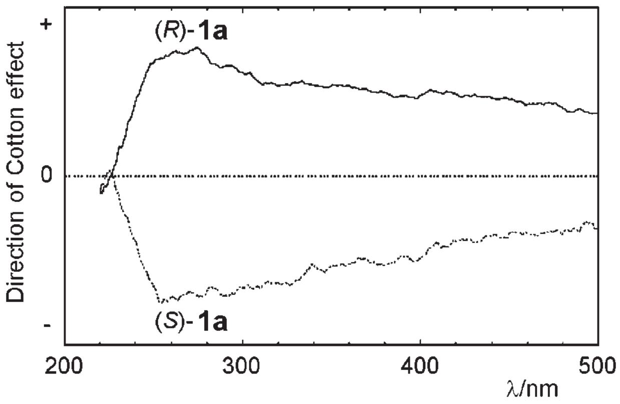


Fig. 1. Circular dichroism spectra of the optical isomers of seleninic acid **1a** in the solid state (KBr disk).

Table 1. Selected Atomic Distances and Bond Angles of **1a**

Atomic distance/Å		Bond angle/°	
Se1–O1	1.753(2)	O1–Se1–O2	103.50(12)
Se1–O2	1.669(2)	O1–Se1–C1	93.59(15)
Se1–C1	1.914(4)	O2–Se1–C1	100.79(15)

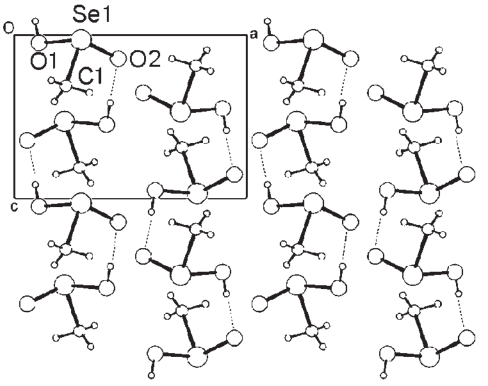


Fig. 2. Crystal packing of (*S*)-**1a**.

lographic analysis of **1a**, which showed a negative Cotton effect, was carried out in order to determine the absolute configuration.[7] The crystal is orthorhombic and belongs to the chiral space group $P2_12_12_1$. The selected atomic distances and bond angles of **1a** are shown in Table 1, and the crystal packing of **1a** is shown in Fig. 2. The two oxygen atoms of the OH and Se=O groups can be discriminated on the basis of the bond distances between the selenium atom and the oxygen atoms {1.753(2) and 1.669(2) Å}, and the hydrogen atom of the OH group was found on the D-map. Thus, the absolute configuration of the seleninic acid showing a negative Cotton effect can be determined to be *S*.

The molecules of **1a** are connected lengthwise via intermolecular hydrogen bonds between the hydrogen atom of OH and the oxygen atom of Se=O (Fig. 2), whereas the molecules of seleninic acid **1e** are known to form dimers via two strong hydrogen bonds in the racemic crystal.[8] The distance between the oxygen of Se=O and the oxygen of OH of the neighboring molecule is 2.548(3) Å, which is slightly shorter than that of acetic acid (2.63 Å),[9] and is almost the same as that of **1e** (2.52 Å).[8]

Stability of Optically Active Seleninic Acid 1a. The circular dichroism and the IR spectra of optically active seleninic acid (*R*)-**1a** (KBr disk made from a single crystal) were monitored for investigating the thermal stability in the solid state. No change was observed in the circular dichroism spectrum or in the IR spectrum after heating the sample at 60 °C for 6 days, indicating that neither racemization nor decomposition of (*R*)-**1a** occurred under the given conditions. However, when the sample was heated at 80 °C for 1 day, the intensity of the Cotton effect in the circular dichroism spectrum decreased together with a decrease in the intensity of the absorption bands (3014, 821, and 682 cm^{-1}) of (*R*)-**1a** on the IR spectrum, indicating that some decomposition of (*R*)-**1a** occurred under the given conditions. The decomposition was completed after 4 days, and dimethyl diselenide and a small amount of selenium were formed.

By contrast, no Cotton effect was observed in methanol solution even within 5 s after the dissolution of (*R*)-**1a** at room temperature, indicating that optically active **1a** racemized very rapidly in solution.

Chiral Crystallization of 1a. The chiral crystallization of **1a** was attempted in order to obtain the optically active seleninic acid in bulk. If only the seed crystals grew on recrystallization when chiral seed crystals of (*R*)-**1a** were used, (*R*)-**1a** would be obtained at higher than 50% yield from the racemic **1a**, because **1a** racemizes rapidly in the mother liquor and the ratio of the enantiomers in solution is maintained at approximately 1:1 during recrystallization.

A chiral single crystal (25 mg) of (*S*)-**1a** was pulverized and seeded in a supersaturated methanol/toluene (1/1) solution of **1a** (500 mg), which was prepared by cooling a hot methanol (1.5 mL) solution of **1a** to room temperature and adding toluene (1.5 mL) to it. The mixture was allowed to stand for 1 day at room temperature, and the crystals precipitated were collected by filtration (355 mg, 68% yield from racemic **1a**). Ten crystals were selected at random from the crystals obtained, and their circular dichroism spectra were measured in the solid state (KBr disk). As a result, all the 10 crystals showed negative Cotton effects (*S*-form), which would suggest that the absolute configuration of all the crystals obtained in the pot is *S*. However, in another recrystallization using (*S*)-**1a** as the seed crystal, 7 crystals showed negative Cotton effects and 3 showed positive Cotton effects. An additional 11 sets of recrystallization were carried out, and at least 6 of the 10 crystals from one pot showed Cotton effects of the same sign as the seed crystals in all cases. However, there were only 3 cases when all 10 crystals from one pot showed the same sign of the Cotton effect as the seed crystals. The crystals originating from the surface of the flask may have caused the low reproducibility. Thus, it is difficult to obtain chiral crystals of the same configuration selectively by this method.

Therefore, the preparation of a large single crystal was attempted in order to obtain a lump of enantiomerically pure **1a**. A chiral single crystal of (*R*)-**1a** (4 mg) was tied with a string and suspended in a supersaturated methanol solution (2 mL) of **1a** (1 g), and allowed to stand for 2 h. A crystal that grew was suspended again in the supersaturated solution that was prepared by dissolving other precipitates in the mother liquor by heating. Finally, the crystal developed into a large chi-

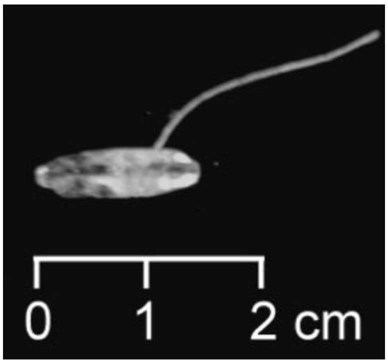
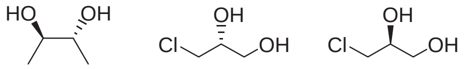


Fig. 3. A lump of crystal of optically active seleninic acid (*R*)-**1a** obtained by chiral crystallization (753 mg).



(2*R*, 3*R*)-**2** (*R*)-**3** (*S*)-**3**

Chart 2.

Table 2. Chiral Crystallization of **1a** in the Presence of Chiral Solvents

Optically active alcohol	Recovery yield/%	Absolute configuration of crystals of **1a** obtained
(2*R*,3*R*)-**2**	65	*R*
(*R*)-**3**	65	*R*
(*S*)-**3**	70	*S*

ral single crystal of enantiomerically pure (*R*)-**1a**. The optical purity of the crystal was confirmed by measuring the circular dichroism spectra (KBr disk) of several crushed pieces of the crystal. As a result, 753 mg of (*R*)-**1a** was obtained as a single crystal in 75% yield from racemic **1a** (Fig. 3). In a similar manner, 701 mg of (*S*)-**1a** was obtained as a single crystal in 69% yield by using a seed crystal of (*S*)-**1a** (11 mg).

Another method for the chiral crystallization of **1a**, which uses not seed crystals but chiral solvents, was examined. Optically active alcohol (2*R*,3*R*)-**2**, (*R*)-**3**, or (*S*)-**3** (Chart 2) (0.2–0.5 mL) was added to a methanol solution (0.5 mL) of **1a** (200–300 mg) and the solution was allowed to stand for a few days. It was confirmed from the IR spectra that the deposited crystals were not mixed crystals that included the chiral solvents but the resulting crystals of **1a**. Ten crystals were selected at random from the crystals obtained in one pot, and the absolute configurations were checked by measuring the circular dichroism spectra (KBr disk). The results are shown in Table 2. In the case of adding (2*R*,3*R*)-**2**, the yield was 65% from racemic **1a** and all of the 10 crystals were *R*-form. In the case of **3**, only the crystals of (*R*)-**1a** were obtained by recrystallization in methanol/(*R*)-**3**, and (*S*)-**1a** was obtained selectively by recrystallization from methanol/(*S*)-**3** at higher than 50% yield. The optically active alcohols can be recovered after recrystallization. In fact, 92% of (*R*)-**3** can be recovered from the mother liquor with ease according to the following procedure: ether was added to the mother liquor and precipitated crystals of **1a** were filtered off, and the filtrate containing the optically active alcohol was finally concentrated under reduced pressure.

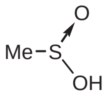


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Chart 3.

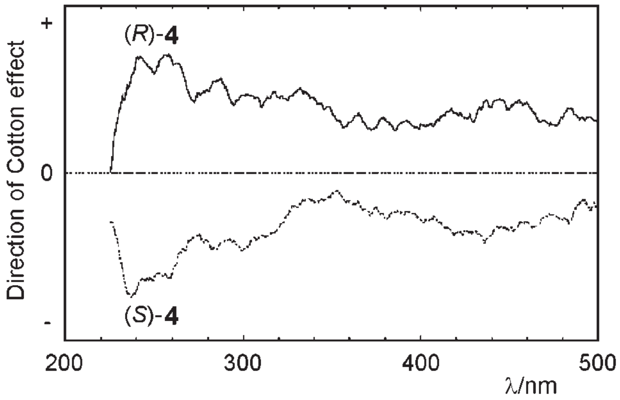

Fig. 4. Circular dichroism spectra of optical isomers of methanesulfinic acid (**4**) in the solid state (neat; powder).

Absolute Configuration of Methanesulfinic Acid. The crystals of methanesulfinic acid (**4**) (Chart 3), which is the sulfur analogue of **1a**, have been reported to belong to a chiral space group.[10] However, neither determination of the absolute configuration nor measurement of the chiroptical property was successful.[11] If the circular dichroism spectra of the chiral crystals of **4** could be measured, the absolute configurations of the optical isomers of **4** would be determined on the basis of the relationship between the absolute configuration and the circular dichroism spectrum of **1a**.

Chiral crystals of **4** were obtained by recrystallization from ether/hexane. Measurement of the circular dichroism spectrum of a single crystal was attempted in the solid state (KBr disk). However, **4** decomposed during the preparation of the KBr disk, perhaps because it is unstable in air.[10] Therefore, the sample for the measurement was prepared at low temperature to prevent decomposition. A single crystal of **4** was sandwiched between two pieces of quartz glass, cooled at −196 °C, and pulverized. Then, the circular dichroism spectrum was measured. The circular dichroism spectrum of one sample showed a negative Cotton effect at around 240 nm, as shown in Fig. 4, and the shape of the spectrum was similar to that of (*S*)-**1a**. On the other hand, another crystal showed a positive Cotton effect in the same region. On the basis of the similarity in the circular dichroism spectra of **4** and **1a**, the absolute configuration of **4** that showed a negative Cotton effect was determined to be *S* and that of the crystal with a positive Cotton effect was determined to be *R*.

Conclusion

The optical isomers of methaneseleninic acid (**1a**) were isolated as stable crystals and the relationship between the absolute configuration and the circular dichroism spectra of **1a** was determined by X-ray crystallographic analysis. Optically active **1a** was found to be stable in the solid state at 60 °C, whereas it decomposed at 80 °C. Optically active **1a** was also found to racemize very rapidly in solution. Two methods for obtaining each enantiomer of **1a** in bulk by chiral crystallization were developed by taking advantage of the rapid racemization in solution. One method involves the use of a seed crystal; a chiral seed crystal of **1a** tied with a string developed into a large chiral single crystal by recrystallization. The other method involves the use of chiral solvents; optically active **1a** was obtained in bulk by recrystallization in the presence of chiral solvent at higher than 50% yield from racemic **1a**. The absolute configuration of optically active methanesulfinic acid (**4**) was clarified by comparing its circular dichroism spectra with those of **1a**.

Experimental

General. All solvents used in recrystallization were of practical grade. Melting points were determined on a Yamato MP-21 Melting point apparatus. IR spectra were measured on a PERKIN ELMER Spectrum GX FT-IR system. ^{1}H, ^{13}C, and ^{77}Se NMR spectra were recorded on a JEOL JNM-EX-500 FT NMR System. Mass spectra (MS) were determined on a JEOL JMS-GCMATE System. Elemental analysis was performed using a PERKIN-ELMER 240-C. Circular dichroism spectra were measured on a JASCO J-725 Spectropolarimeter. Methaneseleninic acid (**1a**) was prepared by oxidation of dimethyl diselenide, according to the literature.[12] Benzeneseleninic acid (**1e**) is commercially available.

Methaneseleninic Acid (1a; Racemate). Mp 124–125 °C (colorless prisms from methanol); ^{1}H NMR (500 MHz, CD_3OD) δ 2.68 (3H, s), 4.86 (1H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 41.3; ^{77}Se NMR (95 MHz, CD_3OD) δ 1294; MS (EI, 70 eV) m/z 128 (M^+, ^{80}Se), 126 (M^+, ^{78}Se), 111 ($M^+ - OH$, ^{80}Se), 109 ($M^+ - OH$, ^{78}Se); IR (KBr) 3014, 2800 (br), 2350 (br), 1750 (br), 988, 821 (Se=O), 682 cm^{-1}; UV (2-propanol) λ_{max} 230 (ε 1.09×10^3), 200 (ε 2.44×10^3) nm.

***(S)*-1a**. Mp 128–130 °C (colorless prisms from methanol/toluene); IR (KBr) 3014, 2800 (br), 2350 (br), 1750 (br), 989, 820 (Se=O), 681 cm^{-1}.

***(R)*-1a**. Mp 128–130 °C (colorless prisms from methanol/toluene); IR (KBr) 3014, 2800 (br), 2350 (br), 1750 (br), 990, 820 (Se=O), 680 cm^{-1}.

General Procedure for Preparation of Seleninic Acids 1b–d. To a DMF (20 mL) solution of sodium diselenide (10 mmol) prepared according to the literature,[13] alkyl bromide (20–25 mmol) was added slowly, and the mixture was stirred until the color of solution changed from violet into green or yellow. To the mixture was added water (20 mL); this combination was extracted with dichloromethane (40 mL × 2); the organic components was washed with 6 M hydrochloric acid (60 mL) and water (50 mL × 2), and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded crude diselenide, which was dissolved in dichloromethane (50 mL); ozone was then bubbled into the solution at −40 °C. After disappearance of color for diselenide, water (10 mL) was added to the solution, and the mixture was stirred vigorously for 1 h at room temperature. Evaporation of solvent and recrystallization of the residue afforded seleninic acid.

2-Methylpropane-1-seleninic Acid (1b).[14] Yield 27%; mp 91–92 °C (colorless film from acetonitrile); ^{1}H NMR (500 MHz, CD_3OD) δ 1.08 (3H, d, $J = 6.72$ Hz), 1.10 (3H, d, $J = 6.72$ Hz), 2.29 (1H, m), 2.82 (1H, dd, $J = 12.2$, 4.75 Hz), 3.00 (1H, dd, $J = 12.2$, 4.75 Hz), 4.84 (1H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 23.5, 25.1, 66.1; ^{77}Se NMR (95 MHz, CD_3OD) δ 1314; MS (EI, 70 eV) m/z 171 ($M^+ + 1$, ^{80}Se), 169 ($M^+ + 1$, ^{78}Se), 154, 152; IR (KBr) 2960, 2900 (br), 2380 (br), 1680 (br), 1460, 1319, 844 (Se=O), 669 cm^{-1}.

2,2-Dimethylpropane-1-seleninic Acid (1c). Yield 23%; mp 123 °C (colorless film from acetonitrile; decomp.); ^{1}H NMR (500 MHz, CD_3OD) δ 1.16 (9H, s), 2.85 (1H, d, $J = 12.1$ Hz), 3.20 (1H, d, $J = 12.1$ Hz), 4.82 (1H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 30.7, 32.0, 72.8; ^{77}Se NMR (95 MHz, CD_3OD) δ 1316; MS (EI, 70 eV) m/z 185 ($M^+ + 1$, ^{80}Se), 183 ($M^+ + 1$, ^{78}Se), 168 ($M^+ - O$, ^{80}Se), 166 ($M^+ - O$, ^{78}Se), 159, 157; IR (KBr) 2963, 2850 (br), 2410 (br), 1680 (br), 1467, 1364, 1322, 842 (Se=O), 670 cm^{-1}; Anal. Calcd for $C_5H_{12}O_2Se$: C, 32.80; H, 6.61%. Found: C, 32.69; H, 6.61%.

Cyclohexaneseleninic Acid (1d). Yield 64%; mp 77–79 °C (colorless film from acetonitrile); ^{1}H NMR (500 MHz, CD_3OD) δ 1.25–1.50 (3H, m), 1.55–1.80 (3H, m), 1.81 (2H, dd, $J = 9.50$, 5.20 Hz), 2.06 (2H, dd, $J = 13.1$, 3.95 Hz), 3.03 (1H, m), 4.84 (1H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 25.7, 25.9, 26.9, 27.1, 27.2, 66.8; ^{77}Se NMR (95 MHz, CD_3OD) δ 1322; MS (EI, 70 eV) m/z 180 ($M^+ - O$, ^{80}Se), 178 ($M^+ - O$, ^{78}Se); IR (KBr) 2927, 2900 (br), 2450 (br), 1446, 1292, 814 (Se=O), 658 cm^{-1}; Anal. Calcd for $C_6H_{12}O_2Se$: C, 36.93; H, 6.20%. Found: C, 36.60; H, 5.89%.

Procedure for Measurement of Circular Dichroism Spectra in Solid State. KBr disk: A mixture of a single crystal of **1a** (ca. 5 mg) and 70 mg of KBr was ground and formed into a disk with a radius of 6.5 mm. Neat: A single crystal of **4** was pinched between a pair of pieces of quartz glass and this combination was cooled by liquid nitrogen for a few seconds. Rubbing the glasses together gave powder of **4**, and which was used for measurement of circular dichroism spectrum.

Typical Procedure for Chiral Crystallization of 1a. Method A: Compound **1a** (500 mg) was dissolved in hot methanol (1.5 mL) and the solution was cooled slowly to room temperature, and then toluene (1.5 mL) was added. The powder of (*S*)-**1a**, prepared by pulverizing the single crystal, was scattered into the solution and the mixture was allowed to stand for 1 day. The crystals that precipitated (68–99%) were filtered and dried in air.

Method B: Compound **1a** (1.00 g) was dissolved in hot methanol (2 mL) and the solution was cooled slowly to room temperature. A single crystal of (*S*)-**1a** (∼10 mg) tied with string was hung in the solution. The crystal that grew was pulled up and then hung again in a solution that was prepared by dissolution of other precipitates in the mother liquor by heating. Repetition of this procedure afforded a lump of enantiomerically pure (*S*)-**1a**.

Method C: Compound **1a** (200–300 mg) was dissolved in hot methanol (0.5 mL) and the solution was cooled slowly to room temperature. Optically active alcohol (0.2–0.5 mL) was added to the solution, and the mixture was allowed to stand for a few days. The crystals that deposited were filtered and dried in air.

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