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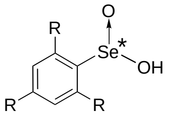
Optically Active Seleninic Acids: Optical Resolution and Stability

Toshio Shimizu, Itaru Watanabe, and Nobumasa Kamigata*

Tricoordinate sulfur compounds are well known to have pyramidal structures, and many chiral tricoordinate sulfur compounds have already been isolated and clearly characterized.[1] Recently, chiral tricoordinate selenium and tellurium compounds, such as oxides,[2] onium salts,[3] ylides,[4] and imides,[5] have also been isolated, and their properties have been studied.[6–8] Chalcogenic acids are also tricoordinate and are considered to have pyramidal structures. However, no studies on optically active chalcogenic acids have been reported. There are at least two possible explanations for this: first, sulfinic acids readily undergo disproportionation[9] to give thiol sulfonates and sulfonic acids. Second, facile racemization of chalcogenic acids may occur via achiral chalcogenate anions with extrusion of a proton and/or by an intra- or intermolecular proton-transfer reaction. Seleninic acids do not disproportionate to the corresponding selenol selenonates and selenonic acids. Therefore, it may be possible to isolate optically active seleninic acids if we could suppress their racemization. We examined the optical resolution of areneseleninic acids by means of liquid chromatography on an optically active column and found that seleninic acid could be optically resolved, although the racemization was fast, especially at high concentrations, and also that bulky alkyl substituents on the benzene ring of areneseleninic acids were effective in retarding racemization. Here we describe the first optical resolution and the stability of seleninic acids.



1: R = H
2: R = Me
3: R = Et
4: R = *i*Pr
5: R = *t*Bu

When the optical resolution of 2,4,6-trimethylbenzeneseleninic acid (**2**) was examined on an analytical scale by liquid chromatography on an optically active column packed with amylose carbamate derivative/silica gel (Daicel Chiralpak AS; 4.6 × 250 mm), two peaks corresponding to he enantiomers were observed on the chromatogram, whereas only one peak was observed in the case of benzeneseleninic acid (**1**), as shown in Figure 1. This result shows that

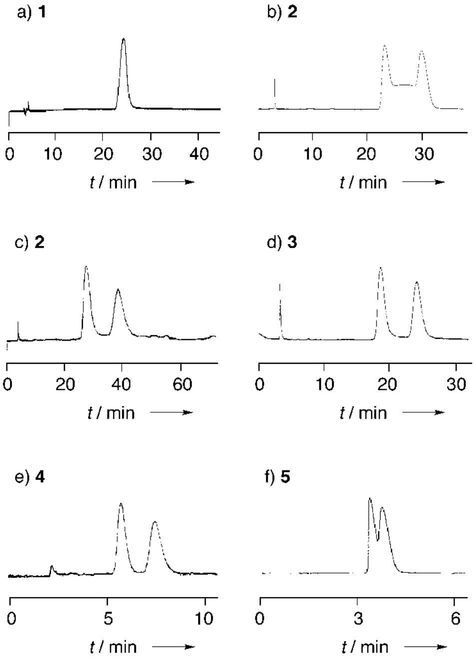


Figure 1. Chromatographic resolution of racemic seleninic acids **1**–**5** on an optically active column packed with amylose carbamate derivative/silica gel (Daicel Chiralpak AS; 4.6 × 250 mm) by HPLC on an analytical scale at 25 °C at a flow rate of 1.0 cm^3 min^{-1}. Eluent: a) hexane/2-propanol (85/15); b) hexane/2-propanol (95/5); c) hexane/2-propanol (90/10) (at 0 °C); d) hexane/2-propanol (98/2); e) hexane/2-propanol (98/2); f) hexane/2-propanol (98/2).

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the hydrogen atom in seleninic acid is fixed to a certain extent to one oxygen atom, at least in the case of substituted benzeneseleninic acids such as **2**. However, the unusual shape of the chromatogram of **2** at 25 °C indicated that racemization occurred on the column. When the chromatographic resolution of **2** was carried out at 0 °C, the two enantiomers could be optically resolved. Similarly, optical resolution of areneseleninic acids **3** and **4**, which have more bulky alkyl substituents on the benzene ring, was also carried out by using the same column. In these cases, satisfactory resolution was obtained even at 25 °C. These results indicate that bulky alkyl substituents on the benzene ring are useful for retarding racemization and also show that failure of the resolution in the case of **1** is due to rapid racemization in the column. However, resolution of **5**, which has the most bulky substituent, was not satisfactory, perhaps due to insufficient recognition of chirality because the bulky alkyl substituents at the *ortho* positions of the benzene ring mask the chiral selenium center of **5**.

The optical resolution of areneseleninic acids **2**–**4** was carried out by HPLC on the same type of optically active column on a preparative scale (10 mm × 250 mm). Optically pure seleninic acids (+)-**2**, (+)-**3**, and (−)-**4** were obtained as first-eluted solutions, and their optical purities were confirmed by HPLC analysis. The second-eluted portions were found to contain (−)-**2**, (−)-**3**, and (+)-**4**, with optical purities of 58, 30, and 68 %, respectively. The inability to obtain optically pure seleninic acids from the latter eluates is due to tailing of the first-eluted enantiomers on a preparative scale. Since concentration of the solution by evaporation under reduced pressure yielded completely racemized seleninic acids, specific rotations were measured on the eluted solution. Concentrations were determined by comparison of the UV spectra with those of authentic racemic samples. The specific rotations of the optically active seleninic acids are summarized in Table 1. Circular dichroism spectra were also measured for the eluted solutions, and the seleninic acids with a positive specific rotation, (+)-**2**, (+)-**3**, and (+)-**4**, showed positive first Cotton effects at 283, 283, and 281 nm, and negative second Cotton effects at 229, 239, and 240 nm, respectively (Figure 2). On the other hand, (−)-**2**, (−)-**3**, and (−)-**4** showed negative first Cotton effects and positive second Cotton effects in the same regions.

Table 1. Specific rotations of optically active seleninic acids **2**–**4**.

Seleninic acid	First-eluted enantiomer *ee* [%]	First-eluted enantiomer $[\alpha]_{435}$	Second-eluted enantiomer *ee* [%]	Second-eluted enantiomer $[\alpha]_{435}$
2	100	709.4 (*c* 0.01)[a]	58	− 337.4 (*c* 0.01)[a]
3	100	471.4 (*c* 0.01)[b]	30	− 131.9 (*c* 0.01)[b]
4	100	− 493.1 (*c* 0.01)[c]	68	395.1 (*c* 0.01)[c]

[a] In hexane/2-propanol (90/10). [b] In hexane/2-propanol (98/2). [c] In hexane/2-propanol (99/1).

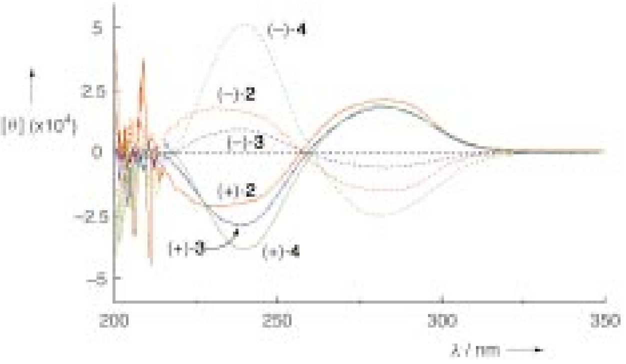


Figure 2. Circular dichroism spectra of optically active seleninic acids **2**–**4**. Solvent: **2** in hexane/2-propanol (90/10); **3** in hexane/2-propanol (98/2); **4** in hexane/2-propanol 99/1.

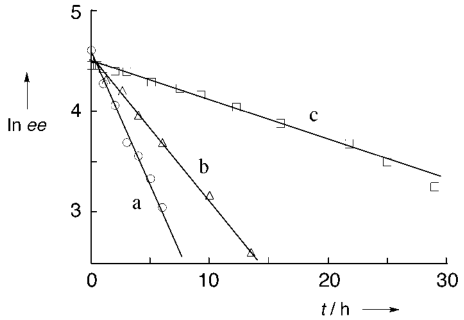
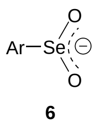


Figure 3. First-order rate plots for the racemization of optically active seleninic acids. a) (+)-**2** (1.52×10^{-4} M) in hexane/2-propanol (90/10); b) (+)-**3** (1.08×10^{-4} M) in hexane/2-propanol (98/2); c) (−)-**4** (1.09×10^{-4} M) in hexane/2-propanol (99/1).

The kinetics of racemization of the optically active seleninic acids were examined in the eluted solutions. The rates of racemization for optically active seleninic acids (+)-**2**, (+)-**3**, and (−)-**4** at 25 °C showed a good linear relationship with first-order rate plots under dilute conditions (Figure 3). The rate constants for (+)-**2**, (+)-**3**, and (−)-**4** were 6.97×10^{-5}, 3.81×10^{-5}, and 1.11×10^{-5} s^{-1}, and the $t_{1/2}$ values were 2.76, 5.05, and 17.3 h, respectively. These results mean that areneseleninic acids with more bulky alkyl substituents are more stable against racemization than those with less bulky substituents, and bulky alkyl substituents on the benzene ring retard racemization of the seleninic acid. (Note, however, that the concentrations and solvent mixtures are different.) There are at least two plausible mechanisms for racemization with a first-order rate constant. One is a pathway via an achiral selenate anion with extrusion of a proton, and the other is vertex (pyramidal) inversion. In tricoordinate sulfur compounds, vertex inversion is known to occur.[1] However, the barriers to vertex inversion for the corresponding selenium analogues are too high for such inversion to occur at room temperature.[6, 10] Therefore, racemization of the seleninic acids may proceed via the corresponding achiral seleninate anions **6** with extrusion of a proton, at least under dilute conditions. It was also found that the rate of racemization increased with increasing concentration in the case of (−)-**4** (1.46×10^{-3} M; initial $t_{1/2} = 2.06$ h), and the rate of racemization deviated from the first-order rate plot, while the half-life increased under high-dilution conditions, and the plots showed a first-order reaction (2.02×10^{-5} M; $k = 5.85 \times 10^{-6}$ s^{-1}, $t_{1/2} = 32.9$ h). These results indicate that racemization by an intermolecular proton-exchange reaction via intermolecularly associated structures also takes



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place at high concentrations, although the order of the reaction could not be determined. This can explain why concentration of the eluate by evaporation of the solvent caused complete racemization of the seleninic acids.

Although the mechanism of racemization is not clear, we have obtained for the first time optically pure seleninic acids from racemic mixtures by optical resolution. The absolute configurations and details of the mechanism of racemization of optically active seleninic acids are currently under investigation. Recently, benzeneseleninic acids have been commonly used in various oxidation reactions.[11] Therefore, the optically active seleninic acids are expected to act as asymmetric oxidizing reagents.

Experimental Section

Preparation of racemic seleninic acids: Racemic seleninic acids **2**–**4** were prepared by oxidation of the corresponding diselenides with ozone at $-30\,^{\circ}C$ in dichloromethane, followed by hydrolysis, in 64, 28, and 72% yields, respectively, according to the literature procedure.[12] Seleninic acid **5** was also prepared according to the literature procedure.[13] All new seleninic acids gave satisfactory spectral data and combustion analyses.

Typical procedure for optical resolution of areneseleninic acids: Racemic areneseleninic acid (50 mg) in eluent (0.3 mL) was charged to an optically active column packed with amylose carbamate derivative/silica gel (Daicel Chiralpak AS; 10×250 mm) and eluted with hexane containing 10 (for **2**), 2 (for **3**), and 1 (for **4**) vol% 2-propanol at a flow rate of $1.0\,mL\,min^{-1}$. About 15 mg of each optically active areneseleninic acid was collected as eluate from the first- and second-eluted portions, and the specific rotations and the circular dichroism spectra were recorded on the eluted solutions, the concentrations of which were determined by comparison of the UV spectra with those of authentic racemic samples. Chemical structures of the optically active seleninic acids were confirmed by mass spectrometry and ^{1}H NMR spectroscopy after concentration, although racemization was occurring during the concentration.

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