Configurational Stability of Optically Active Selenoxides; Racemization via Achiral Hydrate

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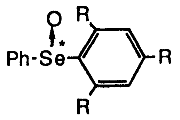
Synopsis. Configurational stabilities of optically active diaryl selenoxides are examined under several conditions such as acidic, basic, or in the presence of water. It is found that the diaryl selenoxide which has two hindered *t*-butyl groups on the ortho positions is relatively stable toward racemization even under acidic conditions. Mechanism of racemization is ascertained to be via formation of the achiral hydrate (R-Se(OH)$_2$-R′) by the observation of oxygen exchange on the selenium atom.

Although optically active sulfoxides have been known for a long time, there has been no example of the isolation of an optically active selenoxide until recently. Davis et al. first reported the preparation of enantiomerically active selenoxides several years ago, although the enantiomeric excesses of the selenoxides were low.[2] Since then several optically active selenoxides were synthesized.[3–7] We reported the synthesis of optically active selenoxides by fractional recrystallization of diastereomeric mixture[4] or chromatographic separation using optically active column.[6] In addition, we obtained optically pure selenoxide as a stable solid by transesterification of the diastereomerically pure selenoxide.[7] The difficulty of the optical resolution of selenoxide has been attributed to its facile racemization.[8] Two mechanisms for the racemization of selenoxide are considered. One is the mechanism by the pyramidal inversion and the other is the mechanism via formation of its achiral hydrate (R-Se-(OH)$_2$-R′). We previously estimated the stability of asymmetric selenoxides toward the pyramidal inversion. Optically active diaryl selenoxides were found to become more stable toward the pyramidal inversion by substitutions of bulky groups on the ortho positions.[9] However, the second mechanism of racemization involving the achiral hydrate is anticipated to be also important. We report here the configurational stability of optically active diaryl selenoxides which possess ortho substituents of various sizes under several conditions such as acidic, basic, or in the presence of water.

Results and Discussion

The optically active selenoxides were prepared by chromatographic resolution (optically active column) of the racemic samples.[6] Racemizations of selenoxides were measured at 26 °C in chloroform or methanol. Progress of the racemization was monitored by means of the circular dichroism spectrum. The racemizations in chloroform were examined, to begin with. However, no racemization was observed and the optical activities of selenoxides **1**—**4** were unchanged even after 5 days. When the racemizations were measured in methanol, selenoxide **1**—**3** were found to racemize. The rate constants of the racemizations of **1**—**3** were 6.00×10^{-6}, 1.85×10^{-6}, 1.33×10^{-6} s^{-1} and the half-lives of the optical activities were 32.1, 104, 145 h, respectively. Larger ortho substituents were found to be more effective for retardation of the racemization. The selenoxide **4** which possessed the most bulky ortho substituents in this series was quite stable in methanol. The rate constants and half-lives of the racemizations are summarized in Table 1.



1 : R = Me
2 : R = Et
3 : R = i-Pr
4 : R = t-Bu

Influences of water, acid, and base were also examined. In the presence of water, racemizations were accelerated in the cases of selenoxides **1**—**3**, however selenoxide **4** was still stable even in the presence of water (Entries 3 and 4). The racemizations of selenox-

Table 1. Rate Constants and Half-Lives of Optical Activities[a]

Entry	Condition	k/s^{-1} ($t_{1/2}$/h)			
		1	**2**	**3**	**4**
1	CHCl$_3$	A[c]	A	A	A
2	MeOH	6.00×10^{-6} (32.1)	1.85×10^{-6} (104)	1.33×10^{-6} (145)	A
3	MeOH+H$_2$O[b]	6.31×10^{-6} (30.5)	2.18×10^{-6} (88.3)	1.40×10^{-6} (138)	A
4	MeOH/H$_2$O(4/1)	3.34×10^{-5} (5.76)	8.59×10^{-6} (22.4)	5.40×10^{-6} (35.6)	A
5	MeOH/H$_2$O(4/1)+HCl[b]	B[d]	B	B	1.85×10^{-5} (10.4)
6	MeOH/H$_2$O(4/1)+NaOH[b]	3.10×10^{-5} (6.21)			

a) Concentrations of selenoxides: 1 mmol l^{-1}. Temp: 26 °C. b) H$_2$O, HCl, NaOH: 30 mmol l^{-1}. c) A: No racemization was observed after 5 days. d) B: Racemization was completed within 1 min.

ides **1**—**3** in dry methanol (distilled after drying with CaH_2) are suspected to be due to the presence of small traces of water in the methanol, because the racemizations were accelerated in aqueous methanol and no racemization occurred in chloroform which was a hydrophobic solvent. Remarkable acceleration of the racemization was observed in all selenoxides under acidic conditions (Entry 5). In the cases of selenoxides **1**—**3**, the racemizations were fast and completed within 1 min. The selenoxide **4** also racemized under these conditions, however, the half-life was long (10.4 h). Therefore, bulky ortho substituents of diaryl selenoxide particularly *t*-butyl groups were found to be effective to retard or prevent the racemization catalyzed by the acid and water. The racemization of selenoxide **1** was also examined in basic media. The racemization of the selenoxide was not accelerated by the addition of sodium hydroxide into aqueous methanol solution (Entry 6).

Since all the racemizations were examined at room temperature and no racemization occurred in chloroform and the racemizations were observed in aqueous conditions, the racemizations of selenoxides under these conditions are considered to proceed via its achiral hydrate. To clarify the mechanism via the hydrate, the racemization of selenoxide **2** with ^{18}O-labeled water was studied. A methanol solution of selenoxide **2** in the presence of $H_2{}^{18}O$ (97 atom%) was stirred at room temperature. The mass spectrum of selenoxide **2** after 10 days indicated the formation of ^{18}O-labeled selenoxide (M^+ 336(^{80}Se), 334(^{78}Se)) (Fig. 1). The high-resolution mass spectrum also supported the formation of the selenoxide-^{18}O. This result indicates the formation of the achiral hydrate. Though the achiral hydrate itself expected to be formed by hydration of the selenoxide **2** could not be detected by mass spectroscopy, it is attributed to the lability of the hydrate.

The results that the racemization was accelerated under acidic conditions and not accelerated in basic media suggest that the protonation on the oxygen atom of the selenoxide is the rate-determining step as shown in Scheme 1. This protonation on the selenoxide corresponds to the protonation of sulfoxide in strong acidic media.[10] The second step of the racemi-

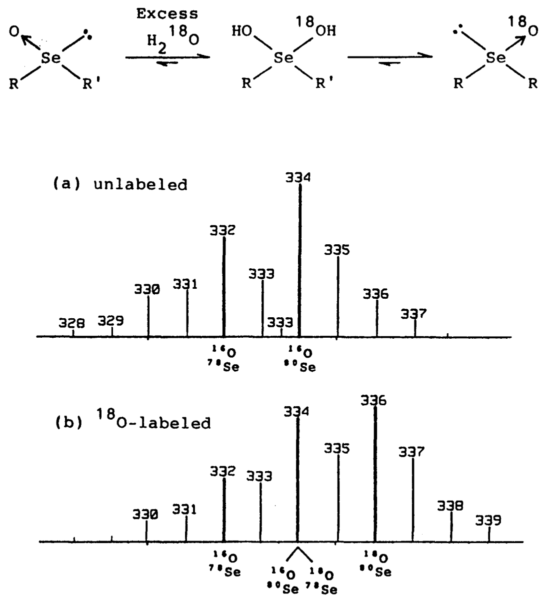
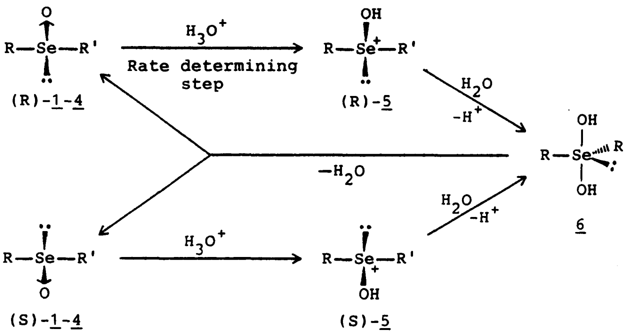


Fig. 1. Mass spectrum analysis of heavy oxygen exchange on selenium atom of selenoxide **2**.



Scheme 1. Mechanism of racemization via achiral hydrate.

$$Ph_2S \rightarrow O \;+\; H_2SO_4 \rightleftharpoons Ph_2S^+{-}OH \;+\; HSO_4^-$$

zation is fast addition of water to the hydroxy selenonium cation (*R*)-**5** or (*S*)-**5**. The addition of water to the hydroxy selenonium ion (*R*)-**5** or (*S*)-**5** followed by elimination of proton to give the achiral hydrate **6**. Finally, dehydration of the achiral hydrate **6** give the racemic mixture of selenoxide (*R*)-**1**—**4** and (*S*)-**1**—**4** resulting the exchange of the oxygen atom.

In conclusion, it was ascertained that the racemization of optically active selenoxides occurred through the achiral hydrate in aqueous media. Configurational stabilities of the optically active diaryl selenoxides toward the racemization via its achiral hydrate were found to be dependent on the ortho substituents.

Experimental

Materials. The optically active selenoxides **1**—**4** were prepared by optical resolution of racemic samples[3,11] using an optically active column.[6] Enantiomeric excesses (e.e.) of optically active selenoxides **1** and **2** were determined by ^1H NMR using $Eu(hfc)_3$ as an optically active shift reagent.[6] In the cases of optically active selenoxides **3** and **4**, e.e. were determined by HPLC using an optically active column.[11] The optical rotations and enantiomeric excesses (e.e.) of selenoxides used in the measurements of racemizations are shown below.

Phenyl Mesityl Selenoxide (1): $[\alpha]_D$ +40.2° (*c* 0.95, chloroform). E.e.=16%.

Phenyl 2,4,6-Triethylphenyl Selenoxide (2): $[\alpha]_D$ −29.0° (*c* 0.90, chloroform). E.e.=12%.

Phenyl 2,4,6-Triisopropylphenyl Selenoxide (3): $[\alpha]_D$ +58.4° (*c* 1.35, chloroform). E.e.=66%.

Phenyl 2,4,6-Tri-*t*-butylphenyl Selenoxide (4): $[\alpha]_D$ +96.5° (*c* 1.30, chloroform). E.e.=49%.

Measurement of Racemization. All racemizations of the selenoxides were carried out in 1 mmol l^{-1} concentration at 26 °C. Progress of the racemization was monitored by means of the circular dichroism spectrum (JASCO J-40A) at ca. 290 nm. The measurements of the racemizations were continued until about one half-life time.

Heavy Oxygen Exchange of Selenoxide. Heavy oxygen exchange of selenoxide **2** was carried out in methanol in the presence of ^{18}O-labeled water (Merck, 97 atom%). Concentrations of selenoxide and the labeled water were 5 mmol l^{-1} and 0.5 mol l^{-1}, respectively. Formation of the ^{18}O-labeled selenoxide **2**-^{18}O was confirmed by the mass spectrum (JEOL JMS-DX300) after 10 days. M^+ 336(^{80}Se), 334(^{78}Se). Exact MS, Found: *m/z* 336.0867 (^{80}Se), Calcd for $C_{18}H_{22}{}^{18}O^{80}Se$: 336.0878. The relative intensities of the mass spectra shown in Fig. 1 are summarized below. Enriched oxygen-18 contained in the selenoxide **2**-^{18}O was estimated by measurements of both its low and high mass spectroscopy. The enriched oxygen-18 was calculated to be 38% by low mass spectroscopy based on intensities of the mass spectrum, *m/z* 328 ($C_{18}H_{22}{}^{16}O^{74}Se$, relative intensity: 3.5) and 338 ($C_{18}H_{22}$-$^{18}O^{82}Se$, relative intensity: 22.3), since these mass numbers do not contain other isotope of oxygen and selenium. The oxygen-18 contained was also estimated to be 46% by high mass spectroscopy based on *m/z* 332 ($C_{18}H_{22}{}^{16}O^{78}Se$), 334 ($C_{18}H_{22}{}^{18}O^{78}Se$ and $C_{18}H_{22}{}^{16}O^{80}Se$), and 336 ($C_{18}H_{22}{}^{18}O^{80}Se$).

m/z	Relative Intensity	
	(a)unlabeled	(b)^{18}O-labeled
328	4.5	3.5
329	6.0	4.1
330	27.1	15.3
331	30.7	19.2
332	65.0	47.2
333	37.5	43.7
334	100	91.5
335	52.7	64.0
336	24.6	100
337	11.1	61.5
338	2.4	22.3
339	—	11.3
340	—	2.2

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