Optical Resolution of Asymmetric Selenoxides by High-Performance Liquid Chromatography Using Optically Active Column

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Synopsis. The optical resolution of asymmetric diaryl selenoxides and the determination of the enantiomeric excess of the partially active selenoxides were found to be possible by HPLC using an optically active column.

Although optically active sulfoxides have been known for a long time, the synthesis of an optically active pure selenoxide has so far been unsuccessful. The reason for the difficulty in isolating the enantiomer of selenoxides has been attributed to either a facile racemization due to the formation of a hydrate or to a rapid pyramidal inversion of the conformation around the selenium atom. In 1983, the preparation of partially optically active selenoxides was reported for the first time, but their optical purities were only 5—11%.[1] Recently, we described a synthesis of the optically pure diastereomeric selenoxide as well as the enantiomeric selenoxide with a high optical activity.[2] The determination of the enantiomeric excess has a vital importance in studies on optical resolution. We have discovered that asymmetric diaryl selenoxides can be resolved into the antipodes and also that the optical purities of the selenoxides, in which optical rotation is unknown, can be determined by HPLC using an optically active column. Details are described in this paper.

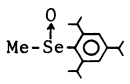
Results and Discussion

Selenides were prepared according to published methods.[3-6] The oxidation of selenides to selenoxides was carried out with *t*-butyl hypochlorite in the presence of methanol and pyridine.[7]

An example of the general procedure is shown for the case of *p*-tolyl 2,4,6-triisopropylphenyl selenoxide (**1**). A chromatographic separation of the racemic selenoxides was performed with a Bakerbond chiral phase HPLC column RP 7103-O (250×4.6 mm) packed with DNBPG/aminopropylsilica (particle size 5 μm), similar to those which have been used for the separation of various optically active compounds,[8] using hexane containing 5 vol% of 2-propanol as the mobile phase at a flow rate of 1.0 ml min^{-1} (Fig. 1). The chromatographic separability factor of the enantiomers, α was calculated to be 1.10. The R_S value was also calculated as 1.46. The integration ratio (lower R_f/higher R_f) was 1.01. This integration value over 1.00 could be attributed to the tailing of higher R_f enantiomer.

Several diaryl and alkyl aryl selenoxides were subjected to HPLC in a similar way using an optically active column; the results are summarized in Table 1. The R_S value and the integration ratio are a measure of the capability for a chromatographic separation of the optical isomers. The R_S values of the selenoxides **1**—**6** were 1.00—1.86 and integration ratios were 1.01—1.05.

In order to investigate the effect of bulky ortho substituents to retard the rate of racemization through a conformational inversion, the separabilities of phenyl 2,4,6-trimethylphenyl selenoxide (**8**), triethyl derivative **7**, triisopropyl derivative **2**, and tri-*t*-butyl derivative **5** in the HPLC with optical active column were compared with each other. All selenoxides were found to be separable into optical isomers; however, as can be seen in Table 1, compared to selenoxides **2** and **5**, the R_S values of selenoxides **7** and **8**, which possess less bulky substituents than isopropyl or *t*-butyl groups, were small. The integration ratios of selenoxides **7** and **8** increased by over 1.00. The decrease of the chromatographic separability of latter selenoxides might be attributed to a decrease in the conformational stability. We have also attempted a resolution of alkyl aryl selenoxide **9** and benzyl aryl selenoxide **10**, which possess bulky ortho substituents. However, contrary to



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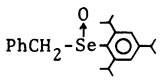

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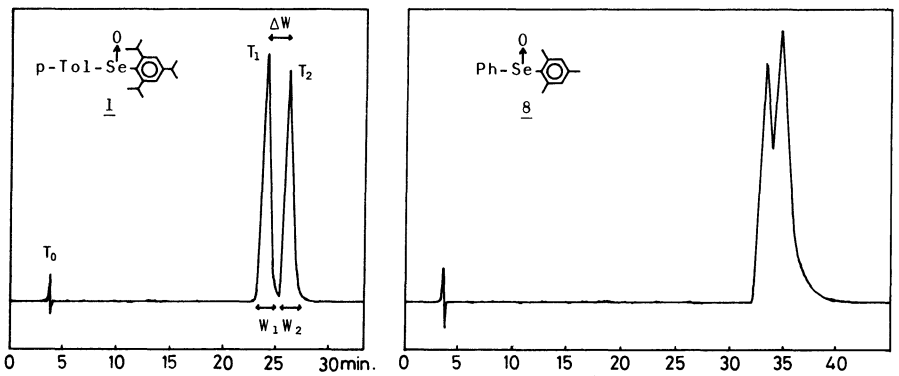
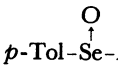
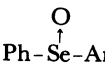
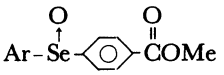
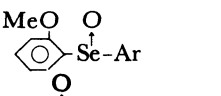
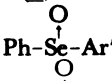
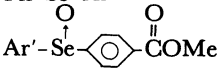
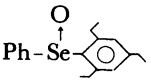
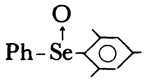
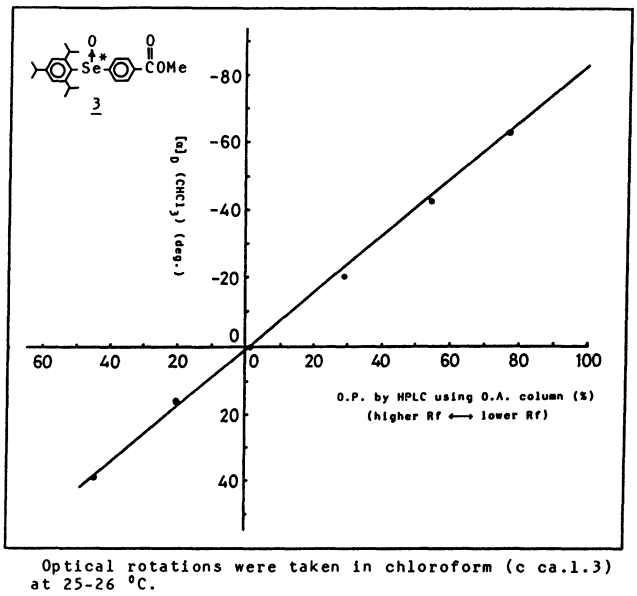


Fig. 1. Chromatographic resolution of enantiomers.

Table 1. Chromatographic Resolution of Selenoxide

	Selenoxide	2-Propanol[c] %	k_1'[d]	α[e]	R_s[f]	Integration ratio[g]
(1)		5	5.17	1.10	1.46	1.01
(2)		5	4.15	1.09	1.35	1.02
(3)		5	7.79	1.12	1.83	1.02
(4)		5	11.8	1.10	1.86	1.02
(5)		3	3.01	1.06	1.00	1.05
(6)		3	4.43	1.07	1.25	1.03
(7)		5	9.33	1.06	0.77	1.18
(8)		10	7.43	1.05	0.51	1.83

a) Ar is 2,4,6-triisopropylphenyl group. b) Ar′ is 2,4,6-tri-*t*-butylphenyl group. c) The volume percentage of 2-propanol in hexane used as a mobile phase. d) k_1' is the capacity ratio for the initially eluted enantiomer; $k_1'=(T_1-T_0)/T_0$. e) The chromatographic separability factor of the enantiomers, α, is the ratio of the capacity ratios of the two enantiomers; $\alpha=k_2'/k_1'$. f) R_s is the peak resolution of the two enantiomers; $R_s=2\Delta W/(W_1+W_2)$. g) The integration ratio of the two enantiomers; lower R_f/higher R_f.



Optical rotations were taken in chloroform (c ca.1.3) at 25-26 °C.

Fig. 2. Correlation of optical rotations and optical purities by HPLC using optically active column.

the diaryl selenoxides, we found that these alkyl aryl selenoxides could not be separated by HPLC using an optically active column.

A plot of the optical rotations $[\alpha]_D$ and the optical purities estimated by HPLC gave a good straight line (Fig. 2) in the case of selenoxide **3**.

In conclusion, HPLC with an optical active column is useful for indicating which selenoxide can be separable into optical antipodes and to determine their optical purities.

Experimental

All melting points were determined on a Yamato MP-21 and were uncorrected. The IR spectra were recorded on a Hitachi 260-10 Spectrometer, ^{1}HNMR spectra with TMS as an internal standard on a JEOL JNM-PMX 60, and mass spectra on a JEOL JMS-DX300 Mass Spectrometer. The optical rotations were measured on a JASCO DIP-140 digital polarimeter. Silica-gel TLC and column chromatography were performed with a Merck Kieselgel 60F_{254} and a Wako Wakogel C-200, respectively. The HPLC system consisted of a Hitachi 655 Liquid Chromatograph equipped with a Rheodyne 7125 sample injector. Elutions were monitored at 265 nm using a Hitachi 638-41 variable-wavelength UV monitor. A Hewlett-Packard 3390A reporting integrator was used to obtain accurate retention times and integration areas at a chart speed of 5 mm min^{-1}.

Materials. Selenoxides (**1, 3, 5,** and **9**) were the known compounds.[1,2,7]

Phenyl 2,4,6-Triisopropylphenyl Selenoxide (2): Selenide was prepared from bis(2,4,6-triisopropylphenyl) diselenide and phenylmagnesium bromide.[3] The oxidation of this selenide to selenoxide **2** was accomplished according to our published method.[7] Mp 148.5—149.5 °C (hexane). IR (KBr) ν=815 cm^{-1} (Se=O). ^{1}HNMR ($CDCl_3$) δ=0.90, 1.24, 1.30 (18H, d, J=6.8 Hz), 2.86 (1H, m), 3.73 (2H, hep, J=6.8 Hz), 6.98 (2H, s), 7.2—7.7 (5H, m). Exact MS, Found: m/z 376.1217 (^{80}Se), Calcd for $C_{21}H_{28}O^{80}Se$: 376.1305.

2-Methoxyphenyl 2,4,6-Triisopropylphenyl Selenoxide (4): Starting selenide was prepared from bis(2-methoxyphenyl) diselenide and 2,4,6-triisopropylphenylmagnesium bromide[3]

and oxidized to selenoxide **4** by *t*-butyl hypochlorite.[7] Mp 154.5—155 °C (benzene–hexane). IR (KBr) ν=825 cm^{-1} (Se=O). ^{1}H NMR ($CDCl_3$) δ=0.86, 1.18, 1.29 (18H, d, J=6.6 Hz), 2.80 (1H, hep, J=6.6 Hz), 3.56 (3H, s), 3.84 (2H, hep, J=6.6 Hz), 6.93 (2H, s), 6.7—8.1 (4H, m). Exact MS, Found: *m/z* 406.1459, Calcd for $C_{22}H_{30}O_2{}^{80}Se$: 406.1411.

4-(Methoxycarbonyl)phenyl 2,4,6-Tri-*t*-butylphenyl Selenoxide (6): A starting selenide was prepared from *p*-ethoxycarbonylphenyl selenocyanate and 2,4,6-tri-*t*-butylphenyllithium in THF[5] followed by the hydrolysis and methylation. The oxidation of the selenide to the selenoxide **6** was performed in a similar method as **4**. Mp 129—129.5 °C. IR (KBr) ν=840 (Se=O) and 1725 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=1.36 (9H, s), 1.45 (18H, s), 3.86 (3H, s), 6.97 and 7.87 (4H, ABq, J=8.6 Hz), 7.49 (2H, s). Mass, M$^+$ 476 (^{80}Se). Exact MS, Found: *m/z* 460.1916 (^{80}Se)(lack of one oxygen, Calcd for $C_{26}H_{36}O_2{}^{80}Se$: 460.1880.

Phenyl 2,4,6-Triethylphenyl Selenoxide (7): Selenide prepared from diphenyl diselenide and 2,4,6-triethylphenylmagnesium bromide[3] was oxidized to the selenoxide **7** as in the case of **4**. Mp 50.5—51.5 °C. IR (KBr) ν=820 cm^{-1} (Se=O). ^{1}H NMR ($CDCl_3$) δ=1.06 (6H, t, J=7.8 Hz), 1.18 (3H, t, J=7.8 Hz), 2.60 (2H, q, J=7.8 Hz), 2.91 (4H, q, J=7.8 Hz), 6.89 (2H, s), 7.2—7.7 (5H, m). Exact MS, Found: *m/z* 334.0841 (^{80}Se), Calcd for $C_{18}H_{22}O^{80}Se$: 334.0836.

Phenyl 2,4,6-Trimethylphenyl Selenoxide (8): Oxidation of the selenide prepared from diphenyl diselenide and 2,4,6-trimethylphenylmagnesium bromide[3] with our published method[7] gave the selenoxide **8** in good yield. Mp 82—82.5 °C. IR (KBr) ν=805 cm^{-1} (Se=O). ^{1}H NMR ($CDCl_3$) δ=2.25 (3H, s), 2.44 (6H, s), 6.81 (2H, s), 7.2—7.7 (5H, m). Exact MS, Found: 292.0287, Calcd for $C_{15}H_{16}O^{80}Se$: 292.0366

Benzyl 2,4,6-Triisopropylphenyl Selenoxide (10): Selenide prepared from bis(2,4,6-triisopropylphenyl) diselenide and benzyl magnesium bromide[3] was oxidized to the selenoxide **10** according to the published method.[7] Mp 132.5—134 °C (hexane). IR (KBr) ν=820 cm^{-1} (Se=O). ^{1}H NMR ($CDCl_3$) δ=1.04, 1.26, 1.27 (18H, d, J=6.8 Hz), 2.88 (1H, m), 3.94 (2H, hep, J=6.8 Hz), 4.38 (2H, s), 6.98 (2H, s), 6.8—7.3 (5H, m).

Optically Active 4-(Methoxycarbonyl)phenyl 2,4,6-Triisopropylphenyl Selenoxide (3): The optically active selenoxide (**3**) was synthesized by the method described in our previous paper.[2] The selenoxide samples with lower enantiomeric excess were prepared by mixing of (+) selenoxide and (−) selenoxide.

References

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