Optical Resolution of Thermodynamically Stabilized Selenoxides by 8-(Dimethylamino)-1-naphthyl Group

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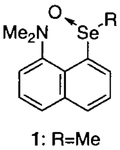
Optically pure selenoxides, stabilized by intramolecular coordination of amino group of 8-(dimethylamino)-1-naphthyl substituent to the selenium atom, were isolated by chromatographic resolution using an optically active column. Stereochemistry of the optically active selenoxides was also examined.

Since the first isolation of selenoxide enantiomers was reported by Davis et al. in 1983,[1] there are several reports on the isolation of optically active selenoxides.[2–6] We first isolated an optically pure diaryl selenoxide that was kinetically stabilized by bulky substituents in 1986,[6] however, an optically pure alkyl aryl selenoxide had not been isolated because optically active alkyl aryl selenoxides undergo racemization more easily than diaryl selenoxides.[5b] Recently, we also reported the isolation of optically pure alkyl aryl selenoxides, (*R*)-(+)- and (*S*)-(–)-2-{(dimethylamino)methyl}phenyl methyl selenoxides, stabilized by intramolecular coordination of amino group to the selenium atom.[7] The selenoxides racemized rapidly in polar solvents although they were stable in solid state. We designed selenoxides **1** and **2** possessing 8-(dimethylamino)-1-naphthyl group which were expected to coordinate more strongly due to the rigid structure and succeeded in isolating the enantiomerically pure selenoxides.



1: R=Me
2: R=Ph

Racemic 8-(dimethylamino)-1-naphthyl methyl selenoxide[8] (**1**) was attempted to optically resolve by HPLC at an analytical scale using an optically active column packed with amylose carbamate derivative/silica gel (Daicel Chiralpak AS; 4.6 × 250 mm, eluent: hexane/ethanol = 90/10). As shown in Figure 1, selenoxide **1** was resolved into two peaks corresponding to each enantiomer. Similarly, racemic 8-(dimethylamino)-1-naphthyl phenyl selenoxide (**2**) could also be resolved into their enantiomers.

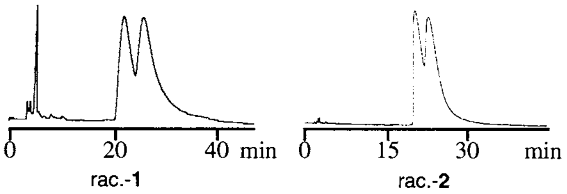
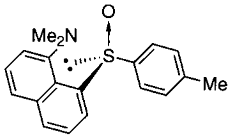


Figure 1. Chromatographic resolution of racemic selenoxides **1** and **2** by means of HPLC using an optically active column (Daicel Chiralpak AS).

The optical resolution of racemic selenoxides **1** and **2** was carried out by HPLC using optically active column (Daicel Chiralpak AS; 10 × 250 mm, eluent: hexane/ethanol = 90/10) at a preparative scale. In the case of selenoxide **1**, both enantiomers were obtained as optically pure form by repeated chromatographic resolution of the first and second fractions. The first eluted enantiomer had a positive specific rotation {(+)-**1**: ee 100%; $[\alpha]_D$ +363.8 (*c* 0.10, $CHCl_3$)}, and the second eluted enantiomer had a negative one {(–)-**1**: ee 100%; $[\alpha]_D$ –350.8 (*c* 0.19, $CHCl_3$)}.[9] Similarly, optically pure selenoxide (–)-**2** {ee 100%; $[\alpha]_D$ –165.4 (*c* 0.19, $CHCl_3$)} was isolated from the first eluent, while optically active selenoxide (+)-**2** was obtained in 80% ee {$[\alpha]_D$ +140.5 (*c* 0.50, $CHCl_3$)} from the second eluent. The inability to isolate optically pure selenoxide (+)-**2** is due to tailing of the first eluted enantiomer.

The absolute configuration of optically active selenoxides (+)-**1**, (–)-**1**, (+)-**2**, and (–)-**2** was estimated by comparison of the CD spectra with that of (*S*)-(–)-8-(dimethylamino)-1-naphthyl 4'-tolyl sulfoxide {(*S*)-(–)-**3**}, which was synthesized by Andersen's method.[10] The CD spectra of optically active selenoxides (+)-**1** and (+)-**2** showed negative first Cotton effects at 318 and 314 nm, respectively, while those of (–)-**1** and (–)-**2** showed positive Cotton effects in the same region, as shown in Figure 2. The CD spectrum of (*S*)-(–)-**3** also showed positive first Cotton effect at 321 nm. Therefore, the absolute configuration of selenoxides (–)-**1** and (–)-**2** is estimated to be *S* and that of (+)-**1** and (+)-**2** is *R*.



(*S*)-(-)-**3**

The stabilities of optically active selenoxides **1** and **2** toward racemization were examined. Optically active selenoxides (–)-**1** and (–)-**2** did not racemize in solid states when these compounds were stored in a desiccator. However, the racemization of optically active selenoxides (+)-**1** and (+)-**2** was observed in methanol, although the selenoxides were stable in chloroform without racemization even after 5 days.[11] The kinetics for the racemization of optically active selenoxides was examined in methanol. The rates for racemization of optically active selenoxides (+)-**1** and (+)-**2** showed a good linear relationship with first-order rate plots, and the rate constants are summarized in Table 1. The rate constants for racemization of selenoxides (+)-**1** and (+)-**2** in methanol were 1.84×10^{-5} and 2.21×10^{-6} s^{-1}, respectively. These results indicate that selenoxide **2** is more stable than selenoxide **1** toward racemization in methanol. The addition of water to the methanol solu-

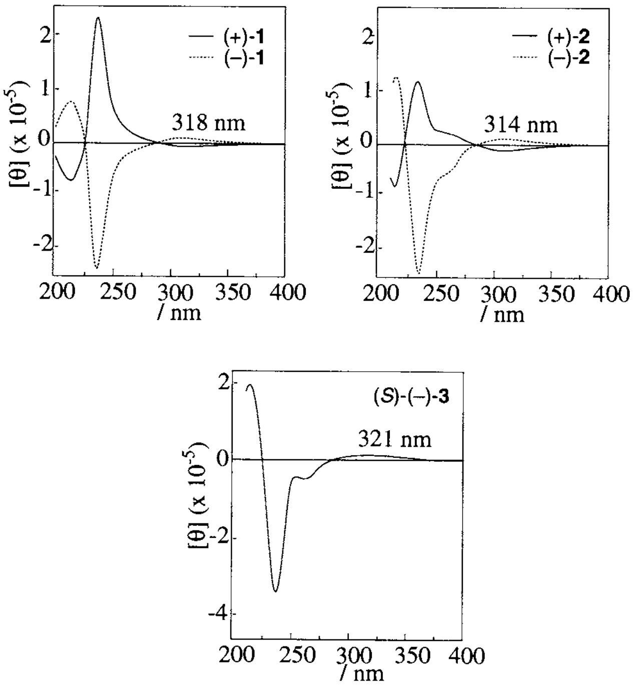
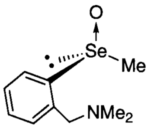
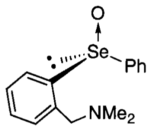


Figure 2. CD spectra of optically active selenoxides (+)-**1**, (−)-**1**, (+)-**2**, and (−)-**2** and sulfoxide (*S*)-(−)-**3** in cyclohexane.



(*S*)-(-)-**4**



(*S*)-(-)-**5**

Table 1. First order rate constants for racemization of optically active selenoxides in solutions[a]

Solvent	k / s^{-1} ($t_{1/2}$ / h)			
	(*R*)-(+)-**1**	(*R*)-(+)-**2**	(*S*)-(-)-**4**[b]	(*S*)-(-)-**5**[b]
$CHCl_3$	A[d]	A	A	A
MeOH	1.84X 10^{-5} (10.4)	2.21 X 10^{-6} (87.1)	2.28 X 10^{-4} (0.844)	5.58 X 10^{-6} (34.5)
MeOH / H_2O[c]	5.21 X 10^{-5} (3.70)	3.70 X 10^{-6} (51.9)	1.23 X 10^{-3} (0.157)	5.13 X 10^{-5} (3.76)

[a]In ca. 5 mM soln. at 26±1 °C. [b]Ref. 7. [c]MeOH/H_2O = 4/1 (V/V). [d]A: No racemization was observed even after 5 days.

tion of (+)-**1** and (+)-**2** accelerated their racemization. Therefore, racemization in methanol is indicated to be occurring due to a trace amount of water which remains in the solvent, despite careful purification. Previously, the rate constants of the selenoxides, (*S*)-(−)-2-{(dimethylamino)methyl}phenyl methyl selenoxide{(*S*)-(−)-**4**} and (*S*)-(−)-2-{(dimethylamino)-methyl}diphenyl selenoxide{(*S*)-(−)-**5**}, in methanol were reported to be 2.28 × 10^{-4} and 5.58 × 10^{-6} s^{-1}, respectively.[7] Therefore, selenoxide **1** was found to be more stable toward racemization than selenoxide **4** in methanol. Similarly, selenoxide **2** was more stable than **5**. These results show that the coordination of amino group of 8-dimethylamino-1-naphthyl moiety to selenium atom is more effective than that of 2-{(dimethyl-amino)methyl}phenyl moiety since naphthyl group is considered to facilitate better intramolecular coordination due to the rigid structure.

References and notes

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9 The optical purities were determined by means of HPLC analysis using an optically active column (Daicel Chiralpak AS).
10 The selenoxide (*S*)-(−)-**3** {ee 96%; $[\alpha]_D$ −134.7 (*c* 1.27, $CHCl_3$} was prepared by the reaction of 8-(dimethyl-amino)-1-naphthyllithium with $(S)_S$-(−)-menthyl-(−)-4-toluenesulfinate according to the literature, see: a) K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Am. Chem. Soc.*, **86**, 5637 (1964). b) S. Colonna, R. Giovini, and F. Montanari, *J. Chem. Soc., Chem. Commun.*, **1968**, 865.
11 Chloroform was distilled from calcium hydride before use. Methanol was distilled from magnesium cake and stored with 3A molecular sieves under nitrogen.