

# Resolution and Chiroptical Characterization of Two 1,8-Bridged Naphthalene Systems: Naphtho[1,8-*cd*]-1,2-dithiole 1-Oxide and 2*H*-Naphtho[1,8-*bc*]thiophene 1-Oxide

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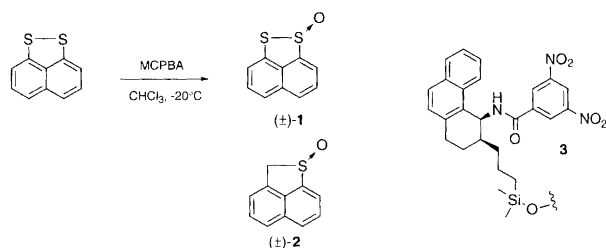
## Dedicated to Professor Göran Bergson on the occasion of his 65th birthday

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The enantiomers of the cyclic thiolsulfinate naphtho[1,8-*cd*]-1,2-dithiole 1-oxide, ( $\pm$ )-**1**, have been obtained by semipreparative chiral liquid chromatography of the racemate and characterized by chiroptical methods. The inherent dissymmetry of the extended chromophore gives rise to a very high specific rotation ( $>1500$  in  $\text{CH}_2\text{Cl}_2$  at 546 nm). The enantiomers of the corresponding sulfoxide, 2*H*-naphtho[1,8-*bc*]thiophene 1-oxide ( $\pm$ )-**2**, showed the chiroptical behaviour expected for an aryl alkyl sulfoxide. CD spectra of **1** and **2** were completely different and could not be used to determine their relative configuration, showing the large effect from substituting S for  $\text{CH}_2$  on the electronic transitions in the system.

The racemization of (+)-**1** was studied at 80 °C and the rate was found to be increasing rapidly with increasing polarity of the solvent, being 55 times higher in water than in 1-propanol.

The sulfoxide group is of great interest in the construction of chiral auxiliaries for asymmetric synthesis.<sup>1–3</sup> However, the present knowledge about the configurational stability of this functionality in different classes of compounds is far from complete and a variety of mechanisms for stereoisomer interconversion have been demonstrated.<sup>4–9</sup> In connection with studies of enantiomerization barriers in the 1,3,2-benzodithiazole 1-oxide ring system,<sup>10,11</sup> it was of interest to prepare the enantiomers of the cyclic thiolsulfinate naphtho[1,8-*cd*]-1,2-dithiole 1-oxide, ( $\pm$ )-**1** (Scheme 1). For comparison, the



Scheme 1.

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related 2*H*-naphtho[1,8-*bc*]thiophene 1-oxide, ( $\pm$ )-**2**, which has recently been resolved into enantiomers by subcritical fluid chromatography on an analytical scale,<sup>12</sup> was also prepared.

These racemates have been obtained previously by oxidation of the corresponding sulfides.<sup>13–15</sup> Furthermore, enantiomeric enrichment via oxidation with (+)-percamphoric acid has been described.<sup>15,16</sup> A number of optically active non-cyclic thiolsulfonates have been prepared, but are known,<sup>17</sup> with few exceptions,<sup>18,19</sup> to be racemized relatively easily. Recently, two diastereomeric dithiirane 1-oxides were each chromatographically resolved into enantiomers and shown to undergo enantiomerization by different mechanisms.<sup>20</sup>

## Results and discussion

*Naphtho[1,8-*cd*]-1,2-dithiole 1-oxide*, **1**. Since direct resolution of ( $\pm$ )-**1** by liquid chromatography on a chiral stationary phase (CSP) operating via aromatic  $\pi$ - $\pi$  interaction was assumed to be a useful technique, a Whelk-O1 column, containing a CSP with the 3,5-dinitro-

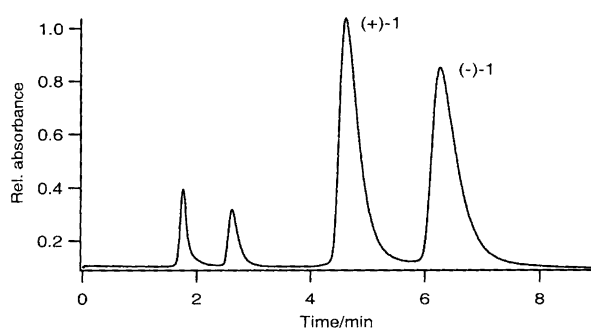


Fig. 1. Analytical chromatogram of  $(\pm)$ -**1** (Whelk-O1, TBME + 2% ethyl acetate).

benzoylated tetrahydrophenanthrylamine structural motif<sup>21</sup> (**3**), was selected for this purpose.

Resolution was readily achieved on an analytical column (Fig. 1) affording an  $\alpha$ -value of 1.6; the separation factor  $\alpha$  being defined as  $\alpha = k'_2/k'_1$ , where  $k'$  (the capacity ratio) is obtained from  $(t_R - t_0)/t_0$ . Separation of the enantiomers by the preparative system showed  $(+)$ -**1** to be the first eluted. CD spectra (Fig. 2) showed three main bands, the one at longest wavelength centered at 342 nm and giving a molar ellipticity  $[\theta] = 2.5 \times 10^5 \text{ deg cm}^2 \text{ dmol}^{-1}$  (60% dioxane). Specific rotations were determined at room temperature in dichloromethane ( $c$  0.3) to be  $[\alpha]_{546} = \pm 1540 \pm 50$  and  $[\alpha]_{465} = \pm 3770 \pm 115$ . The specific rotation was also measured in 60% dioxane giving  $[\alpha]_{546} = \pm 1378 \pm 48$  and  $[\alpha]_{436} = \pm 3317 \pm 110$  ( $c$  0.4). Consequently, the asymmetric oxidation with  $(+)$ -percamphoric acid described previously,<sup>15</sup> giving  $[\alpha]_{546} = +8.2$  (60% dioxane), corresponds to an e.e. of only ca. 0.6%.

The remarkably high specific rotation is obviously a consequence of the inherently dissymmetric chromophore present in this system and its UV absorption at relatively long wavelength.

The optical stability of the enantiomers was studied by monitoring the optical rotation in *tert*-butyl methyl ether (TBME) as a function of time at 50 °C. No significant change was found over a period of 18 h. This stability in non-nucleophilic media is consistent with previous findings.<sup>15</sup> At elevated temperatures (80–100 °C) a measurable loss of optical activity was found, which was shown by enantioselective LC to be

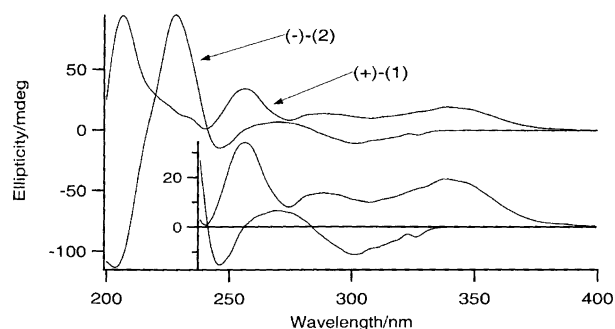


Fig. 2. CD spectra of  $(+)$ -**1** and  $(-)$ -**2** in acetonitrile.

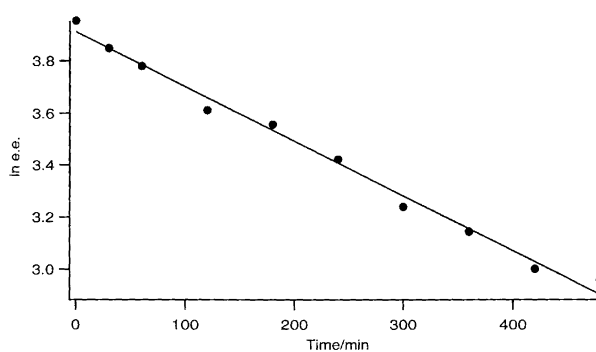


Fig. 3. The racemization process of **1** in 1-propanol followed by LC.

due to racemization. Kinetic studies disclosed a strong dependence on the solvent polarity. At 80 °C first-order rate constants  $k_{\text{rac}} = 1.94 \times 10^{-3} \text{ s}^{-1}$  and  $3.5 \times 10^{-5} \text{ s}^{-1}$  were found in water and 1-propanol, respectively. Figure 3 shows the kinetics of the racemization in 1-propanol. The mechanistic implication of this large solvent effect has to be elucidated by further kinetic studies.

**2H-Naphtho[1,8-bc]thiophene 1-oxide, 2.** Resolution of  $(\pm)$ -**2** on the Whelk-O1 column afforded an  $\alpha$ -value of only 1.22 (TBME + 10% methanol) and the early eluting enantiomer was  $(+)$ -**2**. Preparative separation was performed using a Chiralpak-AD column (hexane + 20% ethanol) yielding baseline separation and an  $\alpha$ -value of 1.32. The second eluted enantiomer was  $(+)$ -**2** which showed a specific rotation  $[\alpha]_{546} = 132$  ( $c$  0.06,  $\text{CH}_2\text{Cl}_2$ ),  $[\alpha]_{436} = 265$  ( $c$  0.06,  $\text{CH}_2\text{Cl}_2$ ) and  $[\alpha]_{\text{D}} = 91$  ( $c$  0.06, methanol). Asymmetric oxidation with  $(+)$ -percamphoric acid previously reported,<sup>15</sup>  $[\alpha]_{\text{D}} = 8.23$  ( $c$  3.76 methanol), thus corresponds to an e.e. of approximately 9%, which is probably a slight overestimate due to concentration differences. CD spectra of the respective enantiomers turned out to be completely different from those of compound **1**. The molar ellipticity of  $(-)$ -**2** was determined to be  $[\theta] = 3800 \text{ deg cm}^2 \text{ dmol}^{-1}$  at 327.8 nm in dichloromethane.

**Kagan oxidations.** Asymmetric oxidations of the sulfides according to the Kagan method [(*R,R*)-diethyl tartrate, titanium tetraisopropoxide, water, cumene hydroperoxide]<sup>22</sup> was performed with modest results. The enantiomeric excess was determined to be 7% for  $(-)$ -**1**, and 37% for  $(-)$ -**2**. When oxidising the dithiole, however, the resulting enantiomeric excess is very sensitive to thiols and other nucleophilic impurities that may be present during the reaction and accordingly cause racemization. Owing to the small amount of dithiole available, further purification was not possible. Thus it cannot be excluded that the true e.e. is significantly higher than that obtained in our experiments.

## Experimental

NMR spectra were recorded on a Varian VXR 400 MHz spectrometer. Mass spectra were acquired using EI (70 eV) on a VG model 7070E double focusing magnetic sector instrument, calibrated with the use of PFK as a mass marker. Optical rotations were obtained with a Perkin Elmer model 341 LC instrument. CD spectra were run on a JASCO model J-715 spectropolarimeter. Analytical scale liquid chromatography was carried out using standard equipment with UV detection.

The preparative separations were performed by means of a Shimadzu mod. LC-8A manual isocratic system. The Whelk-O1 columns used were slurry-packed in our laboratory with the chromatographic sorbent [(3*S*,4*R*)-Whelk-O1; Regis Chem. Co.]. For the preparative resolutions a 10 × 150 mm column was used with TBME containing 2% ethyl acetate as the mobile phase at a flow rate of 6 ml min<sup>-1</sup>. A solution of (±)-**1** in the mobile phase at a concentration of ca. 1.5 mg ml<sup>-1</sup> was used and 1.0 ml was injected in each run, affording ca. 0.7 mg of each enantiomer. After 12 repetitive injections (each run was carried out in less than 8 min) the collected fractions yielded, after evaporation and drying, ca. 8 mg of each enantiomer. The analytical chromatograms were obtained with the use of a 3.0 × 150 mm column using the same mobile phase at 0.6 ml min<sup>-1</sup>. UV detection was at 250 nm. Resolution of (±)-**1** could also be achieved with the use of a 4.6 × 250 mm Kromasil CHI-DMB column<sup>23</sup> (EKA Chemicals Co., Bohus, Sweden). In this case the mobile phase was composed of hexane-TBME (1:1) with 1% of methanol, giving almost baseline separation with an  $\alpha$ -value of 1.15. Chiralpak AD (hexane + 5% isopropyl alcohol) afforded baseline separation and  $\alpha$  = 1.26.

A 250 × 20 mm Chiralpak AD column (amylose-3,5-dimethyl phenyl carbamate coated on silica gel) with a mobile phase composed of 20% ethanol in hexane was used for the resolution of (±)-**(2)**. About 10–20 mg of the racemate could be resolved per injection.

The kinetic studies were performed by thermostating a solution of (+)-**1** (less than 1 mg), from which samples were withdrawn at regular time intervals and analyzed by enantioselective HPLC to determine the enantiomeric composition. The only side reaction observed was the slow formation of the corresponding sulfone, when the racemization was performed in water.

(±) **1** was prepared by oxidation of the dithiole with *m*-chloroperbenzoic acid (MCPBA) in CHCl<sub>3</sub> at -20 °C followed by purification by flash chromatography [silica gel; hexane-ether-chloroform (50:25:25)]. M.p. 87–89 °C (lit.<sup>15</sup> 93–95 °C and lit.<sup>13</sup> 91–92 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.19 (1 H, dd,  $J$  = 8 Hz and 1 Hz), 8.14 (1 H, dd,  $J$  = 8 Hz and <1 Hz), 7.82 (1 H, dd,  $J$  = 8 Hz and <1 Hz), 7.80 (1 H, t,  $J$  = 8 Hz), 7.65 (1 H, t,  $J$  = 8 Hz), 7.60 (1 H, dd,  $J$  = 8 Hz and 1 Hz). <sup>13</sup>C NMR (100.7 MHz, CDCl<sub>3</sub>):  $\delta$  121.8, 110.6, 106.6, 104.8, 102.4, 101.9, 110.7, 100.4, 97.6, 95.05. MS: 206 ( $M^+$ ), 190

( $M^+ - O$ ), 158 ( $M^+ - SO$ , base peak). Exact mass: found,  $M^+ = 205.979$ ; calc. for C<sub>10</sub>H<sub>6</sub>S<sub>2</sub>O: 205.986.

(±)-**2** was prepared by oxidation of the sulfide<sup>16</sup> as described previously.<sup>14</sup> M.p. 121–124 °C (lit.<sup>14</sup> 118–120 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.08 (1 H, dd,  $J$  = 7 Hz and  $J \approx 1$  Hz) 8.06 (1 H, dd,  $J$  = 8 Hz and  $\approx 1$  Hz) 7.85 (1 H, dd,  $J$  = 8 Hz and  $\approx 1$  Hz) 7.74 (1 H, dd,  $J$  = 7 Hz and 8 Hz) 7.64 (1 H, dd,  $J$  = 7 Hz and 8 Hz) 7.53 (1 H, dd,  $J$  = 7 Hz and  $\approx 1$  Hz) 4.93 (1 H, d,  $J$  = 16.8 Hz) 4.38 (1 H, d,  $J$  = 16.8 Hz). MS: 188 ( $M^+$ ), 171 ( $M^+ - OH$ , base peak). Exact mass:  $M^+ = 188.034$ , calc. for C<sub>11</sub>H<sub>8</sub>SO: 188.030.

Kagan oxidations were performed according to the procedure in Ref. 24 on a 0.06 mmol scale, but the treatment with sodium hydroxide was omitted, so as not to risk racemization of the product. The enantiomeric excess was determined using analytical enantioselective chromatography. The disulfide corresponding to **1** was recrystallized three times from ethanol before oxidation.

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