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Determination of absolute configuration using vibrational circular dichroism spectroscopy: the chiral sulfoxide 1-thiochroman *S*-oxide

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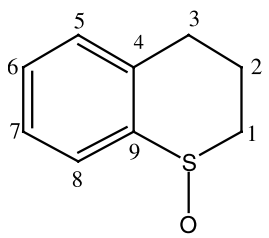
Abstract—We have determined the absolute configuration of the chiral sulfoxide 1-thiochroman *S*-oxide **1** using vibrational circular dichroism (VCD) spectroscopy. The VCD spectrum of a CCl_4 solution of **1** was analyzed using density functional theory (DFT), which predicts three stable conformations of **1**, separated by <1 kcal/mol. The VCD spectrum predicted using the DFT/GIAO methodology for the equilibrium mixture of the three conformations of (*S*)-**1** is in excellent agreement with the experimental spectrum of (+)-**1**. The absolute configuration of **1** is therefore (*R*)-(−)/(*S*)-(+). (+)-**1** and (−)-**1** of high enantiomeric excess (e.e.) were synthesized in high yields via asymmetric oxidation of 1-thiochroman **2** using Ti(*iso*-PrO)$_4$/(*R*,*R*)-1,2-diphenylethane-1,2-diol/H_2O/*tert*-butyl hydroperoxide and Ti(*iso*-PrO)$_4$/L-diethyl tartrate/H_2O/cumene hydroperoxide, respectively.

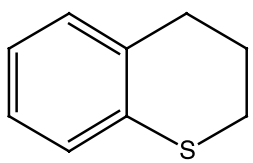
1. Introduction

Chiral molecules exhibit vibrational circular dichroism (VCD).[1] The VCD spectra of enantiomers of a chiral molecule are of identical magnitude but opposite in sign. Recent developments in ab initio density functional theory (DFT)[2] have made possible the reliable prediction of VCD spectra[3] and, hence, the determination of absolute configuration using VCD spectroscopy.[1,4] Here, we report the application of VCD spectroscopy to the determination of the absolute configuration of the chiral sulfoxide, 1-thiochroman *S*-oxide **1**.



1

The sulfoxide **1** was first synthesized in optically active form by Takata et al.[5] via enzymatic oxidation of 1-thiochroman, **2** using rabbit liver cytochrome P-450. (−)-**1** was obtained. Its UV circular dichroism (CD) was similar to that of (−)-2,3-dihydrobenzo[*b*]thiophene-1-oxide, **3**, whose absolute configuration had earlier been determined by Yamagishi et al. to be *R*.[6] In view of the structural similarity of **1** and **3**, Takata et al. therefore assigned the *R*-absolute configuration to (−)-**1**.[5] Optically active **1** was subsequently synthesized by Allenmark and Andersson[7] via enzymatic oxidation of **2** using the chloroperoxidase of the marine fungus *Caldariomyces fumago* and by Andersson et al.[8] via enzymatic oxidation of **2** using the bromoperoxidase of the alga *Corallina officinalis*.



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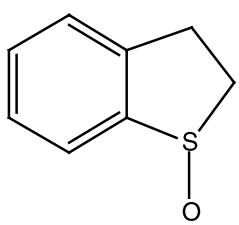

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The absolute configuration of **1** is thus derived from the absolute configuration of **3**. The absolute configuration

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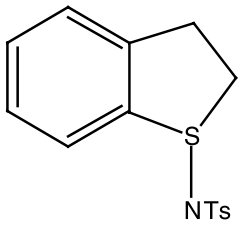
of **3** was assigned by Yamagishi et al.[6] as follows. Sulfoxide (−)-**3** was converted to the corresponding *N*-*p*-toluenesulfonylimide, **4** and the UV ORD of the (−)-**4** obtained compared to that of the sulfonylimide, **5**. The absolute configuration of (+)-**5** had previously been determined by X-ray crystallography to be *R*.[6] The extrema of the ORD of (*S*)-(−)-**5** and (−)-**4** were consignate, leading to the *S* absolute configuration for (−)-**4**. The conversion of (−)-**3** to (−)-**4** was shown by Yamagishi et al.[6] to occur with inversion of configuration, whence the absolute configuration of (−)-**3** is *R*.



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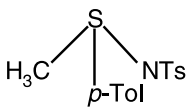

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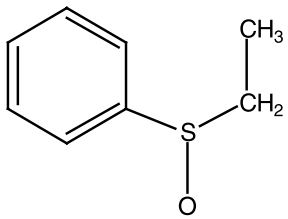
The (*R*)-(−)/(*S*)-(+) absolute configuration of **1** thus rests on the comparison of the UV CD of **1** and **3**. However, the UV CD of **1** could equally be compared to that of phenyl ethyl sulfoxide, **6** whose absolute configuration and UV CD are both well-defined.[9,10]



6

(−)-**1** exhibits negative and positive CD at ~250 and ~220 nm, respectively.[5,6] (*S*)-(−)-**6** exhibits negative and positive CD at ~250 and ~220 nm, respectively.[10] Thus, comparison of the UV CD of **1** and **6** leads to the conclusion that the absolute configuration of **1** should be (*R*)-(+)/(*S*)-(−) opposite to the literature absolute configuration.

In this paper, we report new syntheses of (+)-**1** and (−)-**1** from **2** and the definitive determination of the absolute configuration of **1** via VCD spectroscopy. As discussed above, optically active **1** has previously been obtained using enzymatic methods.[5–7] Here we have obtained (+)-**1** using the Ti(*iso*-PrO)$_4$/(*R*,*R*)-1,2-diphenylethane-1,2-diol(DPED)/H_2O/*tert*-butyl hydroperoxide catalytic sulfoxidation procedure of Rosini et al.[11] and (−)-**1** using the Ti(*iso*-PrO)$_4$/L-diethyl tartrate (DET)/H_2O/cumene hydroperoxide stoichiometric oxidation procedure of Kagan et al.[12] Both procedures lead to **1** in high yield and with high enantioselectivity.

The determination of the absolute configuration of **1** follows a straightforward protocol. The potential energy surface (PES) of **1** is scanned using ab initio DFT in order to define its stable conformations. As we shall document, there are three; their energies span a range of <1.0 kcal/mol. Next, the vibrational unpolarized absorption ('IR') and VCD spectra of these conformations are calculated using DFT. The spectra are summed, weighting each by the fractional population calculated from the DFT energies, giving conformationally averaged spectra. Comparison of predicted and experimental IR spectra yields an assignment of the latter. Comparison of predicted and experimental VCD intensities for unambiguously assigned bands yields the absolute configuration of **1**.

We have previously studied the IR and VCD spectra of a number of chiral sulfoxides of known absolute configuration, including the rigid sulfoxides, *tert*-BuMeSO, PhMeSO, and *p*-TolMeSO and the conformationally flexible sulfoxides, 1-NpMeSO and 2-NpMeSO (Np = naphthyl).[13,14] In addition, we have determined the absolute configuration of the conformationally flexible sulfoxide 1-(2-Me-Np)MeSO.[15] The study reported here further extends the application of VCD spectroscopy to chiral sulfoxides.

2. Results

We have measured the IR and VCD spectra of **1** in CCl_4 solution. The spectra over the frequency range 900–1240 cm^{-1} are shown in Figs. 1 and 2. Analysis of the spectra over this frequency range are sufficient to establish the absolute configuration of **1**. The spectra at frequencies <900 cm^{-1} and >1240 cm^{-1} will be reported and analyzed in a future publication.

The PES of **1** has been scanned at the B3LYP/6-31G* level, varying each dihedral angle C(8)–C(9)–S–C(1) and C(5)–C(4)–C(3)–C(2) independently over the range 105–255° (i.e. −75 to +75° relative to coplanar). Three distinct wells were found. Geometry optimization at the TZ2P basis set level led to three stable conformational structures, which we label **a**, **b** and **c**. Conformation **a** is the lowest in energy. The relative energies of **a**, **b** and **c** are listed in Table 1. The range of conformational energies is less than 1 kcal/mol. The three conformations of **1** are illustrated in Fig. 3. Key dihedral angles are listed in Table 2. In **a** and **c**, the C(1) and C(2) atoms lie on opposite sides of the C(3)–C(4)–C(9)–S plane; in **b**, these atoms are on the same side of the plane. The orientation of the sulfoxide group with respect to the phenyl ring varies considerably among the three conformations. In **a**, **b** and **c** the C(8)–C(9)–S–O dihedral angle is 89.0, 19.6 and 42.5°, respectively.

Harmonic vibrational frequencies, dipole strengths and rotational strengths of conformations **a**, **b** and **c** have been calculated using B3LYP at the TZ2P basis set level. IR and VCD spectra of conformations **a**, **b** and **c** have been derived thence, assuming Lorentzian band shapes. The IR and VCD spectra of the conformational mixture **a**+**b**+**c** were then predicted using percentage

populations of **a**, **b** and **c** obtained from the B3LYP/TZ2P conformational energies (Table 1). The B3LYP/TZ2P IR spectra of **a**, **b** and **c** and of the conformational mixture **a**+**b**+**c** over the frequency range 900–1240 cm^{-1} are shown in Fig. 1. The spectrum of the conformational mixture is in excellent agreement with the experimental spectrum, allowing for a small overall frequency shift due to the neglect of anharmonicity in the calculated spectra.[16] The experimental spectrum can be assigned straightforwardly, as detailed in Fig. 1 and Table 3. The B3LYP/TZ2P VCD spectra of **a**, **b** and **c** and of the conformational mixture **a**+**b**+**c** of (*S*)-**1** over the frequency range 900–1240 cm^{-1} are shown in Fig. 2. Visual inspection shows immediately that the calculated spectrum of the conformational mixture is in excellent qualitative agreement with the experimental spectrum for (+)-**1**, demonstrating that the absolute configuration of **1** is (*R*)-(−)/(*S*)-(+). The 929 cm^{-1} band, assigned to modes 22, exhibits large negative VCD. The 948 cm^{-1} band, assigned to modes 23, exhibits very small negative VCD. The VCD of modes 24 is not observed. The 1007 cm^{-1} band, assigned to modes 25, exhibits large positive VCD. The 1044/1054/1077 cm^{-1} bands, assigned to modes 26–29, exhibit strong VCD with a positive/negative/positive sign pattern. The 1113 cm^{-1} band, assigned to mode 30 of conformation **c** exhibits negative VCD. The 1124 cm^{-1} band, assigned to modes 30 of conformations **a** and **b**, exhibits positive VCD, as does the 1131 cm^{-1} band, assigned to modes 31. The 1159 cm^{-1} band, assigned to modes 32 exhibits weak positive VCD. The 1171 and 1195 cm^{-1} bands, assigned to modes 33 and 34, both exhibit positive VCD. With the exception of mode 32, all observed VCD agrees in sign with prediction. Quantitative agreement of theory and experiment is also excellent, as demonstrated in Table 3 and Fig. 4, where

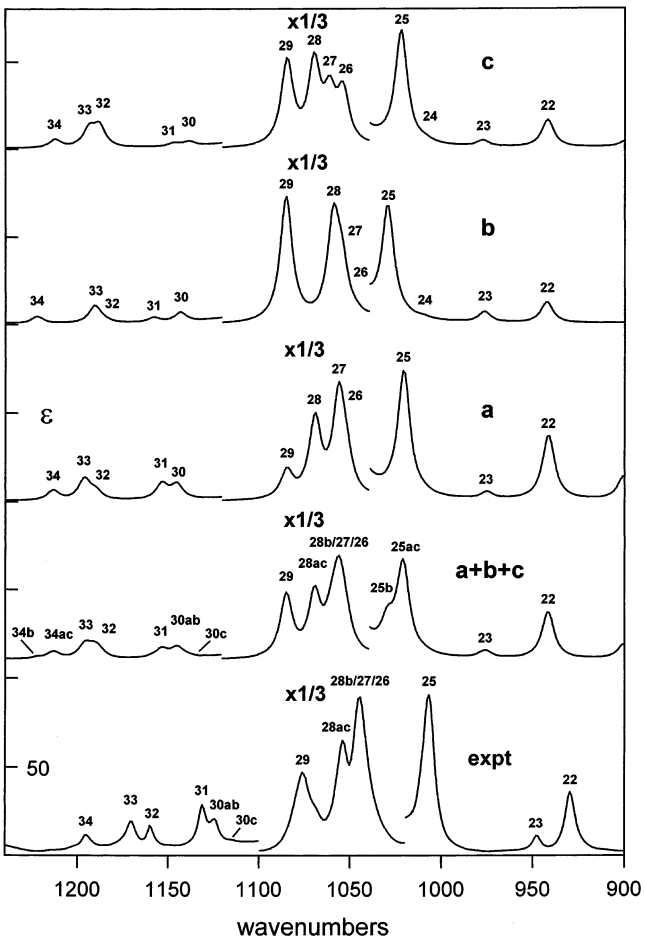


Figure 1. Experimental IR spectrum of (+)-**1** in CCl_4, predicted B3LYP/TZ2P IR spectra of conformations **a**, **b** and **c** of **1** and the predicted IR spectrum of the equilibrium mixture of **a**, **b** and **c**. Calculated spectra use Lorentzian band shapes (γ=4.0 cm^{-1}). Fundamentals are numbered.

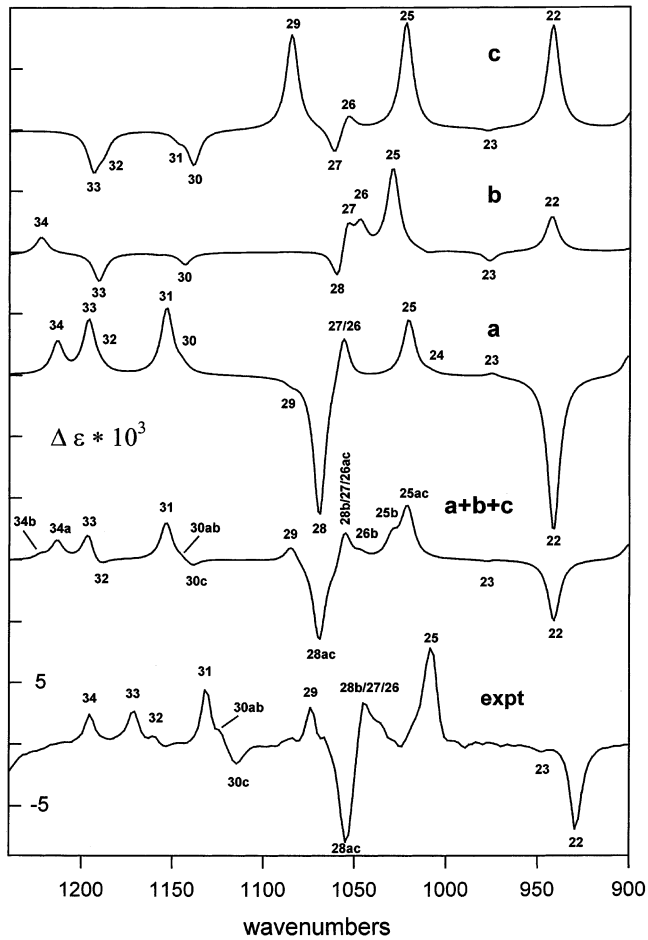


Figure 2. Experimental VCD spectrum of (+)-**1** in CCl_4, predicted B3LYP/TZ2P VCD spectra of conformations **a**, **b** and **c** of *S*-**1** and the predicted VCD spectrum of the equilibrium mixture of **a**, **b** and **c**. The experimental VCD spectrum is the half-difference spectrum: 1/2[$\Delta\varepsilon$(+)–$\Delta\varepsilon$(−)] (see text). Calculated spectra use Lorentzian band shapes (γ=4.0 cm^{-1}). Fundamentals are numbered.

Table 1. B3LYP/TZ2P energies and populations of the conformations of **1**[a]

	a	b	c
E	0	0.50	0.62
P	56.5	24.0	19.5

[a] Energies (*E*) in kcal/mol; populations (*P*) in percent. Populations are calculated from energies assuming Boltzmann statistics.

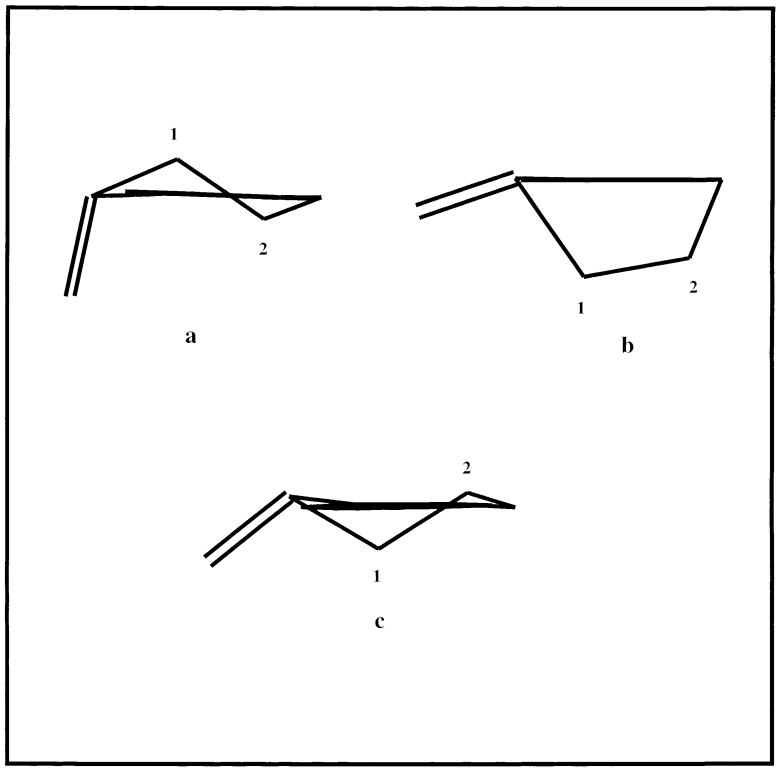


Figure 3. B3LYP/TZ2P structures of the conformations **a**, **b** and **c** of *S*-**1**.

predicted and experimental rotational strengths (the latter obtained by Lorentzian fitting of the experimental VCD spectrum) are compared. This excellent agreement further confirms the reliability of the spectral assignment, the calculated rotational strengths and the percentage populations of **a**, **b** and **c**.

3. Discussion

DFT calculations using the B3LYP hybrid functional predict three stable conformations **a**, **b** and **c** of **1**, differing in the puckering of the C_5S ring and the orientation of the SO group with respect to the phenyl ring. The energies of **a**, **b** and **c** are quite similar; the range of energies is less than 1 kcal/mol. Thus, at room temperature significant populations of all three conformations can be anticipated. In the most stable conformation **a**, the C_5S ring has a 'half-chair' conformation with C(1) and C(2) on opposite sides of the C(3)–C(4)–C(9)–S plane. The SO group is approximately perpendicular to the plane of the phenyl ring (C(8)–C(9)–S–O = 89.0°), with the oxygen atom on the opposite side of the C(3)–C(4)–C(9)–S plane from C(1). In **c**, the C_5S ring is also in a 'half-chair' conformation, but the angle between the SO group and the phenyl ring is much smaller (C(8)–C(9)–S–O = 42.5°) and the O atom is on the same side of the C(3)–C(4)–C(9)–S plane as C(1). The two conformations **a** and **c** can be regarded as deriving from the two enantiomeric forms of 1-thiochroman, **2**, in which the C_5S ring is in the 'half-chair' conformation. In **2**, these two conformations are equi-energetic. For a given configuration of the stereogenic sulfur atom, the presence of the O atom in **1** renders the two conformations distinct and unequal in energy. According to DFT, **a** is more stable than **c**. In the conformation **b** the C_5S ring is in a 'half-boat' conformation, with C(1) and C(2) on the same side of the C(3)–C(4)–C(9)–S plane. The SO group is closer to coplanarity with the phenyl ring than in both **a** and **c** (C(8)–C(9)–S–O = 19.6°). This conformation derives from one of the two enantiomeric 'half-boat' conformations of **2**. According to our DFT calculations, in **1** only one of these two conformations is stable for a given chirality of the SO group. In PhMeSO, the SO group and the phenyl ring are nearly coplanar. DFT calculations predict a barrier to rotation of the SO group by 180° of 4–5 kcal/mol.[14] Our results for **1** demonstrate that the conformational energetics of the C_5S ring predominate, overriding the preference of the SO group for a coplanar orientation with the phenyl ring.

Table 2. B3LYP/TZ2P dihedral angles of the conformations of **1**[a]

	a	**b**	**c**
SC1C2C3	72.0	−20.3	−72.8
C1C2C3C4	−50.6	−39.4	46.0
C4C9SC1	20.9	−50.9	−27.8
C9SC1C2	−51.9	59.0	57.2
C2C3C4C9	15.8	52.6	−11.5
C3C4C9S	−4.6	1.0	7.0
C5C4C3C2	−166.0	−126.5	172.0
C8C9SC1	−161.8	129.2	154.8
C8C9SO	89.0	19.6	42.5

[a] Dihedral angles in degrees for the conformations of (*S*)-**1**. See text for atom numbering.

Table 3. Calculated and experimental frequencies and rotational strengths for modes 22–34 of **1**[a]

Mode	Expt.[b]		Calculation[c]						
			a		**b**		**c**		**a+b+c**
	$\bar{\nu}$	R	$\bar{\nu}$	R	$\bar{\nu}$	R	$\bar{\nu}$	R	R[d]
34	1195	4.5	1214	6.1	1222	3.2	1213	0.0	4.2
33	1171	6.0	1196	10.4	1191	−5.6	1194	−7.2	3.2
32	1159	0.8	1190	0.7	1186	−0.1	1188	−3.2	−0.3
31	1131	7.8	1153	13.4	1158	−0.2	1147	−1.5	7.2
30	1124	2.0	1145	1.4	1144	−2.4			0.2
30	1113	−5.1					1139	−7.0	−1.4
29	1077	6.8	1085	−1.0	1085	0.1	1085	20.8	3.5
28	1054	−23.8	1069	−31.6			1070	0.0	−17.9
28					1059	−8.7			
27	1044	14.3	1056	10.9	1055	7.9	1061	−6.4	6.4
26			1052	−0.8	1047	5.6	1054	3.7	
25	1007	23.0	1021	12.8	1029	19.1	1022	24.6	16.6
24			1009	0.5	1010	−0.8	1009	−0.3	
23	948	−1.0	975	0.9	976	−2.3	978	−0.7	−0.2
22	929	−19.2	941	−39.0	943	8.7	942	25.9	−14.9

[a] Frequencies $\bar{\nu}$ in cm^{-1}; rotational strengths R in 10^{-44} esu^2 cm^2. Experimental rotational strengths are for (+)-**1**; calculated rotational strengths are for *S*-**1**.
[b] From Lorentzian fitting.
[c] B3LYP/TZ2P.
[d] Population-weighted sum of the rotational strengths of **a**, **b** and **c**.

The B3LYP/TZ2P IR spectrum of the conformational mixture **a**+**b**+**c** is in excellent agreement with the experimental spectrum over the frequency range 900–1240 cm^{-1}, leading to an unambiguous assignment of fundamentals 22, 23 and 25–34. The corresponding VCD spectrum for (*S*)-**1** is in excellent agreement with the experimental spectrum of (+)-**1** simultaneously confirming the vibrational assignment and defining the absolute configuration as (*R*)-(−)/(*S*)-(+). The agreement of the calculated and experimental vibrational spectra also supports the DFT conformational analysis.

The vibrational spectra of the conformational mixture **a**+**b**+**c** depend on the populations of **a**, **b** and **c**, which in turn depend on the free energy differences of **a**, **b** and **c**. In our calculations we have used populations calculated from B3LYP/TZ2P energies assuming Boltzmann statistics. The B3LYP/TZ2P energies of **a**, **b** and **c** are not equal to the solution free energies since: (a) the B3LYP/TZ2P energies are not exact; (b) solvent effects are not included; and (c) entropy contributions to free energies are ignored. The excellent agreement of predicted and experimental IR and VCD spectra suggests that the B3LYP/TZ2P energies and solution free energies are in fact not very different.

This work unambiguously determines the absolute configuration of **1** to be (*R*)-(−)/(*S*)-(+). The result is the same as that deduced earlier by empirical comparison of the UV CD of **1** and **3**.[5] However, as noted above, comparison of the UV CD of **1** to that of **6**, an equally plausible reference compound, leads to the opposite absolute configuration (*R*)-(+)/(*S*)-(−). Empirical comparison of the UV CD of **1** to that of other chiral sulfoxides therefore does not provide an unambiguous assignment of the absolute configuration of **1**. The variation of the UV CD from **6** to **3** probably originates in differences in orientation of the SO group with respect to the phenyl ring. In PhMeSO and *p*-TolMeSO, and presumably also in **6**, the SO group is nearly coplanar with the phenyl ring.[14,17] In **3**, the

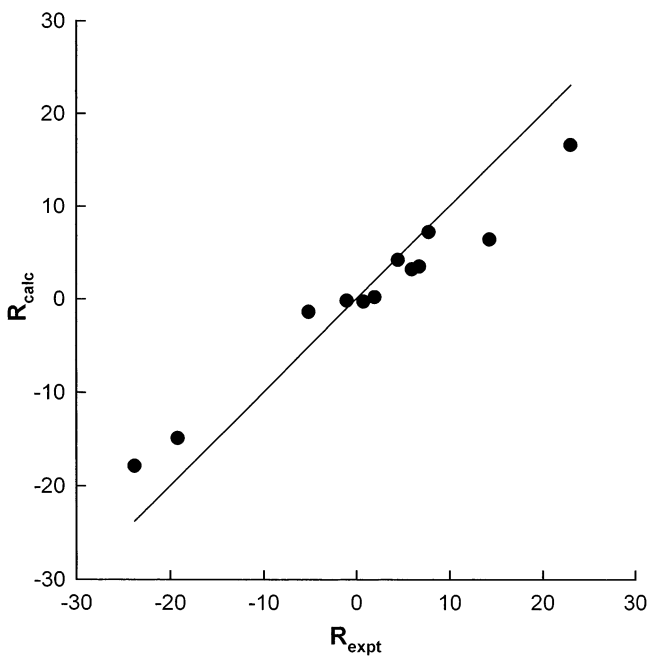


Figure 4. Comparison of calculated and experimental rotational strengths for modes 22–34. Calculated rotational strengths are for *S*-**1**; experimental rotational strengths for (+)-**1**. Rotational strengths are in 10^{-44} esu^2 cm^2. The line is of slope +1.

conformational constraints of the five-membered C_4S ring must lead to a greater angle between the SO group and the phenyl ring. The UV CD of alkyl aryl sulfoxides has been successfully interpreted in terms of coupled oscillator interaction of the SO and aryl groups,[10] and it follows that compounds with substantially different SO group orientations are likely to exhibit substantially different UV CD. The greater similarity of the UV CD of **1** to that of **3** than to that of **6** could be ascribed to a greater closeness in conformation of **1** to **3** than to **6**. However, as we have shown, three conformations are expressed in **1** and the conformations of **3** are as yet undefined; such an argument would therefore be simplistic and premature. More detailed studies are required to analyze the UV CD of **1** in detail; DFT calculations using the TDDFT methodology are under way.[18]

Takata et al.[5] obtained optically active **1** of low e.e. via asymmetric sulfoxidation using the P-450 enzyme. Allenmark and Andersson[7] and Andersson et al.[8] showed that optically active cyclic sulfoxides can be obtained in high e.e. using the chloroperoxidase and bromoperoxidase enzymes. Asymmetric oxidation of cyclic sulfides using purely chemical methods appears to have received relatively little attention. Accordingly, we have investigated the asymmetric oxidation of **2** to **1** using the catalytic protocol of Rosini et al.[11] and the Kagan stoichiometric protocol.[12] *tert*-Butyl hydroperoxide oxidation of **2** using the Ti(*iso*-PrO)$_4$/(*R*,*R*)-DPED/H_2O catalyst led to (*S*)-(+)-**1** of 80% e.e. in 88% yield. The stoichiometric procedure of Kagan et al., employing Ti(*iso*-PrO)$_4$, L-DET and cumene hydroperoxide led to (*R*)-(−)-**1** of 90% e.e. in 51% yield. Thus, we have shown that high e.e. values, comparable to those obtained using enzymatic catalysis, can be obtained using chemical oxidation procedures.

The result that, with the catalytic protocol of Rosini et al. (*R*,*R*)-DPED leads to (*S*)-**1** is in keeping with previous observations that (*R*,*R*)-DPED leads to sulfoxides of (*S*)-absolute configuration,[11] supporting the conclusion that this correlation is valid for both acyclic and cyclic sulfoxides. Likewise, using the procedure of Kagan et al., L-DET preferentially forms (*R*)-**1**, consistent with prior studies.[20]

(*S*)-**1** is eluted after (*R*)-**1** from a Chiralcel OB column, in conflict with previous findings that (*S*)-alkylaryl sulfoxides elute first from this CSP.[19] The empirical correlation between configuration and elution order upon Chiralcel OB CSP thus appears to be limited to open chain alkylarylsulfoxides.

4. Methods

4.1. Synthesis

HPLC analyses were performed at room temperature on Daicel Chiralcel OB (cellulose tribenzoate) chiral stationary phase (CSP). Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. CCl_4 was distilled from CaH_2 and stored over activated 4 Å molecular sieves. Ti(*iso*-PrO)$_4$ (Aldrich) and L-diethyl tartrate (Aldrich) were distilled prior to use under a nitrogen atmosphere. Commercially available *tert*-butyl hydroperoxide (TBHP) (70% in water) and cumene hydroperoxide (80% tech.) were purchased (Aldrich) and used without further purification. Analytical TLC was performed on 0.2 mm silica gel plates (Merck 60 F-254) and column chromatography was carried out with silica gel (Merck 60, 80–230 mesh). Enantiomerically pure (*R*,*R*)-1,2-diphenylethane-1,2-diol (DPED) was prepared by asymmetric dihydroxylation of (*E*)-stilbene.[21] 1-Thiochroman, **2**, was prepared by Clemmensen reduction of 1-thiochroman-4-one (Aldrich), according to a literature procedure.[7,22] Racemic sulfoxide was prepared by oxidation of **2** with 30% hydrogen peroxide following a literature method.[23]

4.1.1. 1-Thiochroman 2. Transparent liquid (61% yield after distillation). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.1 (m, 2H), 2.8 (t, $J=5.9$ Hz, 2H), 3.0 (t, $J=5.9$ Hz, 2H), 6.9–7.2 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.87, 27.56, 29.68, 123.91, 126.39, 126.58, 129.96, 132.86, 133.86; MS (EI) m/z: 150 (M+, 100), 135 (69), 121 (37), 115 (21), 104 (17), 91 (16).

4.1.2. (+)-1-Thiochroman *S*-oxide (+)-1. To a suspension of (*R*,*R*)-DPED (0.2 mmol, 42.7 mg) in CCl_4 (6 mL) under nitrogen was added Ti(*iso*-PrO)$_4$ (0.1 mmol) and the mixture stirred to form a homogeneous solution. Water (2 mmol, 36 μL) and then the sulfide **2** (2 mmol, 300 mg) were added in sequence and stirring was continued for 15 min at 0°C. TBHP (70% in water, 4 mmol, 571 μL) was added and the mixture was stirred at 0°C for ca. 100 min, i.e. until the formation of sulfone was detected (TLC, silica gel, ethyl acetate). The mixture was then diluted with CH_2Cl_2 and dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue was immediately purified by column chromatography (silica gel, ethyl acetate) providing pure sulfoxide (294 mg, 88%). E.e. = 80% (HPLC on Daicel Chiralcel OB (hexane/propan-2-ol 80/20, flow 0.8 mL/min); mp 56–58°C; $[\alpha]_D^{20}=+149$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.05–2.16 (m, 1H), 2.50–2.65 (m, 1H), 2.85–3.17 (m, 4H), 7.24 (d, 1H, $J=7.3$ Hz), 7.36–7.43 (m, 2H), 7.73 (d, 1H, $J=7.3$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.20, 29.59, 46.16, 127.18, 130.24, 130.53, 131.38, 135.59, 138.58; MS (EI) m/z: 166 (M^+, 30), 149 (100), 137 (30), 116 (24), 109 (13).

4.1.3. (−)-1-Thiochroman *S*-oxide (−)-1. To a solution of L-diethyl tartrate (DET) (827 mg, 4 mmol) in anhydrous CH_2Cl_2 (7 mL), Ti(*iso*-PrO)$_4$ (2 mmol, 581 μL) was rapidly added (10 s) at 16°C. After 2.5 min, water (36 μL, 2 mmol) was added slowly (an interruption of 15 s after each drop) with vigorous stirring. The resulting mixture was stirred for 20 min at 16°C, followed by cooling in a freezer without stirring (−22°C) for an additional 20 min. Compound **2** (300 mg, 2 mmol) and

cumene hydroperoxide (740 μL, 4 mmol) were rapidly added and the mixture was stored in a freezer (−22°C) without stirring. After 3 h (absence of sulfide, traces of sulfone by TLC on silica gel, ethyl acetate as eluent) the mixture was poured into a solution of ferrous sulfate heptahydrate (2 g), citric acid (0.67 g), water (20 mL), dioxane (10 mL), diethyl ether (18 mL) and stirred for 15 min. The aqueous phase was extracted with diethyl ether. The combined organic phases were vigorously stirred with aqueous NaOH (2 N, 34 mL), and the aqueous phase extracted with ether. The combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, diethyl acetate) providing 170 mg (51% yield) of pure sulfoxide, e.e. = 90%, $[\alpha]_D^{20} = -167$ (*c* 0.95, $CHCl_3$).

4.1.4. (±)-1-Thiochroman *S*-oxide (±)-1. To a well stirred solution of aqueous H_2O_2 (30% 2.2 mmol, 147 μL) and CH_3COCF_3 (25 mg, 0.22 mmol) was added and the mixture stirred for 15 min at 0°C. A solution of **2** (300 mg, 2 mmol) in $CHCl_3$ (2 mL) was added and the mixture was vigorously stirred for 1.5 h. The two phases were separated, the organic layer was collected and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate) providing pure sulfoxide (249 mg, 75% yield), mp 45–47°C.

4.2. Spectroscopy

IR spectra were measured at 1 cm^{-1} resolution using a Nicolet MX-1 FT spectrometer. VCD spectra were measured at 4 cm^{-1} resolution using a Bomem/BioTools Chiral IR spectrometer. VCD scan times were 1 h. Spectra of solutions of **1** in CCl_4 were obtained using KBr cells of 109, 239 and 597 μm pathlength [ICL]. Concentrations were ~0.3 M. IR spectra, measured at ~0.3 and ~0.02 M concentrations, respectively, were superimposable demonstrating the absence of intermolecular aggregation at the concentrations used in measuring IR and VCD spectra. VCD spectra of (±)-**1** provided the baseline for the VCD spectra of (+)-**1** and (−)-**1**. After conversion to $\Delta\varepsilon$ units, VCD spectra of (+)-**1** and (−)-**1** were normalized to 100% e.e. and the 'half-difference' spectrum, $1/2[\Delta\varepsilon(+)-\Delta\varepsilon(-)]$, calculated to provide the VCD spectrum of (+)-**1**. Experimental frequencies and rotational strengths were obtained from the experimental IR and VCD spectra using Lorentzian fitting.[3b,3c]

4.3. Computation

Ab initio DFT calculations were carried out using GAUSSIAN 98.[24] All calculations used analytical derivative methods and perturbation-dependent basis sets. Atomic axial tensors (AATs) were calculated using GIAO basis sets.[2] Harmonic vibrational frequencies, dipole strengths and rotational strengths were obtained from calculated hessians, atomic polar tensors (APTs) and AATs. IR and VCD spectra were obtained thence, using Lorentzian bandshapes.[3b,3c] DFT calculations used the basis sets 6-31G*[25] and TZ2P[26] and the functional B3LYP.[27]

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