First observable CD spectra from n-σ* excitation: TD-DFT calculation and determination of absolute configuration of 2,6-dithiaspiro[3.3]heptane 2,6-dioxide

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Dedicated to Professor Manfred Schlosser in honor of his scientific achievements

Abstract

Recently we reported that 2,6-dithiaspiro[3.3]heptane 2,6-dioxide **1a** exists as enantiomers at ambient temperature and is able to be resolved. This is because the lone pair(s) on the sulfur atom(s) are rich in s-character, which results in high barrier for flipping the conformation of the four-membered ring, i.e., racemization of the spiro framework of **1a**. During the HPLC analysis, we noticed considerably strong absorption of UV at 210 nm. We expected that the absorbance comes from n-σ* excitation. The acute bond angle of C-S-C leads to high p-character of the C-S bond(s), which lowers the σ* orbital energy. We performed the TD-DFT calculations of a model, constrained dimethylsulfoxide (DMSO) and **1a**. The strong UV absorption of **1a** is reproduced with the TD-DFT calculation. However, there are two sulfoxide groups arranged with chiral position in **1a**, we could expect that the circular dichroism (CD) spectra are observable by coupling of two sulfoxide groups. The TD-DFT calculation showed that the Cotton effects should appear in the observable UV range. We separated the enantiomers of **1a** by HPLC equipped with a chiral stationary phase column. The enantiomers are subjected to the CD analysis. We determined the absolute configuration of **1a**, comparing the calculation and the obtained spectra. This is the first report of the CD spectra of n-σ* excitation.

Keywords: Axial chirality, spiro compounds, TD-DFT calculation, CD spectra

Introduction

Recently, we reported that 2,6-dithiaspiro[3.3]heptane 2,6-dioxide **1a**[1,2] exists as enantiomers at ambient temperature.[1] The spiro[3.3]heptane framework is chiral due to puckering of two four-

membered ring. If flipping of the four-membered ring is quite facile, it racemizes very easily at ambient temperature. For example, commercially available 2,6-diazaspiro[3.3]heptane **2a** is calculated to racemize only with the enthalpy of activation of 5.2 kcal/mol at the B3LYP/6-311+G(d)//B3LYP/6-31G(d) level.[2] However, if the lone pairs of the heteroatom at the 2,6-positions are rich in s-character, the inversion barrier at the heteroatom is high to maintain the absolute configuration without racemization. These circumstances are easily achieved by substitution with heavy atoms. We showed that substitution with phosphorus (**2b**), arsenic (**2c**) and sulfoxide (**1a**), selenoxide (**1b**) and telluroxide (**1c**) led to high barrier for racemization.

(*axS*)-   (*axR*)-
enantiomers
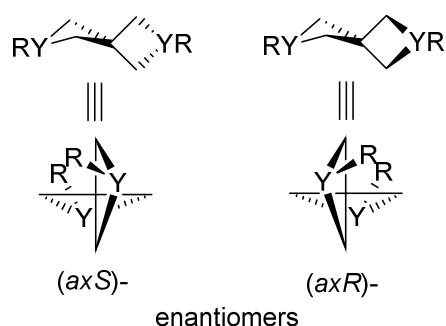
1a YR = SO $\Delta H^{\ddagger}$ = 47.5 kcal/mol
1b YR = SeO $\Delta H^{\ddagger}$ = 53.2 kcal/mol
1c YR = TeO $\Delta H^{\ddagger}$ = 51.1 kcal/mol
2a YR = NH $\Delta H^{\ddagger}$ = 5.2 kcal/mol
2b YR = PH $\Delta H^{\ddagger}$ = 41.0 kcal/mol
2c YR = AsH $\Delta H^{\ddagger}$ = 51.7 kcal/mol

Our initial experiments confirmed that sulfoxide substituted **1a** exists as enantiomers at ambient temperature and is able to resolve with HPLC equipped with a chiral stationary phase column for analytical scale and a preparative scale. However, we wondered that UV absorbance is extremely high at 210 nm in comparison with sulfoxides, such as DMSO. If the absorbance comes from the sulfoxide groups, we expected that we could observe the CD spectra of **1a** because two sulfoxide groups are arranged with chiral position. Previously, the CD spectra with n-σ* excitation was predicted by theoretical calculation[3], and there are some observations of the CD spectra with π-π* excitation of the non-aromatic amides.[4] To date, however, there are no reports on observation of CD spectra of n-σ* excitation. Here we demonstrate the first observation of CD spectra of n-σ* excitation. We performed the TD-DFT calculations to show the possibility of observation of CD spectra, and prepared **1a,** which was resolved into enantiomers. The CD spectra of enantiomers of **1a** were measured to determine the absolute configuration.

Results and Discussion

First, we calculated a model compound, constrained dimethyl sulfoxide (DMSO) (Figure 1). With the narrower bond angles, the bond becomes richer in p-character. Thus, the energy of the σ* orbital should decreased, and the UV absorbance should shift to longer wave length. Hush[5] and Baker[6] calculated **1a** to examine the remote through-bond interaction, and measured the photoelectron spectra. To probe the chirooptical properties of **1a**, we performed the TD-DFT calculations to show whether the UV and CD spectra are observable. Initially, the calculations of constrained DMSO were performed with the dihedral angle of C-S-O-C fixed, which is equivalent to fixation of the C-S-C bond angle. We used the RHF/6-31G(d)//B3LYP/6-311+G** level for the bond orbital energies and the B3LYP/6-311+G** level for TD-DFT calculations (Table 1).[7,8] The σ* orbital energy was obtained using Bond Model Analysis (BMA)[9] and NBO analysis.[10] The σ* energy level is estimated with the diagonal element of a Fock matrix of the bond orbitals (Fii) for BMA. TD-DFT calculations showed that the UV absorbance results from n-σ* excitation. As expected, we noticed that the smaller bond angle of C-S-C resulted in enhanced absorbance with a longer wave-length. A more acute bond angle gives the C-S bond more p-character, which leads to lowering of the σ* energy level of the C-S bond.
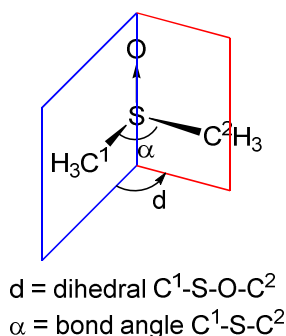

d = dihedral C^1-S-O-C^2
α = bond angle C^1-S-C^2

Figure 1. Constrained DMSO.

We optimized the structure of **1a**, and performed the TD-DFT calculations using the optimized structure at the M06-2X/6-311+G** level (Figure 2). The solvent effect from acetonitrile is included in the calculation with the PCM model. The calculated UV absorbance clearly indicates the absorption (local) maximum at 220 nm, which should be in the observable range of the UV spectra.

Table 1. Bond angle (in deg.) and σ* orbital energy (by BMA and NBO at the RHF/6-31G(d)//B3LYP/6-311+G** level); in a.u.), TD-DFT calculation of UV absorbance of constrained DMSO (B3LYP/6-311+G**).

| Dihedral angle d	Bond angle α	BMA σ* orbital energy (a.u.)	σ* hybrid $sp^n(d^m)$ by NBO on S/C	NBO σ* orbital energy (a.u.)	Calculated ν_{max} (nm)	Calculated absorbance ε
Full optimized 102.5°	96.6°	0.3966	$sp^{5.25}d^{0.11}/sp^{3.62}d^{0.01}$	0.3477	184	6390
95°	90.4°	0.3768	$sp^{5.72}d^{0.21}/sp^{3.69}d^{0.01}$	0.3305	184	7510
90°	86.2°	0.3579	$sp^{6.12}d^{0.21}/sp^{3.77}d^{0.01}$	0.3164	187	8000
85°	81.9°	0.3313	$sp^{6.65}d^{0.21}/sp^{3.89}d^{0.01}$	0.2976	190	8920
80°	77.6°	0.2956	$sp^{7.36}d^{0.13}/sp^{4.04}d^{0.01}$	0.2737	192	10020
75°	73. 1°	0.2491	$sp^{8.39}d^{0.13}/sp^{4.25}d^{0.01}$	0.2439	194	10730
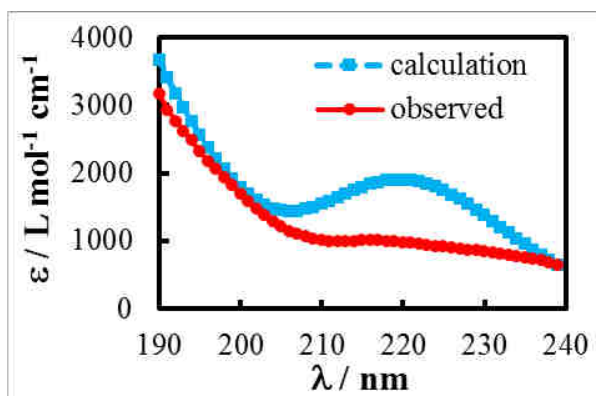
Figure 2. Calculated (blue) and observed (red) UV spec-tra of **1a**.

The HOMO and LUMO of **1a** are shown in Figure 3. The LCBO-MO expression by the BMA analysis showed that the HOMO consists of the lone pair(s) on the oxygen(s) coupled with the lone pair(s) on the sulfur(s) out of phase, and the σ_{C-S} and σ_{C-C} orbitals out of phase. On the other hand, the LUMO mainly consists of the in-phase combination of four each of σ^*_{C-S} and σ^*_{C-C} orbitals. Thus, the UV absorbance resulted from n-σ* excitation.
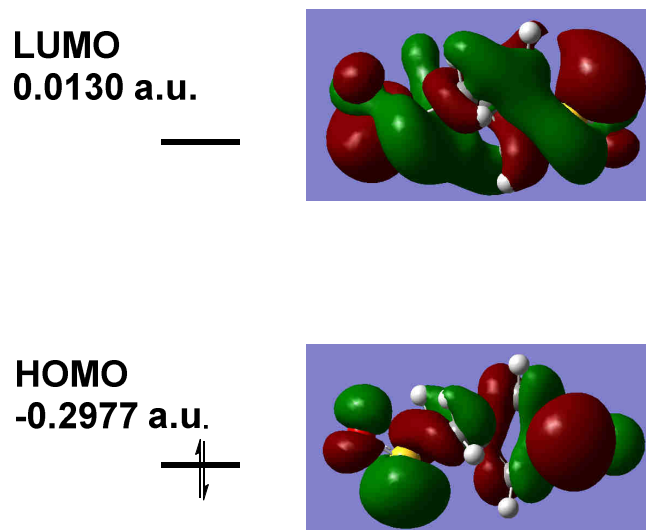
LUMO
0.0130 a.u.

HOMO
-0.2977 a.u.

Figure 3. HOMO and LUMO and the energy levels of **1a** (PCM-M06-2X/6-311+G** (solvent = acetonitrile)).

Furthermore, there are two sulfoxide groups in **1a**, which are arranged in a chiral position. Thus, we could expect that the two sulfoxide groups interact with each other to show CD.[11] To date, there have been many reports on CD spectra from π- π* excitation. However, we believe that there have been no observations of CD spectra from n-σ* excitation. The calculated dihedral angle of O2-S2-S6-O6 for (*axS*)-**1a** is 122.9°, and that for (*axR*)-**1a** is -122.9° (B3LYP/6-311+G**).[12] Thus, a first negative Cotton effect and second positive Cotton effect are expected for (*axR*)-**1a**, and a positive first Cotton effect and second negative Cotton effect should be observed for (*axS*)-**1a**. In fact, the TD-DFT calculations showed CD active. We recalculated **1a** at the PCM-TD-M06-2X/6-311+G** (solvent = acetonitrile) level. The *exo,exo*-**1a** is the most stable and the relative energies of other conformers are shown in Figure 4. From the calculation, the *exo,exo*-(*axR*)-isomer of **1a** should show a negative first Cotton effect at 220 nm ($\Delta\varepsilon$ = -18) and a positive Cotton effect at 188 nm ($\Delta\varepsilon$ = 18), while the (*axS*)-isomer should show a positive first Cotton effect at 220 nm ($\Delta\varepsilon$ = 18) and a negative Cotton effect at 188 nm ($\Delta\varepsilon$ = -18). The simulation weighted on the conformers is shown in Figure 5. Although the simulated CD spectrum is somewhat outside of the observable range (190 nm<), it clearly showed that the absolute configuration could be determined with the CD spectrum.
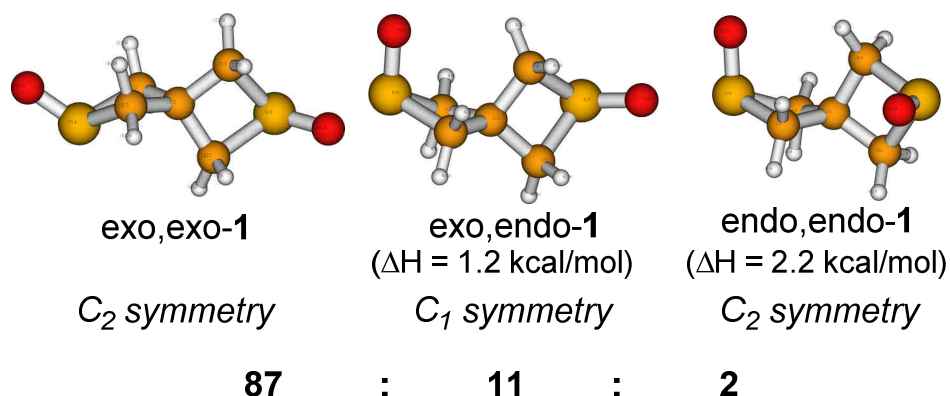
exo,exo-**1**   exo,endo-**1**   endo,endo-**1**
                     (ΔH = 1.2 kcal/mol)   (ΔH = 2.2 kcal/mol)

C_2 symmetry C_1 symmetry C_2 symmetry

87   :   11   :   2

Figure 4. Relative energies and the symmetry point groups of the conformers of **1a**. (PCM-TD-M06-2X/6-311+G** (solvent = acetonitrile)).
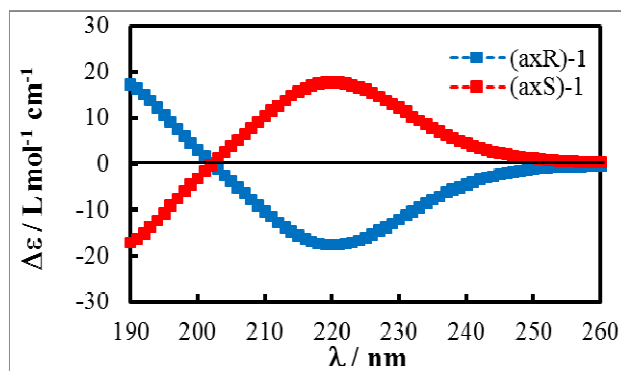

Figure 5. Calculated CD spectra of **1a** (PCM-TD-M06-2X/6-311+G** (solvent = acetonitrile)).

To confirm our calculations, we prepared **1a** from 2,6-dithiaspiro[3.3]heptane **3**.[1,16,17] Treatment of **3** with NaIO$_4$ and repeated recrystallization gave **1a** as a clear solid. As expected, ^{1}H NMR showed two doubled doublets and two doublets. Only one large w-shaped coupling constant (5.1 Hz) is observed (Figure 6). This large coupling constant can be attributed to coupling between the hydrogens at the equatorial 1,3-positions. This is because of the acute bond angle of 94.7° for C1-C4-C3 and the large dihedral angles of 145.2° for H1eq-C1-C4-C3 and -145.2° for C1-C4-C3-H3eq; the other values are too small to observe using a 400 MHz NMR instrument.[18] This observation is in quite contrast of ^{1}H NMR of **3**, which showed only one averaged singlet in toluene-d$_8$ even at -70 °C. It is because the racemization barrier (inversion barrier of the thietane ring) was calculated to be 1.1 kcal/mol at the BMK/6-311+G(d,p)//B3LYP/6-31G(d) level.
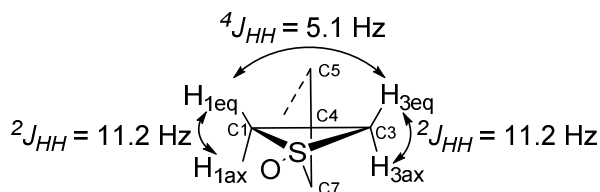
$^4J_{HH}$ = 5.1 Hz

H$_{1eq}$ C5   H$_{3eq}$

$^2J_{HH}$ = 11.2 Hz   C1   C4   C3 $^2J_{HH}$ = 11.2 Hz

H$_{1ax}$ O   S   H$_{3ax}$

C7

Figure 6. Coupling constants for **1a**.

The recrystallized **1a** was examined with a UV spectrometer to obtain the UV absorbance (Figure 2). Although the observed absorbance agrees only qualitatively with the calculation, the maximum absorbance at 216 nm is in accordance with the calculation.

We separated the enantiomers of **1a** using HPLC with a Daicel CHIRALFLASH-IF using methanol as an eluent (Figure 7). The former fraction showed a negative optical rotation $[\alpha]_D^{27}$ = -12.89 (c = 2.13, CHCl$_3$), while the latter had a positive value $[\alpha]_D^{27}$ = 12.60 (c = 0.922, CHCl$_3$). The (-)-isomer of **1a** has a melting point (mp) of 145.3-145.5 °C while the (+)-isomer has mp 144.9-145.2 °C, which is almost the same as that of racemic **1a** (mp 146.4-146.6 °C). To determine the absolute configuration, these enantiomers were subjected to CD spectroscopy. The dihedral angle of O2-S2-S6-O6 for (*axS*)-**1a** is 122.9°, and that for (*axR*)-**1a** is -122.9°. In acetonitrile, the (-)-isomer of **1a** showed a negative first Cotton effect at 224 nm (Δε = -2300) and a positive second Cotton effect at 197 nm (Δε = 1500). On the other hand, the (+)-isomer of 1a showed a positive first Cotton effect at 222 nm (Δε = 1800) and a negative second Cotton effect at 194 nm (Δε = -1400, Figure 8). Thus, the calculations do not quantitatively agree with these observations. However, they do agree qualitatively. Thus, we can conclude that the (-)-isomer is (*axR*)-**1a** and the (+)-isomer is (*axS*)-**1a**.

1st frx   2nd frx

Figure 7. Preparative HPLC with a chiral stationary phase column (Daicel CHRALFLASH-IF, MeOH eluent, 210 nm det.).
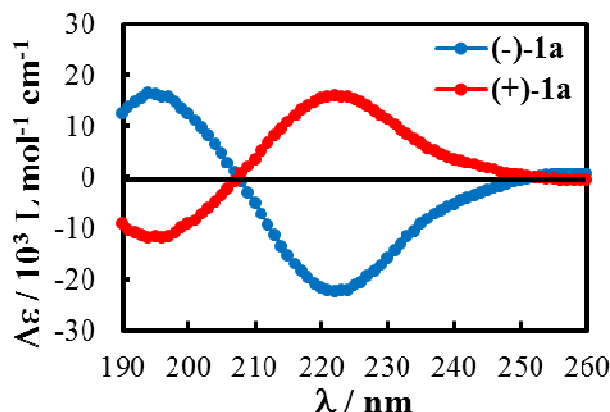
Figure 8. Observed Cotton effect of the enantiomer of **1a** (in acetonitrile).

Conclusions

In conclusion, we have reported the first CD spectra for n-σ* excitation. Due to the high p-character of the σ_{C-C} bond, the σ^*_{C-C} orbital becomes low in energy, which makes the CD spectra in the observable range. We determined the absolute configurations of the enantiomers of **1a**.

Acknowledgements

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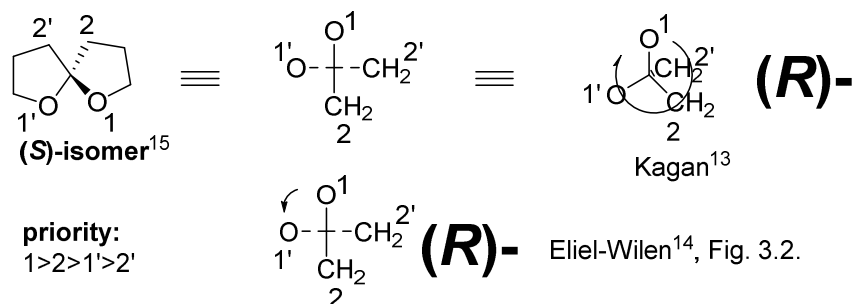
Since the extended Cahn-Ingold-Prelog system is still more common and general (e.g., 1,1-binaphthol, Aldrich catalog Art. No. 246948 and 246956), we used this system. Until now, no replies and comments are yet available from the author[15] on this discrepancy.

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