The First Nonempirical Circular Dichroism Determination of the Absolute Configuration of N-Phthalimidosulfoximines Based on Exciton Coupling Mechanism and a Correlation with the Absolute Configuration of Chiral Sulfoxides

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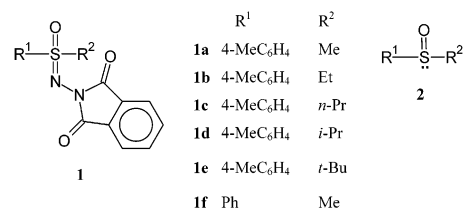**Abstract:** A simple nonempirical method for the assignment of absolute configuration of N-phthalimidosulfoximines and related S-chiral sulfoxides, based on exciton-coupled circular dichroism, is presented.

During the last two decades optically active sulfoxides have been widely recognized as valuable chiral auxiliaries in asymmetric synthesis.[1] Moreover, the sulfinyl moiety is frequently found in bioactive natural products and synthetic drugs.[2] Despite these facts, there have been very few methods to determine their absolute configuration.[3] In particular, only a few examples of correlation between circular dichroism (CD) and structure of optically active sulfoxides have been reported.[4] They are usually based on an empirical rule formulated by the Mislow group after examining the chiroptical properties of several alkyl aryl sulfoxides of known absolute configuration.[5] Very recently this empirical rule has found strong support by a nonempirical analysis of a series of CD spectra of optically active alkyl aryl sulfoxides, using the coupled-oscillator model for nondegenerate transitions.[6] In this paper we would like to report the first nonempirical correlation of the absolute configuration and chiroptical properties of alkyl aryl N-phthalimidosulfoximines based on the analysis of their exciton-split bichromorphoric Cotton effect. This correlation can be

SCHEME 1. Signs of Cotton Effects for Rotamers of N-Phthalomidosulfoximines of (R)-Configuration

A	B	C
(-) C. e.	no exciton C. e.	(+) C. e.
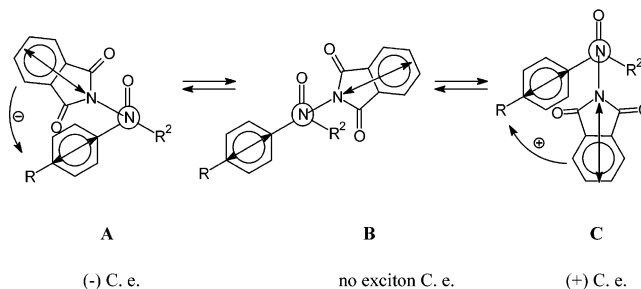
used simultaneously to determine the absolute configuration of the parent alkyl aryl sulfoxides due to the fact that N-phthalimidosulfoximines (**1**) are S-chiral compounds which can be derived from sulfoxides (**2**) via a process believed to proceed with retention of configuration.[7] Knowledge of the absolute configuration of **1** is of great importance not only for verification of the stereochemistry of the above-mentioned transformation but also for determination of the absolute configuration of sulfoxides or sulfoximines. For the most frequently encountered structures of **1**, where R^1 = aryl, there can be envisaged a straightforward method for the assignment of absolute configuration, based on the analysis of the exiton-split bichromophoric Cotton effect.

	R^1	R^2
1a	4-MeC$_6$H$_4$	Me
1b	4-MeC$_6$H$_4$	Et
1c	4-MeC$_6$H$_4$	n-Pr
1d	4-MeC$_6$H$_4$	i-Pr
1e	4-MeC$_6$H$_4$	t-Bu
1f	Ph	Me

In particular, we analyzed a series of N-phthalimidosulfoximines **1** with R^1 = 4-tolyl or phenyl and R^2 = alkyl substituents.[8] For a given R configuration at sulfur atom one obtains a bichromophoric system shown in Scheme 1. There are three rotamers **A**–**C** to be considered, with regard to the rotation about the S–N bond.

To assess the relative population of rotamers **A**–**C** we carried out computations for the model molecule **1f**. First, we selected low-energy conformers of **1f**, with a steric energy difference below 2.4 kcal mol^{-1}. These conformers having varying torsion angles around the bonds Ph–S, S=N, and N–N were found by the MM+ method using HyperChem.[9] The conformers thus determined were divided into the families of rotamers **A**–**C**. The structure of the lowest energy representative of each rotamer **A**–**C** was then fully optimized by the PM3[10] method. The two lowest energy structures had the parameters shown in Table 1.

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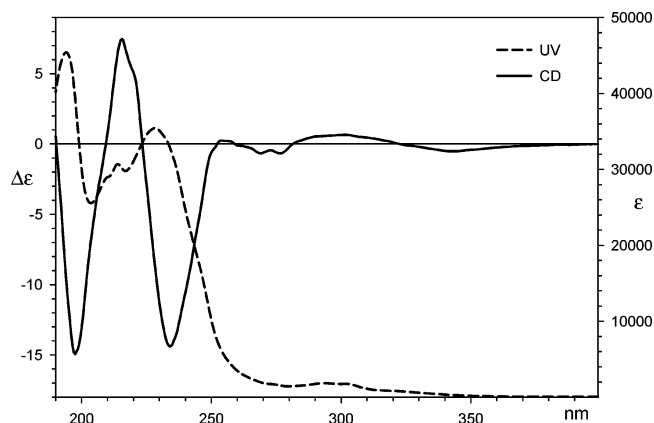
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(9) *HyperChem*, version 6.01, Hypercube 2000.

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TABLE 1. Structural Parameters of the Lowest Energy Rotamers of 1f Computed by the PM3 Method

rotamer	ΔE (kcal mol^{-1})	$C_{ar}-C_{ar}-S-N$ (deg)	$N-N-S-Ph$ (deg)	$S-N-N-C_{C=O}$ (deg)
A	0	152	-116	114
C	1.6	111	34	111

FIGURE 1. CD and UV spectra of (*R*)-**1a** in acetonitrile solution.

TABLE 2. Cotton Effects Used for Absolute Configuration Determination of 1a−f and Their Optical Rotations

compound in CH$_3$CN	$\Delta\epsilon$ (nm)	$[\alpha]_D$ (CHCl$_3$)
(*R*)-**1a**	-14.4 (232)	-159.5
	$+7.4$ (215)	
(*R*)-**1b**	-14.5 (235)	-125.8
	$+6.8$ (216)	
(*S*)-**1c**	$+11.3$ (235)	$+142.7$
	-6.5 (216)	
(*S*)-**1d**	$+14.2$ (233)	$+169.6$
	-6.7 (217)	
(*R*)-**1e**	-16.7 (232)	-150.9
	$+12.6$ (215)	
(*R*)-**1f**[a]	-12.6 (233)	-157.0
	$+9.1$ (214)	

[a] Data corrected to 100% ee.

SCHEME 2. CD Data for 1g (*R*-Configuration, Data Corrected to 100% ee)

$\Delta\epsilon$ +39 (239 nm)

- 19 (229 nm)

Rotamer **A** with a negative N−N−S−Ph angle was found to contribute most abundantly to the population of the rotamers. The next conformer with the energy 1.6 kcal mol^{-1} higher corresponded to the rotamer **C** with a rather small positive N−N−S−Ph torsion angle. For comparison, in the structures of *N*-phthalimidosulfoximines determined by X-ray diffraction analysis (Scheme 1, R^2 = α-naphthyl[11] or *endo*-5-norbornenyl[12]) rotamer **A** is present.

The analysis of exciton coupling in rotamers **A**−**C** is greatly simplified when one considers coupling of the 4-tolyl ^1L_a electric dipole transition moment (belonging to the absorption band at ca. 215 nm) with the electric dipole transition moment of the 220-nm transition of the phthalimide group.[13] Both transitions are polarized along the chromophore long axis, which makes their position independent of the rotation around the S−(4-tolyl) and N−N bonds, respectively. Thus, rotamer **A** generates a negative exciton split Cotton effect for the above-mentioned transitions and the *R* configuration, whereas rotamer **B** essentially does not contribute to the Cotton effects in the 210−230-nm range.

As seen in Figure 1, the CD spectrum recorded for (*R*)-**1a** exhibits a negative Cotton effect at 232 nm and a positive Cotton effect at 215 nm (corresponding to a UV max at 228 nm). This is in full agreement with the established stereochemical model.

The pattern of signs of the Cotton effects appears consistent with the configuration throughout the whole series of investigated compounds **1a**−**f** (Table 2) and is

also consistent for other Cotton effects not shown in the table (see Supporting Information).

Also of interest is to note that the sign of optical rotation (measured in chloroform) reflects consistently the absolute configurations of **1a**−**f**, i.e., it is positive for *S* configuration and negative for *R* configuration.

A derivative **1g** with R$_1$ = α-naphthyl and R$_2$ = methyl groups shows a positive exciton Cotton effect corresponding to the most intense absorption band at 226 nm (ϵ = 58 500). Since this Cotton effect is generated by the coupling of the phthalimide and the naphthalene electric dipole transition moments, both polarized in the direction of the long axis of each chromophore, the geometry of the transition moments is opposite to that of **1a**. Hence, the positive sign of the exciton Cotton effect of **1g** corresponds to *R* absolute configuration (Scheme 2).

In summary we have demonstrated a simple and straightforward method, based on the exciton coupling mechanism, for determining the absolute configuration of alkyl-4-tolyl-substituted *N*-phthalimidosulfoximines, with direct extension to other alkyl−aryl analogues of **1**, as well as to configurationally related sulfoxides **2**. In the latter case the method is complementary to the already existing correlations between the CD spectra and absolute configuration of S-chiral sulfoxides, based on the work of Mislow[5] and Rosini.[6] However, unlike the case of chiral alkyl aryl sulfoxides where a coupled-oscillator mechanism involving the $\sigma-\sigma^*$ transition of the S=O chromophore and the ^1L_a transition of the benzene chromophore is invoked, the present method is based on the coupling of genuine electrically allowed $\pi-\pi^*$ transitions of the phthalimide and the aryl chromophores.

Supporting Information Available: Experimental section with characterization data and full chiroptical data for **1a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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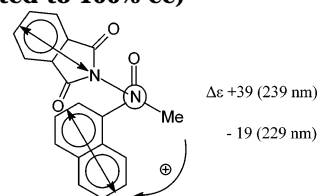
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