Axially Chiral Heteroaromatics. 1. Preparation of Optically Active 1,1'-Biisoquinoline *N,N'*-Dioxide

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A novel optically active heteroaromatic compound, (+)-1,1'-biisoquinoline *N,N'*-dioxide (**1**) and its atropisomer (-)-**1** were prepared and characterized by several spectroscopic methods.

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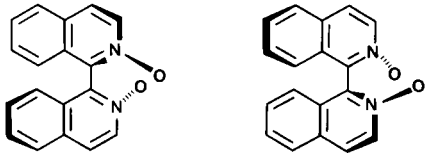
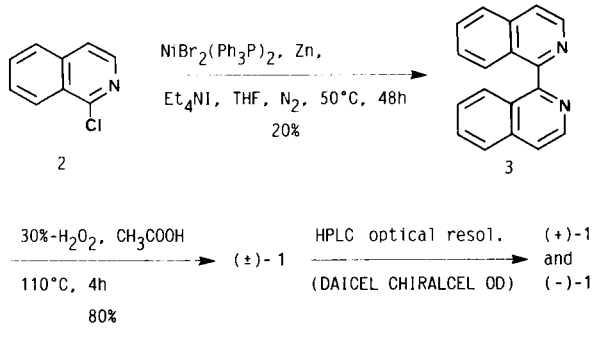
Recently, studies on bipyridines and related compounds and their chelate metal complexes have attracted widespread and distinguished interest in the field of pharmacology, biochemistry, and molecular biology as well as bioorganic and -inorganic chemistry. For instance, trisbipyridine chelate complex of ruthenium(II) has been used as a catalyst for artificial photosynthesis [1], and trisphenanthroline chelate complex of copper(I) or ruthenium(II) has been shown to act as a potential restriction enzyme model and an anti-cancer agent [2]. And in host-guest chemistry, innumerable number of functionalized bipyridines have been investigated as host compounds capable of molecular recognition [3]. It is reasonable to expect that introduction of axial chirality into the bipyridine moiety will open a new aspect for chemistry related to such heteroaromatic ligands and their chelate metal complexes. In the course of our studies on axially chiral heteroaromatic compounds, we now report the first preparation of optically active 1,1'-biisoquinoline *N,N'*-dioxide (**1**) which is expected to act as a chiral ligand to a variety of acceptors such as metal salts and complexes, and organic compounds [4].



(*R*) - 1 (*S*) - 1

Preparation of (+)- and (-)-**1** were achieved as shown in Scheme 1.



Scheme 1. Preparation of (+)-1 and (-)-1

Coupling reaction of 1-chloroisoquinoline (**2**) in the presence of $NiBr_2(PPh_3)_2$ gave 1,1'-biisoquinoline (**3**) in 20% yield [5]. Oxidation of **3** with aqueous 30% hydrogen peroxide in refluxing acetic acid gave (±)-**1** in 80% yield. Both atropisomers of **1** were obtained by preparative hplc with an optically active column (DAICEL CHIRALCEL OD, hexane/ethanol = 70/30, 0.5 ml/minute). One atropisomer having a retention time of 52.55 minutes showed a positive optical rotation of $[\alpha]_D^{20}$ +41.7 (c = 0.144, methanol) and the other having a retention time of 64.16 minutes showed a negative optical rotation of $[\alpha]_D^{20}$ -43.16 (c = 0.18, methanol). The C.D. spectra of thus obtained (+)-**1** and (-)-**1** ensure that these are a pair of enantiomers (Figure 1). Considering the C.D. spectra and uv-vis spectra (Figure 2), it can be revealed that the intense shorter wavelength absorption at 264 nm with transition moments along the long axes of the two isoquinoline nuclei interact with each other to give an exciton-split C.D. spectra with extrema of $\Delta\epsilon_{299}$ -0.946 and $\Delta\epsilon_{263}$ +2.52 (in methanol for (+)-**1** and $\Delta\epsilon_{299}$ +0.946 and $\Delta\epsilon_{263}$ -2.52 for (-)-**1**.

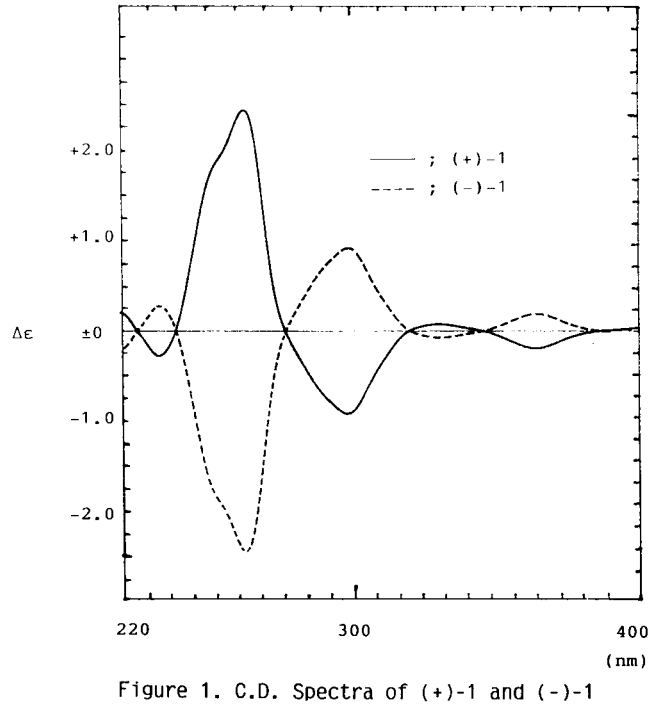


Figure 1. C.D. Spectra of (+)-1 and (-)-1

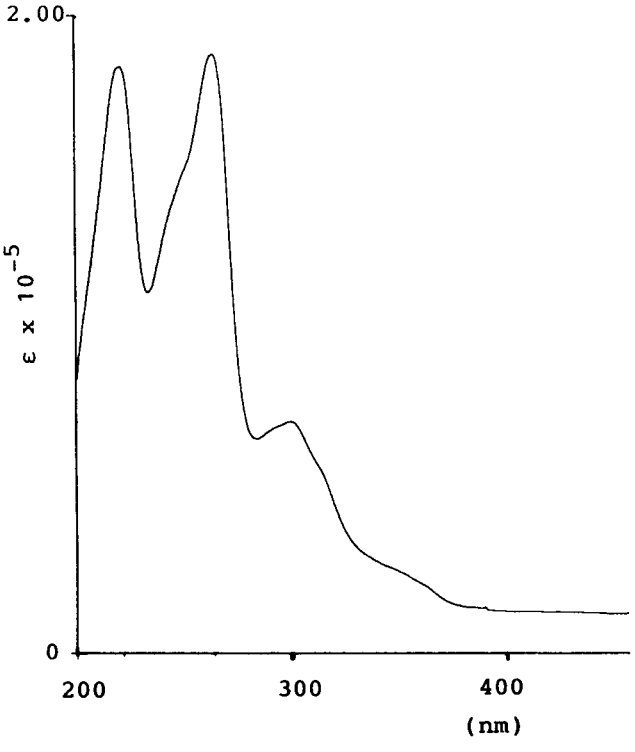


Figure 2. UV-Vis Spectra of 1

Provided that the angle of the planes of the two isoquinoline rings is given, the absolute stereochemistry of (+)-**1** and (-)-**1** will be established according to the exciton chirality method using these split-type Cotton effects [6].

Further studies to determine the absolute configuration (+)-**1** and (-)-**1** by X-ray crystallography and studies on their chelate metal complexes are now in progress in our laboratory.

EXPERIMENTAL

Instruments.

The ^{1}H-nmr spectra were measured at 90 MHz with a Hitachi R-90H FT-NMR spectrometer. Electronic absorption spectra were recorded on a Hitachi U-3200 UV-Vis spectrometer. The C.D. spectra were recorded on a JASCO J-720 spectrometer and optical rotations were measured on a Horiba SEPA-200 polarimeter. Analytic and preparative hplc were performed on JASCO 880-PU with JASCO 870-UV detector equipped with an optically active column DAICEL CHIRALCEL OD, and G.C. analyses were performed on a Shimadzu GC-12A gas chromatograph. The gc-ms were measured on a Hitachi M-80A GC-Mass spectrometer. Elemental analyses were performed with a Yanaco MT-3 elemental analyzer. Melting points were measured on Yanaco MP-5000D micro melting point apparatus.

Materials.

The $NiBr_2(PPh_3)_2$ was prepared by the procedure described in the literature [7]. Zinc powder was treated successively with 2 *M* hydrochloric acid, water, ethanol, acetone, and diethyl ether, and dried at 80° under reduced pressure. Tetraethylammonium iodide, acetic acid, and aqueous 30% hydrogen peroxide were commercially available and used without purification. Solvents were dried and distilled prior to use by conventional procedures. For column chromatography, Merck Silica Gel 60 (70-230 mesh) was used.

1,1'-biisoquinoline (**3**) [5].

A solution of 3.28 g (20 mmoles) of 1-chloroisoquinoline (**2**) in 10 ml of THF was added to a suspension of 4.46 g (6 mmoles) of $NiBr_2(PPh_3)_2$, 1.96 g (30 mmoles) and 5.14 g (20 mmoles) in 30 ml of THF. The mixture was stirred at 50° for 48 hours under a nitrogen atmosphere. To the reaction mixture, 100 ml of 2 *M* aqueous ammonia was added and the solution was extracted with chloroform (3 x 50 ml). The combined organic layer was washed with 100 ml of water and 100 ml of brine, and dried on anhydrous magnesium sulfate. Purification by column chromatography on silica gel (benzene/ether = 1/1) afforded 1.03 g (20%) of **3** as a white crystalline solid, mp 164-165° (lit [8], 164-165°); gc-ms: m/z 256 (M^+); ^{1}H-nmr (deuteriochloroform): δ 7.20-8.25 (m, 10H), 8.60-8.90 (d, 2H, J = 6 Hz); uv-vis (methanol): abs, λ max nm (ε x 10^{-3}) 325 (79), 310 (60), 283 (63), 274 (65).

Anal. Calcd. for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 83.89; H, 4.55; N, 11.02.

1,1'-Biisoquinoline *N,N'*-Dioxide (**1**).

A mixture of 512 mg (2 mmoles) of **3**, 1.5 ml of aqueous 30% hydrogen peroxide, and 5 ml of acetic acid was refluxed with vigorous stirring for 4 hours. Acetic acid was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate as an eluent to give 461 mg (80%) of **1** as a pale yellow crystalline solid, mp 253-259°; gc-ms: m/z 288 (M^+); ^{1}H-nmr (deuteriochloroform): δ 7.05-8.05 (m, 10H), 8.25-8.45 (d, 2H, J = 7 Hz); uv-vis (methanol): (Figure 2) abs, λ max nm (ε x 10^{-3}) 300 (73.3), 264 (188), 222 (184).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.94; H, 4.20; N, 9.72. Found: C, 75.22; H, 4.13; N, 9.51.

Optical Resolution of (±)-**1**.

Optical resolution of (±)-**1** was performed by preparative hplc with an optically active column (DAICEL CHIRALCEL OD, hexane/ethanol = 70/30, 0.5 ml/minute). The first fraction (retention time = 52.55 minutes) showed optical rotation of $[\alpha]_D^{20}$ +41.7 (c = 0.144, methanol) and the second fraction (retention time = 64.16 minutes) showed optical rotation of $[\alpha]_D^{20}$ -43.16 (c = 0.18, methanol); C.D. spectra (methanol): (Figure 1) abs, λ max nm (Δε) (+)-**1**: 263 (+2.52), 277 (0), 299 (-0.946); (-)-**1**: 263 (-2.52), 277 (0), 299 (+0.946).

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