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Preparation, Resolution and Absolute Configuration of 2,2'-Bipyridine-3,3'-dicarboxylic Acid 1,1'-Dioxide and Its Ester

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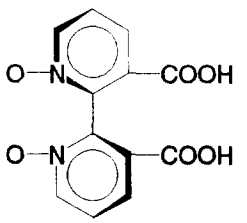
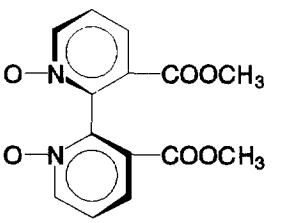
Abstract: The title racemic acid (±)-1, prepared by hydrogen peroxide oxidation of 2,2'-bipyridine-3,3'-dicarboxylic acid, was resolved via the brucine salts. The absolute configuration of acid (+)-1 was determined by X-ray diffraction study of its barium salt using the Bijvoet's anomalous dispersion method. The activation energy $\Delta G^{\neq}$ for interconversion of enantiomers of the dimethyl ester **2** was found to be −106.5 kJ/mol at 50 °C.

In the course of our investigations of axially chiral biaryl systems we successfully employed some biphenyldicarboxylic acids of C_2 symmetry as chiral selectors for HPLC separation of amino alcohol derivatives[1]. Trying to extend this approach to other biaryl systems of C_2 symmetry, we turned attention to the 2,2'-bipyridine system which seemed interesting from the viewpoint of chiroptical behaviour as well as of practical utilization for HPLC.

By analogy to the biphenyl system, 2,2'-bipyridine derivatives should exist as isolable enantiomers when all the four positions (3,3' and 1,1') adjacent to the central connecting bond are substituted. For certain reasons (need of strongly polar groups and synthetic accessibility) we have chosen the 2,2'-bipyridine 1,1'-dioxide system substituted in positions 3 and 3' with carboxy groups. The diacid **1** should be resolvable and capable of ionic anchoring to an aminoalkyl silica carrier. Racemic acid (±)-1 was



(*S*)-(+)-1



(*S*)-(-)-2

prepared by oxidation of 2,2'-bipyridine-3,3'-dicarboxylic acid with hydrogen peroxide in acetic acid. Crystallization of the corresponding brucine salts afforded both enantiomers (−)-**1** and (+)-**1**. Treatment with diazomethane converted the levorotatory acid (−)-**1** into the dextrorotatory methyl ester (+)-**2**. Alternatively, racemate (±)-**2** was easily resolved by preparative chromatography on triacetylcellulose.

Absolute Configuration

To our knowledge, the only hitherto described optically active 2,2'-bipyridine 1,1'-dioxide is 3,3'-dimethyl-2,2'-bipyridine 1,1'-dioxide, obtained by Fuita and coworkers[2] by decomposition of its chiral chromium complex[2,3]. The authors assigned the *S*-configuration to the dextrorotatory enantiomer only on the basis of its CD spectrum. We measured the CD spectrum[6] of our ester (+)-**2** (Fig. 1); however, because of the possible effect of the ester groups, a simple comparison of the two spectra could not afford an unequivocal information on the absolute configuration.

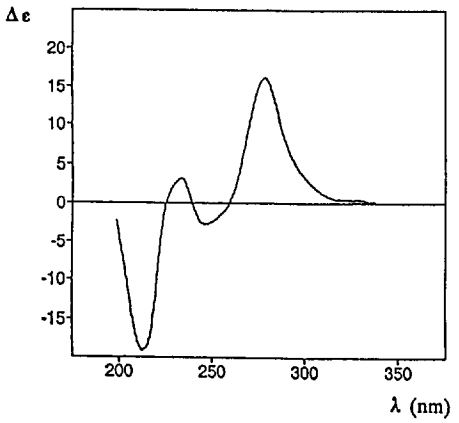


Figure 1. CD spectrum of (+)-**2** (c $1.68.10^{-3}$ M, methanol)

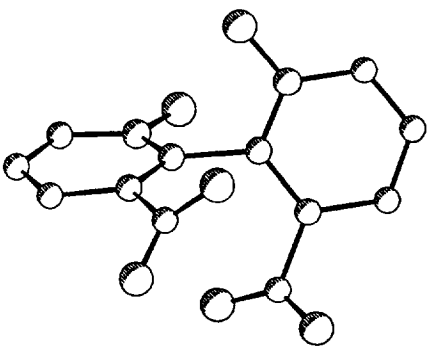


Figure 2. Crystal structure[7] of (+)-**1**

We therefore resorted to a more reliable method and determined the absolute configuration of the barium salt of acid (+)-**1** by X-ray diffraction using the Bijvoet's anomalous dispersion method. This revealed[7] that acid (+)-**1** has the *S*-configuration[8] (Fig. 2).

Configurational Stability

So far, there are no quantitative data available on the configurational stability of the 2,2'-bipyridine 1,1'-dioxide system[10]. We followed the kinetics of racemization of the optically active methyl ester (+)-**2** in dioxane in the temperature range 50 - 70 °C. For interconversion of the enantiomers of **2**, the free

activation energy $\Delta G^{\neq}$ amounted to -106.5 kJ/mol at 50 °C ($\Delta H^{\neq}$ = -94.7 kJ/mol and $\Delta S^{\neq}$ = 0.037 kJ/grad mol). On the other hand, the optically active acid **1** is entirely stable in 0.1 M aqueous NaOH at room temperature; at high temperatures, in the same solvent, it racemized only very slowly ($\Delta G^{\neq}$ = -132.8 kJ/mol at 93.3 °C).

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EXPERIMENTAL

(±)-2,2'-Bipyridine-3,3'-dicarboxylic Acid 1,1-Dioxide ((±)-1). A stirred mixture of 2,2'-bipyridine-3,3'-dicarboxylic acid (2.0 g, 8.2 mmol; prepared from phenanthroline[11]), acetic acid (16 ml) and 30% hydrogen peroxide (16 ml) was heated at 105 - 110 °C. The original suspension dissolved and in 20 min the product began to precipitate. After heating for 3 h, the reaction mixture was cooled and the product was filtered. Yield 2.1 g (92.8%) of the dioxide, not melting up to 360 °C. Anal. Calcd for $C_{12}H_8N_2O_6$: C, 52.18; H, 2.92; N, 10.14. Found: C, 52.38; H, 2.92; N, 10.38.

Optical Resolution of Acid (±)-1. A fine suspension of acid (±)-**1** (2.76 g; 10 mmol) in water (10 ml) was added to a stirred hot suspension of brucine dihydrate (8.6 g; 20 mmol) in water (60 ml) as rapidly as it dissolved. The hot solution was filtered, cooled to 30 °C, inoculated, left aside for 30 min, and filtered. The crystals were pressed, washed rapidly with cold water (3 x 20 ml) and crystallized from water (20 ml). Yield 3.66 g of *brucine salt* of (-)-**1**, decomposing at 210 - 218 °C; $[\alpha]_D^{25}$ -6.8 (c 0.5, DMF). Anal. Calcd for $C_{58}H_{60}N_6O_{14}.4H_2O$: C, 61.25; H, 6.02; N, 7.39. Found: C, 61.45; H, 5.68; N, 7.52. The filtrate was combined with the washings, inoculated and set aside for 4 h at ambient temperature. The separated crystals were collected and washed with cold water (2 x 10 ml). Crystallization from water afforded 2.81 g of pure *brucine salt* of (+)-**1**, melting at 214 - 217 °C; $[\alpha]_D^{25}$ -67.7 (c 0.5, DMF). Anal. Calcd for $C_{58}H_{60}N_6O_{14}.4H_2O$: C, 61.25; H, 6.02; N 7.39. Found: C, 61.19; H 5.69; N, 7.41.

***(R)*-(-)-2,2'-Bipyridine-3,3'-dicarboxylic Acid 1,1-Dioxide ((-)-1).** To a vigorously stirred suspension of the brucine salt of (-)-**1** ($[\alpha]_D^{25}$ -6.8; 3.66 g) in water (10 ml) was slowly added 2 N HCl to pH 2. After stirring the mixture for 3 h, the deposited very fine solid was collected, washed thoroughly with cold water (5 ml) and then with ethanol (10 ml). After drying, the acid was obtained as a microcrystalline powder (832 mg; 60% overall yield), not melting up to 360 °C, $[\alpha]_D^{25}$ -54.6 (c 0.5, 0.1 M NaOH). ^{1}H NMR (200 MHz, NaOD in D_2O) δ 8.44 dd, 2H, J(6,4)=1.2, J(6,5)=6.4 (H-6); 8.14 dd, J(4,6)=1.2, J(4,5)=7.9 (H-4); 7.72 dd, 2H, J(5,6)=6.4, J(5,4)=7.9 (H-5). Anal. Calcd for $C_{12}H_8N_2O_6$: C, 52.18; H, 2.92; N 10.14. Found: C, 51.89; H, 2.87; N 10.16.

***(S)*-(+)-2,2'-Bipyridine-3,3'-dicarboxylic Acid 1,1-Dioxide ((+)-1).** Brucine salt of (+)-**1** ($[\alpha]_D^{25}$ -67.7; 2.81 g), was treated as described in the preceding experiment; yield 618 mg (45% overall yield) of the title acid, not melting up to 360 °C, $[\alpha]_D^{25}$ +54.2 (c 0.5, 0.1 M NaOH). At room temperature, solutions of the optically active acids in 0.1 M NaOH were completely stable at least for 1 month; at 93.2 °C the rate of racemization in the same solvent: $k = 1.76.\ 10^{-6}\ s^{-1}$.

(±)-Dimethyl 2,2'-Bipyridine-3,3'-dicarboxylate 1,1-Dioxide ((±)-2). Acid (±)-**1** (1.5 g, 5.43 mmol) was refluxed for 4 h with a solution of HCl in methanol (saturated at 0 °C). The reaction mixture was concentrated in vacuo and the residue partitioned between saturated solution of sodium carbonate and chloroform. After drying and evaporation, the residue was crystallized from ethanol; yield 1.34 g, m.p. 183 - 185 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.42 dd, 2H, J(6,4)=1.2, J(6,5)=6.4 (H-6); 7.97 dd, 2H,

J(4,6)=1.2, J(4,5)=7.9 (H-4); 7.45 dd, 2H, J(5,6)=6.4, J(5,4)=7.9 (H-5); 3.77 s, 6H (CH_3). Anal. Calcd for $C_{14}H_{12}N_2O_6$: C, 55.26; H, 3.98; N 9.21. Found: C, 54.74; H, 3.94; N, 8.98.

Separation of Ester (±)-2 into Enantiomers. The separation was performed on a triacetylcellulose column (250 g) with ethanol as eluent; injections 60 mg/2 ml, flow rate 5.0 ml/min. Thus, 635 mg of the racemate afforded 189 mg (59%) of (+)-**2** as the first peak (purity >98%) and 208 mg (65%) of (−)-**2** as the second (purity about 90%). The enantiomeric purity was determined by HPLC on an analytical column of triacetylcellulose.

***(R)*-(+)-Dimethyl 2,2'-Bipyridine-3,3'-dicarboxylate 1,1-Dioxide ((+)-2).** Prepared either by chromatographic resolution described above or by treatment of a solution of (−)-**1** in methanol with ethereal diazomethane; m.p. 189 - 192 °C (ethanol), $[\alpha]_D^{25}$ +298.6 (c 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) same as for (±)-**2**. MS(FAB), m/z: 305 (M+H), HR: 305.0739, $C_{14}H_{12}N_2O_6$ requires 305.0774.

Saponification of (+)-2. A solution of (+)-**2** (24.3 mg, $[\alpha]_D^{25}$ +178 (c 0.3, methanol)) in methanol (2.5 ml) was mixed with 0.5 M aqueous NaOH (2.5 ml). After standing for 10 min at room temperature the optical rotation became constant (α −0.201°). A solution of (−)-**1** of the same molarity in the same mixture of methanol and 0.5 M NaOH, showed α −0.255°.

Racemization of Optically Active Esters 2. A solution (25 mg/5 ml) of the studied optically active diester **2** in dioxane was heated at given temperature in a thermostated 10 cm polarimeter cell and optical rotation was measured at appropriate intervals. The racemization first-order rate constants k were obtained from plots of ln α vs time. The racemization rates k for the esters in dioxane were $8.14 \cdot 10^{-5}$ s^{-1} at 50.0 °C, $2.38 \cdot 10^{-4}$ s^{-1} at 60.0 °C and $6.74 \cdot 10^{-4}$ s^{-1} at 70.0 °C. In one experiment, the racemization was brought to completion ($[\alpha]_D$ 0). Subsequent evaporation of the solvent gave pure (HPLC) racemic diester (±)-**2**.

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