# "Marking" the Nitrogen Atoms of Phenyl-(2-pyridyl)-(3-pyridyl)-(4-pyridyl)-methane. Synthesis and Absolute Configuration of the Corresponding Tris(pyridine *N*-oxide)

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*ABSTRACT* To "mark" the nitrogen atoms in phenyl-(2-pyridyl)-(3-pyridyl)-(4-pyridyl)methane (1), we have synthesized the corresponding tris(pyridine *N*-oxide) **2** by oxidation of **1** with *m*-chloroperbenzoic acid. The nitrogen atoms of **2** are unequivocally determined by the Xray crystal analysis of a single crystal of *rac*-**2** whereas the nitrogen atoms cannot be assigned at all in the case of *rac*-**1**. *N*-Oxide **2** can be resolved by chiral high-performance liquid chromatography under similar conditions to those used for the resolution of **1**. The calculated circular dichroism (CD) curve for (*R*)-**2** on the basis of time-dependent density functional theory reproduces the experimental spectra very well to suggest that the second-eluted fraction ([CD(+)283]-**2**) is the *R* isomer, namely (*R*)-[CD(+)283]-**2**. The independent absolute configuration determinations for **1** and **2** are in keeping with the chemical correlation between the two compounds by oxidation of (*R*)-**1** into (*R*)-**2**. *Chirality 23:543–548, 2011.* © 2011 Wiley-Liss, Inc.

*KEY WORDS:* chiroptical properties; chiral separation; configuration determination; density functional calculations; heterocycles

## INTRODUCTION

Many kinds of chiral molecules having outstanding structural features have been successfully synthesized, and their fascinating properties have been disclosed.<sup>1-16</sup> These molecules have attracted much attention not only from the viewpoint of the elucidation of the structure-chiroptical property relationship but also in relation to the potential application in the fields of asymmetric synthesis, host-guest chemistry, and materials science.<sup>17-24</sup> Some of these molecules are important for the understanding of chirality and the origin of life, ultimately. We recently reported the synthesis, optical resolution and chiroptical properties of phenyl-(2-pyridyl)-(3-pyridyl)-(4-pyridyl)methane (1) as a prototypical chiral molecule based on tetraarylmethane framework.<sup>25</sup> As single crystals of 1 were obtained suitable for X-ray analysis, we envisaged a possibility for assigning the absolute configuration of 1 and related compounds. The racemic mixture of 1 (rac-1) crystallized as a racemic compound, that is, equal amounts of the enantiomers were contained in each single crystal. More surprisingly, we could not assign the positions of nitrogen atoms at all; the asymmetric unit was only a half of the molecule. This uncertainty was attributed not only to a random orientation of the aryl groups but also to the 180° rotational disorder of 2- and 3-pyridyl groups in the crystals as the positions of the nitrogen atoms are different from each other by 180° rotation of the corresponding aryl rings. The absolute configuration of **1** was therefore determined by the comparison of time-dependent density functional theory (TDDFT)-calculated CD spectra with the experimental ones. To circumvent the problem of ambiguous assignment of the nitrogen atoms in the crystals of 1, we considered the corresponding tris(pyridine *N*-oxide) **2**, where each nitrogen is "marked" with an oxygen atom and would be easily © 2011 Wiley-Liss, Inc.

determined by X-ray analysis (Scheme 1). Moreover, the stereochemistry at the chirality center would be preserved during the oxidation of 1, therefore the absolute configurations of 1 and 2 are easily correlated. If the absolute configuration of 2 is independently assigned by CD calculations, the two assignments of 1 and 2 would reinforce each other. Further evidence for the absolute configuration of 1 is in fact desirable because of the weakness of its experimental CD spectrum and the molecular flexibility, which affected the CD calculations. Furthermore, as a number of chiral derivatives of pyridine *N*-oxide have been explored for various asymmetric synthesis,<sup>26–29</sup> 2 might be a useful molecule as an asymmetric catalyst. We now report the synthesis, enantioseparation, chiroptical properties and absolute configuration determination of 2 by calculation of CD curve by means of TDDFT.

## EXPERIMENTAL General

Melting points were taken on a Yanaco MP 500D apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JEOL EX-270 (270 MHz) or JEOL LA-500 (500 MHz) spectrometer. Heteronuclear

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Scheme 1. Synthesis of *rac*-2.

multiple-quantum correlation (HMQC) and heteronuclear multiple-bond correlation (HMBC) spectra were recorded on a VARIAN INOVA 600 (600 MHz) spectrometer. Chemical shifts were recorded in unit of parts per million downfield from tetramethylsilane as an internal standard and all coupling constants are reported in Hz. Electronic spectra were taken in hexane/ethanol (1:1 v/v) solution on a JASCO V-570 spectrophotometer. CD spectra were taken on a JASCO J-720W spectropolarimeter. Mass spectra were recorded with a Shimadzu GCMS-QP5050 spectrometer by EI method. High resolution mass spectra were recorded with a QSTAR<sup>®</sup> Elite spectrometer by ESI method. Elemental analyses were performed at the Elemental Analysis Center in Faculty of Science, Osaka University. Commercially available reagents and solvents were purified and dried when necessary.

# Preparation of Rac-(1-oxy-pyridin-2-yl)-(1-oxy-pyridin-3-yl)-(1-oxy-pyridin-4-yl)-phenyl-methane (rac-2)

m-Chloroperbenzoic acid (MCPBA) (248 mg, 1.44 mmol) was added in small portions to a solution of rac-1 (40 mg, 0.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C. The reaction mixture was stirred for 90 min at 0°C, then at room temperature overnight. After concentration of the reaction mixture the residue was purified by column chromatography on alumina eluted with  $CH_2Cl_2$ -MeOH (4:1 v/v) to give rac-2 (> 99%) as pale yellow solid. M.p. > 315°C (dec.). UV/Vis (in EtOH)  $\lambda_{max}/nm$  (log  $\varepsilon)$  276 (4.39). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 8.15$  (ddd, J = 6.5, 1.5, 0.5 Hz, 1H), 8.13 (dd, J = 5.0, 1.5 Hz, 2H), 8.12 (ddd, J = 5.5, 1.5, 1.0 Hz, 1H), 7.98 (t, J = 2.0 Hz, 1H), 7.40 (ddd, J = 8.0, 2.0, 0.5 Hz, 1H), 7.37–7.33 (m, 4H), 7.29 (td, J = 8.5, 1.5 Hz, 1H), 7.25 (dd, J = 8.0, 6.5 Hz, 1H), 7.08 (ddd, I = 8.0, 2.0, 0.5 Hz, 1H), 7.06–7.04 (m, 2H), 7.03 ppm (dd, I =5.0, 1.5 Hz, 2H) ppm. <sup>1</sup>H NMR (600 MHz, methanol- $d_4$ ):  $\delta = 8.25-8.24$ (m, 4H, 4PyNO-2,6H, 3PyNO-6H), 8.22 (dd, J = 6.0, 1.2 Hz, 1H, 2PyNO-6H), 8.10 (s, 1H, 3PyNO-2H), 7.64 (dd, J = 7.8, 3.0 Hz, 1H, 2PyNO-3H), 7.63–7.55 (m, 2H, 2PyNO-4,5H), 7.48 (t, 1H, J = 7.2 Hz, 3PyNO-5H), 7.41-7.38 (m, 3H, 3PyNO-4H, Ph-metaH), 7.35 (t, J = 7.2 Hz, 1H, PhparaH), 7.32 (d, J = 7.2 Hz, 2H, 4PyNO-3,5H), 7.17 ppm (d, J = 7.8 Hz, 2H, Ph-orthoH) ppm. <sup>13</sup>C NMR (67.8 MHz, CDCl<sub>3</sub>):  $\delta = 151.40, 141.20,$ 140.19, 140.03, 139.86, 138.40, 138.25, 137.21, 129.72, 128.84, 128.10, 127.61, 127.41, 127.04, 126.01, 124.79, 124.70, 60.83 ppm. <sup>13</sup>C NMR (150 MHz, methanol- $d_4$ ):  $\delta = 152.60, 143.84, 142.34, 142.00, 141.68, 141.54,$ 139.80, 138.69, 132.38, 131.31, 130.18, 129.86, 129.39, 129.12, 128.87, 128.28, 127.04, 62.58 ppm. MS (FAB) m/z 372 [M+H]<sup>+</sup>. HRMS (ESI): m/z calcd for C<sub>22</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub> 372.1342  $[M+H]^+$ ; found 372.1346, calcd for  $C_{22}H_{17}N_3NaO_3$  394.1162 [*M*+Na]<sup>+</sup>; found 394.1159.  $C_{22}H_{17}N_3O_3$ ·3.2H<sub>2</sub>O (429.04): C 61.59, H 5.50, N 9.79; found C 61.70, H 5.45, N 9.57.

#### **Resolution of Rac-2**

The optical resolution of *rac*-**2** was performed by a high-performance liquid chromatography (HPLC) system consisting of a JASCO PU-2080 plus intelligent HPLC pump, a DG-2080-53 3-Line-Degasser, a CO-2060 plus intelligent column thermostat, a UV-2075 plus intelligent UV/VIS detector, and a CD-2095-K1 plus chiral detector. An HPLC separation was performed by using Chiralcel OD (4.6 or 10 mm  $\phi \times 25$  cm) under the conditions described in the captions of Figures (See below). Fraction 1; [CD(-)281]-**2** CD (hexane-ethanol (1:1 v/v))  $\lambda_{ext}$  333 nm ( $\Delta \epsilon$  -0.2), 306 (+0.9), 281 (-2.7), 264 (+1.2), 244 (-0.7). Fraction 2; [CD(+)283]-**2** 

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CD (hexane-ethanol (1:1 v/v))  $\lambda_{ext}$  331 nm ( $\Delta \epsilon$  + 0.1), 306 (-1.0), 283 (+3.0), 265 (-2.4), 244 (+0.5).

# **COMPUTATIONAL METHODS**

All calculations were performed either on a Linux computer or on the grid server at the Media Information Center of Hiroshima University. Conformational analysis was performed by CONFLEX5 with the MMFF94S<sup>30–33</sup> force field, in which starting structures selected from a set within 50 kcal mol<sup>-1</sup> were converged by applying systematic structural deviations.<sup>34,35</sup>

DFT calculations were run with the Gaussian 03 program (Revision C.02). Geometry optimization of the 12 conformers found by MMFF94S was performed at the B3LYP/631G(d) level.<sup>36,37</sup> For each input structure thus obtained, the first 32 excited states were computed with TDB3LYP/TZVP.<sup>36,38,39</sup> For the conformers that contributed to a greater extent to the average UV-Vis/CD spectra, we verified that all the 32 computed transitions involve virtual orbitals with negative eigenvalues and have energies (within 5.21–5.58 eV) well below the computed ionization potential (5.9–6.1 eV).<sup>40</sup> All rotational strengths (dipole length gauge formulation) obtained from the calculations were converted into Gaussian-type curves adopting a 20-nm band-width value  $\sigma$ , and summed to afford the calculated CD curve for each conformer (see Supporting Information).

## **RESULTS AND DISCUSSION**

The target tris(pyridine *N*-oxide) *rac*-**2** was obtained by oxidation of *rac*-**1** with MCPBA in excellent yield (see Scheme 1) as colorless, hygroscopic solid. (We adopted some modification to the synthetic procedure of *rac*-**1** as described in Ref 25. See Supporting Information.) The <sup>1</sup>H NMR chemical shifts of *rac*-**2** are on the whole observed at higher field than the corresponding ones of *rac*-**1**. In particular, the high field shifts of the *ortho*- and *para*-protons with respect to the *N*-oxide groups are relatively large. These high field shifts are also observed in the parent pyridine *N*-oxide and ascribed to



**Fig. 1.** ORTEP drawing of tris(pyridine *N*-oxide *rac*-**2** (50% probability). Crystal data for rac-2: Molecular formula C22H17N3O3, M = 371.39, triclinic, space group P—1 (No. 2), a = 7.2706(10) Å, b = 9.1391(14) Å, c = 14.682(2) Å,  $\alpha = 78.731(4)^{\circ}$ ,  $\beta = 77.960(4)^{\circ}$ ,  $\gamma = 63.316(4)^{\circ}$ , V = 846.7(2) Å3, Z = 2,  $D_c = 1.457$  g cm<sup>-3</sup>, T = 200 K, total reflections collected 8438, unique reflections = 3865 ( $R_{\rm int} = 0.033$ ), final R1 = 0.0649 ( $R_{\rm w} = 0.2306$  for all data) for 2399 reflections ( $1 > 2\sigma(1)$ ), GOF = 1.105. The structure was solved by direct method and refined by full-matrix least squares by using the SHELXL-97 program. CCDC-790313 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via ccdc.cam.ac.uk/data\_request.cif.



**Fig. 2.** Chromatograms for the optical resolution of *rac*-**2**. Top: UV detection ( $\lambda = 275$  nm). Bottom: CD detection ( $\lambda = 275$  nm). Column: Chiralcel OD (diameter; 4.6 mm), eluent: hexane/ethanol = 1:1 (v/v), flow rate: 1.0 mL min<sup>-1</sup>, temperature: 35°C. After five cycles, the two enantiomers were well-resolved.

electron-donating effect of the *N*-oxide group toward the ring. The <sup>13</sup>C NMR chemical shift of the central carbon in *rac*-**2** is observed at  $\delta$  60.83 ppm (in CDCl<sub>3</sub>), slightly higher field than that of *rac*-**1** ( $\delta$  64.73 ppm in CDCl<sub>3</sub>). A similar high field shift is observed in the central carbon in tetra-



**Fig. 3.** Top: UV spectrum of *rac*-**2** in hexane/ethanol (1:1 v/v). Bottom: CD spectra of the enantiomeric pair of **2** in hexane/ethanol (1:1 v/v). The curves of the first and second eluted fractions are shown by solid and dotted lines, respectively.

kis(2-pyridyl)methane ( $\delta$  72.36 ppm) by oxidation to the corresponding tetra(pyridine *N*-oxide) ( $\delta$  59.63 ppm).<sup>41</sup> Full assignment of the <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts in methanol-*d*<sub>3</sub> was achieved by the acquisition of HMQC and HMBC spectra (see Supporting Information).

TABLE 1. Calculated stability of 12 comformers of (R)-2 by DFT method (B3LYP/6-31G(d) level)

Stability order	Code <sup>a</sup>	Optimized energy (Hartree)	Relative energy (kcal $mol^{-1}$ )	Population at 298 K (%)
1	conf_01	-1238.2892945	0.0000	26.6
2	conf_02	-1238.2887409	0.3474	14.8
3	conf_03	-1238.2886799	0.3857	13.8
4	conf_04	-1238.2879730	0.8292	8.9
5	conf_11	-1238.2879256	0.8590	6.2
6	conf_10	-1238.2878397	0.9129	5.7
7	conf_09	-1238.2878002	0.9376	5.5
8	conf_07	-1238.2877843	0.9477	5.4
9	conf_08	-1238.2876458	1.0346	4.6
10	conf_06	-1238.2873230	1.2371	3.3
11	conf_12	-1238.2871734	1.3310	2.8
12	conf_05	-1238.2870424	1.4132	2.4

<sup>a</sup>The code name "conf\_xx" is based on the order of appearance in the CONFLEX search using MMFF94S.



**Fig. 4.** Boltzmann-weighted average of calculated CD curves for (R)-2 at B3LYP/TZVP level (dotted line) and experimental CD spectrum for the second-eluted enantiomer [CD(+)283]-2 (solid line).

Single crystals of rac-2 were obtained from a solution in methanol by vapor diffusion with ether. The molecular structure of *rac-2* in the crystal (Fig. 1) was in good correlation with the most stable conformation of 2 calculated by the DFT method (vide infra). It is apparent from the space group *P*–1 that **2** crystallizes as a racemic compound; each crystal is composed of the same amounts of (R)- and (S)-enantiomers. Interestingly, there were several short contacts between adjacent molecules causing a mutual arrangement which cancels the molecular dipole moments. Heterochiral pairs are held together by two appreciable C-H-O interactions<sup>42,43</sup>  $(C9-H6...O3 3.289(5) \text{ Å}, \angle C9-H6-O3 150.7(2)^{\circ})$ . A further C-H…O interaction (C6-H4…O2 3.449(4) Å, ∠C6-H4-O2  $166.8(2)^{\circ}$ ) is observed between homochiral pairs. There is a strong C…C contact (C6…C6i 3.122(5) Å, symmetry code: i = -x + 1, -y, -z + 1), which would be the reason for the cancellation of the dipole moments of 1-oxo-pyridin-2-yl groups.



**Fig. 5.** Chromatogram for the analysis of optically pure **2** obtained by the oxidation of the optically pure **1** (first-eluted fraction). Detection: CD at 275 nm, Column: Chiralcel OD (diameter 10 mm), flow rate: 3.0 mL min<sup>-1</sup>, eluent: hexane/ethanol = 1:1 (v/v), temperature  $35^{\circ}$ C.

The enantiomers of **2** were successfully separated by chiral HPLC under conditions similar to the resolution of *rac*-1 (Fig. 2). We expected that the resolution of *rac*-**2** might be easier than those of *rac*-**1** as the differences among the four aryl groups are increased by oxidation. However, recycling was again needed for the optical resolution of *rac*-**2**. The CD spectra of the two fractions in *n*-hexane–ethanol (1:1 v/v) show the typical mirror-image relationship for a pair of enantiomers (Fig. 3). As expected, the shape of CD spectra of **2** was quite different from those of  $\mathbf{1}^{25}$  because of the change in the electronic structure due to the oxidation.

To determine the absolute configuration of 2, we calculated the electronic CD curve of (R)-2 by a quantum-mechanical method for comparison with the experimental ones.44-48 As was observed for (R)-1, the 12 stable conformers, which had been expected considering the three orientations for the phenyl group and two distinct directions for both 1-oxopyridin-2-yl and 3-yl groups, were all obtained. They were subjected to optimization with the density functional theory (DFT) method at the B3LYP/6-31G(d) level, which also afforded relative internal energies used to estimate the Boltzmann populations at 298 K (Table 1). The incentive to oxidation of **1** was originally to alter the molecular polarity to induce crystallization and to reduce the number of stable conformations, and it resulted in a more biased population of all 12 conformers (The population of the most stable conformer of **1** and **2** were 14.8 and 26.6%, respectively). The twelve calculated CD curves, where the rotational strengths were converted to Gaussian curves with a  $\sigma$  value of 20 nm (equivalent to 2900 cm<sup>-1</sup> at 250 nm, see Supporting Information), were Boltzmann-weighted and summed to afford the theoretical CD curve for (R)-2 (Fig. 4). The calculated average spectrum was in good agreement, in terms of sign, position and relative intensity of bands, with the experimental CD recorded for the second eluted enantiomer of 2. Consequently, we could determine the absolute configuration of 2 as (R)-[CD(+)283]-2.

This assignment of absolute configuration was further confirmed by the oxidation of a sample of enantiopure **1**. Thus, 6.3 mg of (*R*)-**1** (first-eluted, configuration assigned by TDDFT method)<sup>25</sup> were converted to (*R*)-**2** (9.1 mg, > 99%). No racemization occurred during the oxidation according to a chiral HPLC analysis (Fig. 5). The retention time (confirmed using the same conditions as described in Fig. 1) and the CD sign of the product were comparable with those of the second-eluted one, which was finally confirmed by its



Fig. 6. Molecular structure of (R)-[CD(+)283]-2.

CD spectrum. It is remarkable that upon oxidation of **1** a reversal of HPLC elution order is observed using identical conditions for the enantioseparation.

# CONCLUSIONS

In summary, we have synthesized tris(pyridine N-oxide) 2, a novel chiral pyridine N-oxide derivative. The compound was resolved by chiral HPLC and characterized by CD spectroscopy. The second-eluted enantiomer [CD(+)283]-2 was determined to have (R)-configuration by the comparison of the theoretical CD curve with the experimental CD spectra (Fig. 6), which was further supported by chemical correlation with (R)-1. The absolute configuration assignments of 1 and 2, based on two independent CD calculations, reinforce each other. The X-ray analysis of racemic crystal of 2 unambiguously revealed the positions of the nitrogen atoms by the "marking" with oxygen atoms. We are now planning to isolate a single crystal of enantiopure 2 to ultimately determine the absolute configuration by X-ray crystallographic analysis and to investigate the potentially interesting nonlinear optical and dielectric properties. In the case that the absolute configuration could not be determined by X-ray crystallographic analysis because of meaningless Flack parameter,<sup>49</sup> we will record the solid-state CD spectrum of the microcrystalline enantiopure 2 and compare it with TDDFT calculation on the X-ray structure.<sup>47</sup> We are also investigating new chiral molecules having tetraarylmethane framework.

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