Absolute Configuration of 8,8'-Dialkyl-1,1'-Biisoquinoline

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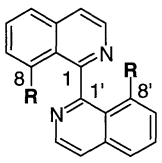
Absolute configurations of 1,1'-biisoquinoline derivatives, in which a series of alkyl groups are introduced at the 8- and 8'-positions, have been determined by using two kinds of well-established methods.

Optical activity based on the high barrier to rotation about σ-bond is designated as "atropisomerism",[1] that is exemplified by a wide range of biaryl compounds both natural and synthetic. One of the important factor making such molecules dissymmetric is substituents adjacent to the rotational axes, and the steric size, shape, and hybridization exert a large influence upon the optical stability of the molecules.[2,3] For instance, 1,1'-biisoquinoline (**1a**) shows very facile racemization due to the small transannular steric hindrance between H-8 (8') and N-2' (2), and therefore, the optical resolution is known to be substantially impossible.[4] By contrast, the *N,N'*-dioxide derivative retains more steric hindrance between the relevant atoms enough to be resolved into both enantiomers.[5] Successful enhancement of the optical stability has been also achieved independently by us[6] and Chelucci[7] with the aid of two methyl groups introduced at the 8- and 8'-positions. Although the optical stability increased in comparison with that of the parent compound **1a**, however, the dimethyl derivative **1b** is still subjected to the gradual racemization process at ambient temperature probably due to the small contribution of the nitrogen lone pairs to the rotational resistance. This foregoing finding intended us to prepare biisoquinolines **1c—e** with a series of alkyl substituents at the 8,8'-positions. During the course of the study on their chemical and physical properties, we succeeded to determine the absolute configurations, which are described in the present communication.



1a (**R** = H)
1b (**R** = Me)
1c (**R** = Et)
1d (**R** = Pr^i)
1e (**R** = Bu^t)

Syntheses of **1c**[8] and **1d**[8] were accomplished in nine steps from the corresponding *o*-alkylbenzaldehydes via the same procedure as that described for **1b**.[6] Despite a great deal of effort, **1e** was not obtained because *tert*-butyl groups were too bulky to incorporate them into the *peri*-positions of 1,1'-biisoquinoline framework.[9] Enantiomeric enrichment of **1b—d** was performed by two kinds of well-known methods, *i.e.*, (1) high performance liquid chromatography (HPLC) equipped with a chiral stationary phase column and (2) optical resolution through transforming to a diastereomeric salt by using a chiral binuclear palladium complex which was reported by Dai[10] and Chelucci.[7] All the biisoquinolines were resolved into both enantiomers and isolated as active forms of 68—98% ee purities. This incomplete enantiomeric resolution was caused by the experimental difficulties mainly due to the moderately facile racemization of **1b—d**.[11]

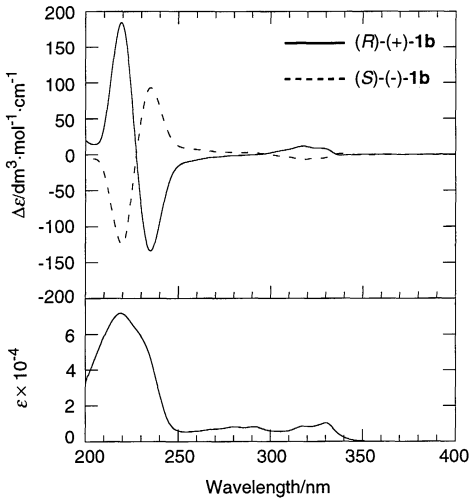


Figure 1. CD (upper panel) and UV-vis (lower panel) spectra of biisoquinoline **1b** in ethanol. Enantiomeric excesses of the samples were 78% ee for (*R*)-(+)-**1b** and 68% ee for (*S*)-(-)-**1b**.

The absolute configurations of a series of biisoquinolines **1b—d** were successfully determined by applying exciton chirality method.[12] Almost the same CD and UV-vis spectra were obtained for the opticaly active **1b—d**, and those of **1b** are shown in Figure 1 as a typical example. Transition moments along the long axes of the isoquinoline rings, which appeared as intense absorption at 219 nm in the electronic spectrum, interact with each other to give the exciton-split CD spectra. Cotton effects for (-)-**1b** were observed positively at 235 nm and negatively at 220 nm, indicating positive exciton chirality. By contrast, the mirror image was obtained for (+)-**1b** although the intensities were slightly different owing to their unequal optical purities. Cotton effect is known to strongly depend on the dihedral angle between chromophores; in analogous 1,1'-binaphthyl systems positive and negative signs are exchanged at dihedral angle of 110°.[13] As can be seen from Figure 2, X-ray structural elucidation revealed almost perpendicular conformations for **1b** and **1c**, of which dihedral angles between two isoquinoline rings were found to be 102° for **1b** and 93.8° for **1c**. Despite a great deal of effort, a single crystal of **1d** appropriate for X-ray crystallography was not obtained. However, AM1-optimized[14] geometry of **1d** retained a dihedral angle of 73.3°, and those of **1b** and **1c** were estimated to be 90.2° and 88.6°, respectively. The X-ray and AM1 results showed slightly different structures, but the dihedral angles for each compounds were found to be less than 110°. Hence, exciton chirality method should be applicable to **1b—d** in a similar way as that for 1,1'-binaphthyl systems, and led to a conclusive assignment that all the (+)-forms corresponded to

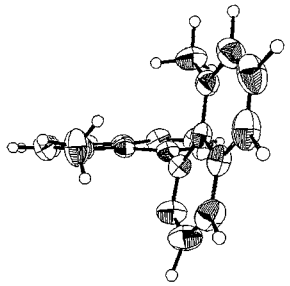


Figure 2. ORTEP drawing of 8,8'-dimethyl derivative **1b**.

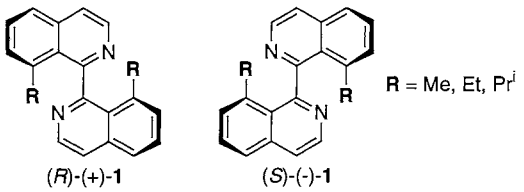


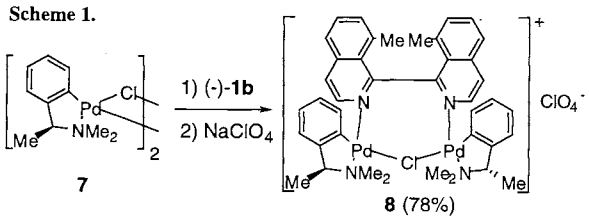
Figure 3. Absolute configuration of 8,8'-dialkyl-1,1'-biisoquinoline.

(*R*)-configurations and (-)-forms to (*S*)-ones as shown in Figure 3.

In order to prove the above assignment, we carried out ^{1}H-NMR measurement of diastereomeric complex **8** which was prepared from (-)-**1b** of 98% ee and a chiral binuclear palladium complex **7**[15] according to Scheme 1. Though **1b** was supposed to racemize partly during the reaction, the initial (-)-enrichment was reflected on the resultant diastereomeric mixture of the palladium complex **8**, of which NMR showed two pairs of all relevant signals in a 19:1 ratio. In particular, the methyl substituents within the phenylethyl groups showed a remarkable difference in the chemical shift; two doublets were observed at 0.38 and 1.03 ppm in a 19:1 ratio. In order to understand the difference in the chemical shift, ZINDO calculations[16] were carried out on the diastereomeric complexes **8**-1 and **8**-2 that were derived from (*R*)- and (*S*)-**1b**, respectively. As can be seen from Figure 4, the methyl groups of **8**-2 were situated just above the aromatic isoquinoline rings, while those of **8**-1 were located 6 Å apart from the same rings. This means that the presence of ring current effect from the isoquinoline rings gave rise to the difference in the chemical shift observed in **8**-1 and **8**-2. Hence, a doublet of high intensity at 0.38 ppm was assigned to the methyl groups of **8**-2, and another doublet at 1.03 ppm to those of **8**-1. Therefore, the starting material (-)-**1b** was concluded to adopt the (*S*)-configuration. As a result, two kinds of determination methods mentioned above led to the same absolute configurations for **1b** as shown in Figure 3.

In summary, we have succeeded in the determination of the absolute configurations of a series of 8,8'-dialkyl-1,1'-biisoquinolines. Further investigations on the physical and chemical properties are in progress and the results will be reported in detail elsewhere.

Scheme 1.



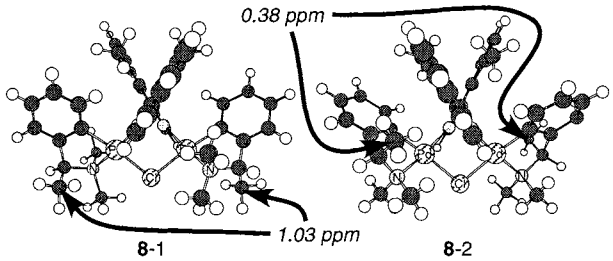


Figure 4. Three-dimensional structures of diastereomeric binuclear palladium complexes **8**-1 and **8**-2 incorporating (*R*)- and (*S*)-**1b**, respectively. Depicted arrows indicate the methyl groups which showed large difference in the chemical shift.

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Reference and Notes

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8 **1c**: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J=7.3 Hz, 6H, CH_2CH_3), 2.14 (m, 2H, CH_2CH_3), 2.27 (m, 2H, CH_2CH_3), 7.43 (d, J=7.1 Hz, 2H, 7-H), 7.65 (dd, J=7.1, 7.8 Hz, 2H, 6-H), 7.74 (d, J=5.6 Hz, 2H, 4-H), 7.79 (d, J=7.8 Hz, 2H, 5-H), 8.52 (d, J=5.6 Hz, 2H, 3-H); MS (EI) *m/z* 312 (M^+); Found: C, 84.75; H, 6.67; N, 8.95%. Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97%. **1d**: ^{1}H NMR($CDCl_3$) δ 0.93 (d, J=6.8 Hz, 6H, CH_3), 1.05 (d, J=6.6 Hz, 6H, CH_3), 2.98 (m, 2H,CH), 7.61 (dd, J=7.1, 1.4 Hz, 2H, 7-H), 7.67 (d, J=5.5 Hz, 2H, 4-H), 7.71 (dd, J=8.1, 7.1 Hz, 2H, 6-H), 7.76 (dd, J=8.1, 1.4 Hz, 2H, 5-H), 8.93 (d, J=5.5, 2H, 3-H); MS (EI) *m/z* 340 (M^+); Found; C, 84.65; H, 7.20; N, 8.04%. Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.10; N, 8.23%.
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