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Unexpected racemization behavior of 8,8′-dialkyl-1,1′-biisoquinoline

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Abstract

The racemization behavior of a series of atropisomeric 8,8′-dialkyl-1,1′-biisoquinolines, in which methyl, ethyl, and isopropyl groups are introduced for enhancing the transannular steric hindrance, is reported. Contrary to prior expectations, their configurational stability was inversely proportional to the steric size of the alkyl groups.

1. Introduction

Optical activity due to the high barrier to rotation about a σ-bond is designated as 'atropisomerism',[1] and is exemplified by a wide range of biaryl compounds both natural and synthetic. One of the important factors making such molecules dissymmetric is substituents adjacent to the rotational axes, and the steric size, shape, and hybridization exert a large influence on the configurational stability of the molecules.[2–5] Admittedly, increasing the bulkiness of substituents tends to cause an enhancement of the configurational stability as a result of steric hindrance. For instance, 1,1′-binaphthyl shows slow racemization at ambient temperature (half-life of ca. 10 h),[6,7] whereas the 2,2′-diol or 2,2′-diphosphine derivatives, which act as useful chiral ligands in asymmetric syntheses,[8,9] gives rise to no racemization at corresponding temperatures.

Another illustration of this kind of substituent effect can be seen in 1,1′-biisoquinoline **1a**, which shows quite facile racemization due mainly to the very small transannular steric hindrance between H-8 (8′) and N-2′ (2) (Fig. 1). Indeed, isolation as the optically active form is known to be essentially impossible.[10] In contrast, the *N*,*N*′-dioxide derivative of **1a** retains enough steric hindrance to be resolved into both enantiomers.[11,12] Successful enhancement of the configurational stability has been also achieved independently by us[13,14] and Chelucci et al.[15] with the aid of two methyl groups introduced at the 8-

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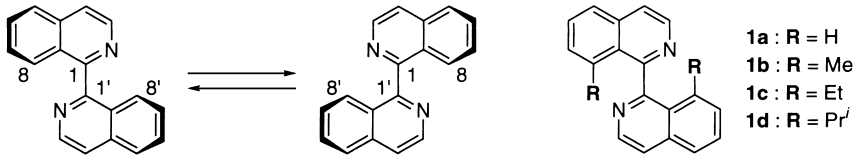

Figure 1.

and 8′-positions; the dimethyl derivative **1b** revealed a half-life of 17 h at 20°C in toluene.[16] However, **1b** is found to undergo gradual racemization at room temperature probably due to the small contribution of the nitrogen lone pairs to the rotational resistance about the pivot bond, although the configurational stability is greatly increased in comparison with that of the parent compound **1a**. This foregoing finding led us to prepare biisoquinolines **1c** and **1d** with bulkier alkyl groups at 8- and 8′-positions and to study how bulky the alkyl groups need to be to freeze the rotation. However, on the contrary, we encountered the unexpected racemization behavior in **1b**–**d** such that the bulkier the alkyl substituent, the lower the configurational stability. In this paper, we wish to report the unexpected reversal of the configurational stability and the racemization mechanism of 1,1′-biisoquinolines **1b**–**d**.

2. Results and discussion

The synthesis and enantiomeric separation of biisoquinolines **1b**–**d** were accomplished according to the previously reported procedures.[13,14] Their racemization rate constants (k) were determined in methanol over the range of 283 to 323 K. Optically active biisoquinolines **1b**–**d** of 52 to 92% ee were used for the kinetic measurements, and the changes in the concentration of both enantiomers were followed by using high performance liquid chromatography (HPLC) equipped with a chiral stationary phase column. Fig. 2 represents a typical example of the concentration changes with time in **1b** at 313 K. The initial enantiomeric excess of 92% gradually decreased to 14% ee after 11 h. Contrary to prior expectations, the bulkier the alkyl substituents, the greater the rate constants. As summarized in Table 1, the rate constants were found to be the largest in **1d** and the smallest in **1b**. Although it is difficult to present a detailed discussion on the decrease in the entropy of activation ($\Delta S^{\ddagger}$) at this moment, the unexpected racemization behavior in **1b**–**d** was clearly reflected in the systematic decrease in the other activation parameters such as the Arrhenius activation energy (E_a), the heat of activation ($\Delta H^{\ddagger}$), and the Gibbs activation energy ($\Delta G^{\ddagger}$); these thermodynamic parameters were inversely proportional to the steric size of the alkyl groups.

In order to understand the unexpected reversal of the sequence in **1b**–**d**, PM3-calculations[17] were carried out for the ground state (GS) and the transition state (TS) during the racemization process, in which a more favorable *anti*-pathway was taken into consideration between the two kinds of possible pathways *syn* and *anti*. Harmonic vibrational frequency calculation gave only one imaginary frequency for each TS structure. The GS and TS geometries of **1b** are shown in Fig. 3 as a typical example. As seen in Fig. 3, the two isoquinoline rings were nearly perpendicular in the GS, but almost coplanar in the TS though both rings were much distorted. The calculated barrier heights ($\Delta\Delta H_f$), that were deduced from the heats of formation in the GS and TS, corresponded almost exactly with the experimental findings as summarized in Tables 1 and 2.

Optically active rotational isomers have sometimes been reported to be more configurationally labile than would be expected from the structures.[2,18] As a good example, Fuji and co-workers[19] recently reported this behavior in 8,8′-disubstituted-1,1′-binaphthyl compounds. Based on X-ray crystallography and theoretical calculations, they concluded that the facile racemization of a compound with a bulkier

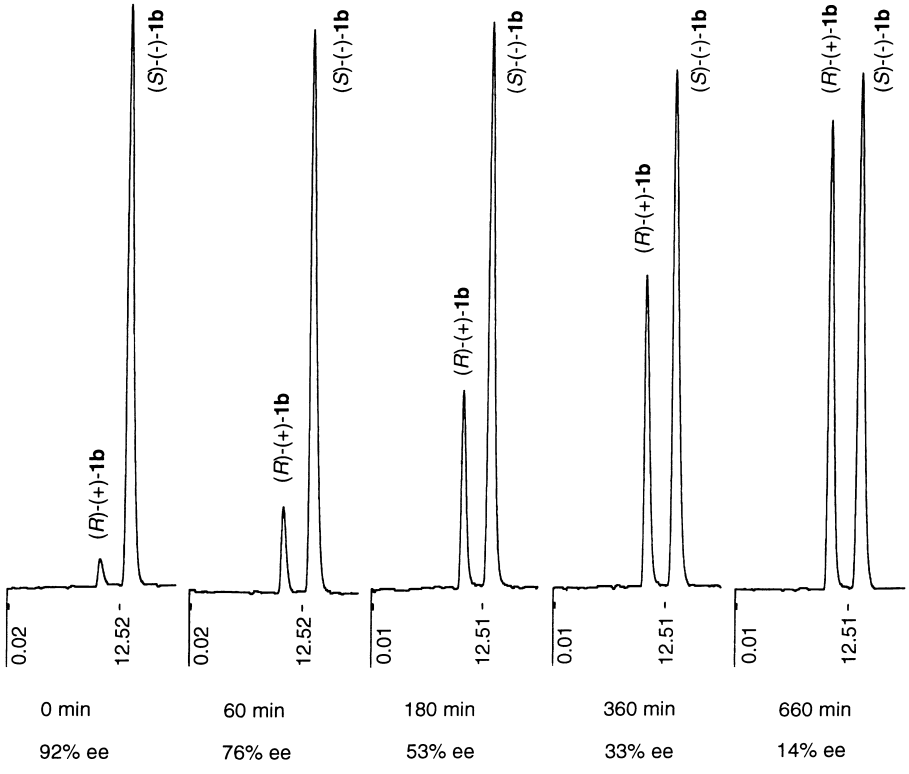

Figure 2. Concentration changes of (*R*)- and (*S*)-**1b** in methanol at 313 K. Column, Chiralcel OD; mobile phase, 30% ethanol–hexane; flow rate, 0.5 ml min^{-1}; λ=280 nm

Table 1
Racemization rate constants at 303 K and activation parameters for racemization in biisoquinolines **1b–d**

Compound	k / sec^{-1}	E_a / kJ·mol^{-1}	$\Delta H^{\ddagger}$ / kJ·mol^{-1}	$\Delta S^{\ddagger}$ / J·mol^{-1}·K^{-1}	$\Delta G^{\ddagger}_{303}$ / kJ·mol^{-1}
1b	5.8×10^{-6}	111	108	11	105
1c	2.2×10^{-5}	105	102	3.2	101
1d	5.3×10^{-5}	95	92	-22	99

substituent was induced by the destabilization of the ground state. On the theoretical side, Schleyer's methodology[20] is helpful to us in examining this possibility. Using the PM3-optimized GS and TS geometries of **1b–d**, their distortional energies were estimated according to the literature method.[20] Fig. 4 schematically represents the procedures for calculating the distortional energies inherent in the biisoquinoline framework. Firstly, the heat of formation was calculated for the 'half' geometry of the biisoquinoline **1b–d** by substituting a hydrogen atom for a unilateral isoquinoline ring; only the newly introduced hydrogen atom at the 1-position was optimized. Secondly, the corresponding partial structure, by contrast, was fully minimized. Thirdly, the distortional energy of the isoquinoline ring was evaluated by subtracting the heat of formation for the fully optimized geometry from that of the partially optimized one. Finally, doubling the resultant answer yielded the rough estimation of the distortional energy inherent in the biisoquinoline framework. The results of the calculations are summarized in Table 2.

What is significant in Table 2 is that the calculated distortional energies in the GS were proportional to

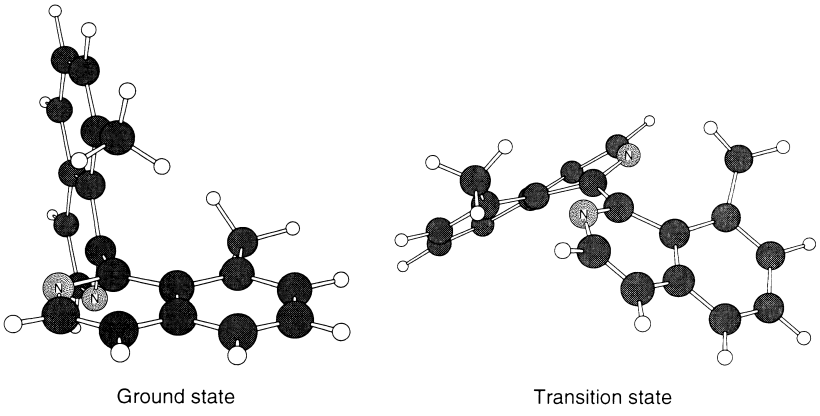

Figure 3. PM3-optimized geometries of the ground and transition states during the racemization process in **1b**

Table 2
PM3-calculated activation barriers for racemization and distortional energies inherent in biisoquinoline frameworks

Compound	$\Delta\Delta H_f$ / kJ·mol^{-1}	Distortional energy / kJ·mol^{-1}	
		Ground state	Transition state
1b	111.6	10.1	94.7
1c	104.9	19.9	89.4
1d	97.9	25.6	94.7

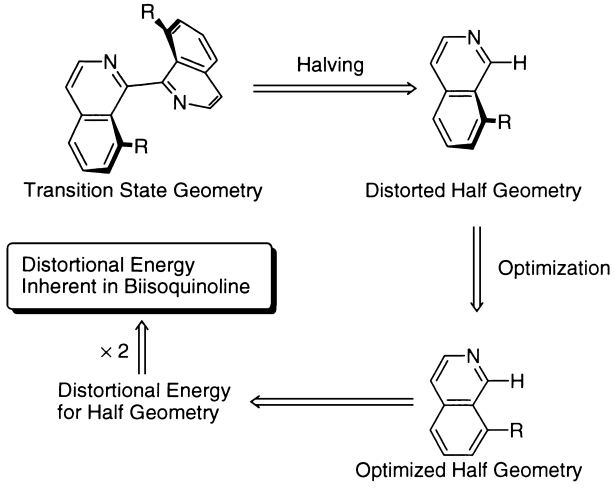

Figure 4. Evaluation procedures of the distortional energy inherent in the 1,1′-biisoquinoline framework. Only the transition state is used here to explain the procedures

the steric size of the alkyl groups, whereas this was not the case for the TS. The Corey–Pauling–Koltun molecular model suggests that a small space exists around the nitrogen lone pairs at 2,2′-positions which is large enough to just accommodate the alkyl groups in the TS, where the alkyl substituents lie in close proximity to the nitrogen lone pairs. This might result in little influence with gain in the steric hindrance, and therefore, the distortional energies in the TS should become almost constant irrespective of the alkyl

groups, while those in the GS increased in proportion to the steric size of the substituents. The systematic increase in the distortional energies in the GS is evident from the X-ray structural elucidation,[14] by which bond angles of N2–C1–C1′ were found to be reduced to 112.1° for **1b** and 110.9° for **1c** due to the steric interaction between the isoquinoline ring and the alkyl group at *peri*-positions. Despite a great deal of effort, a single crystal of **1d** appropriate for X-ray crystallography could not be obtained, but the PM3-optimized geometries of **1b**–**d** showed a similar decrease in the relevant angles that were estimated to be 112.7° for **1b**, 112.2° for **1c**, and 111.3° for **1d**. Here, it is worth noting that the increase in the distortional energies in the GS (+9.8 kJ mol^{-1} for **1b** and **1c**, and +15.5 kJ mol^{-1} for **1b** and **1d**) is approximately reflected in the decrease in the PM3-calculated barrier heights (−6.7 and −13.7 kJ mol^{-1}, respectively), as can be seen from Tables 1 and 2. Equally important, the calculated relative values are in good agreement with the experimental findings such as E_a and $\Delta H^{\ddagger}$ (−6 kJ mol^{-1} for **1b** and **1c**, and −16 kJ mol^{-1} for **1b** and **1d**), although the distortional energies were roughly estimated. This moderate coincidence between the experimental and calculated values means that the unexpected racemization observed in **1b**–**d** would be caused predominantly by the destabilization in the GS. However, one extensive experiment[21] has so far been reported on the transition state stabilization which acts as an alternative mechanism to lower the racemization barrier. The facile racemization via the unfavorable *syn*-pathway in the chiral ruthenium(II) complex of the parent compound **1a** is accounted for by the metal-assisted favorable coordination in the TS,[21] but this kind of special interaction is completely eliminated in the present system. Further work on the non-distortional contribution may be needed to fully understand the mechanism, nonetheless the present result clearly demonstrates that the destabilization in the GS would be the most plausible mechanism for the unexpected racemization behavior observed in biisoquinolines **1b**–**d**.

3. Summary

The racemization behavior of the 8,8′-dialkyl-1,1′-biisoquinolines was found to be inversely proportional to the steric size of the alkyl groups. On the basis of PM3 and X-ray analyses, the unexpected racemization was ascribed to the destabilization of the ground state. Although the detailed mechanism is being investigated in our laboratory, the present work affords one example that shows the curious relationship between the molecular structure and the atropisomerism.

4. Experimental

Mps were determined on a Yanako MP-500D and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a JEOL EX-400 spectrometer for samples in $CDCl_3$ solution with tetramethylsilane as an internal standard. IR and MS were recorded on JEOL FT-IR-230 and JEOL JMS DX-300 spectrometers, respectively. Elemental analyses were performed on a Yanako MT-5. Optical rotations were measured in 1 dm path length cell on a JASCO DIP-370 polarimeter. CD spectra were measured on a JEOL J-720 spectrometer in 1 cm path length cell at concentrations of 1.96×10^{-5}–2.28×10^{-5} mol dm^{-3} in ethanol at 10°C. HPLC analyses were carried out with a JASCO instrument equipped with an 870-UV detector, an 880-PU pump, and a Chromatocorder 12 recorder. Shiseido Ceramospher Chiral RU-1 and Daicel Chiralcel OD were used as chiral stationary phase columns. All chemicals were reagent grade and were used without further purification. Organic solvents were purified by standard procedures. Merck Kieselgel #7734 was used for column chromatography. Semiempirical calculations based on PM3[17]

method were carried out using the MOPAC97 program package implemented in WinMOPAC version 2.0, Fujitsu Limited, 1998.

4.1. 8,8′-Dimethyl-1,1′-biisoquinoline **1b**

Zinc powder (25 mg, 0.37 mmol) was added to a stirred solution of nickel(II) chloride hexahydrate (90 mg, 0.37 mmol) and triphenylphosphine (390 mg, 1.5 mmol) in *N*,*N*-dimethylformamide (6 ml) under argon atmosphere at 50°C. After stirring for 1 h, 1-chloro-8-methylisoquinoline[13] (66 mg, 0.37 mmol) was added. After 5 h, the mixture was poured onto dilute 28% aqueous ammonia and extracted with dichloromethane. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated. Column chromatography on silica gel with hexane:ethyl acetate:methanol (5:4:1 v/v) as an eluent gave crude **1b**, which was recrystallized from methanol to yield **1b** (32 mg, 81%) as colorless prisms, mp 210.0–213.5°C (lit.[15] 207–210°C); MS (EI) m/z 284 (M^+); IR (Nujol) 1600, 1580, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (s, 6H, CH_3), 7.34 (dd, J=6.8, 1.0 Hz, 2H, 7-H), 7.58 (dd, J=6.8, 7.8 Hz, 2H, 6-H), 7.75 (d, J=4.9 Hz, 2H, 4-H), 7.79 (dd, J=1.0, 7.8 Hz, 2H, 5-H), 8.55 (d, J=4.9 Hz, 2H, 3-H). Anal. calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.65; H, 5.67; N, 9.76.

4.2. 8,8′-Diethyl-1,1′-biisoquinoline **1c**

The title compound was prepared in the same manner as that described for **1b**. Yield: 53%. Colorless needles from ethyl acetate–hexane, mp 125.5–126.0°C; MS (EI) m/z 312 (M^+); IR (KBr) 1613, 1594, 1557 cm^{-1}; ^1H 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, 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); ^{13}C NMR ($CDCl_3$) δ 15.4, 28.2, 122.4, 126.6, 127.2, 128.9, 130.7, 138.9, 141.2, 142.3, 161.0. Anal. calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.75; H, 6.67; N, 8.95.

4.3. 8,8′-Diisopropyl-1,1′-biisoquinoline **1d**

The title compound was prepared in 35% yield by following the same procedure described above (for **1b**). Colorless prisms from ethyl acetate, mp 210.8–211.8°C; MS (EI) m/z 340 (M^+); IR (KBr) 1606, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.05 (d, J=6.6 Hz, 6H, $CH(CH_3)_2$), 2.98 (m, 2H, $CH(CH_3)_2$), 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 Hz, 2H, 3-H); ^{13}C NMR ($CDCl_3$) δ 24.8, 25.8, 31.3, 121.9, 126.3, 127.4, 130.9, 139.0, 141.0, 148.4, 160.8. Anal. calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.10; N, 8.23. Found: C, 84.65; H, 7.20; N, 8.04.

4.4. Enantiomeric enrichment

Racemic biisoquinolines **1b**–**d** were partly separated to their enantiomers by HPLC equipped with a chiral stationary phase column (λ 280 nm). Ceramospher Chiral RU-1 (1.0 ml·min^{-1}) was used for the preparative separation of **1b** and **1d** with methanol as eluent, and Chiralcel OD (0.5 ml·min^{-1}) and 10% ethanol–hexane were used for **1c**. The retention times were 25 and 34 min for **1b**, 18 and 24 min for **1c**, and 10 and 12 min for **1d**. The first eluted enantiomers in **1b** and **1d** were (*R*)-forms, while that of **1c** was (*S*). (*R*)-(+)-**1b** (78% ee): $[\alpha]_D^{23}$ +60 (*c* 0.10, $CHCl_3$); CD (EtOH) $[\Delta\varepsilon]_{318}$ +11.4, $[\Delta\varepsilon]_{235}$ −134, $[\Delta\varepsilon]_{219}$ +184. (*S*)-(−)-**1b** (68% ee): $[\alpha]_D^{24}$ −53 (*c* 0.10, $CHCl_3$); CD (EtOH) $[\Delta\varepsilon]_{318}$ −6.9, $[\Delta\epsilon]_{235}$ +92.9,

$[\Delta\epsilon]_{220}$ −125. (*R*)-(+)-**1c** (86% ee): $[\alpha]_D^{26}$ +58 (*c* 0.25, $CHCl_3$); CD (EtOH) $[\Delta\varepsilon]_{319}$ +11.5, $[\Delta\varepsilon]_{235}$ −135, $[\Delta\varepsilon]_{220}$ +190. (*S*)-(−)-**1c** (80.7% ee): $[\alpha]_D^{26}$ −55 (*c* 0.51, $CHCl_3$); CD (EtOH) $[\Delta\varepsilon]_{319}$ −9.85, $[\Delta\varepsilon]_{235}$ +141, $[\Delta\varepsilon]_{220}$ −186. (*R*)-(+)-**1d** (82% ee): $[\alpha]_D^{24}$ +67 (*c* 0.10, $CHCl_3$); CD (EtOH) $[\Delta\varepsilon]_{321}$ +9.6, $[\Delta\varepsilon]_{238}$ −72.1, $[\Delta\varepsilon]_{222}$ +162. (*S*)-(−)-**1d** (71% ee): $[\alpha]_D^{25}$ −56 (*c* 0.10, $CHCl_3$); CD (EtOH) $[\Delta\varepsilon]_{321}$ −10.4, $[\Delta\varepsilon]_{238}$ +92.6, $[\Delta\varepsilon]_{222}$ −188.

4.5. Kinetic measurement

A solution of biisoquinolines **1b**–**d** in methanol (7.9–9.4 mol dm^{-3}) was heated or cooled at a given temperature in a thermostat-controlled water bath. Uncertainty of temperature was within ±0.1°C. Initial enantiomeric excesses were 92% ee for (*S*)-(−)-**1b**, 82% ee for (*R*)-(+)-**1c** and 52% ee for (*R*)-(+)-**1d**. The changes in the concentration of both enantiomers were followed at appropriate intervals by using HPLC (Chiralcel OD, 0.5 ml min^{-1}, λ 280 nm). The mobile phase for **1b**, **1c**, and **1d** was 30, 20, and 10% ethanol–hexane, respectively. First-order rate constants were obtained by analyzing 10–20 concentration data for each sample, and the correlation factors were >0.998. The racemization rate constants *k* were as follows. **1b**: 5.8×10^{-6} s^{-1} at 303 K, 2.4×10^{-5} s^{-1} at 313 K, and 9.1×10^{-5} s^{-1} at 323 K. **1c**: 2.2×10^{-5} s^{-1} at 303 K and 8.3×10^{-5} s^{-1} at 313 K. **1d**: 3.7×10^{-6} s^{-1} at 283 K, 1.5×10^{-5} s^{-1} at 293 K, and 5.3×10^{-5} s^{-1} at 303 K.

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