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Resolution, Enantiomerization Kinetics, and Chiroptical Properties of 7,7′-Dihydroxy-8,8′-biquinolyl

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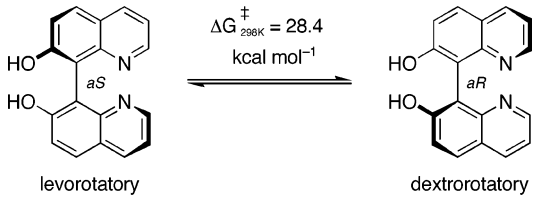

(±)-7,7′-Dihydroxy-8,8′-biquinolyl (**6**) was resolved into its enantiomorphic atropisomers via reverse phase (C18) chromatographic separation of epimeric bismenthyl carbonates, (−)-*lk*-**9** and (+)-*ul*-**9**, derived from **6** and (+)-menthyl chloroformate. The faster eluting diastereoisomer, (−)-*lk*-**9**, was revealed to possess an (*aS*)-configurated biaryl axis by X-ray crystallographic analysis. Saponification of the separated bismenthyl carbonates gave enantioenriched samples of biquinolyl **6**, and absolute stereochemical configurations were assigned to the two optical isomers as (−)-(*aS*)-**6** and (+)-(*aR*)-**6** by correlation with their respective progenitors, (−)-*lk*-**9** and (+)-*ul*-**9**. First-order rate constants for the enantiomerization of **6** in water were obtained over the temperature range 316−366 K, and activation parameters were determined as $\Delta H^{\ddagger} = 34.0$ kcal mol^{-1} and $\Delta S^{\ddagger} = 18.7$ cal mol^{-1} K^{-1} by Eyring plot analysis. A low level (AM1) computational study of the rotational dynamics of **6** showed excellent agreement with kinetic experimental data and suggested that enantiomerization occurs preferentially via a syn pathway. In common with (−)-(*aS*)-1,1′-bi-2-naphthol (BINOL), (−)-(*aS*)-**6** showed positive exciton chirality in its electronic circular dichroism (CD) spectrum and gave a characteristic couplet composed of a positive maximum Cotton effect at 250 nm and a negative minimum at 234 nm ($\Delta\Delta\epsilon = +40$ M^{-1} cm^{-1} at 64% ee).

Introduction

One of the defining properties for any given biaryl molecule is the relative ease with which rotation may occur about the interannular bond.[1] Torsional motion about this axis represents one of the few degrees of conformational freedom available to simple biaryl molecules, and the ground-state dihedral angle is an important determinant for many of the physical attributes of such compounds (e.g., molecular recognition phenomena, phase transition temperatures, solubility, chiroptical behavior, etc.). Crucially, the energy barrier associated with full rotation about the internuclear bond determines whether a biaryl molecule may be usefully resolved into configurationally stable enantiomorphic atropisomers.[2] Those biaryl molecules with sufficiently high rotational barriers for successful atropisomer resolution hold a special place in the historical development of the theory of molecular dissymmetry and optical activity.[3] Over recent decades, certain members of this group, and in particular 2,2′-disubstituted 1,1′-binaphthyls (e.g., BINOL and BINAP),[4] have emerged as a privileged class of chiral bidentate ligands capable of delivering superior levels of enantiocontrol in metal-mediated asymmetric synthesis.

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(2) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(3) For a definitive account of optical activity in the biaryl series, see: Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, *30*, 1671.

(4) Overview: (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. BINOL: (b) Pummerer, R.; Prell, E.; Ricche, A. *Chem. Ber.* **1926**, *59*, 2159. (c) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. (d) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. BINAP: (e) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (f) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

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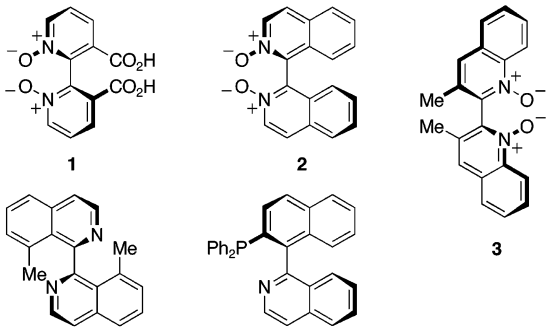

FIGURE 1. Selected axially chiral azacyclic biaryl molecules with resolvable enantiomorphic atropisomers; (*aS*)-configurated enantiomorphs are illustrated. QUINAP = 1-(2′-diphenylphosphino-1′-naphthyl)isoquinoline.

In contrast to the many known carbocyclic biaryl ring systems with robust chirotopic axes, analogous configurationally stable nitrogenous heterobiaryl molecules are comparatively rare (Figure 1). 2,2′-Bipyridyls are arguably the best studied class of azacyclic biaryl molecules; however, the interannular axes of these versatile metal ligands are usually configurationally labile unless at least one of the pyridyl N-atoms is quaternerized (e.g., as an *N*-alkyl pyridinium salt or an *N*-oxide).[5] A majority of the commonly employed chiral 2,2′-bipyridyl ligands are therefore principally dissymmetric due to central and/or planar stereogenic elements rather than by sole virtue of a chirotopic axis.[6] Examples of configurationally stable and purely axially chiral 2,2′-bipyridyls are largely limited to 2,2′-bipyridyl *N*,*N*′-dioxides (e.g., **1**).[7,8] Closely related 2,2′-biquinolyls and 1,1′-biisoquinolyls, which each effectively embed 2,2′-bipyridyl nuclei, also seemingly require *N*-quaternerization to confer useful levels of configurational stability on the molecule. For example, while bis-*N*-oxides **2** and **3** possess high enantiomerization barriers and are easily resolved,[9] 8,8′-dimethyl-1,1′-biisoquinolyl (**4**) was found to racemize with a high-life of only 17 h at 20 °C.[10] The non-C_2-symmetric atropisomeric P,N-ligand QUINAP (**5**), a 1-(naphthal-1-yl)isoquinoline derivative introduced by Brown and co-workers in 1993,[11] lacks *N*-quaternerization and presumably owes it configurational stability to the bulky diphenylphosphino substituent at C2′. QUINAP has emerged as an effective chiral ligand for a wide variety of metal-mediated enantioselective transformations,[12] and a number of analogous P,N-ligand systems have now been developed.[13]

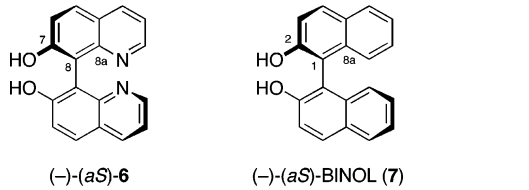

FIGURE 2. 7,7′-Dihydroxy-8,8′-biquinolyl (**6**) and 1,1′-bi-2-naphthol (BINOL, **7**).

Aside from the aforementioned examples (**2**−**4**), few of the large number of possible topologically distinct biquinolyl and biisoquinolyl scaffolds have been studied from an axial chirality standpoint.[14] A priori it is not entirely obvious which of these systems may possess good configurational stability and therefore be of most use in asymmetric synthesis. Nevertheless, in pursuit of new ambifunctional chiral ligand templates with well-defined stereoelectronic properties, we identified 8,8′-biquinol **6** as a promising platform for investigation (Figure 2). In earlier work,[15] we developed optimal methods for the synthesis of this molecule and its 6,6′-disubstituted derivatives in racemic form; however, before moving forward and exploring possible modes of reaction catalysis utilizing these unusual compounds,[16] some study of the interannular conformational mobility of 8,8′-biquinol **6** was clearly required. 7,7′-Dihydroxy-8,8′-biquinolyl (**6**) is an aza-analogue of 1,1′-bi-2-naphthol (BINOL, **7**) and may be expected to retain some of the properties of its better known carbocyclic congener. However, the peri C−H bonds of BINOL, which are largely responsible for the prodigious configurational stability of its enantiomeric atropisomers,[17] are formally replaced by sp^2-hybridized N-atom lone pairs in **6**. The precise effect that this heteroatom placement would have on the configurational stability of **6** versus **7** was unknown at the outset of our studies. Herein, we describe in full our efforts to answer this question and report (a) the resolution of (±)-**6** and assignment of absolute configuration to each optical isomer, (b) the determination of rate constants and associated transition state parameters for the

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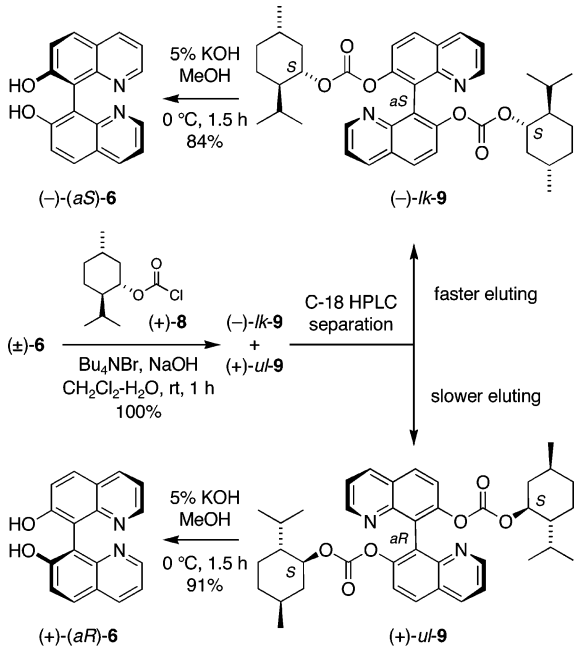
SCHEME 1. Resolution of (±)-7,7′-Dihydroxy-8,8′-biquinolyl (6)



enantiomerization of **6**, and (c) the measurement and interpretation of circular dichroism spectra for **6**.

Results and Discussion

Resolution. Racemic biquinolyl **6** was prepared from 7-hydroxyquinoline according to our previously reported procedure (three steps, 55% overall yield).[15] Initial attempts to resolve this material by fractional crystallization of diastereomeric mixtures of salts/complexes formed from (±)-**6** and various chiral complexation reagents were wholly unsuccessful.[18] Among the many tactics that have been employed for the resolution of BINOL-like molecules, the chromatographic separation of easily prepared diastereomeric bismenthyl carbonate derivatives has proven particularly convenient.[19] Wishing to apply the same approach to the problem at hand, double acylation of (±)-**6** was effected by the agency of excess (+)-menthyl chloroformate (**8**) according to the phase-transfer catalysis method of Wan and co-workers.[19d] This reproducible procedure afforded a 1:1 mixture of epimeric bismenthyl carbonates, (−)-*lk*-**9** and (+)-*ul*-**9**, in quantitative yield (Scheme 1).[20] Following chromatographic separation of the pair of epimers by semipreparative reverse phase HPLC,[21] the structure of the faster eluting isomer, (−)-*lk*-**9**, was determined by X-ray crystallographic analysis (Figure 3). Biquinolyl (−)-*lk*-**9** was so revealed to possess an (*aS*)-configurated chiral axis and seen to exhibit a significantly more transoid solid-state conformational preference than its parent compound **6**.[22] Pleasingly, neither (−)-*lk*-**9** nor (+)-*ul*-**9** showed any sign of axial epimerization after protracted heating in a refluxing solution of toluene (110 °C, 18 h), indicating that each compound has a high level of configurational stability. Removal of chiral auxiliary groups from (−)-*lk*-**9** and (+)-*ul*-**9** was achieved by direct saponification of the alkyl carbonate linkages with methanolic potassium hydroxide and afforded (−)-**6** and (+)-**6**, respectively. Thus, it was readily deduced that the levorotatory form of biquinolyl **6** has (*aS*)-configuration while its dextrorotatory optical isomer is (*aR*)-configurated. Reinstallation of menthyl carbonate units onto samples of freshly prepared enantioenriched 7,7′-dihydroxy-8,8′-biquinolyl (**6**) revealed that closed cycles of saponification and acylation from biscarbonates **9** (i.e., **9** → **6** → **9**) did not occur with complete stereochemical fidelity.[23] Given the rapidity of the double acylation reaction from **6**, the high configurational stability of products *lk*-**9** and *ul*-**9**, and the observed stability of optical rotation values for solutions of **6** in 1 M aqueous sodium hydroxide,[24] loss of stereochemical integrity was attributed to partial racemization during the relatively sluggish saponification step.

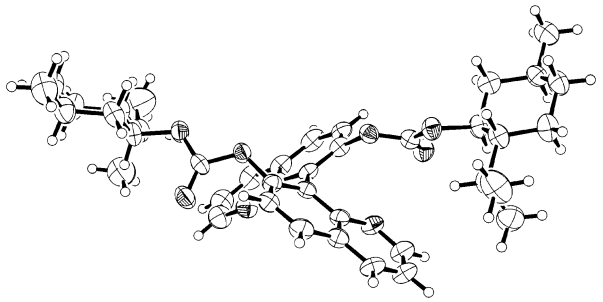


FIGURE 3. ORTEP diagram for (−)-*lk*-**9**. 50% probability ellipsoids are plotted for non-hydrogen atoms.

Enantiomerization Kinetics and Rotational Barrier. With access to enantioenriched samples of 7,7′-dihydroxy-8,8′-biquinolyl (**6**) secured, kinetic experiments were conducted to ascertain its rate of enantiomerization in water as a function of

(18) The following potential resolving agents for (±)-**6** were surveyed unsuccessfully: (+)-camphor sulfonic acid, CuCl/(−)-sparteine complex, and benzylcinchonidinium chloride. For recent applications of the latter two agents in resolution work, see: (a) Zhang, Y.; Yeung, S.-M.; Wu, H.; Heller, D. P.; Wu, C.; Wulff, W. D. *Org. Lett.* **2003**, *5*, 1813. (b) Hu, Q.; Vitharana, D.; Pu, L. *Tetrahedron: Asymmetry* **1995**, *6*, 2123. (c) Wang, Y.; Sun, J.; Ding, K. *Tetrahedron* **2000**, *56*, 4447.

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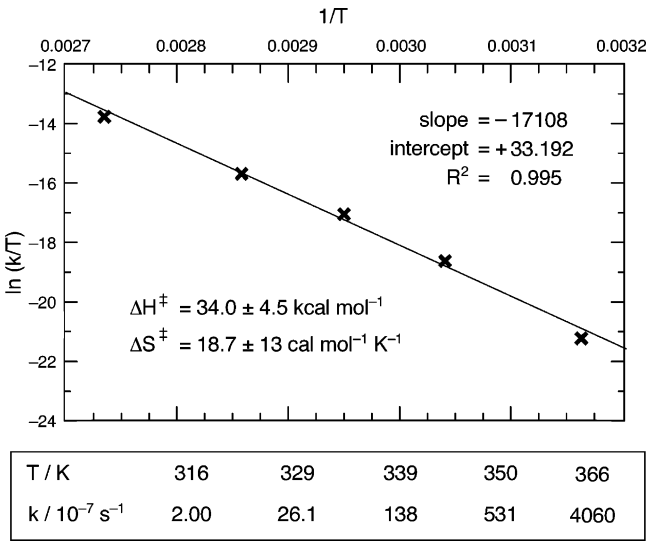
(20) Prefix descriptors, *lk* (like) and *ul* (unlike), refer to configurational relationships between the stereogenic axis and the C1 position of the menthyl moiety within diastereoisomers of **9**. For discourse on this and related terminology, see: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

(21) Diastereoisomers (−)-*lk*-**9** and (+)-*ul*-**9** could not be separated by simple fractional recrystallization, and flash column chromatographic separation proved much inferior to the HPLC-based method.

(22) The angle between the two intersecting least-squares quinolyl ring planes of (−)-*lk*-**9** is 117.7°, as compared to only 104.5° for the same property exhibited in the solid state by (±)-**6**·2MeOH (see ref 15). Both (−)-*lk*-**9** and (±)-**6** are more transoid than crystalline forms of either (±)-BINOL or (+)-(*aR*)-BINOL (angles between intersecting naphthyl ring planes are 90.6° and 101.7°, respectively), see: Mori, K.; Masuda, Y.; Kashino, S. *Acta Crystallogr.* **1993**, *C49*, 1224.

(23) For example, (+)-*lk*-**9** with dr = 75:25 (about axis) was subjected to hydrolysis, and the resulting sample of (+)-(*aR*)-**6** was immediately rederivatized by treatment with excess (−)-**8** to yield (+)-*lk*-**9** with dr = 70:30. Conversion for both steps was essentially quantitative.

(24) Because of the poor solubility of 7,7′-dihydroxy-8,8′-biquinolyl in solvents more commonly used in the measurement of optical rotation data (e.g., $CHCl_3$, EtOH, H_2O, etc.), polarimeter readings were taken from dilute solutions of **6** in aqueous base (1 M NaOH). Optical rotation values in this medium were observed to be invariant at ambient temperature over several hours (20 h).



T / K	316	329	339	350	366
k / 10^{-7} s^{-1}	2.00	26.1	138	531	4060

FIGURE 4. Eyring plot analysis and rate constant data for the enantiomerization of 7,7′-dihydroxy-8,8′-biquinolyl (**6**) in water. Eyring equation: $\ln(k/T) = \Delta S^{\ddagger}/R - \ln(h/k_B) - \Delta H^{\ddagger}/(RT)$. Errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are expressed as 95% confidence limits.

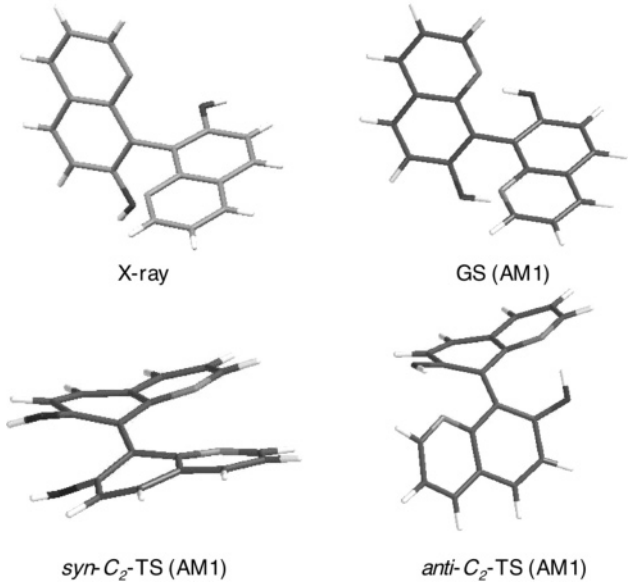


FIGURE 5. Solid-state (X-ray) and computed ground-state (GS) structures for 7,7′-dihydroxy-8,8′-biquinolyl (**6**) and calculated transition states for two possible *syn*- and *anti*-enantiomerization pathways (AM1, Spartan).

TABLE 1. Comparison of Selected Experimental and Calculated Parameters for 7,7′-Dihydroxy-8,8′-biquinloyl (6) and Its Enantiomerization Transition States

parameter source	rel energy /kcal mol^{-1}	torsion angle 8a−8−8′−8a′	torsion angle 7−8−8′−7′	bond length 8−8′/Å
X-ray (ref 15)		104.0°	102.2°	1.493
GS (AM1)	0.0	108.3°	114.0°	1.464
syn-C_2-TS (AM1)	34.1	19.4°	19.2°	1.467
anti-C_2-TS (AM1)	40.3	170.5°	161.5°	1.462

temperature.[25] Unfortunately, a suitable chiral stationary phase for analytical HPLC determination of enantiomeric excess for **6** could not be identified. Instead, to follow the progression of enantiomerization, aliquots of **6** were removed at regular intervals from the isothermal solutions under investigation and the samples converted to bismenthyl carbonates **9** for determination of diastereomeric ratio by ^{1}H NMR spectroscopy.[26] A control experiment verified that conversion of a racemic sample of **6** to *lk*-**9** and *ul*-**9** was complete under the conditions employed for aliquot processing and that dr (**9**) = 1:1 in this case. Thus, neither kinetic nor dynamic kinetic resolution was in operation during derivatization, and %de (**9**) was at the very least linearly related to %ee (**6**), if not equal to it. Despite the laborious nature of our chosen analysis method, we were able to obtain a number of first-order rate constants over a 50 °C temperature range.[27] Subsequent Eyring plot analysis showed excellent goodness-of-fit ($R^2 = 0.995$) to theoretical expectation and allowed extraction of relevant transition state parameters for the enantiomerization process (Figure 4). 7,7′-Dihydroxy-8,8′-biquinolyl (**6**) was so revealed to possess a useful level of configurational stability ($\Delta G^{\ddagger}$ (298 K) = 28.4 kcal mol^{-1}), albeit with a rotational barrier that is significantly lower in energy than that of its carbocyclic congener BINOL (**7**).[28] It is tempting to conclude from these results that the peri-positioned sp^2-hybridized N-atom lone pairs within **6** present less resistance to interannular rotation than the similarly located C−H bonds within **7**. Caution must be exercised in this analysis, however, because various tautomeric forms are accessible to **6** and its enantiomerization may conceivably occur via a vinylogous amide-type structure in which peri-N−H bonds are manifested (i.e., a 7-quinolone).

To gain some insight as to the likely mode of enantiomerization for **6**, its interannular rotational motion was computationally modeled in the gas phase at the AM1 level of theory.[29] Using this method, C_2-symmetric transition state structures for syn and anti enantiomerization pathways for **6** (*syn*-C_2-TS and *anti*-C_2-TS, Figure 5) were successfully located and the former determined to lie 6.2 kcal mol^{-1} beneath the latter (Table 1). Both of the calculated transition states exhibit significant out-of-plane deformation of the quinolyl ring systems. Given the

(25) The appropriate rate law for first-order enantiomerization is: $\ln(\%ee_0/\%ee_t) = 2kt$, where $\%ee_t$ = enantiomeric excess at time *t*. See the Supporting Information for the derivation of this expression. For the distinction between the terms enantiomerization and racemization, see: Ashweek, N. J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R. E.; Haeffner, F.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, *127*, 449.

(26) Following collection, aliquot samples were immediately cooled to room temperature and rapidly derivatized, each in an identical manner, with excess (−)-**8**. Diastereomeric ratio for **9** was determined by ^{1}H NMR spectral analysis (300 MHz, $CDCl_3$, 55 °C) by examination of the integration trace for the well differentiated signals due to protons at C2/2′: δ_H (*lk*-**9**) = 8.76 (1H, dd, *J* = 4.2, 1.8 Hz, *C2/2′-H*), δ_H (*ul*-**9**) = 8.80 (1H, dd, *J* = 4.1, 1.6 Hz, *C2/2′-H*).

(27) On occasion, crystals of **6** would form during enantiomerization experiments, and, in such cases, non-first-order decay in %ee was typically observed. Kinetic data collected from runs in which any inhomogeneity in the reaction mixture was observed were therefore discarded.

(28) The free energy of activation for the enantiomerization of BINOL (**7**) has been determined experimentally as $\Delta G^{\ddagger} = 37.8$ kcal mol^{-1} at 220 °C from diphenyl ether; see ref 17b. Based on our kinetic analysis, the same property for 7,7′-dihydroxy-8,8′-biquinolyl (**6**) at 220 °C would be only 24.8 kcal mol^{-1} ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$).

(29) Satisfactory transition state structures for the enantiomerization of **6** could not be located using density functional theory (B3LYP/6-31G*, Spartan); however, semiempirical calculations at the AM1 level identified transition states exhibiting appropriate single negative eigenvalues (see the Supporting Information for details). Analogous AM1 computations have been demonstrated to give good results in the determination of rotation barriers for 1,1-binaphthyl derivatives, see: Kranz, M.; Clark, T.; Schleyer, P. v. R. *J. Org. Chem.* **1993**, *58*, 3317.

simplicity of our model (i.e., no account of solvent effects, low level of theory), the calculated energy barrier to approach *syn*-C_2-TS from the ground-state geometry of **6** (34.1 kcal mol^{-1}) was in remarkable agreement with our previously determined experimental figure for the enthalpy of activation for enantiomerization of **6** (34.0 kcal mol^{-1}). On the basis of the modeling results, it was postulated that enantiomerization of **6** most likely proceeds via a syn pathway. If this were indeed the case, then doubly charged forms of **6**, that is, either the dianion resulting from deprotonation of each phenolic moiety, or the dication resulting from protonation of each quinoline N-atom, may be expected to experience an increased barrier to interannular rotation because of electrostatic repulsion of like charges in the corresponding transition states for syn enantiomerization pathways (and possibly leading to a preference for alternative anti pathways). To test this hypothesis, both strongly alkaline (pH 13−14, aq NaOH) and strongly acidic (pH 1−2, aq HCl) dilute aqueous solutions of enantioenriched (−)-**6** were prepared and each heated at 75 °C for 20 h. After this time, neither sample of (−)-**6** exhibited measurable deterioration in its enantiomeric excess according to our derivatization-based analysis method (vide supra). Thermolysis of **6** in a neutral aqueous solution under otherwise identical conditions resulted in almost complete racemization, however. Because the rate of enantiomerization for **6** is indeed significantly retarded when this amphoteric compound is doubly charged, we tentatively conclude that a syn pathway for enantiomerization is preferred from the native uncharged form of 7,7′-dihydroxy-8,8′-biquinolyl (**6**). It is noteworthy that our findings relating to **6** stand in stark contrast to the enantiomerization behavior exhibited by BINOL (**7**). BINOL (**7**) is calculated to enantiomerize preferentially via an anti pathway[17b] and has long been known to racemize more rapidly in acidic or basic aqueous solutions than in neutral media.[17a]

Chiroptical Properties. The electronic circular dichroism (CD) spectra of C_2-symmetric biaryl molecules are typically dominated by features arising from exciton coupling between appropriately polarized degenerate transition moments within the two σ-bond isolated chromophores.[30] The sign of exciton chirality for these couplets is sensitive to ground-state dihedral angle, and useful conformational information can be gleaned from CD-spectral analysis where absolute configuration is known (or vice versa).[31,32] With configurational assignments for the two optical isomers of 7,7′-dihydroxy-8,8′-biquinolyl (**6**) secured (vide supra), we therefore elected to further study the chiroptical properties of this molecule to ascertain its solution-phase conformational preference.

Electronic absorption spectra for 7-hydroxyquinoline[33] and 7,7′-dihydroxy-8,8′-biquinolyl (**6**) were collected from aqueous solutions and found to differ only in their intensity (by a factor of 4 molar absorbtivity units in favor of **6**) (Figure 6). This observation indicated a lack of electronic delocalization between the two linked quinolyl moieties within **6** and assured the validity of the usual exciton theory in subsequent CD-spectral analysis. Neutral hydroxyquinoline chromophores may be usefully characterized as derivatives of structurally related naphthols and share very similar transition moments.[34] Accordingly, the four principal absorption bands in the UV spectrum of biquinolyl **6**, λ_{max} = 208, 236, 264, and 328 nm, were assigned respective Platt singlet transition states of ^1B_a, ^1B_b, ^1L_a, and ^1L_b,[35] in analogy to closely related bands exhibited in the electronic spectrum of BINOL (**7**).[36] Exciton coupling between the long-axes polarized ^1B_b transitions of biquinol **6** was manifested in the CD spectrum of its (*aS*)-configurated levorotatory enantiomorph as a moderately intense bisignate band of positive exciton chirality. The couplet was composed of a positive maximum Cotton effect at 250 nm and a corresponding negative minimum at 234 nm ($\Delta\Delta\epsilon$ = +40 M^{-1} cm^{-1} at 64% ee). The expected mirror image bisignate band was displayed in the CD spectrum of (+)-(*aR*)-**6**. Comparison of CD spectra for (−)-(*aS*)-**6** and (−)-(*aS*)-BINOL (**7**) revealed a shared exciton chirality phase, although the latter and better

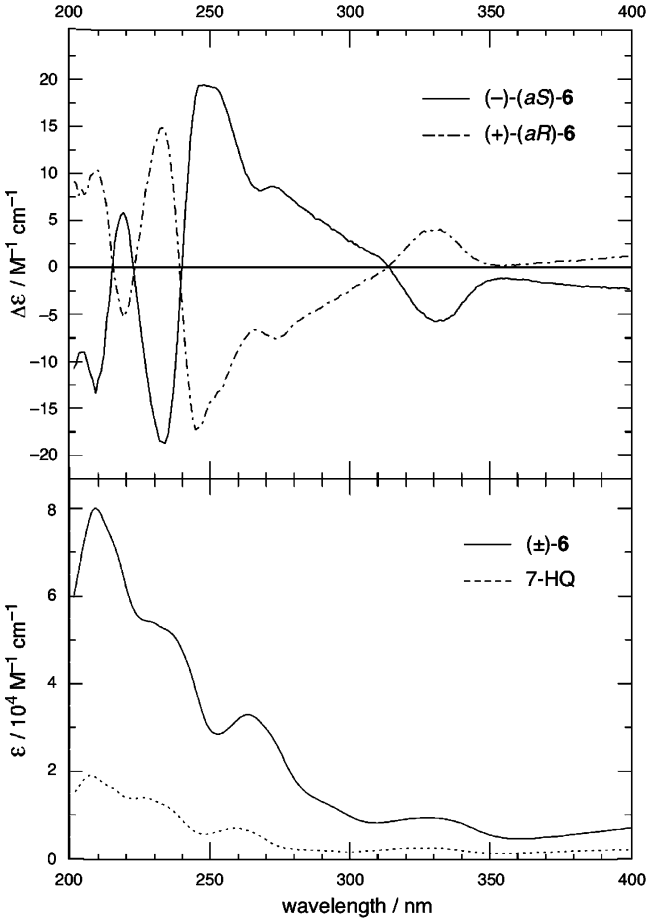


FIGURE 6. CD (upper panel) and UV−visible (lower panel) spectra for 7,7′-dihydroxy-8,8′-biquinoyl (**6**) and UV−visible spectrum for 7-hydroquinoline (7-HQ) collected from H_2O solutions (CD 2.4 mM, UV 0.02 M). Sample enantiomeric excess: (*aS*)-(−)-**6** = 64% ee; (*aR*)-(+)-**6** = 50% ee.

(30) Rodger, A.; Nordén, B. *Circular Dichroism and Linear Dichroism*; Oxford University Press: New York, 1997.

(31) For the quantitative determination of the dihedral angle of 2,2′-homosubstituted 1,1′-binaphthyls by CD-spectral analysis, see: Di Bari, L.; Pescitelli, G.; Salvadori, P. *J. Am. Chem. Soc.* **1999**, *121*, 7998.

(32) For application of the exciton chirality method to the assignment of absolute configuration, see: (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (b) Berova, N.; Nakanishi, K. In *Circular Dichroism: Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley−VCH: New York, 2000.

(33) For a recent ab initio study of the electronic spectrum of 7-hydroxyquinoline, see: Franz, J.; Peyerimhoff, S. D.; Hanrath, M.; Kwon, O.-H.; Jang, D. *Chem. Lett.* **2005**, *34*, 330.

(34) Nishimoto, K.; Forster, L. S. *J. Phys. Chem.* **1967**, *71*, 409.

(35) (a) Klevens, H. B.; Platt, J. R. *J. Chem. Phys.* **1949**, *17*, 470. (b) Platt, J. R. *J. Chem. Phys.* **1951**, *19*, 263.

(36) Pescitelli, G.; Di Bari, L.; Salvadori, P. *Organometallics* **2004**, *23*, 4223.

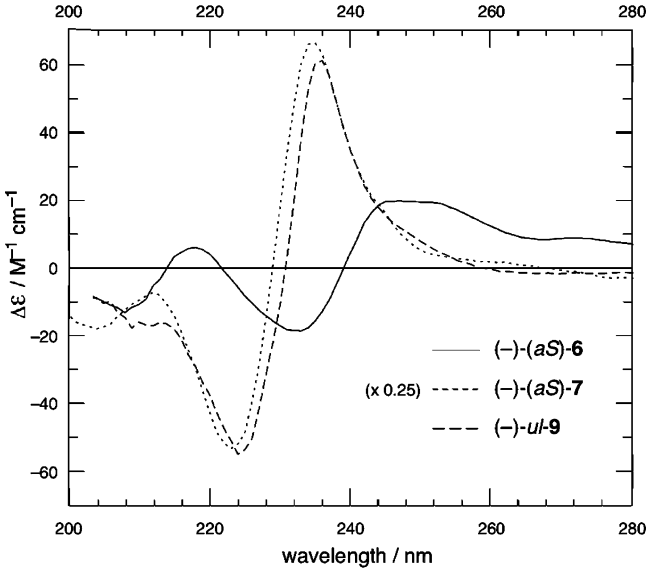


FIGURE 7. Comparison of exciton couplets in the CD spectra of (−)-(*aS*)-7,7′-dihydroxy-8,8′-biquinoyl (**6**, 64% ee), (−)-(a*S*)-1,1′-bi-2-naphthol (BINOL, **7**, >98% ee), and bismenthyl carbonate (−)-*ul*-**9** (≥98% ee, (*aS*)-configuration). CD spectra for (−)-(*aS*)-**7** and (−)-*ul*-**9** collected from MeOH solutions (0.5 and 3.1 mM, respectively), CD spectrum for (−)-(*aS*)-**6** collected from H_2O solution (2.4 mM).

known compound showed more intense band coupling ($\Delta\Delta\epsilon$ = +480 M^{-1} cm^{-1}) (Figure 7). In the case of 1,1′-binaphthyl derivatives, a reversal in the absolute phase of exciton chirality occurs at a dihedral angle of approximately 110°, and the mean internuclear angle for BINOL in solution has been determined to lie well below this threshold.[37] Thus, given that (−)-(*aS*)-**6** and (−)-(*aS*)-**7** both exhibit positive exciton chirality, the ground-state dihedral angle for **6** in (aqueous) solution is unlikely to be significantly more transoid than 110° and probably lies close to its solid-state value of 104.5°.[15] Interestingly, the bisignate exciton couplet of bismenthyl carbonate (−)-*ul*-**9** (prepared from (±)-**6** and (−)-**8** and (*aS*)-configurated) showed close structural homology to that of (−)-(*aS*)-BINOL (**7**) and differed only in its intensity ($\Delta\Delta\epsilon$ = +120 M^{-1} cm^{-1}). It is evident from the above studies that the CD of 8,8′-biquinolyls is closely related to that of analogous 1,1′-binaphthyls and that one may assign absolute configuration to these heterobiaryl compounds by the exciton chirality method with reasonable certainty.[38]

Conclusion

In summary, we have achieved the first resolution of a new axially chiral heterobiaryl molecule, 7,7′-dihydroxy-8,8′-biquinolyl (**6**), and determined that its levorotatory optical isomer is (*aS*)-configurated. Kinetic studies and subsequent Eyring plot analysis enabled measurement of transition state parameters for the enantiomerization of **6** and revealed that this material is significantly less configurationally stable than its carbocyclic congener 1,1′-bi-2-naphthol (BINOL, **7**). Molecular modeling studies (AM1) indicated that biquinol **6** enantiomerizes via a syn rotational pathway and charged forms of **6** were found to possess higher configurational stability than the neutral molecule. The chiroptical properties of **6** were observed to be similar to BINOL (**7**), and both compounds share the same absolute sense of exciton chirality in their CD spectra. Synthetic applications for ambifunctional metal complexes derived from biquinolyl **6** and related compounds are under active investigation and will be reported in due course.

Experimental Section

Preparation and HPLC Separation of Bismenthyl Carbonates (−)-*lk*-9 and (+)-*ul*-9. A solution of (±)-7,7′-dihydroxy-8,8′-biquinolyl (**6**, 302 mg, 1.05 mmol) in aq NaOH (13 mL, 1.5 M) was treated with tetrabutylammonium bromide (TBAB, 137 mg, 0.43 mmol) in CH_2Cl_2 (13 mL) followed by neat (+)-menthylchloroformate (**8**, 2.20 mL, d = 1.03, 2.30 g, 10.5 mmol). The resulting yellow biphasic mixture was stirred for 2 h, during which time the coloration dissipated. H_2O (50 mL) and CH_2Cl_2 (50 mL) were added, and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 30−100% EtOAc in hexanes) to afford a 1:1 diastereomeric mixture of bismenthyl carbonates (−)-*lk*-**9** and (+)-*ul*-**9** (683 mg, 1.05 mmol, 100%) as a colorless solid. The epimers were separated by HPLC on a reverse phase semipreparative column (Hyperprep HS, C18 8 μm, 21.2 mm × 250 mm) employing isocratic elution with 90% MeCN in H_2O (20 mL min^{-1}) to afford (−)-*lk*-**9** (15 min) followed by (+)-*ul*-**9** (17 min), both as colorless crystalline solids. (−)-*lk*-**9**: mp 89−91 °C (cyclohexane); $[\alpha]_D$ = −64.2 (c = 0.98, $CHCl_3$); IR (neat) 2955, 1754, 1452, 1223, 957, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (2H, dd, J = 4.2, 1.8 Hz), 8.20 (2H, dd, J = 8.2, 1.6 Hz), 7.97 (2H, d, J = 9.0 Hz), 7.67 (2H, d, J = 9.0 Hz), 7.34 (2H, dd, J = 8.3, 4.3 Hz), 4.36 (2H, td, J = 10.9, 4.4 Hz), 1.82 (2H, dm, J = 11.8 Hz), 1.63−1.44 (6H, m), 1.42−1.10 (8H, m), 1.00−0.70 (2H, m), 0.86 (6H, d, J = 6.5 Hz), 0.66 (6H, d, J = 6.9 Hz), 0.52 (6H, d, J = 6.8 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6 (2C, 0), 151.0 (2C, 1), 149.8 (2C, 0), 147.7 (2C, 0), 136.0 (2C, 1), 129.2 (2C, 1), 126.6 (2C, 0), 125.0 (2C, 0), 122.5 (2C, 1), 120.8 (2C, 1), 79.0 (2C, 1), 46.6 (2C, 1), 40.4 (2C, 2), 34.1 (2C, 2), 31.4 (2C, 1), 25.7 (2C, 1), 23.2 (2C, 2), 22.1 (2C, 3), 20.7 (2C, 3), 16.3 (2C, 3) ppm; MS (ES+) m/z 653 $(M + H)^+$; HRMS (ES+) m/z 653.3601 (calcd for $C_{40}H_{49}N_2O_6$: 653.3591). Anal. Calcd for $C_{40}H_{48}N_2O_6$: C, 73.59; H, 7.41; N, 4.29. Found: C, 73.55; H, 7.20; N, 4.35. (+)-*ul*-**9**: mp 79−82 °C (MeOH); $[\alpha]_D$ +113.0 (c = 0.22, $CHCl_3$); IR (neat) 2917, 1755, 1452, 1221, 957, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.80 (2H, dd, J = 4.1, 1.6 Hz), 8.22 (2H, dd, J = 8.3, 1.4 Hz), 7.96 (2H, d, J = 9.0 Hz), 7.64 (2H, d, J = 8.9 Hz), 7.34 (2H, dd, J = 8.2, 4.2 Hz), 4.29 (2H, td, J = 10.8, 4.5 Hz), 1.72 (2H, dm, J = 11.9 Hz), 1.65−1.50 (6H, m), 1.40−1.05 (6H, m), 1.00−0.60 (4H, m), 0.85 (6H, d, J = 6.5 Hz), 0.74 (6H, d, J = 7.0 Hz), 0.61 (6H, d, J = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4 (2C, 0), 151.1 (2C, 1), 149.8 (2C, 0), 147.7 (2C, 0), 136.2 (2C, 1), 129.2 (2C, 1), 126.6 (2C, 0), 125.2 (2C, 0), 122.6 (2C, 1), 120.7 (2C, 1), 79.0 (2C, 1), 46.6 (2C, 1), 40.3 (2C, 2), 34.1 (2C, 2), 31.3 (2C, 1), 26.0 (2C, 1), 23.4 (2C, 2), 22.1 (2C, 3), 20.7 (2C, 3), 16.5 (2C, 3) ppm; MS (ES+) m/z 653 $(M + H)^+$; HRMS (ES+) m/z 653.3608 (calcd for $C_{40}H_{49}N_2O_6$: 653.3591).

Hydrolysis of Bismenthyl Carbonates. (−)-(*aS*)-7,7′-Dihydroxy-8,8′-biquinolyl (6). A sample of diastereomerically pure (−)-*lk*-**9** (43 mg, 66 μmol) was treated with 5% w/v methanolic KOH (3.5 mL), and the resulting solution was stirred at 0 °C for 90 min. A yellow coloration developed. H_2O (7 mL) and EtOAc (7 mL) were added, and the layers separated. The basic aqueous

(37) The results of electronic and vibrational circular dichroism analysis place the mean dihedral angle for BINOL between 85° and 100°, see, CD: (a) Hanazaki, I.; Akimoto, H. *J. Am. Chem. Soc.* **1972**, *94*, 4102. vCD: (b) Setnicka, V.; Urbanova, M.; Bour, P.; Kral, V.; Volka, K. *J. Phys. Chem. A* **2001**, *105*, 8931.

(38) Hirao and co-workers reported the assignment of absolute configuration to a series of 1,1′-biisoquinolyls based on CD-spectral analysis; see ref 10d.

phase (pH 13) was washed with EtOAc (2 × 7 mL), and the combined organic washings were extracted once with H_2O (5 mL) before being discarded. The pH of the combined aqueous phases was then adjusted to 7 (with aq 1 M HCl), and the neutral form of biquinolyl **6** was extracted from this solution with EtOAc (3 × 7 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford (−)-(*aS*)-**6** (16 mg, 55.5 μmol, 84%) as a yellow solid: $[\alpha]^{23}_D$ (91% ee) = −111 (*c* = 0.18, 1 M aq NaOH). Reconversion of this material to its bismenthyl carbonate derivatives **9** with (+)-**8** (as above) revealed *lk*-**9**:*ul*-**9** = 95.5:4.5 (by ^{1}H NMR analysis). Spectral data recorded for (−)-(*aS*)-**6** were in complete agreement with those previously reported for (±)-**6**.[15] (+)-(*aR*)-**6** was similarly prepared from (+)-*ul*-**9** (91% yield). Alternatively, (+)-(*aR*)-**6** and (−)-(*aS*)-**6** were also obtained by the respective hydrolysis of (+)-*lk*-**9** and (−)-*ul*-**9**, themselves prepared by acylation of (±)-**6** with (−)-**8** (and as described above for (+)-**8**).

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Supporting Information Available: General experimental conditions, ^{1}H and ^{13}C NMR spectra for (−)-*lk*-**9** and (+)-*ul*-**9**, kinetic data from enantiomerization experiments, details for AM1 modeling study, and CIF file for (−)-*lk*-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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