

Efficient axial chirality induction in biphenyldiol triggered by proton-transferred hydrogen bonding with chiral amine

Hideki Takagi,^a Tadashi Mizutani,^{*b} Takuya Horiguchi,^c Susumu Kitagawa^c and Hisanobu Ogoshi^c

^a Graduate School of Science and Technology, Kobe University, Nada, Kobe, 657-8501, Japan

^b Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto, 610-0321, Japan. E-mail: tmizutan@mail.doshisha.ac.jp; Fax: (81)774-65-6794; Tel: (81)774-65-6623

^c Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto, 615-8510, Japan

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Axial chirality was induced in biphenyldiol upon binding chiral amines with the efficiency of chiral induction much improved at low temperature. At low temperatures, two molecules of amine were bound to biphenyldiol. The value of the dissymmetric *g*-factor increased as proton-transferred hydrogen bonds formed between biphenyldiol and amine. These results indicate that proton-transferred hydrogen bonding plays an important role in constructing a highly ordered chiral assembly.

Introduction

Axially chiral C_2 -symmetric molecules have attracted great attention due to their ability as asymmetric catalysts and chiral recognition hosts.¹ Therefore, chirality control of C_2 -symmetric molecules and their enantioselective preparation have been the subjects of current research.² In particular, use of non-covalent interactions to induce C_2 -symmetric chirality is one of the challenges in supramolecular chemistry.^{3–5} To achieve effective chiral recognition/induction,⁶ intermolecular interactions should be precisely regulated to have maximum control of conformations of the molecules. We previously reported that a C_2 -symmetric chiral diamine can induce axial chirality in a C_2 -symmetric 2,2'-biphenyldiol upon complex formation through hydrogen bonding.⁷

As an interesting feature of hydrogen bond,⁸ Ilczyszyn *et al.*⁹ reported that proton transfer occurs in the hydrogen bonding complex between 2,4-dichlorophenol and triethylamine in C_2H_5Cl at -133 °C. We¹⁰ reported that a solution of the *p*-nitrophenol–diisopropylamine complex in toluene becomes yellow at -80 °C due to phenolic proton transfer to the amine. The tautomeric equilibrium in the hydrogen bonding complex is represented by eqn. (1):



Since it is known that hydrogen bonding between charged groups is stronger than that between neutral groups,¹¹ the tautomeric equilibrium should affect both energetic and geometric features of the hydrogen-bonding complex.^{8,12} In the present study, we report that the combination of these two findings, chiral induction in the phenol–amine complex and proton-transfer in the hydrogen bond, lead to a remarkably efficient system for the preparation of axially chiral biphenyldiol.

Results and discussion

Chiral induction in biphenyldiol at room temperature

We reported that chiral diamines bind to 2,2'-biphenyldiol such as **1** in toluene, with **1** adopting an axially chiral conformation in the complex.⁷ Biphenyldiol **1** racemizes rapidly through rotation along the phenyl–phenyl linkage (Fig. 1, eqn. (2)). Chiral diamine **2** forms a complex with **1** through hydrogen bonding (Fig. 2, eqn. (3)) and one of the enantiomers of **1**

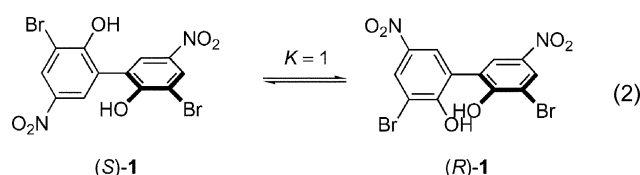


Fig. 1 Atropisomerisation of biphenyldiol **1**.

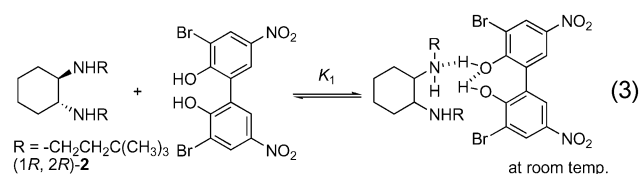


Fig. 2 Binding of diamine **2** to biphenyldiol **1**.

is preferred over the other in the complex. Formation of the hydrogen-bonding complex was confirmed by the UV-visible spectra, which displayed a red shift of the peak maximum of **1** from 295 to 328 nm upon addition of **2** in toluene at 20 °C. The absorption maximum at 328 nm indicates that **1** is in a phenol form: the proton of the OH group is attached to the oxygen in the 1 : 1 complex (Fig. 2, eqn. (3)). The 1 : 1 stoichiometry of **1** and **2** at 20 °C in toluene was established by Job plot analysis (Fig. 3). The estimated value of the association constant, K_1 , of **1** and **2** in toluene at 20 °C is $>10^6 \text{ M}^{-1}$.

We observed exciton-type Cotton effects in the biphenyldiol band (Fig. 4(a)). The magnitude and the sign of the Cotton effects were affected when the alkyl substituents on the nitrogens of the diamine were varied from hydrogen, methyl to 3,3-dimethylbutyl, indicating that there is a significant contribution of van der Waals interaction of the alkyl substituents to the axial chirality induction.⁷ The host–guest van der Waals interaction was also revealed by an intermolecular NOE observed between the *tert*-butyl group on diamine **2** and the aromatic ring protons of **1** in the differential ¹H NMR spectrum. Thus, the hydrogen bonding and van der Waals interaction induce axial chirality in flexible biphenyldiols at room temperature.

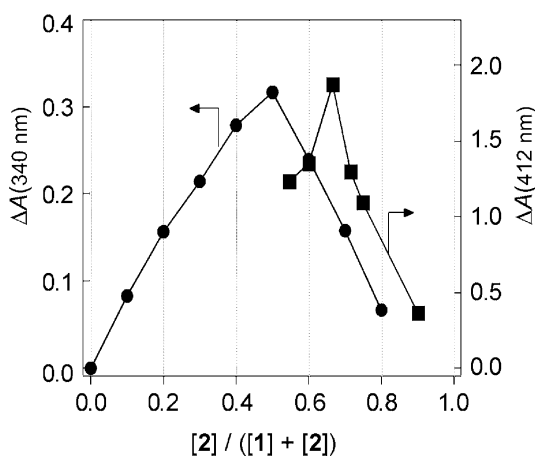


Fig. 3 Job plot for the solution of **1** and **2** in toluene at 20 °C (●) and at -80 °C (■). Absorbances at 340 or 412 nm were plotted against $[2]/([1] + [2])$; $[1] + [2] = 5.6 \times 10^{-5}$ M at 20 °C and 1.5×10^{-4} M at -80 °C.

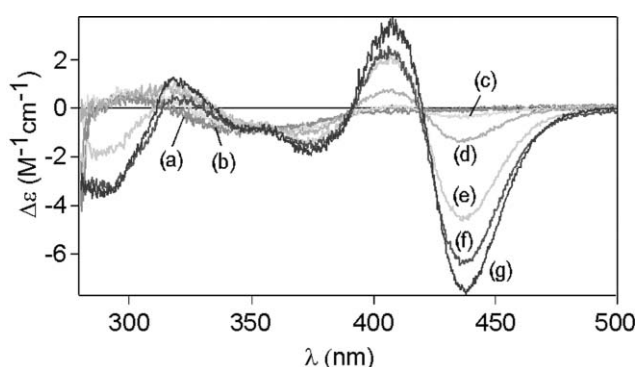


Fig. 4 Variable-temperature circular dichroism spectra of **1** and (1*R*,2*R*)-**2** in toluene: $[1] = 9.0 \times 10^{-5}$ M, $[(1*R*,2*R*)-2] = 3.5 \times 10^{-4}$ M; (a) 22 °C, (b) 0 °C, (c) -20 °C, (d) -40 °C, (e) -60 °C, (f) -70 °C, (g) -80 °C.

Binding of biphenyldiol to amine at low temperatures

Fig. 5 shows that, by lowering the temperature, a new absorption band, increasing in intensity, appears at 412 nm, indicating that the proton is transferred to the amino group and the phenolate is formed.¹³ Observation of the phenolate band in the UV-visible spectrum depended on the molar ratio of **2** to **1**. There was no phenolate band in the UV-visible spectra of this system at -80 °C over a range of 0–1 equivalents of **2** to **1**, indicating that the proton transfer does not occur when $[2]/[1]$ in this range. When 1.2 equivalents or more of **2** was added, the phenolate band was observed at 412 nm. We determined the stoichiometry

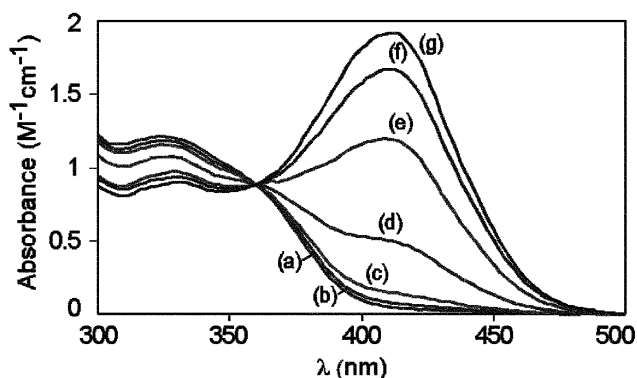


Fig. 5 Variable-temperature UV-visible spectra of a solution of **1** and (1*R*,2*R*)-**2** in toluene: $[1] = 8.7 \times 10^{-5}$ M, $[(1*R*,2*R*)-2] = 3.5 \times 10^{-4}$ M; (a) 22 °C, (b) 0 °C, (c) -20 °C, (d) -40 °C, (e) -60 °C, (f) -70 °C, (g) -80 °C.

of the complex formed at -80 °C by Job plot analysis (Fig. 3), which clearly indicated the proton-transferred complex to be a 1 : 2 (biphenyldiol : diamine) complex. A second amine molecule is thus needed to cause proton transfer. Although we do not definitively know the structure of the 1 : 2 complex,¹⁴ we speculate that the charges developed in the non-polar solvent can be stabilized by interaction with the second amine as schematically shown in Fig. 6 (eqn. (4)). Molecular modeling by using a CAChe conformational search program suggested the proton-transferred hydrogen bonding ternary complex shown in Fig. 7 is formed.

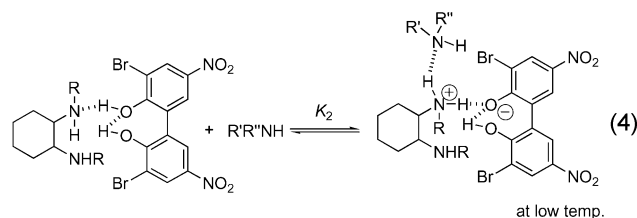


Fig. 6 Ternary complex formation from biphenyldiol **1** and diamine **2**.

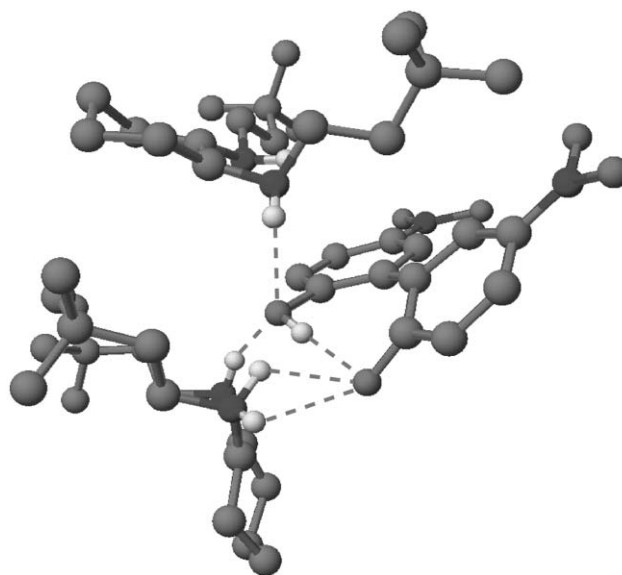


Fig. 7 Structure of one of the possible ternary complexes of **1** and **2**; hydrogens attached to carbons and bromines are omitted for clarity.

Variable-temperature ¹H NMR studies support the successive binding of **2** to **1**. The signals of the biphenyl ring protons of **1** complexed with **2** were shifted downfield as the temperature was lowered from 25 to -80 °C.¹⁵ The complexation-induced shift¹⁶ changed as the stoichiometric ratio was varied from equimolar to 1 : 2. As shown in Fig. 8(a), a solution of **1** and **2** at a 1 : 1 ratio showed the resonances of biphenyl ring protons at 8.53 and 8.30 ppm at -80 °C, which are attributable to the 1 : 1 complex. A solution of **1** and **2** at a 1 : 2 ratio exhibited significantly downfield shifted resonances of the biphenyl ring protons at 9.04 and 8.86 ppm, indicating that the 1 : 2 complex is exclusively formed (Fig. 8(c)). However, at a lower concentration of **1** of 0.87 mM with $[2]/[1] = 2$, two sets of signals corresponding to the 1 : 1 complex and the 1 : 2 complex were observed as shown in Fig. 8(b). Therefore binding of **2** occurs in a stepwise fashion and the second equilibrium constant, K_2 , should be of the order of 10^3 – 10^4 M⁻¹ at -80 °C. A concentration of 0.87 mM of **1** is not sufficient to shift the second equilibrium in eqn. (4) exclusively to the right.

Chiral induction in biphenyldiol at low temperature

A significant feature of a solution of **1** and **2** is that intense Cotton effects are seen in the phenolate band as the temperature

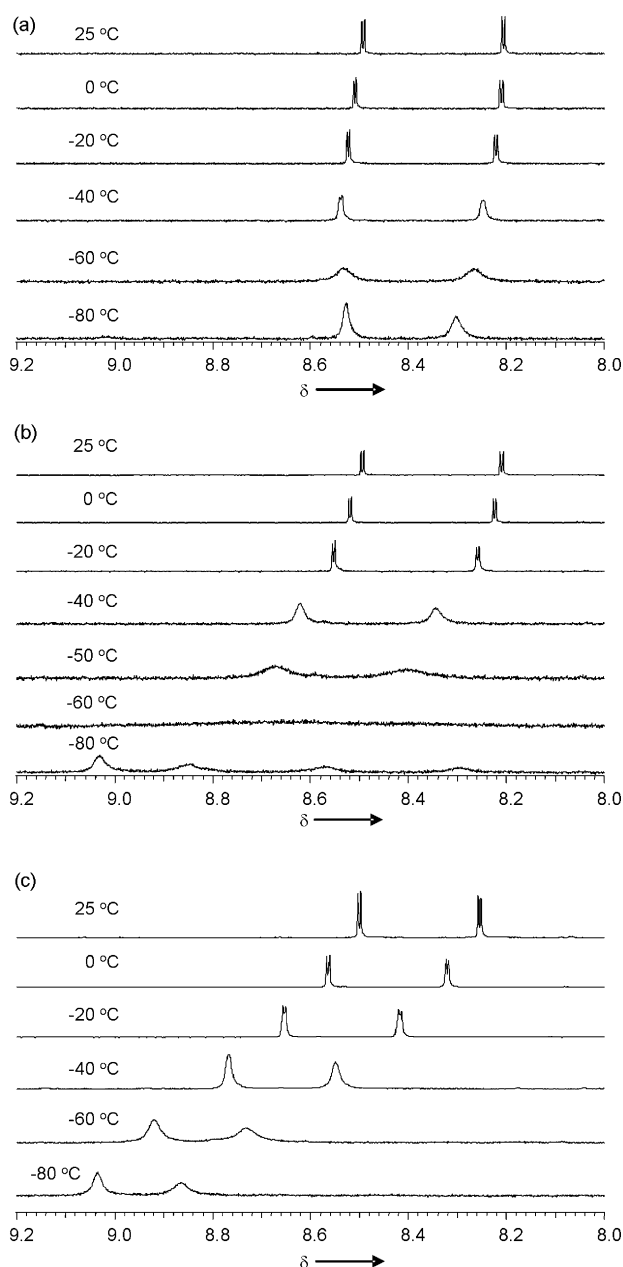


Fig. 8 Variable-temperature ^1H NMR spectra of a solution of **1** and **2** in toluene- d_8 : (a) $[\mathbf{1}] : [(1S,2S)\text{-}\mathbf{2}] = 1 : 1$, $[\mathbf{1}] = 0.99$ mM; (b) $[\mathbf{1}] : [(1S,2S)\text{-}\mathbf{2}] = 1 : 2$, $[\mathbf{1}] = 0.83$ mM, (c) $[\mathbf{1}] : [(1S,2S)\text{-}\mathbf{2}] = 1 : 2$, $[\mathbf{1}] = 9.6$ mM.

is lowered. Fig. 4 shows the variable-temperature CD spectra of a solution of **1** and (1*R*,2*R*)-**2** in a 1 : 4 molar ratio. At 22 °C, weak Cotton effects were seen in the 280–400 nm region, which we ascribed to the 1 : 1 normal hydrogen-bonding complex. The CD spectra remain the same down to -20 °C. Below -40 °C, new Cotton effects were observed in the 380–470 nm region, which clearly show that the proton-transferred phenolate species of **1** adopts a chiral conformation. The temperature dependence is similar to that observed in the UV-visible spectra shown in Fig. 5; only below -40 °C, the phenolate band increased in intensity. We did not observe the Cotton effects in the 380–470 nm region when the $[\mathbf{2}]/[\mathbf{1}]$ ratio is ≤ 1 , the same stoichiometric dependence as observed for the phenolate band in the UV-visible spectra. These CD spectral observations combined with ^1H NMR and UV-visible spectroscopic results, indicate that two molecules of chiral diamine **2** bind to **1** through a proton-transferred hydrogen bonding network and an axially chiral structure is concurrently induced in **1** (Fig. 8).

Since the 1 : 1 complex and the 1 : 2 complex exhibited different UV-visible absorptivity, we can not evaluate the chiroptical properties by simple comparison of the magnitude of the Cotton effects. The ratio, $g = \Delta\epsilon/\epsilon$, the dissymmetric factor,¹⁷ was determined for the 1 : 1 complex and the 1 : 2 complex. We show below that, under some approximations, the g -factor is determined by the geometry of the molecule and is independent of the electronic states of the chromophore. Molar absorptivity ϵ is proportional to the dipole strength:

$$D = |\vec{\mu}|^2 \quad (5)$$

where $\vec{\mu}$ is the electric transition dipole moment, and $\Delta\epsilon$ is proportional to the rotational strength R , that can be expressed using the exciton coupling approximation¹⁸ as:

$$R = \frac{\pi\Delta E}{2hc} \vec{R}_{ij} \cdot (\vec{\mu}_i \times \vec{\mu}_j) \quad (6)$$

Here, ΔE is the electronic transition energy, h is Planck's constant, c is the speed of light, and R_{ij} is the positional vector from the center of chromophore i to chromophore j . From these equations, we obtain:

$$g = \frac{\Delta\epsilon}{\epsilon} \propto \frac{\pi\Delta E}{2hc} \vec{R}_{ij} \cdot (\vec{\mu}_i \times \vec{\mu}_j) \cdot \frac{1}{|\vec{\mu}|^2} = \frac{\pi}{2\lambda} \vec{R}_{ij} \cdot (\vec{e}_i \times \vec{e}_j) \quad (7)$$

where \vec{e}_i and \vec{e}_j are the unit vectors of the transition moments and λ is the wavelength of the electronic transition. Therefore, the g -factor is determined only by the geometry of the two chromophores and λ , and is independent of the magnitude of the transition moment. If we assume that $\vec{R}_{ij} \cdot (\vec{e}_i \times \vec{e}_j)$ is 0.4 nm, g is of the order of 1.5×10^{-3} for $\lambda = 437$ nm.

The g -factor at 354 nm of the 1 : 1 complex at 22 °C was 8.4×10^{-5} . The g -factor at 437 nm was larger and increased as the solution was cooled (Fig. 9). The maximum value of $g = 7.6 \times 10^{-4}$ was obtained at -80 °C, which is an order of magnitude larger than that of the 1 : 1 complex. Therefore, axial chirality is induced in the 1 : 2 complex more effectively than in the 1 : 1 complex.

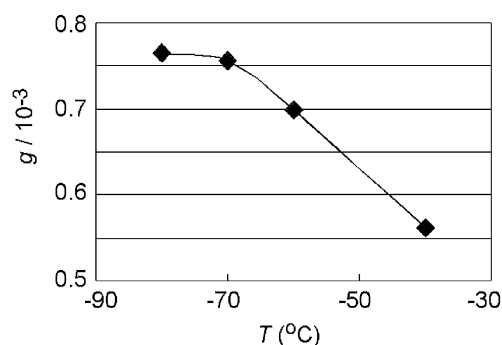


Fig. 9 Plot of the g -value, $\Delta\epsilon/\epsilon$, at 437 nm of a solution of **1** and **2** vs. temperature: $[\mathbf{1}] = 7.5 \times 10^{-5}$ M, $[(1R,2R)\text{-}\mathbf{2}] = 1.5 \times 10^{-4}$ M in toluene.

Chiral induction in biphenyldiol–chiral amine–achiral amine ternary complex

Using the equilibria of the present system, we showed that a solution exhibiting almost no CD can be made CD active by the addition of an *achiral* amine. A toluene solution of **1** and **2** in 1 : 1 ratio showed no phenolate band upon cooling as stated above, nor Cotton effects in the phenolate band. When an equimolar amount of achiral diisopropylamine **3** was added to the 1 : 1 solution, the phenolate band was observed in the UV-visible spectra upon lowering the temperature. Interestingly, this solution exhibited CD signals (Fig. 10) similar in shape to those observed for the 1 : 2 complex. The observed intense Cotton effects can be ascribed to the formation of a 1 : 1 : 1 complex as shown in Fig. 11. From the UV-visible and CD spectra at -80 °C of this solution, the g -factor at 437 nm was calculated to be 3.7×10^{-4} ($[\mathbf{1}] = 9.6 \times 10^{-5}$ M, $[\mathbf{2}] = 9.8 \times 10^{-5}$ M, $[\mathbf{3}]$

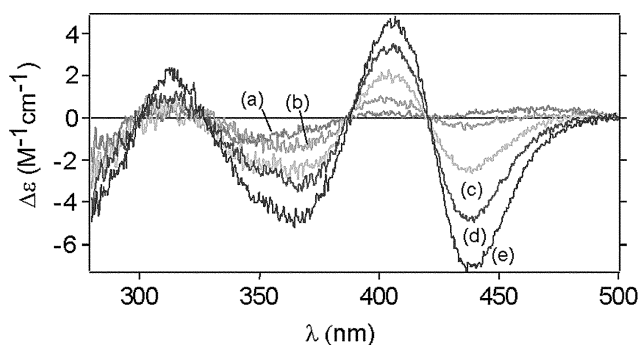
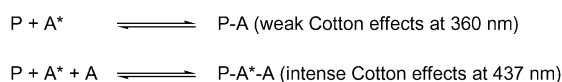


Fig. 10 Circular dichroism spectra of a solution of **1**, **2** and diisopropylamine **3** in toluene at (a) 22 °C, (b) -40 °C, (c) -60 °C, (d) -70 °C and (e) -80 °C: $[1] = 9.6 \times 10^{-5}$ M, $[(1R,2R)\text{-}2] = 9.8 \times 10^{-5}$ M, $[3] = 1.0 \times 10^{-4}$ M.



P: biphenyldiol **1**
 A*: chiral amine **2**
 A: achiral amine **3**

Fig. 11 Ternary complex formation from biphenyldiol, chiral amine and achiral amine.

$= 1.0 \times 10^{-4}$ M). This is almost half of that of a solution of the 1 : 2 complex ($g = 7.6 \times 10^{-4}$ at 437 nm, $[1] = 7.5 \times 10^{-5}$ M, $[2] = 1.5 \times 10^{-4}$ M). Thus, the additional *achiral* amine enhances the *g*-factor from nearly zero to 3.7×10^{-4} .

Conclusions

Complexation of two molecules of diamine with biphenyldiol caused proton-transfer in the hydrogen bonding complex and also effective chiral induction in the biphenyldiol framework. This is the first example of application of proton-transferred hydrogen bonding to supramolecular chemistry, where the proton-transferred hydrogen bonding produces an ordered state, significantly enhancing chiral induction. The tautomeric equilibrium in the hydrogen bonding is thus useful for construction of a highly-ordered supramolecular system with unique functions such as chiral induction and chirality sensing.

Experimental

^1H NMR spectra were recorded using a Jeol A-500 spectrometer. ^1H NMR chemical shifts in toluene- d_8 were referenced to TMS (0 ppm). UV-visible spectra and circular dichroic (CD) spectra were recorded on a Hewlett-Packard 8452 diode array spectrometer and a Jasco J-600 spectropolarimeter, respectively, equipped with a thermostatted cell compartment using a 1 cm path length cuvette. A cryostat (Oxford, DN1704) was used for UV-visible and CD spectral measurements at low temperatures.

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