Dynamic Axial Chirality Control of a Carboxybiphenol through Acid–Base Interaction

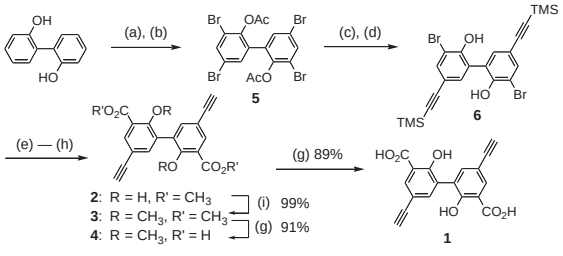
Kohei Morioka, Norio Tamagawa, Katsuhiro Maeda,* and Eiji Yashima*
Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya 464-8603

(Received November 9, 2005; CL-051393; E-mail: maeda@apchem.nagoya-u.ac.jp)

A novel, fluorescent 2,2′-biphenol bearing two carboxyl and two ethynyl groups was found to be sensitive to the chirality of the chiral diamines, thus showing an induced circular dichroism due to an excess single-handed, axially twisted conformation.

The development of achiral or dynamically racemic, chromophoric supramolecular, and macromolecular receptors for the detection and sensing of chirality has recently attracted great interest. This is because the noncovalent binding of a nonracemic guest to the receptors may result in the generation of one of the enantiomeric or diastereomeric twisted or helical conformers, thus producing a characteristic induced circular dichroism (ICD) in the absorption region of the receptors, which can be utilized to determine the absolute configuration of the guest molecules.[1] We previously reported that either a right- or left-handed helix can be induced in an optically inactive, stereoregular poly((4-carboxyphenyl)acetylene) upon complexation with optically active amines. The complexes exhibited a characteristic ICD in the UV–vis region of the polymer backbone because of the prevailing, dynamic one-handed helical conformation.[2] We anticipated that this methodology of a one-handed helicity induction in dynamically racemic helical polymers with specific chiral guests can be applied to rationally designed chromophoric small receptor molecules after the introduction of specific functional groups.[1a,3]

C_2-symmetric 2,2′-biphenols with a dynamic axial chirality were then selected as the chromophoric skeleton to develop a novel chirality-sensing receptor. The unique feature of such axially chiral, but dynamically racemic 2,2′-biphenols has been used for constructing asymmetric catalysts[4] and chirality sensors.[5] We now report the synthesis and chirality-sensing property of a novel 2,2′-biphenol bearing carboxyl and ethynyl groups **1**, which are introduced as additional and more effective binding sites than hydroxy groups for chiral amines and to enhance the effective π-conjugation length, as well as for further applications in a π-conjugated polymer system, respectively.



Scheme 1. Synthesis of **1**–**4**. (a) Br_2, CH_3OH, 0 °C, 63%. (b) Ac_2O, pyridine, Et_2O, rt, 93%. (c) TMSA, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 50 °C, 69%. (d) NH_4OAc aq, THF/CH_3OH, rt, 52%. (e) *n*-BuLi, THF, −25 °C. (f) CO_2, −78 °C. (g) NaOH/CH_3OH, THF, rt. (h) CH_3I, K_2CO_3, acetone, rt, 33%. (i) CH_3I, K_2CO_3, acetone, reflux.

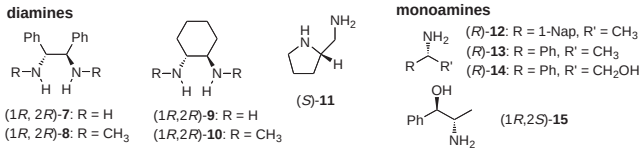


Chart 1. Optically active amines.

The 2,2′-biphenol derivative **1** was synthesized in seven steps from 2,2′-biphenol according to Scheme 1.[6] The corresponding biphenol derivatives (**2**–**4**) with protected hydroxy and/or carboxyl groups[6] were also prepared for comparison in order to investigate the function of the acidic groups on their axial chirality dynamics controlled by a noncovalent interaction with optically active amines.

The carboxybiphenol **1** exhibited split type ICDs in the π-conjugated chromophore region upon complexation with one or four equivalents of the chiral diamines (**7**–**11**) (Figure 1A and Table 1), whereas no apparent CD was observed even in the presence of 50-fold excess optically active monoamines (**12** and **13**) and amino alcohols (**14** and **15**) (Chart 1).[7] The enantiomers of **7** induced ICDs of the mirror images of each other. The ICD intensity increased with an increase in the concentration of (1*R*,2*R*)-**7** in a sigmoidal fashion and reached a maximum value at about [**7**]/[**1**] = 1 ([**1**] = 9.3 mM) accompanied by a significant blue shift of the absorbance maximum, while the further addition of the diamine induced a slight decrease in the ICD intensity (Figure 1B). These results indicate that the complexation involves an acid–base equilibrium and an excess single-handed axially twisted conformer is generated in **1** as a result of the diastereoselective complexation with chiral diamines; the complexation behavior may not be simple and is dependent on the concentrations of **1** and the chiral diamines (see below).

Interestingly, **1** exhibited a green emission, which changed to a blue one upon complexation with mono- and diamines (Figure 1A inset). In sharp contrast to **1**, the other biphenyl derivatives bearing either free hydroxy **2** or carboxyl groups **4** and a fully protected derivative **3** showed no ICDs under the same conditions with chiral amines (**7**–**15**), indicating that both the acidic hydroxy and carboxyl groups located at the ortho and meta positions on the phenyl moieties are essential for the appearance of the ICDs.[8] It is noteworthy that structurally similar chiral diamines of the same configuration (**7**–**10**) had the same Cotton effect signs for **1**, suggesting that **1** may be utilized as a novel chirality sensor for determining the absolute configuration of the chiral diamines.

The Job plot for the **1**–(1*R*,2*R*)-**7** complex using CD showed a 1:1 stoichiometry in which the total concentrations of **1** and **7** remained constant at 18.6 mM in THF.[6] We then performed IR titration experiments under the same conditions as the CD titrations ([**1**] = 9.3 mM in THF) in order to gain further insight into the axial chirality induction mechanism of **1** (Figure 1B), and the

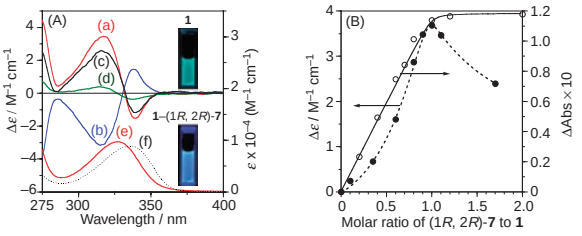


Figure 1. (A) CD spectra of **1** with (1*R*,2*R*)-**7** (a), (1*S*,2*S*)-**7** (b), (1*R*,2*R*)-**8** (c), and (1*R*,2*R*)-**10** (d) ([diamine]/[**1**] = 1) in THF at rt. Absorption spectra of **1** with (e) and without (1*R*,2*R*)-**7** (f) are also shown. [**1**] = 9.3 (a–c, e, and f) and 7.1 mM (d). Inset photographs show the visible difference of **1** with and without (1*R*,2*R*)-**7** in THF under UV-light at 365 nm. (B) Plots of the ICD intensity of the 2nd Cotton effect (●) and the differential IR absorbance (ΔAbs) at 1673 cm^{-1} of **1** (○) as a function of the relative concentration of (1*R*,2*R*)-**7** to **1** ([**1**] = 9.3 mM) in THF. A solid line in the plot is a fit to the theoretical binding curve.[9]

changes in absorbance at 1673 cm^{-1} corresponding to the intramolecularly hydrogen bonded COOH band with the adjacent OH group was followed. The absorbance intensity linearly decreased with the increasing concentration of **7** and almost completely disappeared at [**1**] = [**7**], resulting in the formation of the carboxylate ions (Figure 1B).[9]

On the basis of these observations together with the facts that only the carboxybiphenol **1** is CD active for the chiral diamines among the other analogous biphenyl derivatives, but exhibited no CD upon complexation with the chiral monoamines, we propose a 2:2 cyclic tetramer as a plausible CD active species as shown in Figure 2A, where each amino group of the chiral diamine intermolecularly binds to the carboxyl groups of the different receptors by salt bridges. This tetramer formation may enable a favorable *cisoid* conformation of **1** due to the intramolecular hydrogen bonds between the adjacent hydroxy groups of **1**, thus generating an excess of one of the axially twisted conformers, although the exact structure is not presently clear.[10] On the other hand, chiral monoamines may simply bind to a carboxyl group in a 1:1 fashion, so that the **1**–monoamine complexes may exist as both the interconverting *cisoid* and *transoid* forms (Figure 2B), and a such conformational flexibility may be the reason for no ICD.

As described above, the complexations of **1** with chiral diamines showing ICDs are dependent on the concentrations of **1** and the chiral diamines. At a lower concentration of **1** (0.12 mM) in THF, similar intense ICDs were observed immediately after the addition of (1*R*,2*R*)-**7** ([**7**]/[**1**] = 1) to the solution of **1** (Table 1). However, the ICD intensity was found to be significantly time dependent, and steadily decreased with time and almost completely disappeared after 1 h. Such a decrease in the ICD with time became slower with the increasing concentration of (1*R*,2*R*)-**7** and was negligibly small at [**7**]/[**1**] ≥ 4. We noted that at high concentrations of **1** (7.1 or 9.3 mM), the Cotton effect

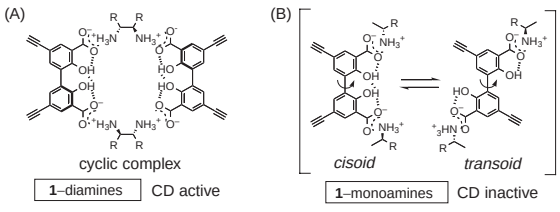


Figure 2. Possible models for complex formation of **1** with chiral diamines (A) and monoamines (B) at [**1**] = 9.3 mM.

Table 1. CD data of **1**–chiral amine complexes in THF at rt[a]

Entry	Diamine	[**1**] /mM	First Cotton effect		Second Cotton effect	
			Sign	Δε (λ)	Sign	Δε (λ)
1	(1*R*,2*R*)-**7**	9.3	−	1.50 (338)	+	3.44 (316)
2		0.12	−	1.98 (338)	+	3.36 (315)
3	(1*S*,2*S*)-**7**	9.3	+	1.46 (338)	−	3.13 (316)
4	(1*R*,2*R*)-**8**	9.3	−	1.18 (339)	+	2.58 (316)
5		0.12	−	0.30 (340)	+	1.03 (319)
6	(1*R*,2*R*)-**9**	9.3	b	b	b	b
7		0.12[c]	−	1.18 (336)	+	0.65 (314)
8	(1*R*,2*R*)-**10**	7.1	−	0.37 (338)	+	0.37 (314)
9		0.12[d]	−	0.52 (339)	+	0.36 (314)
10	(*S*)-**11**	9.3	b	b	b	b
11		0.12[d]	−	3.48 (341)	+	8.72 (313)

[a][Diamine]/[**1**] = 1 (Entries 1, 3, 4, 6, 8, and 10) and 4 (Entries 2, 5, 7, 9, and 11); Δε (M^{-1} cm^{-1}) and λ (nm). [b]Could not be measured because of precipitation of the complex. [c]In THF/$CHCl_3$ = 1/1(v/v). [d]In THF/$CHCl_3$ = 1/9 (v/v).

intensity induced by chiral diamines (**7**, **8**, and **10** in Table 1) showed no change with time, independent of the concentration of the chiral diamines. These concentration and time dependent complexations of (1*R*,2*R*)-**7** with chiral diamines may also support the cyclic tetramer formation, although further studies including the solution and solid-state structure determinations of the acid–base complexes by NMR and X-ray, respectively, are apparently essential.

In summary, we have synthesized a carboxybiphenol that is sensitive to the chirality of the chiral diamines, thus showing an ICD due to an excess single-handed, axially twisted conformation. The carboxybiphenol has reactive ethynyl groups which may be used as a versatile building block for the synthesis of chirality-responsive, π-conjugated helical polymers.

This work was partially supported by Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science, Japan.

References and Notes

1 Reviews: a) E. Yashima, K. Maeda, T. Nishimura, *Chem. Eur. J.* **2004**, *10*, 43. b) S. Allenmark, *Chirality* **2003**, *15*, 409. c) H. Tsukube, S. Shinoda, *Chem. Rev.* **2002**, *102*, 2389. d) J. W. Canary, A. E. Holmes, J. Liu, *Enantiomer* **2001**, *6*, 181.
2 a) K. Maeda, K. Morino, Y. Okamoto, T. Sato, E. Yashima, *J. Am. Chem. Soc.* **2004**, *126*, 4329. b) E. Yashima, T. Matsushima, Y. Okamoto, *J. Am. Chem. Soc.* **1997**, *119*, 6345.
3 a) V. Maurizot, C. Dolain, I. Huc, *Eur. J. Org. Chem.* **2005**, 1293. b) T. Nishimura, K. Maeda, E. Yashima, *Chirality* **2004**, *16*, S12. c) Y. Inai, Y. Ishida, K. Tagawa, A. Takasu, T. Hirabayashi, *J. Am. Chem. Soc.* **2002**, *124*, 2466.
4 a) K. Mikami, M. Yamanaka, *Chem. Rev.* **2003**, *103*, 3369. b) P. J. Walsh, A. E. Lurain, J. Balsells, *Chem. Rev.* **2003**, *103*, 3297.
5 a) H. Takagi, T. Mizutani, T. Horiguchi, S. Kitagawa, H. Ogoshi, *Org. Biomol. Chem.* **2005**, *3*, 2091. b) R. Eelkema, B. L. Feringa, *J. Am. Chem. Soc.* **2005**, *127*, 13480. c) T. Hayashi, T. Aya, M. Nonoguchi, T. Mizutani, Y. Hisaeda, S. Kitagawa, H. Ogoshi, *Tetrahedron* **2002**, *58*, 2803. d) Y. Kubo, T. Ohno, J. Yamanaka, S. Tokita, T. Iida, Y. Ishimaru, *J. Am. Chem. Soc.* **2001**, *123*, 12700. e) T. Mizutani, H. Takagi, O. Hara, T. Horiguchi, H. Ogoshi, *Tetrahedron Lett.* **1997**, *38*, 1991.
6 For details of the synthesis and characterization of **1**–**4** and the Job plot, see the Supporting Information.
7 The optically active compounds used in this study showed no CD above 275 nm.
8 Mizutani, Ogoshi, and co-workers reported that a 2,2′-biphenol bearing bromo and nitro groups exhibited an ICD in the presence of chiral diamines and proposed a ternary complex for axial chirality induction. See refs 5a and 5e.
9 Acceptable fits were observed for a 1:1 complexation of **1** and **7** only when the binding constant (*K*) was greater than 5.0×10^4 M^{-1}, although the *K* value was too large to be precisely estimated under the present conditions.
10 The coldspray ionization (CSI) MS measurement of a 1:1 mixture of **1** (9.3 mM) and (1*R*,2*R*)-**7** in THF operating at −10 °C showed an ion peak at *m*/*z* 1091, which corresponds to $[(\mathbf{1}\cdot\mathbf{7})_2 + Na]^+$.

Published on the web (Advance View) December 21, 2005; DOI 10.1246/cl.2006.110