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Axial Chirality Induction in Flexible Biphenols by Hydrogen Bonding and Steric Interactions

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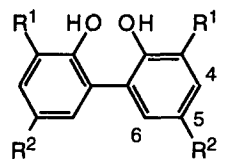
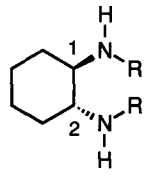
Abstract: Chiral induction in biphenols was studied as a model for intermolecular information transmission. Upon complexation with chiral *trans*-1,2-cyclohexanediamines ($C_6H_{10}(NHR)_2$, R = H, CH_3, $CH_2CH_2Bu^t$), axial chirality was induced in biphenols in toluene, $CHCl_3$ and THF. The induced chirality varies as the alkyl groups on the amino groups vary from H, CH_3 to $CH_2CH_2Bu^t$. The bulky diamine (R = $CH_2CH_2Bu^t$) induced the opposite chirality to that induced by the less bulky diamine (R = CH_3, H). © 1997 Elsevier Science Ltd. All rights reserved.

Information that a molecule has is transmitted from molecule to molecule through intermolecular forces as seen in gene transcription, feedback inhibition and allosteric control. Chiral induction, where a chiral molecule induces chirality in an achiral molecule, is also this kind of process.[1,2] The information transmission processes comprise of, at least, two elementary processes: (1) complex formation and (2) some dynamic processes associated with it such as chemical reactions and conformational changes of interacting molecules.[3] The purpose of our study is to clarify the combination of interactions leading to efficient information transmission. In this paper, we report molecular recognition-triggered chiral induction in biphenol derivatives as a model for such processes.

Biphenols and amines form a complex in solution through hydrogen bonding. The hydrogen bonding between phenolic OH and aliphatic amines has been well studied.[4] We examined the complex formation between biphenols **1–3** and chiral diamines **4–6** by UV-vis and ^{1}H NMR spectroscopy. In the UV-vis spectrum of **1**, upon addition of **4** in toluene, a peak at 310 nm was shifted to 360 nm with an isosbestic point at 330 nm, showing the complex formation through hydrogen bonding to the phenolic hydroxyl groups. Diamine **4** was bound to biphenol **1** in various solvents such as toluene, chloroform, THF and ethanol. In toluene, the Job's plot indicates that the complex has a one-to-one stoichiometric ratio.[5] The binding constant was quite large ($>10^6$ M^{-1}). For instance, 7.7×10^{-5} M of **1** and the same concentration of **4** formed a complex in almost quantitatively. The ^{1}H NMR spectra also indicated the complexation; the resonances for H-1, H-2, and H-1' (of the side chain) were shifted downfield by 0.2 to 0.3 ppm upon complexation with **1**.

We used *p*-nitro derivatives of biphenol since both larger transition moments and lower transition energy than unsubstituted biphenol make UV and circular dichroism (CD) study easier. 2,2'-Biphenol has two





1 $R^1 = Br$, $R^2 = NO_2$ (1*R*,2*R*)-**4** R = $CH_2^{1'}CH_2^{2'}Bu^t$

2 $R^1 = H$, $R^2 = NO_2$ (1*R*,2*R*)-**5** R = CH_3

3 $R^1 = CH_3$, $R^2 = H$ (1*R*,2*R*)-**6** R = H

chiral conformations, both of which rapidly interconverting in a solution at room temperature. Therefore, a solution of **1** shows no CD, while addition of chiral **4** induced CD in **1**. Circular dichroism spectra of the complex of **1**–(1*S*,2*S*)-**4** and its enantiomer are shown in Figure 1. This exciton-type induced CD (ICD) in the 280 nm to 400 nm region due to the biphenol chromophore indicates that axial chirality

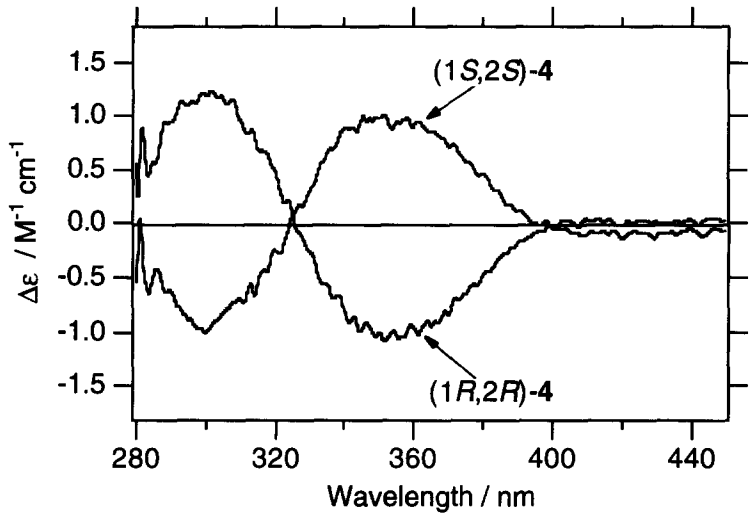


Figure 1. Circular dichroism spectra of the complexes between host **1** and guests (1*R*,2*R*)- and (1*S*,2*S*)-**4** in toluene at 25 °C. [**1**] = 6.83×10^{-5} M, [**4**] = 1.37×10^{-4} M.

was induced in **1** by complexation with chiral **4**. The induced CD intensities observed for complexes between hosts **1**–**2** and diamines **4**–**6** are summarized in Table 1. *N*,*N*'-Dimethylcyclohexanediamine **5**[6] and a simple chiral diamine, *trans*-1,2-diaminocyclohexane (**6**), induced a weaker CD band and its sign was reversed compared to **4** with the same stereochemistry (Figure 2). These observations indicate that the axial chirality induction in **1** is very sensitive to the size of the alkyl groups on the amino groups of the guest.

The ^1H NMR study of the **3**–**4** complex in $CDCl_3$ at 25 °C indicates that intermolecular nuclear Overhauser effects were observed for the aromatic protons, H4, H5, and H6, upon irradiation of the *tert*-butyl protons of **4**.[7] This observation indicates that the alkyl groups on the amino groups were close to the aromatic rings of **3** in the complex. This is consistent with the important role of the alkyl groups in chiral induction, where a direct interaction between the alkyl groups and the aromatic rings should be present.

Table 1. Induced CD in Biphenols **1** and **2** Complexed with Diamines **4** – **6** in Various Solvents at 25 °C

	$\Delta\varepsilon/M^{-1}cm^{-1}$ (wavelength)[a]		
Diamines	**1**	**2**	solvent
(1*R*,2*R*)-**4**	−1.1 (354 nm)		toluene
	0.0 (324 nm)	—[c]	
	1.1 (303 nm)		
(1*S*,2*S*)-**4**	0.6 (354 nm)	0.7 (368 nm)	chloroform[d]
	0.0 (323 nm)	0.0 (317 nm)	
	−0.3 (298 nm)	−0.7 (298 nm)	
(1*R*,2*R*)-**4**	−0.5 (359 nm)	−0.2 (337 nm)	THF
	0.0 (333 nm)	0.0 (315 nm)	
	1.0 (302 nm)	0.4 (298 nm)	
(1*S*,2*S*)-**4**	—[b]	—[b]	acetone
(1*R*,2*R*)-**4**	—[b]	—[b]	acetonitrile
(1*S*,2*S*)-**4**	—[b]	—[b]	ethanol
(1*R*,2*R*)-**5**	0.7 (335 nm)	—[c]	toluene
(1*S*,2*S*)-**6**	0.4 (335 nm)	—[c]	toluene

a) Induced CD was determined after an excess amount of diamines was added and all the biphenols are complexed. b) negligibly small. c) Due to the poor solubility of **2** in toluene, Δε was not determined. d) $CHCl_3$ containing amylene as a stabilizer was used for host **1**, and $CHCl_3$ containing EtOH was used for host **2**, since **2** is hardly soluble in amylene-containing $CHCl_3$.

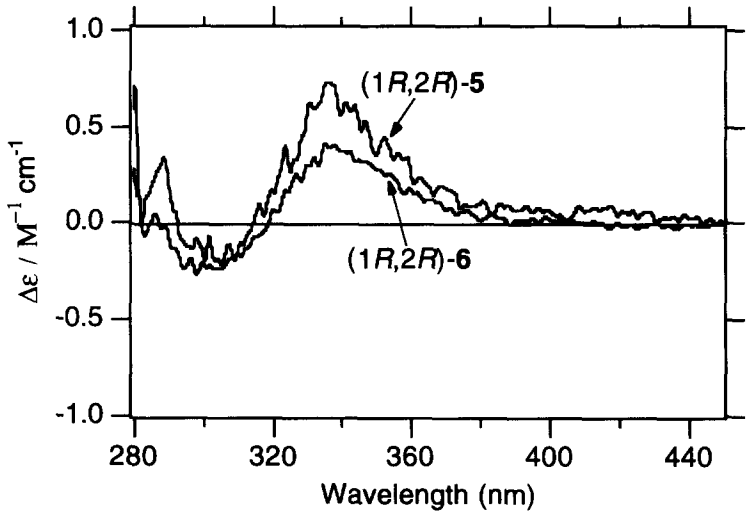


Figure 2. Circular dichroism spectra of the complexes between host **1** and guests (1*R*,2*R*)-**5** and **6** in toluene at 25 °C. [**1**] = 8.91×10^{-5} M, [**5**] = 9.84×10^{-5} M, [**6**] = 9.84×10^{-5} M.

It should be noted that (i) the induced CD diminished in a polar solvent such as acetone, acetonitrile and ethanol, and (ii) induced CD of bromobiphenol **1** was less sensitive to solvent polarity compared to that of **2**, as seen for the larger $\Delta\varepsilon$ of **1**–**4** complex than **2**–**4** complex in THF. The bromine atoms introduced in the proximity of binding site may affect the sensitivity of host-guest hydrogen bonding to the solvent. ^{1}H NMR titration experiments indicate that the binding was strong in acetone, and yet chiral induction was completely suppressed in it. There are at least two interaction modes, one being able to induce chirality and the other being unable to do it. Competitive hydrogen bonding to solvent may alter the hydrogen bonding mode in **1** – **4** complex, leading to diminished chiral induction.

In summary, the size of the alkyl groups and solvent polarity affected the chiral induction. We demonstrated that combination of attractive hydrogen bonding and repulsive van der Waals interactions gives rise to the chiral induction in the present host-guest system.[8]

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5. In $CHCl_3$, the Job's plot indicates that complexes with other stoichiometry than 1:1 also form between **1** and **3**. However, the similar exciton-type induced CD was observed both in $CHCl_3$ and toluene.
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7. Host **3** binds (1*S*,2*S*)-**4** much weakly; the binding constant is 660 M^{-1} in cyclohexane at 25 °C. Induced CD was observed at 305 nm ($\Delta\varepsilon$ = –0.3) and at 273 nm ($\Delta\varepsilon$ = –0.4).
8. We reported that, in a simplified system, the induced chirality varies as the bulkiness of substituents varied, see Mizutani, T.; Takagi, H.; Ogoshi, H. *Tetrahedron Lett.* **1996**, *37*, 2581-2584.

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