Solvent Effect on Helicity Induction of Zinc Bilinone Bearing a Chiral Auxiliary at the Helix Terminal

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Solvent effects on helicity induction in zinc bilinone (ZnBL) derivatives bearing chiral auxiliaries at their 19-positions were investigated by using circular dichroic spectroscopy and ^{1}H NMR experiments. In ZnBLs **1** and **2**, which possess (*R*)-2-methyl-1-phenylpropyloxy and (*R*)-1-phenylethyloxy groups at their 19-positions, respectively, the efficiency of helicity induction was significantly affected by employed solvents (78−95% de in **1** and 33−89% de in **2**). The free energy changes of the *P*−*M* interconversion of **1** and **2** were linearly in proportion to reduction in polarizability of solvents: lower polarizability of solvents led to better efficiency of helicity induction in **1** and **2**. With the support of the ^{1}H NMR study in addition to the molecular modeling previously reported, it was indicated that the solvophobic van der Waals interaction between the alkyl group in the chiral auxiliary and the A-ring of the bilinone skeleton in the preferred conformer plays a crucial role in determining the efficiency of helicity induction in **1** and **2**.

Introduction

Chiral helical structures are widely seen in the living systems as represented by the helical motifs of DNA duplex and α-helix in peptides and have been attracting much attention because such well-defined structures often inspire us to utilize the scaffold for various applications such as stereoselective reactions,[1] optical resolution,[2] molecular recognition,[3] and molecular sensory[4] and memory[5] systems. In this context, much effort has been directed toward constructing chiral helical molecules such as helicenes,[6] metallohelicates,[7] and screw-shaped polymers.[8]

In general, helical chirality, i.e., helicity, is classified into chirality on the basis of the secondary structures[9] and expressed by two forms: right-handed (or *P*) and left-handed (or *M*). When the conformational equilibrium exists between *P*- and *M*-helical structures due to inversion of helicity, one of effective methods to predetermine chirality of the helical secondary structure is introduction of a chiral auxiliary into an appropriate site to generate the difference in thermodynamic stability between the *P*- and *M*-helices through diastereomeric interactions between the chiral group and the helical backbone.[10] The efficiency of helicity induction should be affected by a

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number of external factors such as temperatures,[11] solvents,[12] pressures, pHs, and concentrations. Among those factors, the character of the solvent is quite substantial, because solvent−solute interactions have significant effects on the intramolecular interaction determining the stability of a helical structure. Systematic investigations of solvent effects not only lead to the optimized diastereomeric interactions to control helicity but also provide necessary information on the rational design of enantioselective binding/reaction systems.

We recently reported several approaches to regulation of helicity in zinc bilinones (ZnBLs), zinc complexes of π-conjugated linear tetrapyrroles.[13−17] Bilin derivatives and their metal complexes with Fe(II),[18] Co(II),[19] Mn(III),[19] Ni(II),[20] and Cu(II)[21] often afford helical frameworks due to steric repulsion of the 1- and 19-oxygen atoms, and thus, they are the simplest helical motifs. ZnBL also has a helical structure,[22] and the interconversion of the helix very easily occurs due to the low energetic barrier between the *P*- and *M*-conformers. The helicity can be controlled by coordination of a chiral ligand,[13,14] dimerization of bilinone units,[16] and the covalent attachment of a chiral auxiliary.[15] Especially, introduction of a simple chiral auxiliary at the 19-position, which is a convenient method to control the helicity of the bilinone skeleton, afforded 60−95% diastereomeric excesses (des) of one helical conformer over another one at 288 K.[15,23] In the course of this work, we found that the de of ZnBL is markedly affected by the solvents employed. Here we report the solvent effect on the conformational equilibrium of ZnBL and discuss the mechanism of solvent-controlled helicity induction.

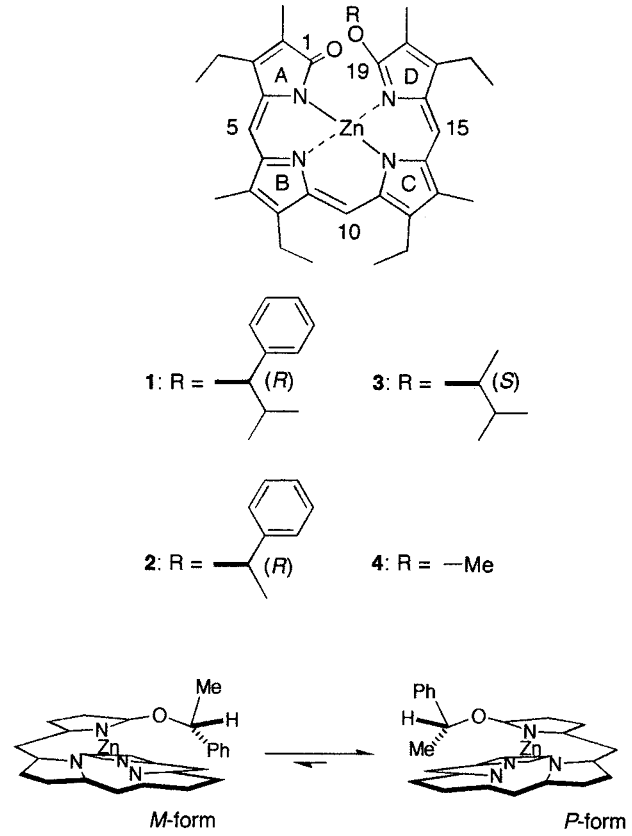

Figure 1. Structures of zinc bilinones employed in the present study, accompanying the numbering scheme. The four pyrrole rings are designated as A, B, C, and D. The lowr portion shows a schematic illustration of the equilibrium between the *P*- and *M*-helical structures.

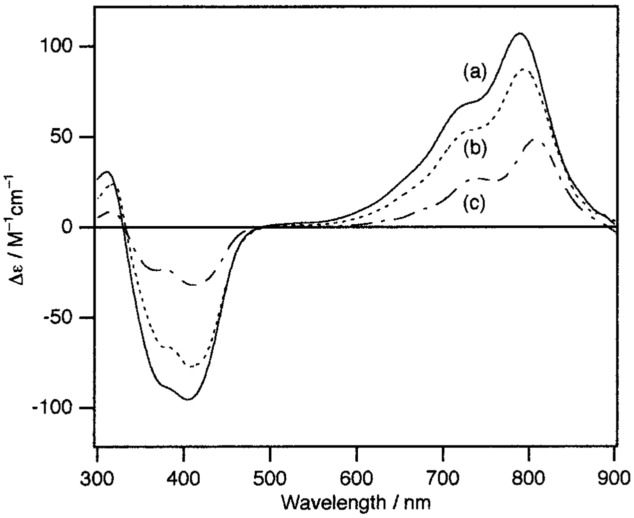

Figure 2. Circular dichroism spectra of **2** in (a) CH_3CN, (b) CH_2Cl_2, and (c) cyclohexane at 288 K. [**2**] = $4.17−4.95 \times 10^{-5}$ M.

Results and Discussion

CD and ^{1}H NMR Spectroscopic Studies on Helicity Induction in ZnBL. The solvent-dependent conformational changes between *P*- and *M*-conformers of ZnBLs were examined for ZnBLs **1**, **2**, and **3**, into which (*R*)-2-methyl-1-phenylpropyloxy, (*R*)-1-phenylethyloxy, and (*S*)-3-methyl-2-butyloxy groups were introduced, respectively (Figure 1). The profiles of helicity induction in these derivatives were previously demonstrated in dichloromethane.[15] We found that the aromatic rings on the

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[23] In the present system, the *P*- and *M*-helical conformers of chiral auxiliary-introduced ZnBLs are diastereomers each other. Therefore, the efficiency of helicity induction is defined as a diastereomer excess (de): when *P*-helicity is predominantly induced, de = {([*P*-conformer] − [*M*-conformer])/([*P*-conformer] + [*M*-conformer])} × 100 (%).

Table 1. CD and UV−Vis Spectral Data and Diastereomeric Excesses for 1−3 in Various Solvents at 288 K

solvent (dielectric constant, polarizability/Å^3)	**1**			**2**			**3**		
	CD $\Delta\epsilon_\lambda$/M^{-1} cm^{-1} (λ/nm)	UV−vis ϵ_λ/M^{-1} cm^{-1} (λ/nm)	de[a] (%)	CD $\Delta\epsilon_\lambda$/M^{-1} cm^{-1} (λ/nm)	UV−vis ϵ_λ/M^{-1} cm^{-1} (λ/nm)	de[a] (%)	CD $\Delta\epsilon_\lambda$/M^{-1} cm^{-1} (λ/nm)	UV−vis ϵ_λ/M^{-1} cm^{-1} (λ/nm)	de[a] (%)
cyclohexane	−110.1 (407)	32 400 (405)	78	−31.9 (411)	28 200 (404)	33	−28.6 (402)	33 000 (404)	20
(2.02, 10.9)	−110.6 (420)						−28.9 (422)		
	139.5 (800)	20 800 (792)		48.7 (808)	14 700 (796)		36.6 (786)	19 000 (787)	
benzene	−126.8 (418)	32 400 (412)	82	−47.7 (416)	29 400 (408)	39	−24.5 (418)	32 900 (408)	21
(2.28, 10.3)	150.7 (801)	20 800 (794)		65.6 (811)	15 800 (795)		30.5 (785)	19 800 (786)	
chloroform	−133.6 (407)	34 300 (405)	80	−42.0 (410)	27 900 (403)	33	−37.7 (401)	35 500 (403)	19
(4.81, 9.50)	149.5 (795)	20 800 (787)		52.5 (801)	13 900 (787)		41.1 (781)	20 000 (779)	
THF	−105.6 (405)	33 800 (405)	84	−48.8 (412)	33 800 (406)	46	−13.0 (399)	34 300 (404)	17
(7.70, 7.93)	124.1 (798)	19 500 (790)		61.2 (805)	16 800 (794)		14.5 (780)	17 800 (787)	
dichloromethane	−142.1 (412)	31 400 (404)	95	−76.7 (410)	30 200 (404)	60	−21.6 (406)	34 500 (402)	7
(9.08, 6.48)	156.9 (788)	17 900 (782)		87.4 (794)	15 600 (785)		23.7 (774)	19 200 (776)	
acetone	−133.2 (409)	32 400 (404)	94	−69.6 (408)	29 600 (402)	67	−16.9 (406)	33 600 (400)	17
(20.7, 6.39)	152.5 (789)	20 100 (782)		84.3 (796)	15 300 (786)		20.5 (772)	19 000 (774)	
acetonitrile	−142.5 (407)	32 200 (402)	>95	−95.7 (405)	29 700 (400)	89	−14.4 (402)	33 200 (400)	11
(38.8, 4.40)	156.3 (785)	19 200 (776)		106.5 (791)	14 600 (781)		16.8 (768)	18 200 (770)	

[a] Determined by ^{1}H NMR spectra.

chiral carbons in ZnBLs **1** and **2** are inevitable for effective helicity induction. The size of the alkyl groups in the chiral auxiliaries in **1** and **2** also affects the helicity induction: by replacing the methyl group of **2** by an isopropyl group, the de increased from 60% to 95% in dichloromethane at 288 K. ZnBL **3**, which possesses no aromatic substituent in its chiral auxiliary, scarcely exhibits a helicity excess (7% de of *P*). As described in our previous paper,[15] the molecular modeling study indicated that the van der Waals interaction between the A-ring and the isopropyl group in **1** gives rise to stabilization of the major conformer to afford quite effective helicity induction. ZnBL **4**, which possesses an achiral substituent at the 19-position, is cited as a reference compound in the later discussion.

Circular dichroism (CD) spectra of **2** in acetonitrile, dichloromethane, and cyclohexane are shown in Figure 2. In cyclohexane, which is the most apolar solvent employed in this study, **2** exhibited relatively small CD intensity, whereas quite a large dichroic absorption was observed in acetonitrile which is the solvent that induces the largest CD signal in this study. The first positive (ca. 800 nm) and second negative (ca. 410 nm) Cotton effects indicate that in these solvents the *P*-helical conformer is preferably induced.[24] We previously found that the CD intensity is directly proportional to the efficiency of helicity induction.[13−15] Therefore, the spectra indicate that helicity induction of ZnBL is much affected by polarity of the solvent: the polar solvent is favorable for helicity induction. Similar solvent-dependent CD behaviors were observed in **1**, although only a marginal solvent effect was observed for CD of **3**.

The diastereomeric excesses of ZnBLs in various solvents were determined by ^{1}H NMR spectroscopy. The rates for the helix inversion of **1**−**3** are fast enough to have an equilibrium mixture of the *P*- and *M*-conformers but are slow on the NMR time scale at 288 K. Thus, taking the result of the CD study into consideration, the ratios of the *P*- and *M*-conformers were determined by comparing their peak integrations. In Figure 3 are shown the expanded region of the ^{1}H NMR spectra of **2** in deuterated acetonitrile, dichloromethane, and cyclohexane, showing the signals of the protons at the 5, 10, and 15 positions and on the chiral carbon. Highly efficient helicity induction was obtained in acetonitrile-d_3 (89% de), whereas the diastereomeric excess in cyclohexane-d_{12} was modest (33% de). As shown in Figure 4, the CD intensities of **2** are almost proportional to diastereomeric excesses determined by ^{1}H NMR, indicating that the CD spectra reflect the efficiency of helicity induction in these solvents: the slope of the line, α, is 1.11, showing a similar $\Delta\epsilon$−de relationship to that obtained for ZnBLs

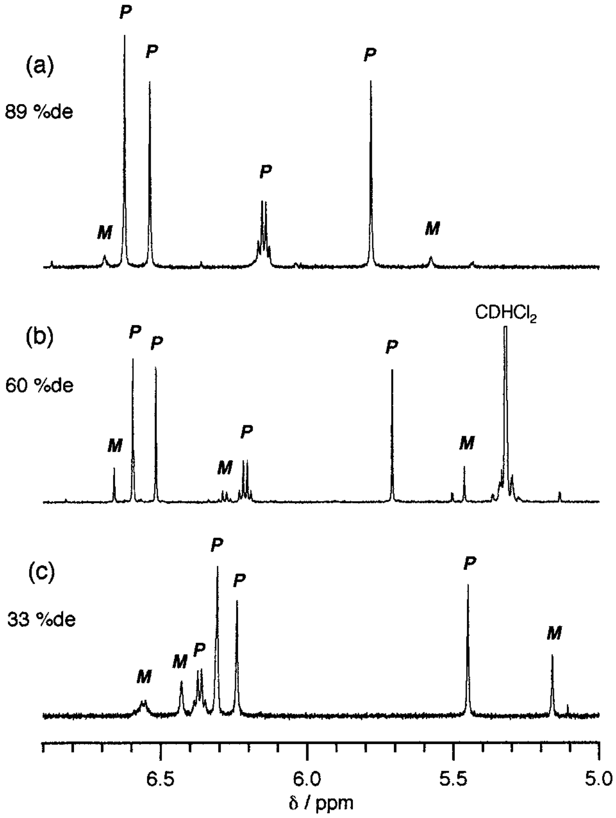

Figure 3. Expanded region of the ^{1}H NMR spectra of **2** in (a) CD_3CN, (b) CD_2Cl_2, and (c) cyclohexane-d_{12} at 288 K. [**2**] = 2.8−3.4 × 10^{-3} M.

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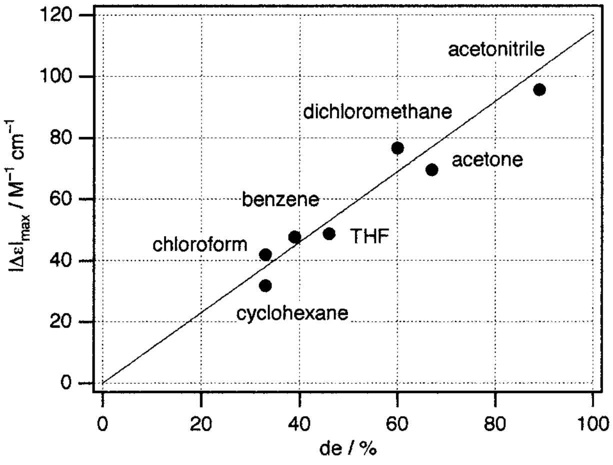

Figure 4. Plot of $|\Delta\epsilon|_{max}$ in the higher energy band against diastereomeric excesses for **2** at 288 K. $|\Delta\epsilon|_{max} = 1.11 \times$ de.

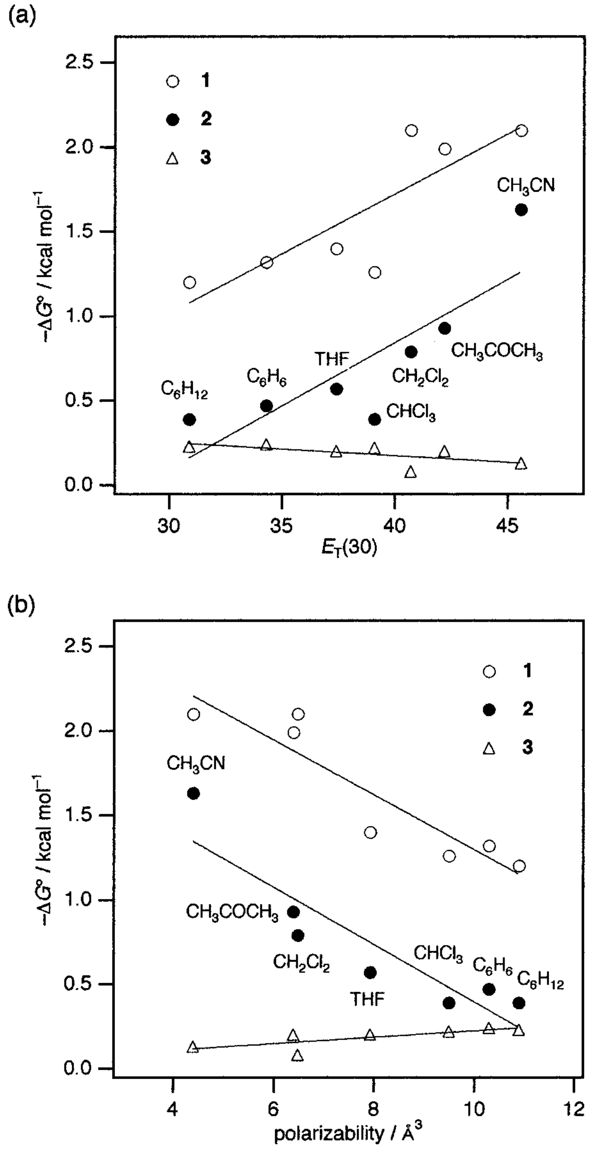

Figure 5. Plots of free energy changes of the interconversion from the *M*- to the *P*-form in ZnBLs **1**−**3** in various solvents at 288 K: (a) against the empirical solvent parameter $E_T(30)$ and (b) against polarizability of solvent molecules. The de of **1** in acetonitrile is defined as 95% because the observed de (>95%) is beyond the identification limit of ^1H NMR spectroscopy.

possessing various chiral auxiliaries at the 19-position ($\alpha = 1.38$, chiral auxiliaries varied)[15] and that obtained for amino ester−zinc 19-methoxybilinone complexes ($\alpha = 1.22$, amino esters varied).[14]

Solvent Effect on Helicity Induction in ZnBL. CD data, UV−vis absorptions, and diastereomeric excesses of ZnBLs **1**−**3** in various solvents are listed in Table 1, along with the parameters of the solvents.[25] In **1** and **2**, the diastereomeric excesses ranged from 78 to >95% and from 33 to 89%, respectively, when the solvent polarity varied. In any solvent, the *P*-conformer is more stable than the *M*-conformer for each ZnBL derivative. Although one might think that solvent molecules possessing Lewis basic activity, such as acetone and acetonitrile, are coordinated to the central zinc, UV−vis spectra in any solvent employed here exhibited a similar spectral profile, and thus the coordination of solvent molecules is not a major factor for solvent effects on helicity induction.[26] When the dielectric constant is taken as a measure of solvent polarity, high diastereomeric excesses were afforded for **1** and **2** in polar solvents, while the decrease in solvent polarity brought about low de values. On the other hand, helicity induction of ZnBL **3** was scarcely affected by changes in solvent.

Although the results described above seemingly imply that the solvent effect on helicity induction in ZnBLs originates from the solute−solvent electrostatic interaction between the permanent dipole of ZnBL and that of the solvent molecule, another possibility lies in the contribution from polarizability of solvents. In Table 1, the order of the increase in polarity of a solvent is almost parallel to the decrease in polarizability of a solvent molecule. Indeed, as shown in Figure 5, both plots of the free energy changes in the *P*−*M* equilibrium of **1** and **2** against the empirical solvent parameter of polarity $E_T(30)$[27] and polarizability of solvent molecules afforded valid linearity. Here, what must be kept in mind is that the mechanism of helicity induction based on solvent polarizability is different in nature from that based on the dielectric property of the solvent: solvent polarizability should significantly affect dispersion forces between ZnBL and solvent molecules to afford some perturbation to intramolecular interactions between the chiral auxiliary and the bilinone framework. That is, when they contact closely with each other through van der Waals interaction as discussed later, it would be weakened by solvation by polarizable solvents. Although the contribution from both of the polarity and polariz-

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(26) When a solvent molecule is coordinated to the zinc in ZnBL, the absorption maximum in the low energy band is expected to exhibit a significant bathochromic shift, as seen in complexation of ZnBL with an amino ester ($\Delta\lambda$ = ca. 30 nm).[13,14] In methanol and ethanol, no remarkable bathochromic shift was observed compared to the spectra in nonpolar solvents, but the spectra in the high energy band exhibited the different shape from those in nonpolar solvents (see Supporting Information for UV−vis absorption spectra of **2** in CH_2Cl_2, methanol, and CH_3CN). To get rid of ambiguity derived from the coordination effect, the data in alcohols were omitted from the discussions. Incidentally, the ^1H NMR titration revealed that the complexation of Gly-O^{t}Bu to **2** induced a bit of decrease in de from 81% to 73% in CD_2Cl_2 at 223 K.

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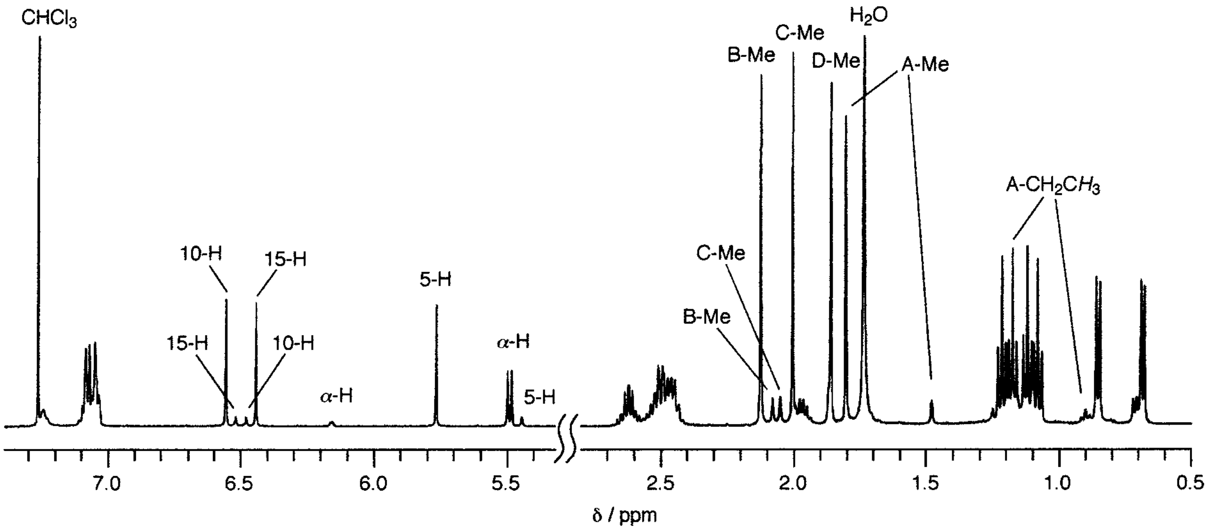

Figure 6. ^{1}H NMR spectra of **1** in $CDCl_3$ at 288 K. [**1**] = 5.3×10^{-3} M. α-H is the proton on the stereogenic carbon in the chiral auxiliary.

ability of solvents looks proper from the $\Delta G° - E_T(30)$ and $\Delta G°$−polarizability plots, the latter is much likely to be a main factor in the solvent effect on the helicity induction from the following reasons: (1) the correlation in the $\Delta G°$−polarizability plot for each ZnBL is better than that in the $\Delta G° - E_T(30)$ plot (the correlation coefficients for ZnBLs **1**, **2**, and **3**: $\Delta G° - E_T(30)$, 0.836, 0.832, and 0.652; $\Delta G°$−polarizability, 0.924, 0.909, and 0.766); (2) any orientation of the chiral auxiliaries in **1** and **2** would not afford a significant difference in the permanent dipole of the whole molecule between the *P*- and *M*-conformers because their partial dipoles are not so large; (3) upon addition of tetrabutylammonium iodide (up to 11 mM) to a CH_2Cl_2 solution of **2**, any remarkable change of the CD spectrum was not found ($\Delta\epsilon_{410} = -76.3$ and $\Delta\epsilon_{794} = 86.2$ M^{-1} cm^{-1} at 288 K), indicating that the helicity induction is scarcely affected by electrostatic perturbation by addition of the electrolyte.[28]

Intramolecular Solvophobic Interaction Determining the Stability of the Preferred Helical Conformer. As reported in our previous work,[15] we proposed the possible structures of the most stable *P*- and metastable *M*-conformers of **1** obtained by the molecular mechanics grid search followed by the ab initio molecular orbital calculations. In the *P*-conformer, the isopropyl group in the chiral auxiliary makes van der Waals contact with the A-ring of the bilinone skeleton. On the other hand, it is positioned at the far site from the bilinone framework in the *M*-conformer and, instead, the phenyl group is placed on the A-ring.

As discussed above, it was concluded that the solvent effect on the helicity induction originates from polarizability of solvent molecules. Thus, in largely polarizable solvents, the molecule of **1** is solvated mainly through dispersion forces with the solvent molecules so that the van der Waals interaction between the chiral auxiliary and the A-ring is reduced, resulting in less thermodynamic stability of the *P*-conformer. In other words, the solvophobic intramolecular interaction in a solvent with low polarizability stabilizes the folded conformation where the alkyl group of the chiral auxiliary is in contact with the bilinone A-ring, and therefore, the equilibrium between the *P*- and *M*-conformers is driven to the preferred one.

Table 2. ^{1}H NMR Chemical Shifts[a] (ppm) for Selected Protons in ZnBLs 1, 2 and 4

	1		2		
protons	*P*	*M*	*P*	*M*	4
5-H	5.77	5.45	5.68	5.41	5.51
10-H	6.56	6.48	6.52	6.51	6.47
15-H	6.44	6.52	6.41	6.54	6.48
A-Me	1.80	1.48	1.83	1.59	1.79
B-Me	2.13	2.08	2.08	2.02	2.00
C-Me	2.01	2.05	2.01	2.09	2.05
D-Me	1.86	1.86	1.79	1.80	1.71
A-CH_2CH_3	1.18	0.90	1.15	0.85	1.12
α-H	5.49	6.16	6.27	6.37	
β-Me[b]			1.43	1.67	

[a] In $CDCl_3$ at 288 K. [b] The protons of the methyl group attached to the stereogenic carbon in the chiral auxiliary.

To attain the experimental support for the structures of the conformers in solution, a detailed ^{1}H NMR analysis was performed. In Figure 6 is shown the ^{1}H NMR spectrum of **1**, and full assignment of all protons was achieved by using NOE, ^{1}H decoupling, and saturation transfer techniques. The chemical shifts for the selected protons in **1** are listed in Table 2, along with those in **2** and 19-methoxy zinc bilinone **4**.[29] The significant differences in the chemical shifts between the *P*- and *M*-conformers ($\Delta\delta > 0.2$ ppm) observed for 5-H, the methyl protons in the A-ring (A-Me), and the methyl protons in the A-ring's ethyl (A-CH_2CH_3) indicate that the chiral auxiliary makes close contact with the A-ring of bilinone and that the orientation of the chiral auxiliary with respect to the bilinone skeleton is quite different between the two diastereomeric conformers. Regarding the spectrum of **4** as a standard, the downfield shift of 5-H in

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(28) Although this experiment was carried out on the basis of the assumption that addition of electrolytes to nonaqueous solvents affects microscopically solvation of ZnBLs to afford electrostatic perturbation around the solvation shell, effects of electrolytes on dielectric properties of solvents have not so far investigated in detail. In addition, not so much examples for the interactions between organic solutes and electrolytes in nonaqueous media have been reported: (a) Lavallee, R. J.; Zimmt, M. B. *J. Phys. Chem.* **1994**, *98*, 4254−4260. (b) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443−12452.

(29) The assignment of the protons in **2** was carried out in a manner similar to that used for **1**.

the *P*-conformer and upfield shifts of A-Me and A-CH_2CH_3 in the *M*-conformer were observed in **1**, although significant differences were not observed for the other protons in both conformers. Especially, the upfield shifts of A-Me and A-CH_2CH_3 in the *M*-conformer ($\Delta\delta$ −0.32 and −0.28 ppm, respectively, compared to those in the *P*-conformer) strongly suggest that the phenyl group is close to the A-ring to give ring current anisotropy to A-Me and A-CH_2CH_3, supporting the proposed structure of the metastable conformer with the phenyl group tilted toward the A-ring.[15]

A similar trend in the ^1H NMR signals of the *P*- and *M*-conformers was observed for **2**: as listed in Table 2, the upfield shifts of A-Me and A-CH_2CH_3 in the *M*-conformer were observed in the ^1H NMR spectrum of **2** (in $CDCl_3$ at 288 K, $\Delta\delta$ −0.24 and −0.30 ppm, respectively, compared to those in the *P*-conformer). In addition, the methyl group attached to the stereogenic carbon (β-Me) in *P*-**2** is shifted upfield by 0.24 ppm compared to that in *M*-**2**, indicating the aliphatic group in the chiral auxiliary in *P*-**2** is placed on the A-ring to receive the magnetic anisotropy from the pyrrole π-electron system. Thus, in the case of **2**, the van der Waals interaction as seen in **1** should still contribute to the stabilization of the preferred conformer. Although the reason for the quite modest solvent dependence of helicity induction in **3** is difficult to explain at this point, it might be agreeable to see that any orientation of the chiral auxiliary with respect to the bilinone skeleton leads to folding via van der Waals interaction more or less to produce relatively small difference in the stability between both conformers.

Conclusions

In summary, we have found that helicity induction in ZnBLs **1** and **2** is largely affected by polarizability of the solvents employed. In cyclohexane, which possesses high polarizability (10.9 Å^3), the efficiency of helicity induction in **1** and **2** was markedly reduced (78 and 33% de at 288 K, respectively), whereas the decrease of polarizability led to more effective helicity induction (for example, >95 and 89% de for **1** and **2** in acetonitrile at 288 K, respectively; polarizability, 4.41 Å^3). This is because the solvation in the solvent with high polarizability breaks the intramolecular van der Waals interaction between the aliphatic group in the chiral auxiliary and the A-ring of the ZnBL skeleton to lead to destabilization of the preferred conformer, i.e., to reduce the efficiency of helicity induction.

It should be noted that the solvophobically driven chiral induction was observed in a wide range of solvents. Solvophobic interactions in nonaqueous media, as observed here, often play major roles in the folding of the oligo(phenylene ethynylene)s into the helical conformers,[30] apolar binding of an aromatic guest by a cyclophane host,[31] the aromatic interaction in metal tris-bipyridine complexes,[32] and so on, and deep insights into these interactions controlling molecular folding in solution will provide understanding of conformational control in biopolymers and rational designs of well-defined higher order structures.

Experimental Section

ZnBLs **1**−**3**[15] and **4**[14] were prepared according to the procedures reported previously. ^1H NMR spectra were recorded at 500 MHz in deuterated solvents. Chloroform-*d*, dichloromethane-d_2, and acetonitrile-d_3 were purchased from Isotec, Inc., and TMS (0 ppm), $CDHCl_2$ (5.32 ppm), and CD_2HCN (1.95 ppm) were used as internal standards, respectively. Cyclohexane-d_{12}, benzene-d_6, THF-d_8, and acetone-d_6 were purchased from Euriso-Top, Inc., CEA group, and $C_6D_{11}H$ (1.38 ppm), C_6D_5H (7.15 ppm), C_4D_7HO (3.58 ppm), and CD_2HCOCD_3 (2.04 ppm) were used as internal standards, respectively. UV−vis absorption and circular dichroism spectra were recorded on a Jasco V-550 spectrometer and a Jasco J-720WI spectropolarimeter, respectively, equipped with thermostated cell compartments. For the preparation of sample solutions for spectroscopic measurements, solutions of zinc bilinones were prepared in volumetric flasks at 15 °C. All solvents of spectroscopic grade were purchased from Nacalai Tesque, Inc. for UV−vis and CD studies.

Supporting Information Available: UV−vis absorption spectra of **2** in dichloromethane, methanol, and acetonitrile at 288 K and 500 MHz ^1H NMR spectrum of **2** in chloroform-*d* at 288 K. This material is available free of charge via the Internet at http://pubs.acs.org.

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