Allosteric Chirality Amplification in Zinc Bilinone Dimer

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Allosteric control of conformation in supramolecular systems has been a topic of active investigations.[1−8] Zinc bilinone is a helical molecule[9] which undergoes racemization between the right-handed (*P*) and left-handed (*M*) conformers in solution. We demonstrated that coordination of a chiral guest to the zinc can induce helical chirality due to the shift in the *P*−*M* equilibrium.[10] In bilinone dimers bearing a flexible achiral spacer, the chirality of one bilinone unit affects the chirality of the other bilinone unit, resulting in an equilibrium mixture of the homochiral and the heterochiral conformers. One would expect that binding of the chiral guest to one zinc bilinone subunit induces the helical chirality in the bilinone (arrow *a*, Figure 1), and then this conformational change can allosterically control the helical chirality of the other bilinone through intramolecular interactions (arrow *b*, Figure 1). To realize a chiral amplification system along this mechanism, we prepared bilinone dimers with varying lengths of oligomethylene bridges and investigated the effects of the helix−helix interactions on the efficiency of chiral induction. We report here that amines trigger a conformational switch from a heterochiral conformation to a homochiral conformation, resulting in efficient helicity induction in the bilinone dimer.

The zinc bilinone dimers were prepared by a nucleophilic ring cleavage of oxoniaporphyrin by alkoxides.[10,11] The dimers were characterized by UV−vis, ^{1}H NMR, and high-resolution mass spectroscopies. We employed L-leucine methyl ester (L-Leu-OMe), L-aspartic acid dimethyl ester (L-Asp(OMe)-OMe), and (*R*)-1-(1-naphthyl)ethylamine ((*R*)-NEA) as chiral guests. The binding constants for these guests were determined by monitoring the absorbance changes at 710 and 780 nm in CH_2Cl_2 at 288 K as a function of guest concentrations and fitting the saturation plot to the 1:1 binding isotherm. The spectroscopic changes exhibited several isosbestic points, indicating that two guest molecules were independently bound to each of the zinc binding sites of the bilinone dimer. The apparent binding constants K_{app} are listed in Table 1. The magnitudes of K_{app} of **3** were approximately the same as those of **4**, but those of **1** and **2** were larger than those of monomer **4**. This suggests that **1** and **2** adopt a conformation different from that of **3** and **4**.

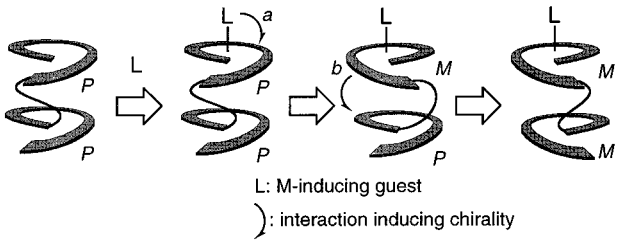
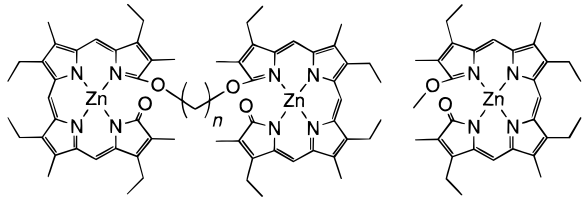


Figure 1. Possible mechanism of chirality amplification in zinc bilinone dimer. Addition of a chiral guest (L), which is able to induce *M*-helicity in bilinone, can convert *PP* conformer to *MM* conformer in a stepwise fashion. For simplicity, only 1:1 complexes between bilinone dimer and guest are shown, although 1:2 complexes are also involved in equilibrium. Arrow *a* represents the interaction between guest chirality and host helicity, and arrow *b* represents the intramolecular interaction between host helicity and host helicity.

Table 1. Apparent Binding Constants (K_{app}, M^{-1}) for Amino Acid Esters and Amine in CH_2Cl_2 at 288 K[a]

	K_{app}, M^{-1}			
	L-Asp(OMe) −OMe	L-Leu-OMe	Gly-O^{t}Bu	(*R*)-NEA
1	122	170	261	577
2	75	102	148	323
3	62	89	130	285
4	64	89	123	291

[a] K_{app} was obtained assuming that dimers consist of two independent zinc bilinones. [**1**−**4**] = 2.4 × 10^{-5} M, [guest] = 0−0.1 M. The standard deviations for the curve fitting were 1−3%.



1: *n* = 2
2: *n* = 3
3: *n* = 4

4

The induced circular dichroism (ICD) was observed in the bilinone band of a complex between **1**−**4** and chiral guests. The sign of the Cotton effects indicated that *M*-helicity is induced in **1**−**4** by L-Asp(OMe)-OMe, L-Leu-OMe, and (*R*)-NEA.[11] The magnitude of the ICD for a given guest increased in the order **2** < **3** < **1** as shown in Table 2. The ^{1}H NMR of **1**−**3** showed two sets of signals, one from a homochiral conformer and another from a heterochiral conformer. The molar ratios *R* of the homochiral conformer to the heterochiral conformer were determined from the ^{1}H NMR spectra. By adding a chiral guest, the signals of these conformers were split into three sets arising from *MM*, *MP*, and *PP* species owing to the diastereomeric complex formation, the ratios of which were also determined by integration of the signals (Figures S5−S7, Supporting Information). The enantiomeric excesses of helices, ee = ([*MM*] − [*PP*])/([*PP*] + [*PM*] + [*MM*]), in the presence of an excess amount of guest at 223 K are listed in Table 2. The enantiomeric excesses for *M*

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Table 2. Differential Dichroic Absorptions (cm^{-1} M^{-1}) and Enantiomeric Excesses (%) of Helices in the Complexes between **1** and **4** and Amino Acid Esters and Amine in Dichloromethane at 223 K[a]

	$\Delta\epsilon$, cm^{-1} M^{-1}			enantiomeric excess (%)		
	L-Asp(OMe)-OMe	L-Leu-OMe	(*R*)-NEA	L-Asp(OMe)-OMe	L-Leu-OMe	(*R*)-NEA
1	88	66	56	86	62	61
2	64	37	26	66	34	24
3	80	50	38	76	43	29
4	78	46	34	75	45	30

[a] $\Delta\epsilon$ was obtained by extrapolation to 100% complexation. Plot of $\Delta\epsilon$ against [complex]/[total bilinone] showed a linear relationship.

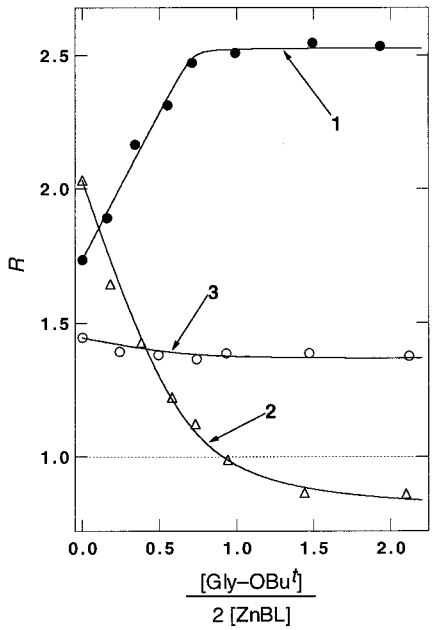

Figure 2. Plots of the ratios of homochiral to heterochiral conformers, R = ([*MM*-**1**−**3**] + [*PP*-**1**−**3**])/[*MP*-**1**−**3**], against the glycine *tert*-butyl ester concentration normalized by the concentration of monomeric unit of zinc bilinone. The ratios R were determined by ^{1}H NMR signal integration in CD_2Cl_2 at 223 K. [**1**−**3**] = 2.5×10^{-3} M. The lines were calculated on the basis of a model in which coordination of one guest causes the shift in the ratio R.

over *P* conformers were increased in the order **2** < **3** < **1**, which is identical to the increasing order of ICD magnitude. The enantiomeric excesses were higher in **1** than in monomer **4**; i.e., L-amino acid esters and (*R*)-amine can induce *M* chirality more efficiently in **1** than in **4**.

Figure 2 shows the plots of the molar ratios of the homochiral conformer to the heterochiral conformer, R, against the ratio of [Gly-O^{t}Bu] to a bilinone unit, i.e., [Gly-O^{t}Bu] /(2[**1**−**3**]). The ratio R increases in the order **3** < **1** < **2** *in the absence of guest*. It is noteworthy that these ratios changed substantially when *achiral* amino acid ester or amine was added. Thus, the ratios R in the presence of an excess amount of Gly-O^{t}Bu increased in the order **2** < **3** < **1**. The homochiral structure was preferentially induced in **1**, while the heterochiral structure was induced in **2** by the addition of Gly-O^{t}Bu. In the plot, a plateau was reached at R = 2.5 for **1** when the molar ratio of Gly-O^{t}Bu to the zinc bilinone unit was less than 1, showing that binding of a Gly-O^{t}Bu molecule to one zinc bilinone induced the same chirality in the neighboring bilinone. A similar behavior is seen for the addition of benzylamine: the ratios R in the presence of 10 equiv of benzylamine were 3.0, 0.8, and 1.5 for **1**, **2**, and **3**, respectively. Modeling studies on **1** and **2** suggest that the homochirality of **1** may arise from a stacking interaction.

The more efficient induction of helical chirality in **1** can be explained by assuming the following thermodynamic scheme. We consider two chiral interaction energies: (1) the point chirality−helical chirality interaction free energy as defined by the free energy difference between the chiral guest−*P*-**1** complex and the chiral guest−*M*-**1** complex ($\Delta\Delta G_1$) (this is schematically illustrated as arrow *a* in Figure 1), and (2) the homochiral and heterochiral interaction energy as defined by the free energy difference between the homochiral conformation and the heterochiral conformation in the **1**−amino acid ester complex ($\Delta\Delta G_2$), which is shown as arrow *b* in Figure 1. For L-Asp(OMe)-OMe, the value of $\Delta\Delta G_1$ was estimated from the diastereomeric excess of L-Asp(OMe)-OMe−**4** complex, and the value of $\Delta\Delta G_2$ was estimated from the homochiral/heterochiral conformer ratio, R, in the presence of Gly-O^{t}Bu. Assuming that these two interactions contribute additively, the relative free energies of *MM*, *MP*, and *PP* conformers are 0, $\Delta\Delta G_1 + \Delta\Delta G_2$, and $2\Delta\Delta G_1$, respectively. Then, the calculated ratio is *MM*:*MP*:*PP* = 1.0:0.11:0.02, while the observed ratio is *MM*:*MP*:*PP* = 1.0:0.13:0.02 in CD_2Cl_2 at 223 K. Therefore, the distribution pattern was reproduced on the basis of this simple model. The higher enantiomeric excess observed in the complex between **1** and L-Asp(OMe)-OMe is thus attributable to the intrinsic tendency of dimer **1** to adopt a homochiral conformer upon complexion with guest. Similarly, the lower enantiomeric excess in the **2**−L-Asp(OMe)-OMe complex is attributable to the tendency of **2** to adopt a heterochiral conformer upon complexation with guest.

In conclusion, we demonstrated that binding of a guest (an allosteric effector) triggers a conformational switch from heterochirality to homochirality, and this allosteric effect is used to amplify the chiral induction in the zinc bilinone dimer.

Supporting Information Available: Synthetic scheme of **1**−**3**, ^{1}H NMR spectra of **1**−**3**, CD spectra of complexes between **1**−**4** and L-Leu-OMe, procedures for calculation of ratios of conformers, ^{1}H NMR spectra of **1**−**3** in the presence of varying concentrations of L-Asp(OMe)-OMe, and stable conformers of **1** and **2** determined by molecular modeling studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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