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Synchronous helicity control in zinc bilinone trimer

Katsushi Hamakubo,[a] Shigeyuki Yagi,[a,*] Hiroyuki Nakazumi,[a] Tadashi Mizutani[b] and Susumu Kitagawa[c]

[a]*Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Gakuen-cho, Sakai, Osaka 599-8531, Japan*
[b]*Department of Molecular Science and Technology, Faculty of Engineering, Doshisha University, Kyotanabe, Kyoto 610-0312, Japan*
[c]*Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8530, Japan*

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Abstract—In order to develop an artificial signal transmission/amplification system triggered by chiral recognition, we synthesized a series of zinc bilinone (ZnBL) trimers bearing a tripodal spacer and investigated homohelicity induction by complexation with chiral α-amino esters. Controlling the length of the peripheral alkyl groups in ZnBL moieties led to preorganization of the trimer to homohelical conformers. In addition, complexation with chiral α-amino esters induced the formation of the chiral homohelical conformer in which three ZnBL moieties adopted the same helicity.

Cooperative behaviors of subunits in multitopic receptors have received much interest, because they are applicable to the construction of signal amplification systems in the development of supramolecular devices such as chemosensors.[1] Lots of multitopic receptors with allosteric functionality have so far been investigated,[2,3] where molecular information of guests are transmitted as integrated spectroscopic signals of the subunits. However, relatively small numbers of examples for chiral guests have been reported.[4–6] In order to realize chiral signal amplification, the most promising strategy is to achieve homochirality induction of racemizing subunits on guest recognition in a multitopic receptor.

We previously reported helicity induction of zinc bilinone (ZnBL), a helical linear tetrapyrrole-zinc(II) complex, by complexation with chiral guests.[7] Although ZnBL racemizes between the right-handed (*P*) and left-handed (*M*) helical conformers, coordination of an α-amino ester to the zinc center induces preferred helicity (*P* for D-amino esters and *M* for L-isomers), where the helicity excess depends on the guest. Here, we report homohelicity induction in ZnBL trimers bearing a tripodal spacer upon complexation with chiral guests. Most remarkably, one of the trimers is converted to a completely regulated homohelicity form.

ZnBL trimers **1**–**4**, in which the peripheral substituents R^1 and R^2 varied, were prepared by nucleophilic ring cleavage of the corresponding [5-oxoniaporphyrinato]zinc(II) chloride by a trialkoxide of trimethylolethane followed by zinc insertion.[8,9] The trimers are expected to be in equilibria among the homohelical (*PPP* and *MMM*) and heterohelical conformers (*PPM* and *PMM*) because of low energetic barrier of helix inversion of ZnBL. The tripodal spacer is expected to give a C_3 symmetrical arrangement of the subunits in the homohelical conformers, while such symmetry should be broken in the heterohelical conformers. Indeed, complicated signals were observed for **1**–**3** in the low field region of the ^{1}H NMR spectra at 223 K,[10] indicating that **1**–**3** consisted of a mixture of the homohelical and heterohelical conformers (see Supplementary data). On the other hand, one set of signals for the 5, 10, and 15-protons and methylene protons –CH_2–ZnBL was observed for **4**, indicating that the highly symmetrical homohelical conformers (a racemic mixture of *PPP* and *MMM*) were predominantly

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* Corresponding author. Tel.: +81 72 2549324; fax: +81 72 2549913; e-mail: yagi@chem.osakafu-u.ac.jp

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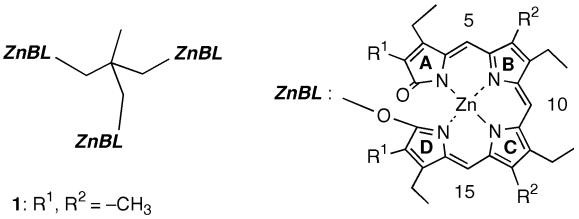
formed (Fig. 3a, discussed below). Thus, introduction of methyl and propyl groups to R^1 and R^2, respectively, led to significant stabilization of the homohelical conformers.



1: R^1, R^2 = –CH_3
2: R^1, R^2 = –$CH_2CH_2CH_3$
3: R^1 = –$CH_2CH_2CH_3$, R^2 = –CH_3
4: R^1 = –CH_3, R^2 = –$CH_2CH_2CH_3$

Me–***ZnBL***
5: R^1, R^2 = –CH_3

The stability of homohelical conformers in **4** was also suggested by a molecular modeling study. The most stable conformer was obtained as a C_3 symmetrical structure as shown in Figure 1.[11] This structure was stabilized by the van der Waals contacts of the 3-ethyl group with the 7-propyl group in the neighboring subunit. Thus, lack of the 7-propyl groups leads to destabilization of the homohelical conformers, as is observed in the trimers **1** and **3**. In the ^{1}H NMR spectrum of **4**, the upfield shift of the 18-Me signal was observed compared to that in **5** ($\Delta\delta$; 0.58 ppm), indicative of magnetic anisotropy from the pyrrole ring. In the molecular modeling structure, the proximity between the 18-methyl group in one subunit and the B-ring in another ZnBL was found. That is, the homohelical conformers of **4** should adopt a compactly folded structure, and thus, one can see that introduction of the 18-propyl groups (trimers **2** and **3**) brings about steric hindrance to disturb compact folding to the C_3-homohelical structure. Therefore, introduction of the 7-propyl and 18-methyl groups is essential to stabilization of the homohelical conformers in the present system.

Homohelicity induction in the ZnBL trimers upon complexation with chiral guests was examined by circular dichroism (CD) spectroscopy. In Figure 2 are shown the high-energy regions of CD spectra of **1**–**5** in the presence of L-Phe-OMe,[12] where the differential dichroic absorption $\Delta\varepsilon$ was normalized by a ZnBL unit. The CD was silent in the absence of any guests, and the induced CD (ICD) was generated by complexation of the ZnBL subunits with the chiral guest molecules. The positive Cotton effect in this region indicated that *M*-helicity of ZnBL was enriched.[7] The CD signal of **4** was extremely enhanced, compared to that of the reference monomer **5**, whereas the ICD for **1**–**3** was not more than that observed for **5** in magnitude. As it is known that the magnitude of the ICD is approximately proportional to the helicity excess (h.e.) of the ZnBL framework, the ZnBL subunits in **4** cooperatively adopted the same helicity to afford the enantiomeric homohelical form, whereas the homohelicity induction in **1**–**3** was not so facilitated. As summarized in Table 1, similar enhanced Cotton effects were observed for other chiral guests in the case of **4**: the values of $\Delta\varepsilon$ reached ca. 120 M^{-1} cm^{-1}, which are regarded as a maximum value of $\Delta\varepsilon$ of the ZnBL framework on the basis of the $\Delta\varepsilon$–h.e. correlation in **5**.[7]

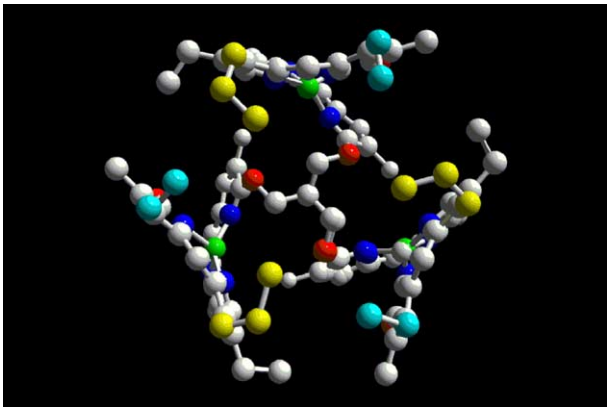


Figure 1. A C_3 symmetric structure of **4** obtained by B3LYP/3-21G calculations, where the C-alkyls as well as the D-ethyl were replaced by hydrogen atoms to simplify geometry optimization. View looking down the C_3 symmetry axis. 7-Propyl and 3-ethyl groups are shown in yellow and light blue, respectively. Hydrogen atoms were omitted for clarity.

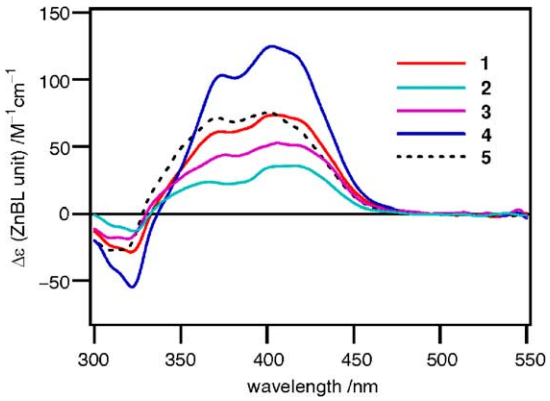


Figure 2. CD spectra in the high-energy region for **1**–**5** in the presence of L-Phe-OMe in $CHCl_3$ at 223 K: [ZnBL unit] = 33.5–45.5 μM, [L-Phe-OMe] = 54.7–61.1 mM. The values of $\Delta\varepsilon$ were normalized by a ZnBL unit.

Further investigation of homohelicity induction in **4** was carried out by ^{1}H NMR titration experiments. In Figure 3 are shown the ^{1}H NMR spectra of **4** in the presence of varying concentrations of L-Phe-OMe in $CDCl_3$ at 223 K. Addition of a small amount of L-Phe-OMe to a solution of **4** gave rise to the complexation-induced chemical shift change (CIS) accompanied by splitting of each signal into two (Fig. 3b), indicating that the complexation–dissociation time scale is faster than the NMR time scale and that the interconversion between the two isomers was slower.[13,14] These two sets of signals were assigned to those of *PPP*- and *MMM*-**4** complexed with the guest molecules, and any heterohelical conformers were not observed, indicating that the equilibria significantly moved to the complexed homohelicity isomers as shown in Scheme 1. As the concentration of L-Phe-OMe increased (Fig. 3c and d), one signal set finally disappeared, whereas the other still remained, accompanied by further CIS. Thus, in combination with the ICD sign, the *MMM*-**4** was found to be exclusively

Table 1. The differential dichroic absorption ($\Delta\varepsilon$) of **1**–**5** in $CHCl_3$ at 223 K upon complexation with various chiral guests: [ZnBL unit] = 0.0335–0.0501 mM, [chiral guest] = 54.5–61.1 mM

Receptor	$\Delta\varepsilon/M^{-1}\,cm^{-1}$ (λ/nm, helicity)[a]			
	(*R*)-NEA[b]	L-Leu-OMe[b]	D-PhGly-OMe[b]	L-Phe-OMe[b]
1	30.4 (397, *M*)	58.0 (403, *M*)	−46.2 (420, *P*)	73.4 (404, *M*)
2	41.0 (398, *M*)	88.8 (397, *M*)	−106.1 (406, *P*)	35.6 (404, *M*)
3	44.6 (401, *M*)	60.5 (402, *M*)	−61.1 (401, *P*)	45.2 (406, *M*)
4	92.4 (402, *M*)	118.2 (400, *M*)	−119.3 (403, *P*)	124.9 (403, *M*)
5	44.2 (397, *M*)	53.8 (401, *M*)	−61.2 (403, *P*)	75.2 (400, *M*)

[a] Helicity predominantly formed.
[b] Abbreviations: NEA, 1-(1-naphthyl)ethylamine; Leu-OMe, leucine methyl ester; PhGly-OMe, phenylglycine methyl ester; Phe-OMe, phenylalanine methyl ester.

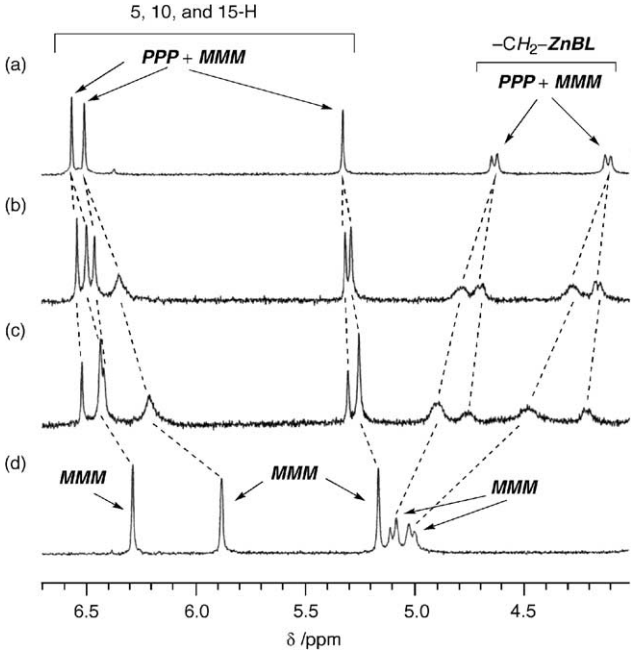
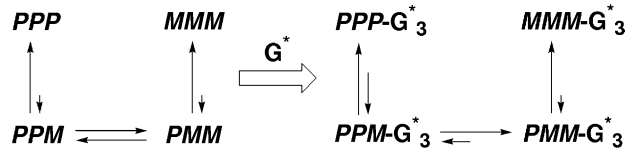


Figure 3. The expanded region of ^1H NMR spectra of **4** in $CDCl_3$ at 223 K: (a) **4** (0.732 mM), (b) **4** (0.732 mM) and L-Phe-OMe (0.722 mM), (c) **4** (0.732 mM) and L-Phe-OMe (1.45 mM), and (d) **4** (0.732 mM) and L-Phe-OMe (10.9 mM).



Scheme 1. A schematic representation of the equilibria among the homohelical and heterohelical conformers in the **4**-chiral guest system.

formed, and this result showed good correspondence with the ICD intensity showing high homohelicity induction. For Leu-OMe and PhGly-OMe, similar NMR behaviors were observed, showing complete regulation of homohelicity of the ZnBL subunits in **4**. In the case of (*R*)-NEA, two sets of signals were still observed with different intensities (*PPP*:*MMM* = 21:79) even when an excess amount of NEA was added. Indeed, the ICD of **4** in the presence of NEA was relatively small ($\Delta\varepsilon$ (ZnBL unit) = 92.4 $M^{-1}\,cm^{-1}$).

Contrary to **4**, **1**–**3** still showed complicated signal patterns even in the presence of any chiral guests, indicating that they consisted of a mixture of the homohelical and heterohelical conformers upon complexation with the chiral guests. It is interesting to note that *PPM*- and *PMM*-**4** were so unstable as to allow direct interconversion between *PPP* and *MMM*, and therefore, the preorganization of the homohelical structures of **4** significantly contributed to synchronous homohelicity induction of the ZnBL subunits.

Two coupling energies are cooperatively or competitively contributing to the synchronous helicity induction; the energy difference between the *PPP* conformer and the *PPM* conformer, ΔE_1, and the energy difference between the *P*-G* complex and the *M*-G* complex, ΔE_2 (G*; chiral guest). ΔE_1 can be called the subunit coupling energy, and ΔE_2 the host–guest chiral recognition energy. In the case of **4**, ΔE_1 is positive, and now ΔE_2 is supposed to be negative as seen in the ZnBL-L-amino ester system.[7a,b] Three equilibria contribute to the homohelicity induction as described by the following equations:

$$PPP\text{-}G_3^* \overset{\Delta E_1+\Delta E_2}{\rightleftharpoons} PPM\text{-}G_3^* \quad (1)$$

$$PPM\text{-}G_3^* \overset{\Delta E_2}{\rightleftharpoons} PMM\text{-}G_3^* \quad (2)$$

$$PMM\text{-}G_3^* \overset{-\Delta E_1+\Delta E_2}{\rightleftharpoons} MMM\text{-}G_3^* \quad (3)$$

where the energy differences for 1, 2, and 3 can be described as $\Delta E_1+\Delta E_2$, ΔE_2, and $-\Delta E_1+\Delta E_2$, respectively. Taking the signs of ΔE_1 and ΔE_2 into consideration, $-\Delta E_1+\Delta E_2$ is obviously smaller than $\Delta E_1+\Delta E_2$, and thus, the *MMM*-G_3^* isomer is predominantly formed. Therefore, for **4**, the subunits are strongly coupled due to the introduction of appropriate alkyl groups as the tail of the tripodal ZnBL trimer.

In conclusion, the ZnBL trimer **4** adopted homohelical conformation, *PPP* and *MMM*, under the present conditions. From CD and ^1H NMR studies, it was found that upon complexation with chiral α-amino esters one of the homohelical structures was exclusively formed. Molecular modeling study indicated that the van der Waals contact of the 3-ethyl group with the 7-propyl group in the neighboring ZnBL subunit contributed to the inter-subunit interaction, and the strongly coupled subunits resulted in the synchronous helicity control.

Acknowledgments

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Supplementary data

Synthetic procedure and characterization for **1**–**4** and ^{1}H NMR titration data for the complexation of **4** with (*R*)-NEA. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.086.

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10. In the present study, ^{1}H NMR and CD spectroscopic measurements were carried out at 223 K because the coordination interaction between ZnBL and α-amino esters was weak at ambient temperature. At ambient temperature, the homohelical and heterohelical conformers were independently observed for **1**–**3** in their ^{1}H NMR spectra, and thus, the homohelical–heterohelical isomerizations were slower than the NMR time scale. For **4**, a small amount of the heterohelical conformers was observed upon raising the temperature ([homohelical]/[heterohelical] = 87/13, at 296 K), where no signal coalescence was observed for the homohelical conformers.
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