Interconversion between Point Chirality and Helical Chirality Driven by Shape-Sensitive Interactions

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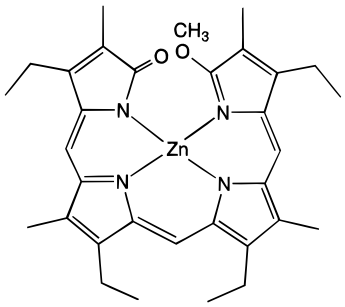
Biologically important molecules such as proteins and DNA have helical structures with a well-defined sense. The helical chirality of these polymers is determined by more basic chirality of constituent monomers, i.e., the point chirality of the asymmetric carbon atom.[1] In view of the importance of helical chirality as structural motif, elucidation of the mechanism of induction of helical chirality by point chirality is of interest and would lead us to understand formation of such biological structures and to design synthetically modified analogs. We now report the investigation of the nature of the interaction driving the helical structure formation, by use of a simplest model system consisting of a guest with *point* chirality and a racemic host with *helical* chirality. Scheme 1 summarizes the dynamic equilibrium of our system, in which degenerate states of a racemic host are perturbed by diastereomeric interactions with a chiral guest. In particular, the helical chirality of a zinc−biliverdin derivative was induced by the interaction with the point chirality of amino acid esters and amines. The chiral induction was driven by shape-sensitive interactions, involving interactions of aromatic groups and a carbomethoxy group of the chiral guest with the biliverdin.

Biliverdin derivatives have the following characteristic properties: (1) a helical surface,[2] (2) conformational flexibility,[3] (3) the characteristic spectroscopic properties (UV−vis, CD, and NMR),[4] and (4) important biological functions[5] (energy transfer in the photosynthetic systems, for example). The zinc complex of biliverdin derivatives **1** consists of a 1:1 mixture of a right-handed helical form and a left-handed helical form in a solution. The UV−vis and NMR studies indicate that amines and amino acid esters form a complex with zinc·biliverdin **1**[6] in a chloroform and dichloromethane solution. The chemical shifts



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Scheme 1

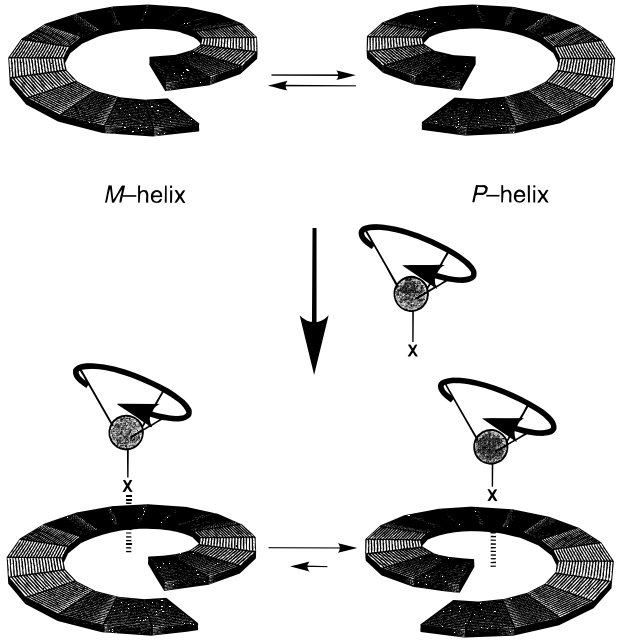

Table 1. Binding Constants (*K*), Diastereomeric Excess (de), and CD Data for Complexes between Host **1** and Amino Acid Esters/Amines in Dichloromethane

guest[a]	K_{288}[b] (M^{-1})	K_{223}[c] (M^{-1})	K_{223}'[c] (M^{-1})	de[d] (%)	$\Delta\epsilon$[e] 288 K	$\Delta\epsilon$[e] 223 K
L-Trp−OMe	115	*f*	*f*	73	46.6	96.4
L-Phe−OMe	96	6470	2190	57	36.7	66.9
D-PhGly−OMe	76	2840	1080	42	−38.8	−66.7
L-Leu−OMe	106	5230	2170	37	37.3	56.5
L-Ile−OMe	91	3530	1220	46	46.8	67.0
L-Val−OMe	54	2690	1170	42	32.5	60.0
L-Ala−OMe	90	5550	3080	42	32.2	58.2
(*R*)−NEA	296	13 200	7480	30	28.3	41.5
(*R*)−PEA	205	8500	7110	14	0.0	−13.7
(*R*)−CHEA	600	35 300	32 100	6	7.9	5.6

[a] Abbreviation: NEA, 1-(1-naphthyl)ethylamine; PEA, 1-phenylethylamine; CHEA, 1-cyclohexylethylamine. [b] Determined by UV−vis titration at 288 K. Standard deviations were within 2%. [c] Determined by NMR titration at 223 K. Standard deviations were within 7%. K_{223} designates the binding constants for the major enantiomer (*M*-**1** for L- and (*R*)-guest except for PEA), and K_{223}' designates those for the minor enantiomer. [d] Determined by the ^{1}H NMR peak integration in CD_2Cl_2 at −50 °C. [**1**] = 2.2 mM, [guest] = 17−24 mM. Under these conditions more than 98% of **1** is complexed with the guest. [e] $\Delta\epsilon$ for the complex in M^{-1} cm^{-1}. Determined under the conditions that more than 87% of **1** is complexed and $\Delta\epsilon$ was corrected for the fraction of complexation. The peak maximum was 400 ± 2 nm except for Ile−OMe being 383 nm at 288 K and Val−OMe being 384 nm at 288 K. Enantiomeric guests showed CD with an inverse sign and almost the same magnitude: at 288 K and 400 nm, $\Delta\epsilon = -35.0$ for D-Phe-OMe; $\Delta\epsilon = -36.1$ for D-Leu−OMe; and $\Delta\epsilon = -28.1$ M^{-1} cm^{-1} for (*S*)-NEA. [f] Not determined since the anomalous chemical shift displacement did not fit to the equation for 1:1 complexation.

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(6) The biliverdin framework of host **1** was prepared according to the Lightner's route: (a) Shrout, D. P.; Lightner, D. A. *Synthesis* **1990**, 1062. (b) Shrout, D. P.; Puzicha, G.; Lightner, D. A. *Synthesis* **1992**, 328. The biliverdin was converted to oxaporphyrin: (c) Fuhrhop, J.-H.; Salek, A.; Subramanian, J.; Mengersen, C.; Besecke, S. *Liebigs Ann. Chem.* **1975**, 1131−1147. (d) Fuhrhop, J.-H.; Kruger, P.; Sheldrick, W. S. *Liebigs Ann. Chem.* **1977**, 339. The oxaporphyrin was then cleaved to yield the 1-*O*-methylbiliverdin derivative: (e) Fuhrhop, J.-H.; Kruger, P. *Liebigs Ann. Chem.* **1977**, 360. (f) Falk, H.; Grubmayr, K.; Thirring, K. *Z. Naturforsch.* **1978**, *33b*, 924. Zinc was inserted to the biliverdin derivative: (g) Falk, H.; Schlederer, T. *Liebigs Ann. Chem.* **1979**, 1560.

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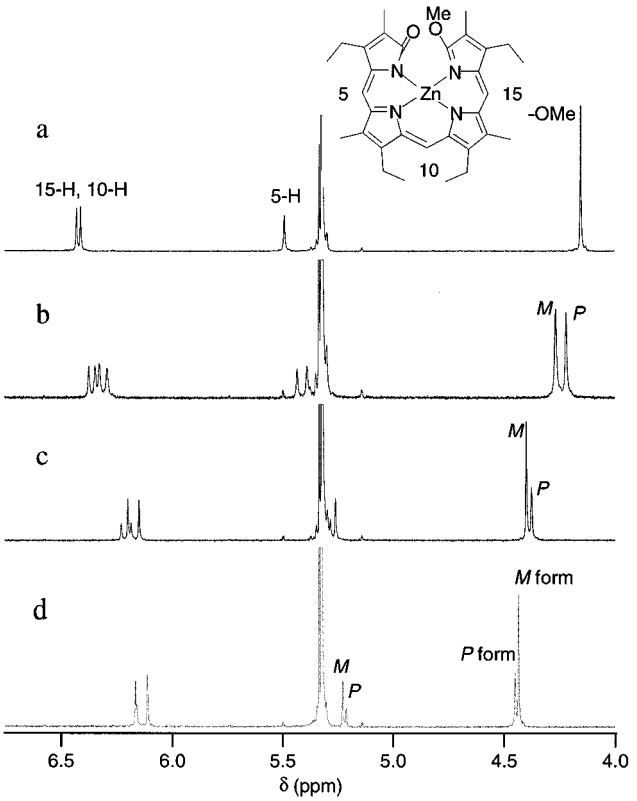

Figure 1. ^{1}H NMR spectra of a solution of host **1** in the presence of varying concentrations of L-Leu−OMe in CD_2Cl_2 at 223 K. The concentrations of Leu−OMe were (a) 0, (b) 8.21×10^{-4} M, (c) 3.24×10^{-3} M, and (d) 2.28×10^{-2} M.

of the NH protons of the guest (NEA) moved from 1.50 ppm of the uncomplexed guest to 3.00 ppm of the complexed guest[7] upon addition of **1** in dry $CDCl_3$ at 296 K, indicating that the amino group of the guest coordinates to zinc of **1**. The signals of **1** are also shifted upon complexation: for example, 0.2−0.3 ppm upfield shifts of the H5, H10, and H15 protons are observed. The complexation-induced shifts in **1** are ascribed to the conformational changes of **1**. The UV−vis titration experiments indicate that **1** and the guest form a 1:1 complex with the association constants ranging from 50 to 600 M^{-1} at 288 K (Table 1).

Circular dichroism (CD) is concurrently induced to the biliverdin absorption band upon complexation of chiral amines and amino acid esters, while **1** itself is CD inactive. L-Amino acid esters induce left-handed helicity (*M*-form) in **1** as deduced from the sign of induced CD[8] (Table 1). Thus, the complex formation directly induces the helical chirality in the zinc·biliverdin host **1**.

Variable-temperature ^{1}H NMR studies of the host−guest systems at 223−288 K revealed the following points: (1) The signal of the free host and the complexed host always coalesced into a single signal, indicating that the complexation reaction occurs faster than the NMR time scale in the temperature range

(7) The chemical shift at 3.00 ppm is the average of the 46% complexed and 54% uncomplexed guest.

(8) (a) Bulke, M. J.; Pratt, D. C.; Moscowitz, A. *Biochemistry* **1972**, *11*, 4025−4031. (b) Blauer, G.; Wagniere, G. *J. Am. Chem. Soc.* **1975**, *97*, 1949−1954. (c) Wagniere, G.; Blauer, G. *J. Am. Chem. Soc.* **1976**, *98*, 7806−7810. (d) Scheer, H.; Formanek, H.; Schneider, S. *Photochem. Photobiol.* **1982**, *36*, 259−272.

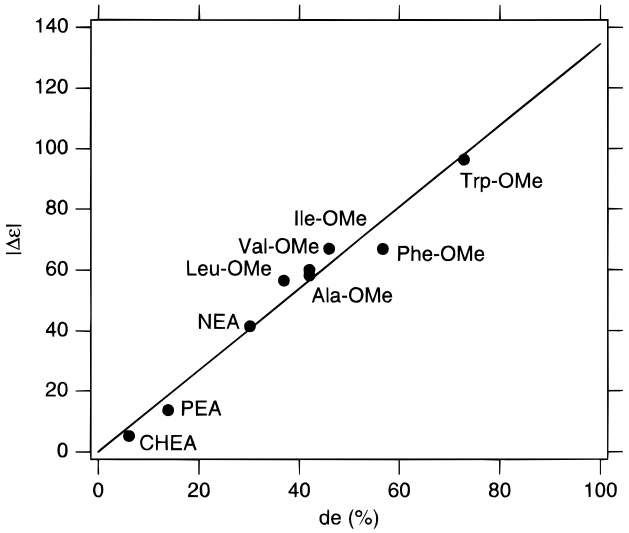

Figure 2. Plot of differential dichroic absorption against diastereomeric excess determined by NMR peak integration. Both the CD and the NMR spectra were recorded at 223 K in dichloromethane. [**1**] = 3.2−3.8 × 10^{-5} M and [guest] = 0.026 M for the CD studies. For the conditions of the NMR studies, see footnote *d* to Table 1.

of 223−288 K. (2) The rate of helix inversion is relatively slow below 253 K and comparable to the NMR time scale (on the order of 10 s^{-1}). Typical ^{1}H NMR spectra of solutions of **1** and varying concentrations of L-Leu-OMe at 223 K are shown in Figure 1.

The diastereomer excess (de) was determined at 223 K by the ^{1}H NMR signal integration on the basis of the fact that the two diastereomeric complexes, *M*-**1**-(*S*)-guest and *P*-**1**-(*S*)-guest, exhibit the methoxy signal of **1** as a completely separated signal (Table 1). A linear relationship is observed between the de's determined by ^{1}H NMR and the differential dichroic absorption ($\Delta\epsilon$) of induced CD (Figure 2). This linear relation supports the NMR assignment that the two signals are from the diastereomeric complexes. It also indicates that the variation in intensity of induced CD among the different guests can be ascribed solely to the de's. The sense of induced helicity was consistent for amino acid esters: all the L-amino acid esters induced *M*-helicity. Thus the chirality at the α-carbon directly determines the helical sense. In contrast, the helicity induction was less effective for amines and the induced helical sense is not consistent. It is noteworthy that the association constants of amines are larger than those of amino acid esters, whereas the helicity induction by amino acid esters is more effective than that by amines. This observation suggests that the carbomethoxy group of amino acid esters plays an important role in helical chirality induction. An indole ring and a naphthyl ring also make contribution to chiral induction as seen for high de's of the aromatic guests. Relatively large diastereomer excess observed for Ala−OMe indicates that the bulkiness of the side chain group of amino acid esters is not a necessary condition for the helicity induction. These interactions sensitive to molecular shape and functional groups are the driving force for the present chiral induction.

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