Phase-Sensitive Supramolecular Chirogenesis in Bisporphyrin Systems**

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To date, the field of supramolecular chirality has attracted much attention in the scientific community, in the context of its direct connection with various natural systems and many practical applications in the areas of catalysis,[1] nonlinear optics,[2] polymer and materials science,[3] molecular recognition,[4] molecular devices,[5] and absolute configuration determination.[6] As noncovalent interactions are the key elements of supramolecular chemistry, there are various external and internal factors controlling chirality induction in these systems. Among these influences, the phase transition, or aggregation state, takes on particular significance in the light of the wide prospective applications of optically active systems in the solid state.[7] However, this important factor has not yet been well investigated and rationalized. Here, by applying supramolecular chemistry, solid-state optical spectroscopy, and exciton chirality principles, we describe a novel and intriguing phenomenon of phase-transition controlled chirality induction in a supramolecular system, which consists of an achiral host and a chiral guest.[8]

Ethane-bridged bis(zinc octaethylporphyrin),[9] which is in a *syn* conformation in nonpolar solvents (see *syn* **ZnD** in Figure 1), was chosen as an achiral host molecule. This compound is well suited for the study of supramolecular chirality induction by chiral ligands (**L**), because of the distinct spectral differences between the initial nonligated *syn* **ZnD** and the ligand-bonded form (*anti* **ZnD** · $\mathbf{L_2}$).[10] This is because of the unique ability of *syn* **ZnD** to switch conformation from a *syn* (face-to-face) form to an extended *anti* form upon complexation with external ligands in nonpolar solvents. In the case of chiral guests, besides the conformational changes, there is another type of structural deformation in the achiral host, which results in the generation of a screw structure by a steric-repulsion mechanism, and hence the transformation of the point chirality of the guest molecules into the supramolecular helical chirality of

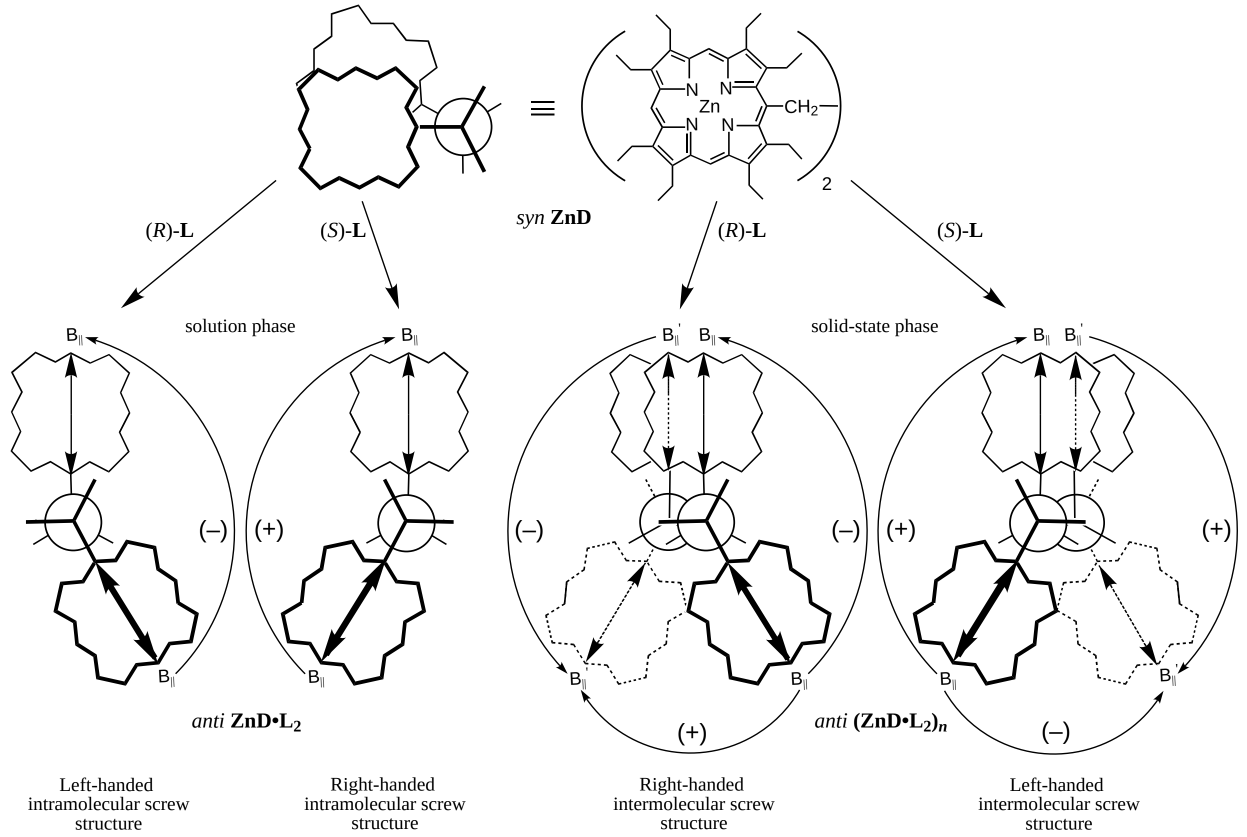

Figure 1. Phase-transition effect on the mechanism of supramolecular chirality induction in achiral *syn* **ZnD** upon interaction with chiral ligands (**L**) in solution and the solid state. The structures of *anti* (**ZnD** · $\mathbf{L_2}$)$_n$ are drawn schematically to show the opposing orientation of the intramolecular and intermolecular couplings (other stacked orientations are possible because of rotations of the *anti* (**ZnD** · $\mathbf{L_2}$)$_n$ monomers against each other).

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the whole system (see the "solution phase" mechanism in Figure 1). The detailed mechanism, driving forces, equilibria, and various controlling factors of this phenomenon have been thoroughly investigated in the solution phase.[11] The most interesting and important feature of this host molecule is that the direction of the screw is dictated solely by the stereochemistry of the guest. Thus, when the bulkiness order of the ligand substituents around the chiral center coincides with the substituent-priority rule which determines the absolute configuration, (*R*)- and (*S*)-guests produce corresponding left- and right-handed twists in *anti* **ZnD**$\cdot$**L**$_2$, affording negative and positive chirality, respectively (see the "solution phase" mechanism in Figure 1). This makes it possible to use optically inactive *syn* **ZnD** as an effective chirality sensor, which can determine the absolute configuration of optically active compounds (particularly amines and alcohols) in nonpolar solvents by using circular dichroism (CD) spectroscopy.

In the present study, to expand the scope of this versatile chirality sensor and to find new prospective applications, the supramolecular chirogenesis behavior of *syn* **ZnD** upon interaction with the chiral amines **1**–**4** (listed in Table 1)[12] has been further investigated in the solid state. The solid-state samples were prepared according to the standard procedure for obtaining a glassy KBr matrix.[13] Thus, *syn* **ZnD** was first ground with amine **1** (or mixed with amines **2**–**4**), and then the mixture was thoroughly ground with KBr crystals to a fine powder, which was pressurized to give a transparent KBr disk suitable for optical measurements. Then UV/Vis and CD spectra were recorded in the solid state and compared with those measured in the solution phase.

In the UV/Vis spectra, the maximum ($\lambda^{\mathrm{UV}}_{\mathrm{max}}$) of the B (Soret) band of the initial *syn* **ZnD** in a KBr matrix without amines is essentially the same as that in the solution phase (Table 1), while their spectral profiles are appreciably different. Thus, in the solid state, the B band is broadened, with a shoulder at 414 nm, and has a full-width-at-half-maximum (fwhm) value which is 2.3 times larger than that in the solution phase. This indicates the formation of an associated species of *syn* **ZnD** in the solid state, without *syn*–*anti* conformational switching. In the presence of chiral amines, there are similar spectral changes to those observed in the solution phase. Typical UV/Vis spectra of the amine-containing systems are shown in Figure 2. These transformations include a bathochromic shift of the B band by 31–38 nm (Table 1) and the relative enhancement of the Q_{X01} transition intensity, which indicates the same *syn*–*anti* conformational switching to yield the corresponding *anti* species as found in the solution phase.[11] However, in sharp contrast to the solution phase, the solid-state spectral pattern exhibits an unsplit B band which is broader by a factor of 1.2–1.3, on comparison of the corresponding fwhm values. Of note is that the maximum of this Soret band is very similar to that of the lowest B transition of the split Soret band seen in nonpolar solvents[14] (except amines **3**). These observations suggest an intermolecular association of the *anti* **ZnD**$\cdot$**L**$_2$ molecules to form a stacked *anti* (**ZnD**$\cdot$**L**$_2$)$_n$ species.

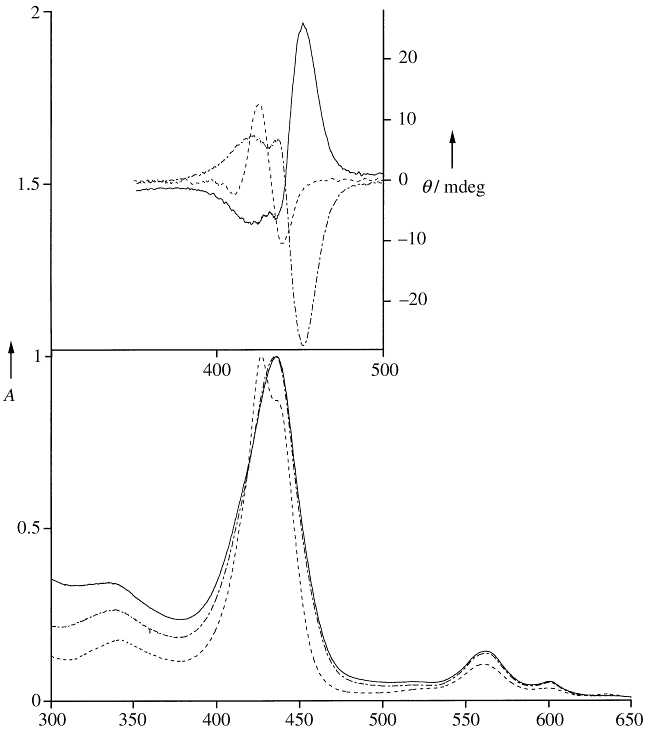

Figure 2. UV/Vis (bottom) and CD (top) spectra of **ZnD** in the presence of **2**$_\mathbf{R}$ in CH_2Cl_2 (–––), **2**$_\mathbf{R}$ in KBr matrix (——), and **2**$_\mathbf{S}$ in KBr matrix (•–•–). The spectra are normalized to the same optical density.

Simultaneous monitoring of the solid-state complexation by CD spectroscopy also reveals induction of optical activity in

Table 1. UV/Vis and CD spectral data of **ZnD** upon interaction with different chiral amines.

Amine (**L**)	Solution phase (CH_2Cl_2)[a] B bands, $\lambda^{\mathrm{UV}}_{\mathrm{max}}$ [nm][c]	Solution phase: First Cotton effect, $\lambda^{\mathrm{CD}}_{\mathrm{max/min}}$ [nm][c]	Solution phase: Dissymmetry factor at $\lambda^{\mathrm{CD}}_{\mathrm{max/min}}$ [$g\times10^3$][d]	Solid-state phase (KBr)[b] B bands, $\lambda^{\mathrm{UV}}_{\mathrm{max}}$ [nm]	Solid-state phase: First Cotton effect, $\lambda^{\mathrm{CD}}_{\mathrm{max/min}}$ [nm]	Solid-state phase: Dissymmetry factor at $\lambda^{\mathrm{CD}}_{\mathrm{max/min}}$ [$g\times10^3$][d]
none	397	–	–	399, 414(sh)	–	–
(*R*)-(+)-bornylamine[c] (**1**$_\mathbf{S}$)[f]	427, 437	439	+0.213	437	450	−1.118
(1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine (**2**$_\mathbf{R}$)[f]	426, 436	439	−0.269	436	452	+1.600
(1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheylamine (**2**$_\mathbf{S}$)[f]	426, 436	439	+0.269	436	451	−1.640
(*R*)-(+)-1-phenylethylamine (**3**$_\mathbf{R}$)	426, 436	439	−0.216	430	446	+1.361
(*S*)-(−)-1-phenylethylamine (**3**$_\mathbf{S}$)	426, 436	439	+0.180	431	445	−1.630
(*R*)-(−)-1-cyclohexylethylamine (**4**$_\mathbf{R}$)	427, 438	439	−0.134	436	451	+0.208
(*S*)-(+)-1-cyclohexylethylamine (**4**$_\mathbf{S}$)	427, 438	439	+0.130	435	452	−0.209

[a] $C_{\mathbf{ZnD}} = 2.9-3.8\times10^{-6}$ M, $C_{\mathbf{L}} = 3.5\times10^{-2}-4.7\times10^{-1}$ M in CH_2Cl_2. [b] The **ZnD**:**L** molar ratio is within the range of 1:1400–1:1700. [c] The solution phase $\lambda^{\mathrm{UV}}_{\mathrm{max}}$ and $\lambda^{\mathrm{CD}}_{\mathrm{max/min}}$ values are from reference [11a]. [d] $g = \Delta\varepsilon/\varepsilon$ (or $g = \Delta OD/OD$ in the case of solid state samples) where $\Delta\varepsilon$ (or ΔOD) is the molar circular-dichroic absorption (or circular-dichroic absorption) of the first Cotton effect obtained from the CD spectrum and ε (or OD) is the molar extinction coefficient (or absorption optical density) at the wavelength corresponding to the first Cotton effect obtained from the UV/Vis spectrum. [e] endo-(1*R*)-2-Amino-1,7,7-trimethylbicyclo[2.2.1]heptane. The subscript ($_\mathrm{R}$ or $_\mathrm{S}$) refers to the absolute configuration of the stereocenter closest to the amine binding group.

the region of the porphyrin B transition,[15] as in the case of the supramolecular chirogenesis in solution.[11] However, the solid-state spectral patterns are remarkably different to those of the solution state. Surprisingly, the first Cotton effects showed the opposite sign with much enhanced intensities and bathochromic shifts of up to 6–13 nm, compared with the corresponding data obtained for identical amines in the solution phase experiments (see Figure 2, top and Table 1). Furthermore, the CD-spectral profile has a complex shape, rather than the simpler bisignate couplet induced in nonpolar solvents; this probably arises from several overlapping excitonic-type couplets, yielding the enhanced first Cotton effect. The intensities of other Cotton effects are markedly diminished, apparently because of mutual cancellation of couplets of opposite sign, located in the high-energy spectral region. As expected, complexation with the guest of opposite chirality gives the mirror-image induced CD spectrum (Figure 2, top).

Although the detailed mechanism of the supramolecular chirality induction in the solid state is not yet well understood, the chirality-inversion phenomenon can be rationalized on the basis of a simple dimerization model of *anti* $\mathbf{ZnD \cdot L_2}$ (Figure 1). As reported previously,[11] in the solution phase the two lowest energy $B_{\|}$ transitions in *anti* $\mathbf{ZnD \cdot L_2}$, the orientation of which determines the sign of the chirality, are coupled intramolecularly in a clockwise fashion upon complexation with *S* amines which, according to the CD exciton chirality method,[16] corresponds to positive chirality. In the case of *R* amines, the dipole's coupling direction is exactly opposite, which results in negative chirality (see the "solution phase" mechanism in Figure 1). In the solid state, as mentioned above, there is an intermolecular association process, which results in formation of the stacked structures, *anti* $(\mathbf{ZnD \cdot L_2})_n$. The simplest stacked species is a dimer of *anti* $(\mathbf{ZnD \cdot L_2})_n$ where $n = 2$; the schematic structure of which is shown in Figure 1 ("solid-state phase"). Although several structural variations of *anti* $(\mathbf{ZnD \cdot L_2})_n$ are possible, this type of aggregation mode is considered to be one of the most credible for the following reasons. It was reported[11a] that supramolecular chirality in the bisporphyrin is induced by the asymmetrical approach of the second ligand to give an atropisomer of *anti* $\mathbf{ZnD \cdot L_2}$, in which the chiral ligands are positioned on the same side of the porphyrin planes. Therefore, stacking of the two *anti* $\mathbf{ZnD \cdot L_2}$ molecules to produce a supramolecular, optically active dimeric species can only occur from the opposite, ligand-free sides. Furthermore, an examination of Corey–Pauling–Koltun molecular models, constructed on the basis of the X-ray data obtained for the relevant *trans* isomer of ethylene-bridged bisporphyrin,[17] reveals that this aggregation mode minimizes intermolecular steric repulsions between the ethyl substituents of the two *anti* $\mathbf{ZnD \cdot L_2}$ molecules.[18] It is obvious that, in *anti* $(\mathbf{ZnD \cdot L_2})_n$, the orientation of the intramolecularly coupling $B_{\|}$ transitions is the same as that of monomeric *anti* $\mathbf{ZnD \cdot L_2}$ in solution. However, the intermolecular coupling between the $B_{\|}$ transition of one molecule and the $B'_{\|}$ transition of another molecule in the stacked structure forms an opposing turn: clockwise for *R* amines and anticlockwise for *S* amines (see the "solid-state phase" mechanism in Figure 1), which produces corresponding positive and negative chirality, according to the CD exciton chirality method.[16] As the directions of the intramolecular and intermolecular couplings are opposing in *anti* $(\mathbf{ZnD \cdot L_2})_n$, it is reasonable to expect a considerable reduction of the induced CD signal[19] in the high-energy spectral region of the intramolecular couplet, which is observed (Figure 2, top). Simultaneously, the lowest energy Cotton effect at 445–452 nm is intense and apparently arises from the intermolecular coupling, because, as mentioned above, the intramolecular coupling in *anti* $\mathbf{ZnD \cdot L_2}$ induces a hypsochromically shifted couplet with the position of the first Cotton effect at 439 nm. It is also likely that the intermolecular dipole–dipole interactions in *anti* $(\mathbf{ZnD \cdot L_2})_n$ induce a more intense CD couplet than intramolecular interactions. Although reliable theoretical treatment of optical activity in bisporphyrins is not yet available, this assumption is supported by a simple dibenzoate model, which shows that the amplitude of the Cotton effects has a parabola-like dependence on the dihedral angle between the coupling transitions, with zero values at 0° and 180°, and a maximum value at around 70°.[16] Assuming that the coupling dipoles follow this tendency, the angle between intermolecular $B_{\|}$ and $B'_{\|}$ transitions falls on the steeper, ascending branch of this curve, whilst the angle between intramolecular $B_{\|}$ transitions is located on the shallower, descending branch of the curve, which results in enhancement of the intermolecular CD amplitude.

To investigate the influence of the amine structure on supramolecular chirogenesis in the solid state, and to make a reliable comparison of these results with the solution-phase data, the anisotropy (g) factors which reflect the pure optical activity of the systems studied are calculated at the wavelength corresponding to the first Cotton effect (Table 1). In general, the g values of the solid-state systems are of opposite sign and considerably enhanced (by a factor of 1.6–9.1) in comparison to those of the solution phase; this is caused by the aggregation effect, as discussed above. More interestingly, the solid-state g factors are inversely proportional to the solution-phase g factors, with a regression line crossing the origin (see Supporting Information). This indicates that, although the apparent cause of the supramolecular chirogenesis is different in solution (intramolecular coupling) and in the solid phase (intermolecular coupling), exactly the same driving forces and controlling parameters (such as ligand structure and binding strength) are operative in both phases. Some deviations from linearity are a result of other factors attributable to the association process and corresponding differences in chirality induction mechanisms.

In summary, this work demonstrates that the phase transition can serve as an effective tool for controlling (and even enhancing) supramolecular chirality induction and inversion in achiral host systems by switching the chirality induction mechanism. Furthermore, correlation of the chirality sign with the absolute configuration of enantiopure ligands opens up an attractive possibility for designing the first chirality sensor in the solid state.

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[12] The same commercially available amines and similar host:guest ratios (Table 1) that were employed in the previous studies[11a] have been selected in this work for reliable comparison of the chirality induction processes in solution and solid-state phases.

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[15] Solid-state CD spectroscopy suffers extensively from interference by optical phenomena other than true CD (such as linear dichroism and optical birefringence) that result from the presence of optical anisotropy in the sample. Using a solid-state specialized universal chiroptical spectrophotometer UCS: J-800 KCM, the corresponding anisotropies of solid-state samples have been measured (for the procedure, see: R. Kuroda, T. Harada, Y. Shindo, *Rev. Sci. Instrum.* **2001**, *72*, 3802–3810). The results have clearly shown that the anisotropies of our samples are negligible (see Supporting Information).

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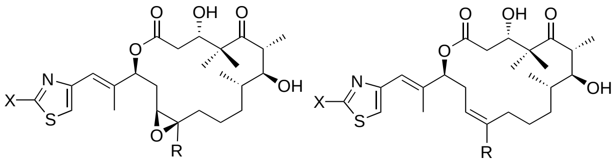
[18] The position of the corresponding ethyl groups is apparently fixed in the solid state. Even in the solution phase, their rotation is relatively slow (see K. M. Smith, *Porphyrins and Metalloporphyrins*, Elsevier, Amsterdam, **1975**).

[19] Inverted orientation of the *anti* **ZnD** · $\mathbf{L_2}$ molecules in *anti* $(\mathbf{ZnD} \cdot \mathbf{L_2})_n$ will result in the same chirality sign caused by the same direction of the intra- and intermolecular coupling dipoles, and thus the overall enhancement of the CD signal rather than the observed reduction.

Stereoselective Total Synthesis of Epothilones by the Metathesis Approach Involving C9–C10 Bond Formation**

Jian Sun and Subhash C. Sinha*

Epothilones A–F (**1**–**6**, Scheme 1), a new family of natural products initially isolated by Höfle et al. from myxobacteria,[1] exhibited remarkably high anticancer activity,[2] especially to taxol-resistant cell lines. These compounds possess a taxol-like mode of action and function through the stabilization of cellular microtubules.[3] The structural novelty of these compounds and the growing awareness of potential advantages shown by them over taxol, including a higher level of cytotoxicity against multidrug-resistant (MDR) cell lines and better water solubility, spurred interest in their total synthesis.[4] In the past six years, a large number of publications have emerged on the partial and total synthesis of epothilones.[5]



1: Epothilone A; R = H, X = Me
2: Epothilone B; R = X = Me
5: Epothilone E; R = H, X = CH_2OH
6: Epothilone F; R = Me, X = CH_2OH

3: Epothilone C; R = H, X = Me
4: Epothilone D; R = X = Me

Scheme 1. Structures of naturally occurring epothilones, **1**–**6**.

Ring-closing metathesis (RCM) is undoubtedly one of the three most successful and efficient methods used to construct the 16-membered macrolide ring of epothilones.[6] Compound **I** and its analogues are metathesized to establish the C12–C13 bond of the corresponding macrolide. The metathesis, however, always yields a ≈1:1 mixture of the *E* and *Z* isomers (**II** and **III**, Scheme 2).[7, 8] Furthermore, the subsequent epoxidation of the C12–C13 double bond in **II** and **III** gives a mixture of α and β-diastereoisomers of **IV**–**VII**, in an approximate ratio ranging from 1:1:1:1 to 3:3:5:1, depending upon the substitution pattern at C12 and C13. Thus, a substantial portion (55–75%) of the precursor is transformed to the undesired products (**V**–**VII**), which limits the usefulness of this approach to the stereospecific synthesis of epothilones.

To circumvent these problems, we decided to explore RCM of dienes such as **7**, to form the C9–C10 bond after all the

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