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DIRECT DETERMINATION OF THE ABSOLUTE CONFIGURATIONS OF CHIRAL CYANOHYDRINS USING BIS(ZINC PORPHYRIN) AS A CD-SENSITIVE BIDENTATE HOST

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Abstract – The absolute configurations of cyanohydrins are readily determined via an exciton-coupled circular dichroism (ECCD) protocol using bidentate bis(zinc porphyrin) host molecule **BP1** as a CD-sensitive chirality probe. UV–vis and NMR studies revealed a monodentate binding mode of cyanohydrin with **BP1**. Based on these studies, a simple working model using a Newman projection of cyanohydrins was established, allowing **BP1** to determine the stereochemistry of various cyanohydrins in a non-empirical and unambiguous manner.

INTRODUCTION

Optically active cyanohydrins are useful chiral synthons that are readily transformed into a diverse range of 1,2-difunctional optically active compounds such as α-hydroxy acids, α-hydroxy esters, α-amino nitriles, and β-amino alcohols.[1] Various methods have been developed for synthesizing optically active cyanohydrins.[2] The absolute configurations of optically active cyanohydrins can be determined by NMR analyses using Mosher's and related methods.[3] However, in addition to requiring milligram-scale samples, these measurements usually involve substrate derivatization. Recently, a supramolecular ECCD protocol using bisporphyrin tweezer host systems attracted significant attention due to its sensitive, non-empirical, derivatization-free, micro-scale determination of the absolute stereochemistry of chiral guest molecules. In this situation, bisporphyrin tweezer host molecules bind chiral guest molecules through ligand-to-metal coordination to form chiral supramolecular complexes, giving bisignate ECCD spectra that reflect the absolute configurations of the substrates. Although several elaborate tweezer systems have been developed for determining various chiral compounds,[4–6] to the best of our knowledge, only one porphyrin tweezer system was used to determine the configurations of cyanohydrins. Borhan and co-workers recently reported a unique bisporphyrin host molecule, MAPOL, having a hydrogen-bonding biphenol

This work is dedicated to Professor Dr. Kaoru Fuji on the occasion of his 80th birthday.

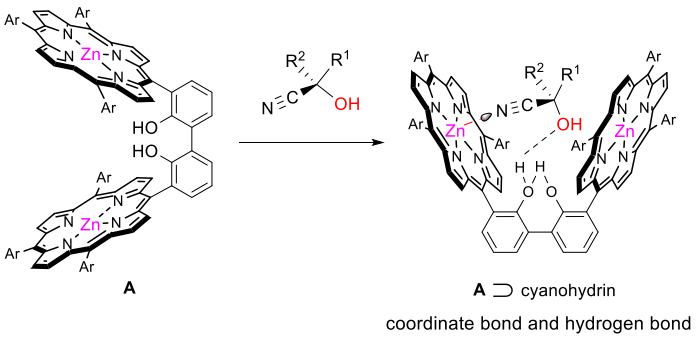


Figure 1. Bisporphyrin host molecule bearing hydrogen-bond core reported by Borhan

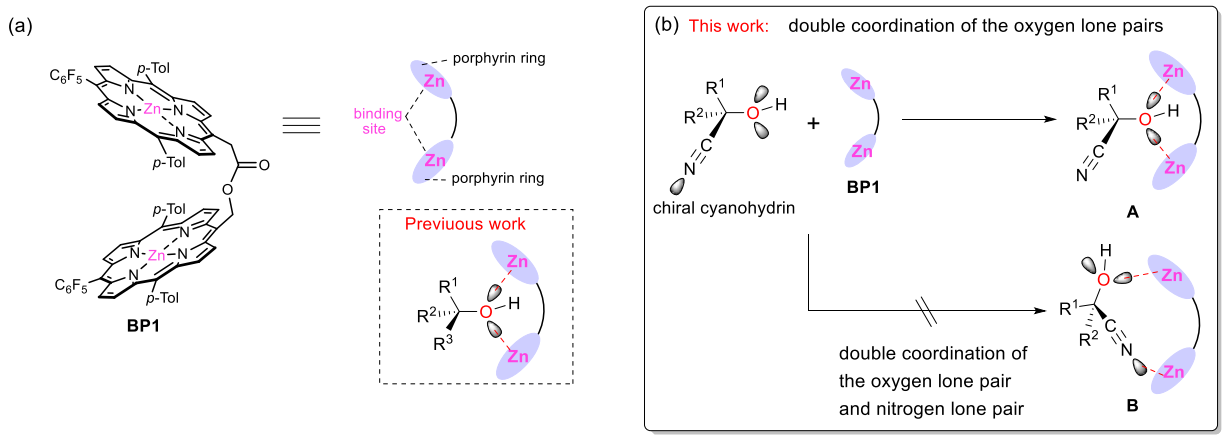


Figure 2. (a) Binding of monoalcohol with **BP1** (b) Possible binding modes of cyanohydrin with **BP1**

unit, as a chiral probe for determining the absolute configurations of cyanohydrins (Figure 1).[7] With this sophisticated host system, the absolute stereochemistry of cyanohydrins can be determined non-empirically without substrate derivatization. However, over 50 equivalents of cyanohydrins with respect to the host molecule were required for the measurements. Therefore, a more sensitive chiroptical method for cyanohydrins is still desired.

Very recently, we reported a chiroptical method for determining the absolute configurations of optically active monofunctional compounds, such as monoalcohols and simple alkyl-substituted epoxides, using bis(zinc porphyrin) host molecule **BP1** having a V-shaped structural motif as a circular dichroism (CD)-sensitive chirality probe (Figure 2a).[8] The binding affinity of V-shaped host molecule **BP1** with monoalcohols and epoxides could be effectively enhanced by double coordination of both the oxygen lone pairs of the hydroxy group to the two central zinc ions. We envisioned that **BP1** would capture the two lone pairs of an oxygen atom of a hydroxy group in cyanohydrin to form a cyanohydrin-containing chiral supramolecular complex, which would provide the corresponding ECCD spectra reflecting the absolute configuration of the guest cyanohydrin (Figure 2b-**A**). In this paper, we report a derivatization-free micro-scale method for determining the absolute configurations of cyanohydrins as a

new application of **BP1**. The absolute stereochemistry of cyanohydrins was readily assigned with less than 5 equivalents of samples in a non-empirical and unambiguous manner through correlation between the sign of the bisignate ECCD signal and the predicted orientation of the porphyrin chromophore based on a simple working model using a Newman projection of the cyanohydrins.

RESULTS AND DISCUSSION

At the beginning of this study, we selected (*rac*)-cyanohydrin **2a** as a model substrate to explore the binding with **BP1**, which was synthesized using a previously reported procedure.[8] The host–guest stoichiometry of the supramolecular complex was investigated by Job's continuous analysis.[9] UV–vis spectral changes at 414 nm of these samples were plotted as a function of the mole fraction of **BP1** to give a peak at 0.5 (Figure 3). These results indicated the formation of 1:1 host–guest complexes for both cyanohydrin **2a** and **BP1**. To investigate the incorporation of cyanohydrin by **BP1**, ^{1}H NMR studies were performed with cyanohydrin **2b**. After complexation with monomeric zincated porphyrin **Zn-5**, the protons of cyanohydrin **2b** showed upfield shifts ($\Delta\delta$ = 0.05–0.01 ppm) compared with those of the free cyanohydrin, whereas larger upfield shifts ($\Delta\delta$ = 0.20–0.06 ppm) were observed when **2b** was bound to bisporphyrin host **BP1** because of the stronger ring current of the two porphyrins of the latter (Figure 4). These observations are consistent with the coordination of the guest cyanohydrin in the cleft of the host. This binding was also observed through the UV–vis titration of **BP1** with cyanohydrin at 25 °C in 5% CH_2Cl_2/hexane. The titration of cyanohydrin **2a** (1–2,800 equiv) complexed with **BP1** exhibited a small bathochromic shift (~1 nm) in the absorption maximum from 414 to 415 nm (Figure 5),[10] whereas a larger bathochromic shift (~5 nm) occurred on binding of cyanohydrin **2a** with monomeric counterpart **Zn-5** (Figure 6). These NMR and UV–vis observations revealed that **BP1** incorporated cyanohydrins into its V-shape cavity, and the slipped-cofacial arrangement of the two porphyrins in **BP1** was well preserved on binding the host molecule that bound the cyanohydrin guest.

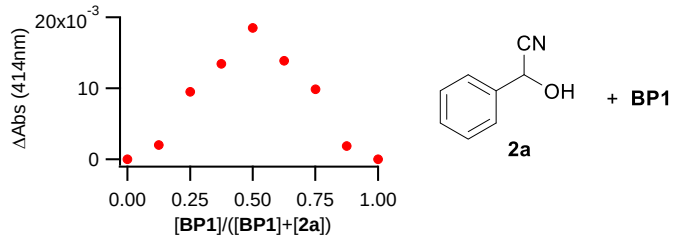


Figure 3. Job's plot. Solutions of bidentate host molecule **BP1** and cyanohydrin **2a** (guest molecule) in 5% CH_2Cl_2/*n*-hexane were prepared with a fixed total concentration of host and guest molecules (3.5×10^{-6} M). The UV–vis spectra were recorded at 0 °C and ΔAbs was monitored at 414 nm. The peak at a mole fraction of 0.5 corresponds to a 1:1 **BP1**/cyanohydrin **2a** complex.

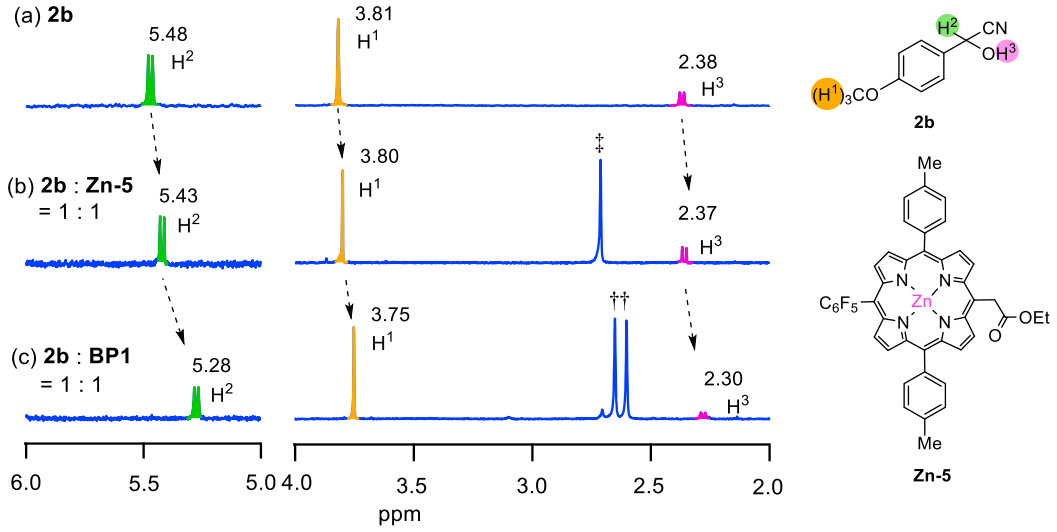


Figure 4. ^{1}H NMR spectra ($CDCl_3$, 25 °C) of cyanohydrin **2b** (a) in the absence of zinc porphyrins, (b) in the presence of monomeric zincated porphyrin **Zn-5** (‡ = methyl proton of the *p*-tolyl group in **Zn-5**), and (c) in the presence of **BP1** († = methyl proton of the *p*-tolyl group in **BP1**). The cyanohydrin signals are color-coded.

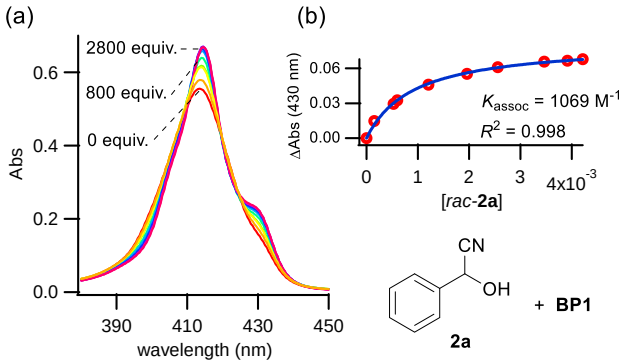


Figure 5. (a) Spectral changes on titrating **BP1** in 5% CH_2Cl_2/*n*-hexane at 25 °C with cyanohydrin **2a**. (b) Changes in ΔAbs at 430 nm for evaluating K_{assoc} ([**BP1**] = 1.5 × 10^{-6} M; [**2a**]/[**BP1**] = 0–2,800).

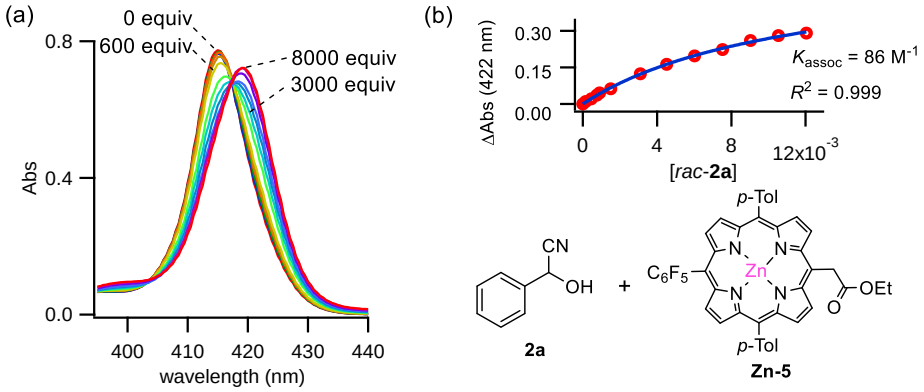


Figure 6. (a) Spectral changes on titrating monomeric porphyrin **Zn-5** with cyanohydrin **2a** in 5% CH_2Cl_2/*n*-hexane at 25 °C. (b) Changes in ΔAbs at 422 nm for evaluating K_{assoc} ([**Zn-5**] = 1.5 × 10^{-6} M; [**2a**]/[**Zn-5**] = 0–8,000).

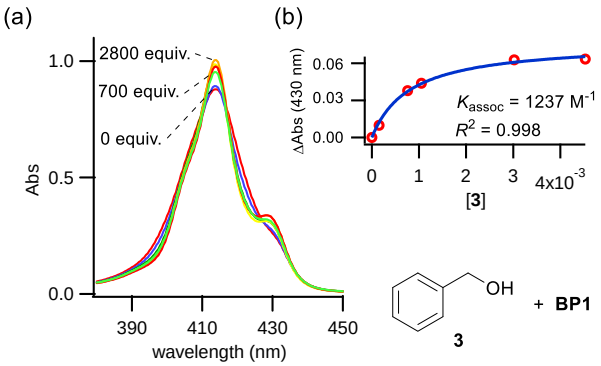


Figure 7. (a) Spectral changes on titrating **BP1** in 5% CH_2Cl_2/*n*-hexane at 25 °C with monoalcohol **3**. (b) Changes in ΔAbs at 430 nm for evaluating K_{assoc} ([**BP1**] = 1.5 × 10^{-6} M; [**3**]/[**BP1**] = 0–2,800).

As mentioned above, we assume that **BP1** binds cyanohydrin by the double coordination of both the oxygen lone pairs of the hydroxy group to the two central zinc ions (Figure 2b-**A**). However, as both the hydroxy and cyano groups could bind with a zincated porphyrin, the bidentate binding of cyanohydrin with **BP1** cannot be excluded (Figure 2b-**B**). To distinguish these binding modes, we compared the association constants of complexation of cyanohydrin **2a** and monoalcohol **3** with **BP1** by UV–vis titration studies (Figures 5 and 7). If the cyanohydrin binds with **BP1** through coordination of the hydroxy and cyano groups, the association constant of cyanohydrin **2** would be greater than that for the complexation of monoalcohol **3** with **BP1**. However, the observed association constant for the complexation of cyanohydrin **2a** with **BP1** (K_{assoc} = 1,069 M^{-1}) was slightly lower than that for the complexation of monoalcohol **3** with **BP1** (K_{assoc} = 1,237 M^{-1}),[11] because of the electron-withdrawing nature of the cyano group. Therefore, **BP1** binds cyanohydrin by simultaneous double coordination of the hydroxy group with two central zinc ions in a monodentate manner (Figure 2b-**A**).

We then investigated the helicity of bisporphyrin **BP1** when complexed with that of chiral cyanohydrin. As expected, consistent ECCD signals centered around the Soret band of porphyrin were observed in the CD spectra of chiral cyanohydrin (*R*)-**2b** with bisporphyrin **BP1** in 5% CH_2Cl_2/hexane at a host/guest ratio of 1:10 (Figure 8a). By reducing the measurement temperature from 25 °C to −10 °C, the intensities of the CD spectra were dramatically increased, and sharp, low-noise, and satisfactory CD spectra were obtained below 10 °C. The effects of the amount of cyanohydrin versus **BP1** on the CD spectra were then examined at 0 °C using 1–500 equivalents of (*R*)-**2b** (Figure 8b). Only 2.5 equivalents of cyanohydrin were required to obtain clear CD signals. The intensity of the CD signal was almost saturated at 400–500 equivalents of (*R*)-**2b**, with clear bisignate CD signals. Excess cyanohydrin did not affect the bisignate CD signal of **BP1**.

Figure 9a shows a working model for predicting ECCD spectra for a chiral cyanohydrin with an *S* configuration complexed with **BP1**. The cyanohydrin is represented by a Newman projection with the

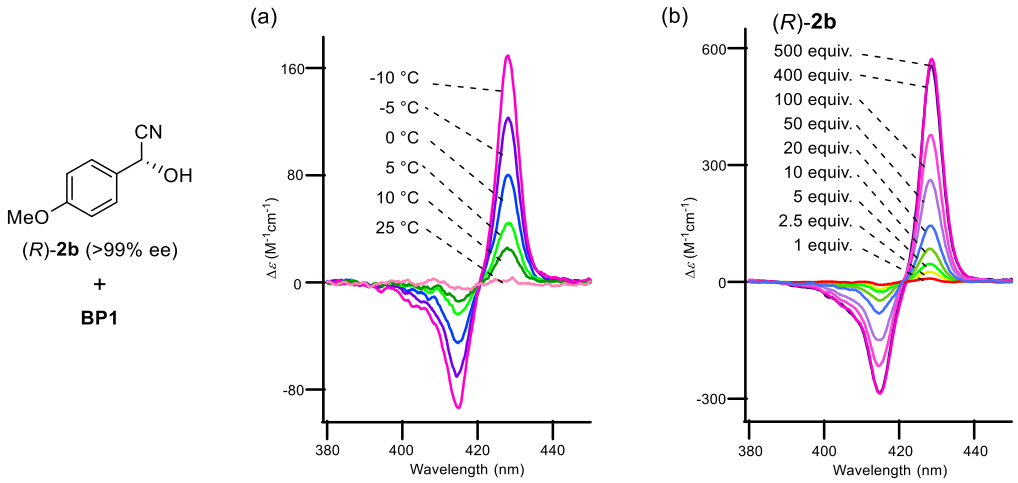


Figure 8. (a) ECCD spectra of **BP1** (1.5×10^{-6} M) complexed with (*R*)-**2b** (10 equiv) at different temperatures (−10 °C to 25 °C) in 5% CH_2Cl_2/*n*-hexane. (b) ECCD titration of **BP1** (1.5×10^{-6} M) with different equivalents of (*R*)-**2b** (5–500 equiv) in 5% CH_2Cl_2/*n*-hexane at 0 °C.

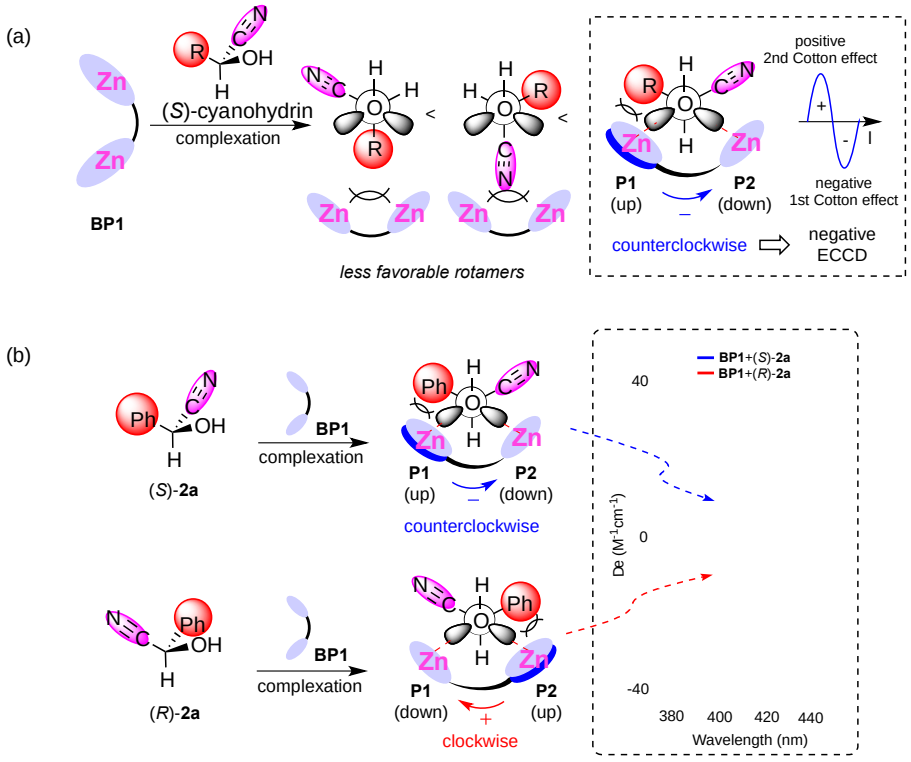


Figure 9. (a) Complexation of bidentate host molecule **BP1** with chiral cyanohydrins and proposed working model for assigning the absolute configuration of the chiral guest. (b) Left: proposed working model for predicting the helicity in complexes of **BP1** and chiral cyanohydrins (*S*)-**2a** and (*R*)-**2a**. Right (dashed box): CD spectra of **BP1** (1.5×10^{-6} M) in the presence (5 equiv) of chiral cyanohydrins (*S*)-**2a** (blue line) and (*R*)-**2a** (red line) in 5% CH_2Cl_2/*n*-hexane at 0 °C.

oxygen atom of its hydroxy group in front and the stereogenic center at the back. We proposed that bidentate host **BP1** approaches the hydroxy group of the *S* cyanohydrin from the side of its smallest group

(H) to capture both hydroxy lone pairs (Figure 9a, dashed box). Porphyrin ring **P1** would rise above porphyrin ring **P2** because of the steric repulsion between **P1** and the largest substituent (R) on the left side. Consequently, **P1** adopts a counter clockwise helicity relative to **P2**, which would produce a negative ECCD spectrum.[12] Figure 9b shows the complexation of chiral cyanohydrin (*S*)-**2a** with **BP1** in 5% CH_2Cl_2/hexane at 0 °C, which leads to the anticipated negative ECCD spectrum in the Soret region, in which the hydrogen atom, CN, and phenyl moieties on the stereogenic carbon correspond to the smallest (H), medium (CN), and largest (R) groups in the working model, respectively.[13] As expected, enantiomer (*R*)-**2a** yielded the opposite ECCD spectrum (Figure 9b, dashed box, red line).

To test the scope of the supramolecular chirogenesis using **BP1** as a CD-sensitive bidentate host molecule, various chiral cyanohydrins with different substituents were investigated. As shown in Table 1 and Figures S1–S7 in the supporting information, all the cyanohydrin substrates examined on complexation with bidentate host **BP1** exhibited the corresponding ECCD signals with acceptable to moderately high amplitudes in 5% CH_2Cl_2/*n*-hexane at 0 °C. In all cases, the predicted ECCD sign based on the binding mode shown in Figure 9 was consistent with the observed ECCD couplet of the cyanohydrin and **BP1** complex. While the cyanohydrins having electron-donating *p*-tolyl (**2c**) and 4-methoxyphenyl groups (**2b**) yielded comparable A_{CD} values to those of the phenyl derivatives, 4-chlorophenyl derivative **2d** showed more intense CD signals.[14] Cyanohydrins bearing a bulky tertiary alkyl (*tert*-butyl), a secondary alkyl (cyclohexyl), and a linear alkyl (*n*-hexyl) group were also compatible with this system (**2e**, **2f**, and **2g**).

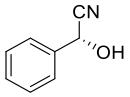
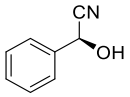
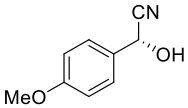
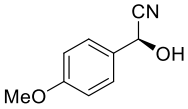
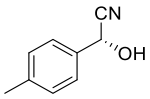
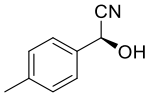
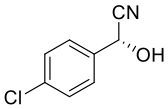
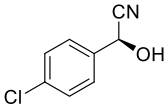
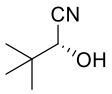
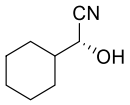
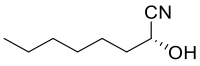
To further demonstrate the utility of this chiroptical protocol, the correlation between the amplitude of the ECCD signal ($A_{CD} = \Delta\varepsilon_{(1st\ Cotton)} - \Delta\varepsilon_{(2nd\ Cotton)}$) and the ee of cyanohydrin **2b** was examined. The measurements were performed using 10 equiv of (*R*)-**2b** (99% ee) ~ (*S*)-**2b** (87% ee) in 5% CH_2Cl_2/*n*-hexane at 0 °C (Figure 10a). As expected, an excellent linear relationship was obtained between the ECCD amplitude and the % ee of cyanohydrin **2b**, with linear regression yielding a correlation coefficient of 0.998 (Figure 10b).[15]

CONCLUSION

In summary, we have demonstrated a highly sensitive and reliable method for determining the absolute configurations of optically active cyanohydrins using bis(zinc porphyrin) host molecule **BP1**. NMR and UV–vis studies revealed that the cyanohydrin binds with **BP1** using the lone pairs of the oxygen atom of its hydroxy group similarly to the optically active monoalcohols we have previously reported.[8] Based on this binding mode, a simple working model was proposed using a Newman projection with the order of the steric bulkiness of the substituents of cyanohydrins, which established a consistent and predictable general trend for various cyanohydrins bearing an aromatic or aliphatic substituent. With this chiroptical protocol using **BP1**, the optical purity of an unknown sample as well as the absolute stereochemistry of

the cyanohydrins can be determined with one measurement.[16] We are currently exploring extending the present method to other functional groups.

Table 1. ECCD Data for Chiral Cyanohydrins **2** with **BP1**[a]

Chiral cyanohydrins (% ee)		Predicted sign	First λ nm ($\Delta\varepsilon$)	Second λ nm ($\Delta\varepsilon$)	A_{CD}[b] (A_{corr})[c]
	(*R*)-**2a** (93)	pos	428 (+35)	414 (−18)	+53 (+57)
	(*S*)-**2a** (92)	neg	428 (−37)	414 (+22)	−59 (−64)
	(*R*)-**2b** (99)	pos	428 (+46)	416 (−26)	+72
	(*S*)-**2b** (86)	neg	428 (−36)	412 (+19)	−55 (−64)
	(*R*)-**2c** (83)	pos	428 (+38)	416 (−23)	+61 (+73)
	(*S*)-**2c** (96)	neg	428 (−40)	413 (+24)	−64 (−67)
	(*R*)-**2d** (95)	pos	428 (+73)	414 (−49)	+122 (+128)
	(*S*)-**2d** (52)	neg	428 (−41)	413 (+24)	−65 (−125)
	(*R*)-**2e** (87)	pos	428 (+105)	415 (−63)	+168 (+193)
	(*R*)-**2f** (81)	pos	428 (+101)	415 (−58)	+159 (+196)
	(*R*)-**2g** (58)	pos	429 (+23)	415 (−13)	+36 (+62)

[a] All CD measurements were performed with 1.5 μM of **BP1** in 5% CH_2Cl_2/*n*-hexane at 0 °C; 5 equiv of chiral cyanohydrin was used. [b] $A_{CD} = \Delta\varepsilon_{(1st)} - \Delta\varepsilon_{(2nd)}$. [c] A_{corr} refers to the amplitudes corrected for the % ee of the samples <99% ee.

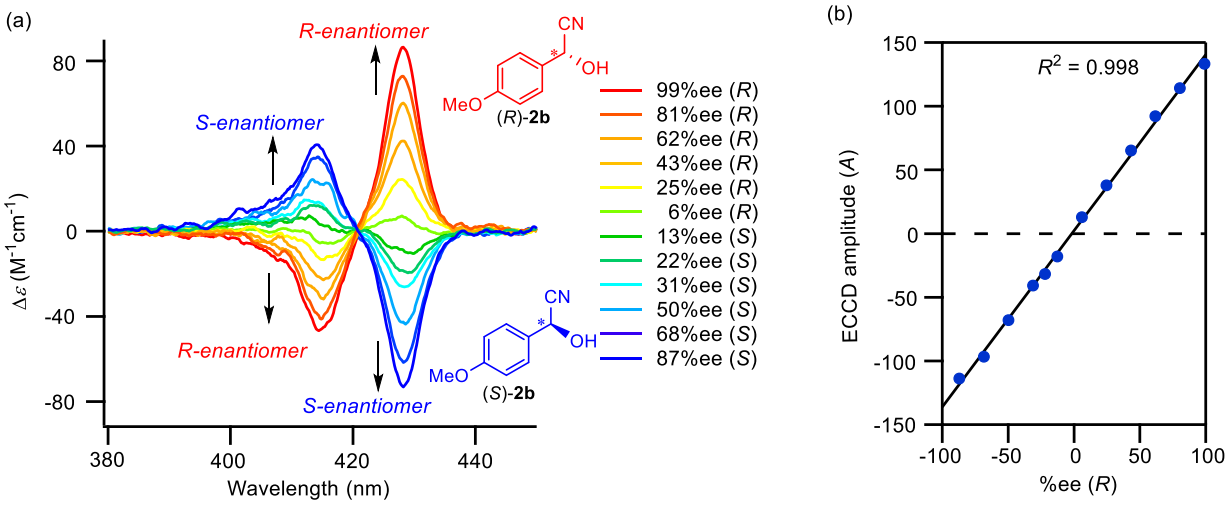


Figure 10. (a) ECCD spectra of **BP1** (1.5×10^{-6} M) complexed with **2b** (10 equiv) at different enantiomeric excesses (ECCD spectra were recorded in 5% CH_2Cl_2/*n*-hexane at 0 °C). (b) Plot of ECCD amplitude ($A = \Delta\varepsilon_{(428\ nm)} - \Delta\varepsilon_{(416\ nm)}$) versus % ee of (*R*)-**2b** in complex with **BP1**.

EXPERIMENTAL

General Methods and Materials. The ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at room temperature on 500, 400, and 300 MHz spectrometers using perdeuterated solvents. The chemical shifts of ^{1}H and ^{13}C NMR spectra are given in ppm relative to the residual protiated solvent and relative to the respective solvent: $CHCl_3$ (δ = 7.24) for ^{1}H NMR, and relative to the central resonance of $CDCl_3$ (δ = 77.0) for ^{13}C NMR. The chemical shifts are reported in δ ppm and the coupling constants *J* are given in hertz (Hz). The following abbreviations are used for signal multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. UV–vis spectra were recorded on a JASCO V-660 dual-beam grating spectrophotometer with a 1 cm cell. IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Mass spectrometry was performed on a JEOL JMS-700 spectrometer. Elemental analysis was conducted using a Yanaco CHN Corder MT-6 elemental analyzer. Optical rotations were measured on a JASCO P-1020 polarimeter. Gas chromatography (GC) analyses were performed with Shimadzu GC-2014 GC systems equipped with a glass capillary column and flame ionization detector. The carrier gas was N_2. The CD spectra were recorded on a JASCO J-820 spectrophotometer with a 1 cm cell. Reactions involving moisture-sensitive reagents were performed under an argon atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under argon before use. Dry THF was purchased for the reactions and used without further desiccation. Bis(zinc porphyrin) **BP1** was prepared as described in the literature.[8] Other chemicals were purchased from commercial sources and used as received unless stated otherwise. Chiral cyanohydrins (*R*)-**2b**, (*R*)-**2c**, and (*R*)-**2d** were commercially available and used without further purification. Chiral epoxides (*R*)-**2a**,[2a] (*S*)-**2a**,[2b] (*S*)-**2b**,[2a] (*S*)-**2c**,[2a] (*S*)-**2d**,[2a] (*R*)-**2e**,[2b] (*R*)-**2f**,[2b] and (*R*)-**2g**[2b] were synthesized according to the reported procedure.

The absolute configurations of cyanohydrins were determined by comparing the measured optical rotations with the reported data.

Spectroscopic Titrations for Evaluation of Association Constants. The association constants K_{assoc} for host–guest complexes were determined by titrating the host molecule **BP1** and its monomeric counterpart **Zn-5** with cyanohydrin **2a** as the guest molecule. K_{assoc} values were calculated using the following equation by applying a non-linear curve-fitting method to the changes in absorbance (ΔAbs) on titrating host molecule **BP1** or **Zn-5** with the guest molecule:

$$\Delta\mathrm{Abs} = \frac{\mathrm{L}[\alpha] - \sqrt{\alpha^2\mathrm{L}^2 - 4K_{\mathrm{assoc}}^2 \cdot \mathrm{A} \cdot \mathrm{X} \cdot \mathrm{L}^2}}{2K_{\mathrm{assoc}} \cdot \mathrm{A}}$$

$$\alpha = K_{\mathrm{assoc}} \cdot \mathrm{X} + K_{\mathrm{assoc}} \cdot \mathrm{A} + 1$$

where X and A represent $[\mathrm{Guest}]_{total}$ and $[\mathrm{Host}]_{total}$, respectively; L denotes ΔAbs at 100% complexation; and L and K_{assoc} are parameters.[11] IGOR Pro (version 6.22) software was used for curve-fitting analysis.

Procedure for Obtaining a Job's Plot. Solutions of bis(zinc porphyrin) **BP1** and cyanohydrin in 5% CH_2Cl_2/*n*-hexane were prepared with a fixed total concentration of host and guest (2.0×10^{-6} M) in 5% CH_2Cl_2/*n*-hexane. Stock solutions of cyanohydrin and **BP1** were prepared in CH_2Cl_2. The molar fractions of host **BP1** were varied from 0 to 1 with intervals of 0.125. UV–vis spectra of all the solutions were recorded at 0 °C. The Job's plot was obtained by plotting the changes in absorbance (ΔAbs) against the molar fractions of host **BP1**.

Procedure for ^{1}H NMR Binding Experiments for Complexation of Bis(zinc porphyrin) BP1 with Cyanohydrins. Solutions of bis(zinc porphyrin) **BP1** and the guest in $CDCl_3$ were prepared with the same concentrations of host and guest.

Typical Procedure for CD Measurement. Anhydrous CH_2Cl_2 and *n*-hexane were dried and redistilled over CaH_2. A bis(zinc porphyrin) **BP1** solution in CH_2Cl_2 (0.2 mM, 50 μL) was diluted to 5 mL with *n*-hexane in a measuring flask to obtain a 2.0 μM **BP1** solution. The background spectrum was recorded using a 1 cm cell from 380 to 450 nm with a scan rate of 50 nm/min at 0 °C. A chiral cyanohydrin (200 μL of a 0.2 mM solution in CH_2Cl_2) was added to the prepared host solution to afford the host–guest complex. The CD spectra were measured immediately (5–30 accumulations). The resultant ECCD spectra recorded in millidegrees were normalized based on the bis(zinc porphyrin) **BP1** concentration to obtain the molecular CD (Mol CD).

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15. The linear regression of $\Delta\varepsilon$ at the first Cotton signal (λ = 428 nm) versus % ee of (*R*)-**2b** also yielded an excellent correlation coefficient of 0.999. See Figure S8 in the supporting information.
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