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One-Pot Enantioselective Extraction of Chiral Fullerene C_{76} Using a Cyclic Host Carrying an Asymmetrically Distorted, Highly π-Basic Porphyrin Module

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Asymmetric recognition is one of the most important recognition events, for which a variety of chiral hosts have been developed to date.[1] However, there are particular types of chiral compounds whose optical resolution is essentially difficult. Representative examples include nonsubstituted chiral fullerenes that are devoid of asymmetric carbon atoms but possess only a distorted π-electronic surface.[2] Among such chiral fullerenes, C_{76} is the smallest homologue that adopts an oval shape (Figure 1a).[2b] On the basis of a report from Okamoto et al.,[3,4b] C_{76} with a small asymmetric distortion seems to be one of the most difficult chiral compounds for enantiomer separation. In fact, we attempted recycling chiral HPLC of racemic (±)-C_{76}, but no enantiomeric peak separation resulted even after 20 cycles (Figure S2).[5] Although separation of its diastereoisomeric derivatives by chiral HPLC[6] or kinetic resolution via asymmetric transformation[7] has been reported, the results are not satisfactory. Here we report a novel π-electronic cyclic host ($\mathbf{1_{2H}}$, Figure 1b) bearing a highly π-basic and asymmetrically distorted N-substituted porphyrin unit that can enantioselectively incorporate C_{76} in its cavity and furnish 7% enantiomeric excess (ee) in a single one-pot extraction.

Host $\mathbf{1_{2H}}$ possesses a *meso*-diaryl-β-octaethylporphyrin ($\mathbf{P_{2H}}$) unit on one side and its *N*-2-acetoxyethyl derivative ($\mathbf{P_{N\text{-}EtOAc}}$) on the other. We have reported that cyclic host $\mathbf{3_{2H}}$, a non-pyrrole-β-substituted version of $\mathbf{1_{2H}}$, and its rhodium complex $\mathbf{3_{Rh}}$ are not enantioselective at all toward C_{76} under NMR conditions and therefore can accurately determine the enantiomeric purity of this chiral fullerene.[4b,c] We anticipated that the enantioselection of C_{76} may be realized by enhancing the π-basicity and distortion of the chiral porphyrin unit in the host. Thus, for the host design, pyrrole-β-substituted $\mathbf{P_{2H}}$ was chosen, since it is electron-rich and also nonplanar because of steric repulsion among the peripheral substituents.[4a,8,9b] Hence, its N-substituted derivative ($\mathbf{P_{N\text{-}EtOAc}}$) could be more π-basic and have a larger molecular distortion than the corresponding unit in **3**. However, optical resolution of structually encumbered $\mathbf{P_{N\text{-}EtOAc}}$ by chiral HPLC was not successful. Meanwhile, we found that its chiral phlorin[10] derivative ($\mathbf{P_{Phl}}$), an unexpected product in the attempted N-hydroxyethylation of lithiated $\mathbf{P_{2H}}$ with epoxyethane, can be separated into enantiomers.[5] Moreover, stereoretentive conversion of $\mathbf{P_{Phl}}$ into $\mathbf{P_{N\text{-}EtOAc}}$ was successful.[5] Thus, compound $\mathbf{2_{2H}}$ (Figure 1b) was synthesized using enantiomerically pure $\mathbf{P_{Phl}}$ and then converted into $\mathbf{1_{2H}}$.[5]

As shown in Figure 2a,[11] the enantiomers of $\mathbf{1_{2H}}$ (blue) clearly exhibited mirror-image circular dichroism (CD) spectra of one another, with a split Cotton effect in the Soret absorption region (400−430 nm). Notably, the CD intensity of $\mathbf{1_{2H}}$ was much larger than that of $\mathbf{3_{2H}}$ (black), suggesting its large molecular distortion caused by steric repulsion among the peripheral substituents.[8,9b] When it was mixed with (±)-C_{76} in toluene at 20 °C, $\mathbf{1_{2H}}$ displayed a bathochromic shift in the Soret absorption band from 412 to 416 nm.[5] This spectral change is typical of metalloporphyrin cyclic dimers upon inclusion of fullerenes.[4,9] Spectroscopic titration of (±)-$\mathbf{1_{2H}}$ with (±)-C_{76} in toluene at 20 °C gave an association constant K_{assoc} of 5.5×10^6 M^{-1}, which is larger than that of $\mathbf{3_{2H}}$ (2.5×10^6 M^{-1}) but smaller than that of $\mathbf{3_{Rh}}$ (1.5×10^7 M^{-1}).[4b,5] Next, we attempted enantioselective extraction of C_{76}. At first, (+)-$\mathbf{1_{2H}}$[11] was mixed with (±)-C_{76} in toluene in a [(±)-C_{76}]/[(+)-$\mathbf{1_{2H}}$] molar ratio of 10, and the mixture was subjected to size-exclusion chromatography (SEC; Bio-Rad Bio-Beads S-XI) using toluene as the eluent. The first fraction containing the inclusion complex

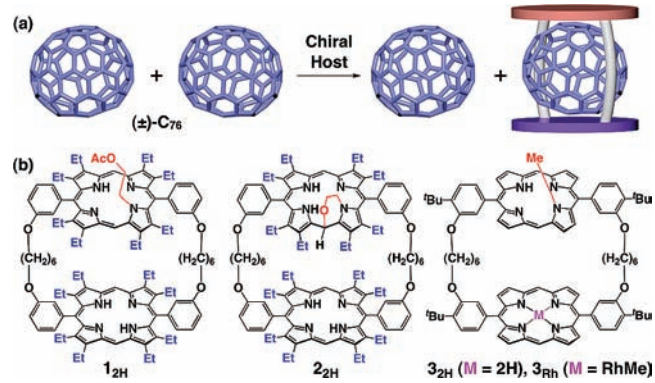

Figure 1. (a) Schematic representation of enantioselective complexation of C_{76} with a chiral host. (b) Molecular structures of chiral hosts $\mathbf{1_{2H}}$, $\mathbf{2_{2H}}$, and **3**.

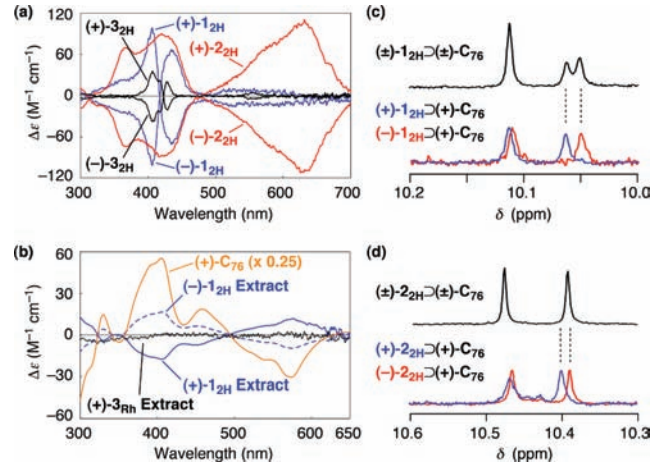

Figure 2. (a) CD spectra of the enantiomers of $\mathbf{1_{2H}}$ (blue), $\mathbf{2_{2H}}$ (red), and $\mathbf{3_{2H}}$ (black) in toluene at 20 °C. (b) CD spectra of C_{76} extracted with $\mathbf{1_{2H}}$ (blue) and $\mathbf{3_{2H}}$ (black) along with that of an almost pure enantiomer of C_{76} (orange) as a reference. (c, d) ^{1}H NMR (500 MHz) spectra (selected region for *meso*-H) of 1:1 mixtures of (+)-host/(+)-C_{76} (blue), (−)-host/(+)-C_{76} (red), and (±)-host/(±)-C_{76} (black) in toluene-d_8 at 20 °C. The hosts for (c) and (d) are $\mathbf{1_{2H}}$ and $\mathbf{2_{2H}}$, respectively. [(+)-C_{76}] = [(±)-C_{76}]/4 = 7.7×10^{-5} M.

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(+)-$\mathbf{1_{2H}}\supset C_{76}$ was collected and then chromatographed on silica gel with toluene as the eluent, where (+)-$\mathbf{1_{2H}}$ in the inclusion complex was protonated and released C_{76}; this was isolated as the first fraction in 51% yield relative to (+)-$\mathbf{1_{2H}}$. As shown in Figure 2b (blue solid curve), the extracted C_{76} was CD-active, with enrichment of (−)-C_{76} (the enantiomer with a negative-signed CD band at 400 nm). By reference to the $\Delta\varepsilon$ value of enantiopure C_{76},[4b] the ee was evaluated as 7.1%. Likewise, the use of (−)-$\mathbf{1_{2H}}$[11] in place of (+)-$\mathbf{1_{2H}}$ for the extraction resulted in enrichment of (+)-C_{76} in 7.0% ee (Figure 2b, blue broken curve). On the basis of the ee values of extracted C_{76}, the enantioselectivity of $\mathbf{1_{2H}}$ (i.e., the ratio of K_{assoc} for the favorable host/guest pair to that for the unfavorable one) was estimated as 1.17. The enantioselective inclusion of C_{76} with $\mathbf{1_{2H}}$ was also confirmed by ^{1}H NMR spectroscopy. Because of the presence of conformational isomers due to its rigid cyclic structure,[4,9] (±)-$\mathbf{1_{2H}}$ alone in toluene-d_8 at 20 °C showed a rather complicated spectral profile.[5] For example, the *meso*-H displayed multiple singlet signals at 9.49−10.53 ppm.[5] However, upon binding with (±)-C_{76}, the spectrum was simplified to give only a few *meso*-H signals at 10.05−10.36 ppm (Figure 2c, black).[5] When (+)-C_{76} was allowed to complex with (−)-$\mathbf{1_{2H}}$ or (+)-$\mathbf{1_{2H}}$ (Figure 2c), either of the two *meso*-H signals at 10.05 (red) and 10.06 (blue) ppm was observed. Therefore, in the upper spectrum (black) of Figure 2c, the signals at 10.05 and 10.06 ppm are assignable to (−)-$\mathbf{1_{2H}}\supset$(+)-C_{76}/(+)-$\mathbf{1_{2H}}\supset$(−)-C_{76} and (+)-$\mathbf{1_{2H}}\supset$(+)-C_{76}/(−)-$\mathbf{1_{2H}}\supset$(−)-C_{76}, respectively. In conformity with the ee value observed for the extraction (Figure 2b), the integral ratio of these *meso*-H signals was 1.2. Likewise, the Ar−H and NH signals of (±)-$\mathbf{1_{2H}}$ in the presence of (±)-C_{76} were split diastereoisomerically.[5]

We also tested $\mathbf{2_{2H}}$ as the potential host, since its chiral phlorin unit $\mathbf{P_{Phl}}$, though nonaromatic, likely adopts a larger molecular distortion than $\mathbf{P_{N\text{-}EtOAc}}$. In fact, successful X-ray crystallography of a phlorin compound identical to the $\mathbf{P_{Phl}}$ unit in $\mathbf{2_{2H}}$ revealed a heavily distorted, nonplanar geometry.[5] The deviation of the O-attached meso carbon atom from the mean plane defined by a dipyrrin moiety bearing a nonsubstituted sp^2 meso carbon atom is the largest among those reported for crystallographically defined phlorins.[5,10] Accordingly, the CD spectra of the enantiomers of $\mathbf{2_{2H}}$ (red) were quite different from those of $\mathbf{1_{2H}}$ and $\mathbf{3_{2H}}$ (Figure 2a). However, despite such a large distortion, the performance of $\mathbf{2_{2H}}$ in enantioselection fell short of our expectations. The K_{assoc} value of 3.8×10^5 M^{-1}, as determined by spectroscopic titration of (±)-$\mathbf{2_{2H}}$ with (±)-C_{76} in toluene at 20 °C,[5] was 1 order of magnitude smaller than that for $\mathbf{1_{2H}}$. Although the ^{1}H NMR spectral profile of the resulting inclusion complex was similar to that of (±)-$\mathbf{1_{2H}}\supset$(±)-C_{76},[5] the *meso*-H signals of (±)-$\mathbf{2_{2H}}$ did not split diastereoisomerically (Figure 2d, black). Notably, authentically prepared (+)-$\mathbf{2_{2H}}\supset$(+)-C_{76} (blue) and (−)-$\mathbf{2_{2H}}\supset$(+)-C_{76} (red) displayed clearly distinguishable *meso*-H signals. Along with the small K_{assoc} value of $\mathbf{2_{2H}}$ toward C_{76}, the nonsplitting feature observed for the *meso*-H signals of the inclusion complex (±)-$\mathbf{2_{2H}}\supset$(±)-C_{76} (black) indicates a dynamic nature of their assembly.[4b,c]

Enantioselective extraction of C_{76} was attempted using as references (+)-$\mathbf{2_{2H}}$, (+)-$\mathbf{3_{2H}}$, and (+)-$\mathbf{3_{Rh}}$,[11] the latter two of which have been reported to be nonenantioselective toward C_{76} under NMR conditions.[4b] We found that only (+)-$\mathbf{3_{Rh}}$ can extract C_{76}, as a result of the very high affinity of the rhodium porphyrin unit toward fullerenes.[4b] However, the extracted C_{76} displayed no detectable optical activity (Figure 2b, black). A possible drawback of non-pyrrole-β-substituted $\mathbf{3_{Rh}}$ is that its chiral *N*-methylporphyrin unit is not basic enough to interact with fullerenes proactively, so the inclusion of C_{76} relies mostly on the high affinity of the achiral rhodium porphyrin unit. In contrast, chiral $\mathbf{P_{N\text{-}EtOAc}}$ in enantioselective host $\mathbf{1_{2H}}$ has an enhanced π-basic character due to the pyrrole-β substitution[4a] and therefore plays a major role in trapping C_{76}.

In conclusion, we have succeeded in one-pot enantioselective extraction of (±)-C_{76} using chiral porphyrin dimer $\mathbf{1_{2H}}$, where even a single extraction produced 7% ee. Control experiments with reference hosts indicated the importance of the high π-basicity and large asymmetric distortion of the $\mathbf{P_{N\text{-}EtOAc}}$ unit in $\mathbf{1_{2H}}$ for enantioselection of C_{76}. This host likely has great potential in HPLC as a chiral stationary phase for optical resolution of nonsubstituted chiral fullerenes. Its separation factor toward (±)-C_{76}, as estimated from the guest/host molar ratio and the optical purity of the extracted C_{76}, is $\alpha = 1.17$,[5] which is, in general, large enough for achieving optical resolution of chiral componds without recycling.[1c]

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Supporting Information Available: Preparation of $\mathbf{1_{2H}}$, $\mathbf{2_{2H}}$, and phlorin; analytical data for their mixtures with C_{76}; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For $\mathbf{1_{2H}}$ and **3**, the symbols (+) and (−) denote the CD signs at their Soret absorption maxima. (+)-$\mathbf{2_{2H}}$ and (−)-$\mathbf{2_{2H}}$ represent the enantiomers of $\mathbf{2_{2H}}$ that afford (+)-$\mathbf{1_{2H}}$ and (−)-$\mathbf{1_{2H}}$, respectively.

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