

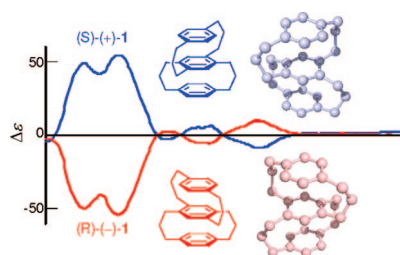
Optical Resolution, Absolute Configuration, and Chiroptical Properties of Three-Layered [3.3]Paracyclophane¹

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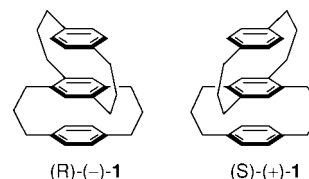
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A racemic mixture of three-layered [3.3]paracyclophane ([3.3]PCP), **1**, has been resolved into two enantiomers, and their absolute configuration was determined from a comparison of experimental chiroptical properties and density functional theory (DFT) calculations. A simple model comprising two *p*-xylenes and 1,2,4,5-tetramethylbenzene (durene) was used to explain the origin of the chiroptical properties of the three-layered cyclophane system.

Cyclophanes are organic compounds consisting of aromatic units and aliphatic chains that form bridges between the aromatic rings.² One of the most interesting properties of cyclophanes is that these molecules can orientate themselves as chiral and helical arrangements. Although studies of chiral cyclophanes have a long history,³ determination of the absolute configurations (AC) of chiral cyclophane systems still needs a great deal of

care: boat-type deformation and transannular interactions of facing aromatic rings cause AC assignment to be laborious, since the chiroptical characteristics of cyclophanes are sensitive to these properties. In recent years, however, computational methods for predicting chiroptical properties such as electronic circular dichroism (CD), vibrational CD, optical rotation, and optical rotatory dispersion (ORD) have been developed and applied successfully to help assign the absolute configurations of rigid chiral molecules including cyclophane systems.⁴



Multilayered paracyclophanes (PCPs) have served as model compounds for investigating transannular delocalization through completely overlapping aromatic π -electrons and the relationship between the magnitude of the delocalization and the number of layers.⁵ Otsubo et al. synthesized multilayered [2.2]PCPs (up to six layers) and studied their structural and electronic properties in detail.⁵ Yamamoto et al. accomplished the synthesis of optically active multilayered [2.2]PCPs (up to six layers) and reported their chiroptical properties.⁶ In the previous paper, we reported the synthesis, structural properties, and transannular π - π interaction of three- and four-layered racemic [3.3]PCPs.⁷ However, elucidation of their chiroptical properties and AC determination are remaining to be resolved. We report here optical resolution, the AC assignment, and chiroptical properties of **1** on the basis of a combined experimental and computational study.

Three-layered [3.3]PCP (\pm)-**1**, which was first reported by Otsubo et al.,⁸ was synthesized by an alternative coupling of the (*p*-ethylbenzenesulfonyl)methyl isocyanide (EbsMIC) method (see Supporting Information).⁷ Resolution of (\pm)-**1** was achieved

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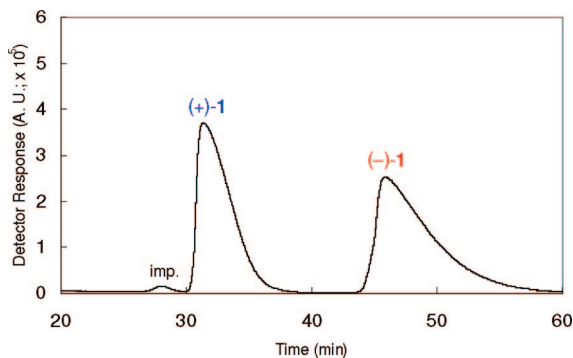


FIGURE 1. Chromatogram of HPLC resolution of (\pm)-**1** in propan-2-ol.

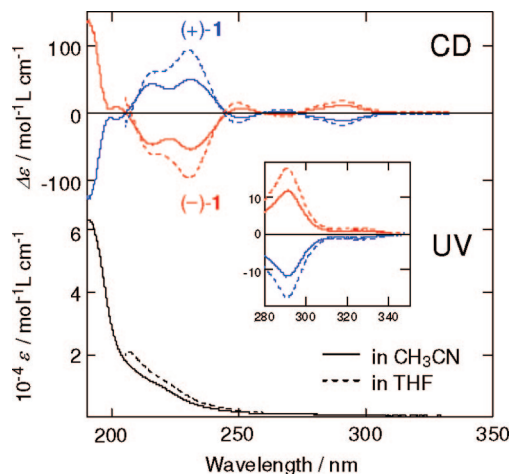


FIGURE 2. CD and electronic spectra of (+)- and (-)-**1** in THF (broken line) and CH_3CN (solid line). (Inset) CD spectra in the longer wavelength region.

by high performance liquid chromatography using a Chiralcel OD column (cellulose tris(3,5-dimethylphenylcarbamate), 10×250 mm) of Daicel Chemical Industries, Ltd. eluting with propan-2-ol at 1.0 mL/min flow speed. The fractions were detected by UV ($\lambda = 254$ nm). About 50 mg of (\pm)-**1** was dissolved in ca. 50 mL of propan-2-ol. Each time, 2 mL of the sample solution was injected and separated. After repeated separations, enantiomers were combined to give (+)-**1** (14.8 mg, retention time 33 min) and (-)-**1** (18.7 mg, retention time 47 min) (Figure 1). The first-eluted sample is (+)-**1** $\{[\alpha]_{\text{D}}^{25} = +125^\circ$ ($c = 0.90$)}, and the second is (-)-**1** $\{[\alpha]_{\text{D}}^{25} = -123^\circ$ ($c = 0.95$)}. The enantiomeric purity was determined by HPLC with Chiralcel OD after recrystallization from $\text{CH}_2\text{Cl}_2/\text{EtOH}$: (+)-**1** 100% e.e.; (-)-**1** 100% e.e.

The CD spectrum of (+)-**1** is a mirror image of that of (-)-**1** in both THF and CH_3CN solution (Figure 2). Solvent effects on the CD spectral pattern were not observed under the present conditions, but the CD signal at ca. 230 nm in the THF solution becomes larger than that in the CH_3CN solution.

The molecular structure of (-)-**1** was further confirmed by X-ray crystallographic analysis.⁹ In the X-ray structure, the [3.3]PCP units take on a boat–boat conformation (Figure 3A), which is comparable to that of (\pm)-**1**,⁷ but different from that of the parent [3.3]PCP¹⁰ with a chair conformation. The three benzene rings are approximately centered with intramolecular distances of 3.260 and 3.284 Å (Figure 3B), which are shorter than that of the parent [3.3]PCP (3.31 Å). The benzene rings

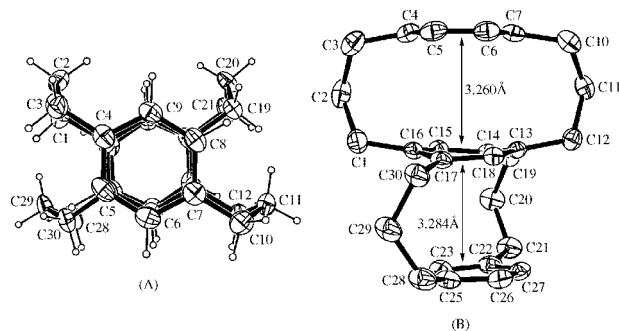


FIGURE 3. Molecular structures of (-)-**1**; top (A) and side (B) views.

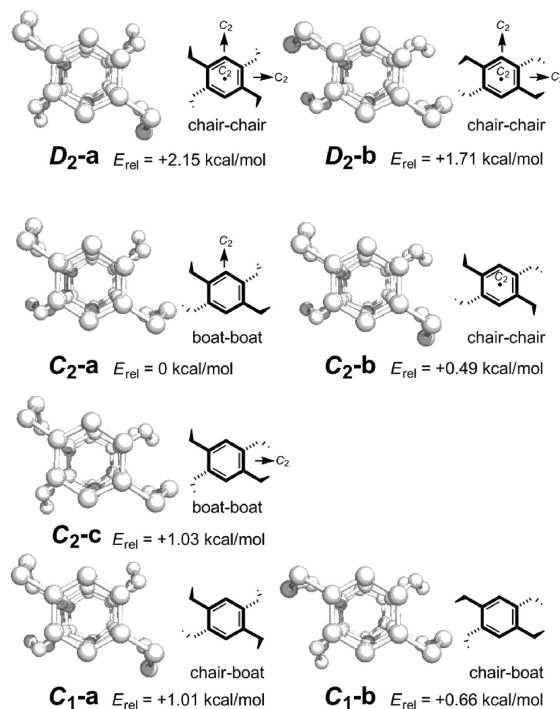


FIGURE 4. B3LYP/TZVP structures of possible conformers of three-layered [3.3]PCP, (*R*)-**1**. The relative energies (E_{rel}) are based on total energies corrected with the zero-point vibrational energies.

of (-)-**1** are almost stacked on each other, maintaining its planarity. It is also noted that the projections of the three aromatic rings do not completely overlap each other. In this respect, the molecule takes a left-handed helical conformation. In the crystal-packing diagram of (-)-**1**, three kinds of CH/π interactions are observed along the *b*-axis [C7–H5 (2.881 Å), C8–C5 (2.837 Å), and C22–H19 (2.712 Å)] (Figure S1, Supporting Information), whereas the CH/π interactions of the benzene rings with the trimethylene protons between (-)-**1** and (+)-**1** isomers are observed in (\pm)-**1**.⁷

It is well-known that [3.3]PCPs are flexible molecules. The ^1H NMR data for (\pm)-**1** show three aromatic signals (δ 5.90, 6.43, and 6.55) in CDCl_3 ,⁷ indicative of an effective D_2 symmetry in solution. This is in contrast to the crystal structure of (-)-**1** which has approximate C_2 symmetry. We therefore carried out conformational analysis of the three-layered [3.3]PCP with *R*-configuration ((*R*)-**1**) at the B3LYP/TZVP level, to gain an insight into the structure in solution. As shown in Figure 4, seven stable conformations, which can be classified into three groups by their symmetry (D_2 , C_2 , and C_1), were obtained. The

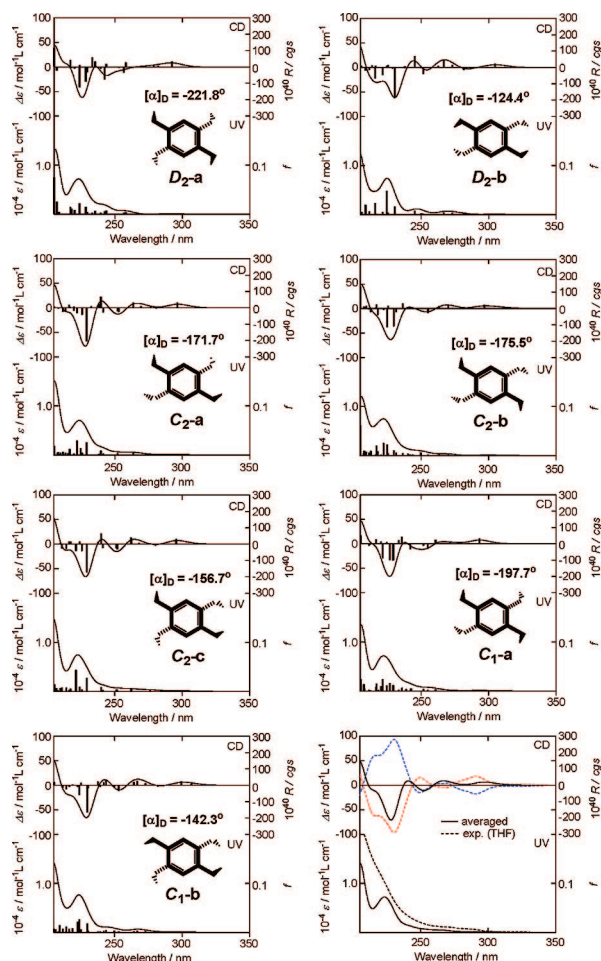


FIGURE 5. Calculated CD and absorption spectra for the possible conformers of (*R*)-**1** and their Boltzmann-averaged spectra. Calculated optical rotation values (B3LYP/TZVP) are also shown. Gaussian bands with a half-bandwidth of 2000 cm^{-1} were used to produce the spectra. $[\alpha]_D$ values in $\text{deg} [\text{dm} (\text{g}/\text{cm}^3)]^{-1}$.

differences in geometry between the conformations lie predominantly in the relative orientation of the carbon bridges. Thus, in all the conformers, the benzene rings are almost stacked maintaining its planarity, as seen in the crystal structure. The interplanar distances of these optimized structures (3.39–3.41 Å, see Supporting Information) are, however, somewhat longer than those of the crystal structure (3.260 and 3.284 Å). This discrepancy probably results from the missing double excitations between the HOMO and LUMO in the DFT approaches, since the geometries of cyclophanes are relatively sensitive to electron correlation effects.¹¹ It should be noted that the geometrical parameters of the lowest-energy conformation, *C*₂-a, were essentially identical to those of the crystal structure.

We have predicted the UV and CD spectra of the possible conformers of (*R*)-**1** at the level of B3LYP/TZVP. For all seven

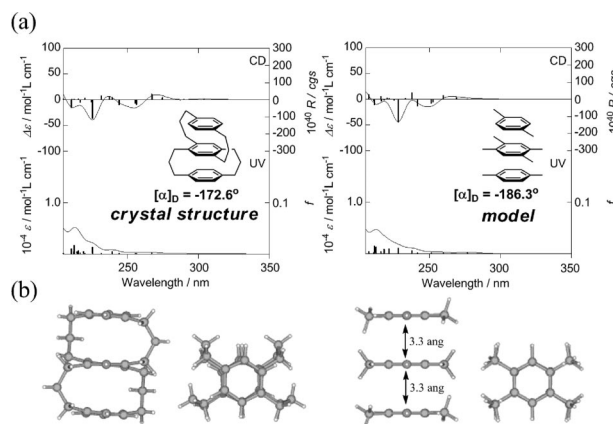


FIGURE 6. (a) Calculated spectra for the crystal structure of (*–*)-**1** and a model benzene trimer comprising two *p*-xylenes and 1,2,4,5-tetramethylbenzene. An interplanar distance of 3.3 Å was used. Calculated optical rotation values (B3LYP/TZVP) are also shown. Gaussian bands with a half-bandwidth of 2000 cm^{-1} were used. $[\alpha]_D$ values in $\text{deg} [\text{dm} (\text{g}/\text{cm}^3)]^{-1}$. (b) Comparison between the geometry of the X-ray structure and the model system.

conformations, 30 excited states were needed to simulate the calculated spectra in the region 205–350 nm. As shown in Figure 5, all of the seven different conformations have an intensely negative CD signal at around 230 nm. The Boltzmann-averaged spectral patterns are in fairly agreement with that observed for (*–*)-**1**, although the calculation seems to overestimate the excitation energies to some extent. Judging from the experimental CD spectrum of (*–*)-**1** (Figure 2 inset), the lowest positive CD signal calculated at ca. 300 nm can be associated with the weak positive CD observed at around 310–340 nm. The intensely negative CD signal around 230 nm can be predicted when using different basis sets (see Supporting Information).

Specific rotation at the sodium D line ($[\alpha]_D$) for each conformer of (*R*)-**1** was calculated at the same level as the CD calculations. Interestingly, all the conformers have negative $[\alpha]_D$ value (-124.4 to -221.8°), which is in agreement with the experimental $[\alpha]_D$ value (-123°) for (*–*)-**1** in CH_2Cl_2 . This is in contrast to the results for the barrellenophane system, where the calculated $[\alpha]_D$ sign is negative or positive depending on the conformation.¹² The calculated $[\alpha]_D$ sign was unchanged when the 6-31G* (-164.6°) and 6-31+G* (-189.2°) basis sets were used instead of TZVP. Thus, the TDDFT prediction is that $[\alpha]_D$ is negative and positive for (*R*)-**1** and (*S*)-**1**, respectively.

From these results, we can conclude that the AC of the three-layered [3.3]PCP is (*R*)-(*–*)/(*S*)-(+). TDDFT calculations (B3LYP/TZVP) of the crystal structure of (*–*)-**1** with an *R*-configuration strongly support this assignment (Figure 6a); the calculated CD spectral pattern agrees well with the experimental spectra, and the calculated $[\alpha]_D$ value (-172.6°) of the crystal structure is in fairly good agreement with the experimental value (-123°). It is noted that the CD sign corresponding to the lowest-energy transition of (*R*)-**1** is positive, although the corresponding CD sign of the three-layered [2.2]PCP with an *R*-configuration is negative.^{6a} This implies that direct comparison between the CD spectra of related systems is insufficient for AC assignment of multilayered cyclophane systems.

Zerner and Canuto reported that the UV spectra of the paracyclophanes could be considered to arise from dimers of

(9) Single crystals of (*–*)-**1** suitable for X-ray analysis were obtained by recrystallization from CH_3CN . Crystal Data: $\text{C}_{30}\text{H}_{34}$, FW = 394.60, crystal system: tetragonal, space group: $P4_32_12$ (#96). Lattice parameters: $a = 10.6091(2)$ Å, $c = 39.7099(14)$ Å, $V = 4469.47(20)$ Å³, $Z = 8$, $D_{\text{calc}} = 1.173\text{ g}/\text{cm}^3$, $F(000) 1712.00$, $\mu(\text{Mo-K}\alpha) 0.655\text{ cm}^{-1}$. Crystallographic data for the structural analyses of (*–*)-**1** has been deposited within the Cambridge Crystallographic Data Center (CCDC) as 644835.

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p-xylene, as long as the interaction is weak.¹³ Although they successfully interpreted the UV spectra of [3.3]PCP using two parallel *p*-xylene molecules at 3.3 Å separation, no investigation to interpret the UV and CD spectra of multilayered cyclophane systems has been reported so far. A detailed molecular orbital (MO) analysis was therefore carried out to comprehensively understand the electronic excited states of the present system.

Although a number of excited states in a relatively small energy window were calculated for the present three-layered [3.3]PCP system, the low-lying excited states associated with absorption bands longer than 200 nm consist of π - π^* transitions from six occupied MOs to six unoccupied MOs (see Supporting Information). The frontier orbitals of **1** consist of linear combinations of the frontier orbitals of the monomeric benzene derivatives. Thus, the HOMO, HOMO-1, LUMO+4, and LUMO+5 are considerably destabilized due to the antibonding interactions between the three benzene units, whereas the LUMO, LUMO+1, HOMO-4, and HOMO-5 are stabilized due to the bonding interactions. The energy shift of the HOMO-2, HOMO-3, LUMO+2, and LUMO+3 are modest, since these orbitals have a nonbonding nature. This splitting of the frontier MOs is responsible for the complicated CD pattern of the present system. Essentially identical frontier MOs were calculated for the other conformers.

Since the TDDFT calculations predict that all the possible conformers have similar chiroptical properties, we have investigated the chiroptical properties of a *p*-xylene-durene-*p*-xylene system with (*R*)-configuration as a simple model. In this model, the benzene rings are stacked while maintaining planarity with an interplanar distance of 3.3 Å, and the projections of the three aromatic rings completely overlap each other (Figure 6). The CD and $[\alpha]_D$ of the model were calculated at the level of B3LYP/TZVP. Interestingly, the calculated spectral pattern for the model system reproduced very well the experimental spectral feature of the three-layered [3.3]PCP ((-)-**1**) and the calculated spectral pattern for the optimized geometries. The calculated $[\alpha]_D$ value of the model system (-186.3°) was also in fairly good agreement with the experimental data and the calculated $[\alpha]_D$ value using the optimized geometries. The frontier MOs of the model system consist of linear combinations of the frontier orbitals of the monomeric benzene derivatives, and the energy ordering is almost identical to the optimized structure of three-layered [3.3]PCP system (see Supporting Information). The

dependence of the excited states on the inter-ring separation was also investigated using the model. The energies of the bonding orbital of the LUMO and antibonding orbital of the HOMO are stabilized and destabilized, respectively, as the inter-ring distance decreases. This gives rise to a red-shifted absorption and CD spectra for the system with shorter inter-ring separation. From these results, it is evident that stereochemistry and transannular interactions of substituted benzene units play a vital role in the chiroptical properties of the present system. In other words, the chiroptical properties are little affected by the position of the bridged carbon atoms, the twist structure, and deformation of the aromatic rings.

In summary, resolution of three-layered [3.3]PCP, (\pm)-**1**, was completely accomplished by a chiral stationary phase with propan-2-ol. The CD and $[\alpha]_D$ of the possible conformers of (*R*)-**1** have been calculated using the TDDFT method. The calculated results for the (*R*)-isomer achieve a very satisfactory agreement with the experimental observations for the (-)-isomer, and therefore the absolute configuration (AC) of the three-layered [3.3]PCP is determined to be (*R*)-(-)/(*S*)-(+). A simple model consisting of benzene derivatives (*p*-xylenes and durene) successfully predicted the observed CD and $[\alpha]_D$. As a consequence, we conclude that the chiroptical properties of the three-layered [3.3]PCP system are little affected by the conformation of the bridged carbon atoms, twisted structure, and deformation of the aromatic rings. The present results imply that the [3.3]PCP system has the potential to facilitate AC studies and CD analyses compared to the more widely investigated [2.2]PCP system. The synthesis and AC assignment of more layered [3.3]PCP systems are in progress.

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Supporting Information Available: Crystallographic data, NMR spectra, and computational data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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