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Tolanophane Revisited – Resolution and Racemization Mechanism of a Twisted Chiral Aromatic Compound

Shinji Toyota,*[a] Katsutoshi Kawai,[a] Tetsuo Iwanaga,[a] and Kan Wakamatsu[a]

Keywords: Cyclophanes / Alkynes / Chiral resolution / Circular dichroism / Conformation analysis / Density functional calculations

Enantiomers of tolanophane consisting of two tolane units were resolved by chiral HPLC, contrary to the previous attempts by Staab et al. Racemization took place rapidly at room temperature, and the barrier to enantiomerization was determined to be 93.2 kJ mol^{-1} at 283 K. This energy barrier was rationally deduced with a mechanism involving rotations about the single and triple bond axes, as revealed by DFT calculations. A tetrahedrane intermediate resulting from a transannular reaction between the two adjacent triple bonds was ruled out.

Introduction

In 1968, Staab et al. reported the first synthesis of tolanophane (**1**),[1] which consists of two tolane (diphenylethyne) units (Figure 1).[2,3] X-ray analysis revealed that this molecule had a twisted structure with D_2 symmetry and a short nonbonding distance between the two triple bonds (2.85 Å).[4] This orientation led to transannular reactions across the triple bonds on treatment with various reagents, such as bromine, to form cyclized products.[2,3] Although the chiral structure suggested the presence of enantiomers, resolution by HPLC on a chiral stationary phase or the formation of diastereomeric salts with enantiopure reagents was unsuccessful. The authors proposed the possibility of the formation of tetrahedrane intermediate **2** to explain the facile racemization of the twisted molecule. However, there was no experimental evidence for the intermediacy: no isomerization, namely scrambling of substituents, was observed for some substituted tolanophanes. As far as we have surveyed, no further studies on this simple yet puzzling molecule have been reported since then.[5] On the other hand, the twisted molecular motif with four *o*-phenylene units has been extensively adopted for the design of nonplanar or helical phenylene oligomers, such as tetraphenylenes and their larger analogues with acetylene linkers.[6–9]

Figure 1. Enantiomers of tolanophane **1** and proposed tetrahedrane intermediate **2**.

HPLC with immobilized chiral stationary phases[10] is a powerful technique to resolve enantiomers of chiral cyclic oligomers and can be used with a wide variety of eluent systems.[11] Enantiomers of various cyclic oligomers were resolved with Daicel CHIRALPAK IA and IC columns,[12] giving valuable information of the chiroptical properties of such hydrocarbon samples. These results inspired us to apply this technique to the resolution of tolanophane in the hope that it could offer convincing clues to solve a stereochemical problem that had remained unsolved for more than 40 years. We herein report the structures, the resolution of enantiomers, and the mechanism of enantiomerization of chiral tolanophane in terms of steric congestion and electronic properties of the triple bonds.

Results and Discussion

Synthesis

Bis(2-bromophenyl)ethyne (**3**) was prepared by the double Sonogashira coupling of 1-bromo-2-iodobenzene and (trimethylsilyl)ethyne in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[13] According to the original procedure,[3] this precursor was treated with BuLi and then $CuCl_2$ to give **1** in 10% yield (Scheme 1). Although we also carried out the coupling of **1** under several conditions with various solvents, additives, and Ni catalyst, the original method gives the best results as far as we know. The ^{1}H NMR spectrum has one set of ABCD signals at δ = 7.3–7.5, and the ^{13}C NMR spectrum has six aromatic signals and one alkyne signal. These signal patterns support a sym-

[a] Department of Chemistry, Faculty of Science, Okayama University of Science,
1-1 Ridaicho, Kita-ku, Okayama 700-0005, Japan
Fax: +81-86-256-9457
E-mail: stoyo@chem.ous.ac.jp

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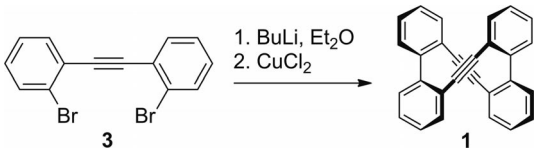
metric structure on the NMR timescale at room temperature. The alkyne carbon signal of **1** (δ = 94.7 ppm) shifted downfield relative to that of the parent tolane (δ = 89.6 ppm).[14] This deshielding is attributable to the bending deformation of sp carbon atoms as well as the anisotropic effect of the nearby triple bond.



Scheme 1. Synthesis of **1**.

X-ray Analysis

X-ray analysis of **1** was performed at –150 °C with a single crystal grown from hexane/dichloromethane. Figure 2 shows the X-ray structures of two independent molecules where solvent molecules (CH_2Cl_2) were omitted. The crystallographic parameters of this crystal, which is tetragonal and in the $I\bar{4}c2$ space group, are similar to those of one of the polymorphs reported by Irngartinger.[4] The asymmetric unit contains two sets of one-quarter of the whole molecule, and the symmetric operation gives two molecules with the same helicity and D_2 symmetry. Selected structural parameters are listed in Table 1. In the acetylene axes, the bond lengths of the triple and single bonds are 1.20 and 1.43 Å, respectively. The bond angles at the alkyne carbon atoms are 171° and 175° in molecules A and B, respectively, and indicate small bending deformations. The dihedral angles between the phenyl groups in the biphenyl moieties, ϕ_1 and ϕ_2, suggest that molecule B (52°) is less twisted than molecule A (58°). The orientation of the two triple bonds can be characterized by two parameters: the distances between their midpoints R and the skew angles between the two axes ρ. The R values for the two independent molecules are 2.86 and 2.83 Å, which are much shorter than the sum of the van der Waals radii of sp carbon atoms (ca. 3.4 Å). Molecule A has a larger skew angle (64.7°) than that of molecule B (56.2°) as a result of the large twist angles in the rigid ring system of the former. Close contact between the two triple bonds is observed in the X-ray structures of tetradehydrodinaphtho[10]annulene (**4**, 2.78 Å, Figure 3) and 5,6,11,12-tetradehydrodibenzo[*a*,*e*]cyclooctene (**5**, 2.61 Å),[15] where the R values shown in parentheses are somewhat shorter than those of **1**. In these planar compounds, the two triple bonds are parallel rather than skewed, corresponding to ρ = 0.

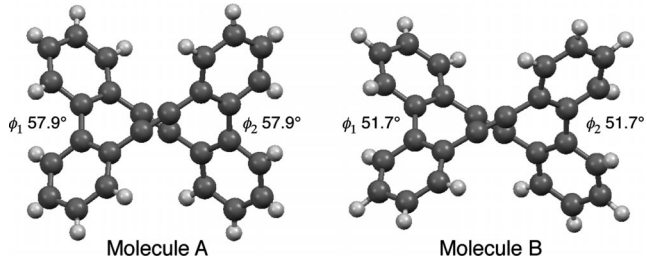


Figure 2. X-ray structures of the two independent molecules of **1**. See Table 1 for the definition of dihedral angles ϕ_1 and ϕ_2.

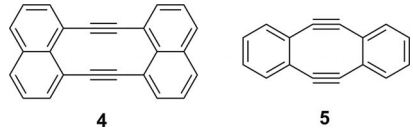
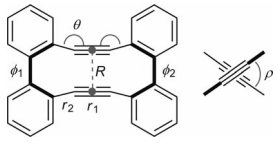


Figure 3. Structures of **4** and **5**.

Resolution of Enantiomers

We performed chiral HPLC with a racemic sample of **1** by using a Daicel CHIRALPAK IA column. The enantiomers were eluted at 29.7 and 37.4 min with hexane/chloro-

Table 1. Structural parameters of the X-ray structures of **1** and calculated structures of **1** and related isomers at the M05-2/6-31G* level.[a]



	Symmetry	N[b]	ΔE [kJ mol^{-1}]	$\Delta G_{298\,K}$ [kJ mol^{-1}]	r_1 [Å]	r_2 [Å]	ϕ_1 [°]	ϕ_2 [°]	θ [°]	R [Å]	ρ [°]
1 X-ray A[c]	D_2	–	–	–	1.203	1.432	57.9	57.9	170.6	2.86	64.7
1 X-ray B[c]	D_2	–	–	–	1.191	1.441	51.7	51.7	174.5	2.83	56.2
1a[d]	D_2	0	0	0	1.210	1.430	56.2	56.2	172.7	2.86	58.9
1b	C_{2h}	1	96.2	97.9	1.213	1.434	–50.1	50.1	161.1	2.98	0.0
1c	C_2	0	96.2	87.1	1.213	1.434	–48.0	51.2	161.1, 161.5	2.97	6.0
1d[c]	C_1	1	96.3	98.7	1.212	1.433	–39.0	51.8	162.5, 163.9	2.92	19.4
1e	D_{2h}	3	159.9	167.3	1.209	1.431	0.0	0.0	169.0	2.76	0.0
2	D_{2d}	0	81.1	86.1	–	–	0.0	0.0	–	–	–
6	D_{2h}	0	–199.1	–192.3	–	–	0.0	0.0	–	–	–

[a] Definitions of structural parameters (see graphic). r_1: C≡C bond length, r_2: C–C bond length, ϕ_1, ϕ_2: dihedral angles between two phenyl groups, θ: bond angle at acetylene carbon atoms, R: distance between midpoints of two triple bonds, ρ: skew angle between two triple bonds. [b] Number of imaginary frequencies. [c] X-ray structures of two independent molecules A and B (see Figure 2). [d] Global minimum. Reference of ΔE and ΔG. [e] Transition state.

form, 10:1, as eluent with almost baseline separation. Preliminary experiments revealed that the enantiomers underwent racemization slowly even at room temperature. By chilling the solvent during chromatography, we successfully obtained almost enantiopure samples of the enantiomers. The resolved enantiomers were circular dichroism (CD) active and their CD curves were mirror images of each other (Figure 4). The first and second fractions gave negative and positive Cotton effects, respectively, at 265 nm.[16]

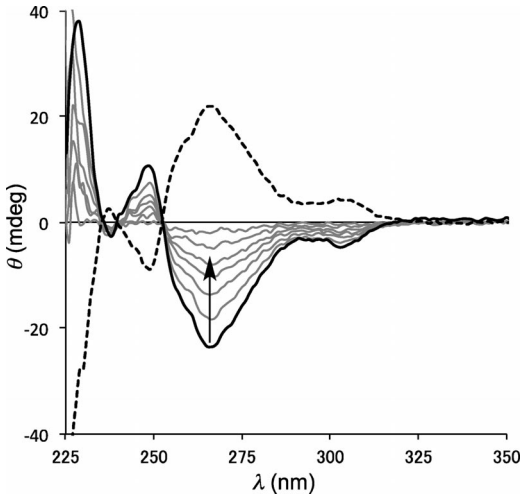


Figure 4. CD spectra of enantiomers of **1** in hexane/chloroform, 10:1. Solid line: first fraction. Broken line: second fraction. Gray lines: decay of CD spectra of first fraction after 1, 2, 3, 4, 6, and 9 h at 10 °C.

The course of racemization could be monitored from the CD spectra measured with an enantiopure sample of the first eluted enantiomer (Figure 4). The rate of enantiomerization was determined by the classical kinetics technique at 10 °C (see Exp. Sect. for the usage of terms, enantiomerization and racemization). The half-life at this temperature was ca. 150 min. Kinetic analysis gave the rate constant $(3.82 \pm 0.10) \times 10^{-5}$ s^{-1}, which corresponds to $\Delta G^{\neq}$ 93.2 kJ mol^{-1} at 283 K. These kinetic data unambiguously show that the unsuccessful resolution reported in the literature was due to facile racemization at room temperature.[3] Nevertheless, the enantiomers can be resolved under appropriate conditions where the exchange becomes slow.

DFT Calculation

In order to obtain information on the racemization mechanism, structures and energies were calculated for various conformations of **1** and related isomers. We adopted the M05-2X/6-31G* level of theory and basis sets because it reasonably reproduced the X-ray structures and energies of π-conjugated compounds.[17] The calculated structures are shown in Figure 5, and the structural parameters and other data are compiled in Table 1. The global minimum structure **1a** is close to molecule A of the X-ray structures.

We adopted the dihedral drive technique for dihedral angle ϕ_1 as the variable parameter, and the other structural parameters were optimized every time with retention of C_2 symmetry. The energy increased monotonically with the decrease of ϕ_1 from 56° (global minimum) to –50°, and became almost constant at 96 kJ mol^{-1} in the range of –30 to –50° (Figure 6). The dihedral angle in the other biphenyl unit ϕ_2 was not affected so much at ca. 50° during the dihedral drive. The calculated structure at ϕ_1 = –50° is **1b**, which has a small bond angle (161°) at the alkyne carbon atoms. Full optimization from structure **1b** gave the less symmetric structure **1c** as the energy minimum, although their energies were almost the same. We also calculated the transition state of the above conformational change to give structure **1d**, which was only slightly less stable than **1b** and **1c**. The energy difference between **1d** and **1a** (98.7 kJ mol^{-1}) is comparable to the observed barrier to enantiomerization. This analysis suggests that **1c** is located at a very shallow hollow in the energy profile and its energy is close to that of transition state **1d**. Fully planar structure **1e** was much less stable than the other nonplanar structures.

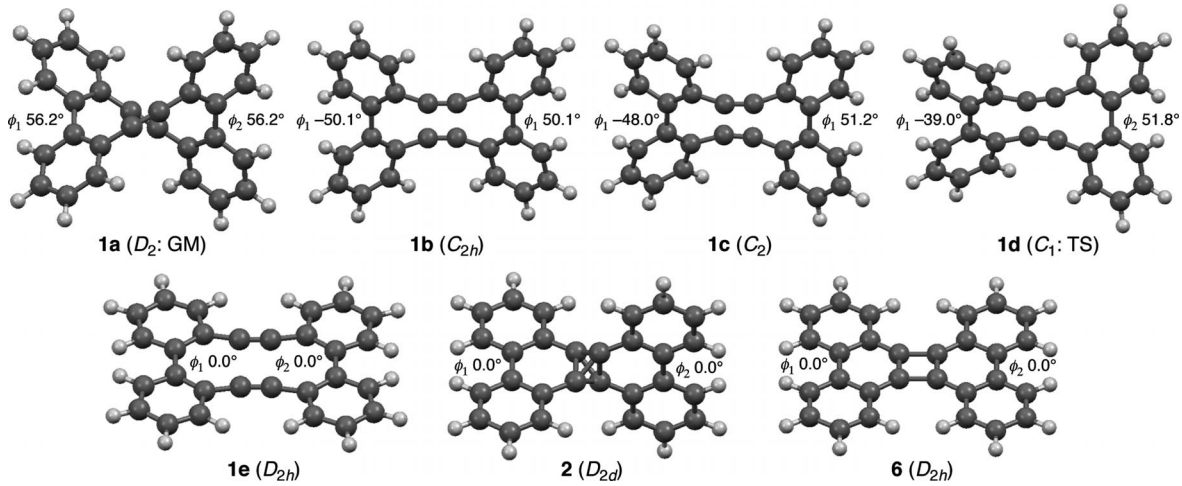


Figure 5. Calculated (M05-2X/6-31G*) structures of various conformations of **1**, tetrahedrane isomer **2**, and cyclobutadiene isomer **6**. See Table 1 for definitions of ϕ_1 and ϕ_2. GM: global minimum, TS: transition state.

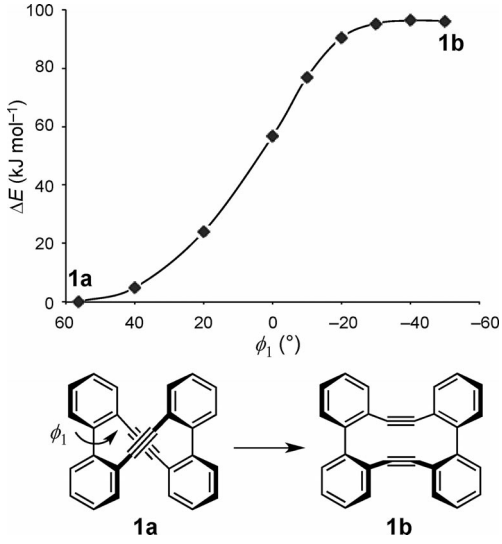
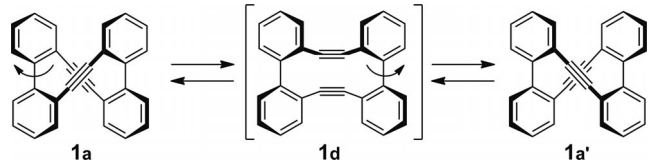


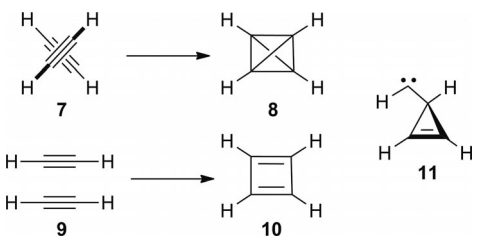
Figure 6. Effects of dihedral angle ϕ_1 on the calculated energies starting from global minimum structure **1a** at the M05-2X/6-31G* level.

We also calculated the isomeric structures of **1**. Tetrahedrane structure **2** was obtained as an energy minimum and found to be more stable by 12.6 kJ mol^{-1} than transition state **1d**. In general, the conversion from the two alkyne units into a tetrahedrane structure was not allowed in terms of MO symmetry, as far as a thermally concerted process was assumed. Then, a conversion process from two acetylene molecules in a crossed arrangement (**7**) into one tetrahedrane molecule (**8**) was analyzed as a model reaction (Scheme 2). This process is symmetrically not allowed according to the calculated orbital correlation diagram (Figure S4 in Supporting Information). If the conversion from **1** into **2** were to occur through nonconcerted mechanisms involving such intermediates as radicals and zwitterions, various side products would be formed. Another possible isomer is cyclobutadiene because some tetrahedrane derivatives are known to isomerize into cyclobutadiene analogues.[18] In the presence of $Fe(CO)_5$, **1** is converted into a $Fe(CO)_3$ complex of cyclobutadiene isomer **6**.[2,3] The calculation suggests that cyclobutadiene **6** itself is thermodynamically much more stable than the other structures. This means that once **6** is formed, it will never revert to the original tolanophane under ordinary conditions. Then we analyzed a model conversion process from two parallel acetylene molecules (**9**) into cyclobutadiene (**10**) in a similar manner (Scheme 2). This process is also symmetrically forbidden under thermal conditions. The course of the isomerization of two acetylene molecules to **8** or **10** was thoroughly investigated by theoretical calculations.[19] The calculations suggested that carbene **11** was a key intermediate in the stepwise routes of the two processes. However, the conversion of two acetylene molecules to **11** would require a large amount of energy (> 200 kJ mol^{-1}).[19a] The above findings suggest that tetrahedrane **2** and cyclobutadiene **6** are highly unlikely to be intermediates during the racemization process of **1**. The observed energy barrier can be rationally explained by the thermal inversion mechanism by bond rotations (Scheme 3).



Scheme 3. Mechanism of racemization between enantiomers **1a** and **1a′** by axis rotation.

The barrier to inversion for tolanophane is much lower than those for tetraphenylene (tetrabenzocyclooctatetraene, **12**) and its derivatives without acetylene linkers (ca. >330 kJ mol^{-1}), which have saddle-shaped twisted structures (Figure 7).[7] On the contrary, expanded tetraphenylene **13** with two acetylene linkers and two diacetylene linkers undergoes rapid enantiomerization with an energy barrier of 39 kJ mol^{-1}.[8a] The dynamic behavior of such processes in cyclic compounds with long linkers occurs too rapidly to allow observation by experimental methods.[8b,8c,20] These tendencies mean that the barrier is effectively lowered by the insertion of acetylene or diacetylene linkers between phenylene units in the tetraphenylene system, which reduces the molecular strain in the transition state.[21] The analogous substituted tolanophane **14** with four *meta*-phenylene units undergoes rapid interconversion between diastereomeric conformers.[5b] Therefore, the sub-



Scheme 2. Model processes from two ethyne molecules to tetrahedrane **8** and cyclobutadiene **10** and theoretically possible intermediate **11**.

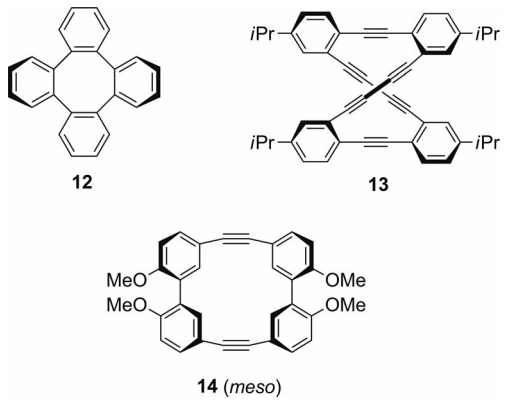


Figure 7. Structures of related compounds **12**–**14**.

stitution position has crucial effects on the conformational distribution and flexibility of the cyclic system.

Conclusions

We were able to resolve the enantiomers of tolanophane **1** and determine the barrier to enantiomerization by classical kinetics. The relatively low barrier was reasonably elucidated by thermal conformational inversion according to DFT calculations, and a mechanism via the tetrahedrane intermediate was ruled out. These findings offer clear evidence to answer the unsolved question raised by Staab et al. Unfortunately, further studies of this interesting compound, in particular, the interactions between triple bonds and transannular reactions to form new aromatic compounds and oligomers, were greatly obstructed by the low yield of the macrocyclization step. The development of an efficient method for the synthesis of this compound and its derivatives, for example, by modern cross-coupling reactions, is in progress.

Experimental Section

General Methods: NMR spectra were measured with a Varian Gemini-300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz). HRMS were measured with a JEOL MStation-700 spectrometer by the FAB method. UV spectra were measured with a Hitachi U-3000 spectrometer with a 10 mm cell. CD spectra were measured with a JASCO J-820 polarimeter with a 10 mm cylindrical cell. GPC was performed with a Japan Analytical Industry Co. LC-908 recycling preparative HPLC system with 20 mmϕ × 600 mm JAIGEL-1H, 2H columns.

Synthesis of 1: To a solution of bis(2-bromophenyl)ethyne (**3**)[13] (1.00 g, 2.98 mmol) in dry ether (35 mL) was added BuLi (4.13 mL of 2.6 mol L^{-1} solution in hexane, 6.61 mmol) at –30 °C under N_2. The solution was stirred for 45 min at that temperature. After cooling to –40 °C, $CuCl_2$ (1.40 g, 10.4 mmol) was added. The reaction mixture was stirred for 30 min at that temperature and then for 2 h at room temp., and heated to reflux for 2 h. The reaction was quenched with dilute HCl (20 mL), and the mixture was extracted with diethyl ether three times. The combined organic solution was washed with aq. $NaHCO_3$ and then aq. NaCl, dried with $MgSO_4$, and the solvents evaporated. The residue was roughly separated by chromatography on silica gel with hexane/chloroform, 8:1 as eluent. The crude product was further purified by preparative GPC with chloroform to give the desired product as colorless crystals (51 mg, 10%); m.p. 209–211 °C (lit. 222–223 °C).[3] ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.32 (m, 4 H), 7.39 (d, J = 7.8 Hz, 4 H), 7.42–7.45 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 94.7 (alkyne), 122.7, 127.0, 128.0, 131.4, 131.7, 143.2 (aromatic) ppm. UV ($CHCl_3$): λ_{max} (ε) = 222 (71000), 241 (68000) nm. HRMS (FAB) calcd. for $C_{28}H_{16}$ [M]$^+$ 352.1252; found 352.1279.

Chiral HPLC and Kinetic Measurement: Chiral HPLC of **1** was carried out with a Daicel CHIRALPAK® IA column (10 mmϕ × 250 mm) with hexane/chloroform, 10:1, as eluent. A solution of a racemic sample (ca. 0.50 mg) in the eluent (0.5 mL) was injected for each batch at a flow rate of 1.0 mL min^{-1}. The enantiomers were eluted at 29.7 and 37.4 min. The eluate of each fraction was used for the CD measurement as obtained. CD (hexane/chloroform, 10:1) λ ($\Delta\varepsilon$) first fraction (5.73 × 10^{-5} mol L^{-1}): 237 (–0.56), 248 (+1.98), 266 (–5.33), 304 (–1.01) nm. Second fraction (5.37 × 10^{-5} mol L^{-1}): 237 (+0.40), 248 (–2.37), 267 (+5.38), 304 (+1.14) nm. Because of the low sensitivity and the ease of racemization, the specific rotations [a] of these enantiomers could not be measured correctly. However, the first and second fractions showed positive and negative optical rotations, respectively, at 589 nm. For the kinetic measurements, all eluents and eluates were cooled in an ice bath. The first eluate was collected and injected again into the column, which contained approximately 5% of the second fraction. The eluate of the first fraction was placed in a CD cell equipped with a thermostat set at 10 °C. The spectra were measured every 30 min while CD intensity was monitored at 266 nm. The data were analyzed as a first-order reversible process expressed as Equation (1), where k_e is the rate of enantiomerization.

$$\text{[CD(+)266]-1} \underset{k_e}{\overset{k_e}{\rightleftharpoons}} \text{[CD(–)266]-1} \quad (1)$$

This rate can be determined from the equation, –1/2 ln([CD]$_t$/[CD]$_0$) = $k_e t$, where t is time (unit: seconds), and [CD]$_t$ and [CD]$_0$ are CD intensities at t and 0, respectively. The least-squares fit of the time and the CD decay gave a rate constant of (3.82 ± 0.10) × 10^{-5} s^{-1} (r = 0.9998) as the slope and the free energy of activation at 93.2 kJ mol^{-1} at 283 K (see Table S1 in the Supporting Information). Racemization is defined as an irreversible conversion from an enantiopure (or enantioenriched) sample into a racemate.[22] Therefore, the rate of racemization k_r is equal to twice the rate of enantiomerization k_e: k_r = 7.64 × 10^{-5} s^{-1} or $\Delta G^{\neq}$ 91.5 kJ mol^{-1} at 283 K for racemization.

DFT Calculations: Calculations were carried out with Gaussian 03[23] on a Linux computer. Structures of various conformations were optimized by hybrid DFT at the M05-2X/6-31G* level of theory. For the dihedral drive analysis, the structure was optimized by varying ϕ_1 in the range 56.2° to –50° with retention of C_2 symmetry. Frequency analyses were performed for all structures and the number of imaginary frequencies is listed in Table 1.

X-ray Analysis: A single crystal was obtained by crystallization from hexane/dichloromethane. Diffraction data were collected with a Rigaku RAXIS-RAPID imaging plate diffractometer with Cu-K_α radiation (λ = 1.54187 Å) to a maximum 2θ value of 68.22° at –150 °C. The structure was solved by the direct method (SHELXS97) and refined by the full-matrix least-squares method (SHELXL97). Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in fixed positions. Formula $2(C_{28}H_{16})\cdot 2(CH_2Cl_2)$, M = 874.67, tetragonal, space group $I\bar{4}c2$ (#120), a = 12.7198(9), c = 25.791(2) Å, V = 4172.8(5) Å^3, Z = 4, D_c = 1.39 g cm^{-3}, μ(Cu-K_a) = 2.90 mm^{-1}. Number of data 22146, number of data used 1917 [$I > 2.0\sigma(I)$], $R1$ = 0.0594, $wR2$ = 0.1646, GOF = 1.143.

CCDC-884577 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR, ^{13}C NMR, and UV spectra, kinetic analysis data, and DFT calculation data.

Acknowledgments

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[1] The systematic name is 9,10,19,20-tetradehydrotetrabenzo[*a*,*c*,*g*,*i*]cyclododecene. Tolanophanes are cyclophanes consisting of tolane units. This term was used in the following articles: a) M. Bauer, M. Nieger, F. Vögtle, *Chem. Ber.* **1992**, *125*, 2533–2538; b) H. R. Darabi, K. Jadidi, A. R. Mohebbi, L. Faraji, K. Aghapoor, S. Shahbazian, M. Azimzadeh, S. M. Nasseri, *Supramol. Chem.* **2008**, *20*, 327–333.

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[4] H. Irngartinger, *Chem. Ber.* **1973**, *106*, 761–772.

[5] This compound was cited in the following articles to date; a) Y. Tobe, R. Umeda, *Sci. Synth.* **2008**, *43*, 393–433; b) K. Utsumi, T. Kawase, M. Oda, *Chem. Lett.* **2003**, *32*, 412–413.

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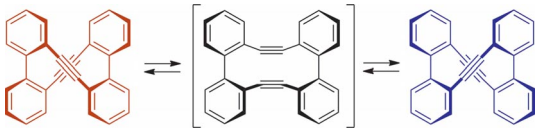
Chiral Cyclophane



Enantiomers of Staab's tolanophane were finally resolved by chiral HPLC. The facile racemization is rationally explained by a bond-rotation mechanism without a tetrahedrane intermediate based on DFT calculations.

Keywords: Cyclophanes / Alkynes / Chiral resolution / Circular dichroism / Conformation analysis / Density functional calculations

