Symmetric Multiple Carbohelicenes

Kenta Kato
Yasutomo Segawa
Kenichiro Itami

Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan
ysegawa@nagoya-u.jp
JST-ERATO, Itami Molecular Nanocarbon Project, Chikusa, Nagoya 464-8602, Japan
itami@chem.nagoya-u.ac.jp
Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Chikusa, Nagoya 464-8602, Japan

Published as part of the 30 Years SYNLETT – Pearl Anniversary Issue

Received: 21.07.2018
Accepted after revision: 24.08.2018
Published online: 26.09.2018

License terms: Open Access

Abstract This account focuses on the synthesis and structures of symmetric multiple carbohelicenes; i.e., fully fused polycyclic aromatic hydrocarbons containing two or more symmetric helicene moieties. Synergies of the multiplexed helicene structures within a π-system generate a number of local minima and transition states between each state. Based on recent studies on multiple helicenes, a systematic molecular design for further multiplexed symmetric helicenes is proposed in the last section of this article.

Key words nonplanar π-systems, polycyclic aromatic hydrocarbons, helicene, multiple helicene

1 Introduction

Helicenes are screw-shaped molecules defined as ortho-fused polycyclic aromatic compounds, in which all aromatic rings are arranged helically.1 This helical structure endows helicenes with chirality even though chiral centers are not present. Based on the helicity rule proposed by Cahn, Ingold, and Prelog in 1966, a right-handed helix is denoted as P (plus) whereas a left-handed helix is denoted as M (minus).2 Such helical π-systems exhibit high values for optical rotation and circular dichroism.3 Moreover, due to the fact that the intrinsic chirality involves a large polyaromatic template, carbohelicenes efficiently induce asymmetry and chirality in organic synthesis and in supramolecular chemistry.4f

The helicity of helicenes can be interconverted thermodynamically with an inversion barrier (ΔG) that depends on the number of fused benzene rings (n). In their ground states (GSs), unsubstituted helicenes exhibit C2 symmetry.3 The transition states (TSs) for the enantiomerization of [n]helicenes (n = 4–7) are shown in Figure 1(a). In the case of [4]helicene, the TS adopts a planar C2v symmetry with a barrier of 4.1 kcal·mol–1, which is small enough for inversion at ambient temperature. The TSs for [5], [6], and [7]helicenes exhibit C2 symmetry with barriers of 23.9, 37.3, and 42.0 kcal·mol–1, respectively (Figure 1(b)). The enantiomerization of [n]helicenes (n ≥ 8) proceeds through multistep mechanisms with higher inversion barriers.3a

Figure 1 (a) Ground states and transition states of [n]helicenes (n = 4–7) together with their symmetry and calculated inversion barriers.4 Experimentally determined inversion barriers are shown in parentheses. (b) Enantiomerization pathway from (P)-[6]helicene to (M)-[6]helicene and its energy diagram (kcal·mol–1).4

SYNLETT 2019, 30, 370–377
Owing to their inversion barriers, \([5]\)helicene racemizes slowly at room temperature, whereas \([6]\)helicene is stable at this temperature. For applications of helicenes in chiral materials, stable substances are required that do not racemize at ambient temperature. Hence, \([6]\)helicene should be a suitable starting point for the design of thermally stable chiral materials.

For the construction of helicene derivatives, four approaches have been reported. The first approach affords helically elongated helicenes with a large number of ortho-fused benzene rings (Figure 2).\(^5\) Generating long helical structures remains challenging in synthetic chemistry, and currently the longest helicene is \([16]\)helicene.\(^5\) The second approach generates laterally \(\pi\)-extended helicenes via a \(\pi\)-expansion in the vertical direction relative to its helical axis.\(^6\) The third approach furnishes heterohelicenes, in which some of the \(\text{sp}^2\)-hydridized carbon atoms of carbohelicenes are replaced with heteroatoms such as B, N, O, Si, P, or S.\(^7\)\(^{–9}\) The optical properties of such heterohelicenes can be tuned by the inherent features of the heteroatoms (e.g., electronegativity, lone pairs, and structural characteristics). The fourth approach concerns multiple helicenes, which contain two or more helicene moieties in a \(\pi\)-conjugated system.\(^10\) Multiple helicenes exhibit highly distorted structures and unique thermodynamic properties that cannot be realized by single helicenes.

![Four types of helicene derivatives](image)

In this account, the synthesis and structures of symmetric multiple carbohelicenes are introduced. Multiple carbohelicenes are categorized by the number of their helicene moieties (multiplicity). With increasing number of helicene moieties, the stereochemistry and the isomerization path-

---

**Biographical Sketches**

**Kenta Kato** was born in Aichi, Japan (1991). He obtained a Master degree in chemistry from Nagoya University in 2016. Currently, he is a postgraduate student in the group of Prof. Kenichiro Itami, focusing on the synthesis of warped nanographenes.

**Yasutomo Segawa** was born in Chiba, Japan (1982). He studied chemistry at The University of Tokyo, Japan, and completed his PhD in 2009 with Prof. Kyoko Nozaki. He then became an Assistant Professor (with Prof. Kenichiro Itami) at Nagoya University in 2009, and became a Group Leader of JST-ERATO Itami Molecular Nanocarbon Project (Designated Associate Professor, Nagoya University) in 2013. His research focuses on the synthesis of novel \(\pi\)-conjugated molecules having non-trivial topologies.

**Kenichiro Itami** was born in Pittsburgh, USA (1971) and raised in Tokyo. He studied chemistry at Kyoto University, Japan, and completed his PhD in 1998 with Prof. Yoshihiko Ito. After being Assistant Professor (with Prof. Jun-ichi Yoshida) at Kyoto University, he moved to Nagoya University as an Associate Professor (with Prof. Ryoji Noyori) in 2005, where he was promoted to Full Professor in 2008. Since 2012 he has also been Director of the Institute of Transformative Bio-Molecules (WPI-ITbM) and since 2013 Research Director of JST-ERATO Itami Molecular Nanocarbon Project. His research focuses on the development of innovative functional molecules with significant structures and properties, and the development of rapid molecular-assembly methods using unique catalysts. Representative achievements are the creation of a range of structurally uniform nanocarbons of fundamental and practical importance by bottom-up chemical synthesis.
ways of multiple helicenes become more complex. In this context, [4]helicene is not considered a helicene moiety, as the inversion barrier of such small helicenes is insufficient to stabilize the helicity. Multiple helicenes containing five-membered rings,\textsuperscript{11} non-aromatic rings and/or heteroatoms\textsuperscript{12} in the helicene structure are also not covered. Moreover, large unsymmetric polycyclic arenes containing helicene moieties are also excluded.\textsuperscript{13} In the final section, we present an outlook on multiple helicene chemistry and the further molecular design of highly multiplexed helicenes.

2 Symmetric Double Carbohelicenes

Symmetric double carbohelicenes contain two helicene moieties that are arranged symmetrically on a π-system. Due to the inherent two helical structures, symmetric double helicenes have three isomers: two enantiomers, the so-called twisted forms \([(P,P)\) and \((M,M)\)], and one diastereoisomer, the so-called meso form \((P,M)\). The first synthesis of double [5]helicene \(1\) was reported by Clar et al. in 1959.\textsuperscript{14} Ohshima, Sakamoto, and co-workers improved the synthesis of \(1\) by using a condensation reaction, and a twisted \(D_2\)-symmetric conformation was assigned (Figure 3(b)) based on \(^1H\) NMR spectroscopy.\textsuperscript{15} Agranat and co-workers reported a computational study of \(1\) in 2007.\textsuperscript{16} S-shaped double [6]helicene \(2\) was synthesized by Laahroven and Cuppen in 1971.\textsuperscript{17} Double helicene \(2\) was synthesized by a photocyclization reaction. The twisted and meso conformers of \(2\) were separated on account of their different solubility. Another type of double [6]helicene, having the shape of the figure of three (3) and its derivative (4) as a double [7]helicene, were synthesized by Martin et al. in 1974 using a photocyclization route.\textsuperscript{18} Based on the NMR and X-ray diffraction analysis of 3 and 4, twisted structures were assigned. In addition to these relatively old reports, three double carbohelicenes (5–7) have been reported in recent years. In 2015, Kamikawa and co-workers synthesized double [5]helicene 5 via a Suzuki–Miyaura cross-coupling reaction.\textsuperscript{19} X-ray diffraction analysis revealed the twisted structure of 5. The meso conformer of 5 is less stable by 5.7 kcal·mol\(^{-1}\) than the twisted one, and the interconversion barrier of 5 was estimated to be 24.2 kcal·mol\(^{-1}\).\textsuperscript{4} Double [6]helicene 6 was synthesized by Itami and co-workers in 2015,\textsuperscript{20} and a mixture of the twisted and meso forms of 6 was obtained by a Scholl reaction. The three isomers were separated by HPLC, and X-ray diffraction analysis revealed a three-dimensional π–π stacking mode for the twisted isomer. The calculated racemization barrier (43.5 kcal·mol\(^{-1}\)) was too high for a kinetic study. Double [7]helicene 7, reported by Müllein and co-workers in 2017, was obtained as an unexpected product of a Scholl reaction of tetra-2-naphthyl-p-terphenyl.\textsuperscript{21} The most stable (twisted) and metastable (meso, 3.2 kcal·mol\(^{-1}\) relative to the twisted conformer) conformers of 7 were isolated by recrystallization, and the racemization barrier of 7 was calculated to be 47.0 kcal·mol\(^{-1}\).\textsuperscript{4}

The structures and enantiomerization pathway of symmetric double helicenes are shown in Figure 3(b) and Figure 3(c), where 1 was selected as a representative example. The most stable conformation of 1 is the \(D_2\)-symmetric twisted form (1a), while the \(C_{m\pi}\)-symmetric meso conformation (1b) is metastable \(\Delta G = 5.1\) kcal·mol\(^{-1}\). The enantiomerization from 1a to 1b proceeds via the meso form and includes two chiral transition states \(\text{TS}_{1ab}\) and \(\text{TS}_{1a*b}\) (\(\text{TS}_{1XY}\): TS between 1X and 1Y). In this pathway, the original chirality \((P,P)\) of 1a is lost upon transformation into the meso intermediate. The energy barrier for enantiomerization of 1 (31.7 kcal·mol\(^{-1}\)) is higher than that of pristine [5]helicene.\textsuperscript{4} The inversion barriers of double helicenes 3–7 are also higher than those of the corresponding pristine \([n]\)helicenes, likely due to the structural interactions of two helicene moieties and the effect of the π-extension.

![Figure 3](image_url)
3 Symmetric Triple Carbohelicenes

Symmetric triple carbohelicenes have four isomers; i.e., two pairs of enantiomers [(P,P,P) and (M,M,M)] as well as (P,P,M) and (P,M,M)]. The most representative member of this class of multiple helicenes is triple [5]helicene 8, which has been well-studied by several groups. The first synthesis of 8 was reported by McOmie and co-workers in 1982 using flash vacuum pyrolysis of cyclobuta[1]phenanthrene-1,2-dione. In 1999, two groups independently reported the synthesis of 8. Pascal and co-workers synthesized 8 by flash vacuum pyrolysis of phenanthrene-9,10-dicarboxylic anhydride, and assigned a D$_3$-symmetric structure (8a) based on X-ray crystallography. Pérez, Guitián and co-workers synthesized 8 by a Pd-catalyzed [2+2+2] cycloaddition of arylene. Later, a conformer of 8 was obtained. In 2003, 8b was structurally characterized by X-ray crystallography by Weng and co-workers. Experimentally, isomerization barriers of 11.7 kcal·mol$^{-1}$ (8b → 8b*, (i) in Figure 4(c)) and 26.2 kcal·mol$^{-1}$ (8b → 8a, (ii) in Figure 4(c)) were determined. In 2011, a hexa-tert-butylated derivative of 8 was reported by Durola and co-workers. In 2017, another type of triple [5]helicene (9) was synthesized by Watanabe and co-workers via a photocyclization reaction. The calculated racemization barrier of 9 was reported as 29.5 kcal·mol$^{-1}$.

The racemization pathway of symmetric triple helicene 8 is shown in Figure 4(c). The most stable conformations of 8 are D$_3$-symmetric structures 8a and 8a*; the metastable C$_s$-symmetric conformations 8b and 8b* are 5.1 kcal·mol$^{-1}$ higher in energy. The enantiomerization from 8a to 8a* proceeds via 8a → 8b → 8b* → 8a*, where the rate-determining step is 8a → TS$_{8ab}$ ($\Delta G = 32.1$ kcal·mol$^{-1}$). In this racemization pathway, the original chirality (P,P,P) of 8a is lost upon transformation into the mirror symmetric (C$_s$) transition state TS$_{8ab}$. This is fundamentally different from the case of double helicene 1, where inversion of chirality occurs via passage through a metastable intermediate (1b). Additionally, due to the higher interconversion barrier for 8b → 8a, the racemization energy of the metastable conformation (8b) could be determined experimentally.

4 Symmetric Quintuple Carbohelicenes

Quintuple [6]helicene 10 was synthesized by Segawa, Itami, and co-workers in 2018 and 10 consists of eight isomers; i.e., four pairs of enantiomers. Even though 10 was initially expected as the product of a Scholl reaction of pentakis(2′-chlorobiphenyl-2-yl)corannulene, this reaction generated warped nanographene due to the rapid formation of seven-membered rings. Alternatively, 11 was synthesized from pentakis(2′-chlorobiphenyl-2-yl)corannulene by a Pd-catalyzed intramolecular cyclization. A single-crystal X-ray diffraction analysis of 10 confirmed a C$_s$-symmetric propeller-shaped structure (10a) with an identical helicity of the five [6]helicene moieties (PPPPP or MMMMM).

The racemization of symmetric quintuple helicene 10 is shown in Figure 5(c). The enantiomerization pathway from 10a to 10$^*$ proceeds via four ground states (10b, 10c, 10c$^*$, and 10b$^*$) and five transition states (TS$_{10ab}$, TS$_{10bc}$, TS$_{10cc^*}$, and TS$_{10bc^*}$). The helicity of five [6]helicene moieties in 10a is inverted via the five TSs, whereby the highest TS on this route is TS$_{10ab}$ (34.5 kcal·mol$^{-1}$ relatively to 10a). This value is in good agreement with the experimentally determined racemization barrier of 10 (34.2 kcal·mol$^{-1}$).

5 Symmetric Sextuple Carbohelicenes

Sextuple [5]helicene 12 was independently reported by two groups in 2017. Tsurusaki, Kamikawa, and co-workers synthesized 12 via a Pd-catalyzed [2+2+2] cyclization reaction of a 12 helicene-based arylene. The cyclization reaction proceeded at room temperature and the metastable conformer 12d was isolated. A kinetic study revealed the isomerization barrier from 12d to 12a and the racemization barrier of 12a as 30.6 kcal·mol$^{-1}$ and 35.4 kcal·mol$^{-1}$, respectively. Coquerel, Gingras, and co-workers synthesized...
K. Kato et al.

Account

Synlett

2019, 30, 370–377

Georg Thieme Verlag Stuttgart · New York — Synlett 2019, 30, 370–377

Synlett

2019, 30, 370–377

K. Kato et al.

Account

and X-ray diffraction analysis revealed a $D_{6v}$-symmetric structure. The theoretically estimated racemization barrier of 13 (52.1 kcal·mol$^{-1}$) is higher than that of pristine [7]helicene (42.0 kcal·mol$^{-1}$). Due to the high barrier, the racemization of 13 was not observed, even after 12 h at 270 °C.

Figure 5 (a) Synthesis of 10 with racemization barrier. Experimentally determined racemization barrier is shown in parentheses. Abbreviations: DMAc = N,N-dimethylacetamide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. (b) Optimized conformers of 10 (10a–d) with the helicity of the [6]helicene moieties (P or M). (c) Structures of TS$^{10ab}$, TS$^{10bc}$, and TS$^{10cc*}$. (d) The lowest racemization pathway of 10 with relative Gibbs free energy values (kcal·mol$^{-1}$).

Figure 6 (a) Sextuple helicenes with racemization barriers. Experimentally determined racemization barrier is shown in parentheses. (b) Structures of conformers and TSs of 12 together with their symmetry. (c) The lowest racemization pathway of 12 with relative Gibbs free energy values (kcal·mol$^{-1}$).

12 via the Ni-mediated homocoupling reaction of a dibrominated [5]helicene. Very recently, another type of sextuple helicene 13 has been reported by Wang and co-workers: the coronene-cored sextuple [7]helicene 13 was synthesized by a Scholl reaction of oligophenylene precursors,
The racemization pathway of sextuple helicene 12 is shown in Figure 6(c). Combining the helicities of the six [5]helicene moieties affords 20 stereoisomers for 12; i.e., ten pairs of enantiomers.28a The most stable structure is D₃-symmetric conformation 12a, in which the inner three [5]helicenes exhibit M and the outer three [5]helicenes exhibit P helicity. Moreover, two possible enantiomerization routes exist: 12a → TS₁₂a → 12b → TS₁₂bc → 12c → TS₁₂d → 12d → TS₁₂c→d → 12c⁺ (or 12c → TS₁₂d → 12d → TS₁₂c⁺ → TS₁₂d → 12c⁺) → TS₁₂c⁺ → 12b⁺ → TS₁₂a → 12a⁺. The rate-determining step is 12a → TS₁₂a → TS₁₂b → TS₁₂c → TS₁₂d → TS₁₂c⁺ → TS₁₂d → TS₁₂c⁺ → TS₁₂c⁺ → TS₁₂b → TS₁₂a → 12a⁺. The energy barrier is higher than that of pristine [5]helicene owing to the steric hindrance of neighboring [5]helicene moieties.

6 Conclusions and Perspective

In this account, we focused on the synthesis and structures of symmetric multiple carbohelicenes and their isomerization pathways. For the synthesis of multiple helicenes with further multiplicity, it is necessary to establish new synthetic strategies to overcome the intermolecular steric hindrance inherent to multiple helicenes.

We propose a novel series of multiple helicenes inspired by 10. As already proposed by Pascal and co-workers in 1999,22b symmetric multiple helicenes can be designed by fusing benzene rings dendritically onto a central benzene ring (Figure 7(a)). Triple [5]helicene 8 can be considered as a benzene ring that contains six fused benzene rings, and the extension of 8 by additional twelve benzene rings affords sextuple helicene 14 with three [5]helicenes and three [7]circulenes. On the other hand, using [n]circulenes as central cores as in, for example, quintuple helicene 10, multiple helicenes with various multiplicities can be designed (Figure 7(b)). Sextuple [6]helicene 15 is obtained from the introduction of six phenanthrene moieties into [6]circulene (coronene). According to preliminary calculations,4 the most stable structure of 15 is the D₃d-symmetric structure. Septuple [6]helicene 16 and octuple [6]helicene 17 can also be designed by a π-extension of [7]- and [8]circulenes, respectively, and theoretical calculations suggest highly warped structures. While a coronene-cored sextuple [4]helicene has already been reported,30 such complex three-dimensional π-systems remain difficult to construct. The further development of multiple helicene chemistry thus requires improvements of the synthetic methods for the generation of such highly strained molecules, before multiple helicenes with unique structural features may potentially be use as chiral materials in future.

Funding Information

This work was supported by the ERATO program from JST (JPMJER1302 to K.I.), the Funding Program for KAKENHI from MEXT (JP16K05771 to Y.S.), a grant-in-aid for Scientific Research on Innovative Areas ‘π-Figuration’ from JSPS (JP17H05149 to Y.S.), and the Naguchi Institute (to Y.S.). K.K. thanks IGERT Program in Green Natural Sciences, Nagoya University and a JSPS fellowship for young scientists. Calculations were performed using the resources of the Research Center for Computational Science, Okazaki, Japan. ITbM is supported by the World Premier International Research Center Initiative (WPI), Japan.

References and Notes


Figure 7 Design of multiple helicenes; (a) Optimized structure of triple helicene 8 and sextuple helicene 14. (b) Optimized structures of multiple helicenes with [n]circulene cores.

(10) For a review on multiple helicenes, see: Li, C.; Yang, Y.; Miao, Q. Chem. Asian J. 2013, 8, 884.


K. Kato et al.


