

Symmetric Multiple Carbohelicenes

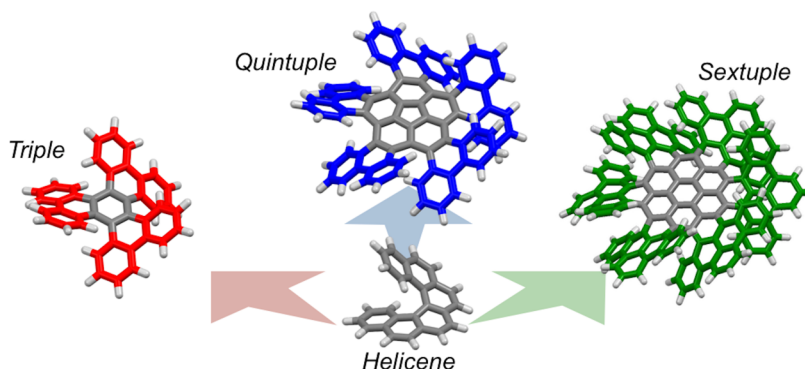
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Abstract: This account focuses on the synthesis and structures of symmetric multiple carbohelicenes, *i.e.*, fully fused polycyclic aromatic hydrocarbons containing two or more helicene moieties symmetrically. Synergies of the multiplexed helicene 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 -system, polycyclic aromatic hydrocarbon, 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.^{1d} 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.^{1e,f}

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 C_2 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 C_{2v} 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 C_s symmetry with barriers of 23.9, 37.3, and 42.0 kcal·mol⁻¹, respectively (Figure 1(b)). The enantiomerization of [n]helicenes ($n \geq 8$) proceeds via multistep mechanisms with higher inversion barriers.^{3a}

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.

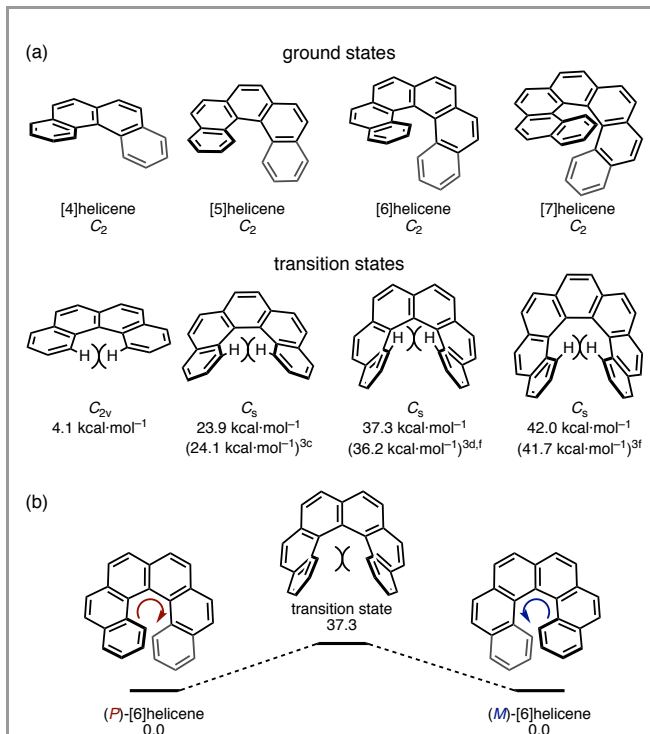
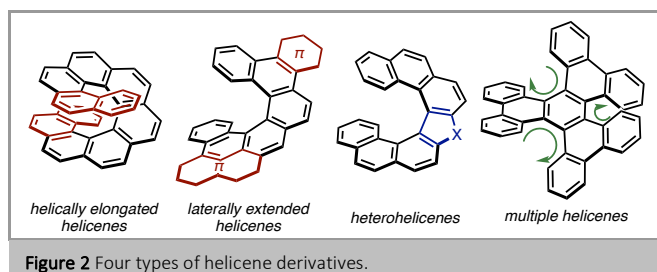


Figure 1 (a) Ground states and transition states of [n]helicenes ($n = 4-7$) together with their symmetry and calculated inversion barriers.⁴ Experimentally determined inversion barriers are shown in parentheses. (b) Enantiomerization pathway from (*P*)- to (*M*)-[6]helicene and its energy diagram (kcal·mol⁻¹).⁴

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.⁵ Generating long helical structures remains challenging in synthetic chemistry, and currently the longest helicene is [16]helicene.^{5e} The second approach generates laterally π -extended helicenes via a π -expansion in vertical direction relative to its helical axis.⁶ The third approach furnishes heterohelicenes, in which some of the sp^2 -hybridized carbon atoms of carbohelicenes are replaced by 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 π -conjugated system.¹⁰ Multiple helicenes exhibit highly distorted structures and unique thermodynamic properties that cannot be realized by single helicenes.



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 pathways of multiple helicenes become more complicated. 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,¹¹ non-aromatic rings and/or heteroatoms¹² in the helicene structure are also not covered. Moreover, large unsymmetric polycyclic arenes containing helicene moieties are also excluded.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 1959.¹⁴ Ohshima, Sakamoto, and co-workers improved the synthesis of **1** using a condensation reaction, and a twisted D_2 -symmetric conformation was assigned (Figure 3(b)) based on ¹H NMR spectroscopy.¹⁵ Agralat and co-workers reported a computational study of **1** in 2007.¹⁶ S-shaped double [6]helicene **2** was synthesized by Laarhoven and Cuppen in 1971.¹⁷ 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.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.¹⁹ An X-ray diffraction analysis revealed the *twisted* structure of **5**. The *meso* conformer of **5** is by 5.7 kcal·mol⁻¹ less stable than the *twisted* one, and the interconversion barrier of **5** was estimated to be 24.2 kcal·mol⁻¹.⁴ Double [6]helicene **6** was synthesized by Itami and co-workers in 2015,²⁰ 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 an 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 Müllen and co-workers in 2017, was obtained as an unexpected product of a Scholl reaction of tetra-2-naphthyl-*p*-terphenyl.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⁻¹.⁴

The structures and enantiomerization pathway of symmetric double helicenes are shown in Figures 3(b) and 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_{2h} -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 **TS**_{1a**b**} and **TS**_{1a**b**'} (**TS**_{1X**Y**}: 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.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.

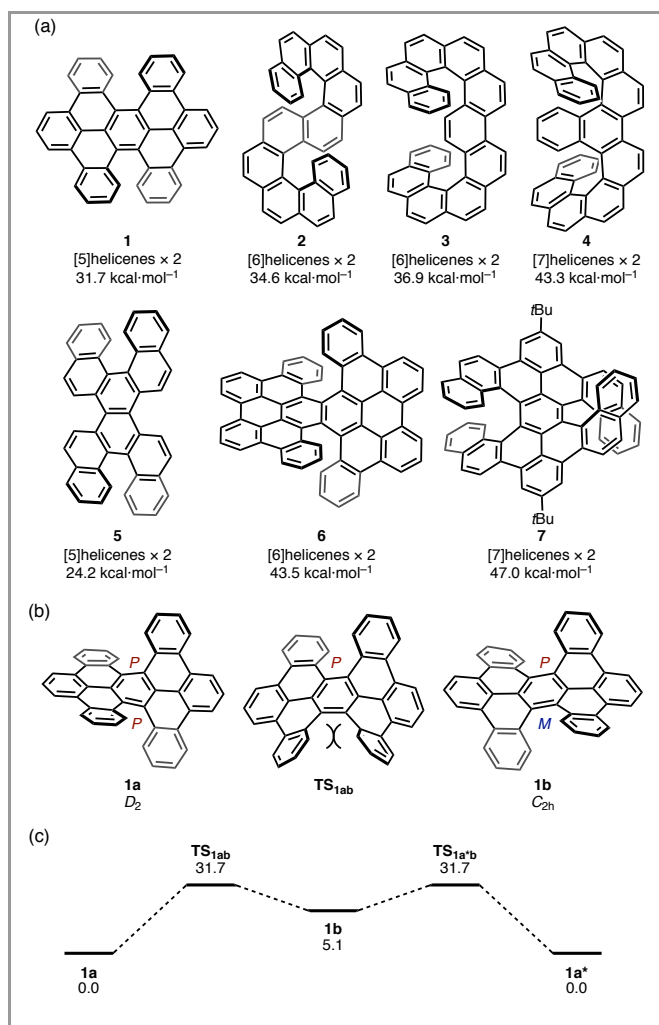


Figure 3 (a) Double helicenes with a racemization barrier. (b) Optimized conformers and transition structures of **1** with the helicity of the [5]helicene moieties (*P* or *M*). (c) Racemization pathway of **1** with relative Gibbs free energy values (kcal·mol⁻¹).⁴

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.²² 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.^{22a} In 1999, two groups independently reported the synthesis of **8**.^{22b,c} Pascal and co-workers synthesized **8** by flash vacuum pyrolysis of phenanthrene-9,10-dicarboxylic anhydride, and assigned a *D*₃-symmetric structure (**8a**) using X-ray crystallography.^{22b} Pérez, Guitián and co-workers synthesized **8** by a Pd-catalyzed [2+2+2] cycloaddition of aryne,^{22c} and a later conformational study of **8** revealed that under these conditions the metastable *C*₂ conformer (**8b**) is obtained.^{22d} In 2003, **8b** was structurally characterized by X-ray crystallography by Wegner and co-workers.^{22e} 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.^{22d} In 2011, a hexa-*tert*-butylated derivative of **8** was reported by Durola and co-workers.²³ In 2017, another type of triple [5]helicene (**9**) was

synthesized by Watanabe and co-workers via a photocyclization reaction.²⁴ 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*₂-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} (Δ*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_{8bb*}. 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.

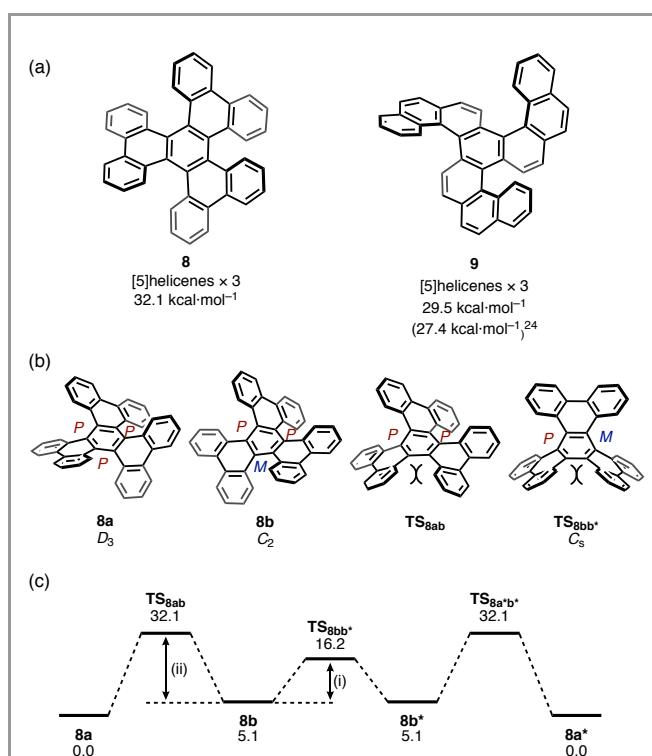


Figure 4 (a) Triple helicenes with racemization barriers. Experimentally determined racemization barrier is shown in parenthesis. (b) Optimized conformers and transition structures of **8** with the helicity of the [5]helicene moieties (*P* or *M*). (c) Racemization pathway of **8** with relative Gibbs free energy values (kcal·mol⁻¹).⁴

4. Symmetric quintuple carbohelicenes

Quintuple [6]helicene **10** was synthesized by Segawa, Itami, and co-workers in 2018,²⁵ 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(biphenyl-2-yl)corannulene, this reaction generated warped nanographene²⁶ due to the rapid formation of seven-membered rings.²⁷ 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_5 -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 **10a*** proceeds via four ground states (**10b**, **10c**, **10c***, and **10b***) and five transition states (**TS_{10ab}**, **TS_{10bc}**, **TS_{10cc*}**, **TS_{10b*c*}**, and **TS_{10a*b*}**).²⁵ 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 relative to **10a**). This value is in good agreement with the experimentally determined racemization barrier of **10** (34.2 kcal·mol⁻¹).

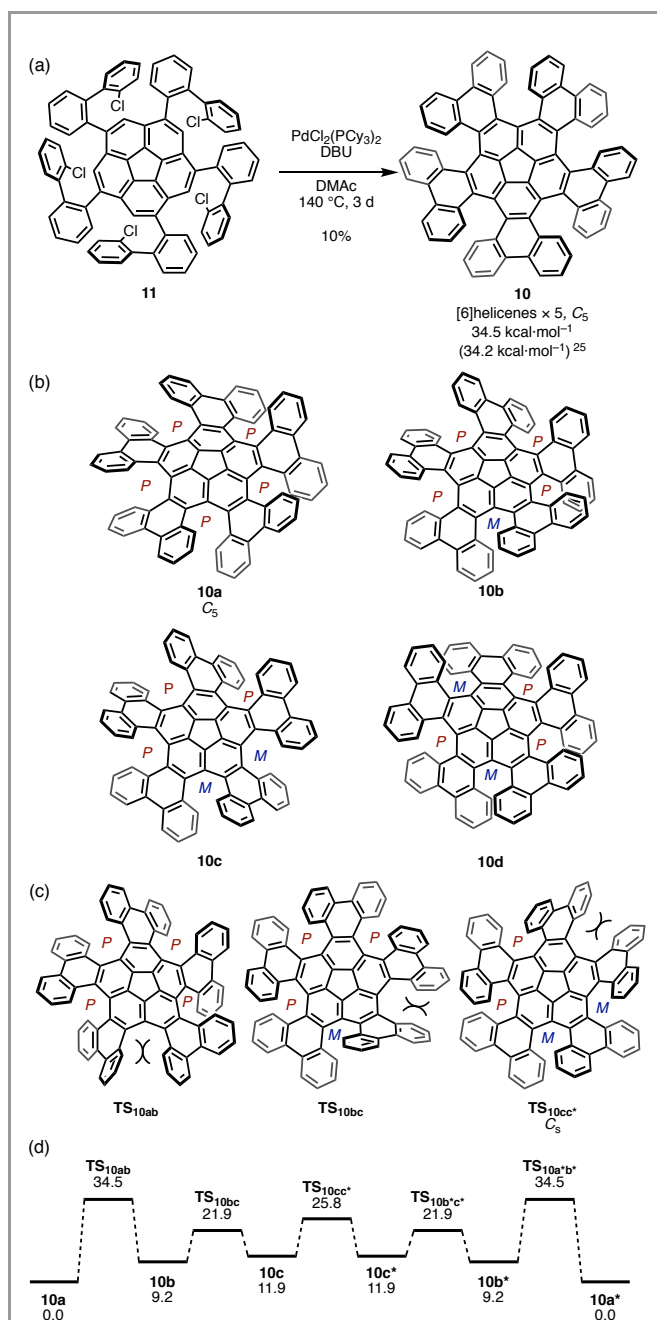


Figure 5 (a) Synthesis of **10** with racemization barrier. Experimentally determined racemization barrier is shown in parenthesis. Abbreviations: DMAc = *N,N*-dimethylacetamide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

(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).

5. Symmetric sextuple carbohelicenes

Sextuple [5]helicene **12** was independently reported by two groups in 2017.²⁸ Tsurusaki, Kamikawa, and co-workers synthesized **12** via a Pd-catalyzed [2+2+2] cyclization reaction of a [5]helicene-based aryne.^{28a} 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 **12** via the Ni-mediated homocoupling reaction of a dibrominated [5]helicene.^{28b} Very recently, another type of sextuple helicene **13** has been reported by Wang and co-workers:²⁹ the coronene-cored sextuple [7]helicene **13** was synthesized by a Scholl reaction of oligophenylene precursors, and an X-ray diffraction analysis revealed a D_6 -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, not even after 12 h at 270 °C.

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 D_3 -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** \rightarrow **TS_{12ab}** \rightarrow **12b** \rightarrow **TS_{12bc}** \rightarrow **12c** \rightarrow **TS_{12cd}** \rightarrow **12d** \rightarrow **TS_{12c*d}** \rightarrow **12c*** (or **12c** \rightarrow **TS_{12cd*}** \rightarrow **12d*** \rightarrow **TS_{12c*d*}** \rightarrow **12c***) \rightarrow **TS_{12b*c*}** \rightarrow **12b*** \rightarrow **TS_{12a*b*}** \rightarrow **12a***. The rate determining step is **12a** \rightarrow **TS_{12ab}** ($\Delta G = 36.3$ kcal·mol⁻¹), and its energy barrier is higher than that of pristine [5]helicene owing to the steric hindrance of neighboring [5]helicene moieties.

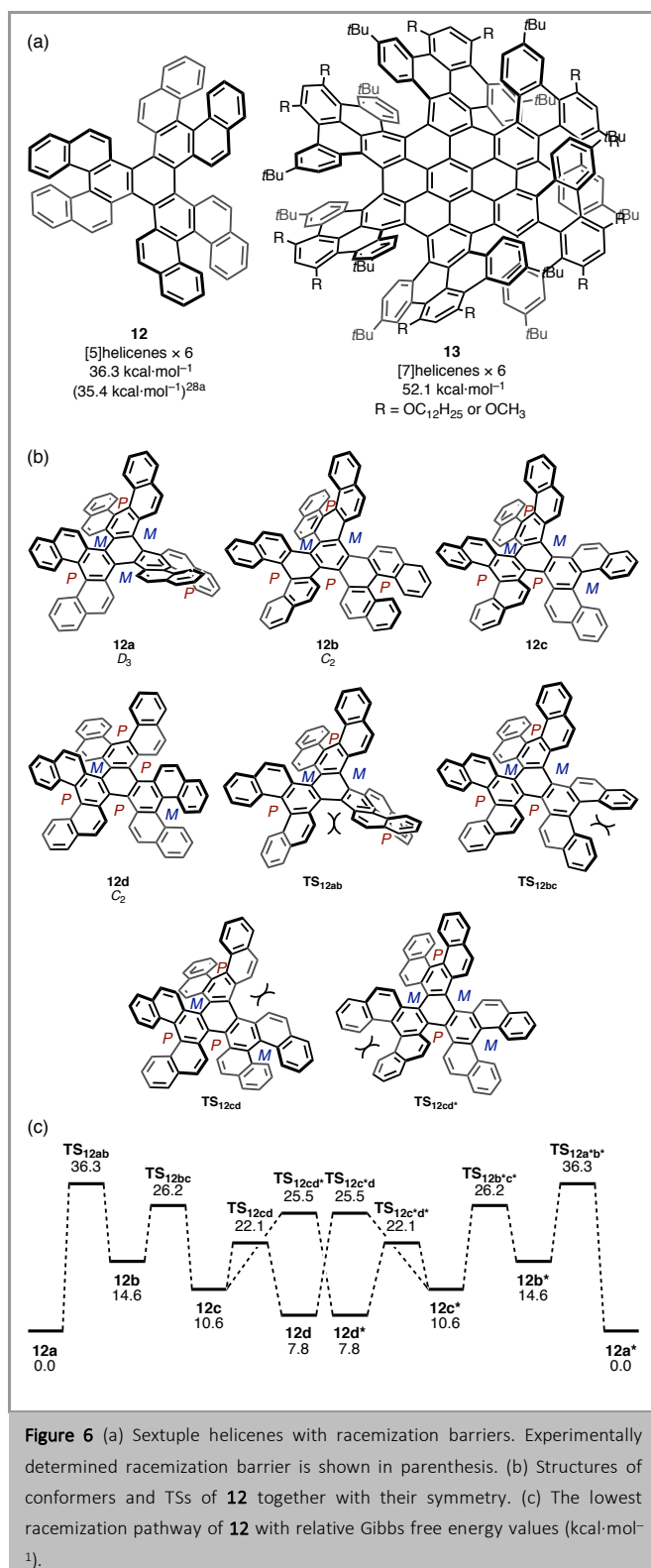


Figure 6 (a) Sextuple helicenes with racemization barriers. Experimentally determined racemization barrier is shown in parenthesis. (b) Structures of conformers and TSs of **12** together with their symmetry. (c) The lowest racemization pathway of **12** with relative Gibbs free energy values (kcal·mol⁻¹).

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 in order 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]helicenes. On the other hand, using [*n*]circulenes as central cores as in *e.g.* 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 D_{3d} -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 complicated 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 used as chiral materials in future.

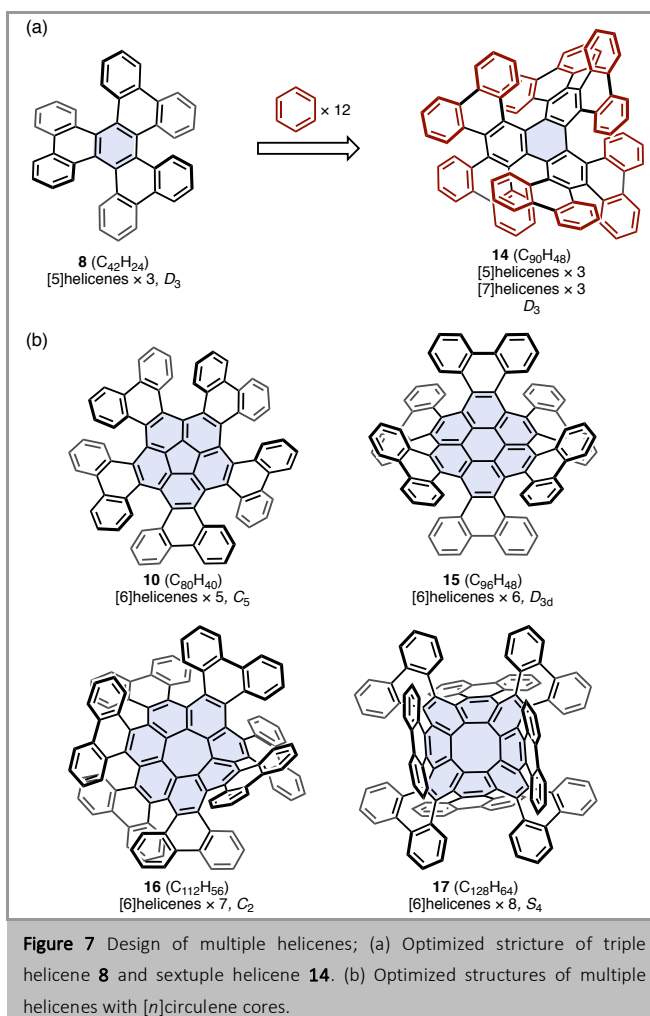


Figure 7 Design of multiple helicenes; (a) Optimized structure of triple helicene **8** and sextuple helicene **14**. (b) Optimized structures of multiple helicenes with [*n*]circulene cores.

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