Synthesis and Thermally Stable Helix-Dimer Formation of Amidohelicene Oligomers

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Optically active amidohelicene monomer to nonamer were synthesized in high yields by a two-directional method. The CD spectra in chloroform exhibited a large difference between dimer and the higher homologs, and vapor pressure osmometry studies revealed the formation of dimeric aggregates for the latter. It is noted that amidohelicene oligomers possessing two-atom linking groups between helicene and *m*-phenylene spacer formed helix-dimers in solution as were ethynylhelicene oligomers. The helix-dimer of the amidohelicene octamer in chloroform was very stable, and did not dissociate at 5×10^{-8} M on heating to 60 °C. The dissociation of the amidohelicene oligomers to random-coil state took place in hydrogen-bonding breaking solvents, DMSO or THF. The equilibrium between helix-dimer and random-coil changed by varying the ratio in the mixed solvents of chloroform and DMSO. Notably, the equilibriums were not affected by temperature for various mixtures of helix-dimer and random-coil. Thus, the sensitivity toward the environment was quite different between the amido- and ethynylhelicene oligomers.

Molecular double-helixes are aggregates formed by two linear molecules through intra- and intermolecular non-covalent bond interactions. Well-known double-strand DNA is constructed via hydrogen-bonding between complementary bases and π–π interactions between aromatic bases, and its reversible association/dissociation plays an important role in the biological function. Thus, it was considered interesting to study synthetic double-helix forming molecules, since the comparison of their aggregation properties would deepen our understanding of the properties of natural double-helixes. In addition, synthetic double-helix molecules can have various applications in materials. Recently, such synthetic oligomers were reported. Lehn and others investigated oligobipyridine ligands coordinated to metal ions forming double-helixes.[1] We reported that ethynylhelicene oligomers form double-helix via π–π interactions.[2] Yashima synthesized two complementary strands linked with amidinium–carboxylate salt bridges,[3] and also oligoresorcinols.[4] Huc showed that oligoamidopyridines formed double-helixes via hydrogen-bonds and π–π interactions.[5] Pyridine–thiazine oligomers associated through self-complementary hydrogen-bonds were also reported.[6] Among the compounds, pyridine–pyrimidine oligomers,[1c] ethynylhelicene oligomers,[2] salts,[3c] oligoresorcinols,[4a,4b,4d] and oligoamidopyridines[5a,5b] changed structure between double-helix and random-coil in response to temperature change, solvent change, or complexation with other molecules. However, such reversible structure change systems are still rare, and the development of novel synthetic double-helix molecules is desired. In particular, it is critical to understand the relationship between the oligomer structure and the double-helix forming property.

We previously synthesized optically active acetylene oligomers containing helicene and *m*-phenylene units. The heptamer (*P*)-**2** was found to form a double-helix in solution,[2a] and π–π interactions between the non-planar aromatic system of the helicene was considered to play an important role in aggregate formation: (*P*)-**2** changed between random-coil by increasing temperature or decreasing concentration;[2b] the hardness and softness of aromatic solvents affected the stability of the double-helix, and the π–π interactions were related to the HSAB (hard soft acid base) principle.

We then decided to examine various derivatives of the ethynylhelicene oligomers to know the relationship between the structure and double-helix formation. It was expected that the systematic study would provide a diversity of double-helix molecules, and comparison of their structures and properties would be used to design molecular systems, which respond to change of environment. We recently reported derivatives, in which the decyloxycarbonyl substituent in the *m*-phenylene units of the ethynylhelicene oligomers was replaced with a perfluorooctyl group.[2d] The pentamer (*P*)-**3** formed a double-helix in solution, but with an inverted twist double-helix from pentamer (*P*)-**1** and heptamer (*P*)-**2**. It was also observed that (*P*)-**3** formed hetero-double-helix with the ethynylhelicene pentamer (*M*)-**1** but not with (*P*)-**1**. Compounds possessing two parts of the ethynylhelicene oligomers were synthesized, which formed intramolecular helix-dimers.[2c] They exhibited different kinetic properties than the intermolecular aggregates.

In the present study, the effect of the linking group in the ethynylhelicene oligomers was examined using amidohelicene oligomers, in which the acetylene moiety of the ethynylhelicene oligomers was replaced with amide group. Both amide

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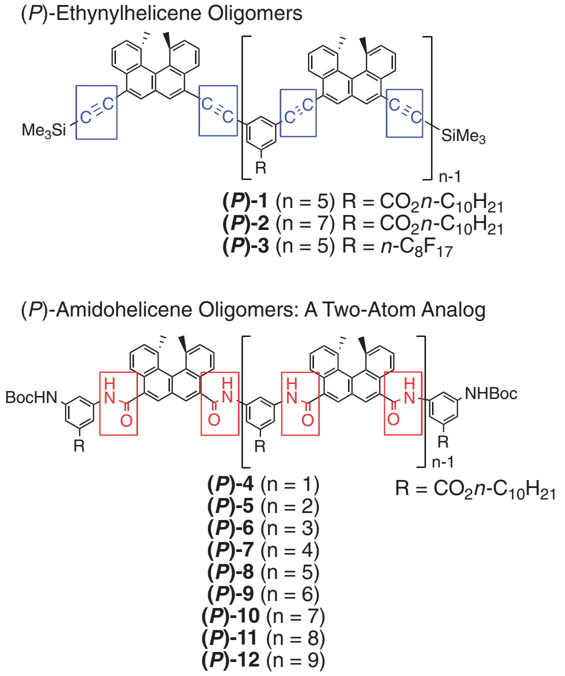
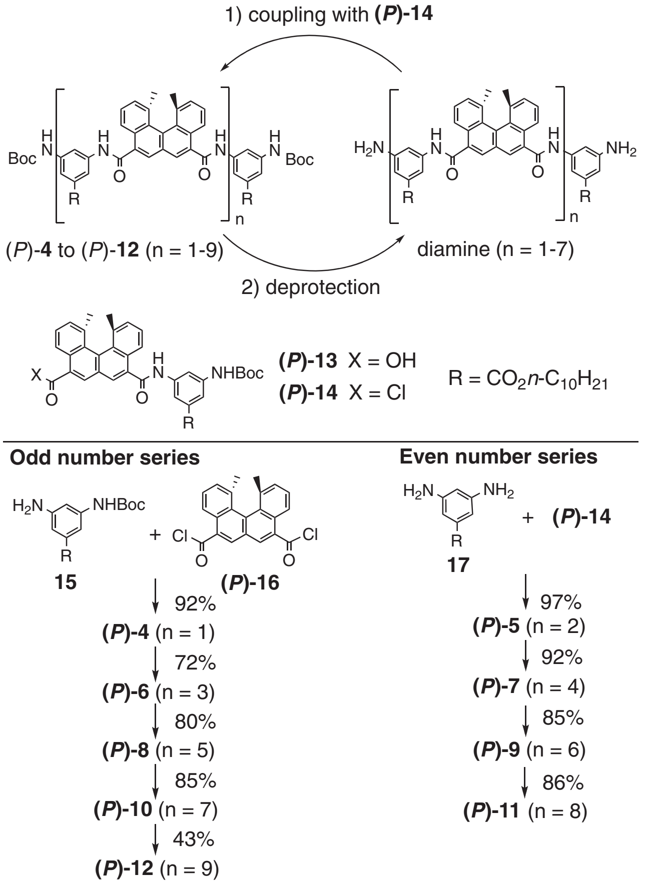


Chart 1.



Scheme 1.

and acetylene are two-atom groups. However, acetylene has a rigid, straight, and non-polar structure, whereas amide has a bond angle of 120° with polar heteroatoms capable of hydrogen-bonding. It was considered interesting to know whether the amidohelicene oligomers could form double-helix, and if this was the case, to know the differences in the double-helix formation.

Amidohelicene monomer (*P*)-**4** to nonamer (*P*)-**12** were synthesized (Chart 1), and trimer and higher oligomers formed helix-dimers in non-polar solvents (see Supporting Information). The dimeric structures of the oligomers were very stable, and did not dissociate by heating even at low concentrations. However, they readily dissociated in hydrogen-bond breaking polar solvents. It was noted that the equilibrium between helix-dimer and random-coil were little affected by temperature. The results contrasted the double-helix of ethynylhelicene oligomers, which readily dissociated on heating.[2]

Results and Discussion

Synthesis. Amidohelicene oligomers were synthesized by repeated amide formation (Scheme 1).[7b] Acid chloride building block (*P*)-**14** was obtained from carboxylic acid (*P*)-**13** by treating with potassium hydroxide and sulfinyl chloride followed by rapid silica gel chromatography. The purification was critical to obtain reproducible results in the subsequent amide formation. Amidohelicene monomer (*P*)-**4** was synthesized by the coupling of 2 equivalents of decyl 3-amino-5-(*t*-butoxycarbonylamino)benzoate **15** and diacid dichloride (*P*)-**16** in 92% yield. Removal of the *t*-butoxycarbonyl group with trifluoroacetic acid and coupling with (*P*)-**14** then gave the trimer (*P*)-**6** in 72% yield in 2 steps. The sequence of synthesis starting from (*P*)-**6** provided pentamer (*P*)-**8**, heptamer (*P*)-**10**, and nonamer (*P*)-**12**. The dimer (*P*)-**5** was obtained by the coupling of decyl 3,5-diaminobenzoate **17** and 2 equivalents of (*P*)-**14**. Diamine formed by deprotection of (*P*)-**5** was then subjected to the coupling sequence giving tetramer (*P*)-**7**, hexamer (*P*)-**9**, and octamer (*P*)-**11** possessing even numbers of the helicene.

Helix-Dimer Formation. The CD spectra of (*P*)-**4** to (*P*)-**12** (5×10^{-6} M, 25 °C) were taken in dimethyl sulfoxide (DMSO) and chloroform (Figure 1). In DMSO, the intensity of the Cotton effect increased linearly with increasing number of helicene units. In chloroform, similar spectra to those in DMSO were obtained for the monomer (*P*)-**4** and dimer (*P*)-**5**. However, the trimer and higher oligomers (*P*)-**6** to (*P*)-**12** provided quite different spectra, which exhibited strong positive and negative Cotton effects at 324 and 297 nm, respectively, indicating the formation of ordered chiral structures. Such chiral structure of (*P*)-**11** was also formed in toluene but not in THF (Figure 2). VPO study in chloroform at 35 °C indicated that tetramer (*P*)-**7** at 1, 5, and 10×10^{-3} M and octamer (*P*)-**11** at 1×10^{-3} M formed bimolecular aggregates, while they were monomeric in THF (5×10^{-3} M) (Figure 3). The infrared spectra of (*P*)-**7** (1×10^{-3} M) provided an amide I carbonyl absorption at 1682 cm^{-1} in THF, and 1654, 1647 cm^{-1} in chloroform. Amide carbonyls were reported to shift to lower frequencies by 20–40 cm^{-1} by forming hydrogen-bonds.[8] It was concluded that amidohelicene oligomers (*P*)-**6** to (*P*)-**12** formed helix-dimers in chloroform and toluene, and random-coil monomers in DMSO and THF. The effect of soft aromatic solvent was small, and no dissociation was observed in $C_6H_5CF_3$, C_6H_5F,

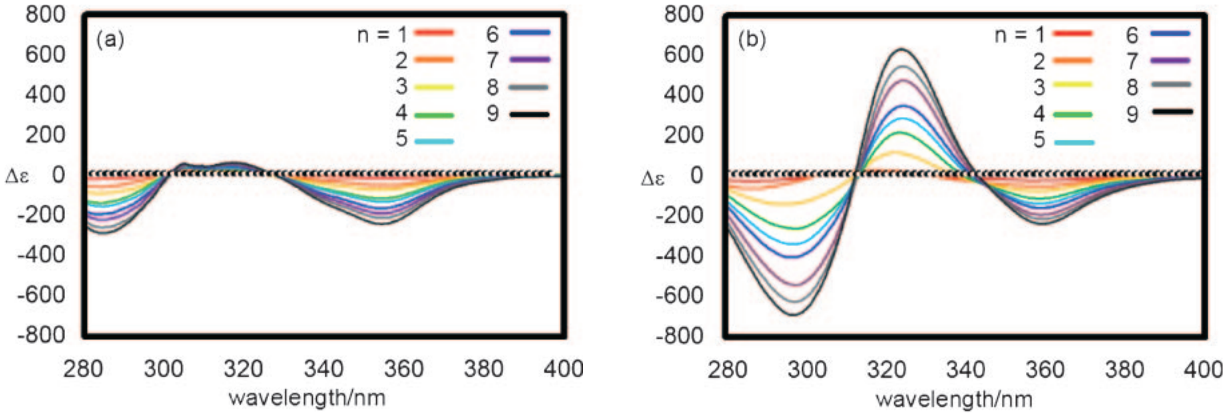


Figure 1. CD spectra (5×10^{-6} M, 25 °C). (a) (*P*)-**4–12** (*n* = 1–9) in DMSO. (b) (*P*)-**4–12** (*n* = 1–9) in chloroform.

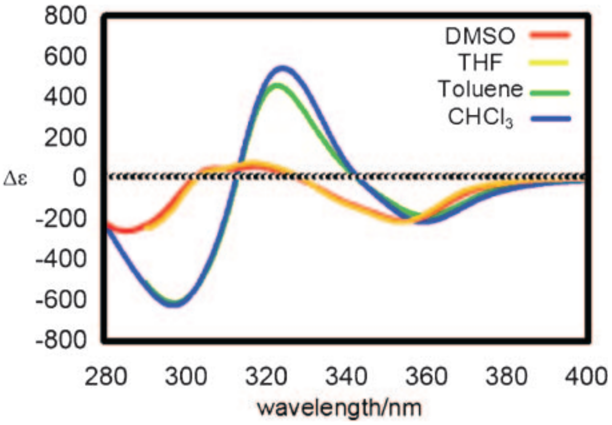


Figure 2. CD spectra (5×10^{-6} M, 25 °C) of octamer (*P*)-**11** in various solvents.

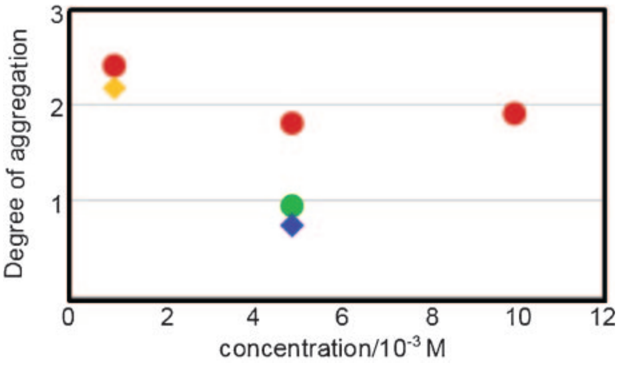


Figure 3. Degree of aggregation determined by VPO. (*P*)-**7** (*n* = 4) in chloroform at 35 °C (red dots), in THF at 45 °C (green dot), and (*P*)-**11** (*n* = 8) in chloroform at 35 °C (yellow dot), in THF at 45 °C (blue dot).

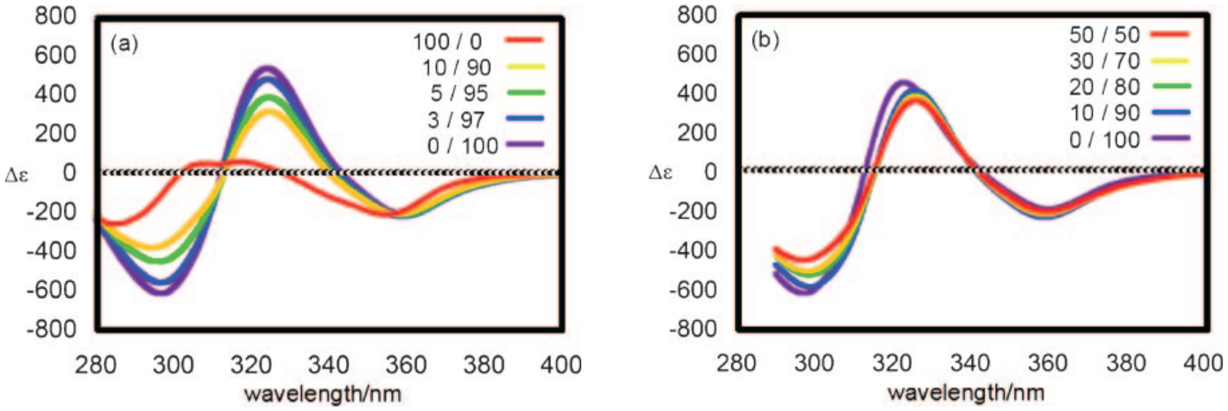


Figure 4. CD spectra of octamer (*P*)-**11** (5×10^{-6} M, 25 °C) in mixed solvents: (a) in DMSO/$CHCl_3$ in various ratios and (b) in 2,2,2-trifluoroethanol/toluene in various ratios.

C_6H_6, $C_6H_5CH_3$, C_6H_5Cl, and C_6H_5I (5×10^{-6} M) at 60 °C, which compared with ethynylhelicene oligomers.[2a]

The effect of the mixed solvent system of a nonpolar solvent and a hydrogen-bond breaking solvent was examined using (*P*)-**11** at 5×10^{-6} M concentration. The equilibrium between helix-dimer and random-coil shifted by changing the ratio of chloroform and DMSO, and the Cotton effect at 325 nm was reduced to a half in 10% DMSO/chloroform compared to that in chloroform (Figure 4a). Another hydrogen-bond breaking solvent however, 2,2,2-trifluoroethanol, did not show notable effect on the CD spectra even at 50% content in toluene (Figure 4b). The driving force of the helix-dimer formation of the amidohelicene olgomers was at least partly ascribed to hydrogen-bonding.

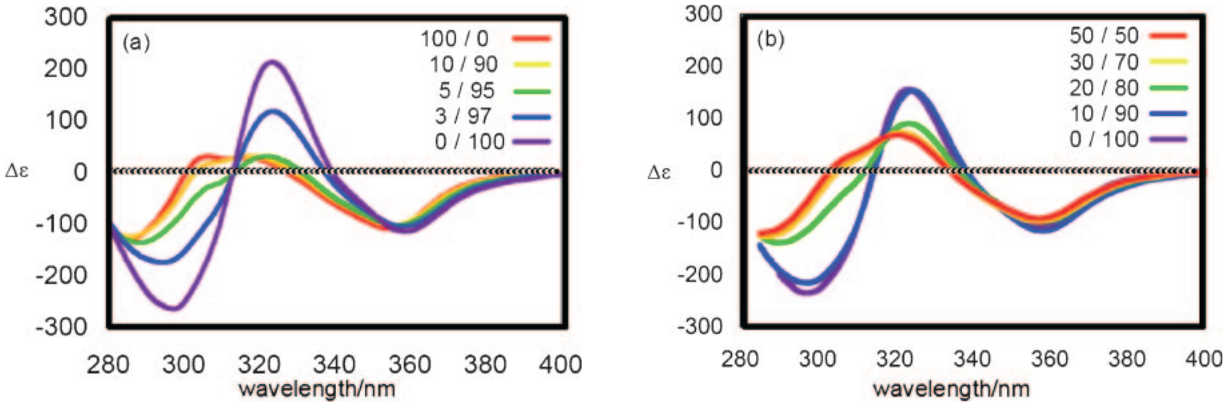


Figure 5. CD spectra of tetramer (*P*)-**7** (5×10^{-6} M, 25 °C) in mixed solvents: (a) in DMSO/CHCl$_3$ in various ratios and (b) in 2,2,2-trifluoroethanol/toluene in various ratios.

It was also observed in the CD spectra under different conditions that $\Delta\varepsilon$ peaks were obtained at 324 nm with 540 $\mathrm{cm^{-1}\,M^{-1}}$ and at 297 nm with $-631\ \mathrm{cm^{-1}\,M^{-1}}$. It may reasonably be concluded that these are the spectra of the pure helix-dimer.

The stability of the helix-dimer of octamer (*P*)-**11** and tetramer (*P*)-**7** was compared. In 10% DMSO/chloroform, the CD spectra of (*P*)-**7** was similar to that in DMSO exhibiting random-coil state (Figure 5a), which contrasted to the partial dissociation of (*P*)-**11** in the same solvents. In 50% 2,2,2-trifluoroethanol/toluene, the equilibrium of (*P*)-**7** considerably shifted to random-coil compared to (*P*)-**11** (Figure 5b). The helix-dimer complexation became stronger as the oligomer elongated.

Several related aromatic amide oligomers were compared in regard to the aggregate formation (Chart 2). Kevlar and Nomex are amide polymers with *m*- and *p*-linked benzenedioic acids and benzenediamines, respectively,[9] and their high thermal resistance is ascribed to sheet formation by intermolecular hydrogen-bonding. Anthranilamide oligomers possessing the trimethoxylated Kevlar structure are monomeric in solution,[10] in which intermolecular hydrogen-bonding is inhibited by intramolecular hydrogen-bonding between the amide protons and the methoxy oxygens. A pyridine version of Kevlar forms a single-helix, in which intrastrand hydrogen-bonding by the pyridine nitrogen and amide proton play an important role.[5b] In nonpolar solvent, the compound forms a double-helix via spring-like extension.[5h] The amidohelicene oligomers in the present work can be regarded as a helicene derivative of Kevlar. The helix-dimer formation and not the polymeric sheet formation of the helicene amides may be ascribed to the chirality. Alternatively, the different distance between two carboxylate groups might also be important. It may be interesting that the change in the aromatic moiety of aromatic amides causes dramatic changes in the aggregate structures.

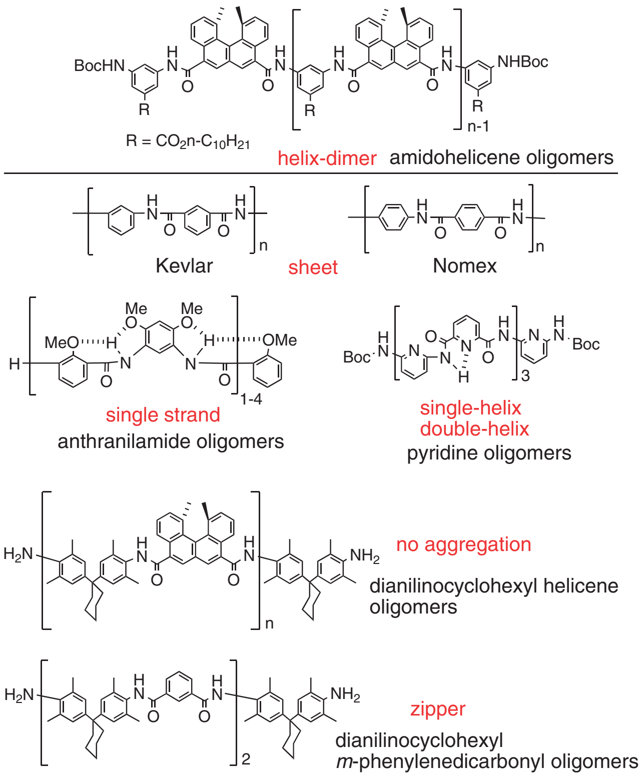


Chart 2.

We previously synthesized amidohelicene monomer to decamer possessing 1,1-dianilinocyclohexyl spacer,[7a,7b] and observed the higher oligomers not to form hydrogen-bonded structure in chloroform. When compared with the present amidohelicene oligomers, the structure of the aniline moiety was shown to be critical for the helix-dimer formation. Notably, using the same dianiline compound, *m*-phenylenedicarbonyl oligomers were reported to form double-strand zipper complexes in solution.[11] The diversity of hydrogen-bonded structures formed from oligomeric aromatic amides indicated the delicate balance between oligomer structure and aggregate structure.

It should also be emphasized that both amidohelicene oligomers and ethynylhelicene oligomers possessing the two-atom linkers, formed helix-dimers in solution. This suggests that chiral oligomers obtained by connecting the helicene and the *m*-phenylene with two-atom linkers could form various helix-dimers.

Equilibrium between Helix-Dimer and Random-Coil. Amidohelicene oligomers formed very strong dimeric aggregates in nonpolar solvents. The CD spectra of octamer (*P*)-**11**

in chloroform at 25 °C did not largely change between the concentrations of 5×10^{-6} and 5×10^{-8} M (Figure 6). The association constant was estimated to be $K > 10^9\,M^{-1}$ by the dimerization at 5×10^{-8} M assuming 90% binding. It compared with the strong dimerization in the pyridinedicarboxamide oligomers by Huc with the estimated $K > 10^7\,M^{-1}$.[5h]

The temperature dependence of the aggregation was next examined. Little change was observed in the CD spectra of octamer (*P*)-**11** between 60 and 5 °C in chloroform at concentration ranging from 1×10^{-6} to 5×10^{-8} M (Figure 7). Such insensitiveness to temperature was observed in toluene at 5×10^{-6} M (Figure S1).

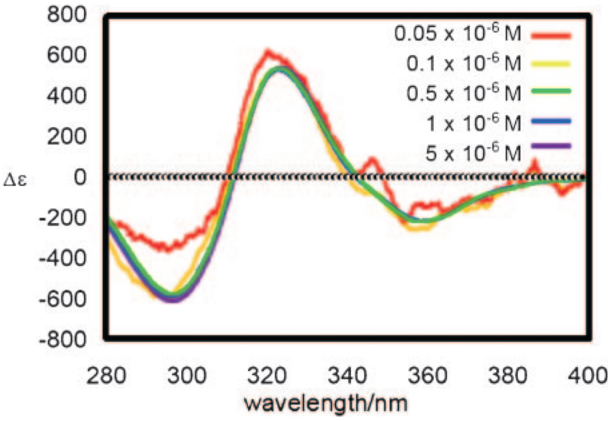


Figure 6. CD spectra of octamer (*P*)-**11** at 25 °C in $CHCl_3$ in various concentrations.

The effect of temperature was examined for various equilibrated states of helix-dimer and random-coil. In 3, 5, and 10% DMSO/chloroform, (*P*)-**11** (5×10^{-6} M) formed mixtures of helix-dimer and random-coil as indicated by the $\Delta\varepsilon$ values (25 °C) at 324 nm: 470, 380, and 310 $cm^{-1}\,M^{-1}$, respectively (Figure 8), being smaller than the value 540 $cm^{-1}\,M^{-1}$ of pure helix-dimer noted above. Notably, essentially no change was observed with these mixtures between 5 and 60 °C, which indicated no change of the equilibrium.

The CD experiments of (*P*)-**7** in mixtures of 5 and 10% CF_3CH_2OH/chloroform and 3% DMSO/chloroform between 5 and 60 °C exhibited little temperature dependence (Figures 9 and S2). Thus, the helix-dimer/random-coil equilibrium of the amidohelicene oligomers in solution turned out to be insensitive to temperature, which was a characteristic feature of these chiral oligomers. This contrasted greatly with the temperature sensitive structure change of ethynylhelicene oligomers.[2]

The structure of ethynylhelicene oligomers and amidohelicene oligomers differed only at the two-atom component linking helicene and *m*-phenylene moieties. Although both formed helix-dimers, their aggregate forming properties were quite different. The helix-dimers of the amidohelicene oligomers were dissociated by hydrogen-bond breaking solvents, and the equilibria were temperature-independent; those of the ethynylhelicene oligomers were dissociated by soft aromatic solvents, and the equilibrium highly temperature-dependent.

The temperature-dependent equilibrium in the bimolecular aggregation/deaggregation of the ethynylhelicene oligomers was ascribed to large entropy changes, ΔS exceeding 100

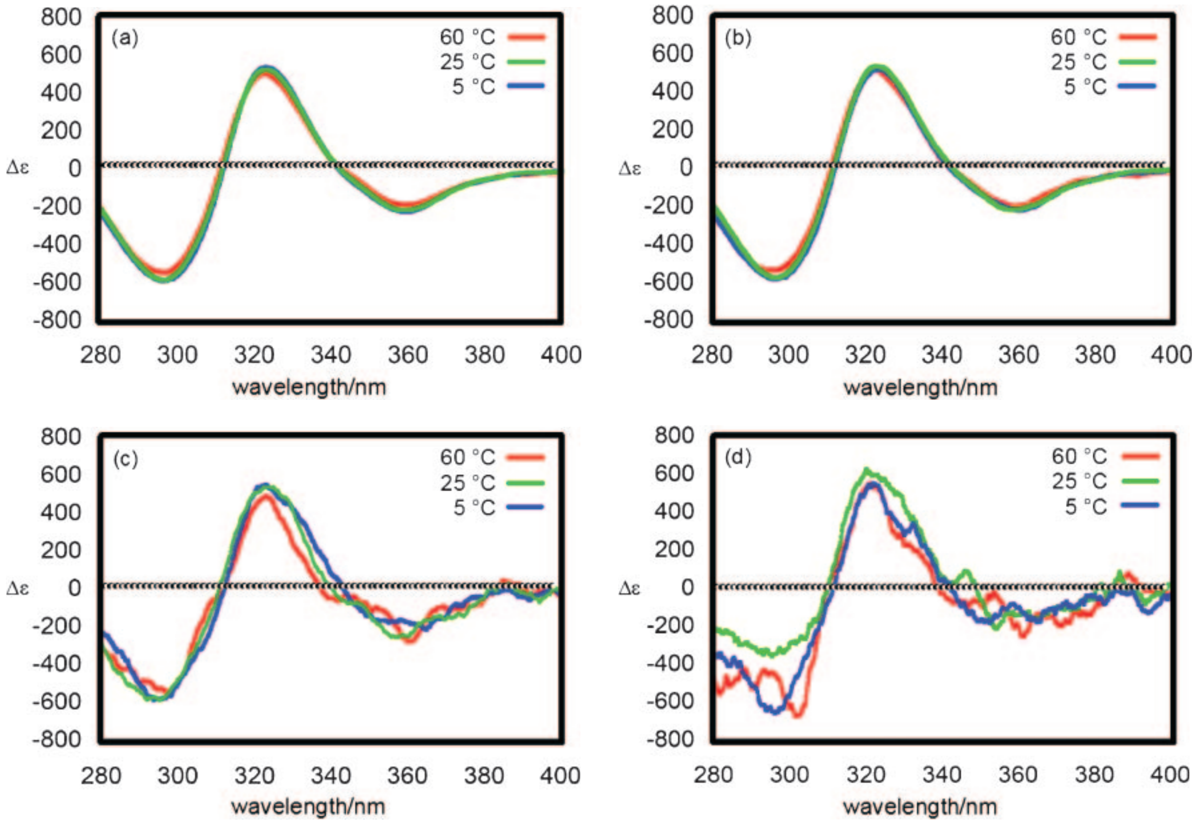


Figure 7. CD spectra of octamer (*P*)-**11** in $CHCl_3$ at various temperatures: (a) 1×10^{-6}, (b) 0.5×10^{-6}, (c) 0.1×10^{-6}, and (d) 0.05×10^{-6} M.

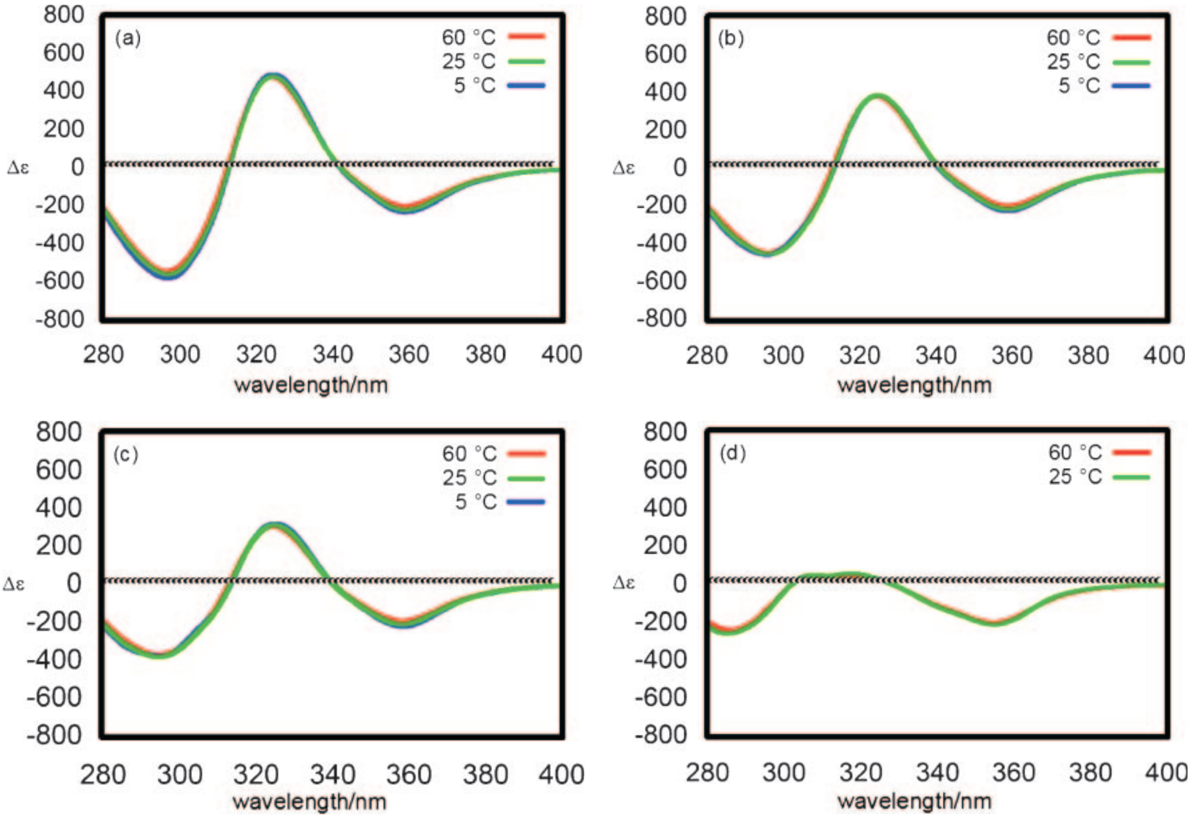


Figure 8. CD spectra of octamer (*P*)-**11** at 5 × 10^{-6} M at various temperatures: (a) in $CHCl_3$ 97% and DMSO 3%, (b) in $CHCl_3$ 95% and DMSO 5%, (c) in $CHCl_3$ 90% and DMSO 10%, and (d) in DMSO 100%.

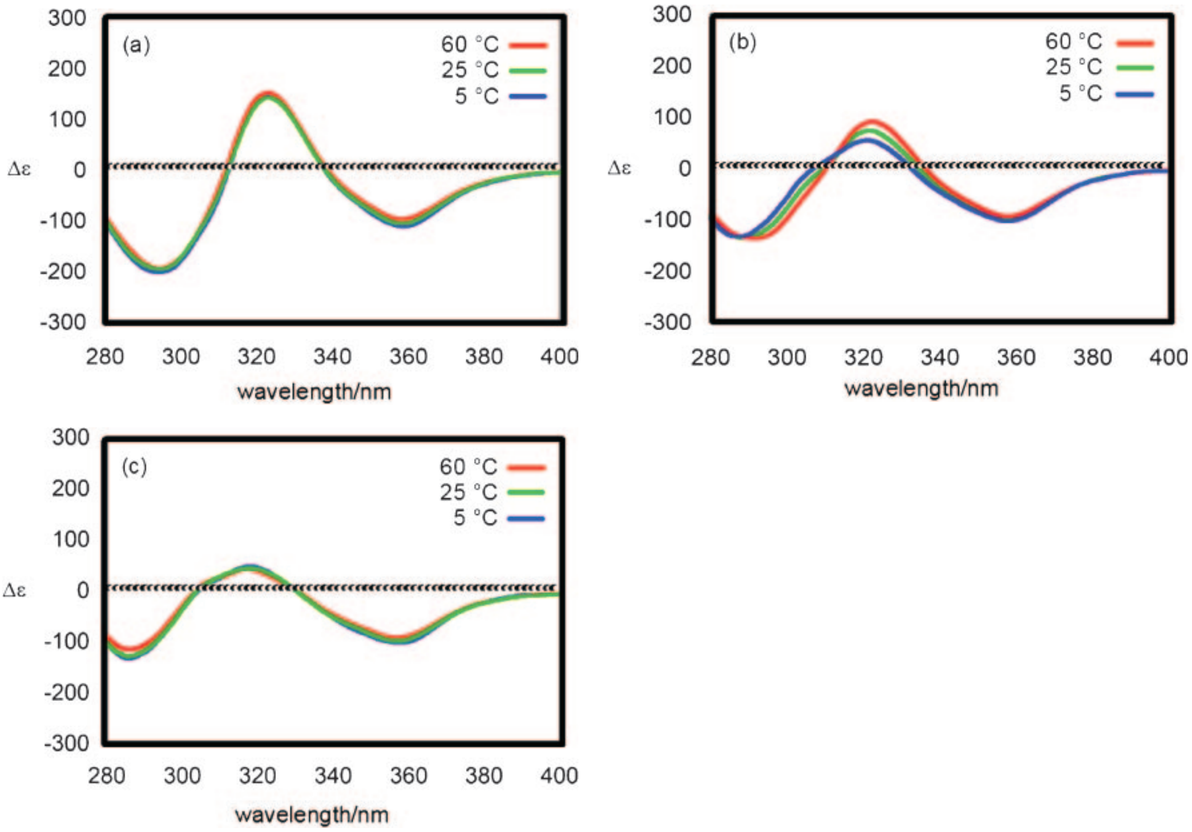


Figure 9. CD spectra of tetramer (*P*)-**7** at 5 × 10^{-6} M at various temperatures: (a) in $CHCl_3$ 95% and CF_3CH_2OH 5%, (b) in $CHCl_3$ 90% and CF_3CH_2OH 10%, and (c) in $CHCl_3$ 80% and CF_3CH_2OH 20%.

$\mathrm{J\,mol^{-1}\,K^{-1}}$ based on the equation $\Delta G = \Delta H - T\Delta S$.[2c] The origin of the temperature-independence in the case of amidohelicene oligomers is notable. Several examples of the association/dissociation equilibrium with small temperature-dependences are known in biomolecules such as proteins,[12] nucleic acids,[13] or oligosugars[14] as well as synthetic oligoacetylenes[15] or oligoamides.[5c] The phenomena were in some cases ascribed to small entropy changes ΔS by solvation/desolvation[14,15] or by formation of preorganized structure in the deaggregated state.[5c,13] Alternatively, temperature dependences of entropy change ΔS and enthalpy change ΔH were discussed.[12] In the present study, preorganized structure for monomeric amidohelicene oligomers may not be likely: The effect of the chain length of the oligomers was not appreciable in CD and ^{1}H NMR spectra in DMSO. If preorganized structures were formed by hydrogen-bonding, their spectra probably exhibited the dependences of oligomer length reflecting the weaker preorganization of smaller oligomers. Solvation/desolvation may not also be appreciable in non-aqueous solvents. The present phenomena of the amidohelicene oligomers probably are a delicate balance of the temperature-dependent ΔH and ΔS, which cancel the effect of temperature.

Conclusion

To summarize, amidohelicene trimer to nonamer formed helix-dimer in non-polar solvents, which dissociated in the presence of hydrogen-bond breaking solvents, DMSO and trifluoroethanol. The aggregation in chloroform was very strong, and the helix-dimer did not dissociate even at low concentrations. Notably, the equilibrium was not affected by temperature, which contrasted to the ethynylhelicene oligomer previously reported. Design of the molecules may be interesting using such different properties in the helix-dimer formation.

Supporting Information

General methods, synthetic procedure and characterization data for (*P*)-**4**–**12**, **13**–**20**, and diamine ($n = 1$–7), CD spectra of (*P*)-**7** and (*P*)-**11** (Figures S1 and S2). This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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