**Linker-Controlled Aggregation**

# [3+3]Cycloalkyne Oligomers: Linking Groups Control Intra- and Intermolecular Aggregation by π–π Interactions**

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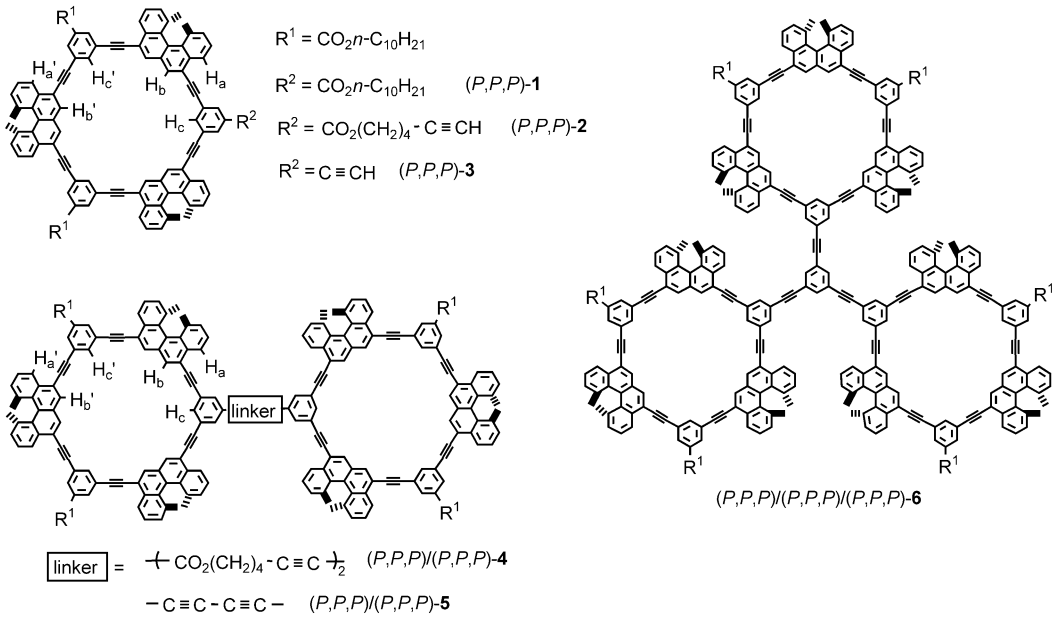
Conjugated π compounds, such as porphyrins,[1] phthalocyanines,[2] and macrocyclic alkynes[3] self-aggregate with face-to-face orientation, which is considered to be due to the π–π interactions between the aromatic ring systems. Such aggregation in organic solvents, however, is weak and nonselective. The compounds are in monomer–dimer equilibrium, and form higher aggregates only under solvophobic conditions in aqueous solvents or in the presence of templates, such as, DNA,[4] peptide,[5] and synthetic bilayer membranes.[6] We previously found that [3+3]cycloalkynes **1**, which are chiral macrocyclic alkynes containing three helicenes and three *m*-phenylene moieties, strongly aggregate in chloroform and benzene.[7] A sharp transition occurs between a monomer and a bimolecular aggregate; (*P,P,P*)-**1** (see Scheme 1) is monomeric below 1 mM in $CHCl_3$, and is dimeric above 1 mM. While the reported π-conjugate compounds required the "external" effects of solvophobic conditions or templates for strong aggregation, the strong aggregation of **1** is caused only by the π–π interactions. Compound **1** forms only a bimolecular aggregate; no higher aggregates are formed. It was therefore considered that the aggregation of the helicene derivative **1** could be used to construct a controlled self-assembly system. Reported herein are the aggregation of oligomeric [3+3]cycloalkynes, two dimers **4, 5**, and a trimer **6** (Scheme 1). In principle, such oligomers can form either an intra- or intermolecular aggregate, the latter of which can be anything from a dimer to a polymer. The aggregate structure in an organic solvent can be controlled by the structure of the linker, that connects the [3+3]cycloalkyne moiety: A dimer **4** with a flexible linker forms a strong intramolecular aggregate, a dimer **5** with a rigid linker equilibrates with a bimolecular aggregate, and a trimer **6** with a rigid linker forms a strong and selective bimolecular aggregate.[8–10]

Dimers (*P,P,P*)/(*P,P,P*)-**4** and (*P,P,P*)/(*P,P,P*)-**5** were synthesized by the oxidative dimerization[11] of (*P,P,P*)-**2**[12] and (*P,P,P*)-**3**,[12] respectively, and the trimer (*P,P,P*)/(*P,P,P*)/(*P,P,P*)-**6** was obtained from (*P,P,P*)-**3** and 1,3,5-triiodobenzene.



**Scheme 1.** Structures of the aggregates.

While $^1$H NMR ($CDCl_3$) and circular dichroism (CD; $CHCl_3$) spectra of (*P,P,P*)-**1** and (*P,P,P*)-**2** are concentration dependent, the $^1$H NMR ($CDCl_3$) spectra of the dimeric (*P,P,P*)/(*P,P,P*)-**4** do not change at concentrations between 0.3 and 1.5 mM (25°C) or at temperatures between 25 and 60°C.[12] The CD ($CHCl_3$, 25°C) spectra of the dimeric (*P,P,P*)/(*P,P,P*)-**4** also do not change between 0.024 and 0.24 mM (Figure 1a). The aromatic $^1$H NMR signals of (*P,P,P*)/(*P,P,P*)-**4** appear considerably upfield of those of the non-aggregated (*P,P,P*)-**1** (0.32 mM) and (*P,P,P*)-**2** (0.31 mM), and are even upfield compared to the aggregated (*P,P,P*)-**1**

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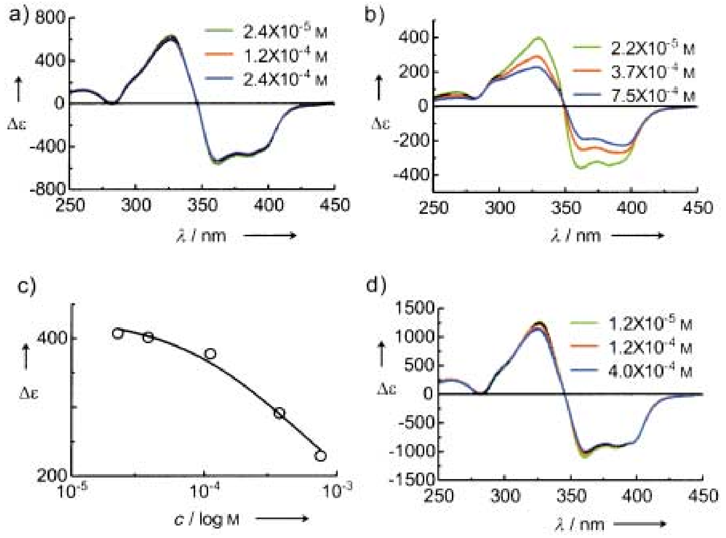

***Figure 1.*** CD spectra of (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4** (a), (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5** (b), (*P*,*P*,*P*)/(*P*,*P*,*P*)/(*P*,*P*,*P*)-**6** (d), and plots of Δε versus concentration at 330 nm for (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5** (c). The curve is the best theoretical fit for the monomer–dimer system, from which the association constant $K = 985\,\text{M}^{-1}$, $R^2 = 0.99$ was obtained.

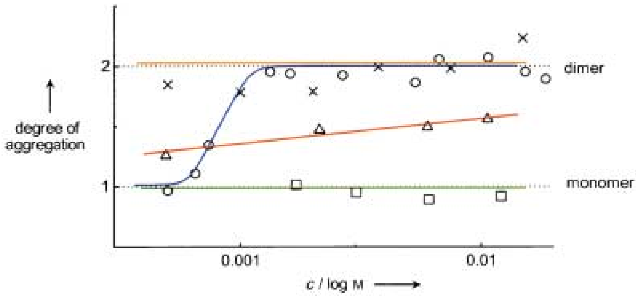

***Figure 2.*** Degree of aggregation by VPO (CHCl$_3$, 35 °C) for (*P*,*P*,*P*)-**1** (○, blue line),[7] (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4** (□, green line), (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5** (△, red line), and (*P*,*P*,*P*)/(*P*,*P*,*P*)/(*P*,*P*,*P*)-**6** (X, orange line). Degree of aggregation = observed molecular weight/molecular weight of monomer.

(12.0 mM) and (*P*,*P*,*P*)-**2** (1.2 mM) (Table 1). The $^1$H NMR observations indicate the aggregate formation of (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4**. In addition, $^1$H NMR resonances of (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4** at H$_a$/H$'_a$ and H$_c$/H$'_c$ (see Scheme 1) separate into two signals in 2:1 ratios, which is in contrast to the $^1$H NMR spectra of (*P*,*P*,*P*)-**2** which show only a single resonance for H$_a$/H$'_a$ and H$_c$/H$'_c$. The magnetic environment of the helicene and the *m*-phenylene units close to the linker moiety differs from the others, which is consistent with the formation of a folded structure at the linker moiety. The molecular weight of (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4** observed by vapor pressure osmometry (VPO) indicates a monomeric nature in solution, which is again concentration-independent (Figure 2). These observations are explained by the strong intramolecular aggregation of (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4**, which folds at the linker moiety. The folded structure named "castanet structure" was determined by Amber calculations,[12] in which the *m*-phenylene moiety is fitted into the groove formed by the helicene as observed in the aggregated (*P*,*P*,*P*)-**1**.[7] While some dyes connected by flexible linkers are reported to adopt a folded conformation in polar or aqueous solvents as a result of solvophobic interactions,[13] one notable aspect of (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4** is that it folds solely by the π–π interactions without such "external" effects.

***Table 1:*** $^1$H NMR (CDCl$_3$, 25 °C) spectroscopic data of (*P*,*P*,*P*)-**1**, (*P*,*P*,*P*)-**2** and (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4**.

| | Conc. [mM] | δ (H$_a$/H$_a'$) [ppm] | δ (H$_b$/H$_b'$) [ppm] | δ (H$_c$/H$_c'$) [ppm] |
|---|---|---|---|---|
| (*P*,*P*,*P*)-**1**[7] | 0.32 | 8.56 | 8.18 | 8.25 |
| | 12.0 | 8.20 | 8.04 | 8.09 |
| (*P*,*P*,*P*)-**2** | 0.31 | 8.53 | 8.18 | 8.25 |
| | 1.2 | 8.34 | 8.08 | 8.11 |
| (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4** | 0.27 | 8.01, 7.96 (1:2) | 7.74 | 7.82, 7.96 (1:2) |
| | 1.5 | 8.01, 7.94 (1:2) | 7.74 | 7.82, 7.97 (1:2) |

The behavior of the dimeric (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5** possessing a rigid linker was examined with the expectation that it would form an intermolecular aggregate, since the linker moiety of this compound cannot fold. Although $^1$H NMR signals in the aromatic regions are broadened in CDCl$_3$, they are slightly concentration-dependent between 0.19 mM and 1.5 mM.[12] CD spectra in CHCl$_3$ are also concentration dependent between 0.75 mM and 0.022 mM, and have isosbestic points at 290 and 350 nm (Figure 1b). Assuming a monomer–dimer equilibrium, the binding constant *K* was obtained using a curve fitting method: $K = 985\,\text{M}^{-1}$ (Figure 1c).[12] The apparent molecular weight of (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5** in CHCl$_3$ obtained by VPO analysis increases at concentrations from 0.5 to 11 mM (Figure 2). It is therefore concluded that (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5** exhibits monomer–dimer equilibrium in CHCl$_3$.

The $^1$H NMR (CDCl$_3$, 23 °C) resonance of the trimeric (*P*,*P*,*P*)/(*P*,*P*,*P*)/(*P*,*P*,*P*)-**6** broadened without any chemical shift change when the concentration was changed from 0.19 to 1.5 mM.[12] CD spectra (CHCl$_3$, 25 °C) also do not change between 0.0012 and 0.4 mM (Figure 1d). The molecular weight measured by VPO (CHCl$_3$, 35 °C) corresponds to the dimer for concentrations between 0.50 and 15 mM (Figure 2). Thus, in CHCl$_3$, (*P*,*P*,*P*)/(*P*,*P*,*P*)/(*P*,*P*,*P*)-**6** exhibits very strong bimolecular aggregation without forming higher aggregates.

These results show that the aggregation structure of di- and trimeric [3+3]cycloalkynes can be controlled by the structure of the linker moiety (Figure 3). A dimer (*P*,*P*,*P*)/(*P*,*P*,*P*)-**4** with a flexible linker forms a strong intramolecular aggregate, and a dimer (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5** and a trimer (*P*,*P*,*P*)/(*P*,*P*,*P*)/(*P*,*P*,*P*)-**6** with rigid linkers form intermolecular aggregates. As was (*P*,*P*,*P*)-**1**, the oligomers exhibit a tendency to form an aggregate containing two [3+3]cycloalkynes without forming higher aggregates. The linker moiety can also affect the strength of the bimolecular aggregate as shown by the aggregates of (*P*,*P*,*P*)-**1**, (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5**, and (*P*,*P*,*P*)/(*P*,*P*,*P*)/(*P*,*P*,*P*)-**6**: (*P*,*P*,*P*)-**1** is monomeric below 1 mM in CHCl$_3$ and forms a strong bimolecular aggregate at concentrations above 1 mM; (*P*,*P*,*P*)/(*P*,*P*,*P*)-**5** exhibits relatively weak monomer–dimer equilibrium; (*P*,*P*,*P*)/(*P*,*P*,*P*)/(*P*,*P*,*P*)-**6**

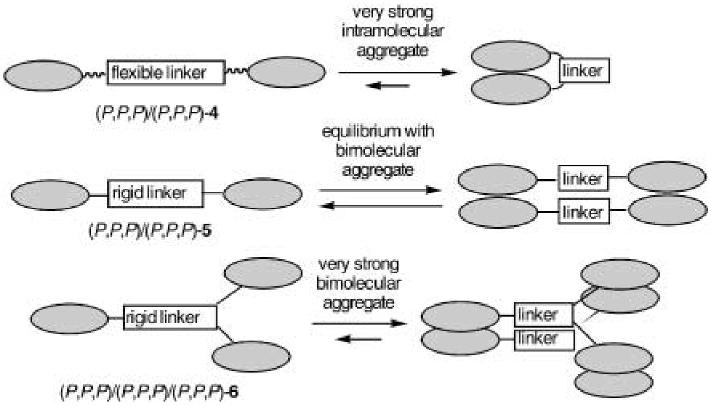

***Figure 3.*** Aggregation behaviors of [3+3]cycloalkyne di- and trimers.

forms a very strong bimolecular aggregate without any indication of monomer or higher aggregate formation. Conformational matching of the nonplanar π-electron system of the [3+3]cycloalkyne moiety, that is, the fitting of the nonplanar π-electron system in the face-to-face π–π interactions,[7] may be important for the formation of these aggregates.

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