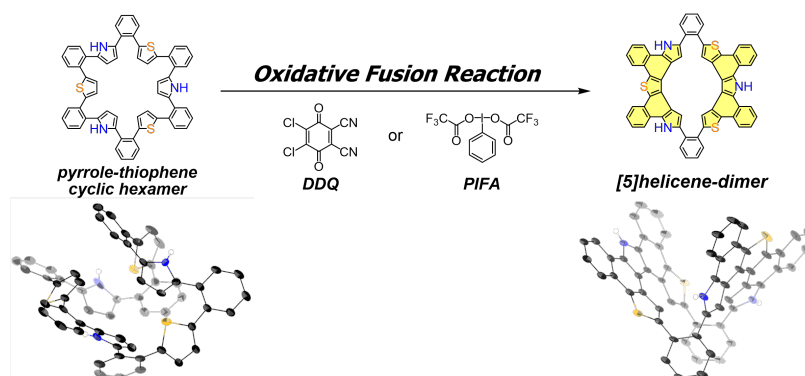# Scholl reaction of *ortho*-Phenylene-bridged Cyclic Pyrrole-Thiophene Hybrid Hexamer

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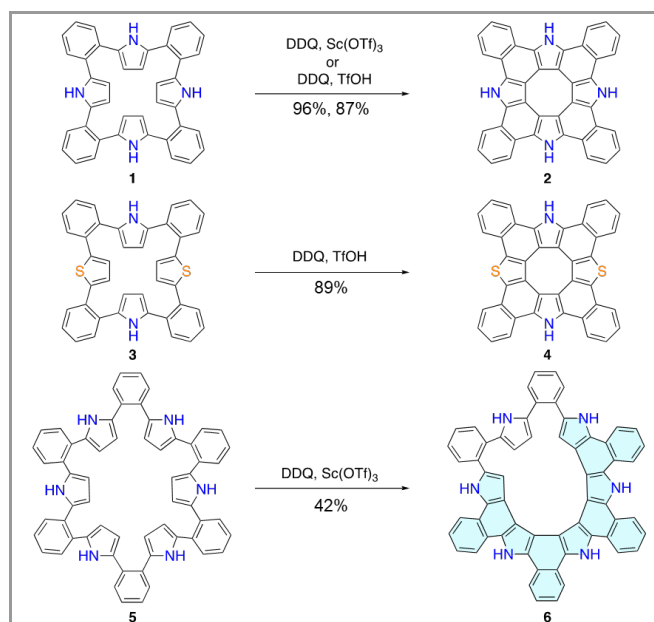
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Abstract Scholl reaction of *ortho*-phenylene-bridged cyclic pyrrole-thiophene hybrid hexamer exclusively gave a cyclophane-type compound of [5]heterohelicenes in 45% yield. The structure was unambiguously revealed by X-ray diffraction analysis. This helicenophane-type compound showed sharp absorption and fluorescence spectra, reflecting its rigid structure. The reaction path was analyzed on the basis of DFT calculations. The reaction path was analyzed on the basis of DFT calculations, and it was found that the formation of **8** is thermodynamically favored and further oxidation is prohibited due to the increased strain energy.

Intramolecular oxidative coupling, also known as the Scholl reaction, is an effective method to obtain polycyclic aromatic hydrocarbons (PAHs) since it does not require prefunctionalization such as halogenation on the substrate.[1] The power of Scholl reaction has been exemplified in the syntheses of a variety of PAHs for more than two decades by using $FeCl_3$ as an oxidant.[2] However, the control of the reaction in terms of regioselectivity and/or suppression of side-reactions is quite tough and the mechanism has been unclear in many cases. [3]

A possible way to control such reactions is the substrate design to facilitate specific bond formation. In this regard, we have recently shown fold-in type oxidative coupling of *ortho*-phenylene-bridged cyclic oligopyrroles and oligothiophenes.[4,5] For example, oxidation of a cyclic tetrapyrrole **1** with DDQ-Sc(OTf)₃ or DDQ-TfOH gave fully fused tetraaza[8]circulenes **2**.[4,6] The same reaction was applied for cyclic pyrrole-thiophene hybrid tetramer **3** to give dithiadiaza[8]circulene **4**. On the other hand, the oxidation reaction for cyclic hexapyrrole **5** gave partly fused closed-aza[9]helicene **6**.[7] These results reflect some important aspects in fold-in type oxidative coupling as follows; i) the β-position of the heterole unit is prone to react unless 1,2-

aryl shift takes place,[7-9] ii) one fusion reaction would cause an increasingly strained structure because of the restriction by the cyclic structure, thus eventually giving a fused product possessing a large strain energy enough to prohibit further reactions. Thus the reaction progress can be correlated with the structural features of the possible intermediates although this hypothesis was not quantitatively analyzed. We thus decided to examine other cyclic heteroaromatic molecules for comparison, and found that a cyclic pyrrole-thiophene hybrid hexamer **7**, which was recently reported by us, might be a good substrate. Here we show the results of the intramolecular oxidative coupling of *ortho*-phenylene-bridged cyclic pyrrole-thiophene hybrid hexamer **7** and study its oxidation mechanism.

Scheme 1. Fold-in type oxidative coupling of *ortho*-phenylene-bridged cyclic hybrids.

In our previous report, cyclic pyrrole-thiophene hybrids were synthesized via Suzuki–Miyaura coupling reaction of 2,5-bis(2-bromophenyl)thiophene and 2,5-bis(pinacolatoboryl)pyrrole with palladium precatalyst (XPhos Pd G2) in the presence of tripotassium phosphate in THF/H$_2$O.[4] The Scholl reaction of cyclic hexamer **7** was examined with DDQ/Sc(OTf)$_3$ at reflux or with PIFA at low temperature following our recent successful cases.[8] Both reactions selectively gave partially fused compound **8** on the basis of MALDI-TOF MS analysis, that displayed a molecular ion peak at m/z = 889.22 (calcd for C$_{60}$H$_{31}$N$_3$S$_3$; m/z = 889.17 [M]$^+$). This result indicates that eight hydrogens were removed from **7** by oxidation. Notably, other fused compounds were not detected, and the isolated yield of **8** was 45% under the DDQ-Sc(OTf)$_3$ conditions and 39% under the PIFA conditions.
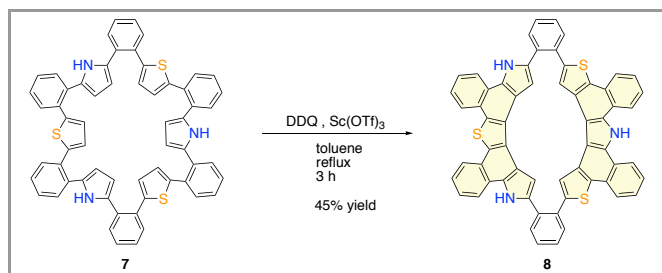
Scheme 2. Oxidation of cyclic pyrrole-thiophene hybrid hexamer.

The structure of **8** has been unambiguously revealed by X-ray diffraction analysis. Different from the aza[9]helicene structure in **6**, **8** displays two hetero[5]helicene structures which are linked via the *ortho*-phenylene bridges. This structure might be also regarded as a cyclophane. Cyclophanes composed of helical moieties are called helicenophane, and its dynamic behavior has been studied so far.[7] In the ^{1}H NMR spectrum of **8**, peaks were observed as sharp signals and there are no significant broadening upon increasing or decreasing temperature. Two [5]helicene units, namely dithiaaza-[5]helicene and thiadiaza[5]helicene, are only slightly helical with average twist angles of 8.21° and 13.99°, respectively.
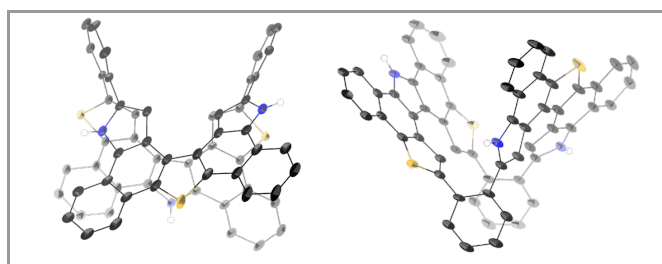

Figure 1. X-Ray crystal structure of **8** with thermal ellipsoids at 50% probability level. Hydrogen atoms except for NHs and solvent molecules were omitted for clarity.

Cyclic hexamer **7** shows broad absorption and fluorescence spectra with the large Stokes shift (14000 cm^{-1}), reflecting its conformational flexibility in solution (Figure 2).[8] On the other hand, cyclophane **8** exhibits sharp absorption band at 401 nm, and its mirror-imaged sharp fluorescence bands at 411 and 434 nm with the small Stokes shift (610 cm^{-1}). This is because the structure of **8** is more rigid than the precursor **7** and no

significant structural relaxation occurs in the excited state. The fluorescence quantum yield of the hetero[5]helicene dimer **8** (Φ_F = 0.037 in THF) is lower than that of aza[9]helicene **6** consisting only of pyrroles (Φ_F = 0.27 in THF) because of the heavy-atom effect of sulfur.[9] TD-DFT calculation has indicated intense degenerated bands with f = 0.10 at 398 nm that is mainly ascribable to the HOMO–LUMO transition (See SI).
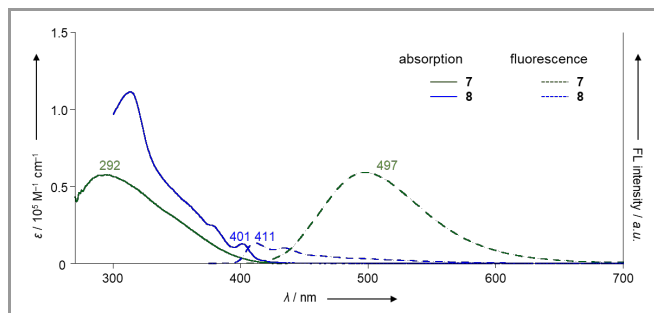

Figure 2. UV/Vis absorption and fluorescence spectra of **7** and **8** in THF.

The reaction path was considered by DFT calculations. Here we set two questions to be answered; i) why the oxidative coupling of **7** gave a [5]helicene dimer, not [9]helicenes like **6**, and ii) why the produced **8** does not react further. For the former question, we have calculated two fragment structures **A** and **B** as well as 2,5-diphenylpyrrole (**DPhP**) and 2,5-diphenylthiophene (**DPhT**) (Figure 3). The HOMO energy level of **A** is higher than that of **DPhP**, which indicates that further oxidation of **A** unit is rather facilitated, giving rise to sequential fusion reaction to give helicene-like structures. On the other hand, the HOMO energy level of **B** is lower than that of **DPhP**. Thus, the next oxidation takes place at the different pyrrolic position to give other intermediates. Among possible intermediates, the formation of dithia[5]helicene **C** is kinetically unfavored, while intermediates **D**, **E**, and **F** could be obtained via oxidation of a **DPhP** unit. The Gibbs free energy comparison suggests that intermediate **E** is the most thermodynamically stable. However, because the intermediates are flexible in solution, tracing the reaction path toward **8** may be less realistic.
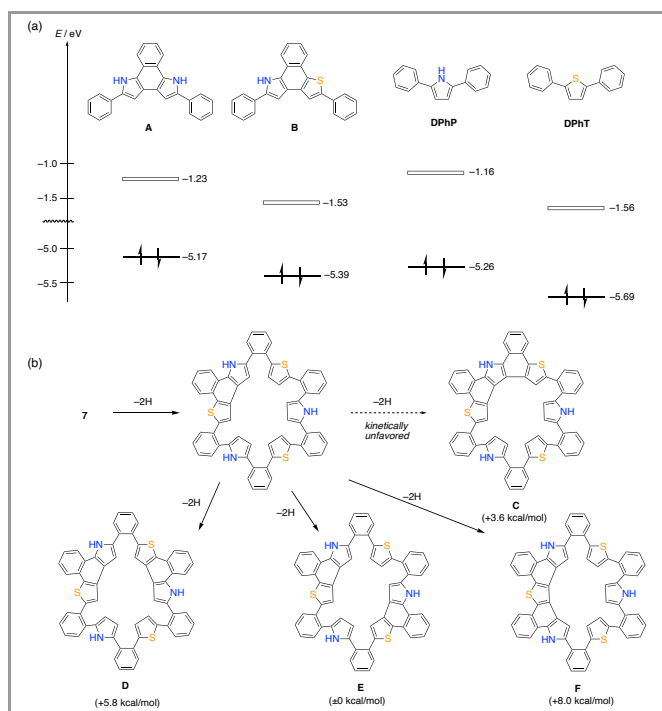
Figure 3. (a) MO diagrams of **A**, **B**, **DPhP**, and **DPhT**. (b) Possible reaction paths and relative Gibbs free energies.

For the second question, we considered the inherent strain energy (See SI for details). To estimate it, homodesmotic reaction model has been adopted for **6** and **8**.[11] According to the model, the strain energy (ΔH) of **6** was calculated to be 12.5 kcal/mol from the thermal energies of **6**, non-cyclic **6**, (*i.e.,* **6'**), 2,5-diphenylpyrrole (**DPhP**), and benzene as follows.

$$\Delta H(\mathbf{6}) = H(\mathbf{6}) - (H(\mathbf{6'}) + H(\mathbf{DPhP}) - 2\,H(\text{benzene}))$$

For comparison, closed-aza[7]helicene (**G**) and closed-aza[11]helicene (**H**) were modeled, and their strain energies were calculated to be 13.5 and 52.5 kcal/mol, respectively (Figure 4). Therefore, a large increase in the strain energy from **6** to **H** may be a reason for the suppression of further reaction from **6**.
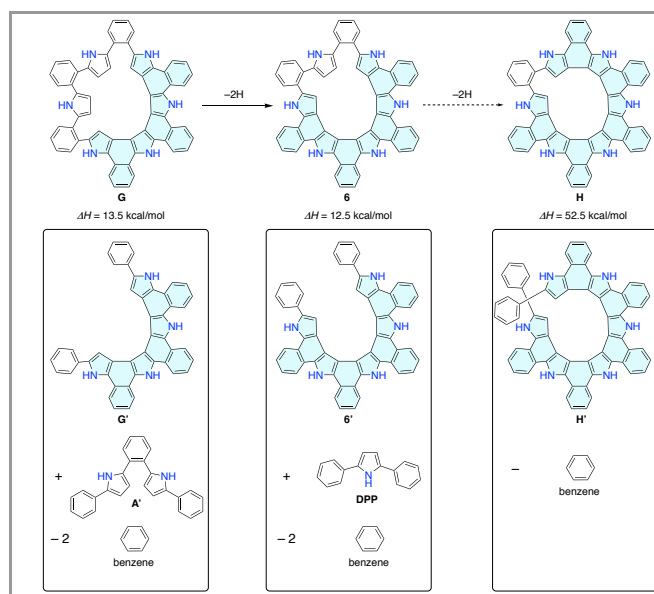

Figure 4. Homodesmotic reaction for **G**, **6**, and **H**.

In the case of **8**, the strain energy was estimated to be 10.9 kcal/mol, that is again much smaller than that of closed trithiatriaza[11]helicene (**K**) (ΔH = 52.4 kcal/mol) (Figure 5). A precursor **I**, that can be obtained from intermediates **D**, **E**, and **F**, have the calculated strain energy of 16.7 kcal/mol. Another precursor **J** has the same degree of strain energy (ΔH = 16.9 kcal/mol), so that the reaction path involving **J** cannot be eliminated (See SI). In both cases, however, the reaction toward other structural isomers of **8**, namely closed dithiatriaza[9]helicene (**L**) and trithiadiaza[9]helicene (**M**), were calculated to be less favored (ΔG = +38.3 and +29.4 kcal/mol relative to **8**, respectively. See SI). Although the detailed transition state has not been investigated, this analysis quantitatively explains the different reaction outcome in **8** from that in **6**.
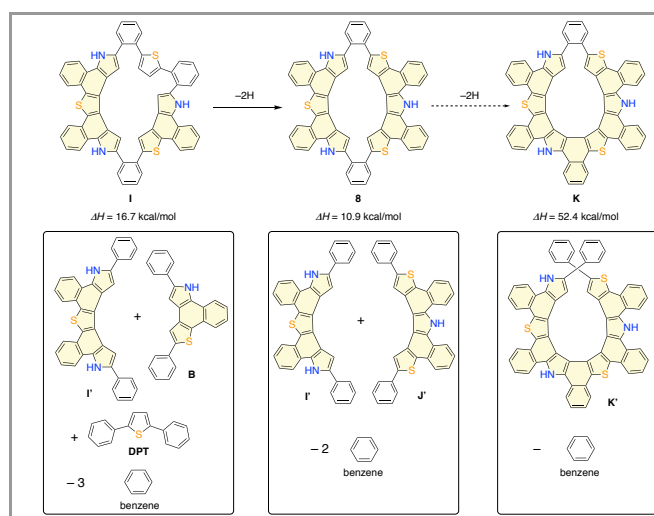

Figure 5. Homodesmotic reactions for **I**, **8**, and **K**.

In summary, Scholl reaction of *ortho*-phenylene-bridged cyclic pyrrole-thiophene hybrid hexamer was investigated, and unique [5]helicene dimer **8** was isolated in moderate yield. The solid-state structure has been unambiguously revealed by X-ray

diffraction analysis. DFT calculations support that the formation of **8** is thermodynamically favored and that further oxidation is prohibited due to the increased strain energy. The fold-in reaction of cyclic hybrid oligomers has been proved to be a unique toolbox for not only helicenes but also helicenophane-type compounds. Further exploration toward unique intramolecular oxidative coupling of cyclic heteroaromatic hybrids are ongoing.

Commercially available solvents and reagents were used without further purification unless otherwise noted.

Dry toluene was used after distillation. The spectroscopic grade solvents were used as solvents for all spectroscopic studies. Silica gel column chromatography was performed on Wako gel C-300 and C-400. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 F254 (Merck 5554). UV-visible absorption spectra were recorded on a Shimadzu UV-3600. Fluorescence spectra were recorded on a JASCO FP-8500 spectrometer. Absolute fluorescence quantum yields were determined on a HAMAMATSU C9920-02S. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA-600 spectrometer (operating as 600 MHz for ^{1}H and 151 MHz for ^{13}C) and chemical shifts were reported as the δ scale in ppm relative to internal standards DMSO (δ =2.50 ppm for ^{1}H, δ =39.52 ppm for ^{13}C). Mass spectra were recorded on a Shimadzu AXIMA-CFRplus using positive-MALDI-TOF method with matrix (TCNQ).

X-Ray Crystallographic Data for Compound 8

Single-crystal of compound **8** was obtained by crystallization from acetone/n-hexane. Single-crystal diffraction analysis data were collected at –180 °C with a Rigaku XtaLAB P200 by using graphite monochromated Cu-Ka radiation (λ = 1.54187 Å). The structures were solved by direct methods (SHELXT-2014/5) and refined with full-matrix least squares technique (SHELXT-2014/7). Crystal Data; $C_{66}H_{45}N_3O_3S_3$, M_W = 1024.23 gmol^{-1}, triclinic crystal system, space group P-1, Z = 2. a = 14.0177(2) Å, b = 14.2006(2) Å, c = 15.1012(5) Å, a = 77.688(11)°, β = 72.469(12)°, γ = 61.882(9)°, V = 2519.0(3) Å^3 and D_{calc} = 1.350 g cm^{-3}. R_1 = 0.0345 ($I > 2\sigma(I)$), wR_2 = 0.0979 (all data), and GOF = 1.083.

Procedures

Cyclophane **8** (oxidation by DDQ/Sc(OTf)$_3$)

A 200 mL three-necked round bottom flask was charged with **7** (45.0 mg, 0.050 mmol), DDQ (47.7 mg, 0.21 mmol, 4.2 eq.), and scandium triflate (103 mg, 0.21 mmol, 4.2 eq.). The reaction flask was evacuated and purged with argon three times. After the mixture was dissolved in dry toluene (50 mL), the reaction mixture was stirred at 115 ˚C for 3 h. After cooled to room temperature, the reaction mixture was diluted with THF and passed through an alumina column with THF as eluent. After removal of the solvents in vacuo, the residue was purified by column chromatography on silica with THF/n-hexane (v/v = 1/1, R$_f$ = 0.36) as eluent to give **8** (20.0 mg, 45% yield) as a pale yellow solid.

Cyclophane **8** (oxidation by PIFA)

A 50 mL two-necked round bottom flask was charged with **7** (20 mg, 0.022 mmol) and dry dichloromethane (15 mL) under argon, which was cooled to –78 °C. Bis(trifluoroacetoxy)iodobenzene (PIFA, 48 mg, 0.11 mmol, 5.0 eq.) was then added, and the reaction mixture was kept at –78 °C for 2 h. Then, the reaction system was allowed to warm to ambient temperature, and stirred for 100 min. After quenched by excess amount of sodium borohydride and methanol, the reaction was stirred for 30 min. The mixture was extracted with dichloromethane three times and the combined organic layers were washed with water and brine, and dried over anhydrous sodium sulfate. After removal of the solvents *in vacuo*, the residue was purified by column chromatography on silica with THF/n-hexane (v/v = 1/1) as eluent to afford **8** (7.4 mg, yield: 39%) as a pale yellow solid.

^{1}H NMR (600.17 MHz, DMSO-d_6) δ = 12.82 (s, 1H, NH), 12.41 (s, 2H, NH), 8.82 (d, J = 8.3 Hz, 2H), 8.42 (d, J = 8.3 Hz, 2H), 8.34 (s, 2H, thiophene), 8.09 (d, J = 7.8 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H), 7.67–7.72 (m, 6H), 7.58–7.65 (m, 6H, benzo/pyrrole), 7.50–7.56 (m, 4H), and 7.46 (t, J = 7.1 Hz, 2H) ppm.

^{13}C NMR (150.91 MHz, DMSO-d_6) δ = 142.52, 134.75, 134.38, 133.69, 132.51, 131.74, 131.24, 131.22, 131.08, 129.91, 129.22, 128.50, 128.44, 128.28, 126.04, 125.86, 125.80, 125.77, 124.88, 124.58, 124.27, 124.13, 123.70, 122.81, 121.66, 121.50, 120.13, 119.52, 113.07, and 106.65 ppm.

MS (MALDI-TOF): m/z $[M]^+$ = calcd for $C_{60}H_{31}N_3S_3$: 889.17; found: 889.22.

UV/Vis (THF): λ_{max} / nm (ε / M^{-1} cm^{-1}) = 314 (1.1 x 10^5), and 401 (1.3 x 10^4). Fluorescence (THF, λ_{ex} = 376 nm) λ_{max} = 411 and 434 nm (Φ_F = 0.037).

Supporting Information

Supporting information for this article is available online at https://doi.org/xxxxxxxx

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