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Helical Structures

A Modular Strategy to Artificial Double Helices**

Yoshie Tanaka, Hiroshi Katagiri, Yoshio Furusho, and Eiji Yashima**

The fascination of the structure, dynamics, and recognition properties of naturally occurring helical polymers, such as the α-helix of peptides and the double helix of DNA structures have prompted chemists to design and synthesize artificial helical polymers and oligomers.[1] Although a number of synthetic polymers and oligomers that fold into single-helical conformations have been reported, only a few structural motifs are available for constructing double-helical structures. The most widely used approach is the utilization of metal-directed self-assembly, in which ligand-containing strands form double-, triple-, or quadruple-helical complexes, that is, helicates;[2] the three-dimensional structures of helicates are determined by the geometry of the template metal ions. Hydrogen-bonding-driven self-assembly is another common approach to constructing supramolecular duplexes.[3] In most cases, however, their three-dimensional structures have been characterized as ladder- or zipperlike linear conformations. It was recently disclosed that some oligoamides give rise to double-helical assemblies by making use of interstrand hydrogen-bonding and aromatic–aromatic interactions.[4] Although the hydrogen-bonding interaction is a readily available and versatile tool for constructing supramolecular assemblies,[5] it is still difficult and challenging to design double helices with predictable structures.[4c] Herein, we describe the design and synthesis of hydrogen-bonding-driven double helices by a modular strategy in which intertwined supramolecular binary complexes are employed.

Our strategy is based on the crescent-shaped *m*-terphenyl derivatives (Figure 1). Crescent-shaped molecules, such as bipyridine and phenanthroline derivatives, have often been used to construct intertwined supramolecular complexes and

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[*] Dr. Y. Tanaka, Dr. H. Katagiri, Dr. Y. Furusho, Prof. E. Yashima
Yashima Super-structured Helix Project
Exploratory Research for Advanced Technology (ERATO)
Japan Science and Technology Agency (JST)
Creation Core Nagoya 101
2266-22 Anagahora, Shimoshidami
Moriyama-ku, Nagoya 463-0003 (Japan)
Fax: (+81) 52-739-2081
E-mail: furusho@yp-jst.jp
yashima@apchem.nagoya-u.ac.jp

Prof. E. Yashima
Institute for Advanced Research
Nagoya University
Chikusa-ku, Nagoya 464-8601 (Japan)
Fax: (+81) 52-789-3185

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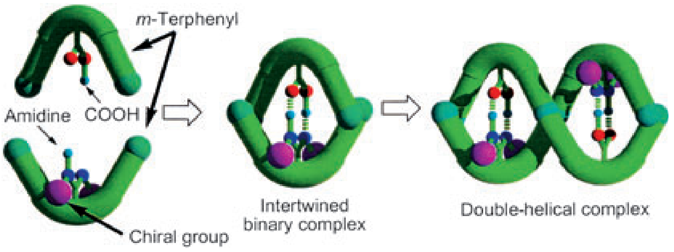
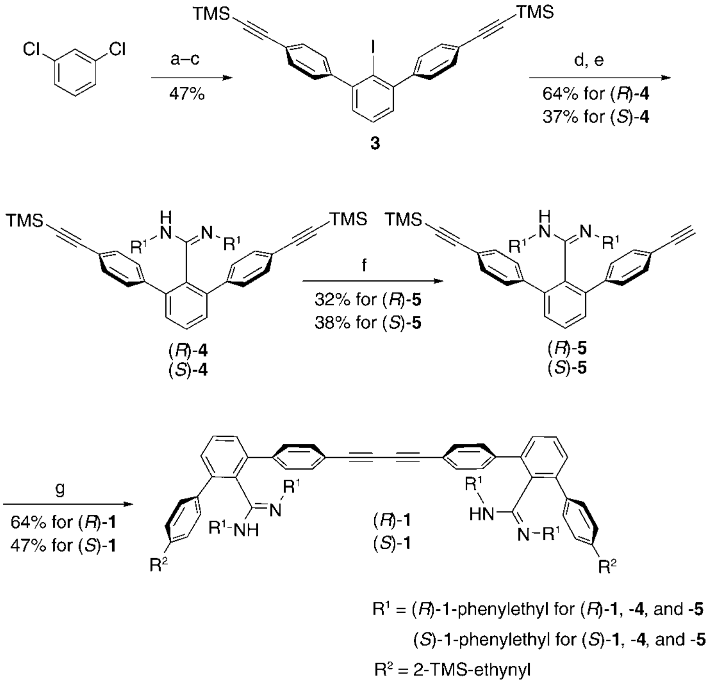


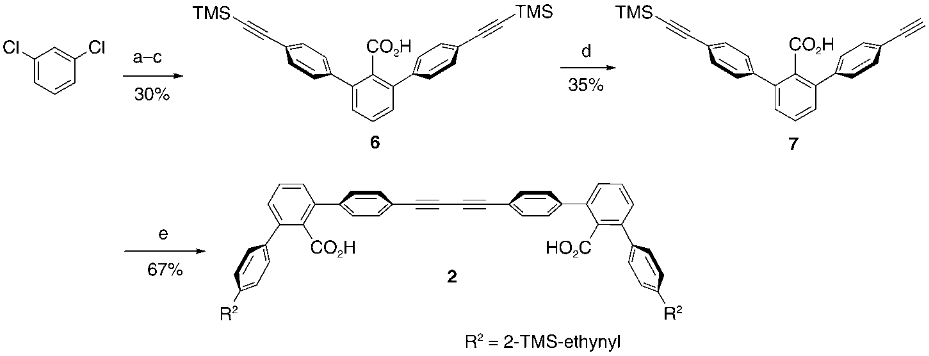
Figure 1. Schematic illustration of the modular strategy for the construction of artificial double-helical assemblies.



Scheme 1. Synthesis of diamidines **1**: a) *n*BuLi/THF, −78 °C; b) 4-trimethylsilylethynylphenylmagnesium bromide, −78 °C to RT; c) I_2, RT; d) *n*BuLi, TMEDA/Et_2O, 0 °C; e) *N*,*N*′-bis[(*R*)-1-phenylethyl]carbodiimide for (*R*)-**4**, *N*,*N*′-bis[(*S*)-1-phenylethyl]carbodiimide for (*S*)-**4**/THF, RT; f) nBu_4NF/THF, 0 °C; g) $[PdCl_2(PPh_3)_2]$, CuI, Et_3N/THF, RT. TMEDA = *N*,*N*,*N*′*N*′-tetramethyl-1,2-ethanediamine.

interlocked molecules.[6] We chose amidinium–carboxylate salt bridges as the supramolecular junction for the *m*-terphenyl derivatives because the charge-assisted hydrogen bonding between amidines and carboxylic acids is quite strong even in polar solvents and has a well-defined geometry.[7] Chiral groups were introduced onto the nitrogen atoms of the amidine moieties to control the chirality of the double helices. The formation of the salt bridge leads to a supramolecular binary complex, in which the two *m*-terphenyl derivatives are intertwined around the salt bridge (Figure 1). Connecting the intertwined complexes together should result in the formation of the double-helical structure.

The chiral diamidine (*R*)-**1** and its antipode (*S*)-**1** were prepared according to Scheme 1.[8] The iodide **3** was obtained by the Hart coupling of *m*-dichlorobenzene with 4-trimethylsilylethynylphenylmagnesium bromide followed by quenching with iodine.[9] Iodide **3** was lithiated and then treated with *N*,*N*′-bis[(*R*)-1-phenylethyl]carbodiimide[10a] to yield the amidine (*R*)-**4**.[11] (*R*)-**4** was treated with tetra-*n*-butylammonium fluoride (TBAF) to give the monosilane (*R*)-**5**, which was dimerized by oxidative coupling using the Sonogashira reagents to afford the diamidine (*R*)-**1**. The antipode (*S*)-**1** was synthesized in a similar manner except that *N*,*N*′-bis[(*S*)-1-phenylethyl]carbodiimide was used.[10b] Similarly, the dicarboxylic acid **2** was prepared according to Scheme 2. Carboxylic acid **6** was obtained by Hart coupling using CO_2 as the quencher. The monodesilylation of **6** was achieved by treatment with TBAF to yield the monosilane **7**, which was subsequently dimerized by oxidative coupling to afford **2**.



Scheme 2. Synthesis of dicarboxylic acid **2**: a) *n*BuLi/THF, −78 °C; b) 4-trimethylsilylethynylphenylmagnesium bromide, −78 °C to RT; c) CO_2, RT; d) nBu_4NF/THF, 0 °C; e) $[PdCl_2(PPh_3)_2]$, CuI, Et_3N/THF, RT.

Complexation of the diamidine (*R*)-**1** with the dicarboxylic acid **2** was first investigated by ^1H NMR spectroscopy (Figure 2). The ^1H NMR spectrum of **1** in $CDCl_3$ was complicated at 25 °C, because of the presence of several conformers originating from the *E*–*Z* isomerism of the C=N double bonds and the restricted rotation about the C–C bond between the amidine and the *m*-terphenyl groups.[11] In contrast, the ^1H NMR spectrum of the complex (*R*)-**1**·**2** showed a simple spectrum, thus indicating the presence of only one isomer. This result is consistent with the formation of a salt bridge between (*R*)-**1** and **2**, through which the geometry around the amidine residues is fixed in the *E* configuration. The resonances of the NH protons (c′ and c″) were observed as two doublets at a low magnetic field of approximately $\delta = 13.5$ ppm, which is indicative of the formation of a salt bridge. The CH_3 protons of the amidine groups (d′ and e′) were also evident. The non-equivalency of these signals is attributed to the formation of a duplex between (*R*)-**1** and **2**, which was also supported by 2D NMR spectroscopic and electrospray ionization mass spectrometry (ESI-MS) studies.[8] The association constant of **1** and **2** at

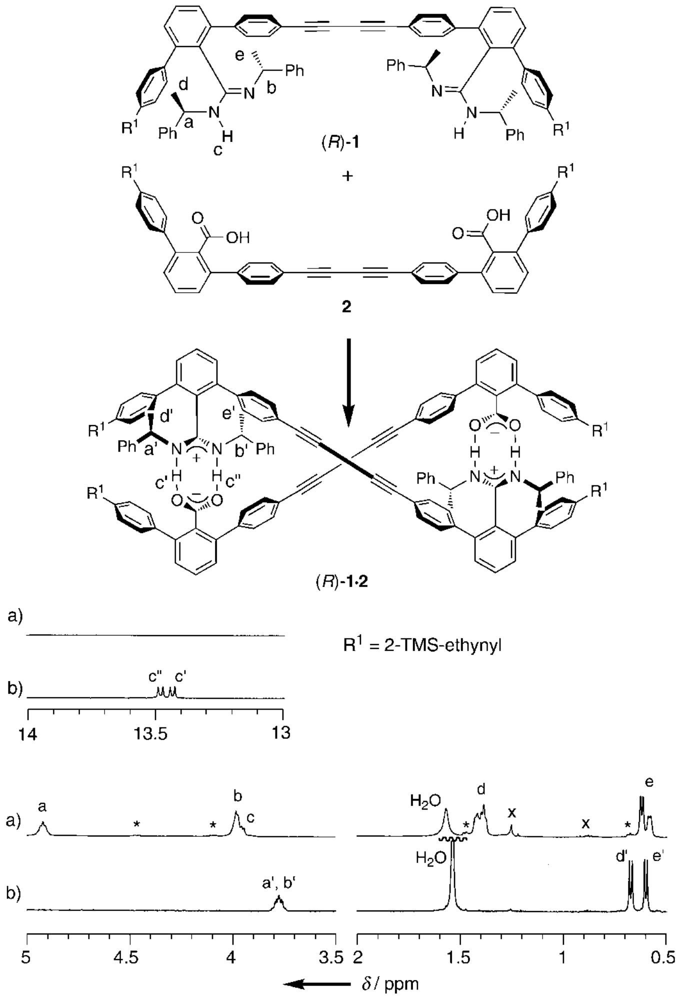


Figure 2. Partial ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) spectra of a) diamidine (*R*)-**1** (7.1 mM) and b) complex (*R*)-**1**·**2** (0.4 mM). The asterisks denote the signals for the corresponding *Z* isomer of (*R*)-**1**. "x" indicates impurities.

25 °C in $CDCl_3$ was estimated to be $> 10^6\,\text{M}^{-1}$ by ^{1}H NMR spectroscopy.[8]

The X-ray structural analysis unambiguously revealed that the complex (*R*)-**1**·**2** adopted a right-handed double-helical structure in the solid state (Figure 3).[8,12] The amidine and carboxy groups formed two identical salt bridges with two hydrogen bonds for each and average N···O distances of 2.73 Å. The two amidinium–carboxylate salt bridges enabled the two strands to be held together. All the benzene rings of the *m*-terphenyl groups were chirally twisted clockwise by about 48–61°, and the two strands were wound up to form the right-handed double-helical structure.

Circular dichroism (CD) measurements were then performed to examine if the complexes (*R*)- and (*S*)-**1**·**2** maintained their single-handed double-helical structures in solution (Figure 4). Both enantiomers of **1**·**2** showed intense mirror-image CD signals between approximately 260 and 370 nm in $CHCl_3$, whereas (*R*)- and (*S*)-**1** exhibited very weak Cotton effects in this region. The significant enhancement of the Cotton effects for the complexes **1**·**2**, especially in the absorption region of the diacetylene linkages (ca. 300–370 nm), indicates that the single-handed double-helical structures of (*R*)- and (*S*)-**1**·**2** are likely retained in $CHCl_3$. This presumption was supported by the variable-temperature ^{1}H NMR spectroscopic measurements of (*R*)-**1**·**2** in $CDCl_3$; no signals corresponding to the opposite diastereomeric left-handed double helix were observed, even at temperatures as low as −60 °C. Thus, (*R*)-**1**·**2** seems to adopt a predominantly right-handed double-helical structure, although the possibility that the inversion of the double helices is still fast on the NMR time scale even at −60 °C can not be ruled out.

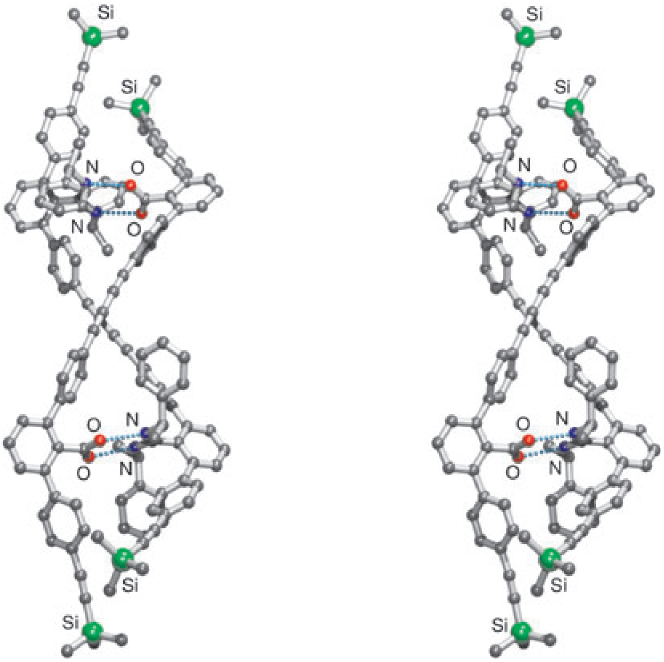


Figure 3. Stereoview of the crystal structure of (*R*)-**1**·**2**. The hydrogen atoms and included solvents are omitted for clarity. The intermolecular hydrogen bonds between N and O are shown by dashed lines.

It should be noted that (*R*)-**1**·**2** even exhibited intense Cotton effects in DMSO, although the intensities were reduced to 67 % of those in $CHCl_3$ (Figure 4). The ^{1}H NMR

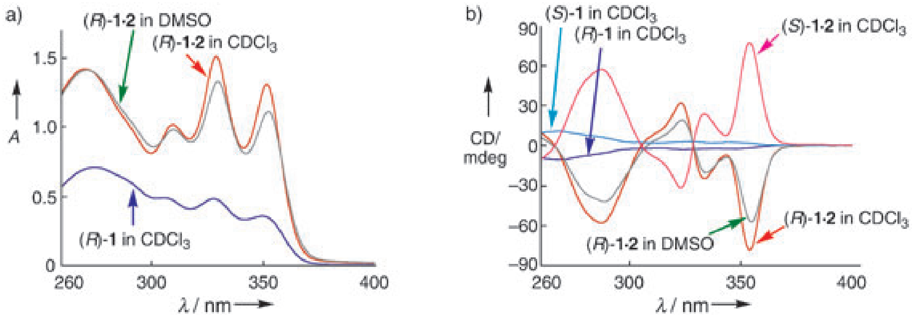


Figure 4. a) UV/Vis spectra (0.1 mM, 20 °C) of amidine (*R*)-**1** in $CDCl_3$ (blue), and complex (*R*)-**1**·**2** in $CDCl_3$ (red) and in DMSO (green). b) CD spectra (0.1 mM, 20 °C) of (*R*)-**1** (blue), (*S*)-**1** (light blue), (*R*)-**1**·**2** (red), and (*S*)-**1**·**2** (pink) in $CDCl_3$, and (*R*)-**1**·**2** in DMSO (green).

spectrum of **1·2** showed that 60 % of the complex **1·2** retained its duplex structure, whereas the rest of **1·2** underwent dissociation into **1** and **2** in [D$_6$]DMSO (0.1 mM, 25 °C).[8] In sharp contrast, (*R*)-**4·6**, a simple model for (*R*)-**1·2**, showed a weak CD spectrum similar to that of (*R*)-**4** in DMSO.[8] In fact, it was shown by ^{1}H NMR spectroscopic analysis that **4·6** dissociated into **4** and **6** in [D$_6$]DMSO.[8] Consequently, the complexation of **1·2** was more stable than that of the simpler **4·6**.

In summary, we have successfully prepared the first artificial single-handed double helices through formation of salt bridges between chiral diamidines ((*R*)- and (*S*)-**1**) and the achiral dicarboxylic acid **2.** Both single-handed double helices are stable in the solid state as well as in solution. The modular strategy, we believe, can act as a new design rationale for the formation of hydrogen-bond-driven double helices in which the three-dimensional structures including the helix sense are predictable.

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[12] Crystal data for (*R*)-**1·2** ($C_{141}H_{140}N_4O_9Si_4$): $M_r = 2147.03$, crystal dimensions $0.30 \times 0.24 \times 0.14$ mm^3, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $\rho_{calcd} = 1.132$ g cm^{-3}, $\mu(\mathrm{Cu}_{K\alpha}) = 8.92$ cm^{-1}, $F(000) = 4568$, $2\theta_{max} = 136.4°$ were $a = 13.6965(5)$, $b = 22.7967(11)$, $c = 40.3486(17)$ Å, and $V = 12598.2(9)$ Å^3. A total of 124842 reflections were collected, of which 22862 reflections were independent ($R_{int} = 0.044$). The structure was refined to final $R_1 = 0.072$ for 15968 data [$I > 2\sigma(I)$] with 1430 parameters and $wR_2 = 0.2360$ for all data, GOF = 1.039, and residual electron density max./min. = 0.49/−0.32 e Å^{-3}. CCDC-266647 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.