A hetero-stranded double helix composed of *m*-diethynylbenzene-based complementary molecular strands stabilized by amidinium-carboxylate salt bridges†

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A hetero-stranded double helix with a controlled helix sense was designed and synthesized from an optically active dimeric amidine and its complementary achiral dicarboxylic acid strand with conjugated *m*-diethynylbenzene backbones, being stabilized by the salt bridges.

Helical structures are the central structural motifs for biomacromolecules, such as DNA, proteins, and polysaccharides, and also direct the sophisticated functions of these macromolecules in living systems. Since the inspirational discovery of the DNA double helix by Watson and Crick,[1] chemists have been prompted to design and synthesize artificial polymers and oligomers that fold into a helical conformation.[2] In contrast to a wide variety of synthetic single helical polymers and oligomers, the structural motifs available for constructing double helices are limited in number.[2h,m,3] Of particular importance is the driving force for intertwining two molecular strands, which includes metal–ligand coordination,[4] aromatic interactions,[5] hydrophobic effects,[6] and hydrogen-bonding interactions.[7,8] The hydrogen-bonding interaction is a useful tool for assembling various supramolecular complexes.[9] However, most supramolecular duplexes stabilized by hydrogen-bonding interactions fail to form double helical conformations, resulting in the formation of ladder- or zipper-like duplexes.[10] We have recently reported hetero-stranded double helices with a controlled helix sense that consist of optically active dimeric amidine strands and their complementary, achiral carboxylic acid strands, of which the formation relies on the salt bridge formation.[7] The amidinium-carboxylate salt bridge has been widely used as supramolecular junctions, because of its high association constants and well-defined geometry due to its doubly bridged hydrogen bonding nature.[11] The helical sense of the double helices can be controlled by the optically active substituents on the amidine groups. Another key feature of this design is the use of *m*-terphenyl skeletons that facilitate the formation of intertwined duplexes. However, the preparation of *m*-terphenyl skeletons bearing functional groups at the 2′-position requires the cumbersome Hart coupling involving the formation of organolithium intermediates that restrict further molecular design.[12] In the field of supramolecular chemistry, simpler *m*-diethynylbenzene skeletons have been widely employed for constructing various supramolecular complexes including single and double helices, because of their well-defined geometry as well as shape-persistent nature.[13] In addition, *m*-diethynylbenzene skeletons can be constructed through the Sonogashira coupling that requires relatively mild conditions, which extends the possibility for the further design of artificial double helices. We now report the design and synthesis of a new, more compact double helix stabilized by salt bridges by replacing the *m*-terphenyl groups with simpler *m*-phenylene ones (Fig. 1).

The optically active amidine and achiral carboxylic acid strands that are complementary to each other ((*R*)-**1** and **2**) were synthesized according to Scheme 1. An amidine group was introduced by treating the iodide **3**[14] with *n*-BuLi, followed by *N*,*N*′-bis[(*R*)-1-phenylethyl]carbodiimide.[7,15] During the reaction, the TMS groups were partially lost because of the highly basic conditions, and the mono-silylated amidine, (*R*)-**4**, was isolated by SiO_2–NH_2 column

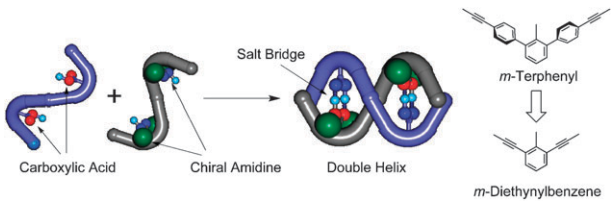
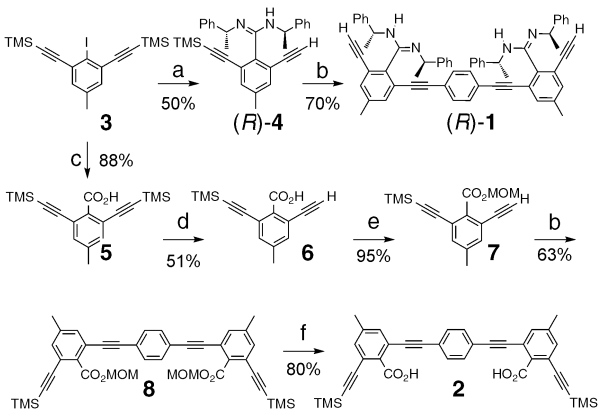


Fig. 1 Schematic illustration of the strategy for the design of short double helices.



Scheme 1 Synthesis of diamidine (*R*)-**1** and dicarboxylic acid **2**. *Reagents and conditions*: (a) (i) *n*-BuLi, TMEDA; (ii) *N*,*N*′-bis[(*R*)-1-phenylethyl]carbodiimide; (iii) H_2O, (b) 1,4-diiodobenzene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, rt, 6 h, (c) (i) *n*-BuLi, TMEDA; (ii) CO_2, rt, 12 h; (iii) H_3O^+, (d) TBAF, THF, 0 °C, 1 h, (e) MOMCl, Et_3N, THF, 0 °C, 10 min, (f) HCl, THF, 45 °C, 4 h.

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chromatography. The dimeric amidine strand, (*R*)-**1**, was obtained by the Sonogashira coupling of (*R*)-**4** and 1,4-diiodobenzene. The dicarboxylic acid **2** was similarly prepared from the iodide **3**. The iodide **3** was lithiated and then treated with CO_2 to yield the carboxylic acid **5**, of which one TMS group was removed by treatment with tetrabutylammonium fluoride (TBAF) to give the monosilyl **6**. During the deprotection, a base-catalyzed intramolecular cyclization proceeded under the basic conditions to produce a lactone as a by-product (Fig. S9, ESI†).[16] The direct coupling of **6** and 1,4-diiodobenzene under the Sonogashira conditions failed to afford the corresponding dimeric acid strand because of the base-catalyzed intramolecular cyclization that took place, giving the lactone as the major product. To prevent the undesirable side reaction, the carboxyl group was protected as a methoxymethyl (MOM) ester. After protection of the carboxyl group of **6**, the monosilyl **7** was dimerized by the Sonogashira coupling with 1,4-diiodobenzene to afford the dimeric strand, **8**, of which the methoxymethyl (MOM) groups were removed by hydrolysis with hydrochloric acid to yield the dicarboxylic acid **2**.

Complexation of the diamidine (*R*)-**1** with the dicarboxylic acid **2** was first investigated by ^{1}H NMR spectroscopy (Fig. 2). The ^{1}H NMR spectrum of (*R*)-**1** in $CDCl_3$ was highly broadened at 25 °C owing to 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 ethynylene linkers. In contrast, the ^{1}H NMR spectrum of (*R*)-**1**·**2** showed very simple signals, thus indicating the presence of only one isomer. This result is consistent with the formation of salt bridges between (*R*)-**1** and **2**, and the geometry around the amidines residues is likely fixed in the *E* configuration. The resonances of the NH protons were observed as two sharp signals at the low magnetic fields of 13.83 and 13.77 ppm, which are indicative of the formation of salt bridges. Furthermore, the formation of the duplex (*R*)-**1**·**2** was also confirmed by ESI-MS measurements; the ESI-MS spectrum of a $CHCl_3$ solution of (*R*)-**1**·**2** showed signals at *m*/*z* 1440.6 corresponding to $[(R)\text{-}\mathbf{1}\cdot\mathbf{2}\text{–H}]^-$ (Fig. S1, ESI†).

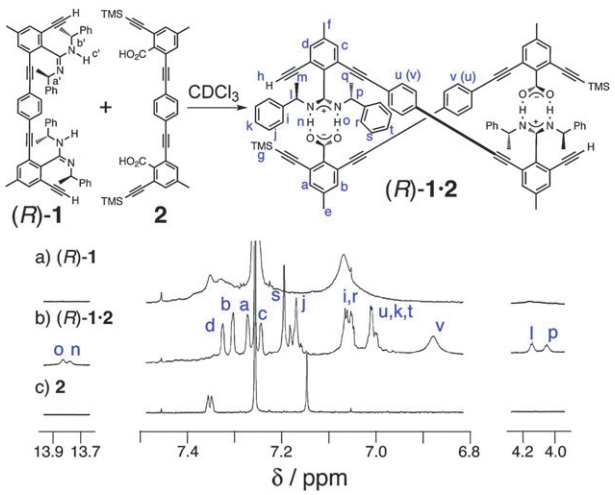

Fig. 2 Partial ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) spectra of (a) (*R*)-**1** (5.0 mM), (b) (*R*)-**1**·**2** (2.0 mM), and (c) **2** (2.0 mM).

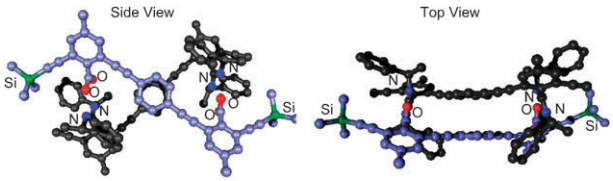

Fig. 3 Capped-stick drawings of the energy-minimized structure for the right-handed conformation of (*R*)-**1**·**2** obtained by the DFT calculation. The hydrogen atoms are omitted for clarity.

Repeated attempts failed to produce crystals of (*R*)-**1**·**2** suitable for an X-ray crystallographic study. The density functional theory (DFT) calculations were then conducted to obtain more information about the three-dimensional structure of the duplex (*R*)-**1**·**2** (Fig. 3 and Fig. S8, ESI†). The calculation results suggested that (*R*)-**1**·**2** more likely adopted a right-handed double helical conformation than a left-handed one, as in the case of the double helices bearing *m*-terphenyl groups with (*R*)-1-phenylethyl substituents.[7a] In the calculated structure, the two *p*-phenylene linkers stack together with a centroid distance of 3.6 Å, which indicates the presence of π–π stacking interactions between the linkers. The absorption spectrum of the duplex showed a remarkable hypochromicity with a blue shift, which also supports the aromatic interactions between the two linkers in solution (Fig. 4a). The 2D NMR studies including the COSY and ROESY measurements of (*R*)-**1**·**2** also supported the right-handed double helical structure (Fig. S2–S4, ESI†). The circular dichroism (CD) spectrum of the duplex (*R*)-**1**·**2** showed intense CD signals above 250 nm in $CHCl_3$, whereas (*R*)-**1** exhibited rather weak Cotton effects in this region (Fig. 4a). The significant enhancement of the Cotton effects of the (*R*)-**1**·**2** complex, especially in the absorption region of the *p*-diethynylbenzene conjugated linkers (*ca.* 280–370 nm), indicates that (*R*)-**1**·**2** likely adopts a preferred-handed double helical structure induced by the chiral (*R*)-1-phenylethyl substituents on the amidine groups. The CD spectrum of (*R*)-**1**·**2** in $CHCl_3$ showed a slight temperature dependence between −10 and 50 °C: the Cotton effect intensities slightly increased with decreasing temperature, reflecting the dynamic nature of the double helix (Fig. S5, ESI†). The ^{1}H NMR signals of (*R*)-**1**·**2** in $CDCl_3$ did not show chemical shift changes nor splits due to the diastereomeric pairs over the

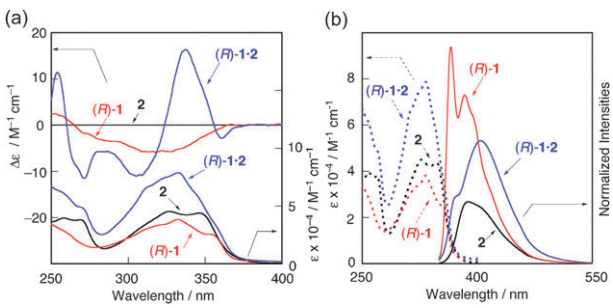

Fig. 4 (a) CD and absorption spectra of (*R*)-**1**, **2**, and (*R*)-**1**·**2** in $CHCl_3$ (0.2 mM, cell length = 0.1 cm) at 25 °C. (b) Absorption (dashed lines) and fluorescence (solid lines) spectra of (*R*)-**1**, **2**, and (*R*)-**1**·**2** measured in $CDCl_3$ (3.8 μM, 1 cm cell) at 25 °C excited at 330 nm. The signal intensities have been normalized.

temperature range of 55 to −60 °C, and thereby it is not possible to quantify the twist-sense bias of the double helix. The association constant (K_a) of the monomeric amidine and carboxylic acid was estimated to be 4.73×10^5 M^{-1} in $CHCl_3$ at 25 °C by CD titration experiments, while that of (*R*)-**1**·**2** was evaluated to be much higher than 10^8 M^{-1} (Fig. S6 and S7, ESI†).

The fluorescence spectra of (*R*)-**1**, **2**, and (*R*)-**1**·**2** measured in $CDCl_3$ at 25 °C are shown in Fig. 4b. When excited at 330 nm, both (*R*)-**1** and **2** exhibited a strong fluorescent emission over the range of 350 to 550 nm, arising from their conjugated backbones. The duplex, (*R*)-**1**·**2**, showed a red shifted fluorescence, which suggested the formation of an inter-strand excimer.

In summary, we have designed and synthesized a novel hetero-stranded double helix with a controlled helix sense that consists of an optically active dimeric amidine strand and its complementary achiral dicarboxylic acid strand based on simple *m*-diethynylbenzene backbones. Although the present system has a slightly less stability than the prototype bearing *m*-terphenyl backbones, it has a greater advantage than the *m*-terphenyl-based one from the viewpoint of the synthetic accessibility. The present results described in this report will expand the design possibility of synthetic double helices, due no longer to the need of cumbersome *m*-terphenyl skeletons.

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