Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

# Hydrogen-Bonded Duplexes with Lengthened Linkers

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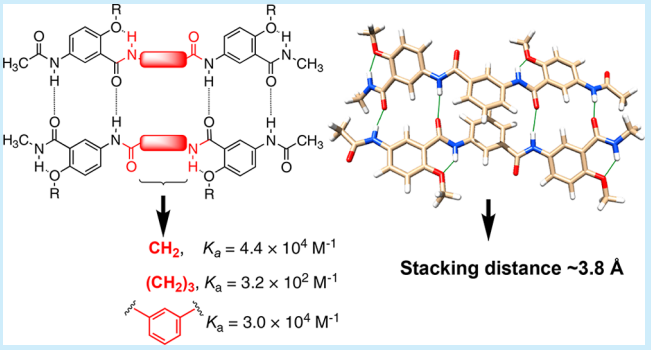
Supporting Information

**ABSTRACT:** Connecting basic hydrogen-bonding units with lengthened flexible or rigid linkers generates oligoamide strands that carry new H-bonding sequences and association specificity, leading to H-bonded homo- and heteroduplexes with association constants in the $10^4$ $M^{-1}$ range in chloroform. Computational and experimental studies indicate that in duplexes with rigid aromatic linkers the oligoamide strands adopt bent conformations that allow the formation of interstrand H-bonds and accommodate the introduced aromatic liners, offering a new series of association units.




The control of molecular association is essential for implementing noncovalent synthesis, i.e., predictably organizing molecular components into supramolecular assemblies.[1] Many H-bonded complexes, such as those first studied by Jorgensen and Zimmerman[2] and soon developed by Zimmerman and Meijer[3] and many others,[4] are known. The majority of these complexes are based on heterocycles and have evolved from those having limited strength and being complicated by interconverting tautomers to ones with great strength and high specificity.[4] For example, highly stable H-bonded complexes[5,6] served as association units in constructing supramolecular polymers[1b,f,7] and other molecular architectures.[8]

We developed a series of H-bonded duplexes consisting of linear oligoamide strands.[1d,9,10] Basic H-bonding units linked via glycine residues result in oligoamide strands having H-bonding sequences defined by arrays of H-bond donors (D) and acceptors (A). An oligoamide specifically pairs with another strand carrying a complementary H-bonding sequence, leading to self-complementary duplexes such as the quadruply H-bonded **1·1**, **2·2**, or heterocomplementary duplexes such as **3·4** (Figure 1) and their longer analogues.[9]

Our H-bonded duplexes are free of tautomerism that typically accompanies heterocycle-based complexes. Secondary electrostatic interactions, which accompany most known H-bonded complexes and result in association strengths that rely on both the number of H-bonds and the specific H-bonding sequences,[11] are absent in our system. Thus, the stabilities of our duplexes are proportional to the number of interstrand H-bonds. In $CHCl_3$, duplexes with four interstrand H-bonds have

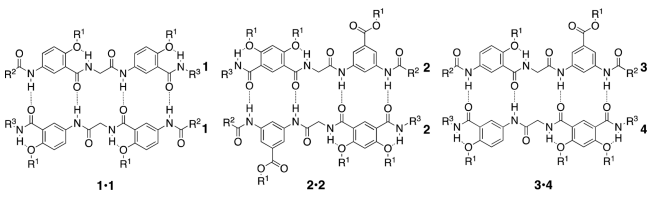



**Figure 1.** Examples of known H-bonded duplexes with four interstrand H-bonds.

association constants ($K_a$'s) in the $10^4$ $M^{-1}$ range, while those with six H-bonds have $K_a$'s in the $10^9$ $M^{-1}$ range.

In addition to binding strength, the effectiveness of H-bonded complexes as association units also depends on their specificity. Our H-bonded duplexes allow the tuning of association specificity by combining different types of H-bonding benzene units;[9] or by replacing benzene units with naphthalene residues.[12] With their tunable affinity and sequence-specificity, our H-bonded duplexes, along with related systems developed by others, have instructed the formation of $\beta$-sheets,[13] supramolecular (noncovalent) block copolymers,[1b,f,h,7,14,15] the specification of chemical reactions,[16] and other applications.[17]

Rather than varying the arrangement of H-bond donors and acceptors to generate new H-bonding sequences, which requires the incorporation of multiple types of H-bonding units, such as those derived from naphthalene, that offer limited

**Received:** January 26, 2018





DOI: 10.1021/acs.orglett.8b00283
Org. Lett. XXXX, XXX, XXX–XXX

availability, duplexes with new association specificity may be generated by adjusting the spacing between linked basic H-bonding units that are readily available. Specifically, replacing glycine residues with longer linkers will widen the spacing between adjacent H-bonding units, which will generate new association specificity, including new sequences.

Oligoamide **5a** was first designed and examined (Figure 2). Based on coupling steps we reported before for preparing

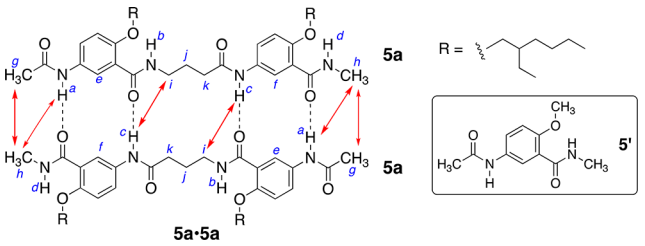



**Figure 2.** Oligoamide strand **5a** and its H-bonded duplex **5a·5a**. The structure of previously reported **5′**[10a] is also shown. Cross-strand NOEs revealed by the NOESY are shown with double-headed red arrows.

strands **1** through **4**,[10] H-bonding units derived from 5-aminosalicylic acid were connected with a linker derived from 4-aminobutyric acid into **5a** (Scheme S1 and the Supporting Information (SI)). With its ADAD array, strand **5a** should dimerize into H-bonded duplex **5a·5a**.

At 10 mM in $CDCl_3$, the $^1$H NMR signals of amide protons *a* (at 9.24 ppm) and *c* (at 9.76 ppm) of **5a** move downfield with respect to the aniline NH signal (at 7.91 ppm) of **5′** that undergoes very weak self-association,[10a] suggesting that protons *a* and *c* engage in enhanced H-bonding interactions. The involvement of protons *a* and *c* in intermolecular H-bonding is demonstrated by the shifts of their signals with concentrations. As shown in Figure 3a, from 0.10 to 50 mM, the resonances of

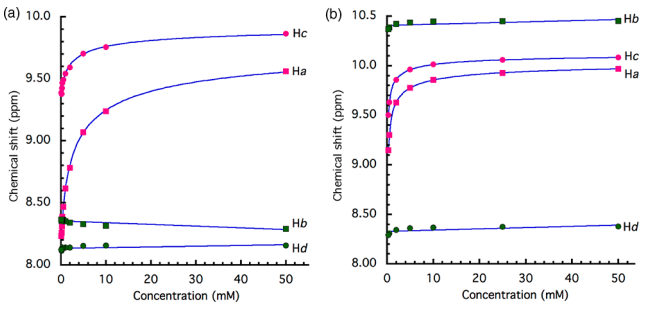



**Figure 3.** Concentration-dependent change in the chemical shifts of protons *a*, *b*, *c*, and *d* of (a) **5a** and (b) **5b**. Each of the chemical shift values is the average of those from triplicate runs.

protons *a* and *c* show downfield shifts of 1.3 ppm and ~0.5 ppm, respectively. In contrast, protons *b* and *d*, which form intramolecular H-bonds, have negligible shifts in the same concentration range. Nonlinear regression analysis[10] of the concentration-dependent chemical shift values of proton *c* yielded a dimerization constant of 322 ± 10 $M^{-1}$ for **5a** (Table 1) that is much larger than that of **5′** (~25 $M^{-1}$ in $CDCl_3$).[10a] The formation of duplex **5a·5a** is confirmed by the NOESY spectrum of **5a** (10 mM) recorded in $CDCl_3$ (Figure S1), which revealed cross-strand NOEs between protons *a* and *h*, *c* and *i*, and *g* and *h*, that are consistent with the expected antiparallel alignment of two strands of **5a** (Figure 2).

**Table 1. Association Constants Obtained from $^1$H NMR Dilution Experiments**[a]

| complex | $K$ ($M^{-1}$) | complex | $K$ ($M^{-1}$) |
|---|---|---|---|
| **5′·5′**[b] | 25 | **6·6** | (2.6 ± 0.4) × $10^2$ |
| **5a·5a** | (3.2 ± 0.1) × $10^2$ | **7·7** | (1.8 ± 0.2) × 10 |
| **5b·5b** | (3.0 ± 0.5) × $10^4$ | **6·7** | (4.3 ± 0.8) × $10^4$ |

[a]Measured based on dilution experiments in $CDCl_3$ at room temperature. Errors are based on values of association constants obtained from triplicate runs. [b]Value from ref 10a.

Our original quadruply H-bonded duplexes have association constants that are 2 orders of magnitude, i.e., in the $10^4$ $M^{-1}$ range,[10] larger than the dimerization constant of **5a·5a**. The low stability of **5a·5a**, which impairs its effectiveness as an association unit, can be attributed to the linker based on 4-aminobutyric acid. Compared to glycine, this longer linker increases the conformational freedom of **5a** and thus enhances the entropic barrier for forming **5a·5a**.

To address the low stability of **5a·5a** and its analogues, strands **5b**, **6**, and **7** were designed by connecting basic H-bonding units derived from 5-aminosalicylic acid with linkers based on the readily available *m*-aminobenzoic acid, isophthalic acid, and *m*-phenylenediamine (Figure 4). These rigid linkers

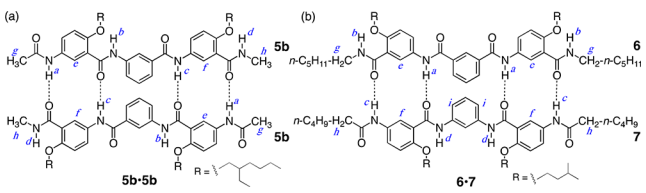



**Figure 4.** Design of oligoamide strands (a) **5b**, and (b) **6**, and 7 and their corresponding H-bonded duplex **5b·5b** and **6·7**.

should reduce conformational flexibility and also ensure extended conformations on the oligoamide strands, which facilitate the pairing of these strands into duplexes. Duplex **5b·5b**, like **5a·5a**, shares the same H-bonding sequence (ADAD) with **1·1** while having association specificity different from **1·1** because of the widened spacing between its two basic H-bonding units. Another advantage of incorporating the rigid aromatic linkers is that H-bonding sequences, such as ADDA and DAAD, of **6** and **7**, that cannot be generated with our previous designs based on glycine linkers, are now available.

A potential problem with **5b·5b** and **6·7** is that the two benzene rings that serve as the linkers in each duplex could impose steric hindrance that may obstruct the formation of the duplex. This possible complication was ruled out computationally. The energy-minimized structures of **5b·5b** and **6·7**, obtained by calculation at the B3LYP/6-31G(d,p) level of theory with chloroform as the solvent (Figure 5), indicate that

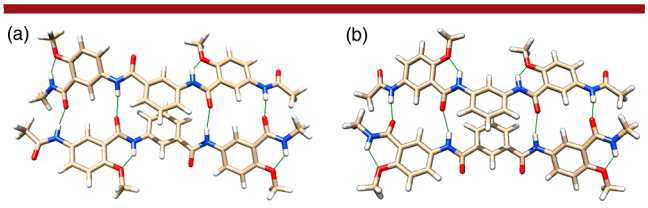



**Figure 5.** Energy-minimized structures of (a) duplex **5b·5b** and **6·7**. All side and end groups are replaced with methyls. H-bonds are indicated as dashed green lines.



DOI: 10.1021/acs.orglett.8b00283
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the two benzene rings of the central linker indeed face each other, but with one ring being "lifted" and the other being "pushed down". This leads to bent conformations for the individual strands, which accommodate both the interstrand H-bonds and the stacking of the aromatic linkers. In each duplex, the benzene rings of the linkers are parallel and within stacking distance (~3.8 Å), which may provide additional stability.

Strands **5b**, **6**, and **7** were synthesized based on procedures similar to those we reported before[10] (Scheme S1 and the SI).

In $CDCl_3$, the $^1H$ resonances of protons *a* and *c* (9.86 and 10.01 ppm) of **5b** (10 mM) show significant downfield shifts relative to the aniline NH resonance of compound **5′** (at 10 mM, 7.91 ppm), indicating the involvement of these protons in intermolecular H-bonding interactions.

Diluting **5b** in $CDCl_3$ (from 50 to 0.16 mM) revealed significant shifts of amide protons *a* and *c* (Figure 3b). In contrast, the $^1H$ signals of intramolecularly H-bonded protons *b* and *d* exhibit negligible shifts in the same concentration range (Figure 3b). Nonlinear regression analysis of the concentration-dependent changes in the chemical shifts of proton *c* yielded a dimerization constant of $(3.0 \pm 0.5) \times 10^4$ $M^{-1}$ (Table 1). Thus, replacing the flexible linker of **5a** with a rigid aromatic one results in strand **5b** with a dimerization constant that is in line with those of quadruply H-bonded duplex **1·1**, **2·2**, or **3·4**.

Upon mixing **6** and **7** (1:1, 2.5 mM/strand) in $CDCl_3$, amide proton *a* of **6** moved downfield, from 9.00 ppm for the single strand to 10.00 ppm for the 1:1 mixture. Proton *c* of **7** also showed a downfield shift from 7.27 ppm of the single strand to 9.22 ppm of the 1:1 mixture. In contrast, protons *b* and *d*, which are intramolecularly H-bonded, experienced much smaller shifts (0.32 and 0.12 ppm) between the single strands and the 1:1 mixture. These observations demonstrate that **6** and **7** associate via intermolecular H-bonding.

The $^1H$ NMR signal of an aromatic proton located near (≤7 Å) another aromatic ring is known to move upfield[18] that indicates parallel stacking of the two aromatic rings.[19] The resonance of proton *e* shifts 0.43 ppm upfield, from 7.56 ppm of single strand **6** to ppm 7.13 of duplex **6·7**. Aromatic proton *f* of **7** should undergo similar shift upon mixing **6** and **7** although its signal could not be assigned due to signal overlap. The upfield shift of proton *e* demonstrates that the aromatic rings of the linkers are brought into close proximity, which is consistent with the optimized structure of **6·7**.

The 1:1 mixture of **6** and **7** in $CDCl_3$ was diluted from 40 mM to 0.078 mM, and the concentration-dependent shifts of amide proton *a* of **6** was fitted to a 1:1 binding motif,[10,20] which revealed an association constant of $(4.3 \pm 0.8) \times 10^4$ $M^{-1}$ (Table 1). The self-association of strands **6** or **7** was probed by diluting a solution of either strand in $CDCl_3$ from 40 mM to 0.156 mM. The concentration-dependent shifts of proton *a* of **6** and proton *c* of **7** led to "dimerization" constants of $260 \pm 44$ $M^{-1}$ for **6** and $18 \pm 2$ $M^{-1}$ for **7** (Table 1). In comparison to the association constant of **6** and **7**, the self-association of **6** or **7** is either much weaker or negligible, and thus has little effect on the formation of heteroduplex **6·7**.

The difference in the chemical shifts ($\Delta\delta$) of amide proton *c* of **7** in a series of solutions with different molar fractions of **7** ($X_7$) and that of single strand **7** in $CDCl_3$ was monitored, while the total molar concentration of the two strands was held constant at 5 mM. The values of $\Delta\delta \cdot X_7$, which is proportional to the complex of **6** and **7**,[21] are plotted against $X_7$ (Figure 6). The resultant Job plot exhibits a peak with $X_7$ being 0.5, which confirms the 1:1 stoichiometry for the association of **6** and **7** and thus the formation of duplex **6·7**.

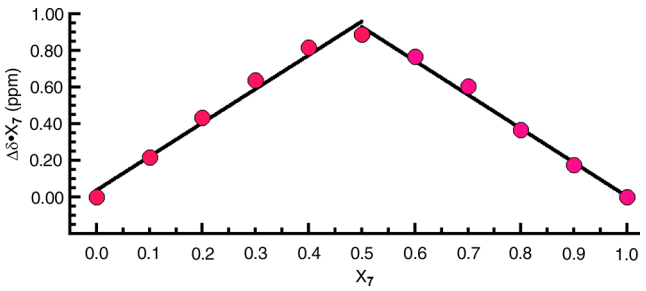


**Figure 6.** Job plot of **6** and **7** in $CDCl_3$. The total concentration of **6** and **7** was kept at 5 mM.

The NOESY spectrum of **5b·5b**, measured in $CDCl_3$ (10 mM, 400 MHz, 300 K, mixing time = 0.3 s), reveals NOEs between protons *a* and *f*, *c* and *e*, and *g* and *h* (Figure S2). The ROESY spectrum of **6·7**, measured in $CDCl_3$ (5.5 mM of each strand, 400 MHz, 298 K, mixing time = 0.3 s), shows ROEs between protons *a* and *f*, *a* and *i*, *e* and *f*, and *g* and *h* (Figure S3). Since within each single strand the distance between each pair of protons is too long to give the observed NOE or ROE cross-peak, the detected cross-peaks must correspond to interstrand contacts between otherwise remote protons that are placed into close proximity in the duplexes.

By widening the spacing between basic H-bonding units, oligoamide strands carrying H-bonding sequences that defined new association specificity are generated. The limitation of a linker derived from 4-aminobutyric acid, which results in lowered stability and thus renders duplex **5a·5a** and its analogues ineffective as association units, is overcome by incorporating aromatic linkers based on *meta*-disubstituted benzene residues. Instead of introducing steric hindrance that would obstruct the association of the individual strands, the aromatic linkers, being placed within stacking distances, do not compromise the formation of H-bonded homoduplexes **5b·5b** and heteroduplex **6·7**. The H-bonded duplexes described herein have expanded the diversity of H-bonded duplexes with new association specificity or new H-bonding sequences. More interestingly, this series of duplexes, with their aromatic linkers that can be further tuned electronically, may provide a platform for incorporating and specifying noncovalent forces besides H-bonding, which may lead to the creation of association units that operate in media in which H-bonding is ineffective.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00283.

Synthetic procedures; analytical data; NMR spectra; computational details (PDF)

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DOI: 10.1021/acs.orglett.8b00283
Org. Lett. XXXX, XXX, XXX−XXX

### Author Contributions

⊥Y.Z. and R.C. contributed equally.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the US National Science Foundation (CBET-1512164), American Chemical Society-Petroleum Research Fund (PRF No. 58364-ND7), and Biomedical Research Council, Agency for Science, Technology and Research of Singapore, for support.

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DOI: 10.1021/acs.orglett.8b00283
*Org. Lett.* XXXX, XXX, XXX−XXX