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Intramolecular hydrogen bonding of nucleobases

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Abstract—The intramolecular hydrogen bonding of a series of linked uracil, thymine and adenine derivatives is described. The nucleoside bases have been linked by semi-flexible spacers and the chemical shifts and $\Delta\delta NH/\Delta T$ values for the nucleoside NH protons confirm the strong intramolecular hydrogen bonding motif.

The design of artificial DNA-like complementary purine–pyrimidine base pairs has enabled a better understanding of the relationship between structural variations and complex stability.[1–3] The design of ligands and receptors that will preferentially bind a specific DNA motif requires a detailed understanding of the hydrogen bonding ability of purine and pyrimidine bases, including normal and reversed Watson–Crick as well as Hoogsteen bonding (Fig. 1).[4] Artificial systems that lack some form of conformational rigidity and exhibit poor solubility often display weak binding for dimerization.[1,5] In addition to the traditional duplex formation associated with AT(U) or CG complementary base pairs, the formation of localized triplet structures has been recognized as an important contributor for the binding of oligonucleotides to double stranded DNA.[5–7] We report in this paper the preparation and hydrogen bonding properties of a series of nucleobases containing spacers with both a rigid ethynylbenzene and a flexible alkyl chain.

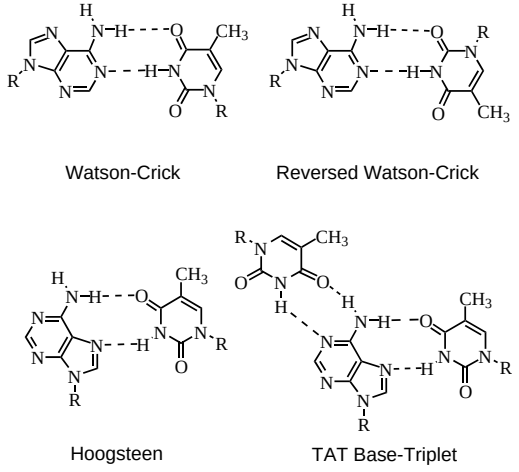

Figure 1. Hydrogen bonding in nucleoside bases.

The preparation of receptors **4**–**7** commenced with the alkylation of 1,10-decanediol with 3-iodobenzylbromide in the presence of sodium hydride to give **1** in 30% yield (Scheme 1). Subsequent coupling of **1** with trimethylsilylacetylene in the presence of $Pd(PPh_3)_4$ and CuI[8] gave **2** in 99% yield, and desilylation with Bu_4NF yielded **3** in 89% yield. Palladium-catalyzed coupling of an excess of **3** with 3′,5′-diacetoxy-5-iodo-deoxyuridine gave a mixture of bis-coupled product **4** in 23%[9] and mono-coupled product **5** in 39% yield. Similarly, palladium catalyzed coupling of an excess of **3** with 2′,3′,5′-triacetoxy-8-bromoadenosine gave a mixture of bis-coupled product **6** in 14% and mono-coupled product **7** in 27% yield. The mono-coupled product **5** was subsequently coupled with 2′,3′,5′-triacetoxy-8-bromoadenosine to give **8** in 17% yield.

The preparation of DNA base pair triplet models commenced with the alkylation of thymine with various alkynyliodides in the presence of potassium carbonate as described in Scheme 2 and the alkylation of adenine with 3,5-diiodobenzylbromide in aqueous NaOH in the presence of Aliquat 336 to give **10** (Scheme 3).[10] The palladium catalyzed coupling of **10** with alkynylthymines **9a**–**f** then gave **11a**–**f**[11] (Scheme 3).

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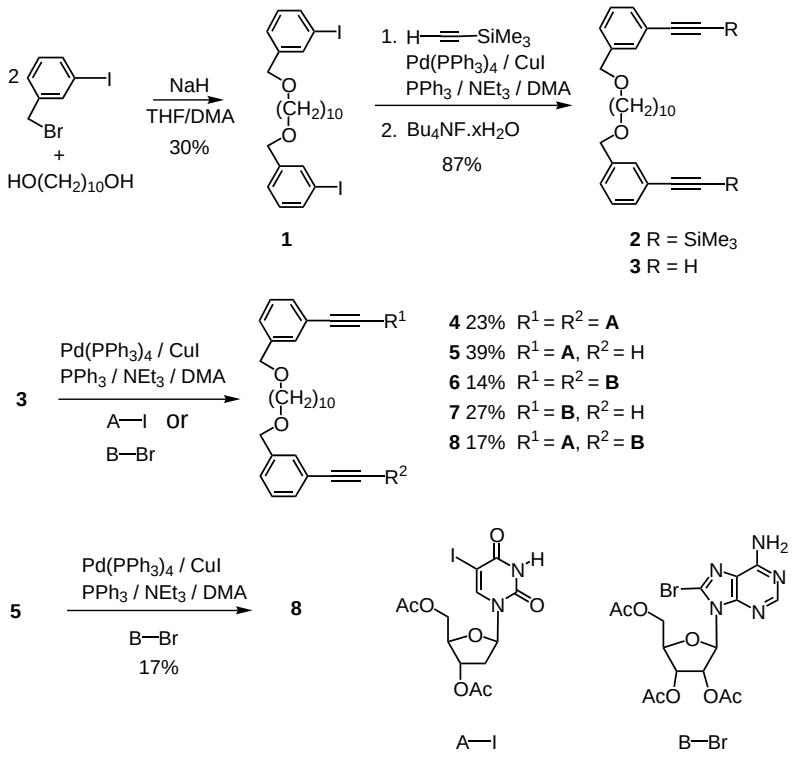
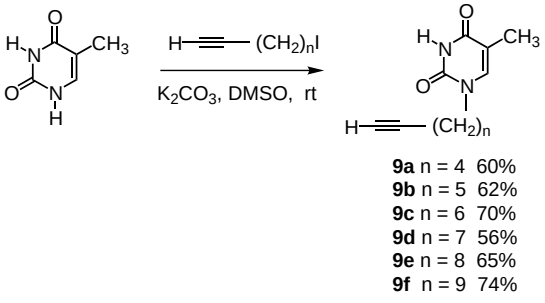


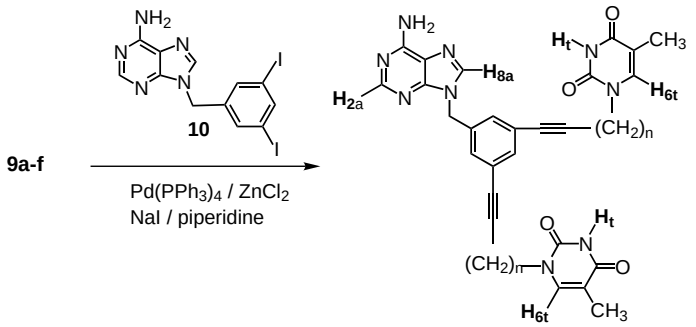
Scheme 1. Preparation of DNA base pair models **4**–**8**.



Scheme 2. Preparation of alkynylthymines **9a**–**f**.

Compound **5** was not capable of forming intramolecular hydrogen bonds as it contains only one nucleobase, so the ^{1}H NMR chemical shift for the uracil NH proton at 8.05 ppm could be used as a standard. The chemical shift for the NH protons in bis-2′deoxyuridine derivative **4** was 8.86 ppm (1 mM at room temperature in $CDCl_3$) under conditions known to minimize intermolecular hydrogen bonding,[12] indicating that the two uracil residues were capable of intramolecular hydrogen bonding. Compound **8**, containing both a purine and a pyrimidine residue, displayed a NH resonance for uracil at 9.65 ppm, again reflecting a strong intramolecular hydrogen bond. The chemical shift for the NH_2 protons at 5.66 ppm for mono-adenine derivative **7**, under similar conditions, could also be used as an internal standard. The chemical shift for the adenine NH_2 protons for bis-adenine **6** was 5.89 ppm, indicative of a weak intramolecular hydrogen bond between the two adenine units. The $\Delta\delta NH/\Delta T$ values for the NH protons were obtained by variable temperature NMR experiments from −60 to 60°C. Compound **8** displayed an extraordinarily high value of 42.6 ppb/K for the NH proton of the uracil component, much larger than the corresponding value of 23.2 ppb/K for **4**. Furthermore, the $\Delta\delta NH/\Delta T$ value for the amino group of the adenine residue in **8** was 21.1 ppb/K, while the corresponding value for compound **6** was only 9.6 ppb/K, confirming the presence of an efficient hydrogen bonding arrangement involving the complementary base pairs.

Fig. 2 shows the downfield region of the ^{1}H NMR spectra for compounds **11a**–**f** at 2 mM in $CDCl_3$. The ^{1}H NMR signals for the thymine H-6 protons and the protons of the central phenyl ring appear almost at the same position in compounds **11a**–**f**. The chemical shifts for the adenine H-8 protons vary with the length of the alkyl spacer between the uracil rings, whilst the signal for the adenine H-2 protons appeared relatively constant. The alternating changes in the chemical shifts for the thymine H-6 and the adenine H-8 protons from **11a** through to **11f** indicates that when the alkyl chain contains an odd number of carbons the intramolecular hydrogen bonding increases and that when the alkyl chain contains an even number of carbons the intramolecular hydrogen bonding decreases.



Scheme 3. Preparation of DNA base pair triplet models **11a**–**f**.

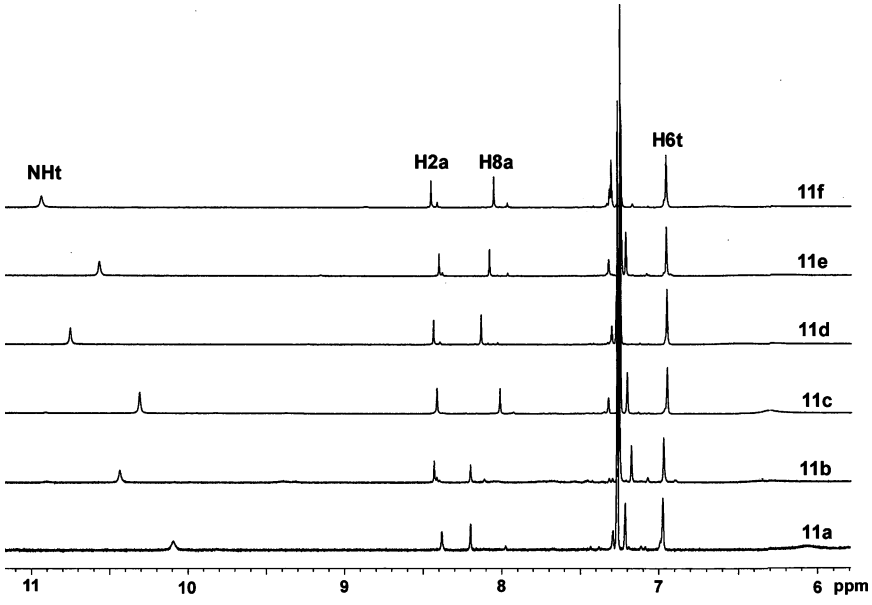


Figure 2. ^{1}H NMR spectra of **11a**–**f** at 2 mM in $CDCl_3$.

References

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9. **1,10-(Decandiol)-di{3-[5-(3′,5′-di-*O*-acetyl-2′-deoxy uridine)ethynyl]benzyl} ether (4)**
   To a solution of 3′,5′-diacetoxy-5-iododeoxyuridine (0.248 g, 0.5 mmol) and PPh_3 (0.026 g, 0.10 mmol) in NEt_3/DMA (20 ml; 1:5) under N_2, were added $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol), CuI (0.019 g, 0.10 mmol) and **3** (0.320 g, 0.8 mmol), respectively. The dark red solution was heated at 80°C for 2 h. The reaction solvents were removed in vacuo. The residue was purified on silica gel (MeOH:acetone:CH_2Cl_2; 1:5:70) to give **4** (0.060 g) and **5** (0.112 g), in an overall yield of 57%. For **4** ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 1.19 (m, 16H, CH_2); 1.61 (m, 4H, CH_2); 2.13 (s, 6H, CH_3); 2.19 (s, 6H, CH_3); 3.45 (t, 4H, $J=6.6$ Hz, CH_2); 4.32, 4.39 (m, 4H); 4.39 (s, 4H, CH_2); 5.28 (m, 2H); 6.35 (m, 2H); 7.32 (m, 8H, Ar); 7.90 (s, 2H); 8.92 (s, 2H, NH). Calcd for $[M+H]^+$ $C_{54}H_{63}N_4O_{16}$: 1023.4238. Found: 1023.4190.
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11. **9-{3,5-Di[(11-undecyn-1-yl)-1-thyminyl)]-1-benzyl} adenine (11f)**
    To a solution of 1-(3,5-diiodo-1-benzyl)adenine (0.108 g,

0.25 mmol) and PPh_3 (0.026 g, 0.10 mmol) in piperidine (5 mL) under N_2, were added $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol), $ZnCl_2$ (0.0136 g, 0.10 mmol), NaI (0.015 g, 1.0 mmol) and *N*-9-undecynylthymine (0.143 g, 0.50 mmol), respectively. The dark red solution was heated at reflux (110°C) for 1 h. The solvent was removed in vacuo and the residue was purified on silica gel (MeOH:CH_2Cl_2; 10:90) to give **11f** as a white solid (0.129 g, 67%). ^1H NMR ($CDCl_3$, 2 mM, rt, 600 MHz): δ (ppm) 1.33, 1.54, 1.55, 1.67, 1.89 (m, CH_2); 1.93 (s, 6H, CH_3); 2.37 (t, 4H, $J=6.6$ Hz, CH_2); 3.69 (t, 4H, $J=7.8$ Hz, CH_2); 5.27 (s, 4H, CH_2); 6.70 (s, 2H, NH_2); 6.97 (s, 2H, CH, thymine); 7.32, 7.33 (m, 4H, Ar); 8.06 (s, 1H, H8, adenine); 8.46 (s, 1H, H2, adenine); 10.94 (s, 2H, NH, thymine). Calcd for $[M]^+$ $C_{44}H_{55}N_9O_4$: 773.4377. Found: 773.4373.

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