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Substituent Control over Dimerization Affinity of Triply Hydrogen Bonded Heterodimers

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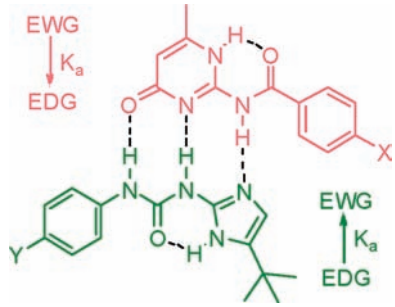
ABSTRACT



Linear arrays of hydrogen bonds represent important elements of the supramolecular toolkit for receptor design, assembly of supramolecular polymers, and other well-defined supramolecular structures. It is illustrated that remote substituent effects control dimerization affinity in a predictable manner using a conformer independent ureidoimidazole DDA motif and its amidoisocytosine based AAD partner.

The design and synthesis of linear arrays of hydrogen bonds,[1−5] capable of high affinity and high fidelity interaction[6,7] with complementary partners, is a key area in modern supramolecular chemistry. Such motifs form important components of supramolecular polymers[5,8−10] and other well-defined supramolecular assemblies.[11] A number of strategies and control features can be employed to tune the dimerization affinity of both homo and heterocomplementary arrays.[1,2,5] In addition to the number of hydrogen bonds, the arrangement[12−14] and spacing between donors (D)/acceptors (A)[15] within an array play a key role, as do the tauto-

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meric[16−18] and conformational preferences.[19−23] It has been shown that tautomeric and conformational preferences of linear arrays can be modulated through remote substituent effects.[16,20,24] In contrast, the ability to predictably control dimerization affinity through electronic substituent effects has not been demonstrated; however, this feature has been noted to play a role. As early as 1967, Kyogoku and co-workers[25] noted variation in the stability of adenine-thymine/uracil pairs incorporating substituents directly attached to the pyrimidine/purine ring systems. Meijer and co-workers also highlighted a prominent role for acylation, in controlling dimerization affinity of synthetic DAD-ADA arrays.[26] Although some systems exhibit the expected increase in dimerization affinity due to addition of the electron-withdrawing acyl group, others do not because of changes in the preferred conformation that result upon acylation. Herein we illustrate experimentally that remote substituent effects control dimerization affinity in a predictable manner for a series of DDA-AAD arrays. In addition, we present theoretical evidence from molecular modeling studies to support our findings.

In this study we exploited the ureidoimidazole **2a** and amidoisocytosine **1a** motifs previously introduced by our group.[23] The ureidoimidazole motif **2a** is suitable for studying remote electronic substituent effects because although the hydrogen-bonding array may adopt two tautomeric configurations, these are very similar and either of the conformations that must be adopted as a consequence of the enforced intramolecular hydrogen bonding presents a DDA array (Figure 1). For **1a**, intramolecular hydrogen bonding limits the tautomeric and conformational diversity available to the amidoisocytosine motif. Two different tautomers are possible, only one of which presents the required AAD array. Similarly to the syntheses of AAD **1a** and conformer independent DDA **2a**,[23] we synthesized a series of these compounds with different substituents in the *para* position of the aromatic ureido/amido ring system as illustrated in Scheme 1 (see Supporting Information for details). The ^{1}H NMR spectra of all compounds exhibit broad resonances for the NH protons, which is consistent with fast interconversion between all possible tautomers and conformers.

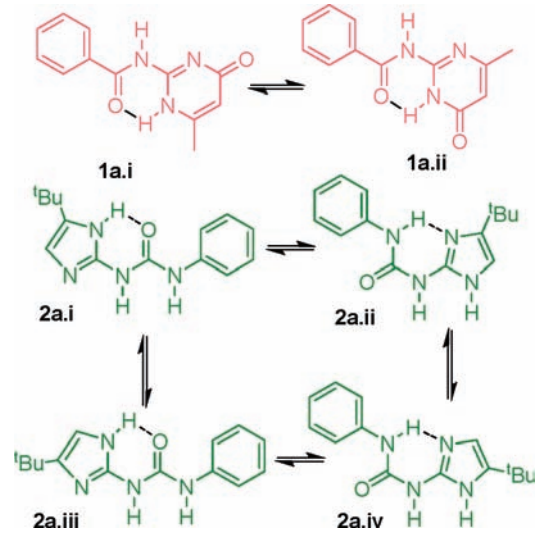
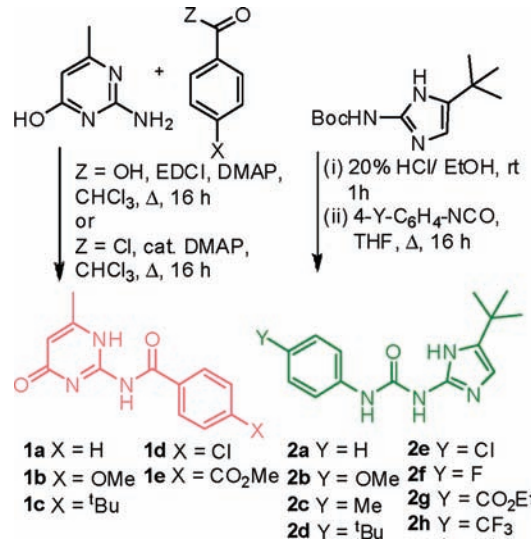


Figure 1. Possible tautomeric and conformational configurations available to compounds **1a** and **2a**.

Scheme 1. Syntheses of Compounds **1** and **2**



^{1}H NMR titrations were performed in deuterated chloroform and analyzed using HypNMR[27] (see Supporting Information for procedural details). Dimerization constants were also obtained for each compound (see Supporting Information); however, in concordance with our earlier observations for the parent compounds **1a** and **2a**, all of the compounds were found to exhibit negligible self-association/dimerization. This factor was therefore not considered further in our determination of the association constants. With the available compound set, we were able to perform a sufficient number of titrations with both amidoisocytosine **1a** (X = H) and ureidoimidazole **2a** (Y = H), where the substituent

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Table 1. Association Constants Determined by ^{1}H NMR Titrations (300 MHz, $CDCl_3$) for the Interaction between Compounds **1** and Compounds **2**

complex	$K_a \times 10^3$ M^{-1}	complex	$K_a \times 10^3$ M^{-1}
1a·2a	33 ± 16	**1a·2b**	3.8 ± 2.1
1b·2a	41 ± 3.9	**1a·2c**	3.8 ± 2.2
1c·2a	25 ± 20	**1a·2d**	1.9 ± 0.8
1d·2a	18 ± 13	**1a·2e**	16 ± 8.4
1e·2a	10 ± 7.9	**1a·2f**	8.1 ± 2.8
		1a·2 g	84 ± 22
		1a·2 h	86 ± 34

on the complementary partner is varied, to establish a trend in each case. Each titration was performed in triplicate with the standard deviation given as the error. For the amidoisocytosine series association toward **2a** ranges from 40,000 M^{-1} (Y = OMe) to 10,000 M^{-1} (Y = CO_2Me) (Table 1); this 4-fold variation represents a minor effect. In contrast, the variation in association constants for binding of **1a** to the ureidoimidazole series is much more dramatic, covering almost 2 orders of magnitude from 3800 M^{-1} (Y = OMe) to 86,000 M^{-1} (Y = CO_2Me).

The error in determining association constants using ^{1}H NMR titration can be high; indeed, an order of magnitude variation in the association constants determined for the thymine-diamidopyridine interaction has been reported.[26,28] However, for this internally consistent set of experiments, the ureidoimidazole series *qualitatively* correlates with the Hammett parameter σ (Figure 2).[29] For the ureidoimidazole series a simplistic explanation for the effect can be made on the basis of electron-withdrawing substituents on the phenyl ring of the ureidoimidazole stabilizing negative charge development on the nitrogen atom of the NH donor, making it a more effective hydrogen bond donor and leading to a higher K_a. For the amidoisocytosine series the situation is more complicated. It has previously been suggested that the

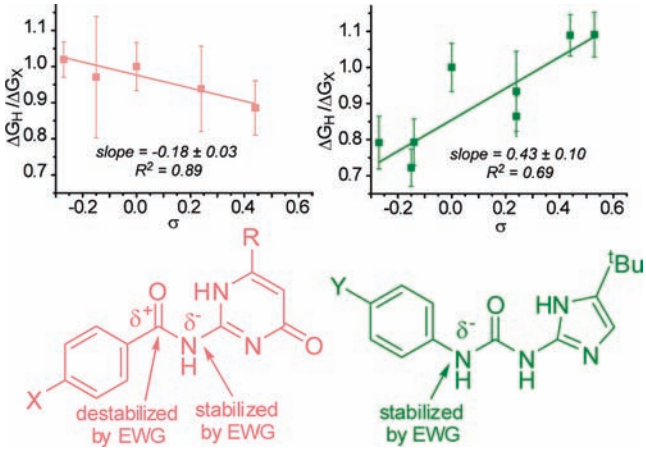

Figure 2. Hammett plots for the interaction of **2a** with **1a**−**1e** and for the interaction of **1a** with **2a**−**2h** (conditions for determination of association constants as for Table 1).

amide bond insulates against electronic substituent effects,[30] and this seems reasonable here; electron-withdrawing groups destabilize positive charge development on the carbonyl carbon, making it a poorer intramolecular hydrogen-bond acceptor, but stabilize negative charge development on the NH nitrogen, making it a better hydrogen-bond donor. The two properties effectively cancel one another, and there is little meaningful change across the series.

In the absence of detailed structural information, we turned to molecular modeling to provide support for these results. Calculations at B3LYP/6-31G* basis set using Gaussian03[31] on the binding conformation of the monomers were performed, and electrostatic potential surfaces were added (Figure 3). The potential along the recognition face of the ureidoimidazole series varies significantly depending on the substituent present, whereas there is less of a change for the amidoisocytosine series. The amidoisocytosine pyridone functional group has a significant negative potential that is unaffected by proximal substituents. In contrast the ureidoimidzaole has a positive potential centered on the urea group that changes considerably depending on the substituent. Mulliken analysis[32] (see Supporting Information) supports the visual confirmation of the effect.

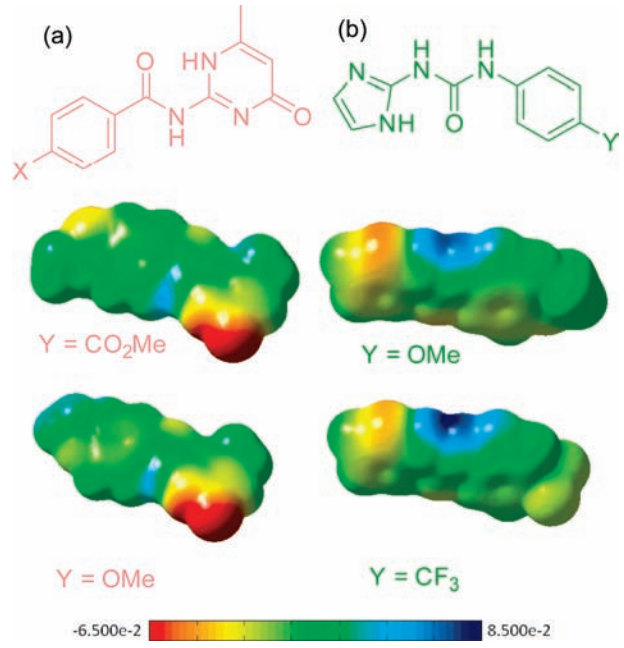

Figure 3. Electronic potential surfaces for (a) amidoisocytosine and (b) ureidoimidazole series with different substituents (^{t}Bu group on ureidoimidazole not included in electronic structure calculations).

In conclusion we have illustrated that dimerization affinity of linear arrays can be predictably controlled through remote substituents. We expect these observations to be broadly applicable to other linear arrays. In terms of using such arrays for supramolecular assembly, the implications are 2-fold: (a) the ability to systematically control dimerization affinity means an appropriate array from the available toolkit can be selected and functionalized as necessary without recourse

to design and synthesis of new motifs, and (b) an appropriate choice of linking chemistry to the array can be selected that has a predictive effect when the array is to be employed as a component of a self-assembling system. For instance, given the key role of dimerization affinity in supramolecular polymers[5,8−10] and the use of ester[33] and ether[34−36] linkages to append hydrogen bonding groups to polymer chains, this is likely to have a significant effect on polymer properties. It is worth noting in this context that high affinity motifs are not a prerequisite for supramolecular polymerization; supramolecular polymers have previously been described where dimerization constants are smaller than the magnitude of the effects described in the current study.[37] Our group will explore this avenue of investigation in the future.

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Supporting Information Available: Synthetic procedures, characterization, details of electronic structure calculations, details of binding studies, and additional titration curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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