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Designed Molecular Switches: Controlling the Conformation of Benzamido-diphenylacetylenes

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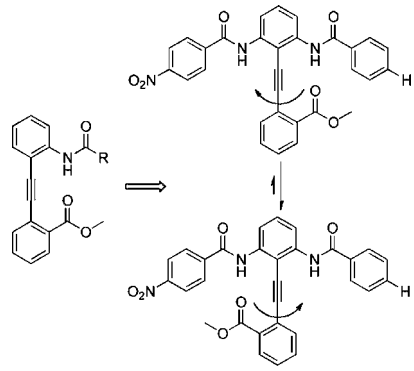
ABSTRACT



With the goal of creating a molecular switch, the hydrogen-bonded diphenylacetylene structure has been modified such that an equilibrium now exists between two intramolecular H-bonded states. Through X-ray crystallography and ^{1}H NMR analysis it is shown that this equilibrium can be biased in a predictable manner by modulating the relative acidity of the amide NH's.

Molecules that can change conformation in a stimulus-dependent fashion are valued synthetic targets due to their potential use as logic gates,[1−3] information storage systems,[4,5] sensors,[6] and as stepping stones toward the design of angstrom scale machines.[7] In light of the myriad applications for switches, many structural motifs have been pursued in the past 15 years that exhibit a conformational change based upon a variety of stimuli.[7−17]

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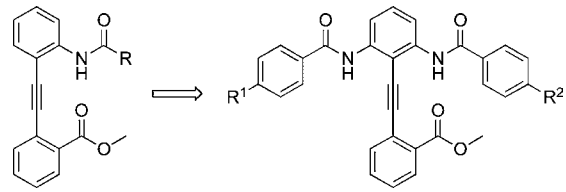


Figure 1. Conceptual transformation of the classical hydrogen bonded diphenylacetylene into a molecular switch.

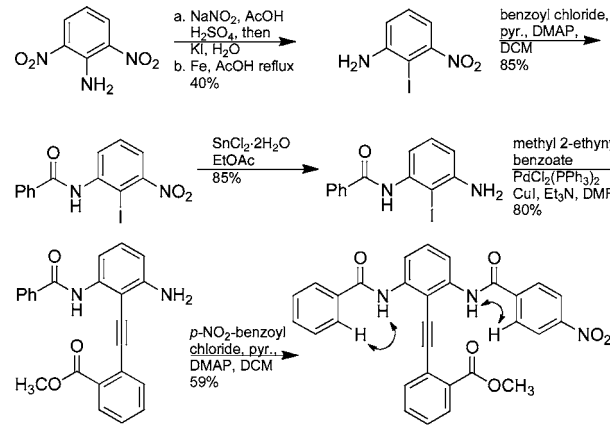
Our interest in the design of β-strand mimetics stabilized by an intramolecular hydrogen bond across an alkyne spacer[18] prompted us to investigate the use of this system as a new switching entity. The key feature of this scaffold is the 10-membered H-bonded ring first described by Kemp[19,20] (Figure 1), which increases the rotational barrier around the phenyl-alkyne bond from 0.6 to 7.19 kcal/mol.[21,22] The utility of this intramolecular interaction has been established in the stabilization of helical foldamers,[22−24] molecular wires,[25] a proteomimetic,[18] and an ion sensor.[26]

Transforming the H-bonded diphenylacetylene unit into a switch requires that we (i) set up a conformational equilibrium between two forms, (ii) demonstrate that the equilibrium can be biased in a predictable fashion, and (iii) show that this bias can be altered through the application of a stimulus. Herein we report our synthetic and analytical stratagem for accomplishing parts i and ii.

Addition of a second amide, *ortho* to the alkyne spacer (Figure 1), opens up the required equilibrium providing two donors for intramolecular H-bonding. We can potentially bias the benzoate H-bond acceptor to prefer one amide over the other by conjugating electron-withdrawing and -donating groups to the amide carbonyls. If the carbonyl is electron-rich, the NH bond should be less acidic thus making the amide a weaker H-bond donor. Conversely, an electron-poor carbonyl will increase the acidity of the NH making it a stronger H-bond donor.

para-Substituted benzoic acids are ideal electron-modulating groups because of the range of available derivatives with well characterized σ-Hammett values.[27] These values can be used to quantify the effect of subsitution on acidity and, in 4-substituted benzamides, the strength of H-bond donation.[28,29] Accordingly, we should be able to use the $\Delta\sigma$ between the two benzamides in our system to predict which NH is the preferred H-bond donor.

Scheme 1. Synthesis of **1**



1

To test this idea, compound **1**, which balances pNO$_2$-benzamide with benzamide, was assembled from 2,6-dinitroaniline according to Scheme 1. The pNO$_2$-amide has less electron density than benzamide, as described by $\Delta\sigma = 0.78$, and so the pNO$_2$-amide should be the preferred H-bond donor.

Single crystal X-ray diffraction of **1** (Figure 2) shows that the preferred H-bond donor is indeed the pNO$_2$-benzamide with a NH···OC distance of 2.23 Å. There is also a steric clash between the methyl ester and the pNO$_2$-phenyl that creates a 50° dihedral angle between the ring and the amide carbonyl.

With this result in hand, we expanded our analysis to the solution phase using ^{1}H NMR. The spectrum of **1** shows the pNO$_2$-NH at 9.43 and the benzamide NH at 9.07 ppm (4 mM, CDCl$_3$). These resonances are assigned by the NOE between these peaks and the aryl protons *ortho* to each carbonyl (Scheme 1).

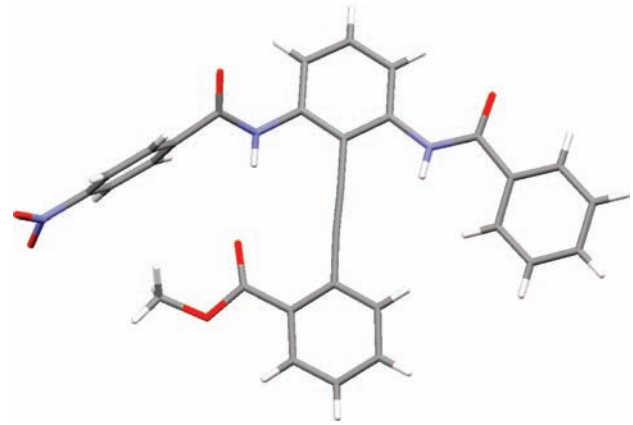


Figure 2. Single crystal X-ray structure of **1**.

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Kemp-type diphenylacetylenes show proton spectra with non-H-bonded amide resonances around 8 ppm and H-bonded amide resonances from ~9 to 9.2 ($CDCl_3$).[22,24] That both amides in our compound resonate around this latter range suggests that each could be involved in a hydrogen bond. Intermolecular H-bonding, a concentration-dependent phenomenon, is ruled out by the fact that the NH shifts of **1** stay constant as the solution is diluted from 16 to 0.063 mM ($CDCl_3$). Thus, the downfield shift of both NH's must be due to an equilibrium between the conformations of the benzoate acceptor.

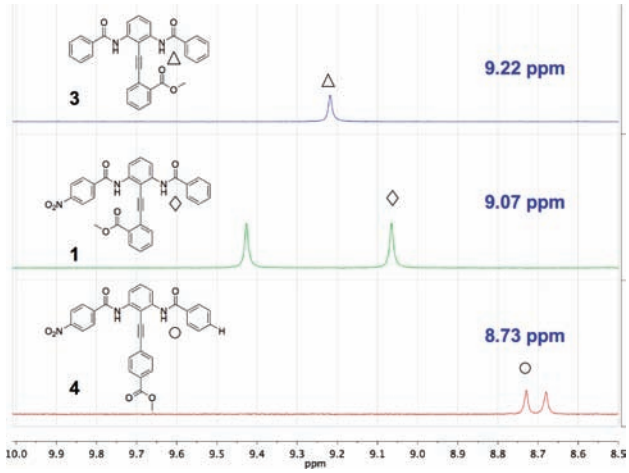

Figure 3. ^{1}H NMR amide resonances of compounds **3**, **1**, and **4** from top to bottom (4 mM in $CDCl_3$). The benzamide resonances are denoted by △, ◇, and ○ for **3**, **1**, and **4**, respectively, and the chemical shifts are also reported.

To determine the position of that equilibrium, two reference compounds were designed. The first reference positions an unsubstituted benzamide on both sides (**3**, Figure 3) and has a $\Delta\sigma = 0$. As such, the methyl ester must partition equally between the amides, providing a definition of the benzamide NH chemical shift in a system where no conformational preference exists (50/50 definition). The second reference compound (**4**, Figure 3) juxtaposes *p*NO_2-benzamide with benzamide; however, in this molecule the ester is *para* to the acetylene linker. Because the ester cannot influence the amide chemical shifts (again intermolecular association is ruled out by the same dilution assay), these values represent the resonances of **1** if they are not H-bonded (100/0 definition).

We expect that if the *p*NO_2-NH is preferred in solution, then the other NH will be more shielded, as the result of a decrease in H-bonding, and will resonate between our two definitions. Figure 3 shows that the benzamide resonance for **1** does appear between that of **3** and **4**, demonstrating that the conformational equilibrium is biased toward the *p*NO_2-benzamide.

This analysis also determines the magnitude of the conformational bias from the degree to which the benzamide NH has shifted upfield. Dividing the difference in chemical shift between **3** and **1** by the difference in chemical shift between **3** and **4**, we find that this initial system has a preference of 30.6% for the NO_2−NH.

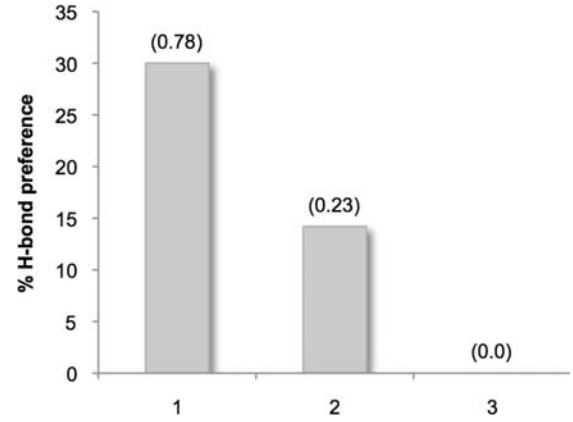

Figure 4. Comparison of the % H-bond preference for compounds **1**−**3**. The $\Delta\sigma$ values appear at the top of each bar.

Having shown that the solid-state and solution-phase conformations can be biased in a predictable manner, we next investigated the sensitivity of conformational preference toward a varying $\Delta\sigma$. Toward this end, compound **2** (Figure 1, $R^1 = H$, $R^2 = Cl$) was prepared and analyzed in the same fashion as **1**. Comparison of **2** with its appropriate control molecules (Figure S2 in Supporting Information) shows that decreasing $\Delta\sigma$ from 0.78 to 0.23 attenuates the H-bond preference from 30.6% to 14.2% (Figure 4).

In summary, we have shown (i) evidence of a conformational equilibrium in these bis(benzamido)-diphenylacetylene molecules and (ii) that electronic modulation can be used to attenuate or enhance benzamide H-bond donation strength, resulting in a measurable conformational bias. Indeed, the sensitivity of the conformational equilbrium toward a varying $\Delta\sigma$ suggests the utility of this scaffold for dynamic switching, and we are currently working to develop this facet.

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Supporting Information Available: General experimental methods, procedures, NMR spectra, and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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