Molecular Switches

DOI: 10.1002/anie.201106241

pH-Dependent Conformational Switching in 2,6-Benzamidodiphenylacetylenes**

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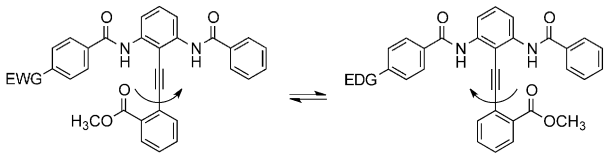
The conformational dynamism of macromolecules in response to changing pH is essential to the maintenance of many biological systems.[1] However, due to the complexity of such systems the elements essential to conformational switching can be difficult to discern. Molecular switches, which are relatively easier to prepare and analyze, can help to identify these essential elements and employ them in new contexts.[2] With this application in mind we now report a pH-dependent switch based on our 2,6-benzamidodiphenylacetylene system.

Many structural motifs have been explored that behave as switches in response to changes in pH.[3] With a notable exception,[3d] these molecules tend to utilize intramolecular hydrogen-bonds to stabilize a particular conformation. Direct protonation of one H-bond acceptor changes that group to a H-bond donor, forcing the system to reconfigure to a new conformation.

While these studies characterize direct protonation as a tool for controlling conformation, an alternative approach employs remote protonation. The protein rhodopsin, for example, uses a conjugated π-system to link a basic imine to the spatially removed photo-switchable olefin. Thus, addition of a proton to the basic site electronically controls the absorption wavelength of the switch.[1a] In this way, it should also be possible to manipulate a H-bonded equilibrium through electronic modulation. A system of this type would involve a basic site, such as an electron-donating amine, that is removed from the H-bond network but linked through conjugated π-bonds. Addition of a proton to the basic site could then be communicated electronically to the H-bond network, causing it to switch conformation.

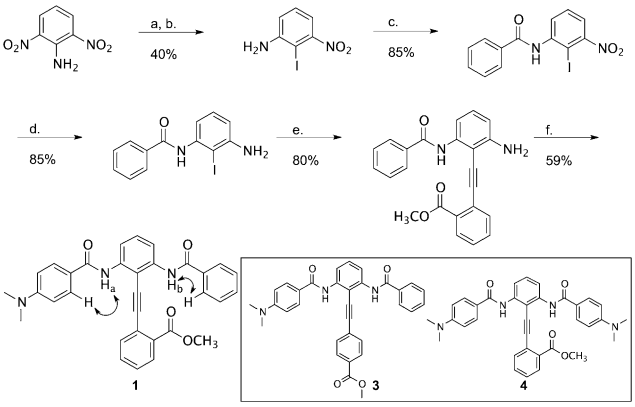
We have designed a H-bonded 2,6-benzamidodiphenylacetylene system that offers the ability for remote protonation (Scheme 1). Based upon Kemp's singly H-bonded β-sheet mimetic,[4] our scaffold contains two potential H-bond donors. The balance between the two conformations should be biased toward the amide NH that offers the strongest H-bond.



Scheme 1. Conjugation of electron-withdrawing (EWG) or -donating groups (EDG) to the H-bonded network can control the conformational equilibrium by increasing or decreasing the NH acidity.

The strength of a H-bond can be controlled by increasing or decreasing the acidity of the amide proton. For this task, 4-substituted benzamides provide a wide variety of electron-withdrawing or -donating groups spatially separated from the H-bond donors. Additionally, *para* substituted benzoic acids have well characterized Hammett values (σ_p)[5] that correlate acidity to the electronegativity of the *para*-substituent.[6]

To test this idea we prepared compound **1** according to Scheme 2. This compound compares the electron-donating *p*-NMe_2-benzamide ($\sigma_p = -0.83$) with benzamide ($\sigma_p = 0.00$).



Scheme 2. The synthesis and NOE contacts observed for **1** as well as the structures of **3** and **4**. Reagents and conditions: a) $NaNO_2$, H_2SO_4, AcOH then KI and H_2O, 70 °C; b) Fe^0, AcOH, reflux; c) benzoyl chloride, pyr., DMAP, DCM; d) $SnCl_2 \cdot 2H_2O$, EtOAc; e) methyl 5-alkynyl-benzoate, $[PdCl_2(PPh_3)_2]$, CuI, DMF, NEt_3, 80 °C; f) *p*-NMe_2-benzoyl chloride, pyr., DMAP, DCM.

The electron-donating character of *p*-NMe_2 should lower the acidity of its associated amide NH (NH_a) rendering it a weaker H-bond donor relative to the benzamide NH (NH_b). The X-ray crystal structure of **1** (Figure 1a) shows that the electron-donating *p*-NMe_2 group causes the H-bond acceptor to prefer the NH_b with a CO···N distance of 3.1 Å in the solid state. This structure also displays a steric interaction between the methyl benzoate and the benzamide ring causing a rotation of 49° out of the amide plane.

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[**] The authors would like to thank Dr. Sam Thompson (Oxford) and Prof. Marc Adler (N.I.U.) for helpful insights; Drs. Amber Thompson and Christopher Incarvito for crystallography; NSF (CHE-0750357) and the University of Oxford for funding.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106241.

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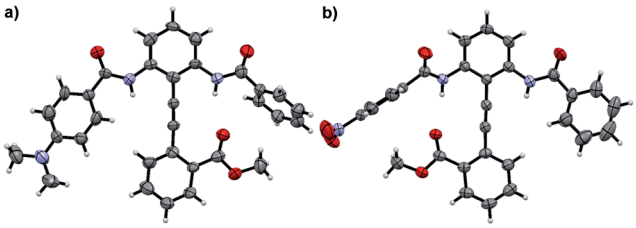
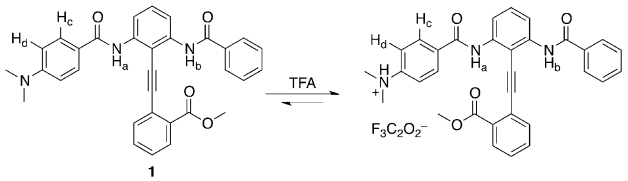


Figure 1. a) The solid-state structure of **1** depicting the methyl benzoate H-bonded to the benzamide NH; b) The solid-state structure of **2** depicting the methyl benzoate H-bonded to the *p*-NO_2-benzamide NH. The ORTEP ellipsoids are shown at the 50% probability level. Blue N, grey C, red O, white H.

We have previously reported that electron-withdrawing groups can be used to control the H-bonded conformation of our diphenylacetylene system. Compound **2**, which juxtaposes *p*-NO_2-benzamide ($\sigma_p = 0.78$) with benzamide ($\sigma_p = 0.00$), should prefer to form a H-bond with the more acidic *p*-NO_2-benzamide. Figure 1b shows that the benzoate carbonyl is H-bonded to the *p*-NO_2-amide NH in the solid state, with a CO···N distance of 3.1 Å.[4i]

It is also possible to determine the position of the conformational equilibrium in solution.[4i] By this procedure (see Supporting Information for details) we find that the conformational equilibrium of **1** in solution (CD_2Cl_2, 8 mM, 298 K) is biased toward the benzamide NH in a ratio of 1.3:1. The conformational equilibrium of **2** in solution is biased toward the *p*-NO_2-benzamide in a ratio of 1.9:1.

Having demonstrated the ability to predictably influence the H-bonded equilibrium by modulating spatially removed functional groups we returned to remote protonation. Compound **1** provides a basic dimethylamine ($pK_b \approx 11$ in MeCN/H_2O)[7] that is conjugated to the H-bond network. When deprotonated, electron donation from the *p*-NMe_2 biases the conformation toward the benzamide NH in the solid state and the solution phase. However, protonation to form the dimethyl-ammonium ion should transform it into an electron-withdrawing group, leading to a conformational switch (Scheme 3).



Scheme 3. The proposed pH-dependent molecular switch based upon compound **1**.

The ^{1}H NMR spectra of **1** (8 mM, CD_2Cl_2) in the presence of 0–6 equiv of trifluoracetic acid (TFA) are shown in Figure 2. The spectrum in the absence of acid depicts two singlets at 9.26 and 8.95 ppm that can be assigned to NH_b and NH_a in Scheme 3. Additionally the two doublets assigned to H_c and H_d in Scheme 3 resonate at 7.87 and 6.72 ppm. Upon addition of 6 equiv of TFA, the NH_a resonance migrates $\Delta\delta =$ 0.43 ppm downfield. The resonance corresponding to NH_b shifts $\Delta\delta = 0.04$ ppm upfield after 3 equiv then begins to move downfield again upon addition of 4–6 equiv. The resonances of the aryl protons H_c and H_d also shift downfield by 0.31 and 0.94 ppm, respectively. NOE and COSY experiments after the addition of 0, 2, and 3 equiv of TFA confirm the identity of the salient peaks.

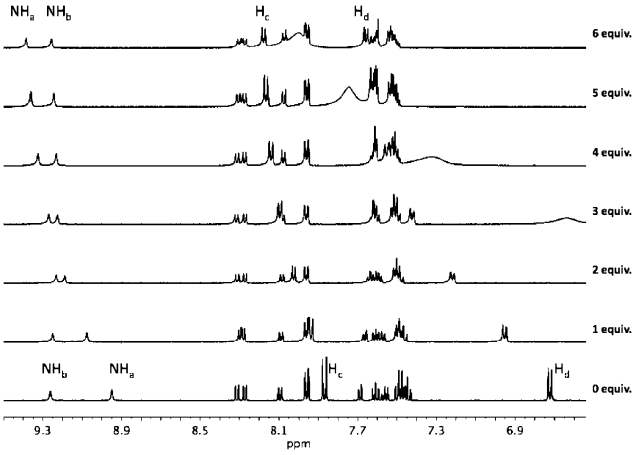


Figure 2. ^{1}H NMR spectra of **1** (8 mM, CD_2Cl_2) with 0–6 equiv of TFA. The peak labels correspond to the assignments in Scheme 3.

The downfield shift of H_c and H_d suggests that the dimethyl-ammonium ion is acting as an electron-withdrawing group whose influence is distance dependent, as demonstrated by the greater shift of H_d compared with H_c. The shift of NH_a beyond NH_b suggests that a conformational switch may be occurring. Further analysis of the amide resonances is complicated by the competing influences of the changing H-bond equilibrium and the electronic effect of protonating the NMe_2 group.

Titration of compound **3** (Scheme 2) serves to isolate the electronic effect of protonation by removing the intramolecular H-bond. Addition of 0–6 equiv of TFA causes the *p*-NMe_2-benzamide and benzamide NH signals in **3** to migrate 0.04 and 0.05 ppm downfield (See Supporting Information).

Figure 3 compares the shift of the amide resonances in **1** and **3**. Subtracting the shift of the *p*-NMe_2-NH of **3** from that of **1** yields the migration of NH_a due only to the changing conformational equilibrium (triangular markers, Figure 3). The line in Figure 3 at $\delta = 9.00$ ppm corresponds to the amide resonance of **4** in the absence of TFA (Scheme 2). Compound **4** balances two *p*-NMe_2-benzamides and as such its amide resonance should approximate the shift of NH_a when the conformational equilibrium ratio is 1:1. After 1 equiv of TFA, NH_a's corrected resonance has moved downfield of the line, indicating that the H-bonded equilibrium is now biased toward the *p*-$N(H)Me_2^+$-benzamide. Using a similar method as in the neutral case the equilibrium ratio in the presence of 6 equiv of TFA is calculated to be 99:1 toward the dimethylammonium-benzamide.

These results in solution and the solid state support the presence of a conformational equilibrium between two H-bonded configurations. The position of this equilibrium can be predictably biased by conjugating electron-donating or

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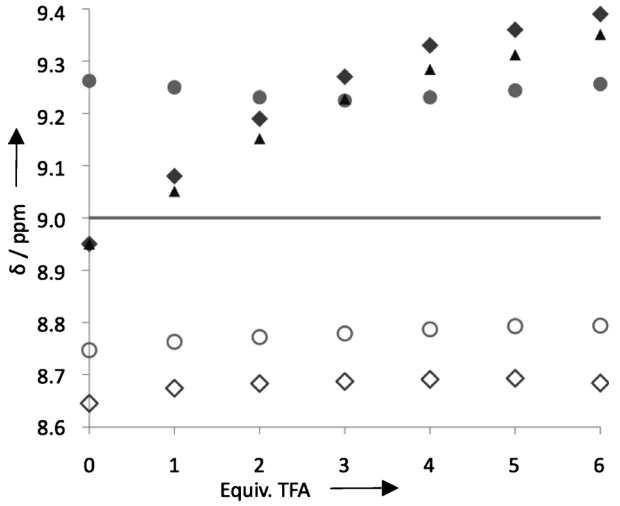

Figure 3. The change in chemical shift of NH_a (◆) and NH_b (●) of **1** as well as that for *p*-NMe_2-NH (◇) and *p*-H-NH (○) of **3** upon addition of 0–6 equiv of TFA (8 mM, CD_2Cl_2). The ▲ markers represent the shift of NH_a minus the shift of *p*-NMe_2-NH of **3**. The line at $\delta = 9.00$ ppm represents the amide resonance of **4** in the absence of TFA.

-withdrawing groups to the H-bond network. Furthermore, we show that the pH-dependent conversion of a donating group to a withdrawing group is communicated to the remote H-bond network, triggering a conformational switch.

Received: September 2, 2011

Keywords: conformational dynamics · diphenylacetylene · hydrogen bonding · molecular switch · pH dependence

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