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Designed Molecular Switches: Controlling the Conformation of Benzamido-diphenylacetylenes

Ian M. Jones and Andrew D. Hamilton*

Department of Chemistry, Yale University, P.O. Box 20810, New Haven, Connecticut 06520, and Department of Chemistry, Oxford University, 12 Mansfield Road, Oxford OX1 3TA, U.K.

andrew.hamilton@chem.ox.ac.uk

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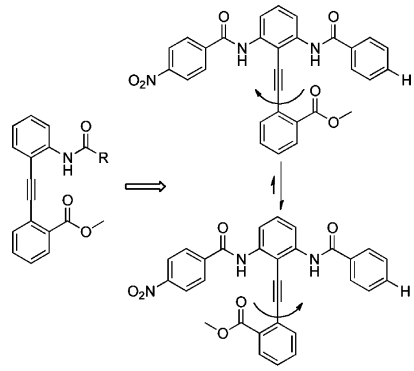
ABSTRACT



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]

(1) Gust, D.; Moore, T. A.; Moore, A. L. *Chem. Commun.* **2006**, 1169–1178.
(2) Collier, C. P.; Wong, E. W.; Belohradsky, M.; Raymo, F. M.; Stoddart, J. F.; Kuekes, P. J.; Williams, R. S.; Heath, J. R. *Science* **1999**, *285*, 391–394.
(3) de Silva, A. P.; McClenaghan, N. D.; McCoy, C. P. In *Molecular Switches*; Feringa, B. L., Ed.; John Wiley and Sons: New York, 2001; pp 339−361.
(4) Irie, M. *Chem. Rev.* **2000**, *100*, 1685–1716.
(5) Berkovic, G.; Krongauz, V.; Weiss, V. *Chem. Rev.* **2000**, *100*, 1741–1753.
(6) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
(7) Chatterjee, M. N.; Kay, E. R.; Leigh, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 4058–4073.
(8) Deetz, M. J.; Jonas, M.; Malerich, J. P.; Smith, B. D. *Supramol. Chem.* **2002**, *14*, 487–489.
(9) Hu, H. Y.; Xiang, J. F.; Yang, Y.; Chen, C. F. *Org. Lett.* **2008**, *10*, 1275–1278.
(10) Brazdova, B.; Zhang, N. R.; Samoshin, V. V.; Guo, X. *Chem. Commun.* **2008**, 4774–4776.
(11) Ashton, P. R.; Ballardini, R.; Balzani, V.; Baxter, I.; Credi, A.; Fyfe, M. C. T.; Gandolfi, M. T.; Gomez-Lopez, M.; Martinez-Diaz, M. V.; Piersanti, A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 11932–11942.
(12) Bissell, R. A.; Cordova, E.; Kaifer, A. E.; Stoddart, J. F. *Nature* **1994**, *369*, 133–137.
(13) Onoda, A.; Haruna, H.; Yamamoto, H.; Takahashi, K.; Kozuki, H.; Okamura, T.; Ueyama, N. *Eur. J. Org. Chem.* **2005**, 641–645.
(14) Spruell, J. M.; Paxton, W. F.; Olsen, J.-C.; Benìtez, D.; Tkatchouk, E.; Stern, C. L.; Trabolsi, A.; Friedman, D. C.; Goddard, W. A.; Stoddart, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11571–11580.
(15) Norikane, Y.; Tamaoki, N. *Org. Lett.* **2004**, *6*, 2595–2598.

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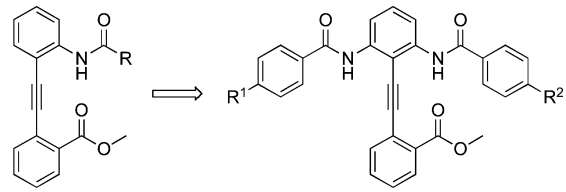


Figure 1. Conceptual transformation of the classical hydrogen bonded diphenylacetylene into a molecular switch.

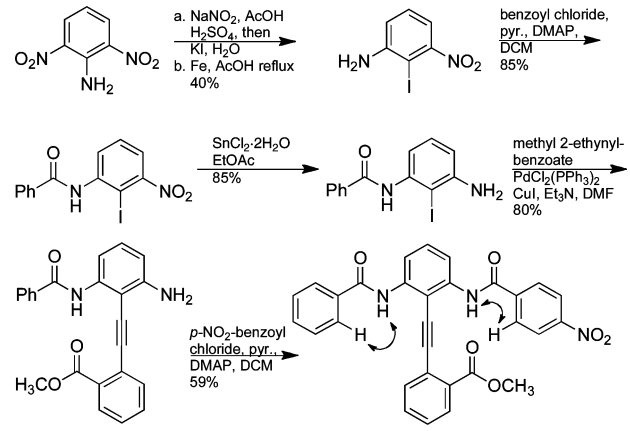
Our interest in the design of β-strand mimetics stabilized by an intramolecular hydrogen bond across an alkyne spacer[18] prompted us to investigate the use of this system as a new switching entity. The key feature of this scaffold is the 10-membered H-bonded ring first described by Kemp[19,20] (Figure 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**



To test this idea, compound **1**, which balances *p*NO_2-benzamide with benzamide, was assembled from 2,6-dinitroaniline according to Scheme 1. The *p*NO_2-amide has less electron density than benzamide, as described by $\Delta\sigma = 0.78$, and so the *p*NO_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 *p*NO_2-benzamide with a NH···OC distance of 2.23 Å. There is also a steric clash between the methyl ester and the *p*NO_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 *p*NO_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).

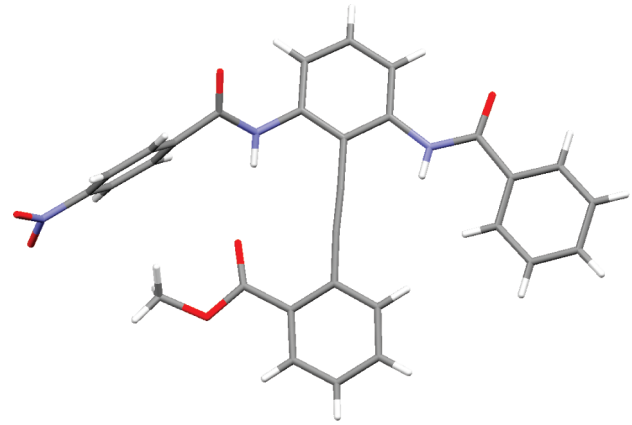


Figure 2. Single crystal X-ray structure of **1**.

(16) Tie, C.; Gallucci, J. C.; Parquette, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1162–1171.
(17) Aaron, S. L.; Michael, R. W. In *Molecular Switches*; Feringa, B. L., Ed.; John Wiley and Sons: New York, 2001; pp 1−35.
(18) Wyrembak, P. N.; Hamilton, A. D. *J. Am. Chem. Soc.* **2009**, *131*, 4566–4567.
(19) Kemp, D. S.; Li, Z. Q. *Tetrahedron Lett.* **1995**, *36*, 4175–4178.
(20) Kemp, D. S.; Li, Z. Q. *Tetrahedron Lett.* **1995**, *36*, 4179–4180.
(21) Okuyama, K.; Hasegawa, T.; Ito, M.; Mikami, N. *J. Phys. Chem.* **1984**, *88*, 1711–1716.
(22) Yang, X. W.; Yuan, L. H.; Yamamoto, K.; Brown, A. L.; Feng, W.; Furukawa, M.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2004**, *126*, 3148–3162.
(23) Cary, J. M.; Moore, J. S. *Org. Lett.* **2002**, *4*, 4663–4666.
(24) Yang, X. W.; Brown, A. L.; Furukawa, M.; Li, S. J.; Gardinier, W. E.; Bukowski, E. J.; Bright, F. V.; Zheng, C.; Zeng, X. C.; Gong, B. *Chem. Commun.* **2003**, 56–57.
(25) Hu, W.; Zhu, N. B.; Tang, W.; Zhao, D. H. *Org. Lett.* **2008**, *10*, 2669–2672.
(26) Jo, J.; Lee, D. *J. Am. Chem. Soc.* **2009**, *131*, 16283–16291.

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.

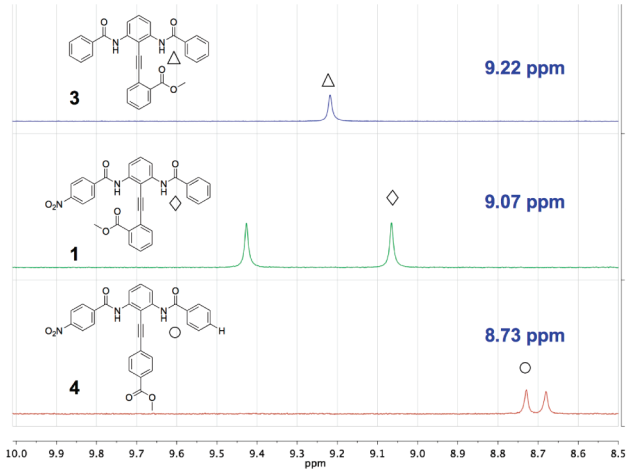


Figure 3. ^{1}H NMR amide resonances of compounds **3**, **1**, and **4** from top to bottom (4 mM in $CDCl_3$). The benzamide resonances are denoted by △, ◇, and ○ for **3**, **1**, and **4**, respectively, and the chemical shifts are also reported.

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.

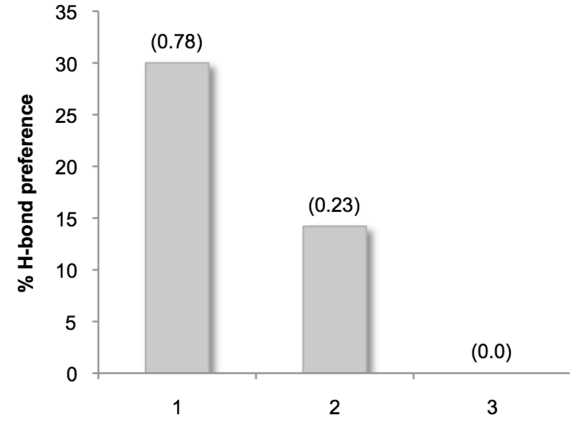


Figure 4. Comparison of the % H-bond preference for compounds **1**−**3**. The $\Delta\sigma$ values appear at the top of each bar.

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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(27) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.
(28) Krueger, P. J.; Smith, D. W. *Can. J. Chem.* **1967**, *45*, 1611–1618.
(29) Hobbs, M. E.; Bates, W. W. *J. Am. Chem. Soc.* **1952**, *74*, 746–749.