Molecular Switches

DOI: 10.1002/ange.201100144

Anion-Dependent Switching: Dynamically Controlling the Conformation of Hydrogen-Bonded Diphenylacetylenes**

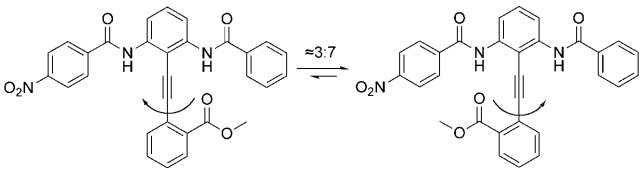
*Ian M. Jones and Andrew D. Hamilton**

Molecules that can switch conformation in a stimulus-dependent fashion are intriguing chemical species because of their many potential uses.[1] In particular, switches that respond to an anionic stimulus[2] have received increasing attention due to the importance of anions in nature.[3] With this utility in mind, we now report the development of an anion-dependent switch based on an intramolecularly H-bonded diphenylacetylene system.[4]

The field of anion recognition has rapidly expanded over the last 20 years leading to the design and study of many receptor motifs.[5] A common strategy involves the use of H-bond donors such as amides and ureas to coordinate a prospective anion.[6] Of these H-bond donors, complexation strength follows the trend: amides < ureas < thioureas owing to the increasing NH acidity[7] and the formation of secondary H-bond interactions.[8]

This pattern of increasing H-bond potential provides an entry point in creating a molecular switch using a diphenylacetylene scaffold. We have previously shown that appending two differentially functionalized benzamides *ortho* to the acetylene linkage creates a controllable equilibrium between two H-bonded conformations[4i] with the more stable conformer formed to the more acidic H-bond donor (Scheme 1).

Another way of controlling that equilibrium is to add additional secondary H-bond interactions. Thus, replacing one amide with a bidentate group, such as a urea, would considerably bias that equilibrium toward the urea conformer. However, ureas are also known to form strong complexes with anions. In this way a dynamic conformational switch is possible since addition of anions should preferentially chelate the urea site, causing the H-bond acceptor to change conformation to the available NH group (Figure 1).



Scheme 1. A bisbenzamido–diphenylacetylene scaffold where the conformational equilibrium is biased by the differential acidity of the flanking benzamides.[4i]

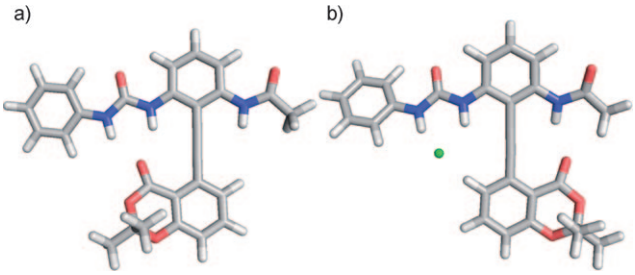


Figure 1. a) The lowest-energy conformation of **1** without added anion. b) The lowest-energy conformation of **1** with added NBu_4Cl (the cation has been removed for clarity). These minima were found by a molecular mechanics (MM) conformational search followed by an AM1 single-point minimization.

To test this hypothesis, compound **1** (Scheme 2) was designed to juxtapose an acetamide and a phenylurea above a benzodioxanone carbonyl group. This bicyclic benzodioxanone was chosen to provide a less sterically demanding H-bond acceptor relative to the s-*trans* methyl ester in Scheme 1.

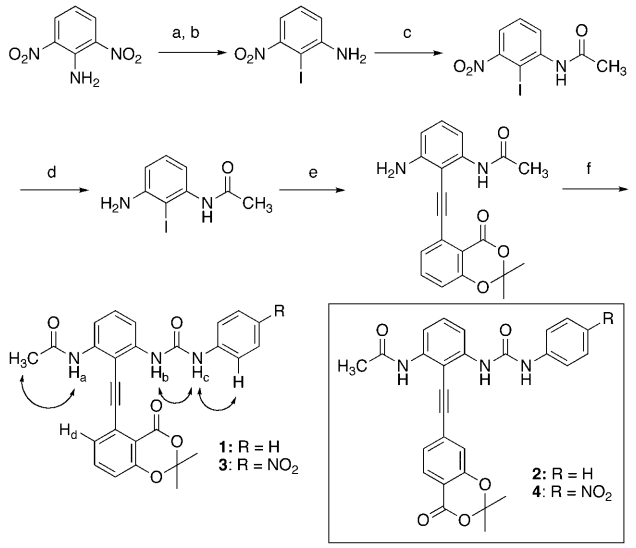
To gain initial insight on the competency of this system toward conformational switching, the H-bonded equilibrium of **1** was modeled in the absence and presence of 1 equiv NBu_4Cl (Figure 1). These studies were carried out using a molecular mechanics conformational search (MMFF94x force field) followed by an AM1 single point minimization using a commercially available software package (see Supporting Information for details).[9] The results show that the H-bond acceptor of **1** should prefer the urea by -3.4 kcal mol^{-1}, but upon addition of NBu_4Cl the carbonyl should switch such that an intramolecular H-bond with the acetamide is favored by -9.7 kcal mol^{-1}.

Compound **1** was prepared according to Scheme 2. The ^1H NMR spectrum of **1** (5 mM, $CDCl_3$, 298 K), shown in Figure 2, has three NH peaks at $\delta = 7.89$, 8.43, and 8.79 ppm, which by COSY and NOE experiments (Scheme 2) can be assigned to NH_a, NH_c, and NH_b, respectively. In addition to the NH resonances, the spectrum also has a doublet of note at $\delta = 7.25$ ppm that can be assigned to H_d, (Scheme 2) by the ^1H COSY spectrum of **1**.

[*] I. M. Jones, Prof. A. D. Hamilton
Department of Chemistry, University of Oxford
12 Mansfield Road, Oxford, OX1 3TA (UK)
and
Department of Chemistry, Yale University
P.O. Box 20810, New Haven, CT 06520 (USA)
E-mail: andrew.hamilton@chem.ox.ac.uk

[**] We thank Drs. Sam Thompson, Marc Adler (University of Oxford), and Andrew Jamieson (University of Leicester) for their insights as well as the University of Oxford and the NSF (CHE-0750357) for funding.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201100144.



Scheme 2. The synthesis and observed NOE contacts in **1** and **3** as well as the structures of **2** and **4**. Reagents and conditions: a) $NaNO_2$, AcOH, and H_2SO_4, then KI and H_2O, 64%; b) Fe^0 and AcOH, reflux 51%; c) AcCl, pyr., DMAP, DCM, 67%; d) $SnCl_2{\cdot}2H_2O$, EtOAc, 68%; e) 5-alkynylbenzodioxinone,[10] $[PdCl_2(PPh_3)_2]$, CuI, DMF, NEt_3, 71%; f) 4-R-PhNCO, pyr., DCM, 61%. DMAP = dimethylaminopyridine; DCM = dichloromethane, pyr. = pyridine.

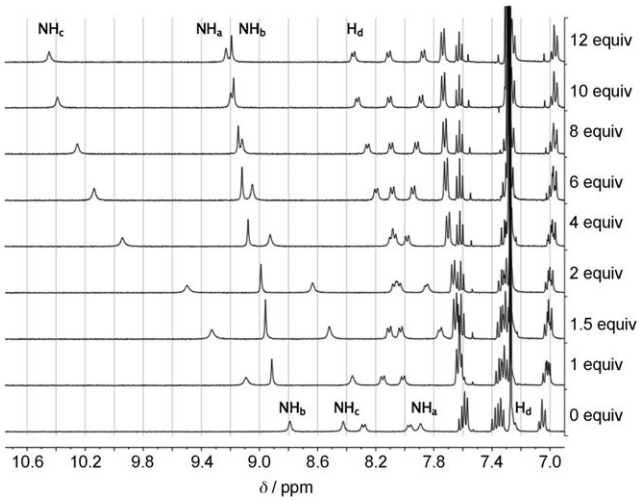


Figure 2. The ^1H NMR spectra of **1** (5 mM, 298 K, $CDCl_3$) upon addition of 0–12 equiv of NBu_4Cl. Peaks at $\delta = 7.25$, 7.89, 8.43, and 8.79 ppm correspond to H_d, NH_a, NH_c, and NH_b (Scheme 2), respectively.

The molecular modeling results suggest that anion binding should result in strong downfield shifts of the NH_c and H_d ^1H NMR signals because of a direct interaction with the halide. The NH_a peak should also experience a downfield migration due to interaction with the HB acceptor carbonyl.

Indeed, Figure 2 shows that titration of **1** with NBu_4Cl causes the resonances corresponding to NH_a, NH_b, and NH_c to shift downfield by $\Delta\delta = 1.35$, 0.40, and 2.03 ppm, respectively. It is noteworthy that NH_b, which swaps an intramolecular H-bond for an intermolecular interaction with the anion, shifts downfield the least. Association of **1** with Cl^- also causes H_d to migrate $\Delta\delta = 1.10$ ppm downfield.

Fitting the equation for a 1:1 binding isotherm (stoichiometry confirmed by Job's plot) to the shift of NH_c gives the association constant for the binding to Cl^- to **1** as $78\,M^{-1}$ (Table 1). Changing the anion from Cl^- to Br^- gives, in all cases, a weaker downfield shift of the urea NH resonance and modest decrease in the corresponding K_a value.

Table 1: A comparison of the K_a data obtained from the shift of NH_c in **1**–**3** upon titration with NBu_4Br and NBu_4Cl.

Compound	K_a Br^- [M^{-1}]	K_a Cl^- [M^{-1}]
1	29 ± 6	78 ± 6
2	300 ± 100	950 ± 60
3	96 ± 3	238 ± 5

To assess the proposed conformational switching mechanism (shown in Figure 1) we prepared a control derivative (**2**) in which the H-bond accepting carbonyl group is shifted to the *para* position of the lower phenyl ring. This derivative maintains the electronic characteristics of **1** while removing the potential for intramolecular H-bonding. This molecule should assay the relative contributions of anion binding and conformational switching on the downfield shift of NH_a in **1**.

Figure 3 shows that, upon addition of 12 equiv of Cl^-, the amide NH resonance in **2** shifts $\Delta\delta = 0.89$ ppm, which is significantly less than that for NH_a in **1**. This confirms that the downfield shift of NH_a is affected both by anion binding and a change in the conformation of the molecule. The increased K_a for Cl^- binding to **2** (Table 1) shows that removing the energetic cost of breaking the intramolecular H-bond increases anion affinity by more than an order of magnitude over compound **1**.

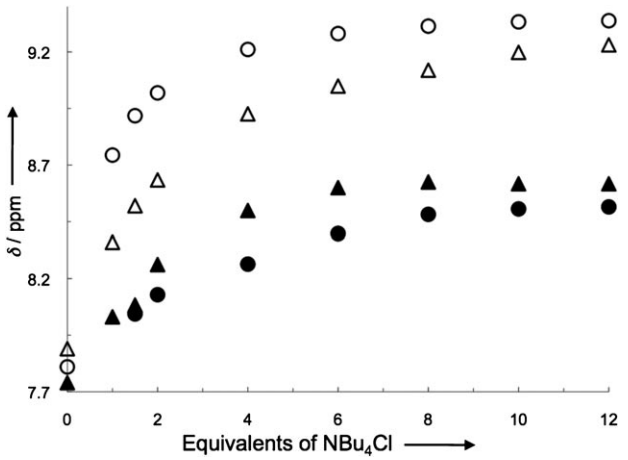


Figure 3. The change in chemical shift of the acetamide NH protons upon titration of **1** (△), **2** (▲), **3** (○), and **4** (●) with an increasing number of equivalents of NBu_4Cl. All titrations are at 500 MHz with 5 mM solutions of **1**, **2**, **3**, or **4** in $CDCl_3$ at 298 K.

Further evidence for the proposed switching mechanism came from compounds **3** and **4**, which are analogous to **1** and **2**

but incorporate a *p*-nitro group onto the phenylurea. This electron-withdrawing substituent should increase the acidity and thus the H-bond donation capability of the urea. The resulting increase in affinity should stabilize both the intramolecular H-bond as well as association of anion with the urea. Correspondingly, this stabilization should be reflected in the shift of the acetamide-NH resonance if a conformational switch is present.

In fact, the ^{1}H NMR spectrum of **3** shows that the acetamide resonance is shifted by $\Delta\delta = 0.1$ ppm upfield compared to that of **1** (see 0 equiv, Figure 3). This change is indicative of a shift of the H-bonded equilibrium away from NH_a toward the urea protons. Furthermore, addition of the *p*-nitro group increases the anion affinity, determined from the urea resonances, by two- to three-fold compared to **1** (Table 1), and causes an increased downfield shift of the acetamide NH signal at lower equivalents of Cl^- (see 2–6 equiv, Figure 3). It is also noteworthy that both NH_a signals in **1** and **3** appear to saturate at the same point, indicating that they are experiencing the same H-bond interaction.

Solubility problems in $CDCl_3$ precluded the measurement of spectra for **4** with 0 and 1 equiv of Br^- or Cl^-. However, the *p*-nitro group in **4** causes increased anion affinity as evidenced by a larger downfield shift of the urea resonances compared to those of **2** (see 1.5–12 equiv, Figures S16 and S19). Despite this increase in affinity, Figure 3 shows a *reduced* downfield shift of the acetamide resonance in **4** compared to that of **2**, indicating that a conformational shift, and not direct anion binding, is the cause of the increased shift of NH_a in **3**. These differences in the downfield shifts of the acetamide signals of **1**–**4** confirm that molecules **1** and **3** are anion-dependent molecular switches.

It is possible to quantify the magnitude of the conformational shift by comparing δ_{NHa} at a given [Cl^-] with the corresponding chemical shifts of NH_a when it is completely H-bonded and not H-bonded. The value of the fully H-bonded NH_a can be obtained by fitting the titration data to the equation for the 1:1 binding isotherm and is estimated to be $\delta = 9.49$ ppm. The chemical shift of NH_a when it is not H-bonded is estimated as the acetamide shift in **2**, which is $\delta =$ 7.74 ppm. From these values the equilibrium position at a given [Cl^-] is determined by dividing the difference between δ_{NHa} and 7.74 ppm by the difference between 9.49 and 7.74 ppm. By this method we find that in the absence of anion the H-bond acceptor prefers the urea in a ratio of 9:1. Upon addition of 12 equiv of Cl^-, that ratio becomes nearly 5:1 in favor of the acetamide (Figure 4).

The importance of anion binding in biology and chemistry has stimulated the development of systems that can elucidate and monitor this phenomenon. We have modified our H-bonded diphenylacetylene scaffold, such that it now juxtaposes an amide and a urea. Through the use of molecular modeling and ^{1}H NMR spectroscopy we have determined that addition of Cl^- causes the conformation of the H-bond acceptor to switch from the urea protons to the amide proton. This discovery suggests the use of diphenylacetylenes of this type as possible fluorescent anion sensors and we are currently working to develop this capability.

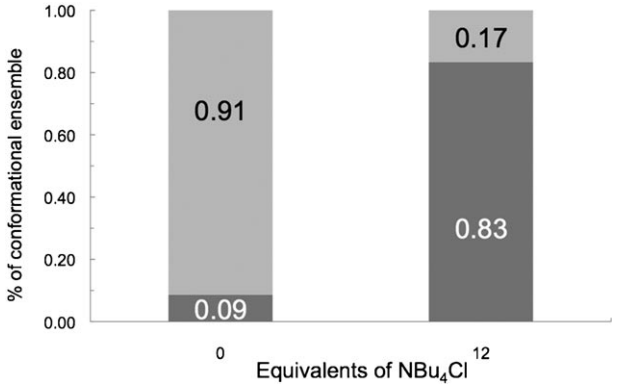


Figure 4. The change in the equilibrium position upon increasing the number of equivalents of NBu_4Cl from 0 to 12. Light gray bars correspond to the percent of molecules adopting the urea H-bonded conformation, while the dark gray bars represent the percent of the population in the acetamide H-bonded state.

Received: January 8, 2011
Published online: April 14, 2011

Keywords: anion binding · diphenylacetylene · molecular switch

[1] a) D. Gust, T. A. Moore, A. L. Moore, *Chem. Commun.* **2006**, 1169–1178; b) C. P. Collier, E. W. Wong, M. Belohradsky, F. M. Raymo, J. F. Stoddart, P. J. Kuekes, R. S. Williams, J. R. Heath, *Science* **1999**, *285*, 391–394; c) A. P. de Silva, N. D. McClenaghan, C. P. McCoy in *Molecular Switches* (Ed.: B. L. Feringa), Wiley-VCH, Weinheim, **2001**, pp. 339–361; d) M. Irie, *Chem. Rev.* **2000**, *100*, 1685–1716; e) G. Berkovic, V. Krongauz, V. Weiss, *Chem. Rev.* **2000**, *100*, 1741–1753; f) A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515–1566; g) M. N. Chatterjee, E. R. Kay, D. A. Leigh, *J. Am. Chem. Soc.* **2006**, *128*, 4058–4073.

[2] a) C. M. Keaveney, D. A. Leigh, *Angew. Chem.* **2004**, *116*, 1242–1244; *Angew. Chem. Int. Ed.* **2004**, *43*, 1222–1222; b) Y.-L. Huang, W.-C. Hung, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Angew. Chem.* **2007**, *119*, 6749–6753; *Angew. Chem. Int. Ed.* **2007**, *46*, 6629–6633; c) M. Montalti, L. Prodi, *Chem. Commun.* **1998**, 1461–1462; d) M. J. Chmielewski, J. Jurczak, *Chem. Eur. J.* **2006**, *12*, 7652–7667; e) C.-F. Lin, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Chem. Eur. J.* **2007**, *13*, 4350–4355; f) J. Raker, T. E. Glass, *J. Org. Chem.* **2002**, *67*, 6113–6116; g) B. W. Laursen, S. Nygaard, J. O. Jeppesen, J. F. Stoddart, *Org. Lett.* **2004**, *6*, 4167–4170; h) T.-C. Lin, C.-C. Lai, S.-H. Chiu, *Org. Lett.* **2009**, *11*, 613–616; i) M. J. Chmielewski, A. Szumnaa, J. Jurczak, *Tetrahedron Lett.* **2004**, *45*, 8699–8703.

[3] a) G. Novarino, S. Weinert, G. Rickheit, T. J. Jentsch, *Science* **2010**, *328*, 1398–1401; b) C. F. Yocum, *Coord. Chem. Rev.* **2008**, *252*, 296–305; c) J. P. McEvoy, G. W. Brudvig, *Chem. Rev.* **2006**, *106*, 4455–4483.

[4] a) D. S. Kemp, Z. Q. Li, *Tetrahedron Lett.* **1995**, *36*, 4175–4178; b) D. S. Kemp, Z. Q. Li, *Tetrahedron Lett.* **1995**, *36*, 4179–4180; c) J. M. Cary, J. S. Moore, *Org. Lett.* **2002**, *4*, 4663–4666; d) X. Yang, A. L. Brown, M. Furukawa, S. Li, W. E. Gardinier, E. J. Bukowski, F. V. Bright, C. Zheng, X. C. Zeng, B. Gong, *Chem. Commun.* **2003**, 56–57; e) X. Yang, L. Yuan, K. Yamato, A. L. Brown, W. Feng, M. Furukawa, X. C. Zeng, B. Gong, *J. Am. Chem. Soc.* **2004**, *126*, 3148–3162; f) W. Hu, N. Zhu, W. Tang, D. Zhao, *Org. Lett.* **2008**, *10*, 2669–2672; g) P. N. Wyrembak, A. D.

Hamilton, *J. Am. Chem. Soc.* **2009**, *131*, 4566 – 4567; h) J. Jo, D. Lee, *J. Am. Chem. Soc.* **2009**, *131*, 16283 – 16291; i) I. M. Jones, A. D. Hamilton, *Org. Lett.* **2010**, *12*, 3651 – 3653.

[5] A. Brown, K. M. Mullen, J. Ryu, M. J. Chmielewski, S. M. Santos, V. Felix, A. L. Thompson, J. E. Warren, S. I. Pascu, P. D. Beer, *J. Am. Chem. Soc.* **2009**, *131*, 4937 – 4952, and references therein.

[6] a) E. Fan, A. V. Arman, S. Kincaid, A. D. Hamilton, *J. Am. Chem. Soc.* **1993**, *115*, 369 – 370; b) J. Scheerder, M. Fochi, J. F. J. Engbersen, D. N. Reinhoudt, *J. Org. Chem.* **1994**, *59*, 7815 – 7820; c) D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, *J. Org. Chem.* **2005**, *70*, 5717 – 5720.

[7] F. G. Bordwell, D. J. Algrim, J. A. Harrelson Jr, *J. Am. Chem. Soc.* **1988**, *110*, 5904 – 5906.

[8] J. Pranata, S. G. Wierschke, W. L. Jorgensen, *J. Am. Chem. Soc.* **1991**, *113*, 2810 – 2819.

[9] *MOE*, Chemical Computing Group, Montreal, Quebec, Canada, **2010**.

[10] a) R. C. Dushin, S. J. Danishefsky, *J. Am. Chem. Soc.* **1992**, *114*, 655 – 659; b) A. Hadfielda, H. Schweitzera, M. P. Trovab; K. Green, *Synth. Commun.* **1994**, *24*, 1025 – 1028; K. Green, *Synth. Commun.* **1994**, *24*, 1025 – 1028; c) G. A. Molander, F. Dehmel, *J. Am. Chem. Soc.* **2004**, *126*, 10313 – 10318; d) J. S. S. Rountree, P. V. Murphy, *Org. Lett.* **2009**, *11*, 871 – 874.

