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ARTICLE

Remote Conformational Control of a Molecular Switch *via* Methylation and Deprotonation

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Exacting control over conformation in response to an external stimulus is the central focus of molecular switching. Here we describe the synthesis of a series of diphenylacetylene-based molecular switches, and examine their response to covalent modification and deprotonation at remote phenolic positions. A complex interplay between multiple intramolecular hydrogen bond donors and acceptors determines the global conformation.

Introduction

The control of molecular switching has the potential to achieve targeted drug delivery, and is the basis of a new generation of molecular sensors.[1–4] For example, encapsulating drug cargo in a pH-responsive molecular container provides a vehicle to deliver therapy specifically to the acidic environment that surrounds solid tumours, potentially lessening the deleterious off-target effects of traditional chemotherapies.[5,6] Increasing the scope of stimuli for molecular switches is therefore an important endeavour, and will facilitate their deployment in an expanded set of applications.

The post-translational modification of macromolecules, such as proteins and nucleic acids, exerts an additional layer of conformational regulation.[7–9] Two such reversible events are protonation and methylation. The latter has attracted particular attention, and is central to normal genetic regulation as well as maladies such as cancer, diabetes, and Alzheimer's disease.[7,10] The reversible protonation of proteins is responsible for modulating regulatory processes, but is also implicated as an aggravating factor in amyloid disease.[11]

Inspired by these systems, we were curious to explore the effects of deprotonation and methylation on the conformational behaviour of a molecular switch. Specifically we wished to provide insights into the effect these modifications have on hydrogen-bonded networks. We have previously employed a bis-benzamido diphenylacetylene (DPA) system to examine the effects of anions, Brønsted-, and Lewis acids on internal conformational dynamics (Figure 1).[12–14] In these systems the key determinant of conformation is an intramolecular H-bond between the methyl benzoate carbonyl and one of the two amide NH's. The H-bond acceptor is predictably biased toward the most electron-deficient H-bond donor. Structurally similar acetylene-based compounds have previously been deployed as specific anion receptors,[15] and as components of switchable helical foldamers.[16,17]

Building on our previous work we set out to incorporate two phenolic sites at the periphery of the scaffold, which are connected through a hydrogen-bonding network to a proximal benzamide N-H. Each of these remote positions may be deprotonated or methylated before studying the global conformational change (Figure 1).

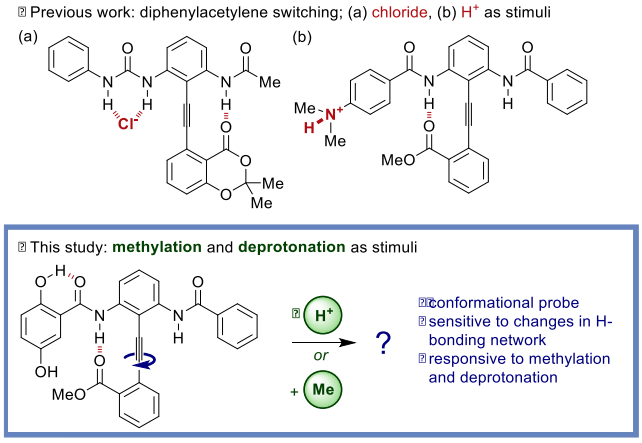
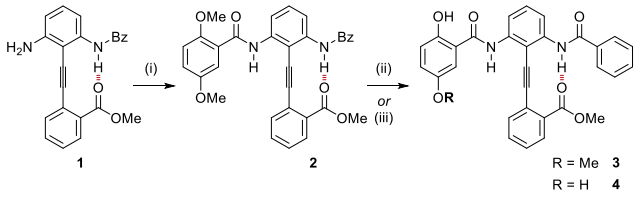


Figure 1. Study outline: conformational change upon methylation and deprotonation.

Results and Discussion

The synthesis of switch compound **2** was achieved in 73% yield upon treatment of aniline **1**[18] with 2,5-dimethoxybenzoyl chloride. The effects of methylation state on the conformation of the DPA were initially investigated by sequential chemical demethylation of dimethoxybenzamide **2** with $BBr_3 \cdot OEt_2$. At

cryogenic temperatures mono-demethylation to give **3** proceeded in 94% yield and with complete regioselectivity for the 2-methoxy group. Conversely, performing the reaction at room temperature with a larger excess of boron tribromide, dihydroxy phenol **4** was obtained as the sole product in 71% yield.



(i) 2,5-dimethoxybenzoyl chloride (2 eq.), pyridine, DMAP, CH_2Cl_2, rt, 30 min, 73%; (ii) $BBr_3{\cdot}OEt_2$ (1.5 eq.), -30 °C, 15 min, 94%; (iii) $BBr_3{\cdot}OEt_2$ (5 eq.), rt, 30 min, 71%. Bz = benzoyl.

Scheme 1. a) The synthesis of dimethoxy, monomethoxy and dihydroxy switch compounds **2**, **3** and **4**.

The solution-phase conformation of each switch molecule was examined by comparing the ^{1}H NMR chemical shift of the benzamide NH (δ_{sw}) with those of two control molecules, one of which is incapable of forming an intramolecular hydrogen bond (0% control, δ_0) and one which is assumed to solely adopt a conformation in which the intramolecular hydrogen bond exists (100% control, δ_{100}, Figure 2).[18–20] A measure of the position of the conformational equilibrium, ε, is then obtained by employing equation (1). Application of this assay to dimethoxy compound **2** indicates that hydrogen bonding occurs predominantly between the ester and the unsubstituted benzamide (a ratio of 11:2, ε = 0.85). This result is consistent with the formation of an NH···O hydrogen bond between the *ortho*- methoxy substituent and amide, effectively blocking hydrogen bonding from this amide to the ester.

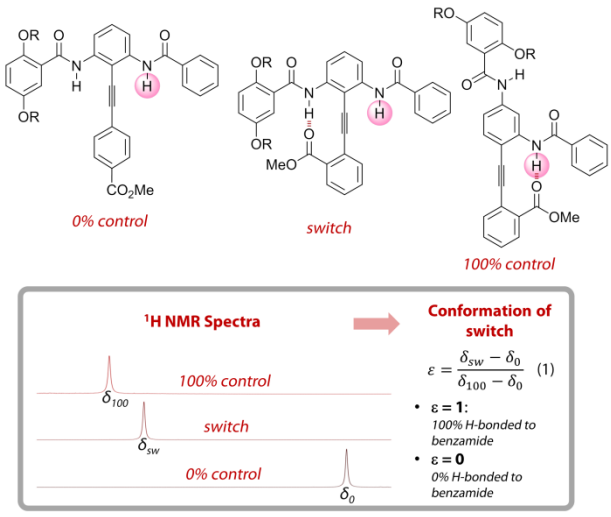


Figure 2. Generic switch, 0% and 100% control molecule structures and NMR assay of conformation. R = H, CH_3. The benzamide proton examined by ^{1}H NMR is highlighted in pink.

This postulate is further borne out by the X-ray crystal structure of **2**, and by its calculated lowest energy conformation (Figure 3).[21]

The same analysis was applied to the monomethoxy compound **3**, and suggested a significant conformational change. A large upfield shift in the benzamide NH relative to dimethoxy compound **2** indicated a 4:3 ratio in favour of the conformation in which the unsubstituted benzamide is engaged in a hydrogen bond (ε = 0.57). The increased propensity for hydrogen bonding to the substituted benzamide (relative to **2**) is likely a consequence of hydrogen bonding between the *ortho*-hydroxy donor and amide carbonyl acceptor, enhancing the donor ability of the amide N-H in a cooperative manner.[22] X-ray crystallographic analysis provides evidence for this strong O-H···O hydrogen bond (Figure 4a), and supports the slight solution-phase preference for the unsubstituted benzamide engaging in a hydrogen bond with the ester. The structure also exhibits the out-of-plane twisting of the benzamide engaged in hydrogen bonding characteristic of these systems (Figure 4b).[13]

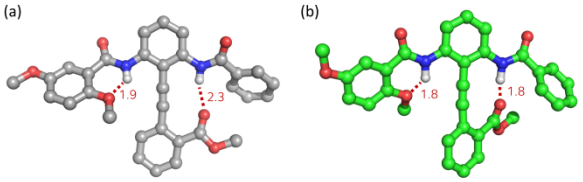


Figure 3. a) X-ray crystal structure of **2**, showing a NH···O hydrogen bond with the *ortho*-methoxy substituent; b) computed lowest energy conformation of **2**. Bond lengths (in Å) are indicated in red.

Lastly the solution-state conformational preference of dihydroxy switch compound **4** was examined.† As with the removal of one methyl group to form **3**, removal of a second methyl group elicited an upfield shift in the unsubstituted benzamide proton, consistent with a weaker intramolecular hydrogen bonding interaction with the ester. ^{1}H NMR analysis indicated a 2:1 preference for the conformer in which the substituted benzamide is engaged in a hydrogen bond (ε = 0.32). This observation suggests that the *meta*-hydroxyl group – known to be electron-withdrawing in benzoic acid model systems[23] – is increasing the acidity of the corresponding amide NH, causing it to be preferred over the unsubstituted benzamide. Interestingly, both **3** and **4** exhibited strong solvent-dependent switching behaviour: when placed in 9:1 $CDCl_3$:d_6-DMSO (*v*/*v*), their preference towards hydrogen bonding to the unsubstituted benzamide was increased dramatically from the values observed in pure $CDCl_3$, to 18:1 and 17:1 respectively (ε_3 = 0.95; ε_4 = 0.94). Dimethoxy compound **2**, on the other hand, exhibited virtually no change (8:1 preference, ε_2 = 0.89). This dramatic difference is likely due to increased solvation of the hydroxyl groups in **3** and **4**, breaking the key structural OH···O=C hydrogen bond.

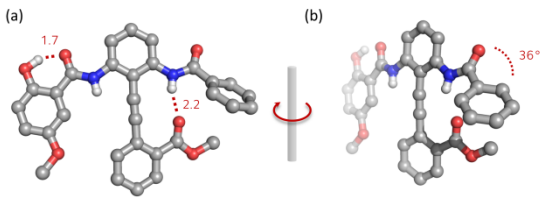


Figure 4. X-ray crystal structure of **3**; (a) side view, distances (in Å) indicated in red; b) edge view, C_{ortho}-C-C-O dihedral angle indicated in red.

We proceeded to investigate the dynamic behaviour of this system upon treatment with base. Dihydroxy switch **4** was unsuitable for this study, since quantitative assaying was confounded by its poor solubility. Therefore studies were carried out solely on **3**. We postulated that base would deprotonate the acidic phenol, giving a phenolate that would hydrogen bond to the adjacent amide, blocking it from bonding to the ester. An NMR titration experiment was carried out by adding DBU in small portions to $CDCl_3$ solutions of **3** and its corresponding control compounds in turn. As expected the unsubstituted benzamide NH shifted markedly downfield, consistent with its increased involvement in H-bonding. The second amide proton was immediately broadened to the extent that it could no longer be observed after the addition of 0.3 eq. DBU, consistent with its undergoing rapid exchange in the presence of the base.

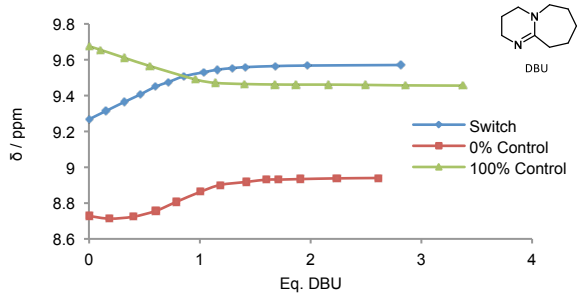
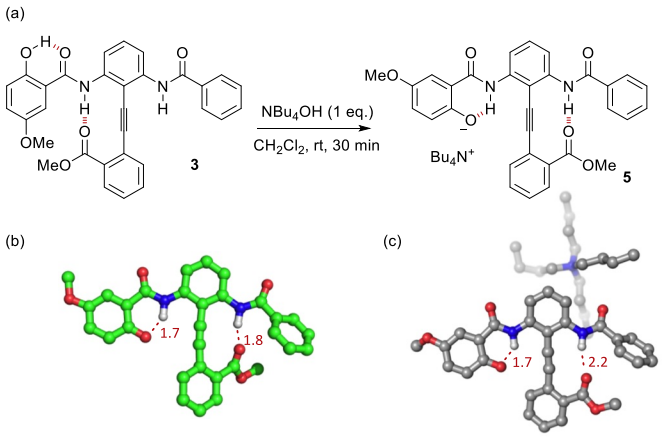


Figure 5. ^{1}H NMR titration (600 MHz) of **3** (3.2 mM) with DBU (1,8-diazabicycloundec-7-ene) in $CDCl_3$.

Quantitative analysis of switching as a function of base was not possible, since after the addition of *ca*. 1 eq. DBU the switch NH chemical shift moved downfield beyond the shift of the 100% control, rendering equation (1) inapplicable. Nonetheless, the significant, dose-dependent downfield shift of the benzamide proton provides compelling evidence of switching behaviour. To confirm the preferred conformation of the phenolate, *n*-$Bu_4N^+OH^-$ was added to a solution of **3** in anhydrous dichloromethane to generate tetrabutylammonium salt **5** (Scheme 2a).



Scheme 2. (a) Deprotonation of **3** to examine the solid-state conformational preference of the corresponding phenolate **5**. (b) Computed lowest energy conformer of **5** (counter-ion not modelled). (c) X-Ray crystal structure of **5**. Distances (in Å) indicated in red.

Diffraction quality crystals were obtained by recrystallization from acetonitrile, and the salt **5** was observed to adopt the predicted conformation, with the phenolate H-bonding to the adjacent amide, thus blocking it from hydrogen bonding to the methyl ester (Scheme 2c). This structure is similar to **2**, wherein the *ortho*-methyl ether participates in an analogous intramolecular H-bond. The computed lowest energy conformation is in good agreement with this structure; the alternative rotamer in which the hydrogen bond is formed between the ester and substituted benzamide lies more than 12 kcal·mol^{-1} ($K \approx 6.8 \times 10^8$) higher in energy (Scheme 2b).

Lastly, we investigated the fluorescence properties of the three methylation states – **2**, **3** and **4** – to determine whether they could be characterized by a change in emission spectra. Compound **2** has a single emission band at λ_{max}=410 nm, which is likely due to excited-state intramolecular proton transfer (ESIPT), an effect previously observed for salicylamide.[24] When the system is conformationally unlocked by mono-demethylation to form **3**, λ_{max} redshifts to 515 nm (Figure 6). This is a significant change, and may be a consequence of the availability of the phenol OH to participate in an alternative ESIPT reaction with the adjacent amide, generating a transient excited enol-phenoxide tautomer.[25] Upon removing the second methyl group to generate **4** λ_{max} remains the same – consistent with the same mechanism of fluorescence being in operation – but its intensity is quenched. This is in agreement with the conformational changes indicated by NMR analysis, where **4** exists primarily with the 2,5-dihydroxybenzamide engaged in a hydrogen bond with the ester. In this conformation, intramolecular collisional quenching of the excited state is favoured by the proximity of the ester, and a reduction in fluorescence quantum yield is therefore expected. Thus, both the position and intensity of fluorescence peaks provide a semi-quantitative metric for molecular conformation.

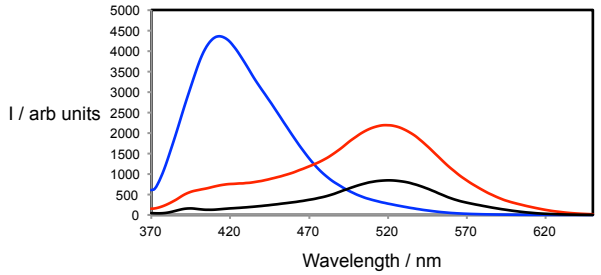


Figure 6. A comparison of the fluorescence spectra **2** (blue), **3** (red), and **4** (black).

Conclusions

Seeking to expand the scope of stimulus-responsive molecular switching we have developed a system to observe how methylation and deprotonation can affect the interplay of H-bond donors and acceptors and lead to a global conformation change. Using molecular mechanics models, X-ray crystallography and ^{1}H NMR, we have observed three conformational states that are dependent on the degree of methylation. These states also have definitive fluorescence characteristics, which enable their rapid identification. Whilst methylation and demethylation are static states with relatively long lifetimes, protonation and deprotonation are dynamic, fluxional processes. We have demonstrated that similar conformational changes can be brought about both by methylation and deprotonation. These stimuli provide a novel means by which to control the global conformation of molecular switches, and should inform future developments in the field.

Experimental Details

The synthesis of **1** has previously been reported.[26] For full experimental details describing the synthesis of the control molecules, please refer to the ESI.

Synthetic Procedures

Methyl 2-((2-benzamido-6-(2,5-dimethoxybenzamido)phenyl)ethynyl)benzoate (2). Oxalyl chloride (0.15 mL) was added dropwise over 1 min to a solution of 2,5-dimethoxybenzoic acid (157 mg, 0.43 mmol) in dichloromethane (5 mL) and *N*,*N*-dimethylformamide (2 drops). The reaction was stirred for 40 min. After this period the solution was concentrated *in vacuo* and then re-suspended in dichloromethane (2 mL). In another flask, methyl 2-((2-amino-6-benzamidophenyl)-ethynyl)benzoate **1** (160 mg, 0.43 mmol) and 4-dimethylaminopyridine (ca. 2 mg) were added to a mixture of dichloromethane (2 mL) and pyridine (0.24 mL, 0.65 mmol). This solution was stirred for 0.5 h before the solution of acid chloride in dichloromethane was added to the amine over 3 min. The reaction was stirred for 30 min after which time the solution was diluted with dichloromethane and the organic layer washed with 2 M HCl and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, dichloromethane:ethyl acetate, 20:1) to give **2** (167 mg, 73 %) as a viscous yellow oil that solidified upon standing; R_f 0.45 (9:1 chloroform/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 10.67 (s, 1H), 9.50 (s, 1H), 8.42 (d, *J* 8.4, 1H), 8.38 (dd, *J* 8.4, 0.7, 1H), 8.08 (dd, *J* 8.0, 1.1, 1H), 8.03 (s, 1H), 7.96 (d, *J* 7.1, 2H), 7.86 (d, *J* 3.2, 1H), 7.69 (dd, *J* 7.8, 1.1, 1H), 7.57 (td, *J* 7.6, 1.3, 1H), 7.48 (d, *J* 8.0, 2H), 7.42 (t, *J* 7.9, 2H), 7.09 (d, *J* 3.3, 1H), 6.96 (d, *J* 9.0, 1H), 3.88 (s, 3H), 3.70 (s, 3H), 3.43 (s, 3H); δ_C (126 MHz, $CDCl_3$) 167.1, 165.6, 163.4, 154.4, 151.9, 140.7, 140.4, 135.8, 133.8, 132.4, 131.6, 131.0, 130.6, 128.8, 128.4, 128.2, 123.4, 123.0, 120.3, 115.9, 115.7, 115.5, 114.1, 102.9, 101.5, 86.9, 57.4, 56.0, 52.2; HRMS (ESI): found 535.1863; $C_{32}H_{27}N_2O_6$ $[M+H]^+$ requires 535.1791.

Methyl 2-((2-benzamido-6-(2-hydroxy-5-methoxybenzamido)phenyl)ethynyl)benzoate (3). Boron tribromide (1 M in dichloromethane, 140 µL, 0.14 mmol) was added dropwise to a stirred -30 °C solution of **2** (50 mg, 0.094 mmol) in dichloromethane (4 mL). After 15 min the reaction was quenched by the cautious addition of water (5 mL) and diluted with dichloromethane (10 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel, dichloromethane:ethyl acetate, 50:1) to afford **3** (46 mg, 94%) as a white powder. δH ($CDCl_3$, 400 MHz): 11.27 (1H, s), 9.27 (1H, s), 9.18 (1H, s), 8.40 (1H, dd, *J* 8.3, 0.5), 8.18 (1H, dd, *J* 8.3, 0.6), 8.09 (1H, dd, *J* 7.9, 1.0), 7.97 (2H, d, *J* 7.1), 7.70 (1H, dd, *J* 7.8, 0.9), 7.60−7.52 (2H, m), 7.51−7.44 (4H, m), 7.25 (1H, d, *J* 2.8), 7.07 (1H, dd, *J* 9.1, 2.9, 6.99 (1H, d, *J* 9.0), 3.70 (3H, s), 3.50 (3H, s); δC ($CDCl_3$, 101 MHz): 168.4, 166.5, 165.4, 155.8, 151.9, 140.4, 138.8, 135.3, 133.3, 132.5, 131.8, 131.0, 130.9, 129.1, 128.5, 127.8, 122.8, 121.0, 119.4, 115.9, 115.7, 115.2, 111.3, 103.1, 103.0, 85.6, 56.0, 52.2; HRMS (ESI): found 521.1591; $C_{31}H_{25}N_2O_6$ $[M+H]^+$ requires 521.1634.

Methyl 2-((2-benzamido-6-(2,5-dihydroxybenzamido)phenyl)ethynyl)benzoate (4). Boron tribromide (1 M in dichloromethane, 0.20 mL, 0.20 mmol) was added dropwise to a stirred RT solution of **2** (20 mg, 0.037 mmol) in dichloromethane (2 mL). After 2 h the reaction mixture was quenched by the cautious addition of water (5 mL) and diluted with dichloromethane (5 mL). The layers were separated and the aqueous layer was extracted exhaustively with 3:1 chloroform:isopropanol (*v*/*v*, 6 x 5 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (silica gel, dichloromethane:ethyl acetate, 4:1→1:1) to afford **4** (13.5 mg, 71%) as a white powder. δ_H (400 MHz, $CDCl_3$) 11.37 (s, 1H), 9.08 (s, 1H), 9.02 (s, 1H), 8.39 (d, *J* 8.3, 1H), 8.13 (d, *J* 8.4, 1H), 8.07 (d, *J* 7.6, 1H), 7.97 (d, *J* 7.4, 2H), 7.66 (d, *J* 2.8, 1H), 7.59 (d, *J* 7.0, 2H), 7.56 (d, *J* 7.3, 1H), 7.48 (p, *J* 8.5, 7.9, 4H), 7.08 (dd, *J* 9.0, 2.8, 1H), 6.93 (d, *J* 9.0, 1H), 3.82 (s, 3H); δ_H

(75 MHz, $CDCl_3$) 168.7, 167.8, 165.7, 156.5, 150.9, 140.0, 138.7, 135.1, 133.1, 133.0, 132.3, 131.2, 131.0, 130.3, 129.2, 129.0, 127.4, 123.3, 120.5, 119.0, 116.7, 115.7, 115.3, 114.3, 110.2, 103.5, 103.1, 85.8, 77.4, 57.1; HRMS (ESI): found 507.1461; $C_{30}H_{23}N_2O_6$ $[M+H]^+$ requires 507.1478.

Tetra-*n*-butylammonium 2-((3-benzamido-2-((2-(methoxycarbonyl)phenyl)ethynyl)phenyl)carbamoyl)-4-methoxyphenolate (5). A solution of tetrabutylammonium hydroxide (1.0 M in methanol, 10 µL, 0.01 mmol) was added dropwise to a RT solution of **3** (5 mg) in anhydrous dichloromethane (0.5 mL) under argon. The solution immediately changed from colourless to a bright yellow colour. After 30 min the reaction vessel was connected *via* tubing to a reservoir containing hexane (~3 mL) under argon to facilitate vapour diffusion crystallization. After 72 h only yellow oily film was observed, which was taken up in acetonitrile (0.5 mL) and immediately formed yellow crystalline plates, which were used for X-ray crystallographic analysis. *The yield was not determined.* MP: 165-167 °C (acetonitrile).

Conformational Analysis

In general, the position of the conformational equilibrium exhibited by switch molecules **2**, **3** and **4** was examined by comparison of the position of the ^{1}H NMR signal corresponding to the unsubstituted benzamide NH with its position in the 0% and 100% control molecules. By applying equation (I), a value ε is obtained whose value reflects the position of the equilibrium.

Equation (I) $$\varepsilon = \frac{\delta_{sw}-\delta_0}{\delta_{100}-\delta_0}$$

In extremis, ε assumes values of zero where the switch does not hydrogen bond to the benzamide, and unity where it exclusively does so.

DBU-Mediated Switching

A solution of switch **3** (1.0 mg, 0.0019 mmol) in $CDCl_3$ (600 µL) was placed in an NMR tube, and an initial ^{1}H NMR spectrum acquired. A solution of 1,8-diazabicycloundec-7-ene (0.05 M in $CDCl_3$) was subsequently added in portions (10 x 8 µL, 2 x 16 µL, 1 x 50). After each addition the NMR tube was shaken vigorously, and an additional ^{1}H NMR spectrum was acquired. The precise concentration of DBU at each stage was determined by integration of the DBU CH_2 multiplet at ~2.5 ppm relative to the switch compound's CH_3 signal at ~3.7 ppm. Repeating the experiment and analysis described above for the control compounds and plotting the position of the benzamide NH vs. equivalents of base generated the data presented in Figure 5.

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Notes and references

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† Due to low solubility in $CDCl_3$, modified control molecules were employed, see electronic supplementary information.

Electronic Supplementary Information (ESI) available: [^{1}H & ^{13}C NMR – including spectra, HRMS, IR, optical rotation]. See DOI: 10.1039/c000000x/. Crystallographic data (excluding structure factors) for **2**, **3** and **5** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1017646, 1017647 and 1017648 respectively) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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