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A Lewis acid-mediated conformational switch

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Molecules that change conformation in response to a stimulus have numerous uses, such as artificial chemoreceptors, novel drug delivery strategies and liquid crystal technology. Here we describe the design, synthesis and conformational behaviour of an isonicotinamide-substituted diphenylacetylene upon recognition of Lewis-acids, including metalloporphyrins. Binding of these at a remote site – the pyridyl nitrogen – increases hydrogen-bond donor ability of the proximal amide NH, causing an increased preference for the alkyne rotamer in which this hydrogen bond is maintained.

Introduction

Dynamic control of molecular conformation by the application of an external stimulus is a field that has attracted much interest in recent years,[1–6] with diverse stimuli such as Brønsted acids,[7–16] metal cations,[17–24] halide anions,[25–30] light[31–36] and redox couples[37–39] being employed. The potential applications of such molecules are equally diverse, including sensors,[40–42] liquid crystal displays,[8] and targeted drug delivery.[43] Induced conformational change also frequently occurs in biological systems, for example in the signal transduction carried out by G protein-coupled receptors,[44,45] and has been implicated in the protein misfolding and aggregation associated with some forms of amyloidosis.[46] The study of conformational changes in synthetic model systems can therefore give insight into the forces that govern these important cellular and extracellular processes, and inform future therapeutic strategies.

The diphenylacetylene motif is well-suited to the investigation of conformational equilibria since the low barrier for rotation about the acetylene allows rapid interchange between conformers.[47] Building on the seminal work of Kemp,[48,49] we have previously demonstrated that 2,6-bis(amido)-2'-alkylbenzoates are competent molecular balances, with the relative H-bond donor ability of the two amides dictating the conformational preference, and that this conformation can be perturbed by changes in pH or halide concentration.[50–52] We postulated that isonicotinamide **1** would be susceptible to conformational change under the influence of Lewis acids: the basic pyridine nitrogen should enhance the Brønsted acidity of the corresponding amide, increasing its hydrogen bond donor strength, and thus favouring the conformation in which it is hydrogen bonded to the ester (Figure 1).

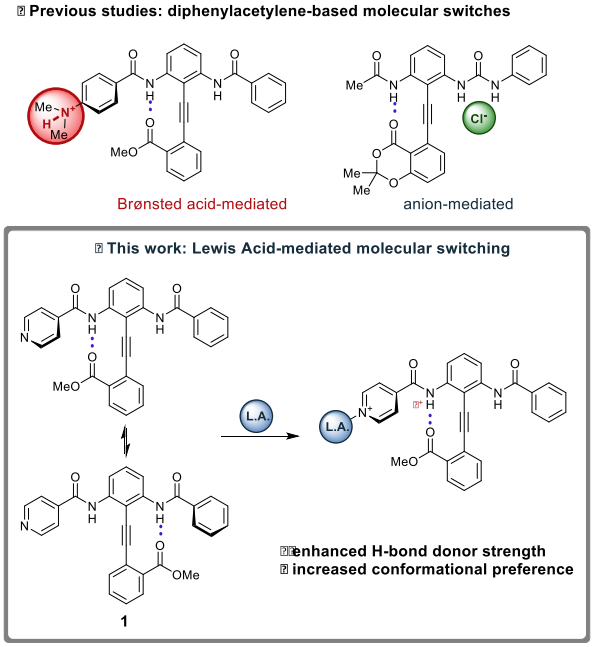
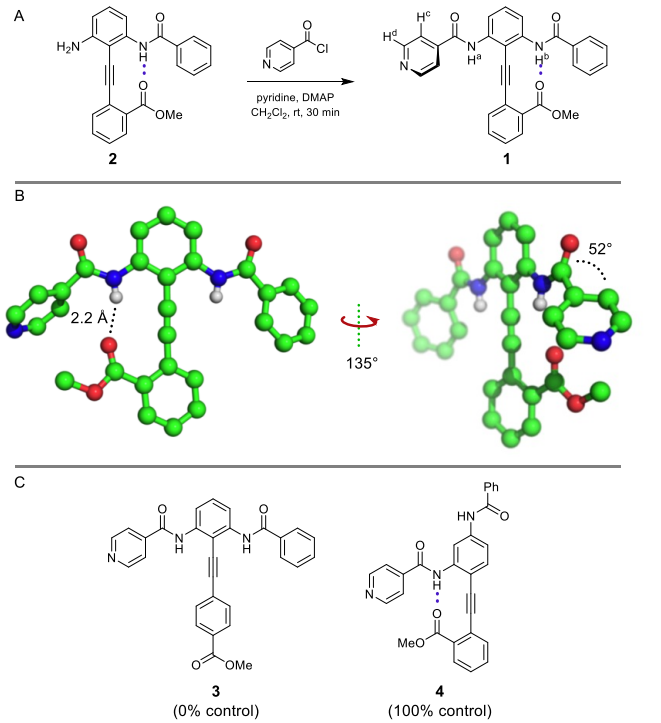


Figure 1. Conformational switching of diphenylacetylenes upon application of a stimulus: (a) Brønsted acid; (b) an anion; (c) Lewis acids.

Results and Discussion

Treatment of aniline **2** (prepared in a convergent manner from 2,6-dinitroaniline and methyl-2-iodobenzoate)[39,51] with isonicotinoyl chloride afforded the desired switch **1** in 65% yield (Scheme 1). The corresponding control compounds **3** and **4** were generated in an analogous manner (see ESI for full experimental detail).



Scheme 1. A: synthesis of **1**. B: X-ray crystal structure of **1** shown from two perspectives. The intramolecular N-H···O bond distance and dihedral angle between the carbonyl group and pyridine ring are indicated. C: structures of control molecules **3** and **4**. DMAP = 4-dimethylaminopyridine, rt = room temperature.

In the absence of an external stimulus, solution-phase data suggested that diphenylacetylene **1** exhibits a 2:1 bias in favour of hydrogen bonding to the isonicotinamide N-H (*vide infra*), consistent with its single crystal X-ray structure which displays an N-H···O bond distance of 2.2 Å (Scheme 1).[†] Congruent with previous studies,[51] hydrogen bonding to the ester causes a steric clash, leading to a 52° twist of the pyridine ring out of the plane of the diphenylacetylene.

Having demonstrated the conformational bias in the absence of an applied stimulus we investigated the conformational switching achieved upon recognition of Lewis acids. The addition of $BF_3{\cdot}OEt_2$ to a solution of **1** in $CDCl_3$ led to two discrete species observable in solution (see Figure 2, middle spectrum: 0.5 eq.), as opposed to protonation studies on similar systems in which rapid proton transfer led to a single, time-averaged set of signals.[51,53] The peak-broadening and small chemical shift changes observed for **1** upon addition of a sub-stoichiometric quantity of BF_3 are indicative of slow exchange between bound (**1**·BF_3) and unbound (**1**) states on the NMR time scale. Upon addition of one equivalent of the Lewis acid, a downfield shift was observed in H^a, from 9.41 to 9.70 ppm, whilst H^b moved upfield from 9.08 to 8.90 ppm (Figure 2). H^c and H^d experienced a downfield shift consistent with withdrawal of electron density when the pyridine lone pair is acting as a Lewis base. When the corresponding shifts in the control compounds **3** and **4** are considered, this equates to a 4:1 bias of switch **1** in favour of hydrogen bonding to H^a. These compounds are taken to define the chemical shift of H^a in the extreme cases where it is not hydrogen bonded (**3**, 0% control), and is entirely hydrogen bonded (**4**, 100% control) to the methyl ester acceptor,[54] and that the position of the conformational equilibrium is well-approximated by the chemical shift of H^a relative to these extremes.[51,55]

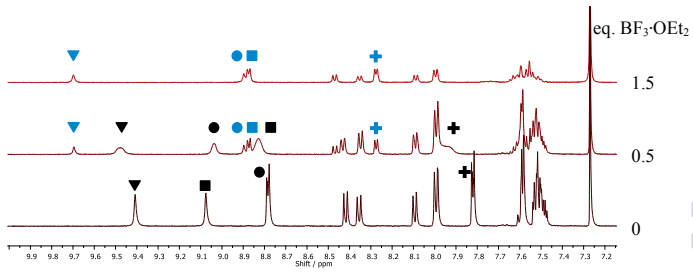


Figure 2. ^{1}H NMR spectral comparison of **1** (bottom) and **1**·BF_3 (top) in $CDCl_3$. H^a (▼), H^b (■), H^c (✚) and H^d (●) are indicated. Black markers indicate unmodified **1**, blue corresponds to **1**·BF_3.

Given the well-known propensity of pyridines to bind zinc(II) porphyrins,[56] we were intrigued as to whether the addition of **5** would elicit conformational change in our system. Zinc(II) porphyrin **5**, prepared from 3,5-di-*tert*-butyl benzaldehyde, pyrrole and zinc(II) acetate, was added to a solution of switch **1** in $CDCl_3$.[57] Both amide (H^a and H^b) and pyridine (H^c and H^d) hydrogens experienced a significant upfield shift due to their proximity to the porphyrin ring current (Figure 3). Whilst these shifts are diagnostic of zinc:pyridine binding, analysis of the conformational behaviour (with reference to controls **3** and **4**) shows minimal change (a ratio change from 2:1 to 7:3). This is likely due to unfavourable steric repulsion between the ester and porphyrin in the conformer of complex **1**·**5** when the isonicotinoyl amide hydrogen bond is engaged. Such behaviour reinforces the hypothesis that hydrogen bond donor strength is not the sole determinant of conformation, and that other non-covalent interactions must be considered during the design stages.[55]

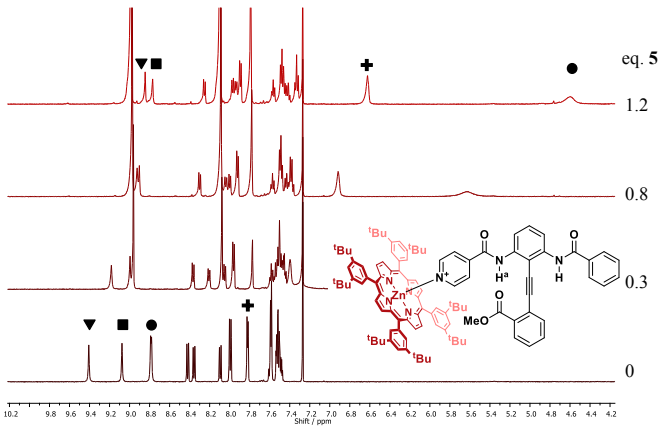


Figure 3. ^{1}H NMR spectral conformational analysis of **1** by chemical shifts of H^a (▼), H^b (■), H^c (✚) and H^d (●) on the addition of **5** in $CDCl_3$. The stoichiometry of **5** is calculated by integration relative to the pyrrole C-H singlet.

Given our previous work with conformational switching of diphenylacetylene-based compounds in the presence of a

Brønsted acid stimulus we were intrigued to see whether the pyridyl system would undergo analogous behaviour. Accordingly trifluoroacetic acid (TFA) was titrated into a solution of **1** in $CDCl_3$, and the position of the ^1H peak corresponding to N-H^a was examined as a function of the TFA equivalence.[58] An immediate downfield shift in H^a (▼) was observed upon the addition of TFA, concomitant with an upfield shift in H^b (■), and consistent with an increased bias towards the conformer in which H^a is hydrogen-bonded to the methyl ester. To assess the extent to which the change in shift was due to conformational change, as opposed to acidification alone, the titration experiment was performed on controls **3** and **4**. As the concentration of TFA is increased, the ^1H shift of H^a tends towards that of the 100% control **4**, consistent with a conformational change in favour of the isonicotinoyl amide. Prior to the addition of the acid, the conformation lies slightly in favour of this side, whereas upon addition of 3 eq. of TFA, the bias is increased to 4:1. This result suggests a comparable conformational bias with that obtained with Lewis acids. Both proton environments on the pyridine (H^c and H^d; ✚ and ● respectively) also move markedly downfield (from 7.82 to 8.28 ppm, and 8.78 to 8.87 ppm respectively) supporting the postulate that the pyridine nitrogen is undergoing protonation (Figure 4).[59]

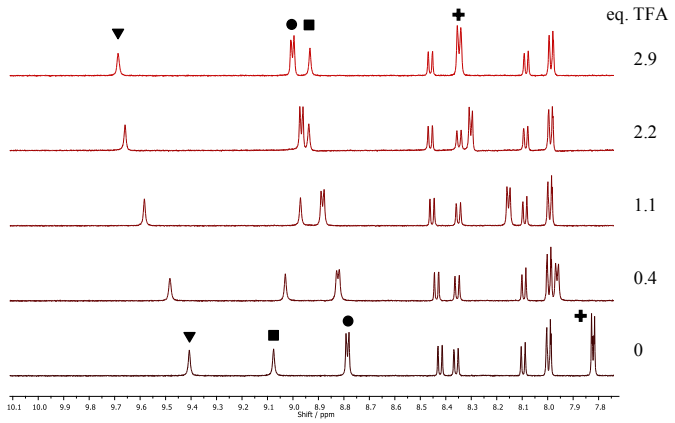


Figure 4. ^1H NMR spectral conformational analysis of switch **1** by chemical shifts of H^a (▼), H^b (■), H^c (✚) and H^d (●) on the addition of TFA in $CDCl_3$. The stoichiometry of TFA is calculated precisely by integration relative to an internal ^1H NMR standard.[58]

Conclusions

We have demonstrated that the conformational equilibrium of an isonicotinamide diphenylacetylene switch can be biased in response to a range of stimuli. This process is mediated remotely at the pyridine nitrogen atom; the resulting pyridinium ion enhances the adjacent amide as a hydrogen bond donor, leading to a conformational preference for the rotamer in which this N-H···O hydrogen bond is maintained. Switching molecules of this kind have fascinating potential applications in stimulus-responsive medicines and materials, and the ability to sense both Brønsted- and Lewis-acids provides a powerful tool for further investigations.

Experimental Details

For full experimental details for the synthesis of **2**, and for control compounds **3** and **4** by analogous routes to that described for **1**, please refer to the ESI.

Synthetic Procedures

Methyl 2-((2-benzamido-6-(isonicotinamido)phenyl)ethynyl) benzoate (1).[†] Thionyl chloride (139 μL, 1.6 mmol) was added to a solution of isonicotinic acid (100 mg, 0.81 mmol) in dichloromethane (3 mL). A drop of dimethylformamide was added, causing the reaction mixture to bubble vigorously for several minutes. After gas evolution had ceased (*ca.* 10 min) the reaction mixture was concentrated under a stream of nitrogen gas. The solid residue was taken up as a suspension in dichloromethane (2 mL) and pyridine (130 μL, 1.6 mmol) was added. The supernatant solution was removed *via* syringe and added to a stirred suspension of **2** (100 mg) and 4-dimethylaminopyridine (0.5 mg) in dichloromethane (2 mL). All solids were observed to dissolve immediately upon addition of the acid chloride solution. After 30 min the reaction mixture was diluted (dichloromethane, 25 mL) and water (10 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 petrol:ethyl acetate) to give **1** (83 mg, 65%) as a white powder. X-ray diffraction quality crystals were grown by vapour diffusion (chloroform/hexane); δ_H ($CDCl_3$, 500 MHz) 9.41 (1H, br s, H17), 9.07 (1H, br s, H22), 8.78 (2H, d, *J* 6.0, H21), 8.41 (1H, d, *J* 8.8, H13/H15), 8.35 (1H, d, *J* 8.2, H13/H15), 8.09 (1H, d, *J* 7.9, H4), 7.99 (2H, d, *J* 7.3, H25), 7.83–7.80 (2H, m, H20), 7.60–7.57 (3H, m, H6, H7 & H27), 7.54–7.45 (4H, m, H5, H14 & H26), 3.44 (3H, s, H1); δ_C ($CDCl_3$, 126 MHz) 165.8 (C23), 165.3 (C2), 164.9 (C18), 150.4 (C21), 142.6 (C19), 140.0 (C12/C16), 139.7 (C12/C16), 135.1 (C24), 132.9 (C6/C7), 132.6 (C6/C7), 132.0 (C27), 131.2 (C5), 131.1 (C4), 130.2 (C3), 129.0 (C5), 128.7 (C26), 127.4 (C25), 122.9 (C8), 121.8 (C20), 115.5 (C13 & C15) 103.1 (C9), 102.5 (C11), 85.6 (C10), 52.1 (C1); ν_{max} (neat): 3398, 2952, 1719, 1684, 1583, 1487, 1469, 1304, 695; HRMS (ESI): found 498.1417; $C_{29}H_{21}N_3NaO_4$ $[M+Na]^+$ requires 498.1424; MP: 197-199 ˚C (chloroform/hexane).

Zinc(II) Tetra(3,5-di-*tert*-butyl)phenylporphyrin (5). Based on a literature procedure,[60] pyrrole (83 μL, 1.3 mmol) was added to a solution of 3,5-di-*tert*-butylbenzaldehyde (250 mg, 1.15 mmol) in propionic acid (15 mL), and the resulting mixture was heated to reflux. After 3 h the reaction was allowed to cool to room temperature and was concentrated *in vacuo*. Residual propionic acid was removed by azeotrope with toluene (3 x 25 mL), and the resulting brown solid was taken up in dichloromethane, triethylamine (0.25 mL) was added and the mixture was stirred for 30 min. The solution was then passed twice through a plug of silica (eluent: dichloromethane) to remove polymeric impurities. The purple

residue was concentrated *in vacuo* and re-dissolved in chloroform (40 mL), and a solution of zinc(II) acetate dihydrate (0.25 g, 1.15 mmol) in methanol (5 mL) was added in one portion. The reaction mixture was stirred for 2 h then concentrated *in vacuo* and re-dissolved in dichloromethane:petrol (1:1 v/v). This solution was passed over a plug of silica (1:1 dichloromethane:petrol) and concentrated *in vacuo* to afford a purple solid. This was dissolved in chloroform (3 mL) and triturated by layering with methanol (3 mL) to give **5** (88 mg, 27 %) as a lustrous purple crystalline solid. δ_H ($CDCl_3$, 400 MHz) 9.02 (8H, s), 8.11 (8H, d, *J* 1.7), 7.79 (4H, t, *J* 1.8), 1.53 (72H, s).

Conformational Studies

BF_3-Mediated Switching

A stock solution of boron trifluoride diethyl etherate (0.507 M) was initially made up in $CDCl_3$. Switch **1** (2.4 mg, 0.005 mmol) was dissolved in $CDCl_3$ (0.6 mL), and an initial ^{1}H NMR spectrum was acquired. The stock solution of $BF_3{\cdot}OEt_2$ was added volumetrically (3 x 0.5 μL; 3 x 0.5 eq.), and a new ^{1}H NMR spectrum was acquired after the addition of each aliquot. The same procedure was carried out for control compounds **3** and **4**. The conformation at a given concentration of BF_3 was calculated on the basis of the position of H^b (see scheme 1) in the switch molecule **1**, relative to its position in the two control molecules **3** and **4** (see ESI for full details).

Zinc Porphyrin **5**-Mediated Switching

Switch **1** (2.4 mg, 0.005 mmol) was dissolved in $CDCl_3$ (0.6 mL), and an initial ^{1}H NMR spectrum was acquired. Zinc(II) porphyrin **5** was added in portions (6 x *ca.* 1 mg, 6 x *ca.* 0.17 eq.), and a new ^{1}H spectrum was acquired after the addition of each aliquot. The precise stoichiometry of **5** was calculated by integrating its 8H singlet at 8.97 ppm relative to the methyl group of the switch. The procedure was repeated for **3** and **4**, and the conformation at a given concentration of **5** was determined in an analogous manner to that described for the BF_3-mediated switching.

TFA-Mediated Switching

A stock solution containing trifluoroacetic acid (0.1 M) and 1,3,5-trimethoxybenzene (0.01 M, added as a ^{1}H NMR standard for integration) was made in $CDCl_3$. Switch **1** (1.0 mg) was dissolved in $CDCl_3$ (0.6 mL), and an initial ^{1}H NMR spectrum was acquired. The stock solution of TFA was added volumetrically (5 x 4 μL then 3 x 8 μL), and a new ^{1}H NMR spectrum was acquired after the addition of each aliquot. The precise stoichiometry of TFA added was determined by integrating the peak corresponding to the aromatic 3H singlet of 1,3,5-trimethoxybenzene relative to the 3H singlet corresponding to the ester in the switch **1**. The procedure was repeated for **3** and **4**, and the conformation at a given concentration of **5** was determined in an analogous manner to that described for the BF_3-mediated switching.

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Notes and references

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† The X-ray data for **1** has been deposited in the Cambridge Crystallographic Data Centre (CCDC 993562).

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