# Protonation activates anion binding and alters binding selectivity in new inherently fluorescent 2,6-bis(2-anilinoethynyl)pyridine bisureas†

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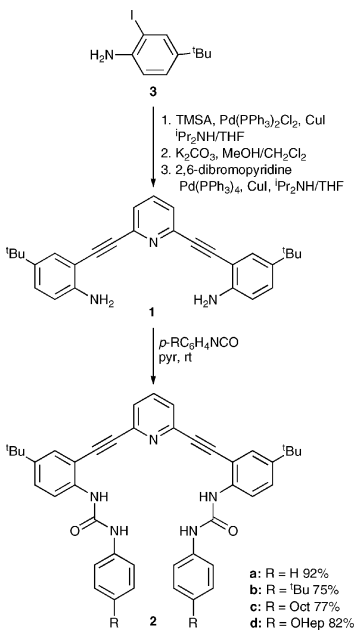
**A new class of 2,6-bis(2-anilinoethynyl)pyridine-based bisureas forms 1 : 1 complexes with halides; protonation enhances binding by over one order of magnitude, alters the binding selectivity, and provides a colorimetric indication of anion binding.**

The synthesis and study of hydrogen bonding receptors for anions is an engaging challenge because of the design difficulties associated with targeting such relatively diffuse, weakly basic and highly solvated analytes.[1] The prevalence of systems in both biological and supramolecular research whose behaviour is dictated by their hydrogen bonding ability with simple ions has also generated increased attention in this field.[2] We are developing a modular design strategy for the preparation of ion and molecule receptors based on an arylacetylene core, a well-known chromophore and fluorophore which lends itself to facile synthetic modification. The adaptation of phenylacetylene scaffolding to supramolecular chemistry has yielded a surprising array of host–guest and coordination complexes.[3] This rigid and linear motif has provided suitable geometric dimensions for both macrocyclic and acyclic ligands in transition metal complexes. Among the benefits of such core structures is the degree of preorganization resulting from use of the rigid, conjugated components. Given the elegant metal cation sensors that have been developed utilizing molecules such as these,[4] a modular receptor class that targets anions based on fluorescent cores may offer new applications in anion sensing. Ureas show well-known affinities for anions in solution,[5] and can easily be coupled to a modular synthetic scaffold built upon the 2,6-bis(2-anilinoethynyl)pyridine core **1** (Scheme 1). Furthermore, the ethynylpyridine core has the added feature that the protonation state of the pyridine nitrogen can regulate binding geometries and selectivities.[6]

We previously reported two sulfonamide-based ethynylpyridine receptors that showed promise as rigid receptors for anions and/or water in a [2 + 2] binding mode.[7] Both solid-state and serial dilution experiments revealed that these receptors form helical homodimers around two halide or water guests, as well as heterodimers incorporating both a halide and a water guest, depending upon the protonation state of the pyridine nitrogen. Unfortunately, the complicated equilibria present in solution prevented unambiguous determination of the host–guest stoichiometry in solution. We reasoned that an increase in the number of hydrogen bonding sites within a convergent receptor binding pocket would likely favour [1 + 1] complexation. To that end, we report herein the synthesis of the bisurea analogues **2a–d** derived from **1** and the solution and solid-state data of **2a** that confirm this binding hypothesis.

Key intermediate **1** can be synthesized easily on a multi-gram scale from known iodoaniline **3** (Scheme 1).[8] Sonogashira cross-coupling with (trimethylsilyl)acetylene, protiodesilylation in basic MeOH, and a second cross-coupling with 2,6-dibromopyridine affords bis-aniline **1** in >70% overall yield. Treatment of **1** with a variety of commercially available isocyanates gives bisureas **2a–d** in very good to excellent yields. Although our synthetic method allows for the facile preparation of a variety of these compounds, our focus for solution and solid-state studies has thus far been on the phenylurea derivative **2a**.

Slow evaporation of a MeOH solution of **2a** yielded crystals suitable for X-ray diffraction (Fig. 1).‡ Unlike the sulfonamide [2 + 2] dimers,[7] in which the "arms" wrap around the guest




**Scheme 1** Synthesis of urea receptors **2a–d**.

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† Electronic supplementary information (ESI) available: Experimental details and spectral data for **1**, **2a**, and **2a**·**TFA**, DFT calculated energies and structures for **2a**·**TFA**, titration data and binding isotherms. CCDC 717899 (**2a**·**MeOH**) and 717900 (**2a**·**HCl**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b901643k

 

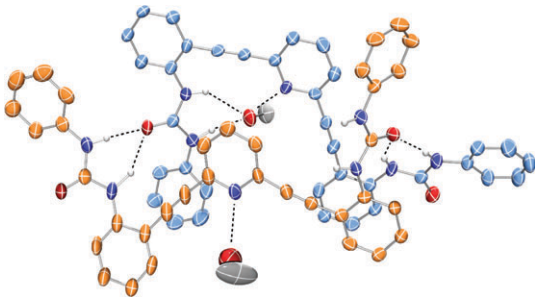

**Fig. 1** ORTEP representation (50% probability ellipsoids) of the two conformers of **2a·MeOH** with two solvent molecules in different H-bonding motifs. The "W" conformer (orange) and the "S" conformer (light blue) show half of the "SWWS" tetrameric repeat unit. The *tert*-butyl groups have been omitted for clarity. The N···O distances (2.889–3.291 Å) are typical for H-bonds (dashed lines). H atoms have been omitted.

molecules, the solid-state structure revealed that receptor **2a** adopts two different conformations—a backwards "S" and a "W" which stack in an "SWWS" fashion with the bottom "SW" in a centrosymmetrical arrangement with respect to the top "WS". In the W form, a MeOH guest donates a hydrogen bond to the pyridine nitrogen while both urea arms are pointed away from the MeOH. In the S form, a second MeOH donates a hydrogen bond to the pyridine nitrogen and accepts two hydrogen bonds from the urea N–H of one arm. Intermolecular urea N–H···O=C contacts make up the remainder of the [4 + 4] "tetrameric" repeat unit. There are no additional H-bonds between these "isolated" units.

As in the case of the neutral sulfonamide receptors,[7] the neutral bisurea receptors show an affinity for neutral guests (*e.g.*, MeOH, Fig. 1). Protonation of the central pyridine nitrogen activates strong anion binding in this system as well. To perform binding constant measurements, the trifluoroacetate and tetrafluoroborate salts were prepared under the assumption that these weakly basic, larger anions would not strongly compete for the binding pocket in this receptor. (Preliminary molecular models had indicated halides were appropriately sized guests.) Fortunately, **2a·TFA** proved easy to prepare on large scale as an anhydrous, analytically pure crystalline solid. While a crystal structure of the TFA-protonated urea has so far proven elusive,[9] DFT modelling of this complex indicated that the urea backbone was flexible enough to partially accommodate the $CF_3CO_2^-$ counter-ion, with one oxygen stabilized by three hydrogen bonds between the central pyridine, and one urea arm (Fig. 2).[10] Nonetheless, the binding pocket in this model is sufficiently compact that the receptor arms must twist significantly from planarity to allow the receptor to accommodate such a large guest. While smaller oxoanions may fit more easily into the binding pocket of protonated **2a**, we reasoned that any competition between the trifluoroacetate and halide guests would favour the guest with the greater number of stabilizing hydrogen bonds, *i.e.*, the halide.

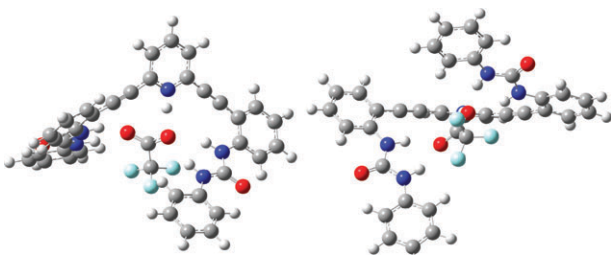

**Fig. 2** Top (left) and side (right) views of the DFT calculated position of the trifluoroacetate anion in protonated **2a**.

UV-Vis spectrophotometric titrations of protonated **2a·TFA** with $Bu_4NCl$, $Bu_4NBr$ and $Bu_4NI$ were carried out, and the data individually fit with the HyperQuad 2006 suite of programs (see ESI†).[11] In comparison with the TFA salt, titration with the tetraalkylammonium salts showed a new absorbance band at 422 nm which increased in intensity and shifted bathochromically. Isosbestic behaviour was observed when sufficient time was allowed between aliquots for the system to reach equilibrium (less than 3 min). Binding constants for **2a** were obtained *via* titrations using $^1$H-NMR spectroscopy since the UV-Vis spectra of the neutral receptor did not exhibit any significant spectroscopic handle. These latter data were fit to a [1 + 1] model using HypNMR 2006.[11]

As shown in Table 1, protonation of **2a** activates the halide binding ability of this receptor class. Whereas unprotonated **2a** obeys the classic Hofmeister series, protonated **2a** strongly binds all three halides in the range of 42 700–83 200 $M^{-1}$. In fact, the binding constants for bromide and iodide are two and four orders of magnitude larger in the protonated receptor compared to the neutral receptor. However, these are apparent binding constants and a decrease in the observed binding values from competition with the trifluoroacetate counter-ion in the **2a·TFA** receptor must be taken into account.[12]

Evidence of our target [1 + 1] binding behaviour was confirmed in the solid state. X-Ray quality crystals of **2a·HCl** were grown by addition of HCl to a solution of **2a** in hexanes–EtOAc.‡ In contrast to the free-base receptor, the two urea arms of **2a·HCl** envelop the chloride ion affording a [1 + 1] host–guest complex with a total of five N–H···Cl hydrogen bonds (N···Cl distances 3.03–3.66 Å, Fig. 3).

The neutral receptor relies entirely upon the urea functionality for its hydrogen bonding capabilities, and thus shows preference for the more basic guests. The arms in the neutral receptor seem to be too far apart to participate effectively in cooperatively stabilizing the guest, and exhibit both the S and W forms, while the U-shaped [1 + 1] complex is not observed. In contrast to the neutral receptor, **2a·TFA** has a well-defined binding pocket. The pyridinium hydrogen provides a third point of contact, which anchors the receptor arms in the desired conformation upon guest binding and converges all available hydrogen bonds to the binding pocket.

**Table 1** Calculated Ka ($M^{-1}$) fit to a [1 + 1] model.[11] Average values from triplicate measurements are shown. Experimental errors are *ca.* ±10%

| Guest | **2a**[a] | **2a·TFA**[b] |
|---|---|---|
| $Cl^-$ | 2100 | 42 700 |
| $Br^-$ | 400 | 61 700 |
| $I^-$ | Not measurable | 83 200 |

[a] $^1$H-NMR data. [b] UV-Vis data.

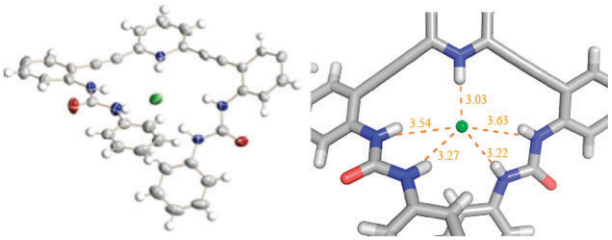


**Fig. 3** ORTEP representation of the protonated receptor **2a·HCl** with ellipsoids at the 50% probability level. On the right, the dashed lines indicate N–H···Cl hydrogen bonds.

This disrupts the intermolecular hydrogen bond network that held the neutral tetrameric complex intact and yields the [1 + 1] complex while disfavouring our previously observed [2 + 2] dimeric and SWWS tetrameric complexes.[7] The slight preference for the less basic $Br^-$ and $I^-$ anions over $Cl^-$ could be attributed to a larger binding pocket in the U-shaped conformation, which mitigates the traditional bias in binding more basic anions to favour the larger halides.

In conclusion, we have synthesized and performed a preliminary analysis on a new class of hydrogen bonding receptors for halide anions, based on an inherently fluorescent arylacetylene core. Bisurea receptor **2a** binds chloride, bromide and iodide and fits with good agreement to a [1 + 1] model, which significantly simplifies the solution studies of this receptor class relative to the previously reported sulfonamide analogues. Protonation of the pyridyl nitrogen in the receptor increases the association constant by more than an order of magnitude over the free-base receptor, and alters the selectivity between the larger halides and chloride. The increasing discovery of anionic contaminants in the environment, and the facile mobility of anions in natural systems, make developing new approaches for anion sensing and binding vitally important. These modular receptors offer potential long-term applications in the design of new materials for remediation and sensing and the development of new molecular probes for anions.

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## Notes and references

‡ X-Ray diffraction data were collected at low temperature on a Bruker APEX diffractometer with MoKα-radiation ($\lambda$ = 0.71073 Å). Absorption corrections were applied by SADABS. The structures were solved using direct methods. All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms involved in H-bonds were found on the residual densities and refined with isotropic thermal parameters. Other H atoms were treated in calculated positions in a rigid group model. One of the *t*-Bu groups in **2a·HCl** is disordered over two positions and refined with restrictions on its geometry. The investigated compounds crystallized as thin plates which provided weak reflections at high angles. The large $R_{int}$ values are a result of weak reflections at high angles. All calculations were performed by the Bruker SHELXTL package.

Crystal data for **2a·MeOH**: $C_{44}H_{45}N_5O_3$, $M$ = 691.85, triclinic, 0.32 × 0.14 × 0.04 mm, $P\bar{1}$, $a$ = 15.977(4) Å, $b$ = 17.510(5) Å, $c$ = 17.934(5) Å, $\alpha$ = 115.738(6)°, $\beta$ = 92.041(5)°, $\gamma$ = 115.933(5)°, $V$ = 3903.6(18) Å$^3$, $Z$ = 4, $T$ = 173 K, $\rho_{calcd}$ = 1.177 g cm$^{-3}$, $\mu$(MoKα) = 0.075 mm$^{-1}$; $2\theta_{max}$ = 50°, 28 502 reflection measured, 13 659 reflections independent [$R_{int}$ = 0.0842], 981 parameters, $R_1$ = 0.0836, w$R_2$ = 0.1940 (reflections with $I > 2\sigma(I)$), GooF = 1.006, max/min residual electron density +1.135/−0.213 e Å$^{-3}$.

Crystal data for **2a·HCl**: $C_{43}H_{42}ClN_5O_2$, $M$ = 696.27, 0.25 × 0.12 × 0.02 mm, triclinic, $P\bar{1}$, $a$ = 12.237(2) Å, $b$ = 17.221(3) Å, $c$ = 20.026(3) Å, $\alpha$ = 107.216(3)°, $\beta$ = 101.613(4)°, $\gamma$ = 103.090(4)°, $V$ = 3759.5(11) Å$^3$, $Z$ = 4, $T$ = 203 K, $\rho_{calcd}$ = 1.230 g cm$^{-3}$, $\mu$(MoKα) = 0.145 mm$^{-1}$; $2\theta_{max}$ = 50°, 27 464 reflection measured, 13 172 reflections independent [$R_{int}$ = 0.1307], 955 parameters, $R_1$ = 0.0856, w$R_2$ = 0.1078 (reflections with $I > 2\sigma(I)$), GooF = 0.945, max/min residual electron density +0.371/−0.275 e Å$^{-3}$.

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