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Polarisation effects on the H-bond acceptor properties of sulfonamides†

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The strengths of H-bonding interactions in networks are affected by cooperativity between the interacting sites. Compounds with an intramolecular H-bond between a sulfonamide NH group and pyridine nitrogen were used to measure the magnitude of cooperative effects on intermolecular H-bonding interactions with the sulfonamide oxygen. X-ray crystallography and ¹H NMR experiments confirm the presence of the intramolecular H-bond and show that it is maintained in the 1:1 complex formed with perfluoro-*tert*-butanol (PFTB) in *n*-octane solution. Association constants for formation of 1:1 complexes with PFTB were determined using UV/Vis absorption titrations for a series of compounds equipped with different pyridine groups. Substituents on the pyridine were used to tune the strength of the intramolecular H-bond and investigate the effects on the strength of the intermolecular H-bond. Electron-donating groups on the pyridine that increase the strength of the intramolecular H-bond were found to increase in the strength of the intermolecular interaction with PFTB. The results were used to determine the H-bond acceptor parameters, β , for the sulfonamide oxygen group, and the values show a linear relationship with the value of β for the pyridine nitrogen. The slope of this relationship corresponds to the cooperativity parameter, κ , which is +0.16. The positive cooperativity observed in H-bonded sulfonamides is comparable to the value measured previously for the amide group ($\kappa = +0.20$).

Non-covalent interactions are key in determining the properties and structures of biomolecules,¹ materials,² and supramolecular systems.³ To a first approximation the thermodynamic properties of a non-covalent interaction can be predicted according to the properties of the individual, isolated molecules.⁴ However, polar interactions such as H-bonding can alter the molecular charge distribution leading to cooperative effects in multiply H-bonded

networks.⁵ Cooperativity in supramolecular assemblies containing alcohols^{5,6} and amides has been studied previously.^{7–9} Formation of an interaction with the H-bond donor site polarises the functional group, so that the H-bond acceptor site becomes a stronger H-bond acceptor. The resulting positive cooperativity has been investigated in H-bonded networks using computational approaches to make theoretical predictions,^{10–17} and using experimental techniques such as calorimetry,^{18–20} NMR,^{6,8,21,22} and IR spectroscopy.^{23–26} We have developed an experimental approach for quantifying H-bond cooperativity by measuring the interplay between an intramolecular and intermolecular H-bond. Here we apply this approach to sulfonamides.

Sulfonamides are of interest due to their widespread use in the pharmaceutical industry as anti-bacterial agents, and quantification of cooperative effects in H-bonded networks may have implications in drug design.²⁷ Fig. 1 shows the approach. Molecular mechanics conformational searches and density functional theory (DFT) calculations suggest that this framework should favour an intramolecular H-bond between the pyridine acceptor and the sulfonamide NH group. The H-bond acceptor properties of the pyridine can be tuned by using the X substituent, and the methylene spacer ensures there is no through bond communication between the sulfonamide and pyridine units. The relationship between pyridine substituent X and the H-bond acceptor properties of the sulfonamide can be quantified by measuring association

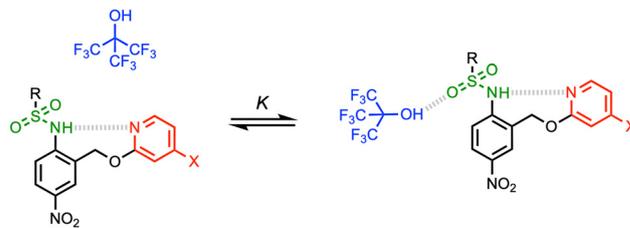


Fig. 1 Interaction of a H-bonded sulfonamide group (green) with perfluoro-*tert*-butanol (PFTB, blue). X is a substituent that modulates the H-bond acceptor properties of the pyridine (red), and R is a solubilising group.

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constants (K) for formation of 1 : 1 complexes with a strong H-bond donor, perfluoro-*tert*-butanol (PFTB), in *n*-octane solution.

The experiment in Fig. 1 requires a set of sulfonamides equipped with different pyridine derivatives (Scheme 1). Compound **1** is a reference compound with no intramolecular H-bond, which was synthesised by condensation of commercially available 2-methyl-4-nitroaniline and 1-octanesulfonyl chloride (Scheme 1(a)). Compound **2** was prepared by reaction of the previously reported aniline with 1-octanesulfonyl chloride,⁹ and this compound was then used in an S_NAr reaction to obtain compound **3** (Scheme 1(b)). Compounds **4–7** were synthesised by reaction of the previously reported aniline-pyridine conjugates with 1-octanesulfonyl chloride (Schemes 1(c) and (d)).⁹ Although the yields were very low, sufficient material was obtained for UV/Vis and ¹H NMR titration experiments.

The three-dimensional structure of compound **3** was determined by single crystal X-ray diffraction, and the intramolecular H-bond illustrated in Fig. 1 is clearly present (Fig. 2). Fig. 3 shows the ¹H NMR spectra of compounds **3–8** recorded in chloroform, which indicate that this interaction is also present in solution. The chemical shift of the signal due to the sulfonamide NH proton in compound **1** is 6.75 ppm, but the presence of the pyridine ring in compounds **3–8** leads to a downfield shift of between +4 and +7 ppm in chloroform. Similar behaviour was observed in *n*-octane solution (see δ_f values in Table 1), and ¹H NMR dilution experiments showed no evidence of self-aggregation (see ESI†). The large increases in NH chemical shift compared with compound **1** suggest that there is an intramolecular H-bond between the sulfonamide NH group and the pyridine nitrogen in all of compounds **3–8**. The size of the downfield shift depends on the nature of the pyridine X substituent, and there is a good correlation

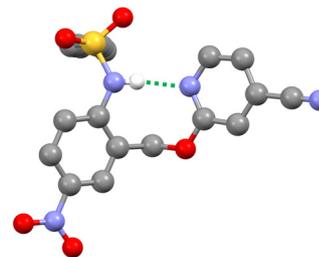


Fig. 2 Molecular structure of **3** taken from the X-ray crystal structure. The intramolecular H-bond is shown as a dotted line.

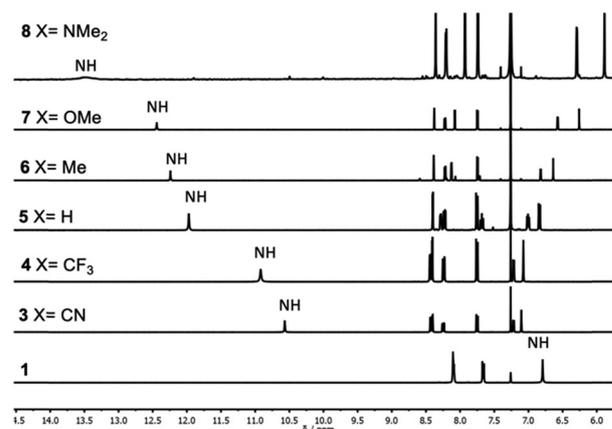
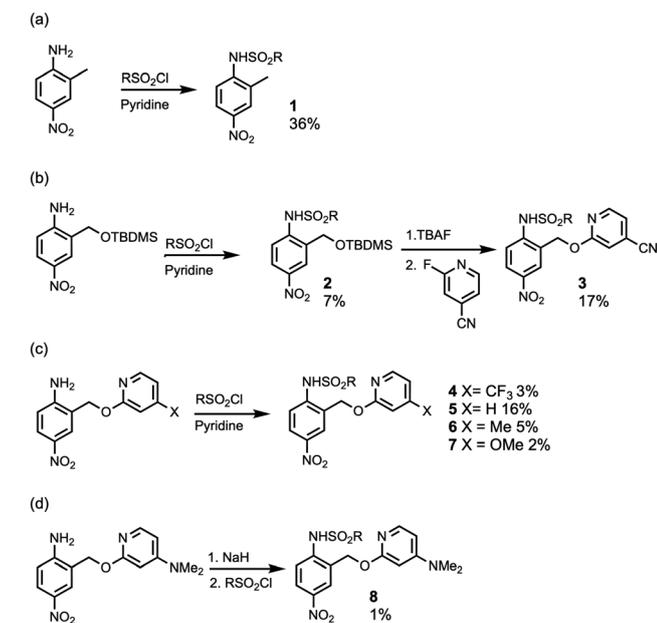


Fig. 3 Partial 400 MHz ¹H NMR spectra of compounds **1** and **3–8** (2–50 mM) recorded in chloroform-*d* at 298 K. The signal due to the sulfonamide NH proton is highlighted.

Table 1 Association constants for formation of 1 : 1 complexes with PFTB measured by UV/Vis absorption titrations^a and limiting chemical shifts of the signal due to the sulfonamide NH proton (ppm) measured by ¹H NMR titrations in *n*-octane at 298 K

Compound	X	$\beta(\text{pyridine})^b$	K_1/M^{-1}	δ_f	δ_b
1	—	—	47 ± 7	6.18	6.22
3	CN	5.4	46 ± 7	10.60	10.74
4	CF ₃	5.8	52 ± 12	10.82	10.97
5	H	7.2	69 ± 11	11.66	11.95
6	Me	7.7	76 ± 19	11.86	12.22
7	OMe	7.8	92 ± 6	— ^c	— ^c
8	NMe ₂	9.5	123 ± 12	12.79	— ^c

^a Errors are quoted as two standard deviations based on at least three different experiments. ^b Values from ref. 9. ^c Signals not visible in the NMR spectra.



Scheme 1 Synthesis of compounds **1–8**. R = *n*-octyl.

($R^2 = 1.00$) with the H-bond acceptor parameters of the corresponding 4-X-pyridines, $\beta(\text{pyridine})$. These observations suggest that the properties of the intramolecular H-bond in compounds **3–8** depend on the H-bond acceptor properties of the pyridine nitrogen.

The interaction with perfluoro-*t*-butanol (PFTB) was investigated using UV/Vis absorption spectroscopy titrations in *n*-octane. Fig. 4 shows the data for titration of PFTB into **5**,



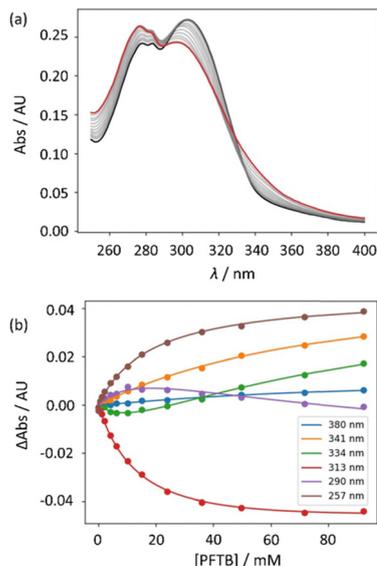


Fig. 4 (a) UV/Vis absorption spectra for the titration of PFTB into **5** (0.0278 mM in *n*-octane at 298 K). The spectrum of **5** and the final point of the titration are reported in black and in red, respectively. (b) Fit of the absorbance at six different wavelengths to a 1:2 binding isotherm ($K_1 = 69 \text{ M}^{-1}$, $K_2 = 14 \text{ M}^{-1}$).

which is representative of the data obtained for all of the sulfonamides (see ESI†). Addition of PFTB lead to disappearance of the band at 310 nm and appearance of a new band at 270 nm. We have previously shown that H-bonding of PFTB to the nitro group of 2-methyl-4-nitroaniline leads to a red shift of the absorbance maximum, so the blue shift in Fig. 4a suggests that PFTB binds to the sulfonamide oxygen.⁹ There is no well-defined isosbestic point in Fig. 4a, which indicates that this is not a simple two-state equilibrium. The UV/Vis titration data fit well to a 1:2 binding isotherm (Fig. 4b) with a weak second binding interaction. The association constants for formation of the 1:1 PFTB complexes (K_1) are reported in Table 1 (see ESI† for K_2 values). The values of K_1 increase with the electron donating ability of the substituent on the pyridine ring, as measured by the H-bond acceptor parameter of the corresponding 4-X-pyridine, $\beta(\text{pyridine})$, which indicates that there is positive cooperativity between the intramolecular and intermolecular H-bonds in these complexes.

To ascertain whether intermolecular H-bonding with PFTB competes with the intramolecular H-bond in compounds **3–8**, ^1H NMR titrations were carried out in *n*-octane. The data for titration of PFTB into **3** is shown in Fig. 5 (see ESI† for other compounds). The NMR titration data for all compounds were fit to a 1:2 binding isotherm using the association constants determined from the UV/Vis titrations in order to determine the complexation-induced changes in chemical shift. For the 1:1 complex, the limiting complexation-induced change in ^1H NMR chemical shift (difference between the free chemical shift, δ_f , and bound chemical shift, δ_b , in Table 1) of the signal due to the sulfonamide NH proton was positive in all cases (+0.14 to +0.36 ppm). When a similar titration was carried out using compound **1**, which does not have an intramolecular H-bond,

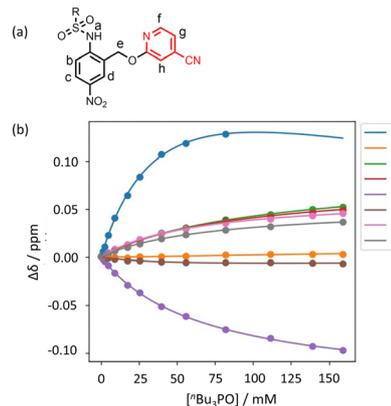


Fig. 5 (a) Proton labelling scheme for compound **3**. R = 1-octyl. (b) Fit of the ^1H NMR chemical shifts measured in *n*-octane at 298 K to a 1:2 binding isotherm.

the corresponding change in chemical shift for formation of the 1:1 complex was less than +0.1 ppm. The increase in the chemical shift of the signal due to the sulfonamide proton suggests that the intramolecular H-bond in compounds **3–8** is stabilised by formation of the intermolecular H-bond in the 1:1 PFTB complex. The other proton that showed a large complexation-induced change in ^1H NMR chemical shift in the 1:1 complex was proton b, which is *ortho* to the sulfonamide group (Fig. 5, see ESI†). The upfield shift of 0.05–0.07 ppm suggests that proton b is in close proximity to PFTB in the 1:1 complex, which is consistent with the structure of the complex illustrated in Fig. 1.

The X-ray crystal structure and NMR data show there is an intramolecular H-bond between the sulfonamide NH and the pyridine nitrogen in compounds **3–8**, and that this interaction is maintained on formation of a 1:1 complex with PFTB. The association constants for formation of the 1:1 complexes in Table 1 can therefore be used to quantify the effect of the intramolecular H-bond on the intermolecular H-bond. The β parameters that describe the H-bond acceptor properties of the sulfonamide group in compounds **3–8** were determined using eqn (1).⁴

$$\Delta G^\circ/\text{kJ mol}^{-1} = -RT\ln(K_1/2) = -(\alpha - \alpha_s)(\beta - \beta_s) + 6 \quad (1)$$

where α is H-bond donor parameter for PFTB (4.9),²⁸ and α_s and β_s are the H-bond parameters of the solvent (1.2 and 0.6 respectively for *n*-octane).²⁹

The factor of two in eqn (1) accounts for the degeneracy of the 1:1 complex in which the H-bond donor can bind to one of two different oxygens in the sulfonamide group.³⁰ Fig. 6 shows that there is a linear relationship between the value of the H-bond acceptor parameter for the sulfonamide group in compounds **3–8** and the H-bond acceptor parameter for the corresponding 4-X-pyridine. The slope of the line of best fit is +0.16, which is defined as the cooperativity parameter, κ , of the sulfonamide group.^{6,9} This value is slightly lower than the value of κ previously measured for the amide group using the same approach, +0.20,^{7,9} and much lower than the value measured



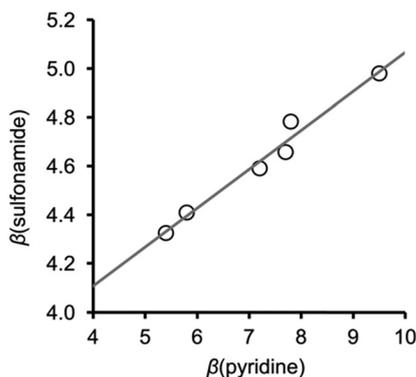


Fig. 6 Relationship between the H-bond acceptor parameter of the sulfonamide group in compounds **3–8**, $\beta(\text{sulfonamide})$, and the H-bond acceptor parameter of the corresponding 4-X-pyridine, $\beta(\text{pyridine})$. The line of best fit is $y = 0.16x + 3.5$ ($R^2 = 0.97$).

for the phenol OH group, +0.33.⁶ It has been postulated that the positive cooperativity observed for the amide group is due to polarisation of the π -electron density away from the nitrogen and towards the oxygen when a H-bond is formed.^{11,31} The slightly lower value of κ measured for sulfonamides may be related to the reduced π -delocalisation compared with amides.

Compounds containing an intramolecular H-bond between a pyridine and a sulfonamide NH group were synthesised to quantify the cooperativity between two H-bonding interactions with a sulfonamide group. X-ray crystallography and ¹H NMR experiments confirmed the presence of the intramolecular H-bond and showed that this interaction is maintained on formation of a 1:1 complex with perfluoro-*tert*-butanol (PFTB) in *n*-octane. UV/Vis absorption titrations were used to measure the association constants for binding of PFTB to a series of compounds in which the H-bond acceptor properties of the intramolecular H-bond were tuned using substituents in the 4-position of the pyridine ring. These association constants were used to determine the H-bond acceptor parameters of the sulfonamide groups, β , and a linear correlation was found with the corresponding H-bond acceptor parameters of the pyridine groups. The cooperativity parameter, κ , measured from this relationship was +0.16, which indicates positive cooperativity that is similar in magnitude to the positive cooperativity observed for amides ($\kappa = +0.20$).^{7,9}

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Data availability

All supporting data is provided in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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