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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 ^{1}H 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 (κ = +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

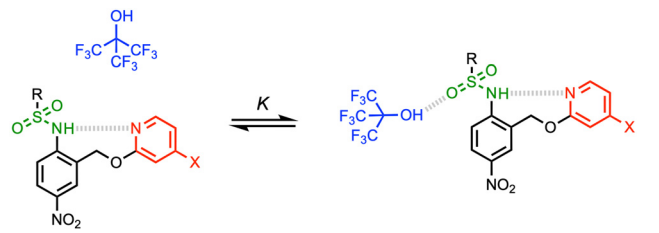

Fig. 1 Interaction of a H-bonded sulfonamide group (green) with perfluoro-*tert*-butanol (PFTB, blue). X is a substituent that modulates the H-bond acceptor properties of the pyridine (red), and R is a solubilising group.

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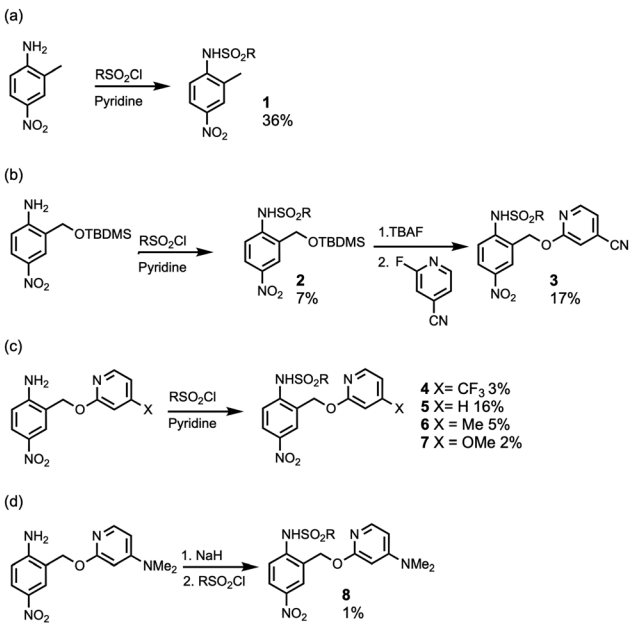
† Electronic supplementary information (ESI) available: Materials and methods, synthetic procedures, full characterization of all compounds, ^{1}H NMR and UV/Vis absorption titration data, and X-ray crystallography data are available in the Supplementary Material. CCDC 2352883. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4cc03530e

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 ^{1}H 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 ^{1}H 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 ^{1}H 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



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

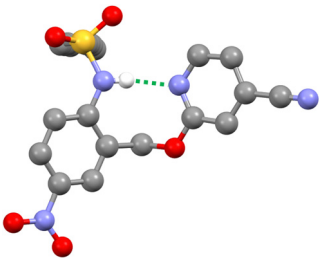


Fig. 2 Molecular structure of **3** taken from the X-ray crystal structure. The intramolecular H-bond is shown as a dotted line.

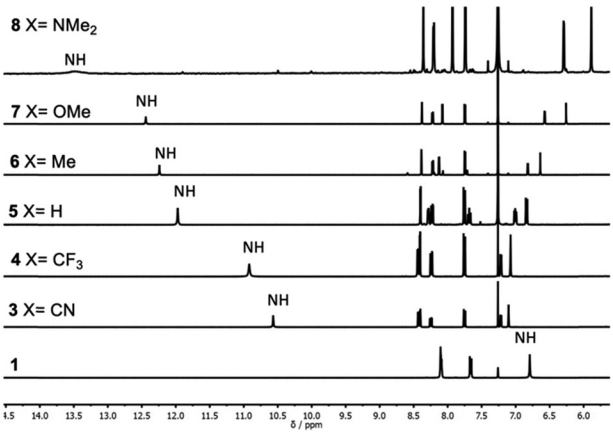


Fig. 3 Partial 400 MHz ^{1}H NMR spectra of compounds **1** and **3**–**8** (2–50 mM) recorded in chloroform-*d* at 298 K. The signal due to the sulfonamide NH proton is highlighted.

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 ^{1}H NMR titrations in *n*-octane at 298 K

Compound	X	β(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.

(R^2 = 1.00) with the H-bond acceptor parameters of the corresponding 4-X-pyridines, β(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**,

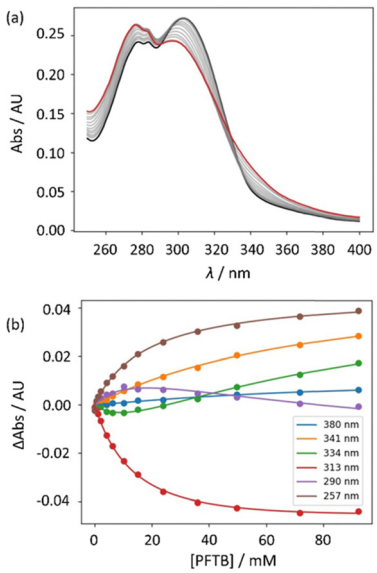


Fig. 4 (a) UV/Vis absorption spectra for the titration of PFTB into **5** (0.0278 mM in *n*-octane at 298K). The spectrum of **5** and the final point of the titration are reported in black and in red, respectively. (b) Fit of the absorbance at six different wavelengths to a 1 : 2 binding isotherm (K_1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

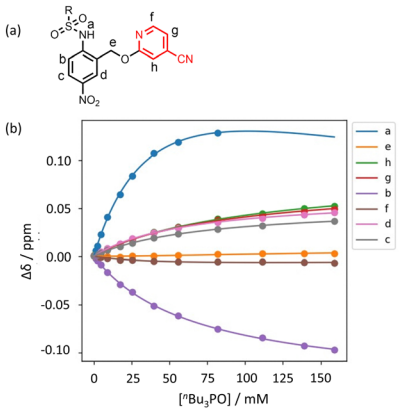


Fig. 5 (a) Proton labelling scheme for compound **3**. R = 1-octyl. (b) Fit of the ^{1}H NMR chemical shifts measured in *n*-octane at 298 K to a 1 : 2 binding isotherm.

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, β(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**, ^{1}H 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 ^{1}H 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, 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 ^{1}H 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]

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

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

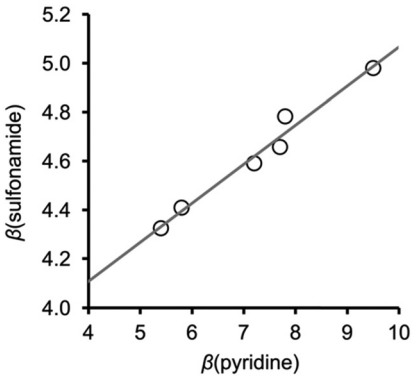


Fig. 6 Relationship between the H-bond acceptor parameter of the sulfonamide group in compounds **3–8**, β(sulfonamide), and the H-bond acceptor parameter of the corresponding 4-X-pyridine, β(pyridine). The line of best fit is $y = 0.16\,x + 3.5$ ($R^2 = 0.97$).

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 ^{1}H 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 (κ = +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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