How strong is a π-facial hydrogen bond?

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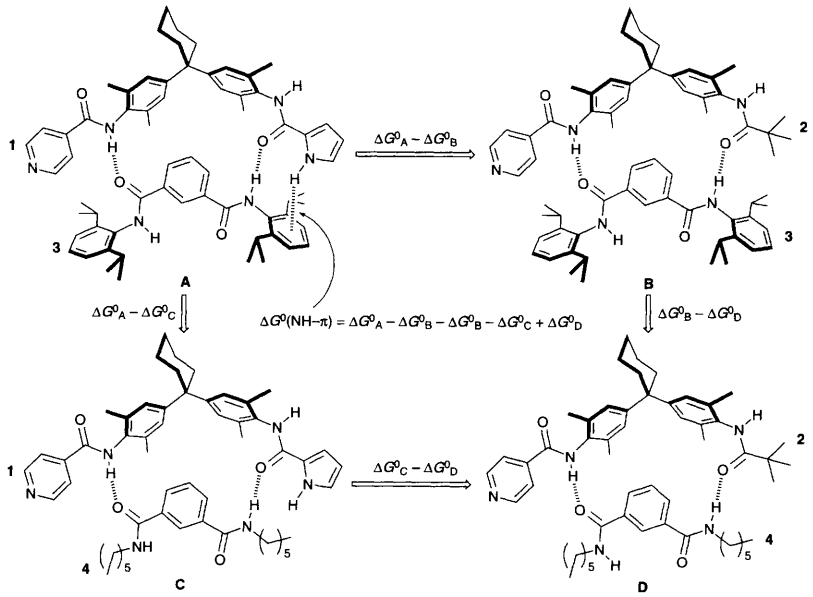
Functional group substitutions (chemical mutations) in a molecular zipper complex have been used to construct a thermodynamic cycle for estimating the strength of a π-facial H-bond between an NH group and an aromatic ring resulting in a lower limit of −4.5 ± 0.5 kJ mol^{-1} for the magnitude of the intermolecular NH-π interaction in chloroform.

Cooperation between multiple, weak non-covalent interactions is responsible for the exquisite specificity found in the folding and recognition properties of biopolymers. The fundamental interactions which govern these processes have therefore been the subject of much investigation over many years. There is structural and spectroscopic evidence that suggests that the concentration of π-electron density on the faces of aromatic rings allows them to act as acceptors in H-bonding interactions with donors such as amide NH groups.[1–5] However, such structural studies do not provide any information on how strong these interactions are and whether, in competition with other interactions such as conventional H-bonds, they have any practical significance for molecular recognition processes in solution.[6] We have therefore used chemical double mutant cycles to obtain quantitative thermodynamic information about the magnitudes of these weak non-covalent functional group interactions,[7] and here report the application of this approach to an NH–π H-bond.

The double mutant principle is illustrated in Scheme 1. The complexes are based on the molecular zipper motif which was described previously and tolerates a range of functional group substitutions.[7] We want to quantify the NH–π interaction in complex **A**. Comparing the stability of complex **A** with complex **B** can give us some idea of the magnitude of the interaction, but this chemical mutation not only removes the interaction of interest, it also removes secondary interactions such as the repulsion between the amide NH of **3** and the pyrrole NH of **1**.† The magnitude of such secondary interactions can however be quantified by comparing complexes **C** and **D**. Thus with the two single mutants (**B** and **C**) and the double mutant (**D**), we can construct a thermodynamic cycle which allows us to measure the NH–π interaction (strictly the pyrrole–π interaction) in the absence of secondary effects.[8]

The structure of complex **A** was determined from the limiting complexation-induced changes in chemical shift in ^{1}H NMR titration experiments and a ROESY experiment (Fig. 1). These observations are characteristic of a zipper structure with the isophthaloyl ring of **3** bound in the cavity formed by the bis(aniline) fragment of **1**. The large upfield shift observed for the signal due to the pyrrole NH proton clearly shows that it lies over the ring current on the face of the aniline π-system in compound **3**. Moreover, the change in the chemical shift of this signal is much larger than the changes in chemical shift observed for the signals due to the other pyrrole protons. This shows that the point of contact is the pyrrole NH not the neighbouring CH group, and so the interaction is dominated by the NH–π interaction rather than CH–π (or π–π) interactions. The behaviour of the amide signals is also informative. The signal due to the pyridine amide experiences a large downfield shift, which indicates that it forms an H-bond to one of the carbonyl oxygens of **3**. In contrast, the signal due to the pyrrole amide is unaffected by complexation, suggesting that this NH is



Scheme 1 Chemical double mutant cycle for measuring the terminal NH–π interaction in complex **A**. ΔG°_A, ΔG°_B, ΔG°_C and ΔG°_D denote the changes in standard Gibbs free energy for association of the complexes **A**, **B**, **C** and **D**.

not involved in H-bonding. Thus the downfield shift observed for the amide signal of **3** must be due to an H-bond between one of the amide NHs and the carbonyl oxygen of the pyrrole amide of **1**. NOEs show that the pyrrole NH is *trans* to the pyrrole amide NH (Fig. 1), and so these observations are also consistent with an NH–π interaction.

Although we have been unable to obtain single crystals of complex **A**, we have crystallised the single compound **5** which contains all the key interaction sites.‡ The geometric relationship between two molecules in the crystal structure is shown in Fig. 2. The structure shows exactly the same features as discussed above for complex **A** in solution. In particular, the pyrrole is oriented at 90° to the plane of the aniline π-system, and the pyrrole NH is directed towards the π-electron density on the face of the ring. The pyrrole NH hydrogen was located in the difference Fourier map and lies 2.83 Å above the plane of the π-system (the shortest H–C distance is 2.88 Å). The pyrrole CH

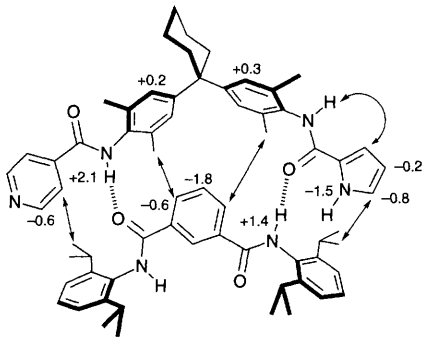


Fig. 1 Limiting complexation-induced changes in ^{1}H NMR chemical shift for complex **A** in chloroform. Selected NOEs observed for a 1 : 1 mixture of **1** and **3** in a ROESY experiment are also shown.

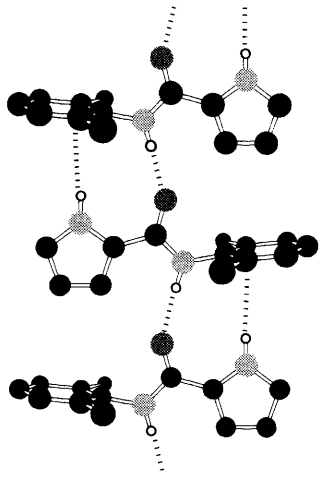


Fig. 2 The molecular structure of **5**, and the interactions between three molecules of **5** found in the X-ray crystal structure. The H-bonded amide N–O distances are 2.79 Å.

Table 1 Association constants (K_a)[a] and the corresponding changes in standard Gibbs free energy (ΔG^0) in chloroform at 298 K

Complex	Composition	K/dm^3 mol^{-1}	ΔG^0/kJ mol^{-1}
A	**1+3**	159±8	−12.6±0.1
B	**2+3**	36±3	−8.9±0.2
C	**1+4**	8±1	−5.1±0.3
D	**2+4**	11±2	−5.9±0.4

[a] Average values from at least three separate experiments. Titration data for 4–6 different signals were used to determine the association constant in each experiment. Errors are quoted as twice the standard error from the weighted mean (weighting based on the observed change in chemical shift).

groups are significantly further away from the face of the π-system; the closest contact is with the pyrrole α-proton which is 4.57 Å above the plane of the π-system. Thus the observed interaction is essentially a π-facial H-bond with little contribution from CH–π (or π–π) interactions.

^{1}H NMR titrations gave very similar complexation-induced shifts for complexes **A**, **B** and **D** which implies that they have essentially the same structure in solution. However, differences were observed for complex **C** which suggests that the adverse secondary interactions discussed above force a change in the conformation of this complex. The association constants measured for the four complexes in chloroform are given in Table 1 and applying the double mutant equation in Scheme 1 yields a value of −4.5 ± 0.5 kJ mol^{-1} for the NH–π interaction. In fact, this value is a lower limit on the magnitude of the interaction because complex **C** does not adopt the conformation shown in Scheme 1 and the experimentally determined binding constant is for a different lower energy structure. The π-facial H-bond (> −4.5 ± 0.5 kJ mol^{-1}) is significantly larger than the edge-to-face π–π interaction we have measured previously (−1.4 ± 0.8 kJ mol^{-1})[6] and is consistent with a model in which the magnitude of these interactions is determined essentially by electrostatics; the N–H bond dipole is much larger than the C–H dipole and so interacts more strongly with the negatively-charged π-electron density.[9] The magnitude observed for this interaction should be compared with conventional H-bonding interactions in chloroform of −7 kJ mol^{-1}.[10,11] In organic solvents, it appears that π-facial H-bonds may be just as important as conventional H-bonds in thermodynamic terms.

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Footnotes

† It has already been shown that the *tert*-butyl–π interaction is negligible in this system (ref. 7).

‡ *Crystal data* for $C_{13}H_{14}N_2O$: a = 7.351(3), b = 21.783(10), c = 8.129(4) Å, β = 103.07(4)°, T = 293(2) K, space group *C*/*c*.

Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/124.

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