Structure of Amido-Pyridinium Betaines: Persistent Intermolecular C-H···N Hydrogen Bonding in Solution

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**Abstract:** A Hydrogen bonding of the type C-H···X (where X = O and N) is known to influence the structure and function of chemical and biological systems in solution. Whilst C-H···O hydrogen bonding in solution has been extensively studied, both experimentally and computationally, equivalent thermodynamic parameters have not been enumerated experimentally for C-H···N hydrogen bonding. This is in part due to the lack of systems that exhibit persistent C-H···N hydrogen bonds in solution. Herein is described a class of molecule based on a biologically active norharman motif that exhibits unsupported intermolecular C-H···N hydrogen bonds in solution. Pairwise interaction leads to dimerization giving bond strengths of ca. 7 kJ mol-1 per hydrogen bond, which is similar to chemically and biologically relevant C-H···O hydrogen bonding. The experimental data is supported by computational work which provides additional insight into the hydrogen bonding by consideration of electrostatic and orbital interactions and allowed a comparison between calculated and extrapolated NMR chemical shifts.

Introduction

Hydrogen bonding is pervasive throughout chemistry and is fundamental to our understanding of the structure and function of molecules and ions. What constitutes a hydrogen bond has been a topic of debate and the definition has continued to evolve. As recently as 2009, IUPAC agreed updated terminology.[1] The most common and strongest hydrogen bonds are characterised by an X-H···Y interaction between an hydrogen atom and two electronegative elements X and Y, where typically, X and Y are oxygen, nitrogen, or Y = halide.[2] Substituting X for a less electronegative atom such as carbon leads to a weaker interaction, giving what has been called, amongst others, weak, non-traditional, non-conventional, or non-classical hydrogen bonding.[3] There has been some debate about whether weak C-H hydrogen bond donor interactions should be described as simply dispersive Van der Waals forces, or directional interactions with orbital contributions akin to classical strong hydrogen bonds.[4] A reduction in hydrogen bond strength for C-H···Y bonds compared to X-H···Y bonds is most simply interpreted as reduction of an attractive electrostatic interaction X**--H**+···Y**-, due to the less polar C-H bond, but the role of



**Figure 1** Norharman derivative (**1**) and structurally related phenyl pyridinium amide (**2**), showing the formal neutral resonance form present for **1** but absent for **2**.

covalency and dispersion forces in hydrogen bonds should not be neglected.[4a-d] Regardless of terminology, the interaction between C-H hydrogen-bond donors and acceptors is increasingly being recognized as important as they have been shown to direct structure and mediate reactivity in biology, catalysis and functional materials.[5]

Since the 1960s, single crystal X-ray and neutron diffraction data has been the primary method used to identify C-H hydrogen bonding, with C-H···X interactions characterised by a short donor-acceptor distance.[6] Interpretation of solid- state structures is problematic, because it can be difficult to discriminate between true hydrogen bonding interactions and close contacts between atoms due to crystal packing. In the solution state several models have been developed to place hydrogen bond acceptors and hydrogen bond donors on an universal scale,[7]These empirical models allow the free energy of hydrogen bond association to be estimated based on experimental and/or computational data, which is now available for many organic compounds.[7c, 8] However, the vast majority of C-H···X hydrogen bonds observed in the solid state do not persist in solution, making it difficult to determine the energetics of these interactions.[9]

The focus of this work is C-H···N hydrogen bonding. C-H···N motifs are far less common than those for C-H···O, which is perhaps surprising given the relatively small difference in electronegativity for oxygen and nitrogen.[10] Furthermore, very few C-H···N hydrogen bonds have been identified in solution because weak bonding is displaced by solvation or thermal activation for the weakest cases. Of the C-H···N bonds studied in solution, the hydrogen bond is underpinned by either proximal traditional strong hydrogen bonding or a restricted geometry promoting an intramolecular C-H···N interaction.[11]

Herein we describe structural, solution NMR, and quantum chemical experiments that show the presence of unsupported intermolecular C-H···N hydrogen bonding in the solid state and solution for a class of compound derived from N-heterocyclic norharman (**1**) and betaine (**2**) (Figure 1). Norharman and related -carbolines alkaloids are found in plants, animals, tobacco smoke, instant coffee, and cooked meats and are implicated in a range of neurological effects in humans including Parkinson’s disease.[12]

In previous computational work the electronic structures of **1** and **2** were investigated using natural bond orbital (NBO) and natural resonance theory (NRT) approaches.[13] Examination of the different resonance forms of **1** and **2** showed that both exhibit charge density at the central nitrogen atom indicative of an amido-like N atom (**1’** and **2** in Figure 1), which is reflected in their metal coordination chemistry.[13] The synthesis of **1** and **2** has been described, however **2** was not isolated, and the single crystal structures of **1** and **2** were not determined. During exploratory synthetic work it was noted that the 1HNMR chemical shift of the pyridinium proton between the nitrogen atoms of **1** and **2** varied considerably in comparison to other signals. This suggested a significant perturbation on coordination of the amido-like nitrogen atom or that the C-H moiety was acting as a hydrogen bond donor. For compound **2** restricted rotation about the pyridinium-amido C-N bond could also result in large chemical shift differences,[13] but this is clearly impossible for **1**.We were therefore motivated to determine the solid-state structure of **1** and **2** and investigate their solution NMR behavior in more detail.

Results and Discussion

The kinetic stability of betaines is largely dependent on the stabilization of the formally localized charge. While compound **1** is air and water stable, the structurally related compound **2** is air and moisture sensitive. To avoid contamination by water all reactions and manipulations of **1** and **2** were performed under an inert atmosphere. Compound **1** was prepared using a previously reported method[13] and single crystals of **1** were grown from slow evaporation of a THF solution. Attempts to grow single crystals of **2** directly were unsuccessful, however crystals of **2** suitable for an X-ray structure determination were grown at -20 oCby addition of 12-crown-4 to a solution of the metal salt adduct [(**2**)Li(-I)(THF)]2 in diethylether to extract LiI (ESI).

For both **1** and **2** hydrogen atoms engaged in the C-H···N interactions, were located in the electron difference map and their position refined without restraint. The single-crystal X-ray structure of **1** contains two molecules in the asymmetric unit with essentially identical molecular metrical data. The bond lengths about the heterocyclic structure are typical for aromatic *N*-heterocycles.[14] These include those at N(1) (Figure 2a) which are C(2)-N(1) = 1.366(2) and C(9)-N(1) = 1.374(2) Å, respectively. The two molecules in the asymmetric unit are primarily distinguished by their intermolecular interactions and by the orientation of the *i*Pr group with respect to the other molecule of the dimer. Both exhibit pairwise C-H···N contacts resulting in a dimeric motif. One molecule exhibits C-H···N contacts, with N(3)···H(15\*) = 2.556(2) Å, d(C(1)···N(1’)) = 3.542(2) Å and (C(1)-H(1)-N(1’)) = 156.72(9)°, whereas the other exhibits significant deviation from coplanarity of the *N*-heterocycles with N(1)···H(1’) = 2.730(2) Å, d(C(1)···N(1’)) = 3.364(2) Å and (C(1)-H(1)-N(1’)) = 124.82(9)°.



**Figure 2** Molecular structure and intermolecular dimeric motif arising from C-H…N interactions for a) **1** and b) **2**. All H atoms are omitted for clarity except those participating in C-H···N bonding.

For **2**, the asymmetric unit contains one molecule of **2** and notable features of the molecular structure (Figure 2b) are the asymmetric bond lengths at N(1) (in contrast to **1**)and the planarity of the atoms about the C(2)-N(1) bond. The bond lengths of C(2)-N(1) and C(9)-N(1) are 1.337(2) and 1.3917(17) Å respectively, which are between typical imine (1.28 Å) and C(sp2)-N(sp3) (1.42 Å) bonds respectively, indicating significant C(2)-N(1) -bonding. The intermolecular structure is again characterized by a dimeric motif arising from C-H···N interactions between the N(1) and C(1’)-H(1’) hydrogen atom, where N(1)···H(1’) = 2.524(2) Å, d(C(1)···N(1’)) = 3.440(2) Å and the angle at H(1) (C(1)-H(1)-N(1’)) = 161.96(9)°.

Dimeric motifs such as those observed for **1** and **2** have been reported in the solid state structures of several other aromatic *N*-heterocycles such as benzimidazole as well as imine derivatives.[14] X-ray parameters including hydrogen atoms are inherently imprecise due to the low electron density about the H nucleus. It is, therefore, more reliable to compare the C···N distances with literature values when evaluating the C-H···N interaction. The C···N distances found for **1** and **2** are amongst the shortest reported, where typically values > 3.6 Å are found.[14] However, the solid state interactions of **1** and **2** are not considered particularly remarkable, in themselves.



**Figure 3** Dimer-monomer equilibrium of **1** and variable temperature 1H NMR spectra of **1** in a) [D8]THFand b) CD2Cl2.

More interestingly, solution NMR spectroscopy of **1** and **2** indicates that C-H···N hydrogen bonding persists in solution. The most notable feature of the 1H NMR spectra of **1** and **2** are the solvent, concentration, and temperature dependence of the signals attributable to the H(1) proton (Figure 3 and 4), which in the solid state participates in the C-H···N interaction. At all temperatures and concentrations a single set of signals is observed for **1** and **2** which isindicative of rapid exchange on the NMR timescale.The 1H NMR spectra of **1** in [D8]THF (Figure 3a) at a concentration of 26.9 mM show a significant chemical shift change (**) of 1.08 ppm for the H(1) signal between 8.94 and 10.02 ppm at 330 and 205 K respectively. The remaining proton signals exhibit much smaller changes to lower field of less than



**Figure 4** Dimer-monomer equilibrium of **2** and variable temperature 1H NMR spectra of **2** in [D8]THF.

** = 0.4 ppm. In addition, at lower temperatures the signal attributed to H(1) exhibits the greatest broadening. The chemical shift change to lower field on reducing the temperature is consistent with a monomer-dimer equilibrium exhibiting fast exchange on the NMR timescale with the concentration of hydrogen-bonded dimer increasing at lower temperature.[1b]

The NMR data are also solvent dependent. Similar temperature-dependent chemical shift changes are observed in toluene-d8, however precipitation at lower temperatures prevented quantitative analysis (*vide infra*). In contrast, the chemical shift change in CD2Cl2 between 295 and 195 K is less than 0.05 ppm, with H(1) observed at *ca.* 8.8 ppm (Figure 3b). The data are consistent with the solvation of **1** in dichloromethane preventing dimerization of **1** at the temperatures studied. The dielectric permittivity[15] of THF (7.5) and dichloromethane (8.9) are of a similar magnitude indicating that specific interactions between **1** and dichloromethane result in a different solvated structure in dicholoromethane compared to THF. Indeed, solid-state structures are known that exhibit a CH2Cl2 molecule bridging a *sp*2 nitrogen and aryl hydrogenmoiety in quinoline derivatives via N···H and Cl···H hydrogen bonding interactions[16] resulting in support the hypothesis that **1** and **2** can form specific H-bonded complexes with dicholoromethane (see ESI for details). C-H···N interactions have also been implicated in the 1H NMRspectra of nitrogenous bases dissolved in liquid haloforms such as chloroform.[17]

Analogous 1H NMR spectra were acquired for compound **2** (Figure 4). At 23.4 mMin [D8]THF, ** = 0.51 ppm is observed for the H(1) signal between 7.26 and 7.77 ppm at 330 and 205 K respectively. The remaining proton signals exhibit changes to lower field of less than ** = 0.2 ppm.

To the best of our knowledge thermodynamic parameters and equilibrium constants for unsupported C-H···N hydrogen bonding have not been reported previously. Under fast exchange the observed chemical shift is a number weighted average of the dimer **D) and monomer (**M) chemical shifts.[18] Values for **D and **M and the enthalpy (*H*0) and entropy (*S*0) of reaction for the dimer-monomer equilibrium can be determined by fitting VT chemical shift data acquired at a range of concentrations (ESI).[18c] The chemical shift ofH(1) was used to determine **D, **M, *H*0 and *S*0 for **1** and **2** (Table 1).

**Table 1**. NMR and thermodynamic parameters determined from the VT NMR data of **1** and **2**.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **D (ppm) | **M (ppm) | *H*0  (kJ mol-1)[a] | *S*0  (J K-1 mol-1)[a] | *G*0  (kJ mol-1)[a] |  |  |  |  |
| **1**-exp[b] | 10.64 | 8.78 | 14.0 ± 0.5 | 31 ± 4 | 4.7 ± 0.5 |  |  |  |  |
| **1**-calc | 12.0[c] | 8.7[c] |  |  | +1[d] |  |  |  |  |
| **2**-exp[b] | 9.51 | 7.20 | 14.2 ± 0.4 | 55 ± 4 | -2.2 ± 0.4 |  |  |  |  |
| **2**-calc | 9.8[c] | 6.9[c] |  |  | -1[d] |  |  |  |  |

[a]dissociation of dimer to monomer,[b] in [D8]THF, [c]DFT, [d] Hunter model

The enthalpy and entropy for the formation of monomeric species from the dimers (Figure 3 and 4) are of comparable magnitude for **1** and **2**, as may be expected for molecules of similar structure. The enthalpy differences are within error, whereas the dissociation entropy of [**2**]2 is significantly greater than for [**1**]2. The X-ray structure of **2** (Figure 1)shows that the phenyl and pyridinium moieties are not coplanar, whereas for **1** the structure enforces coplanarity, and therefore entropy difference can be explained by relief of restricted rotation of the pyridinium and phenyl moieties present in [**2**]2.

Values of *H*0 and *S*0 can be compared to other dimers exhibiting pairwise hydrogen bonding in non-aqueous solution. For example, traditional strong hydrogen bonding exhibited by benzoic acid in benzene *H*0 = 31.9 kJ mol-1 and *S*0 = 54 J K-1 mol-1;[19] and 2-pyridone in CD2Cl2 *H*0 = 30.5 kJ mol-1 and *S*0 = 50 J K-1 mol-1 [20] exhibit greater *H*0 and comparable *S*0. These correspond to a *G*0298Kof 15.8 and 15.6 kJ mol-1 and equilibrium constants of 1.6 and 1.8 mM, respectively. For weaker C-H···O hydrogen bonding there are a limited number of experimental studies enumerating thermodynamic parameters based mainly on vibrational data of liquid benzaldehydes typically giving *H*0 = 3 to 9 kJ mol-1 for dimer-monomer equilibria (*S*0 not determined).[21] In contrast C-H···O dimers of liquid cyclohexenone give H0 = 18.5 kJ mol-1 and *S*0 = 76 J K-1 mol-1 (*G*0298K = 4.1 kJ mol-1),[22] and the dimerization of fluoroenaminoketones in CCl4 was reported as having surprisingly large values of *H*0 = 35.1 kJ mol-1 and *S*0 = 93.7 J K-1 mol-1 (*G*0298K = 12.1 kJ mol-1).[23] Theoretical methods have been applied extensively to many C-H···O interactions particularly relevant to biological systems and typically give *H*0 = *ca.*  5 - 12 kJ mol-1 per C-H…O bond.[24]

The *G*0 (Table 1) and equilibrium constants for dimer to monomer (Figure 3 and 4) at 298 K are 4.7 and -2.2 kJ mol-1 and 0.15 M and 2.42 M for **1** and **2**,respectively, indicating that dimerization is more favourable for **1** in comparison to **2**, for primarily entropic reasons.

In order to gain additional insight into this system a DFT study (see ESI for full details) was undertaken on the monomer-dimer equilibria for **1** and **2**. As expected, both the structural and energetic results of these studies were influenced by the choice of computational methodology, in particular by the addition of empirical dispersion corrections and the inclusion of solvation.[25] On balance, the (RI‑)PBE0/def2-TZVPP (with COSMO solvation in THF *ε* = 7.58) level gave the best agreement between experiment and theory (considering the metric parameters and dimerization enthalpies for [**1**]2 and [**2**]2) and discussion of the computational results will focus on this level of theory unless otherwise specified.



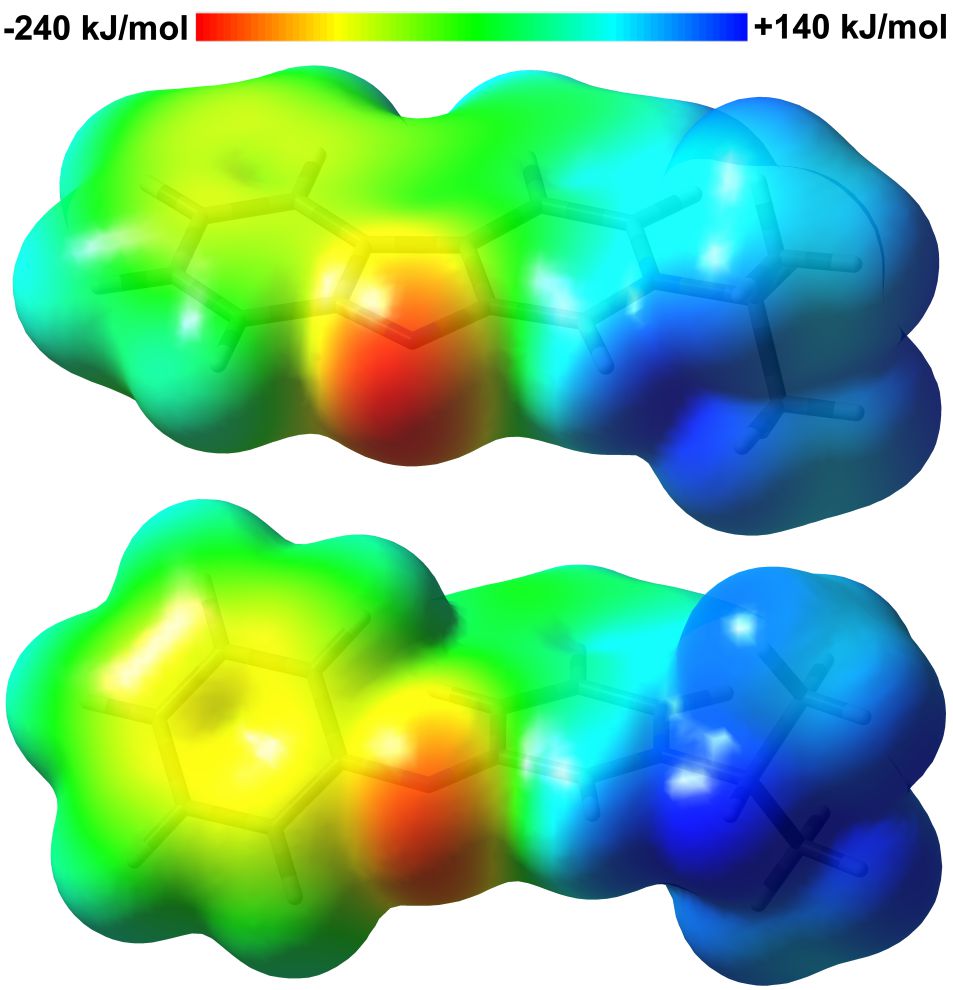
**Figure 5.** Optimised structures of **[1]2\_iso1** (above) and **[2]2\_iso2** (below).

With respect to structure, two conformational isomers were found for each dimer (and their corresponding monomeric forms). For [**1**]2\_iso1 the *ipso* C-H bond of each *i*Pr group points away from the other molecule in the dimer (Figure 5). In the other (iso2) this bond points towards the core of the dimeric unit. For [**1**]2 both isomers are essentially isoenergetic at this level of theory, but for [**2**]2, the structure iso2 is favoured by around 10 kJ mol-1. This is presumably due to an unfavourable steric interaction between the *i*Pr Me groups and the Ph ring of the opposite molecule of **1** for iso1. This is consistent with the solid-state structures of [**1**]2 and [**2**]2 (Figure 2), where both isomers are observed for [**1**]2, but only iso2 is observed for [**2**]2. Comparison of the calculated (*vide infra*) and experimental NMR chemical shifts for the *i*Pr *ipso* C-H protons (see ESI for details) suggests that in solution [**1**]2 is found predominantly as iso1 (in iso2 the calculations predict a significant deshielding of this proton, which is not seen experimentally) and [**2**]2 is found predominantly as iso2. The following discussion will therefore focus on [**1**]2\_iso1 and [**2**]2\_iso2 unless otherwise stated.

The calculated C-H···N bond distances in [**1**]2 and [**2**]2 compare favourably with the experimental solid-state structures (with deviations of 0.003 Å and 0.036 Å respectively for the C-N distances) (Figure 5). For [**1**]2 the longer-range interactions, such as those between the *i*Pr group on one molecule and nitrogen atom on the other, are also quite well described. However, while the metric parameters for [**1**]2 are generally in good agreement with experimental data, for [**2**]2 it seems that there may be a dispersive interaction between the *i*Pr and the Ph groups on opposite molecules (see Figure 5 for the relative orientation of these groups) that is not well modelled by the PBE0 functional. This leads to a greater separation of *i*Pr and Ph groups in the calculations compared to the solid state (e.g. C(7’)···C(9) is 0.14 Å longer in the calculations). Introducing empirical dispersion corrections during geometry optimisation (PBE0-D3/def2-TZVPP level) did bring the *i*Pr and Ph groups closer together, as expected, but the distance between these groups was then significantly shorter than in the solid state (e.g. C(7)···C(9) is 0.27 Å shorter in the calculations), suggesting that dispersive interactions in the solid state in this system may be overestimated when empirical dispersion corrections are applied to gas-phase optimisations in this way.

DFT studies were also used to probe the structures of CH2Cl2 complexes of **1** and **2**, which may form when these species are dissolved in CD2Cl2 (*vide supra*) (Figure S8). The calculations suggest that C-H···N and C-H···Cl interactions, sufficiently strong to inhibit dimerization, are possible which is consistent with the temperature insensitive 1H NMR spectra of **1** and **2** in CD2Cl2.

DFT calculations were used to determine NMR shielding tensors for the monomeric and dimeric forms of **1** and **2**, calculated using the GIAO approach (at the PBE0/IGLO-III level, with COSMO solvation in THF, *ε* = 7.58). Chemical shifts for **1** and **2** were calculated using the observed 1Hchemical shifts of H(12) (Figure S1 and S4) on the phenyl moiety as an internal reference, which is relatively independent of temperature for both compounds. For **2** there is a very good agreement (deviations of 0.3 ppm) between the experimental and calculated chemical shifts for the monomer and dimer (Table 1), which gives added confidence in the experimental extrapolations and corroborates that at 205 K, a 23.4 mM solution of **2** in [D8]THF (Figure 4) contains a significant proportion of the dimeric species. However, while the agreement between the calculated monomer chemical shifts for **1** is also very good (deviation of 0.1 ppm) there is a 1.4 ppm difference in the predicted chemical shift for the dimer (12.0 ppm) compared to the extrapolated value (10.6 ppm). This may be due to specific solvent-solute interactions that are not well modelled by the COSMO solvation model or potentially some conformational flexibility of the *i*Pr group of **1**. In any case, the chemical shift observed at 205 K for a 26.9 mM solution of **1** in [D8]THF (Figure 3a) is substantially different from the predicted chemical shift of the monomeric form, supporting the hypothesis that a significant proportion of [**1**]2 is present.



**Figure 6**. Electrostatic potentials (in kJ mol-1.) for **1** (top) and **2** (bottom) mapped onto their electron densities (isosurfaces at 0.002 a.u.) at the B3LYP/6-31G\* level.

To probe hydrogen bonding and solution-phase free energy (vide infra) the electrostatic potentials for **1** and **2** (Figure 6) were determined, which show regions of negative charge density at the nitrogen atom H-bond acceptors and positive charge density at the C-H donor (in addition to the isopropyl C-H bonds). This charge distribution is consistent with the observed hydrogen bonding motif seen in the dimeric species and suggests a significant electrostatic contribution to H-bonding in these species. These data also allow an estimation of the solution-phase free energy of hydrogen bonding in this system using a model developed by Hunter *et al.*[7c, 7e, 26] This is desirable, as it is difficult to accurately calculate dimerization energies in solution for such weakly bound systems directly from gas-phase DFT studies. H-bonding interactions in any solvent can be expressed using Equation 1.



where  and  are the hydrogen bond donor and acceptor constants for solute molecules and **s and **s are the corresponding values for the solvent. The +6 kJ mol-1 term accounts for an energetic penalty for bringing two molecules together in solution at 298 K to form a non-covalent complex.[8] Eqn. 1 is derived for individual acceptor and donor molecules that exhibit a single hydrogen bonding interaction. For a single molecule exhibiting dimerzation via a pairwise hydrogen bonding interaction, Equation 1 can be simply modified to give Equation 2.



The values of ** and **were derived from the electrostatic potentials calculated for **1** and **2** (Figure 6).[26] The  parameters, which were calculated from the maximum electrostatic potential at H(1) (113 kJ mol-1 for **1** and 108 kJ mol-1 for **2**), were 1.43 and 1.36 for **1** and **2** respectively, which are similar to N-heterocycles such as pyridine as weak hydrogen bond donors.[7e] Calculation of *β* parameters from the minimum electrostatic potential at N(1) was less clear cut, as an empirical functional-group-dependent scaling factor, *c*, is required. This relates to the chemical structure of the functional group of interest (e.g. primary amine, nitrile, ether-type oxygen etc) and betaines such as **1** and **2**, which have mixed imido/amido-type character, have not been parameterised. Using a value of *c* for secondary amines and the minima on the electrostatic potentials (-240 kJ mol-1 for **1** and -222 kJ mol-1 for **2**) gave β values (12.14 and 10.82 for **1** and **2** respectively) that seemed appropriate for these strong H-bond acceptors. For THF **s = 0.9 and **s = 5.3,[7c] which gives a calculated free energy of association of -1 and +1 kJ mol-1 for **1**  and **2**,respectively. This is broadly consistent with the experimental data, -4.7 and +2.2 kJ mol-1 for **1** and **2**, but the difference between the two systems is more pronounced in the experiment, which we attribute to the different entropic contributions to dimerization in **[1]2** and **[2]2** that are not accounted for in this model. What is clear is that the hydrogen bond donor abilities of **1** and **2** are rather similar, and they are weak H-bond donors, as expected. However, their hydrogen bond acceptor properties are influenced by the structure of the molecules. We have seen similar behaviour in the ligand properties of these systems.[13]

Finally, in order to explore the orbital basis of C-H···N bonding in these species in more detail an NBO analysis was undertaken (see ESI for details) on [**1**]2 and [**2**]2. When comparing similar conformational isomers (e.g. [**1**]2-iso2 with [**2**]2-iso2) the donation of electron density from a nitrogen lone pair on one molecule to the C-H σ\* acceptor orbital on the other is more significant in [**1**]2 compared to [**2**]2. (occupation of a C-H σ\* orbital = 0.033 vs 0.028 e-; stabilisation energy = 23 vs 15 kJ mol-1, respectively), and both are weaker than the same interaction in a classical H-bonded dimer e.g. [2-aminopyridine]2 (occupation of σ\* orbital = 0.058 e-; stabilisation energy = 82 kJ mol-1).§ These data suggest that the underlying C-H…N bonding in [**1**]2 is stronger than in [**2**]2, presumably due to the more charge-dense N-lone pair in **1**. This difference may be overcome by a dispersive interaction between the *i*Pr and Ph groups in [**2**]2, ultimately leading to very similar enthalpies of dimerization.

Conclusions

The experimental and computational data collectively show that the norharman motif leads to C-H···N hydrogen bonding in solution. Typically the C-H···N bond strength would be derived from Δ*H*0, giving a bond strength of ca. 7 kJ mol-1 per hydrogen bond. This is comparable to typical C-H···O hydrogen bonding found in chemical and biological systems that mediate structure and function, such as that found in asymmetric catalysis, proteins and nucleic acid polymers. However, our computational studies suggest there may also be a dispersive contribution to Δ*H*0 arising from non-H-bonding interactions, particularly in [**2**]2. Where inherently weak hydrogen bonding is the focus, any quantification based on Δ*H*0 should be considered collectively with other weak attractive (or indeed repulsive) interactions that can have comparable magnitude. It remains difficult to quantitatively assess the relative contributions of different interactions to the total ΔH0 for systems of this size in solution. Nevertheless, the data for **1** and **2** suggest that both dispersive interactions between alkyl and aryl substituents and hydrogen bonding contribute to the observed Δ*H*0. As such, the 7 kJ mol-1 contribution to Δ*H*0 per hydrogen bond observed experimentally is an upper limit and the true H-bond energies in this system are likely to be slightly lower than this. Of course similar arguments can be applied more generally to other systems exhibiting weak hydrogen bonding. Finally, although C-H···N hydrogen bonds are less ubiquitous than C-H···O in biological systems, this work supports the contention that a comparable enthalpic contribution can occur in hydrogen bonding networks. Thus there exists an opportunity to exploit C-H···N hydrogen bonding in the development of functional materials and selective chemical processes.

Experimental Section

**General**

All manipulations were performed in a nitrogen-filled drybox. General solvents and NMR solvents were dried and distilled over the following agents; ethers and toluene over potassium metal, dichloromethane over calcium hydride. All solvents and drying agents were purchased from Sigma-Aldich. Compound **1** and [(**2**)Li(-I)(THF)]2 were prepared using literature procedures.[13]

**Crystal Growth and Data for 1**

Yellow crystals of **1** were grown by slow evaporation of a saturated THF solution (*c.a.* 1 mL) over several days at -20 ◦C in a drybox refrigerator. 2(C14H14N2), Mr = 210.28, *a* = 8.8720(5), *b* = 11.1494(5), *c* = 11.5584(7) ̊A, α = 95.771(4), β = 92.775(5), γ = 91.946(4), V = 1135.34(11) ̊Å3, T = 110.0 K, triclinic, space group P-1, *Z* = 4, 21173 reflections measured, 4425 independent reflections (Rint = 0.0327). The final R1 values were 0.0423 [I ≥ 2s(I)] . The final *w*R(F2) values were 0.1005 [*I* ≥ 2*s*(*I*)] . The final R1 values were 0.0529 (all data). The final *w*R(F2) values were 0.1074 (all data).

**Crystal Growth and Data for 2**

To a glass vial (5 mL) containing [(**2**)Li(μ-I)(THF)]2 (20 mg, 0.04 mmol) dissolved in diethylether (1 mL) was added 12-crown-4 (9 mg, 0.05 mmol). The reaction was stirred for 10 min giving a white precipitate and red supernatant. The mixture was filtered through celite and the solution stored at -20 ◦C in a drybox refrigerator for several days giving red crystals. C14H16N2, Mr = 212.30, *a* = 6.8655(4), *b* = 99.795(6), *c* = 11.6640(6) Å, α = 90, β = 92.775(5), γ = 90, V = 1161.27(17)Å3, T = 110.0 K, monoclinic, space group P21/*c*, *Z* = 4, 4169 reflections measured, 2326 independent reflections (Rint = 0.0228). The final R1 values were 0.0432 [*I* ≥ 2*s*(*I*)] . The final *w*R(F2) values were 0.0937 [I ≥ 2s(I)] . The final R1 values were 0.0542 (all data). The final *w*R(F2) values were 0.1011 (all data).

**X-ray Diffraction**

Diffraction data for compounds **1** and **2** were collected at 110 K on an Agilent SuperNova diffractometer with MoKα radiation (λ = 0.71073 Å). Data collection, unit cell determination and frame integration were carried out with CrysalisPro. Absorption corrections were applied using crystal face indexing and the ABSPACK absorption correction software within CrysalisPro. Structures were solved using the Olex2 suite using Charge Flipping and refined using olex2.refine.[27] All non-hydrogen atoms were refined anisotropically. Carbon bound hydrogen atoms were placed using a riding model and included in the refinement at calculated positions with the exception of the H atoms engaged in the C-H···N interactions, which were located in the electron difference map and their position refined without restraint.

**General computational details**

**Optimised structures and energies**

All calculations were performed using the TURBOMOLE V6.40 package using the resolution of identity (RI) approximation.[28] Initial optimisations of the monomer and dimer structures of **1** and **2** were performed at the (RI-)BP86/SV(P) level, followed by frequency calculations at the same level. Further optimisations and vibrational frequency calculations were performed on these structures at the (RI-)PBE0/def2-TZVPP level. All minima were confirmed as such by the absence of imaginary frequencies. No symmetry constraints were applied during optimisations.

Electronic energies were corrected for the zero point energies, thermal energies and entropies of each state (obtained from frequency calculations at the same level of theory used for geometry optimisations). Gas-phase entropies from frequency calculations were converted to standard-state concentration of 1 mol dm-3. Solvation effects were modelled using the COSMO module of TURBOMOLE at the same level of theory used for the geometry optimisations.[25c] The dielectric constants used were dichloromethane (8.93 at 298 K) and tetrahydrofuran (7.58 at 298 K).[29] As part of some methodologies, single-point DFT-D3 corrections were applied at the PBE0-D3 level using Grimme’s DFT-D3 V3.0 Rev 2 program (with BJ-damping).[25a, 25b] Basis-set superposition errors were estimated using the Counterpoise method. Electrostatic potentials for **1** and **2** were derived from B3LYP/6-31G\* single point calculations (on the PBE0/def2-TZVPP optimized structures) that were performed using Gaussian 09.[30]

**NMR chemical shifts and NBO analyses**

Single-point calculations on the previously optimised (BP86/SV(P)-level) structures of **1**, **2**, **[1]2** and **[2]2** were performed using Gaussian 09 [30] (at the BP86/IGLO-III and PBE0/IGLO-III levels; basis set information was obtained from the EMSL basis set exchange).[31] NMR shielding tensors were calculated using the GIAO approach. Additionally, single-point calculations at the PBE0/def2-TZVPP-level (basis set information was obtained from the EMSL basis set exchange)[31] with Gaussian 09, were used to prepare input for NBO analysis by the NBO 5.9 package.[32] NMR chemical shifts were obtained from isotropic shielding tensors using the following relationship.



Where σ is the calculated isotropic shielding tensor for the proton of interest; **ref for **1** and **[1]2** is the chemical shift of H20 (fig S7), which is experimentally observed to be essentially temperature independent in THF solution and appears at 7.3 ppm and *σ*ref was the calculated isotropic shielding tensor for this proton. **ref for **2** and **[2]2** is the chemical shift of H22 (Figure S7), which is experimentally observed to be essentially temperature independent in THF solution and appears at 6.6 ppm and *σ*ref was the calculated isotropic shielding tensor for this proton.

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**Keywords:** hydrogen bonds • aggregation • betaines • bond energy • nitrogen heterocycles

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