Weak Intermolecular CH…N Hydrogen Bonding: Determination of $^{13}\text{CH}^{15}\text{N}$ Hydrogen-bond Mediated $J$ couplings by Solid-state NMR Spectroscopy and First-principles Calculations

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Abstract

Weak hydrogen bonds are increasingly hypothesised to play key roles in a wide range of chemistry from catalysis to gelation to polymer structure. Here, $^{15}\text{N}/^{13}\text{C}$ spin-echo magic-angle spinning (MAS) solid-state NMR experiments are applied to “view” intermolecular CH…N hydrogen bonding in two selectively labelled organic compounds, $4-[^{15}\text{N}]$ cyano-4’-$[^{13}\text{C}_2]$ ethynylbiphenyl (1) and $[^{15}\text{N}_3,^{13}\text{C}_6]$,2,4,6-triethyl-1,3,5-triazine (2). The synthesis of $2^{15}\text{N}_3,^{13}\text{C}_6$ is reported here for the first time via a multistep procedure, where the key element is the reaction of $[^{15}\text{N}_3]$,2,4,6-trichloro-1,3,5-triazine (5) with $[^{13}\text{C}_2]$-([trimethylsilyl]ethynyl)zinc chloride (8) to afford its immediate precursor $[^{15}\text{N}_3,^{13}\text{C}_6]$,2,4,6-tris([trimethylsilyl]ethynyl)-1,3,5-triazine (9). Experimentally determined hydrogen-bond mediated $^2hJ_{\text{CN}}$ couplings (4.7 ± 0.4 Hz (1), 4.1 ± 0.3
Hz (2)) are compared with density functional theory (DFT) gauge-including projector augmented wave (GIPAW) calculations, whereby species independent coupling values $^{2h}K_{CN}$ (29.0 (1), 27.9 (2) $\times 10^{19}$ kg m$^{-2}$ s$^{-2}$ A$^{-2}$) quantitatively demonstrate the $J$ couplings for these “weak” CH…N hydrogen bonds to be of a similar magnitude to those for conventionally observed NH…O hydrogen-bonding interactions in uracil ($^{2h}K_{NO}$: 28.1 and 36.8 $\times 10^{19}$ kg m$^{-2}$ s$^{-2}$ A$^{-2}$). Moreover, the GIPAW calculations show a clear correlation between increasing $^{2h}J_{CN}$ (and $^{3h}J_{CN}$) coupling and reducing C(H)…N and H…N hydrogen bonding distances, with the Fermi Contact term accounting for at least 98% of the isotropic $^{2h}J_{CN}$ coupling.

**Introduction**

Hydrogen bonds are known to play a crucial role in directing the assembly of organic molecules into supramolecular structures and feature highly throughout structural chemistry and biology.$^{1,2}$ There is increasing interest in so-called ‘weak’ CH…A (where A = N or O) hydrogen bonds$^{3-5}$ whereby key roles in, for example, catalysis through the stabilisation of transition states,$^{6-12}$ or in promoting supramolecular gelation$^{13}$ or helical folding of peptides$^{14}$, or in the structure of cellulose polymorphs,$^{15,16}$ a high-mobility donor-acceptor copolymer$^{17}$ or poly($\varepsilon$-caprolactone)$^{18}$ have been proposed. In this context, note that Jeffrey makes a distinction (see Tables 2.1 and 2.2 in Ref.$^{19}$) between moderate (including NH…N and NH…O) and weak (with a CH donor) hydrogen bonds, with a D…A hydrogen bonding distance cut-off between the moderate and weak categories of 3.2 Å. While CH…A proximities can be identified in crystal structures obtained by diffraction, this approach alone cannot conclusively answer the question as to whether a close contact between a potential donor and acceptor is a bonding interaction that contributes to stabilizing the structure or is rather the result of other packing constraints.$^{4,20-23}$

NMR probes the local structure around a nucleus and is thus a powerful method for identifying and quantifying intermolecular interactions. Previous papers have demonstrated the sensitivity of the $^1$H chemical shift as a probe of weak CH…A hydrogen bonding. Specifically, Brown and coworkers have demonstrated, using an approach that combines experimental solid-state magic-angle spinning (MAS) NMR with gauge-including projector augmented wave (GIPAW) density-functional theory (DFT)-based calculations,$^{24-27}$ significant (up to 2 ppm) molecule to crystal changes in the $^1$H chemical shift due to intermolecular CH…A hydrogen bonding for sp$^3$, sp$^2$ and sp hybridized CH donors in maltose anomers, uracil and 4-cyano-4’-ethynylbiphenyl,
respectively. For maltose, the largest $^1$H chemical shift changes are associated with a short H…O distance (< 2.7 Å) and a CHO bond angle greater than 130°. In uracil, the chemical shift changes due to CH…O hydrogen bonding of 2.0 and 2.2 ppm are ~40% of those due to conventional NH…O hydrogen bonding (5.1 and 5.4 ppm). In solution-state NMR, Solà et al. have observed a shift to low ppm of 2.1 ppm for a CH $^1$H resonance between the syn and anti conformers of an organometallic complex, with intramolecular CH…O hydrogen bonding only being possible for the syn conformer.

Hydrogen-bond mediated $J$ couplings constitute a direct means of identifying a specific pair of hydrogen-bonded nuclei as well as quantifying the strength of a particular hydrogen bond. Following their observation by solution-state NMR, the adoption of specific NH…N intramolecular hydrogen bonding arrangements has been demonstrated in the solid state by the observation in two-dimensional refocused INADEQUATE MAS NMR spectra of cross peaks corresponding to $^{2h}J_{NN}$ couplings. Moreover, the measurement of $J$ couplings using a spin-echo MAS NMR experiment allows the quantitative determination of these $^{2h}J_{NN}$ couplings, and hence the strength of the corresponding NH…N hydrogen bonds. It has also been shown that $^{2h}J_{NO}$ couplings due to intermolecular NH…O hydrogen bonds in uracil can be measured using a heteronuclear $^{15}$N-$^{17}$O MAS spin-echo experiment. Schanda et al. have further detected small $^{3h}J_{NC}$ couplings (average value 0.5 Hz) across C=O…HN hydrogen bonds in the protein ubiquitin using a three-dimensional HNCO MAS experiment. In solution-state NMR, very small $^{3h}J_{CC}$ couplings of 0.2 to 0.3 Hz have been measured across CH…O=C hydrogen bonds in $\alpha$-sheet regions of a small protein. Moreover, cross peaks due to $J$ couplings for CH…$\pi$ interactions have been observed between methyl and aromatic side chains or carbonyl groups in proteins by Plevin et al. and Perras et al., where DFT calculation predicts $J$ coupling magnitudes of ~0.1 Hz.

This paper investigates weak intermolecular CH…N hydrogen bonding in the solid-state structures adopted by 4-cyano-4’-ethynylbiphenyl, 1, and 2,4,6-triethynyl-1,3,5-triazine, 2, for which diffraction structures are available in the Cambridge Structural Database (CSD). In both cases, the hydrogen-bond donor is a sp hybridized alkyne moiety, while the acceptor is a nitrogen atom in a nitrile group in 1 or in a triazine ring in 2. In order to focus on the intermolecular CH…N hydrogen bonds, the molecules 1 and 2 were synthesized with selective isotopic labelling: specifically, both carbons in the alkyne group were $^{13}$C labelled, while all nitrogens were $^{15}$N.
labelled. Note that the synthesis of 2-$^{15}$N$_3$-$^{13}$C$_6$ is reported here for the first time. Scientists are striving for the ability to view directly hydrogen bonds: in this work, we apply a combined experimental and calculation approach to observe and measure, for what we believe to be the first time in the solid state, $J$ couplings across weak intermolecular CH…A hydrogen bonds.

**Methods**

**General Synthesis.** Column chromatography was performed on silica gel (Merck 60, 70-230 mesh). Solution-state NMR spectra were recorded at 300 K on a Bruker DRX 400 (9.4 T, 400.13 MHz for $^1$H, 100.62 Mz for $^{13}$C and 40.56 MHz for $^{15}$N) spectrometer with a 5 mm inverse detection H-X probe equipped with a z-gradient coil for $^1$H, $^{13}$C and $^{15}$N. Chemical shifts ($\delta$ in ppm) are given from internal DMSO-$d_6$ solvent, (2.49) for $^1$H and (39.5) for $^{13}$C, and external CH$_3$NO$_2$ (0.00) for $^{15}$N NMR.

**Reagents.** $[^{15}$N$_2]$-urea (3) was purchased from Chemotrade and $[^{13}$C$_2]$-trimethylsilyl acetylene (6) from Isotec Inc. Unlabelled chemicals were obtained from Sigma-Aldrich.

$[^{15}$N$_3]$-Cyanuric acid (4): Ammonium chloride (0.48 g, 8.97 mmol) and $[^{15}$N$_2]$-urea (3) (1.0 g, 16.12 mmol) were fused at 250 °C and heated for 25 min. The crude reaction mixture was dissolved in boiling water, and the solution was allowed to cool. The precipitate was filtered and washed with water, giving $[^{15}$N$_3]$-cyanuric acid (4) (50% yield).

$[^{15}$N$_3]$-2,4,6-Trichloro-1,3,5-triazine (5): A mixture of $[^{15}$N$_3]$-cyanuric acid (4) (1.0 g, 7.57 mmol) and PCl$_5$ (4.73 g, 22.71 mmol) was heated at 200 °C. Then the reaction mixture was distillated to afford the crude product which was treated with water. The filtered solution was concentrated to afford the product (19%).

$[^{13}$C$_2]$-Lithium 2-(trimethylsilyl)acetylide (7): To a solution of $[^{13}$C$_2]$-trimethylsilyl acetylene (6) (0.55 g, 5.35 mmol) in dry tetrahydrofuran (5.5 mL), 3.3 mL (5.35 mmol) of 1.6 M n-butyllithium in hexane was slowly added at −78 °C, under nitrogen atmosphere. The solution was allowed to warm up to 0 °C and stirred for 2 h. The solvent was removed under vacuum and the product isolated as a white solid (quantitative yield).
[\textsuperscript{13}\text{C}_2]-[\text{Trimethylsilyl}ethynyl]\text{zinc chloride} (8): To a solution of [\textsuperscript{13}\text{C}_2]-lithium 2-(trimethylsilyl)acetylide (7) (0.57 g, 5.35 mmol) in dry tetrahydrofuran (15 mL), a solution of zinc chloride (0.73 g, 5.35 mmol) in 5.5 mL of dry tetrahydrofuran was slowly added at \(-78\) °C, under nitrogen atmosphere. Once the mixture thus obtained had been stirred for 5 min at \(-78\) °C, it was warmed up to \(0\) °C for 30 min. The solvent was removed under vacuum and the product was isolated as solid (quantitative yield).

[\textsuperscript{15}\text{N}_3,\textsuperscript{13}\text{C}_6]-2,4,6-Tris[(trimethylsilyl)ethynyl]-1,3,5-triazine (9): To a solution of [\textsuperscript{15}\text{N}_3]-2,4,6-trichloro-1,3,5-triazine (5) (0.20 g, 1.07 mmol) in 6 mL of dry tetrahydrofuran, were added tetrakis(triphenylphosphine)palladium (0.062 g, 0.053 mmol) and a solution of [\textsuperscript{13}\text{C}_2]-[trimethylsilyl]ethynyl]zinc chloride (8) (1.07 g, 5.34 mmol) in 9 mL of dry tetrahydrofuran. The mixture was then stirred under nitrogen atmosphere at \(30\) °C for 3 h. Afterwards 11 mL of 0.1 N HCl was added and the reaction mixture was extracted with ethyl ether (3 x 22 mL). The combined organic layers were washed with brine (22 mL) and dried over MgSO\(_4\). The solvent was evaporated, and the crude product was purified by column chromatography with the following eluents: 1:400 AcOEt-hexane to afford [\textsuperscript{15}\text{N}_3,\textsuperscript{13}\text{C}_6]-2,4,6-tris[(trimethylsilyl)ethynyl]-1,3,5-triazine (9) (46%). Some amount of the hydrolyzed compound described next was also subsequently isolated with 1:10 AcOEt-hexane.

[\textsuperscript{15}\text{N}_3,\textsuperscript{13}\text{C}_6]-2,4,6-Triethynyl-1,3,5-triazine (2): To a solution of [\textsuperscript{15}\text{N}_3,\textsuperscript{13}\text{C}_6]-2,4,6-tris[(trimethylsilyl)ethynyl]-1,3,5-triazine (9) (0.061 g, 0.16 mmol) in 4 mL of methanol-tetrahydrofuran (1:1), was added potassium fluoride (0.035 g, 0.60 mmol). The mixture was stirred at room temperature for 1 h. After removal of the solvents, the product was extracted with dichloromethane and purified by sublimation to afford [\textsuperscript{15}\text{N}_3,\textsuperscript{13}\text{C}_6]-2,4,6-triethynyl-1,3,5-triazine (2) (99%). \textsuperscript{1}H NMR (DMSO-\(d_6\)) \(\delta\) 4.97 (\(^1J_{\text{C-H}} = 253.5\) Hz, \(^2J_{\text{C-H}} = 56.1\) Hz); \textsuperscript{13}C NMR (DMSO-\(d_6\)) \(\delta\) 159.1, 85.3, 79.9; \textsuperscript{15}N NMR (DMSO-\(d_6\)) \(\delta\) \(-99.1\) (\(^2J_{\text{C-N}} = 10.9\) Hz).

Solid-state NMR spectroscopy Experiments were performed on a Bruker AVANCE III NMR spectrometer, operating at \(^1\text{H}, \text{ }^{13}\text{C}\) and \(^{15}\text{N}\) Larmor frequencies of 500, 125 and 50 MHz, respectively, using a Bruker 3.2 mm triple-resonance MAS probe and a spinning frequency of 10 kHz.
$^{15}\text{N}/^{13}\text{C}$ heteronuclear spin-echo experiments were performed using the pulse sequences shown in Figure 1. An 8-step phase cycle was used: $\varphi_1 = -x, +x$; $\varphi_2 = +y, -y, x, -x, +x, +y$; receiver $= +x, -x, +x, +x, -x, +x$ to select $\Delta p = \pm 1$ and $\pm 2$ on the $^{1}\text{H} \pi/2$ ($\varphi_1$) and $^{15}\text{N} \pi$ pulses ($\varphi_2$), respectively, where $p$ is the coherence order. $^{15}\text{N} \pi$ pulses of 10.0 $\mu$s corresponding to a nutation frequency ($v_1$) of 50 kHz were used, along with $^{13}\text{C} \pi$ pulses of 8.0 $\mu$s duration ($v_1 = 62.5$ kHz) and $^{1}\text{H} \pi/2$ pulses of duration of 2.5 $\mu$s ($v_1 = 100$ kHz). Ramped ($^{1}\text{H}/^{15}\text{N}$) cross polarisation (CP) was employed with a contact time of (1) 5.0 ms and (2) 6.0 ms and (10), [U-$^{13}\text{C},^{15}\text{N}$] histidine·HCl, purchased from Sigma Aldrich, UK and used without further recrystallisation or purification, for which results are presented in the Supporting Information) 1.0 ms. SPINAL-64 heteronuclear decoupling was used with $v_1(^{1}\text{H}) = 100$ kHz and pulses of duration (1) 4.90 $\mu$s, (2) 4.84 $\mu$s and (10) 4.85 $\mu$s.

**Figure 1.** Pulse sequences for the $^{15}\text{N}/^{13}\text{C}$ heteronuclear spin-echo experiment, whereby non-selective (top) or Gaussian-shaped selective (bottom) $\pi$ pulses are applied to the $^{13}\text{C}$ channel. For the case of homonuclear spin-echo experiments, the $^{13}\text{C} \pi$ pulse is omitted.

For non-selective heteronuclear spin-echo experiments, $\pi$ pulses on $^{13}\text{C}$ (top option in Figure 1) were applied with the $^{13}\text{C}$ carrier frequency in the centre of the spectrum, whereas for selective $^{13}\text{C}$ inversion, a Gaussian shaped pulse (bell shape, bottom option in Figure 1) of length, $\tau_P$, (2) 4.0 ms or (10) 2.0 ms was used, whereby the $^{13}\text{C}$ carrier frequency was centred on the carbon resonance of interest. Thus, for selective heteronuclear spin-echo experiments, the initial $\tau = 0$ case corresponds to $\tau_P$. Following the procedure described in ref52, the data obtained using selective $^{13}\text{C}$
pulses was fit to equations (see below) containing a shifted echo term, \((\tau - \tau_{sh})\), to account for the evolution which occurs during the length of the selective pulse, where \(\tau_{sh} = (2)\) 0.96 ms or \((10)\) 0.48 ms. \(^{15}\)N homonuclear spin-echo experiments were performed by omitting the \(\pi\) pulse on the non-observe, \(^{13}\)C channel. Experiments were interleaved such that each set of homonuclear and heteronuclear spectra were recorded consecutively for each evolution interval, \(\tau\), and all echo delays were rotor synchronised. \((1)\) 768, \((2)\) 320 and \((10)\) 32 transients were co-added for each \(\tau\) increment for \((1, 2)\) (16 s recycle delay) and \((10)\) (12 s recycle delay), respectively.

\(^{13}\)C CP MAS spectra were recorded with ramped \((\text{H}-^{13}\text{C})\) CP of contact time \((1, 10)\) 1.0 ms and \((2)\) 2.5 ms and an acquisition time of \((1, 2)\) 10 ms and \((3)\) 20 ms. \((1, 10)\) 8 and \((2)\) 128 transients were co-added and a recycle delay of \((1)\) 30 s, \((2)\) 3 s and \((10)\) 2.5 s was used.

\(^{15}\)N chemical shifts were referenced indirectly to neat liquid nitromethane (CH\(_3\)NO\(_2\)) by using powdered \([^{15}\text{N}]\)glycine as an external secondary reference (\(\delta_{\text{iso}} = -347.4\) ppm). To convert to the chemical shift scale frequently used in protein NMR, where the alternative IUPAC reference (see Appendix 1 of Ref. 53) is liquid ammonia at \(-50^\circ\)C, it is necessary to add 379.5 ppm to the given values.\(^{54}\) The \(^{13}\)C chemical shifts were referenced to tetramethylsilane (TMS, Si(CH\(_3\))\(_4\)) by using powdered L-alanine as an external secondary reference (\(\delta_{\text{iso}} = 177.9, 51.0, 20.5\) ppm) – this is equivalent to using adamantane at 38.5 ppm that corresponds to TMS at 0 ppm.\(^{55}\)

\(S_{\text{HET}}(\tau)\) and \(S_{\text{HOM}}(\tau)\) integrals were taken over the respective resolved peaks after Fourier transformation with respect to \(t_2\) and quotients, \(S_Q(\tau) = S_{\text{HET}}(\tau)/S_{\text{HOM}}(\tau)\), determined. \(S_Q(\tau)\) was normalized such that \(S_Q(\tau = 0) = 1.00\). Uncertainties, \(\sigma_{\text{HET}}\) and \(\sigma_{\text{HOM}}\), were estimated for \(S_{\text{HET}}\) and \(S_{\text{HOM}}\) data points, respectively, based on the signal to noise ratios observed for heteronuclear \(^{15}\)N/\(^{13}\)C spin-echo spectra obtained at \(\tau = 0\) and uncertainties, \(\sigma_q\), in \(S_Q\) were calculated using eq 1.

\[
\sigma_q = S_Q \sqrt{\left( \frac{\sigma_{\text{HET}}}{S_{\text{HET}}} \right)^2 + \left( \frac{\sigma_{\text{HOM}}}{S_{\text{HOM}}} \right)^2} \quad (1)
\]

Errors on fitted parameters were determined using the covariance method as described in Ref\(^{40}\). The analysis assumes that there is no deviation from the magic angle that would lead to a residual
In this respect, note that the dipolar coupling constant corresponding to a $^{13}$C and $^{15}$N spin pair at a distance of 3.25 Å is less than 100 Hz: as shown in section S6 of Ref. 56, a deviation of more than 2° from the magic angle would be required to see a noticeable change in the spin-echo evolution for such a small dipolar coupling. This work used the carboxylate $^{13}$C linewidth of L-alanine in a $^{13}$C CP MAS experiment to check the setting of the magic angle, which, as discussed in section S5 of Ref. 56, ensures a setting to within a small fraction of a degree from the magic angle.

**DFT Calculations of J Couplings** First-principles J couplings were calculated using a pre-release version of the 8.0 CASTEP software package. CASTEP implements density functional theory using a plane-wave basis set. Calculations of the J couplings used Vanderbilt’s Ultrasoft pseudopotentials, as described by Green and Yates and based on the approach introduced by Joyce et. al. The pseudopotentials used are the CASTEP 8.0 default set. The exchange-correlation functional employed was the Perdew-Burke-Ernzerhof (PBE) implementation of the generalized gradient approximation.

The geometry optimized crystal structure of 1 (all atoms relaxed) as described in ref, as generated starting from the crystal structure with CSD reference code and number JOQSEN and 112101, was used for J-coupling calculations. For 2, a geometry optimization was performed upon the crystal structure with CSD reference code and number HULSEM and 193181. The calculations used Ultrasoft pseudopotentials, planewaves up to a maximum energy of 600 eV and a Brillouin Zone sampling of 0.2 $\times$ $2\pi$ Å$^{-1}$. An initial partial geometry optimisation was performed allowing only the hydrogen atoms to move. However, the forces on the carbon atoms were as large as 4.5 eV/Å, thus, a full optimisation was carried out allowing all atoms to move. Note that while the published crystal structure of 2 has $Z' = 1$, symmetry was not imposed during the DFT calculations, and the resulting geometry-optimised structure (allowing all atoms to move) has $Z' = 2$ (see Supporting Information). However, note that the differences between the two molecules are very small, for example there are no differences (to two decimal places for distances in Å and to one decimal place for the angles in degrees) in the intermolecular CH…N hydrogen bonding distances discussed below.

For 10, geometry optimization was performed upon the crystal structure with CSD reference code
A partial geometry optimisation (only hydrogen atom positions) was performed, since the forces remaining on the non-hydrogen atoms after partial optimisation were all less than 1.0 eV/Å.

$J$-coupling calculations were performed with a plane-wave cut-off of 750 eV and a k-point sampling grid density of 0.07 (1) or 0.1 (2, 10) × 2π Å$^{-1}$. The $J$ couplings are computed by considering one nucleus as a perturbation and it is therefore necessary to multiply the size of the original crystal unit cell until the values of the couplings are converged. A 1×1×1 (200 atoms), 1×2×2 (120 atoms) or 1×2×2 (200 atoms) supercell was found to be sufficient for the $J$ couplings to be well converged within ±0.1 Hz. The calculation time for the $J$ couplings varied between 0.5-2 hours on 2 Intel Xeon X5650 12 core 2.66 GHz nodes at the University of Warwick.

The outputs of the GIPAW calculations of NMR parameters are .magres files for which the software Magresview allows the ready linking to the crystal structure.

**Results and Discussion**

The structure of this paper is to describe experimental results first followed by DFT GIPAW calculations. Within the experimental section, there is first a description of the synthesis of the selectively labelled compounds followed by a description of the hydrogen bonding in the crystal structures, before the experimental MAS NMR data is presented.

**Synthesis** The synthesis of [$^{13}$C≡$^{13}$CH,$^{15}$N≡C] 4-cyano-4′-ethynylbiphenyl, 1 (specifically, 1-$^{15}$N,$^{13}$C$_2$, IUPAC name: 4′-($^{13}$C$_2$)ethynylbiphenyl-4-($^{15}$N)carbonitrile) is described in Ref. The synthesis of [$^{13}$C≡$^{13}$CH,$^{15}$N] 2,4,6-triethynyl-1,3,5-triazine, 2 (specifically, 2-$^{15}$N$_3$,$^{13}$C$_6$) was achieved for the first time in this work according to the multistep procedure depicted in Scheme 1, where the key element is the reaction of [$^{15}$N$_3$]-2,4,6-trichloro-1,3,5-triazine (5) with [$^{13}$C$_2$]-[trimethylsilyl]ethynyl]zinc chloride (8) to afford [$^{15}$N$_3$,$^{13}$C$_6$]-2,4,6-tris[(trimethylsilyl)ethynyl]-1,3,5-triazine (9). Powder X-ray diffraction (PXRD) patterns for the samples of 1 and 2 are presented in section S1 of the Supporting Information. The Supporting Information also shows PXRD and NMR spectra for 1 and 2 at natural isotopic abundance (Figures S1 to S3), for which the same synthetic methodology was followed using the corresponding unlabelled reagents.

In overview, [$^{15}$N$_3$]-cyanuric acid (4) was obtained by cyclotrimerization of [$^{15}$N$_2$]-urea (3), and then nucleophilic substitution of the hydroxyl groups by chlorine gave the [$^{15}$N$_3$]-cyanuric
chloride or $[^{15}\text{N_3}]2,4,6$-trichloro-1,3,5-triazine (5). Treatment of lithium 2-(trimethylsilyl)acetylide (7) with a solution of anhydrous zinc chloride in tetrahydrofurane yielded $[^{13}\text{C_2}]-[(\text{trimethylsilyl})\text{ethynyl}]\text{zinc chloride (8)},$ which was reacted with $[^{15}\text{N_3}]2,4,6$-trichloro-1,3,5-triazine (5) in the presence of tetrakis(triphenylphosphine)palladium to afford $[^{15}\text{N_3},^{13}\text{C_6}]2,4,6$-tris[(trimethylsilyl)ethynyl]-1,3,5-triazine (9). Further hydrolysis of the latter compound with potassium fluoride in CH$_3$OH-THF resulted in $[^{15}\text{N_3},^{13}\text{C_6}]2,4,6$-triethynyl-1,3,5-triazine (2-$^{15}\text{N_3},^{13}\text{C_6}$). Crystals of 2-$^{15}\text{N_3},^{13}\text{C_6}$ were grown by sublimation, the melting point being the same as the one described in reference$^{47}$ for the non labeled compound.

![Scheme 1. Synthesis of 2-$^{15}\text{N_3},^{13}\text{C_6}$](image)

**CH…N Hydrogen Bonding in the Geometry Optimised Crystal Structures.** There is a single unique entry in the CSD for both 1 and 2. For 1 (CSD reference code: JOQSEN$^{46}$), the intermolecular hydrogen bonding between the alkyne CH and the nitrile nitrogen shown in Figure 2 (top) leads to the formation of linear chain-like arrangements, with there being four distinct molecules in the asymmetric unit cell ($Z' = 4$). Table 1 lists the hydrogen bonding parameters (after...
geometry optimization), namely the C(H)...N and H...N distances and the CHN angle, for the four
distinct molecules in 1 (see also Figure 3 of Ref. 29). The average C(H)...N and H...N distances
are 3.28 Å and 2.21 Å, respectively, with an average CHN angle of 173°.

For 2 (CSD reference code: HULSEM47), each molecule has three hydrogen-bonding donor CH
groups and three hydrogen-bonding acceptor nitrogens, leading to a hexagonal structure as shown
in Figure 2 (bottom). Note that there is a single mirror plane through one of the ring nitrogen atoms
(N^A in Figure 2), such that there are two distinct ring nitrogen atoms (N^B and N^C are equivalent in
Figure 2) in the asymmetric unit (and hence, also, two distinct ring carbon atoms and two distinct
alkyne groups). Table 1 lists the hydrogen bonding parameters (after geometry optimization),
namely the C(H)...N and H...N distances and the CHN angle, for the two distinct nitrogen sites
in 2. The average C(H)...N and H...N distances are 3.25 Å and 2.17 Å, respectively, with an
average CHN angle of 177°.

Table 1. CH...N hydrogen bonding parameters\textsuperscript{a} and GIPAW calculated $^2J_{CN}$ and $^3J_{CN}$ couplings
for 1 and 2

| d(C...N) / Å | d(H...N) / Å | \( \angle \text{CHN} / ^\circ \) | $^2J_{CN}$ / Hz | % FC\textsuperscript{b} | $^3J_{CN}$ / Hz | % FC\textsuperscript{b} |
|---|---|---|---|---|---|---|
| Four distinct molecules (and hence) nitrogen sites in the asymmetric unit cell of 1 |
| 3.23 | 2.16 | 177.1 | −10.1 | 99.9 | −1.8 | 97.0 |
| 3.28 | 2.21 | 171.2 | −9.0 | 99.1 | −1.6 | 96.5 |
| 3.28 | 2.21 | 172.8 | −8.8 | 99.4 | −1.6 | 96.6 |
| 3.31 | 2.25 | 167.9 | −7.6 | 99.4 | −1.3 | 96.2 |
| Two distinct nitrogen sites in 2 |
| 3.24 | 2.15 | 180.0 | −8.9 | 98.4 | −1.7 | 97.0 |
| 3.26 | 2.18 | 173.7 | −8.2 | 98.5 | −1.6 | 97.0 |

\textsuperscript{a}After geometry optimisation, starting from the CSD structures with reference codes JOQSEN\textsuperscript{46}
and HULSEM.\textsuperscript{47} \textsuperscript{b}The full listing of the four Ramsey contributions: Fermi Contact (FC), Spin
Dipolar (SD), Paramagnetic Orbital (Para) and Diamagnetic Orbital (Dia) are given for 1 and 2 in
Tables S4 and S5, respectively, in the Supporting Information.
The Introduction has referred to previous studies where significant molecule to crystal changes in the calculated $^1$H chemical shift were observed for maltose$^{28}$ and uracil$^{29}$, whereby hydroxyl and carbonyl groups are the hydrogen bonding acceptor sites, respectively, in intermolecular CH···O hydrogen-bonding interactions. A consideration of Table 1 shows that the CH···N hydrogen bonding distances in 1 and 2 are similar to those in uracil (C(H)···O = 3.21 Å, 3.29 Å; H···O = 2.16 Å, 2.25 Å, $\angle$CHO = 161°), but with bond angles closer to 180°, while the hydrogen bonding distances are significantly longer in maltose: C(H)···O = 3.56 Å, H···O = 2.48 Å, $\angle$CHO = 168° for the largest molecule to crystal change in the calculated $^1$H chemical shift.

**Figure 2.** Representations of the geometrically optimised (CASTEP) crystal structures of 1 and 2 (CSD reference codes: JOQSEN$^{46}$ and HULSEM$^{47}$) with red dashed lines indicating intermolecular CH···N hydrogen bonds. Solid and dashed arrows distinguish intramolecular $^2$J$_{CN}$ and $^3$J$_{CN}$ couplings (for 2 only) from intermolecular hydrogen-bond mediated $^{2h}$J$_{CN}$ and $^{3h}$J$_{CN}$ couplings. For 2, there is a mirror plane, shown as a yellow thick vertical line, such that there are only two distinct nitrogen atoms in the asymmetric unit of the X-ray crystal structure.$^{47}$ Isotopically enriched $^{13}$C sites (for the alkyne groups, denoted C2 and C3 in 2) are shown in black with the
unlabelled carbon atoms (specifically the ring carbons in 2) in grey, while the $^{15}$N atoms (of the nitrile group in 1 and in the ring in 2) are in blue, with hydrogen atoms in white.

**One-dimensional MAS NMR.** Figure 3 presents one-dimensional $^{15}$N and $^{13}$C solid-state NMR spectra of 1 and 2 obtained via CP from $^1$H at a $^1$H Larmor frequency of 500 MHz and a MAS frequency of 10 kHz. Similar spectra of 1 (at a $^1$H Larmor frequency of 300 MHz) have been presented in Figure 4 in Ref. 29: it is not possible to resolve distinct $^{15}$N resonances for the four distinct molecules in the asymmetric unit cell (Figure 3a), and there is only a single lineshape with a clear shoulder at lower ppm in the $^{13}$C spectrum (Figure 3b) corresponding to the two $^{13}$C labelled carbon atoms of the alkyne group for the four distinct molecules in the asymmetric unit cell (i.e., a total of eight overlapping resonances).

For 2, one separate resonance is observed in Figure 3c for the $^{15}$N spectrum, while two separate resonances in the $^{13}$C spectrum (Figure 3) are observed that correspond to the two alkyne atoms, labelled C2 and C3 in Figure 2. The CP efficiency is different for the protonated C3 CH moiety as compared to the non-protonated C2 carbon, hence explaining the different relative intensity in Figure 3d. As noted above, the mirror symmetry in the CSD crystal structure of 2 (see the thick vertical yellow line in Figure 2) means that two distinct nitrogen resonances as well as two distinct C2 and two distinct C3 resonances would be expected in Figure 3c and 3d, respectively. This may be the origin of the unusual lineshapes in these spectra. However, for such labelled compounds, unusual lineshapes (such as those observed in Figure 3d) can also arise from the cross correlation of chemical shift anisotropy and dipolar couplings as well as J couplings, as noted previously for cis-azobenzene-$^{15}$N$_2$ dioxide$^{68}$ and fully $^{13}$C-labelled L-alanine.$^{69}$ For comparison, $^{13}$C CP MAS NMR spectra for samples 1 and 2 at natural isotopic abundance are presented in Figure S3 in the Supporting Information.
Figure 3. Solid-state MAS (10 kHz) NMR spectra of (top, a and b) 1 and (bottom, c and d) 2, recorded at a $^1$H Larmor frequency of 500 MHz. (left) Heteronuclear $^1$H-$^{15}$N {$^{13}$C} CP MAS spin-echo spectra for (a) 1 and (c) 2 (both recorded with $\tau = 0$ and $\tau_P = 4$ ms, see pulse sequence in Figure 1). The noise level is calculated as (a) 0.9% and (c) 0.6%. (right) $^1$H-$^{13}$C CP MAS spectra of (b) 1 and (d) 2.

Spin-echo MAS NMR. In solution-state NMR, $J$ couplings manifest themselves in the observation of multiplet patterns. In solid-state MAS NMR, it is usually not possible to read off $J$ couplings from such multiplet patterns; however, $J$ couplings that are (often much) smaller than the observed linewidths can be determined from spin-echo experiments\textsuperscript{38-41,70-78} that exploit the much longer spin-echo dephasing time, $T_2^\ast$.\textsuperscript{33} In particular, Duma et al. have shown that homonuclear $J$ couplings can be reliably determined\textsuperscript{38} even for regimes where unusual broadened lineshapes are observed in the direct dimension, as commented on above.
In the spin-echo (\(\tau/2 - \pi - \tau/2\)) pulse sequences employed in this work, \(^{15}\)N magnetization is created by CP and subsequently evolves under \(^1\)H decoupling. As shown in Figure 1, three variants of this pulse sequence are applied. In a \(^{15}\)N homonuclear (HOM) spin-echo experiment, a \(\pi\) rf pulse is applied only to the \(^{15}\)N spins, such that there can only be evolution under homonuclear \(^{15}\)N-\(^{15}\)N J couplings as well as a loss of signal characterized by \(T_2'\). In a \(^{15}\)N/\(^{13}\)C heteronuclear (HET) spin-echo experiment, a rf pulse with \(\pi\) flip angle is applied to both \(^{15}\)N and \(^{13}\)C spins, such that there can also be evolution under heteronuclear \(^{15}\)N-\(^{13}\)C J couplings. If there is resolution in the observed \(^{15}\)N NMR spectrum, separate (HOM and HET) spin-echo curves can be extracted for distinct nitrogen sites. However, as noted above, in this study, there is no resolution of distinct nitrogen sites for 1 (Figure 3a) or for 2 (Figure 3c). If there is resolution of distinct \(^{13}\)C resonances, the \(^{13}\)C \(\pi\) pulse in a \(^{15}\)N/\(^{13}\)C HET spin-echo experiment can be applied non-selectively or selectively, i.e., to invert the spin states of all \(^{13}\)C spins or only those corresponding to one resolved \(^{13}\)C resonance, respectively.\(^{75}\) In this way, the experimental spin-echo curves can be encoded with all heteronuclear \(^{15}\)N-\(^{13}\)C J couplings or only specific \(^{15}\)N-\(^{13}\)C J couplings.

For 1, there is no resolution of distinct carbon sites (Figure 3b), thus, the HET spin-echo modulation will depend on all \(^{15}\)N-\(^{13}\)C J couplings, with the added complication that a superposition of the distinct (HOM and HET) spin-echo curves for the four distinct molecules in the asymmetric unit cell will be observed. For 2, there are resolved \(^{13}\)C resonances in Figure 3d for the C2 and C3 resonances at ~75 and ~85 ppm, respectively, thus selective \(^{15}\)N/\(^{13}\)C heteronuclear spin-echo experiments allow the evolution under distinct \(^{15}\)N-\(^{13}\)C J couplings to C2 or to C3 to be observed. However, there is again still the complication that, for the CSD structure, two distinct nitrogen resonances (labelled \(N_A\) and \(N_B\) in Figure 2) as well as two distinct C2 and two distinct C3 resonances are expected. These are not resolved in Figure 3c and 3d, such that there will be a superposition of the (HOM and HET) spin-echo curves for the distinct sites.

Using the method presented in Ref.\(^{41}\), the quotient of the heteronuclear and homonuclear spin-echo signals, \(S_Q(\tau) = S_{\text{HET}}(\tau)/S_{\text{HOM}}(\tau)\), depends only on the heteronuclear J coupling(s), with the evolution under any homonuclear J coupling cancelling out. Trébosc et al. utilized a similar approach to analyse \(^{15}\)N-\(^{13}\)C heteronuclear spin-echo data for L-histidine.HCl.H\(_2\)O.\(^{75}\) By analogy to the REDOR experiment,\(^{79}\) the analysis of Trébosc et al. makes the simplification of assuming that the dephasing time for a homonuclear and heteronuclear spin echo are the same, i.e., there is
a cancelling of the spin-echo dephasing time, $T_2'$. However, as shown in Ref. 41, the dephasing time for a homonuclear and heteronuclear spin echo can be different, thus, an exponential term, $\exp(-\tau/ \Delta T_2')$, should be included in the $S_Q(\tau)$ expression, where $1/ \Delta T_2'$ equals $(1/ T_2'_{\text{HET}}) - (1/ T_2'_{\text{HOM}})$. Note that this difference in dephasing times is small, such that the fitted $\Delta T_2'$ values in Ref. 41 for the quotient of $^{15}\text{N}-^{17}\text{O}$ heteronuclear and $^{15}\text{N}$ homonuclear spin-echo data sets recorded for uracil are 294 and 585 ms for the two distinct $^{15}\text{N}$ resonances, corresponding to a very slow decay of $S_Q(\tau)$.

Figures 4a and c show the $S_{\text{HET}}(\tau)$ and $S_{\text{HOM}}(\tau)$ spin-echo signal (integrated intensities over the $^{15}\text{N}$ resonance, after Fourier transformation with respect to the acquisition time, $t_2$) as a function of evolution time, $\tau$, for 1 and 2, respectively. In both cases, clear differences are observed between the spin-echo curves for the homonuclear and heteronuclear experiments, indicating the presence of $^{15}\text{N}-^{13}\text{C} J$ couplings. Specifically, for 1, a zero crossing is observed for $S_{\text{HET}}(\tau)$ between $\tau = 100$ ms and 110 ms in Figure 4a, while only a slow signal decay is observed for $S_{\text{HOM}}(\tau)$. For 2, faster decay is observed, as compared to $S_{\text{HOM}}(\tau)$, for the two $S_{\text{HET}}(\tau)$ curves corresponding to selective pulses on the C2 and C3 resonances, though none of the curves exhibit a zero crossing. The analysis here is for the corresponding quotients, $S_Q(\tau) = S_{\text{HET}}(\tau)/S_{\text{HOM}}(\tau)$, as plotted in Figure 4b for 1 and Figure 4d for 2 (selective spin echoes for C2, black, C3, grey).
Figure 4. $^{15}$N homonuclear (open diamonds) and $^{15}$N/$^{13}$C heteronuclear (filled diamonds) $^1$H-$^{15}$N CP MAS spin-echo (\(\tau/2-\pi-\tau/2\)) intensities for (a) 1 and (c) 2, as a function of the total spin-echo duration, \(\tau\). Experiments were carried out at a $^1$H Larmor frequency of 500 MHz and a MAS frequency of 10 kHz. The error bars for the experimental intensities were determined to be (a) ± 0.009, (c) ± 0.006 and are omitted for clarity of presentation. The quotients \(S_Q(\tau) = \frac{S_{\text{HET}}(\tau)}{S_{\text{HOM}}(\tau)}\) for (b) 1 and (d) 2 (C2, black, C3, grey), together with the best fits (solid lines, see Table 2) to (b) eq 2, (d) eq 3 (black) and eq 4 (grey). \(S_Q(\tau)\) has been normalized such that \(S_Q(\tau = 0) = 1.00\): Experimentally, the ratio of the integrated intensities \(S_{\text{HET}}(\tau = 0)/ S_{\text{HOM}}(\tau = 0)\) equalled 0.998 for 1 and 1.003 and 1.002 for C2 and C3 selective experiments of 2, respectively.
A spin-echo ($\tau/2 - \pi - \tau/2$) curve with a zero crossing allows the reliable determination of the largest $J$ coupling, with its $\cos(\pi J \tau)$ modulation giving a first zero crossing at $\tau = 1/(2J)$. As shown in section S3 in the Supporting Information, modulation due to additional $J$ couplings (of magnitude less than or equal to the first $J$ coupling) does not change the time at which zero crossings occur, but the additional modulation does change the shape of the modulation. If the spin-echo curve corresponds to the superposition of more than one $\cos(\pi J \tau)$ modulation, i.e., corresponding to the case of overlapping resonances that exhibit different $J$ couplings, section S3 in the Supporting Information further shows that the first zero crossing is observed at the average of the different $J$ couplings. With this in mind, best fits of the three $S_Q(\tau) = S_{\text{HET}}(\tau)/S_{\text{HOM}}(\tau)$ curves to three different equations are shown in Figure 4b for 1 (to eq 2) and Figure 4d for 2 (selective spin echoes for C2, black and C3, grey, to eq 3 and 4, respectively):

1. $S_Q(\tau) = A \cos(\pi J_{NC1} \tau) \cos(\pi J_{NC2} \tau) \exp(-\tau/\Delta T_2')$ (2)
2. $S_Q(\tau) = A \cos^2(\pi J_{NC}(\tau - \tau_{sh})) \exp(-\tau/\Delta T_2')$ (3)
3. $S_Q(\tau) = A \cos(\pi J_{NC}(\tau - \tau_{sh})) \exp(-\tau/\Delta T_2')$ (4)

Note in eq 3 and 4 that a time-shift, $(\tau - \tau_{sh})$, takes into account the length of the selective pulse.$^{52}$ It is evident that good fits are obtained in all three cases, with the fit parameters being listed in Table 2 (see also the listing of correlation coefficients in Table S1 in the Supporting Information). As noted above, the fit functions in eq (2) to (4) include an exponential term, $\exp(-\tau/\Delta T_2')$, to take into account the difference in dephasing time for a homonuclear and heteronuclear spin echo. However, for 1, this term was set equal to one (otherwise, correlation coefficients with magnitude above 0.9 are observed), while the large errors bars on the fitted $\Delta T_2'$ parameters for 2 are indicative of large correlation coefficients, between 0.8 and 0.9 (see Table S1 in the Supporting Information), in all cases, showing that the small difference in dephasing time for homonuclear and heteronuclear spin echo cannot be reliably determined for these spin-echo curves.
For 1, a zero crossing is observed for $S_Q(\tau)$ in Figure 4b, allowing the reliable determination of the largest $^{13}$C-$^{15}$N heteronuclear $J$ coupling. As shown in Figure S4 in the Supporting Information, a better fit is obtained when an additional modulation to a second $J$ coupling is included, i.e., the best fit of $S_Q(\tau)$ in Figure 4b is for two $J$ couplings of 4.7 and 2.9 Hz. The two $S_Q(\tau)$ curves in Figure 4d corresponding to selective spin echoes for the C2 (black) and C3 (grey) resonances of 2 are best fit to a $\cos^2(\pi J \tau)$, eq 3, and a single $\cos(\pi J \tau)$, eq 4, modulation, with fitted $J$ couplings of 4.7 and 4.1 Hz, respectively. The change in shape of the $S_Q(\tau)$ curve for the case of modulation due to two equal $J$ couplings as compared to a single $J$ coupling is evident in Figure 4d (see also Figure S4 in the Supporting Information).

Table 2. Parameters extracted from the fits of the experimental $^{15}$N/$^{13}$C spin-echo ($\tau/2-\pi-\tau/2$) intensities in Figure 4: Comparison of experimentally determined and calculated (GIPAW) $J$ couplings (see Figure 2)$^a$

| Data set | $J_{CN}$ | $J_{CN}/Hz$ | $A$ | $\Delta T'_2$/ms$^b$ | $[\varepsilon]^c$ |
|----------|---------|-------------|-----|-----------------|-----------------|
| $S_Q(1)$ | $^2bJ_{CN}$ | 7.6 to 10.1 | 4.7 ± 0.4 | 1.02 ± 0.01 | —$^f$ | 0.001 |
|          | $^3bJ_{CN}$ | 1.3 to 1.8 | 2.9 ± 0.8 | | | |
| $S_Q(2)$ | $^2cJ_{CN}$ | 10.9, 11.3 | 4.7 ± 0.2 | 1.03 ± 0.01 | 397 ± 180 | 0.011 |
|          | $^2hJ_{CN}$ | 8.2, 8.9 | 4.1 ± 0.3 | 1.02 ± 0.01 | 930 ± 762 | 0.003 |

$^a$ Intermolecular hydrogen-bond mediated $J_{CN}$ couplings are given in bold typeface. $^b$ $1/\Delta T'_2 = (1/T'_{2het}) - (1/T'_{2hom})$. $^c$ $\varepsilon^2 = \sum (I_{fit}(n) - I_{exp}(n))^2 / \sum I_{exp}(n)^2$. $^d$ The range of calculated $J_{CN}$ values for the four molecules in the asymmetric unit of 1 is stated (see Table 1). $^e$ Fit of the $S_Q(\tau)$ data in Figure 4b to eq 2, $I_{exp}(-\tau/\Delta T'_2)$ was set to 1 (otherwise correlation coefficients greater than 0.9 were obtained). $^f$ The calculated $J_{CN}$ values correspond to the two distinct nitrogen atoms, see Table 1 and S5. $^g$ Fit of the $S_Q(\tau)$ data in Figure 4d (solid and grey black line to eq 3 and 4, respectively), where $\tau_{sh} = 0.96$ ms.

GIPAW $J$ coupling calculations. The calculation using density functional theory of NMR $J$ couplings represents a valuable resource that complements experimental measurement.$^{80-83}$ This
section compares the experimentally determined $J$ couplings to those calculated using the GIPAW method\textsuperscript{58,59} for the geometry-optimised crystal structures in the CSD (reference codes: JOQSEN\textsuperscript{46} for 1 and HULSEM\textsuperscript{47} for 2). The application of GIPAW calculation to complement experimental solid-state NMR measurements has been previously employed for $2hJ_{NN}$ and $2hJ_{NO}$ hydrogen-bond mediated couplings,\textsuperscript{41,84,85} as well as $^{29}$Si-$^{31}$P, $^{11}$B-$^{11}$B, $^{31}$P-$^{77}$Se and $^{31}$P-$^{31}$P $J$ couplings in inorganic materials.\textsuperscript{86-89}

Before comparing the experimental and calculated $J$ couplings in Table 2, it is important to consider powder X-ray diffraction (PXRD) analysis for the two solid-state samples of 1 and 2 for which experimental solid-state NMR results are presented in this paper. Figure S1 and S2 (for 1 and 2, respectively) in the Supporting Information compare the experimental PXRD patterns with predicted patterns for the CSD structures (reference codes: JOQSEN\textsuperscript{46} for 1 and HULSEM\textsuperscript{47} for 2). For 1, there is excellent agreement. However, for 2, while there are experimental peaks in the PXRD pattern corresponding to those predicted for the HULSEM\textsuperscript{47} CSD structure, there are a number of peaks in the experimental PXRD pattern in Figure S2 that are not in the predicted pattern for the CSD structure. Since solution-state NMR has confirmed the synthesis of the correct molecular structures (see experimental details above), the PXRD pattern in Figure S2 shows that our sample of 2 is likely a mixture of a new solid-state form (or forms) and the CSD solid-state structure. Efforts are ongoing to identify the new solid-state form(s) of 2 by structure determination from this PXRD pattern.

Table 1 above lists the GIPAW calculated $2hJ_{CN}$ and $3hJ_{CN}$ couplings corresponding to the distinct intermolecular CH...N hydrogen bonds for the geometry-optimised crystal structures in the CSD, reference codes: JOQSEN\textsuperscript{46} for 1 and HULSEM\textsuperscript{47} for 2. For 1, the experimental $S_Q(\tau)$ data in Figure 4b corresponds to the superposition of spin-echo modulation for the four distinct, but not resolved, $^{15}$N resonances (N1 to N4 in Table 1). For each $^{15}$N resonance, Figure 1 and Table 1 both suggest that there should be two $\cos(\pi J \tau)$ modulations corresponding to the $2hJ_{CN}$ and $3hJ_{CN}$ couplings, noting that there is no resolution of the resonances in the $^{13}$C spectrum in Figure 3b for the two chemically distinct carbons in the alkyne bond. As shown in section S3 in the Supporting Information, the consequence of the superposition of the spin-echo modulation for the four distinct $^{15}$N resonances is that an average $2hJ_{CN}$ and an average $3hJ_{CN}$ coupling is extracted from fitting the experimental $S_Q(\tau)$ data in Figure 4b to eq 2. While there is not perfect agreement between
experiment and calculation in Table 2 in that the calculated values are larger than the experimental ones by approximately a factor of two, the calculations confirm that it is to be expected that experiment observes \( J \) couplings across the weak intermolecular CH…N hydrogen bonds. Moreover, it is observed in both experiment and calculation that, in 1, the \( J \) coupling across the intermolecular hydrogen bond is bigger for the nearer carbon (\( ^2hJ_{CN} > ^3hJ_{CN} \)). Note that the spin-echo experiments cannot determine the sign of the \( J \) couplings.

For 2, the GIPAW calculation for the CSD structure HULSEM\(^{47} \) reveals that there are intramolecular \( ^2J_{CN} \) and \( ^3J_{CN} \) couplings between the ring \(^{15}\)N nuclei and the labelled \(^{13}\)C nuclei of the alkyne groups that are of similar magnitude to the intermolecular \( ^2hJ_{CN} \) and \( ^3hJ_{CN} \) couplings, respectively (see Tables 1 and 3). For 2, distinct resonances are resolved in the \(^{13}\)C spectrum for C2 and C3 (see Figure 3d), thus separate \( S_0(\tau) \) data is presented in Figure 4d corresponding to selective spin echoes applied to the C2 and C3 resonances. The GIPAW calculation for the CSD structure HULSEM\(^{47} \) predicts that, for the C2 resonance, the dominant spin-echo modulation is \( \cos^2(\pi J \tau) \) for the two approximately equal intramolecular \( ^2J_{CN} \) couplings (see Table 3 and Figure 2), while, for the C3 resonance, the dominant spin-echo modulation is \( \cos(\pi J \tau) \) for the intermolecular \( ^2hJ_{CN} \) couplings (see Table 1 and Figure 2). There are also three-bond intramolecular \( ^3J_{CN} \) (see Table 3) and intermolecular \( ^3hJ_{CN} \) couplings (see Table 1) that are calculated to be significantly smaller than the \( ^2J_{CN} \) and \( ^2hJ_{CN} \) couplings.

Table 3. GIPAW calculated\(^{4} \) intramolecular \( J_{CN} \) couplings (magnitude > 1 Hz) for 1, 2 and 10

| \( J_{iso} \) / Hz | % FC of \( J_{iso} \) | next largest term |
|------------------|------------------|------------------|
| type             | % of \( J_{iso} \) |
|\(^1\)J\(_{CN}\)^b | −12.0            | 73.0             | SD                  | 36.9 |
|\(^1\)J\(_{CN}\)^b | −11.8            | 73.7             | SD                  | 36.9 |
|\(^1\)J\(_{CN}\)^b | −11.8            | 73.6             | SD                  | 37.2 |
|\(^1\)J\(_{CN}\)^b | −11.7            | 73.9             | SD                  | 37.8 |
|\(^2\)J\(_{CN}\)^b | 3.3              | 75.9             | Para               | 20.9 |
|\(^2\)J\(_{CN}\)^b | 3.3              | 76.3             | Para               | 21.2 |
Two distinct nitrogen sites in 2 (see Figure 1)

|   |   |   |   |   |
|---|---|---|---|---|
| $^2J_{CN}$ | 3.2 | 78.6 | Para | 21.7 |
| $^2J_{CN}$ | 3.4 | 76.4 | Para | 21.7 |

[{$^2J_{CN}$ (N$^A$ to C$^2_A$)} | $-11.3$ | 101.4 | Para | $-1.5$ |}
[{$^2J_{CN}$ (N$^A$ to C$^2_C$)} | $-11.2$ | 101.3 | Para | $-1.4$ |}
[{$^2J_{CN}$ (N$^B$ to C$^2_A$)} | $-10.9$ | 101.5 | Para | $-1.6$ |}
[{$^2J_{CN}$ (N$^B$ to C$^2_B$)} | $-10.9$ | 101.4 | Para | $-1.5$ |]
[{$^3J_{CN}$ (N$^A$ to C$^3_A$)} | $-1.9$ | 84.0 | SD | 15.1 |]
[{$^3J_{CN}$ (N$^A$ to C$^3_C$)} | $-1.9$ | 84.9 | SD | 15.5 |]
[{$^3J_{CN}$ (N$^B$ to C$^3_A$)} | $-1.9$ | 85.3 | SD | 15.4 |]
[{$^3J_{CN}$ (N$^B$ to C$^3_B$)} | $-1.9$ | 84.9 | SD | 15.4 |]
[{$^1J_{CN}$ (N$^A$ to C$^{ring}_B$)$^b$} | 4.6 | $-12.4$ | Para$^c$ | 118.9 |]
[{$^1J_{CN}$ (N$^A$ to C$^{ring}_B$)$^b$} | 4.9 | $-6.7$ | Para$^c$ | 112.7 |]
[{$^1J_{CN}$ (N$^B$ to C$^{ring}_B$)$^b$} | 4.4 | $-16.8$ | Para$^c$ | 123.9 |]
[{$^1J_{CN}$ (N$^B$ to C$^{ring}_B$)$^b$} | 4.9 | $-16.0$ | Para$^c$ | 122.9 |]
[{$^3J_{CN}$ (N$^A$ to C$^{ring}_B$)$^b$} | $-2.5$ | 69.4 | SD | 22.7 |]
[{$^3J_{CN}$ (N$^B$ to C$^{ring}_B$)$^b$} | $-2.6$ | 69.8 | SD | 22.0 |]

[U-$^{13}$C,$^{15}$N] L-histidine.HCl.H$_2$O (10)

|   |   |   |   |   |
|---|---|---|---|---|
[{$^1J_{CN}$ (NH$_3$ to CH)} | $-3.2$ | 69.8 | SD | 24.6 |]
[{$^1J_{CN}$ (NH$_3$ to CH$_2$)} | $-1.2$ | 107.3 | Para | $-9.6$ |]
[{$^1J_{CN}$ (NH to CH)} | $-11.3$ | 137.8 | Para | $-42.5$ |]
[{$^1J_{CN}$ (NH to C)} | $-6.6$ | 148.7 | Para | $-53.6$ |]
[{$^2J_{CN}$ (NH to CH$_2$)} | $-3.1$ | 105.3 | Para | $-8.7$ |]
[{$^2J_{CN}$ (NH to CH)} | $-2.8$ | 105.6 | Para | $-6.8$ |]
[{$^1J_{CN}$ (NH to CH)} | $-12.8$ | 132.5 | Para | $-36.7$ |]
[{$^1J_{CN}$ (NH to CH)} | $-9.1$ | 134.0 | Para | $-37.0$ |]
[{$^2J_{CN}$ (NH to C)} | $-3.5$ | 100.6 | Para | $-5.0$ |]
The full listing of the four Ramsey contributions: Fermi Contact (FC), Spin Dipolar (SD), Paramagnetic Orbital (Para) and Diamagnetic Orbital (Dia) are given for 1, 2 and 10 in Tables S4, S5 and S9, respectively, in the Supporting Information. These $J$ couplings are not observed in this work because of the selective $^{13}$C labelling of only the alkyne carbons. In this case, the Para term is the largest contribution to the total isotropic $J$ coupling.

As noted above, the $S_Q(\tau)$ data in Figure 4d for C2 (black) and C3 (grey) is fit (see Table 2) to the $\cos^2(\pi J \tau)$ and $\cos(\pi J \tau)$ modulation of eq 3 and 4, respectively. While the fit function could be extended to include extra spin-echo modulation, i.e., due to smaller $^3J_{CN}$ or $^3hJ_{CN}$ couplings, it would not be possible to reliably fit the extra modulation since there is not an observed zero crossing. The analysis and comparison of experiment to GIPAW calculation for 2 is complicated by the PXRD pattern in Figure S2 in the Supporting Information showing the presence of a new solid-state form as well as the HULSEM$^{47}$ CSD structure. However, the intramolecular $J$ couplings are expected to be similar in all solid-state forms of 2 since there are no torsional degrees of freedom in the molecular structure. Moreover, the fits of the $S_Q(\tau)$ curves in Figure 4d allow us to hypothesise that the same intermolecular CH…N hydrogen bonding is also adopted in the (yet uncharacterised) new solid-state form(s) of 2.

For 2, while there is again not perfect agreement between experiment (and noting the above discussion of the different solid-state forms of 2) and calculation in Table 1 in that the calculated values are larger than the experimental ones by approximately a factor of two, the calculations confirm that it is to be expected that experiment observes $J$ couplings across the weak intermolecular CH…N hydrogen bonds. Specifically, for the HULSEM$^{47}$ structure of 2, the intermolecular hydrogen-bond mediated $^2hJ_{CN}$ couplings are calculated to be of similar size to the intramolecular $^2J_{CN}$ coupling, as is observed for the $J$ couplings extracted from the experimental data (see Tables 1 to 3).

Considering the calculated intermolecular hydrogen-bond mediated $^2hJ_{CN}$ and $^3hJ_{CN}$ couplings for both 1 and 2 in Table 1, there is a clear correlation between the magnitude of the $^2hJ_{CN}$ (and also $^3hJ_{CN}$) coupling and the CH…N hydrogen bonding distances, namely the shorter the C…N (and H…N) distance, the greater the $^2hJ_{CN}$ (and also $^3hJ_{CN}$) coupling. A similar trend has been
established for the extensively investigated $2hJ_{NN}$ couplings across NH…N hydrogen bonds between nucleobases.$^{90-93}$

The GIPAW calculations provide the four Ramsey contributions: Fermi Contact (FC), Spin Dipolar (SD), Paramagnetic Orbital (Para) and Diamagnetic Orbital (Dia) – see the full listing of the calculated $J$ couplings for 1 and 2 in Tables S4 and S5, respectively, in the Supporting Information. Table 1 shows that the FC term dominates the calculated $2hJ_{CN}$ and $3hJ_{CN}$ couplings for both 1 and 2, namely accounting for at least 98% and 96% of the total isotropic $J$ coupling for $2hJ_{CN}$ and $3hJ_{CN}$, respectively. Such an observation has also been made for $2hJ_{NN}$ couplings.$^{90,91,93-96}$

Hydrogen bond mediated $2hJ_{CN}$ couplings can be visualised using coupling deformation density (CDD) maps of Malkina and Malkin,$^{97}$ as shown in Figure 5 for 2 (our implementation of CCD maps is described, for through-space Se-P $J$ couplings, in Ref. 88, see section S5). As for a $2hJ_{CN}$ coupling in a model NCH…NH$_3$ interaction (see Figure 5 in Ref. 97), the directionality of the hydrogen bond mediated $2hJ_{CN}$ couplings in 2 is evident in Figure 5.
The Supporting Information also compares experimentally determined $J_{CN}$ couplings (see section S5) to the nitrogen sites for [U-$^{13}$C,$^{15}$N] L-histidine.HCl.H$_2$O to those calculated using the GIPAW approach (see Table S9). Reasonable agreement, noting that the calculated one-bond $J$ couplings are smaller than in experiment, is observed (see Table S10), noting also the experimental $^{13}$C-$^{15}$N $J$ couplings determined by Trébosc et al$^{75}$ as well as intramolecular $^{2}J_{NN}$ couplings of 0.9 Hz measured by Thureau et al.$^{78}$ It is informative to compare the $^{2}J_{CN}$ couplings determined experimentally and by calculation in this work for the intermolecular CH…N hydrogen bonds in 1 and 2 to other hydrogen bond mediated $J$ couplings for conventional NH…O and NH…N intermolecular hydrogen bonds that have been experimentally determined by solid-state NMR and calculated using the same GIPAW method. Specifically, Table 4 compares the experimental and calculated $^{2}J_{CN}$ couplings for 1 and 2 to $^{2}J_{NO}$ couplings in uracil$^{41}$ and $^{2}J_{NN}$ couplings in two
guanosine derivatives. The through-bond $J$ coupling between two nuclear magnetic moments depends on the gyromagnetic ratio of the two coupled nuclei, thus, when comparing calculated $J$ couplings between different pairs of nuclear isotopes, it is necessary to consider the reduced spin coupling constant, $K_{xy} = \frac{2\pi J_{xy}}{\hbar \gamma_x \gamma_y}$ (given in units of $10^{19}$ kg m$^{-2}$ s$^{-2}$ Å$^{-2}$), so as to obtain a measure of the scalar coupling that is independent of the nuclear species. Considering the calculated reduced spin coupling constants, while those for the NH…N hydrogen bonds in the guanosine derivatives are about two times bigger than those for the CH…N hydrogen bonds, it is observed that the values for the CH…N hydrogen bonds in 1 and 2 are of similar magnitude to those for the NH…O hydrogen bonds in uracil, even though the C…N distances are significantly longer than the N…O distances (2.8 Å in uracil).
Table 4. Comparison of experimental $J$ and calculated (GIPAW) $J$ and $K$ hydrogen-bond mediated coupling constants$^a$ in 1, 2 and guanosine derivatives

| Donor $(i)$ | Acceptor $(j)$ | Expt $2hJ_{ij}$ | Calc $2hJ_{ij}$ | Calc $2hK_{ij}$ / Å |
|------------|--------------|-----------------|-----------------|------------------|
| C$^b$      | N            | 4.7 ± 0.4       | −8.9            | 29.0             | 3.28            |
| C$^c$      | N            | 4.1 ± 0.3       | −8.5            | 27.9             | 3.25            |
| N3$^d$     | O3           | 4.8 ± 0.5       | 4.6             | 28.1             | 2.84            |
| N1$^d$     | O3           | 6.7 ± 0.4       | 6.1             | 36.8             | 2.83            |
| N1a$^e$    | N7b          | 6.2 ± 0.4       | 6.5             | 52.7             | 2.88            |
| N1b$^e$    | N7a          | 7.4 ± 0.4       | 7.7             | 62.4             | 2.81            |
| N2$^f$     | N7           | 5.9 ± 0.3       | 7.1             | 57.5             | 2.91            |

$^a$ The $J$ coupling constant has units Hz, while the reduced spin coupling constant, $K_{XY} = 2\pi J_{XY} / h\gamma_X\gamma_Y$, is given in units of $10^{19}$ kg m$^{-2}$ s$^{-2}$ Å$^{-2}$ (see Table S11 in the SI for conversion factors).$^b$ 4-cyano-4'-ethynylbiphenyl, 1 (this work, see Tables 1 and 2), where an average is taken over $Z' = 4$ molecules.$^c$ 2,4,6-triethynyl-1,3,5-triazine, 2 (this work, see Tables 1 and 2), where an average is taken over two nitrogen sites.$^d$ Uracil from ref$^{41}$. $^e$ 3',5'-bis-O-propanoyl-2'-deoxyguanosine from refs$^{40,84}$ / 3',5'-bis-O-decanoyl-2'-deoxyguanosine from refs.$^{40,85}$

Table 4 highlights the greater discrepancy with respect to solid-state NMR experiment for the GIPAW calculated $2hJ_{CN}$ couplings in this work as compared to previous reports of GIPAW calculated $2hJ_{NN}$ and $2hJ_{NO}$ couplings. The only other case where a similar approximately factor of two discrepancy between experiment and GIPAW calculation has been noted is for through-space intermolecular $J_{PP}$ couplings in two organochalcogen systems.$^{89}$ By comparison, good agreement between GIPAW calculation and experiment has been observed for similar through-space $J_{PSe}$ couplings in peri-substituted napthalenes$^{88}$ as well as for $2J_{PSi}$ couplings of P-O-Si connectivities in silicophosphates and calcium phosphates.$^{86}$

Conclusions

The results presented in this work demonstrate that, using ($^{15}$N/$^{13}$C) heteronuclear spin-echo NMR experiments, we are able to measure the small intermolecular $2hJ_{CN}$ couplings that occur in 1 and 2, whereby the hydrogen-bond donor is a sp hybridized alkyne moiety, while the acceptor is a nitrogen atom in a nitrile group in 1 or in a triazine ring in 2. We believe this to be the first solid-
state determination of NMR $J$ (scalar) couplings across ‘weak’ CH···N hydrogen bonds. As well as adding a new category to the range of observed hydrogen-bond mediated $J$ couplings, see for example Figure 7 of Ref.98, what is noteworthy is that the magnitude of the experimentally fitted intermolecular $2hJ_{CN}$ couplings (4.7 and 4.1 Hz for 1 and 2, respectively) is comparable to that for extensively studied $2hJ_{NN}$ couplings for NH…N hydrogen bonds adopted by nucleobases (between 6 and 11 Hz). As such, these are an order of magnitude larger than measurements by solution-state NMR of $3hJ_{CC}$ couplings of 0.2 to 0.3 Hz for CH…O=C hydrogen bonds in α-sheet regions of a small protein43 as well as for $J$ couplings due to CH…π interactions that have been observed between methyl and aromatic side chains or carbonyl groups in proteins by Plevin et al.44 and Perras et al,45 where DFT calculation predicts $J$ coupling magnitudes of ~0.1 Hz. We further note that, following previous ab initio predictions,99,100 $J_{CC}$ couplings between 0.2 and 0.5 Hz have recently been measured for through-space van der Waals interactions between aliphatic side groups of the GB3 protein.101

In this work, $J$ couplings have been calculated using the GIPAW method.58,59,84 By comparison with previously presented calculations for conventional NH···N, NH···O hydrogen bonds,41,84,85 it is observed that the reduced spin coupling constants (that are independent of the magnetogyric ratio of the coupled nuclear spins) for the so-called CH…N weak hydrogen bonds, $2hK_{CN}$, are of similar magnitude to those for conventional (NH…O and NH…N) intermolecular hydrogen bonds, $2hK_{NO}$ and $2hK_{NN}$. As for $2hJ_{NN}$ couplings for NH…N hydrogen bonds adopted by nucleobases,90-93 for both 1 and 2, the GIPAW calculations show that a larger $2hJ_{CN}$ (and also $3hJ_{CN}$) coupling is correlated with a shorter C…N (and H…N) intermolecular hydrogen bonding distance. We hence argue that experimentally accessible $2hJ_{CN}$ couplings are well suited for “viewing” weak CH…N hydrogen-bonding interactions, noting the increasing recognition that close CH···N proximities can correspond to structure-determining interactions, playing important chemical roles, for example in the stabilisation of transition states in catalysis.7,12 Noting that, as early as 1963, it has been shown that the formation of C-H…N bonds upon adding pyridine causes the C-H stretching frequency in the IR spectrum of 1,3,5-trichlorobenzene to be lowered by 35 cm$^{-1}$,102 future work could seek to correlate the measurement of $2hJ_{CN}$ couplings with insight from IR and or Raman spectroscopy.
Supporting Information. PXRD analysis; Additional MAS NMR analysis for 1 and 2 (at natural abundance); Comparison of different spin-echo modulations; Correlation coefficients for spin-echo fits for 1 and 2; Experimental MAS NMR spin-echo data with fits for 3; Full listings of DFT calculated J couplings (pdf)

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