Electronic Supplementary Information (ESI)

Probing intermolecular interactions and nitrogen protonation in pharmaceuticals by novel ^{15}N edited and 2D ^{14}N-^{1}H solid-state NMR

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I. Pulse sequences

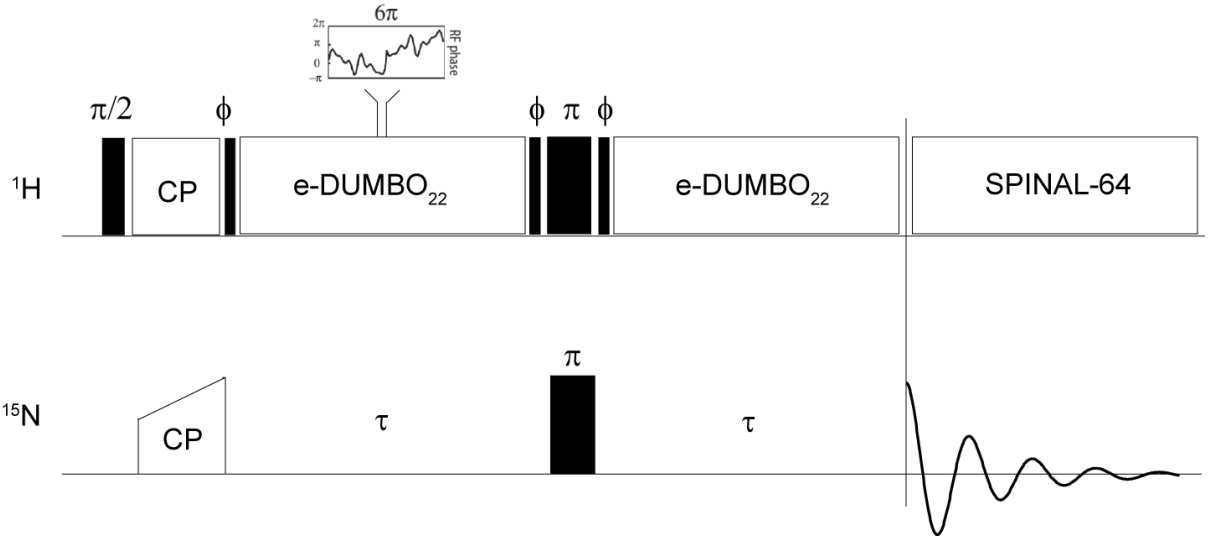

Figure S1. Pulse sequence for $^{1}J_{15N\text{-}1H}$ spectral editing experiments.

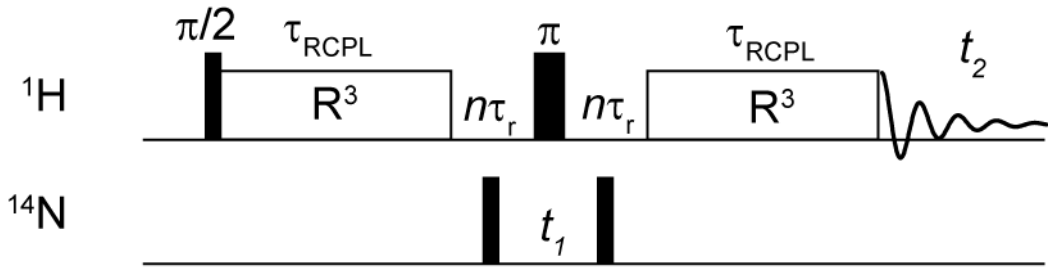

Figure S2. Pulse sequence for ^{14}N-^{1}H HMQC experiments.

II. Confirmation of Form A of cimetidine by PXRD and ^{13}C SSNMR

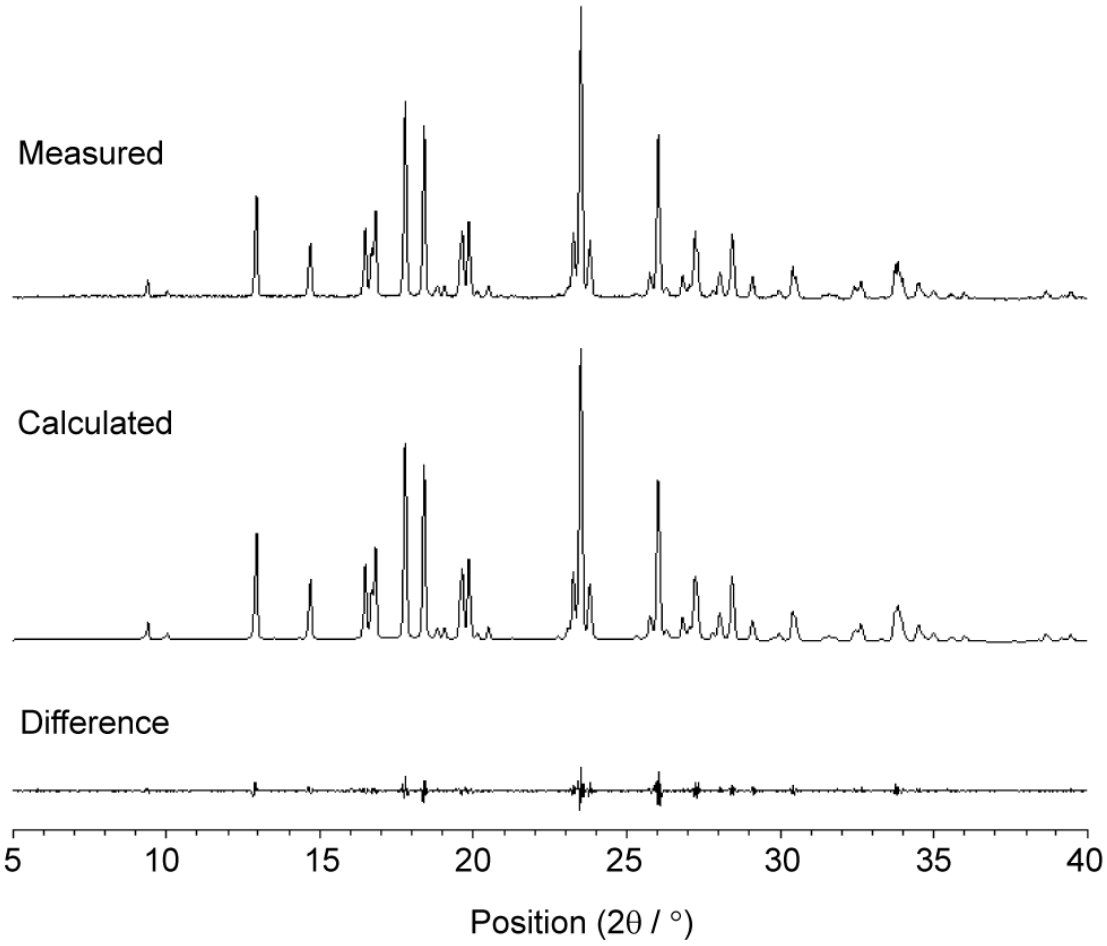

Figure S3. Pawley refinement of the powder X-ray diffraction pattern of the cimetidine sample used in this study against the reported Form A crystal structure (CSD refcode CIMETD). The agreement between the calculated and experimental patterns confirms the phase identity as Form A. The diffraction pattern was collected using an X'Pert Pro diffractometer equipped with a real-time multistrip X'Celerator detector (Panalytical, Eindhoven, The Netherlands). Samples were scanned in continuous mode from 2 to 40 °θ with a 2θ step size of 0.0167°, using CuKα radiation (1.54 Å) with a generator power and current of 40 kV and 40 mA, respectively. The calculated pattern was obtained from the Pawley refinement.[1] The refinement was performed using Materials Studio version 5.5 (Accelrys, San Diego, USA) and achieved a weighted profile R-factor (R_{wp}) of 6.75%.

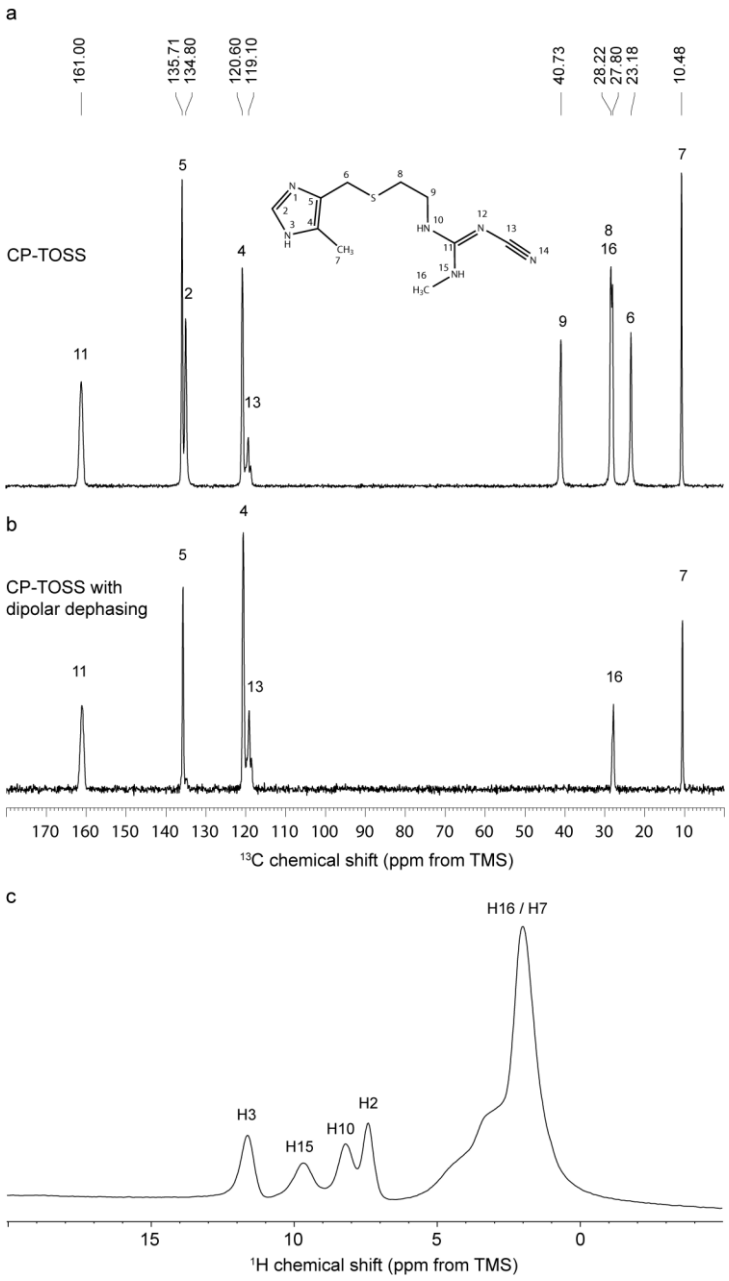

Figure S4. (a, b) ^{13}C CP-TOSS spectra of cimetidine Form A powder used in this study. The top ^{13}C spectrum was obtained using a five-pulse TOSS sequence.[2] The middle spectrum was obtained using the TOSS sequence with three additional shifted-echo rotor periods without ^{1}H decoupling, causing dipolar dephasing of CH and CH_2 carbon signals. Spectra were obtained at 11.7 T and 273 K using an MAS frequency of 8 kHz. 1944 transients were coadded for a recycle delay of 10 s. A 50% ramped CP contact time of 2 ms was used. SPINAL-64 ^{1}H decoupling at a ^{1}H nutation frequency of 100 kHz was applied during t_2. ^{13}C chemical shifts are referenced with respect to hexamethylbenzene at 17.36 ppm,[3] corresponding to TMS at 0 ppm. (c) ^{1}H (60 kHz, 850 MHz) one-pulse spectrum of cimetidine Form A.

III. ^{1}H-^{15}N HETCOR spectra of cimetidine Form A

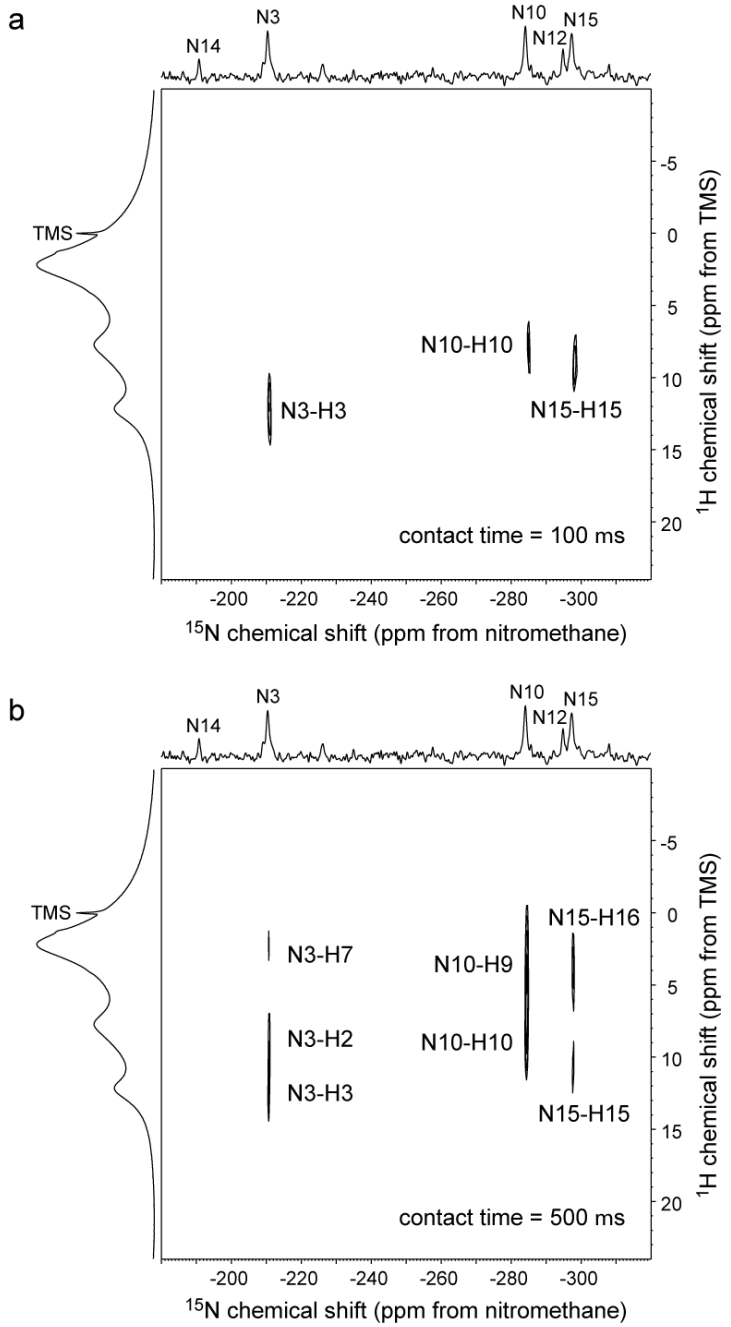

Figure S5. ^{1}H-^{15}N 2D CP-HETCOR spectra of cimetidine Form A obtained using the pulse sequence with FSLG ^{1}H homonuclear decoupling during t_1, as presented by van Rossum *et al.*[4] The contact time made use of a ramp on the ^{1}H channel and used the durations given in the Figure. A 1D ^{15}N CP-MAS spectrum is plotted along the horizontal (F_2) axis and a single-pulse ^{1}H MAS spectrum is plotted along the vertical (F_1) axis. All spectra were obtained at 11.7 T and 273 K using an MAS frequency of 14 kHz. The base contour levels are at (a) 62% and (b) 42%. As in the ^{14}N-^{1}H spectrum in Figure 3b, longer-range correlations are observed in Figure S5b corresponding to the longer contact time, however no correlation peaks are observed for the non-protonated nitrogens.

IV. GIPAW calculated chemical shielding tensors

Table S1 lists the chemical shielding tensor components as calculated by the GIPAW approach.[5, 6] The principal components are labelled according to the Haeberlen convention: $|\sigma_{zz} - \sigma_{iso}| \geq |\sigma_{xx} - \sigma_{iso}| \geq |\sigma_{yy} - \sigma_{iso}|$. The isotropic chemical shielding is given by:

$$\sigma_{iso} = (\sigma_{XX} + \sigma_{YY} + \sigma_{ZZ}) / 3 \quad \text{(S1)}$$

while the reduced chemical shift anisotropy is defined as:

$$\delta_{ANISO} = \sigma_{ZZ} - \sigma_{iso} = (2/3)\,\sigma_{ZZ} - (1/3)\,(\sigma_{XX} + \sigma_{YY}) \quad \text{(S2)}$$

The asymmetry is defined as:

$$\eta_{CSA} = (\sigma_{YY} - \sigma_{XX}) / (\sigma_{ZZ} - \sigma_{iso}) \quad \text{(S3)}$$

Table S1. ^{1}H, ^{13}C and ^{15}N NMR parameters calculated from the single-crystal structure of cimetidine by using the GIPAW method.

Nucleus	σ_{xx}	σ_{yy}	σ_{zz}	σ_{ISO}	δ_{ANISO}	η_{CSA}	δ_{ISO}(calc)[a]	δ_{ISO}(exp)
H7a	24.25	26.40	32.17	27.61	6.84	0.47	2.0	2.0
H7b	25.43	27.67	34.57	29.22	8.02	0.42	0.4	2.0
H7c	23.79	25.08	35.22	28.03	10.78	0.18	1.6	2.0
H16a	23.44	27.16	37.14	29.25	11.84	0.47	0.4	2.0
H16b	23.73	27.69	33.03	28.15	7.32	0.81	1.5	2.0
H16c	21.07	25.45	34.64	27.05	11.38	0.58	2.6	2.0
H8a	25.53	27.39	31.85	28.26	5.39	0.52	1.3	2.0 - 4.0
H8b	23.97	26.05	38.16	29.39	13.15	0.24	0.2	2.0 - 4.0
H9a	23.49	25.69	32.57	27.25	7.98	0.41	2.4	2.5 - 3.4
H9b	30.43	28.73	21.66	26.94	–7.92	0.32	2.7	2.5 - 3.4
H6a	22.62	23.98	32.09	26.23	8.79	0.23	3.4	4.0 - 4.5
H6b	21.74	25.98	32.14	26.62	8.28	0.77	3.0	4.0 - 4.5
H2	19.64	21.08	26.91	22.54	6.55	0.33	7.1	7.4

H10	12.35	18.52	33.32	21.40	17.88	0.52	8.2	8.2
H15	8.44	17.98	33.68	20.04	20.47	0.70	9.6	9.7
H3	10.10	11.90	31.05	17.68	20.05	0.13	11.9	11.6
N1	–194.62	–98.48	195.02	–32.69	341.57	0.42	–132.5	–128.1
N3	–51.07	28.96	146.44	41.44	157.50	0.76	–206.6	–210.7
N10	164.51	153.59	46.44	121.51	–112.61	0.15	–286.7	–284.6
N12	171.18	141.76	80.99	131.31	–75.48	0.58	–296.5	–295.4
N14	–99.70	–50.16	224.23	24.79	299.16	0.25	–190.0	–191.3
N15	184.12	154.90	51.23	130.08	–118.27	0.37	–295.3	–297.7
C2	–46.77	24.71	106.97	28.30	118.00	0.91	136.2	134.8
C4	–29.33	39.09	121.57	43.78	116.69	0.88	120.7	120.6
C5	–32.89	9.13	106.48	27.57	118.37	0.53	136.9	135.7
C6	155.74	152.69	118.58	142.34	–35.63	0.13	26.8	23.2
C7	175.65	163.77	139.82	159.75	–29.84	0.60	9.4	10.4
C8	121.91	133.92	158.11	137.98	30.19	0.60	31.2	27.8
C9	161.50	139.75	97.94	133.06	–52.68	0.62	36.1	40.8
C11	–32.89	–22.88	89.25	11.16	117.13	0.13	153.4	161.0
C13	–72.82	–68.78	263.25	40.55	334.06	0.02	124.0	119.1
C16	111.60	138.53	176.82	142.31	51.75	0.78	28.2	28.2
S7	575.46	525.87	358.85	486.73	–191.82	0.39	--	--

[a] $\delta_{iso} = -[\sigma_{iso} - \sigma_{ref}]$, where σ_{REF} = 169.2 ppm (high-ppm) or 164.5 ppm (low ppm), 29.6 and –165.2 ppm for ^{13}C, ^{1}H and ^{15}N, respectively. The σ_{ref} values are calculated from addition of the mean average of the experimental isotropic chemical shifts and the mean average of σ_{iso} values. Due to limited resolution of the methyl and aliphatic protons only CH and NH experimental values were included for ^{1}H σ_{ref} calculations. Separate calculations of σ_{ref} for high and low ppm regions of the ^{13}C were used. The different values agree with previous studies that have shown over-estimation of calculated shifts in high-ppm regions and under-estimation of low-ppm regions. [7-9]

V. GIPAW calculated electric field gradients

Table S2 lists the ^{14}N electric field gradient tensor components as calculated by the GIPAW approach. The principal components are ordered such that: $|V_{zz}| \geq |V_{yy}| \geq |V_{xx}|$. The quadrupolar coupling constant, C_Q (in units of Hz), is given by:

$$C_Q = (V_{zz}.\, eQ) / h = (e^2qQ) / h \quad \text{(S4)}$$

where Q is the nuclear quadrupole moment and q is the electric field gradient.

The asymmetry is defined as:

$$\eta_Q = (V_{xx} - V_{yy}) / V_{zz} \quad \text{(S5)}$$

The quadrupolar product is defined as:

$$P_Q = C_Q \sqrt{[1 + (\eta_Q^2/3)]} \quad \text{(S6)}$$

Considering the quadrupolar interaction to second-order perturbation theory, there is an isotropic second-order quadrupolar shift (in ppm) given by:[10, 11]

$$\delta^Q_{iso} = -(3/40)\,(P_Q/\nu_0)^2\,[I(I+1) - 9m(m-1) - 3] / [I^2\,(2I-1)^2] \times 10^6 \quad \text{(S7)}$$

$$= (3/40)\,(P_Q/\nu_0)^2 \times 10^6 \qquad \text{when } I = 1 \text{ and } m = 0 \quad \text{(S8)}$$

where ν_0 is the Larmor frequency in Hz.

Table S2. ^{14}N quadrupolar parameters calculated from the single crystal structure of cimetidine by using the GIPAW method

Nucleus	V_{xx}	V_{yy}	V_{zz}	C_Q/MHz	η_Q	P_Q/MHz	δ^Q_{iso}/ppm
N1	0.29	0.41	–0.70	–3.31	0.17	3.32	221.2
N3	0.10	0.30	–0.41	–1.92	0.49	1.99	79.6
N10	0.22	0.59	–0.82	–3.86	0.45	3.99	319.2
N12	–0.29	–0.46	0.74	3.52	0.23	3.55	252.6
N14	0.11	0.33	–0.44	–2.06	0.51	2.15	92.6
N15	0.16	0.60	–0.75	–3.55	0.59	3.75	281.6

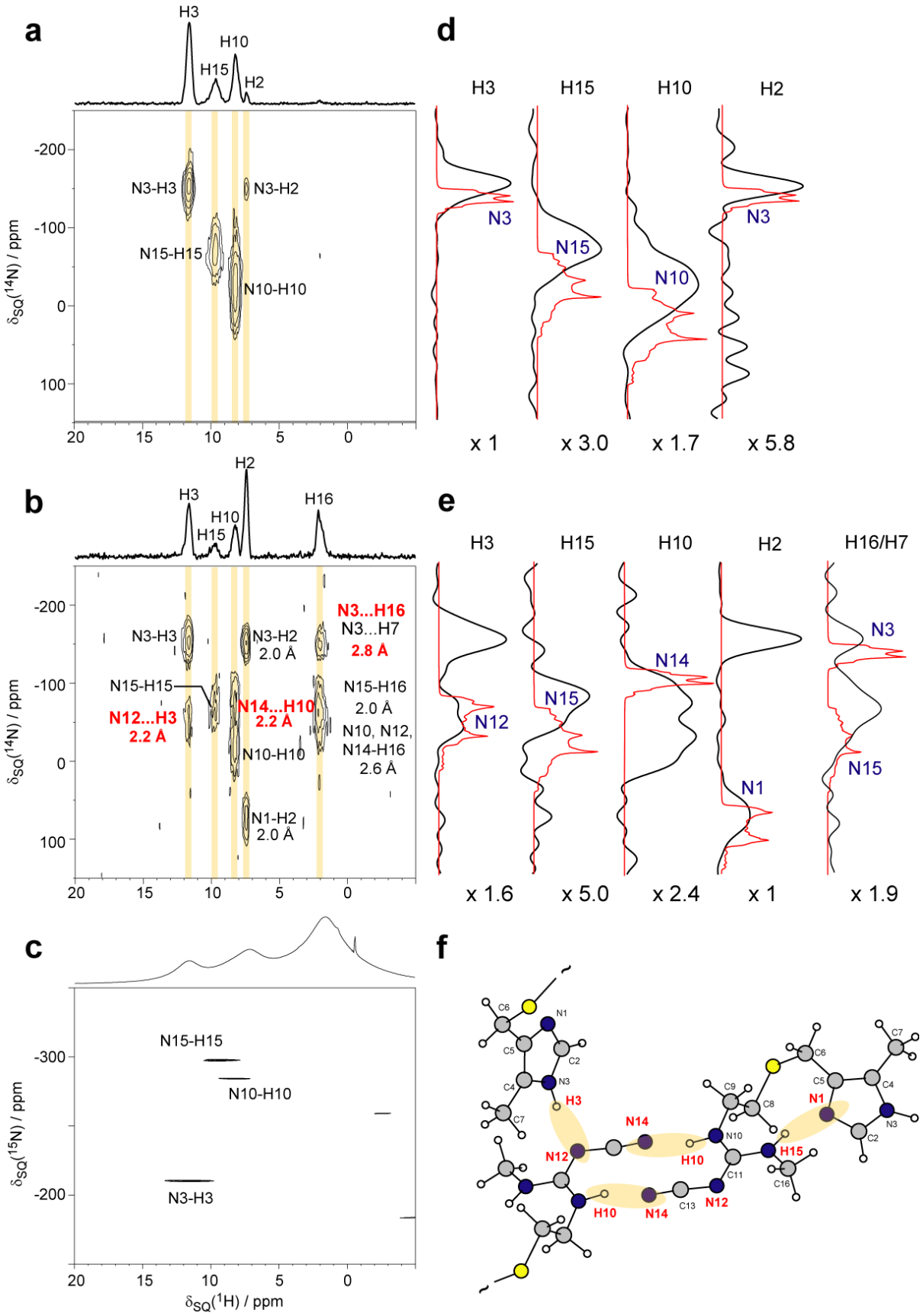

Figure S6. A reproduction of Figure 3 except that no scaling has been applied to the calculated C_Q values used to simulate the ^{14}N lineshapes.

VI. Hydrogen-bonding geometry

Table S3. NH…N Hydrogen bonding distances and angles in **I**, as determined from the geometry optimised (CASTEP) crystal structure.

Hydrogen Bond	N…N / Å	NH / Å	H…N / Å	NHN Angle / °
N15H…N1	2.85	1.05	1.84	159.8
N3H…N12	2.91	1.04	1.88	168.7
N10H…N14	2.87	1.04	1.88	157.5

Table S4. NH distances within 3 Å proximity taken from the geometry optimised (CASTEP) crystal structure of cimetidine Form A. One-bond correlations are denoted in bold and intermolecular correlations shown in italic.

Sites	Distance (Å)	Sites	Distance (Å)
N1-H15	1.84	**N3-H3**	**1.04**
N1-H2	2.16	N3-H2	2.15
N1-H8a	2.42	N3-H7b	2.81
N1-H6a	2.78	*N3-H16a*	*2.88*
N1-H16a	*2.99*	N3-H7c	2.93
N10-H10	**1.04**	**N15-H15**	**1.05**
N10-H9a	2.07	N15-H16a	2.06
N10-H9b	2.08	N15-H16c	2.12
N10-H16a	2.61	N15-H16b	2.12
N10-H8a	2.72	N15-H9b	2.62
N10-H8b	2.80	N15-H8a	2.95
N12-H3	*1.88*	*N14-H10*	*1.88*
N12-H10	2.61	N14-H16c	2.59
N12-H16b	2.63	*N14-H6a*	*2.93*
N12-H7a	*2.92*	*N14-H9b*	*2.97*

VI. Conformation differences between X-ray calculated crystal structure and geometry optimised crystal structure of cimetidine

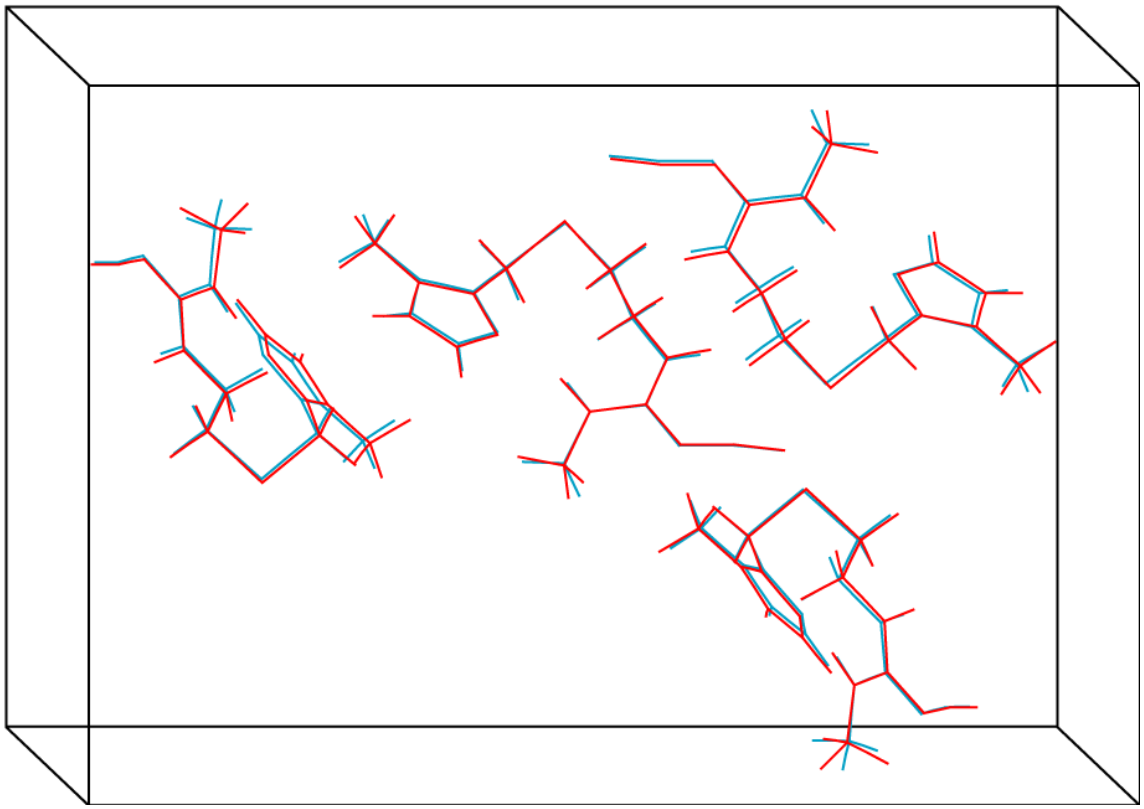

Figure S7. Cimetidine crystal structure (CIMETD)[12] showing: before (blue) and after (red) geometry optimisation. The single molecule used for calculations presented in Table 2 was extracted from the geometry optimised full crystal structure without further optimisation.

References

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