^{15}N NMR and crystal structure studies of 5-(2-pyridylmethylene)-pseudothiohydantoin;† dipolar dephasing experiments for establishing the preferred tautomer in the solid and solution states

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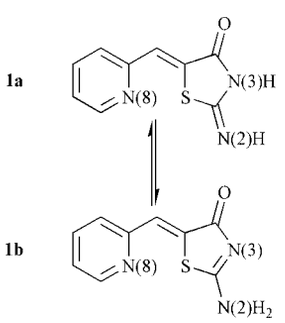
The preferred tautomeric form of 5-(2-pyridylmethylene)pseudothiohydantoin **1** in the solid and solution states has been determined by natural abundance high-resolution ^{15}N NMR studies and by a single crystal X-ray structural analysis.

We have shown that transition-metal complexes of the bifunctional ligand, 5-(2-pyridylmethylene)hydantoin (HPYHY), are capable of generating novel supramolecular transition-metal–organo networks based on coordinate and hydrogen bonds.[1] A synthetic strategy has been developed to extend the range of ligands of this type by substitution of the hydantoin moiety by similar five-membered heterocyclic rings and thereby vary (i) the potential complementary hydrogen bond donor (**D**) and acceptor (**A**) groups and (ii) the coordinating atom (N or S). 5-(2-Pyridylmethylene)pseudothiohydantoin, **1**, is a ligand capable of providing either **ADD** (**1a**) or **AAD** (**1b**) hydrogen bonding sites depending on the tautomer adopted. Pseudo-



thiohydantoin (the five-membered ring component of **1**) has been shown to have pharmacological activity by lowering blood pressure in rats who have had hypertension induced artificially.[2] It has also been shown to have some anti-thyroid activity.[3]

Early single crystal X-ray structural analyses of pseudothiohydantoin carried out by Amirthalingham[4] and Ananthamurthy[5] proposed an *imino* tautomeric configuration, whereas a recent study by Steel[6] showed pseudothiohydantoin to exist as the *amino* tautomer. Hence, it is clear that a cautious approach must be taken when determining the hydrogen bonding capabilities of **1** in the solid state. Our present study, however, provides an unambiguous determination of the tautomeric preference of **1** in the solid state using a combination of single crystal X-ray structural analysis and natural abundance high-resolution ^{15}N NMR spectroscopic methods using dipolar dephasing techniques. 2D ^{1}H–^{15}N correlation NMR spectroscopy has been used to determine the prefered tautomer in the solution state.

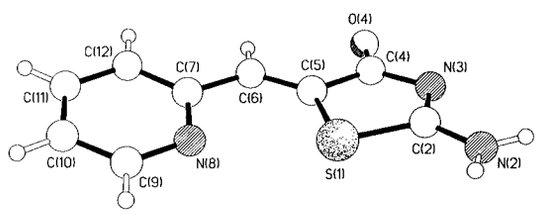


Fig. 1 The solid state structure of **1**. Selected bond lengths (Å): S(1)–C(2) 1.768(2), S(1)–C(5) 1.741(2), C(2)–N(2) 1.307(2), C(2)–N(3) 1.329(2), N(3)–C(4) 1.357(2), C(4)–C(5) 1.495(2), C(4)–O(4) 1.223(2), C(5)–C(6) 1.338(3). The C(5)–C(6)–C(7) angle is 125.2(2)° and the associated non-bonded S(1)···N(8) distance is 2.81 Å.

Results and discussion

The synthesis of the ligand **1** was achieved by adapting a procedure outlined in the patent literature[7] from pyridine-2-carbaldehyde and pseudothiohydantoin. The compound is soluble in methanol, acetic acid, pyridine, DMF and DMSO. Crystals suitable for X-ray diffraction studies were obtained from slow evaporation of a DMSO solution. The X-ray structure (Fig. 1) confirms the *Z* configuration of the ligand and shows the molecule to adopt a near planar geometry for the pyridine and the pseudothiohydantoin rings (there is a torsional twist of *ca.* 9° about the C(6)–C(7) bond). The unambiguous location and successful refinement of the two hydrogen atoms attached to N(2) coupled with the absence of a hydrogen atom attached to N(3) establishes the *amino* (**1b**) rather than *imino* (**1a**) nature of N(2) and therefore the adoption of tautomer (**1b**) in the solid state (*vide infra*).

The pseudothiohydantoin amino C–N distance is short [C(2)–N(2) 1.307(2) Å] and consistent with a pronounced double bond character. The ring amido C–N distance is in contrast fairly long [N(3)–C(4) 1.357(2) Å]. Thus, of the two possible resonance forms of (**1b**), namely (**1c**) and (**1d**) both of which have N(2) carrying a positive charge, the one where N(3) bears a formal negative charge (**1d**) best fits the experimentally observed bond lengths.

† The 1UPAC name for pseudothiohydantoin is 2-iminothiazolidin-4-one.

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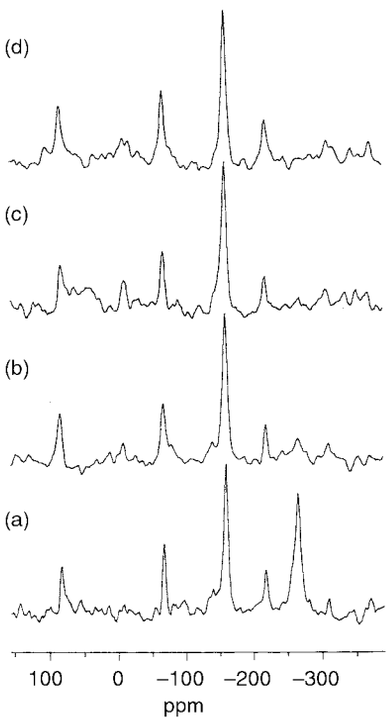
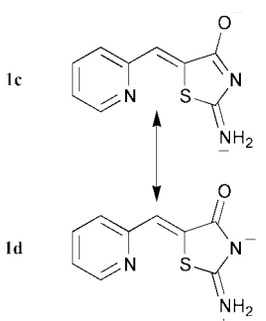


Fig. 2 (a) High-resolution solid-state ^{15}N NMR solid state spectrum for a natural abundance sample of **1**. (b)–(d) Spectra from the dipolar dephasing experiments obtained for **1** with dephasing delay 50 μs (b), 75 μs (c) and 100 μs (d).



Similar bond lengths have been observed in unsubstituted pseudothiohydantoin,[6] though in the latter structure the C=NH_2 distance is slightly longer at 1.317(1) Å.

To complement and reinforce the characterisation of the preferred tautomer, we have carried out natural abundance CPMAS solid-state ^{15}N NMR studies of **1**; the relevant spectra are shown in Fig. 2. The ^{15}N isotropic resonances at 68, −160 and −266 ppm in the spectrum [Fig. 2(a)] were unambiguously assigned to N(8), N(3) and N(2) respectively by comparison to similar compounds[8] and by repetition of the experiment using a second spinning frequency. In order to establish the structure of **1** we have made use of the fact that the number of non-protonated nitrogens in the imino and amino tautomers is different, and, therefore, the number of strongly dipolar coupled ^1H, ^{15}N spin pairs is different. Dipolar dephasing experiments have been used previously in ^{15}N NMR spectroscopy in order to distinguish protonated and non-protonated ^{15}N nuclei.[9–13] As can be seen from Fig. 2, the use of the dephasing delay in the range 50–100 μs was sufficient to suppress the signal at −266 ppm. This confirmed that only N(2) is protonated in the solid state and hence that the ligand has the **AAD** hydrogen bonding pattern established by the single crystal X-ray structural determination.

The tautomeric preference has a direct influence on the hydrogen-bonding and packing arrangement in the solid state and results in the formation of tapes that extend in the crystallographic *a* direction. Centrosymmetrically related pairs of molecules are linked by N–H···N hydrogen bonds between one of the amino hydrogen atoms of one molecule and the pseudothiohydantoin ring nitrogen of another and *vice versa* (labelled *a* in Fig. 3). These pairs of molecules are further linked by N–H···O hydrogen bonds involving the "other" amino hydrogen atom in one molecule and the carbonyl oxygen atom of a lattice translated counterpart (labelled *b* in Fig. 3). Adjacent centrosymmetrically related tapes in the crystallographic *b* direction are oriented such that the pyridine ring within one tape is positioned over the pseudothiohydantoin ring of another and *vice versa*, the pyridyl nitrogen atom in one molecule being positioned almost orthogonally with respect to the amino carbon atom C(2) of the next (the N···C distance is 3.65 Å).

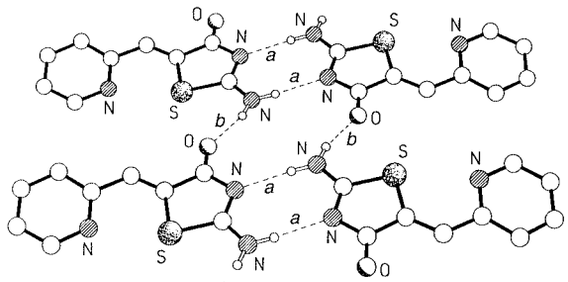


Fig. 3 Part of one of the hydrogen bonded tapes of molecules present in the crystals of **1**. Hydrogen bonding geometries: type *a*, N···N, H···N distances 2.93, 2.03 Å, N–H···N angle 174°; type *b*, N···O, H···O 2.79, 1.92 Å, N–H···O 163°. N–H distances have been fixed at 0.90 Å.

Natural abundance ^{15}N NMR studies were also carried out on a 0.33 M d_6-DMSO solution of **1** using correlation *via* double inept transfer techniques.[14] The results illustrated in Fig. 4 clearly show both proton signals correlating to the same nitrogen atom which is formally assigned to N(2) based on the solid state NMR experiments. No proton correlation is observed for N(3). This suggests that tautomer **1b** is also preferred in d_6-DMSO. Comparison of solid and solution state ^{13}C NMR data show no significant difference in chemical shifts (180.0 and 180.8 for C(2) in solution and solid state respectively) which also supports the presence of the same tautomer in both physical states.

Conclusion

The single crystal X-ray structural analysis of **1** reveals the ligand to adopt the tautomer with an **AAD** hydrogen bonding arrangement. Furthermore, the successful application of dipolar dephasing solid state ^{15}N NMR experiments provides a promising possibility[15] of establishing the preferred tautomers in a wide range of organo-nitrogen compounds. The solution state natural abundance ^{15}N NMR study has unambiguously shown that **1b** is the preferred tautomer in d_6-DMSO solution.

Experimental

Solvents were of reagent grade and the commercially available substrates were used without further purification. Infra-red spectra were recorded on a Matteson Infra-red Fourier Transform Spectrometer between 4000 and 260 cm^{-1} as KBr pellets. ^1H, ^{13}C and $^{13}C\{^1H\}$ NMR spectra were recorded on JEOL JNM-EX270 (^1H at 270 MHz and $^{13}C\{^1H\}$ at 67.5 MHz) and Bruker DRX-400 (^1H at 400 MHz and $^{13}C\{^1H\}$ at 100 MHz) Fourier-Transform NMR spectrometers. ^1H and ^{13}C NMR were referenced internally to the residual non-deuterated solvent. Chemical shifts are reported in parts per million (δ) relative to TMS ($\delta = 0$) using $(CD_3)_2SO$ ($\delta_H = 2.52$) unless stated. ^{13}C NMR data are referenced to $(CD_3)_2SO$ ($\delta_C = 43.5$).

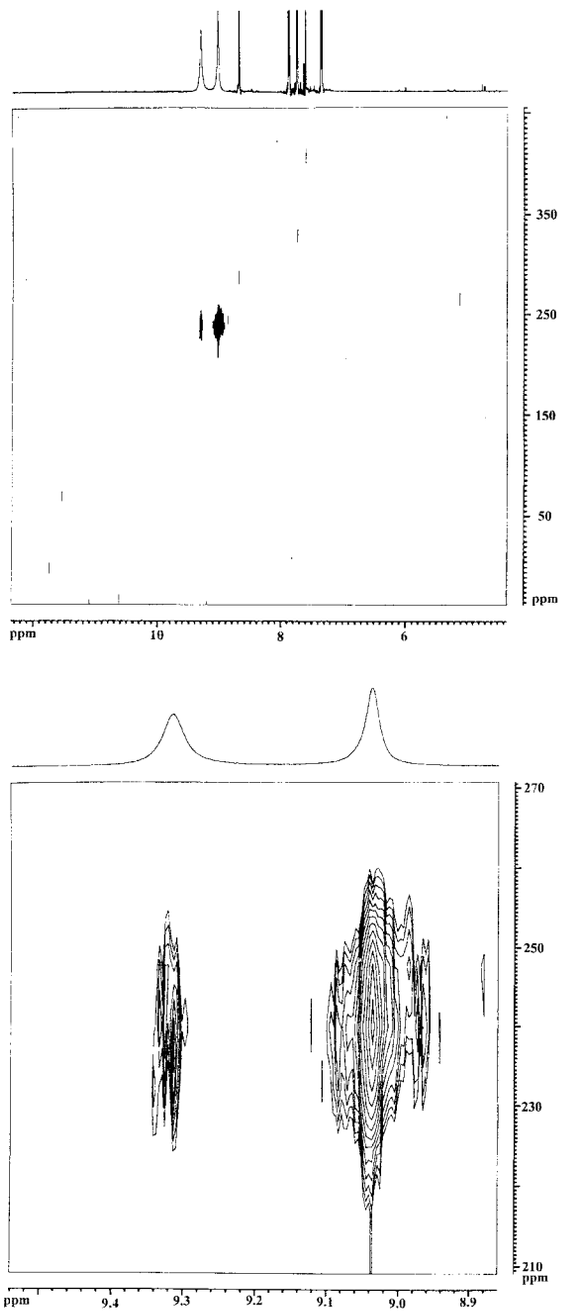


Fig. 4 High-resolution solution-state 2D ^{1}H–^{15}N correlation *via* double INEPT transfer NMR spectrum for a natural abundance sample of a 0.33 M d_6-DMSO solution of **1**.

Coupling constants are reported in Hz. The solid state ^{13}C NMR spectra were recorded on a Bruker MSL300 spectrometer ($^{13}C\{^{1}H\}$ at 75.5 MHz) and the solid state ^{15}N spectra were recorded on the same spectrometer at 30.4 MHz using magic-angle spinning (MAS), high-power ^{1}H decoupling and ^{1}H–^{15}N cross-polarization (CP). A spinning frequency of 4.7 kHz was employed. The ^{1}H 90° pulse length was 6.3 μs. A contact time of 10 ms was used with a recycle delay between acquisitions of *ca.* $3 \times t_1(^{1}H)$. ^{1}H spin-lattice relaxation time, $t_2(^{1}H)$, was measured *via* inversion-recovery ^{1}H–^{13}C CP experiments and is equal to *ca.* 30 s. Total acquisition times were in the range 20–25 hours. Chemical shifts are given relative to external liquid nitromethane using solid $^{15}NH_4NO_3$ as a secondary reference. The solution state two dimensional ^{1}H–^{15}N chemical shift correlation NMR experiments were performed on a Bruker AMX 600 spectrometer at 300 K with ^{1}H and ^{15}N frequencies at 600.13 and 60.82 MHz respectively. All spectra were recorded using a 5 mm txi triple resonance probe equiped with a *z*-gradient and the phase sensitive (echo–antiecho) 'invieagssi' pulse program.[16] This inverse detected pulse program utilises a double INEPT transfer and gradient coherence selection. The ^{1}H spectral width was 4803.1 Hz and the ^{15}N spectral width was 1249.3 Hz and the aquisition time was 0.47 s with a relaxation delay of 1.5 s. 128 ^{1}H spectra scans were acquired each with 140 transients. GARP[17] decoupling was used during acquisition and the experiment was optimised for the one bond coupling assumed to be 90 Hz. One order of zero-filling was used in each dimension and cosine-bell squared window functions applied before Fourier Transformation. Positive ion FAB mass spectra were recorded on a VG AutoSpec-Q using 3-NBA (3-nitrobenzyl alcohol) as matrix.

Preparation of 2-imino-5-(2-pyridylmethylene)thiazolidin-4-one 1

Pyridine-2-carbaldehyde (0.50 g, 4.66 mmol) was added dropwise to a flask containing pseudothiohydantoin (0.54 g, 5.21 mmol), glycine (0.35 g, 4.66 mmol), and sodium carbonate (0.25 g, 2.33 mmol) followed by distilled water (1 ml). Upon stirring, vigorous effervescing was observed. As this subsided, a further addition of water (1.5 ml) was made and the mixture stirred at room temperature for 1 h. The yellow–orange precipitate was collected and washed with water, ethanol, diethyl ether and dried *in vacuo* to give an off-white powder which did not require further purification. Yield: 0.89 g, 90%; mp 260–263 °C (decomp.). Found: C, 52.7; H, 3.4; N, 20.3%. Calc. for $C_9H_7N_3OS$: C, 52.7; H, 3.4; N, 20.5%. ^{1}H NMR (d_6-DMSO, 0.09 M): δ 7.4 (t, 1H), 7.6 (s, 1H), 7.8 (d, 1H), 7.9 (t, 1H), 8.7 (d, 1H), 9.2 (br, 2H). $^{13}C\{^{1}H\}$ NMR (d_6-DMSO, 0.09 M): δ 180.5 (C4), 180.0 (C2), 151.9 (C7), 149.2 (C11), 137.3 (C9), 133.4 (C5), 127.0 (C12), 125.8 (C6), 123.3 (C10). $^{13}C\{^{1}H\}$ NMR (solid state): δ 183.6 (C4), 180.8 (C2), 152.9 (C7), 149.7 (C11), 136.2 (C9), 132.1 (C5), 129.5 (C12), 127.9 (C6), 124.5 (C10). IR (ν_{max}/cm^{-1}): 3197, 2967, 2828, ν(N–H); 1670, ν(C=O); 1617, ν(C=C); 1582, ν(N=C, pyridine); 1146, ν(C–N–C); 895, ν(C–S); 1375, δ(N–H); MS-FAB^{+}(NBA) (*m*/*z*): 206 $[M + H]^{+}$; 228 $[M + Na]^{+}$.

Structure determination

Crystals of **1** suitable for X-ray diffraction studies were obtained from the slow evaporation of a DMSO solution of **1**. Crystal data: $C_9H_7N_3OS$, $M = 205.2$, triclinic, space group $P\bar{1}$ (no. 2), $a = 6.677(1)$, $b = 8.191(2)$, $c = 9.319(2)$ Å, $\alpha = 71.48(2)$, $\beta = 79.50(2)$, $\gamma = 73.31(2)°$, $V = 460.6(2)$ Å^3, $Z = 2$, $D_c = 1.480$ g cm^{-3}, μ(Cu-Kα) = 28.7 cm^{-1}, $F(000) = 212$; dichroic yellow–red prismatic needles, 0.51 × 0.10 × 0.09 mm, 1493 independent measured reflections; refinement based on F^2 to give $R_1 = 0.035$, $wR_2 = 0.094$ for 1406 independent observed absorption corrected reflections ($|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 126°$) and 136 parameters. CCDC reference number 188/268. See http://www.rsc.org/suppdata/p2/b0/b004368k for crystallographic files in .cif format.

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