3(5)-(1-Adamantyl)pyrazoles: chemistry and molecular structure †

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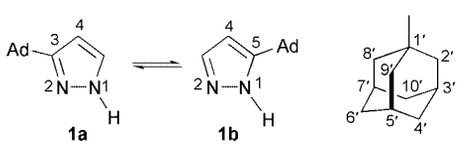
The synthesis and molecular structure of 3(5)-(1-adamantyl)-4-bromopyrazole (**2**) are reported. The compound crystallizes in tetramers formed by units of the 5-adamantyl tautomer **2b**, linked by N–H · · · N hydrogen bonds. The results are discussed in the light of other tetramers found in *N*-unsubstituted pyrazoles. The comparison between ^{13}C and ^{15}N in the solid state, CPMAS, and solution NMR spectra shows that tautomer **2b** is also dominant in solution. Nitration of 3(5)-(1-adamantyl)pyrazole occurs at position 4 of the pyrazole ring but it is accompanied of oxidation of the adamantyl substituent at position 3′.

Introduction

Some years ago we reported and discussed in this journal the structure of 3(5)-(1-adamantyl)pyrazole (**1**).[1] This compound presents the very rare case, at least in pyrazoles, of the simultaneous presence of both tautomers **1a** and **1b** in the crystal. We wanted to know whether derivatives of this compound bearing substituents at the 4-position also present this phenomenon. Besides, being interested in the packing mode of *N*-unsubstituted pyrazoles,[2] we decided to explore the effect of bulky substituents, which appear to determine the N–H · · · H hydrogen-bond (HB) network.[3]



Pyrazoles unsubstituted on the nitrogen (1*H*-pyrazoles) crystallize forming four classes of N(1)–H · · · N(2) HB networks: dimers, trimers, tetramers and catemers (chains).[3] A simple rule, based on the molar refractivity (MR) values of the substituents at positions 3 and 5, predicts correctly the class for more than fifty pyrazoles and related compounds, if one groups trimers and catemers in one class and dimers and tetramers in the other. One of the rare exceptions is compound **1**. For this compound, the model predicts that it should crystallize in dimers and tetramers and experimentally, the compound, which is a mixture of tautomers **1a** and **1b** in the solid state, crystallizes forming a catemer.[3] Therefore, we decided that it would be interesting to find out whether this is an exception, or if our model has some flaw. To this aim, we decided to prepare two derivatives substituted at position 4 because, according to the model, the substituent at this position (or its absence) has no effect on the HB network.

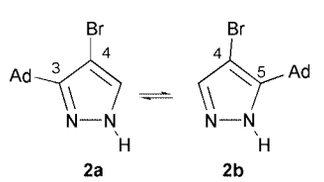
A subsidiary aspect is to determine if the 1-adamantyl substituent "prefers" position 3 (**a**) or the position 5 (**b**) in the solid state. Compound **1**, being a 1 : 1 mixture of **1a** and **1b**, cannot be used, but its 4-substituted derivatives could, perhaps, answer this question. In another publication (based on ^{13}C CPMAS NMR experiments) we concluded that alkyl groups "prefer" the 5 position in solid 1*H*-pyrazoles, and the bulkier the alkyl group, the clearer the preference.[4]

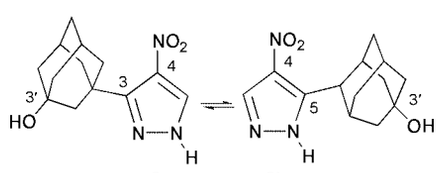
Results and discussion

Chemistry

Previously, we prepared 3(5)-(1-adamantyl)pyrazole (**1**) by adamantylation of pyrazole, under microwave conditions.[5] This is a rather tedious procedure, since the compound was obtained mixed with the 4-adamantyl derivative. In the present work, we have used the standard method to obtain 3(5)-substituted pyrazoles [for instance, 3(5)-phenyl or 3(5)-*tert*-butyl][6–8] starting from methyl R ketones (R = phenyl, *tert*-butyl or 1-adamantyl).

On compound **1** we carried out two reactions that usually lead to 4-substituted compounds:[9–11] bromination, using bromine, and nitration, using a sulfuric acid–nitric acid mixture. In the first case we obtained, as expected, 3(5)-(1-adamantyl)-4-bromopyrazole (**2**) in 98% yield. In the second case, the expected nitration was accompanied by the oxidation of the 3′ position of the adamantyl ring, and compound **3** was obtained in 75% yield. We had already observed a similar behavior in the nitration of *N*-(1-adamantyl)pyrazoles.[12]





† Detailed experimental procedures and structural analysis for **1**–**3** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b004690f/

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X-Ray crystallography

Of the two derivatives, it was decided to study only **2**, because the supplementary OH group at the 3′ position of compound **3** would complicate the HB network by making O–H···N bonds. Compound **2** crystallizes in tetramers formed by four **2b** tautomers. Therefore, our two main questions were answered simultaneously: the 1-adamantyl group (MR = 2.82)[3] both directed the structure to dimers or tetramers (here, a tetramer) and favors the 5-substituted tautomer in the solid state. That means that the parent compound, **1**, is a double exception, because it is a catemer and because tautomer **1b** is present. Whether these two facts are related is, for the moment, a question that we are not able to answer.

To discuss in more detail the structure of the tetramer we will again use the centroids of the pyrazole rings to represent and compare the structures published in the literature.[3] When the four centroids belonging to pyrazoles connected by N–H···N HBs (Fig. 1) are linked, a non planar quadrilateral (quadrangle) is formed. To simplify the problem, we will use the average values for the distances between centroids (*di*) and the angles between centroids (ψi) (Table 1). Then, the more symmetrical situations will correspond either to a planar square ($\psi i = 90°$) or to a regular tetrahedron ($\psi i = 60°$). Compound **2b** is very close to the second possibility ($\psi i = 58.5°$) with a $di = 4.98$ Å.

An examination of literature results (eleven tetramers)[3] shows that *di* ranges from 4.91 to 5.16 Å (average = 5.06 Å) and ψi ranges from 41.5 to 64.0° (average 50.9°). Therefore, compound **2b** is closer to a tetrahedron with shorter inter-centroid distances.

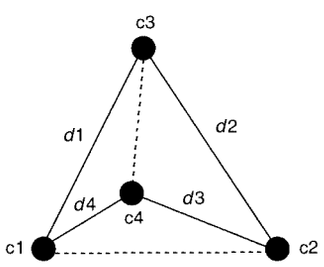

Fig. 1 Description of the structure of **2b** in terms of centroids.

Table 1 Distances and angles between centroids of pyrazoles connected by HBs

		d/Å			ψ/°
c1—c3	*d*1	5.103(6)	c2—c1—c4	ψ1	63.3(1)
c2—c3	*d*2	5.077(6)	c3—c2—c4	ψ2	63.9(1)
c2—c4	*d*3	4.904(6)	c1—c3—c2	ψ3	52.7(1)
c1—c4	*d*4	4.818(7)	c3—c1—c4	ψ4	54.1(1)
Average	*di*	4.976	Average	ψi	58.5

DSC experiments

We have recorded the differential scanning calorimetry (DSC) plots of compounds **1**, **2** and **3** to search for any phase transition frequent in adamantane derivatives.[13] However, none was observed between 20 and 175 °C for **1** (melting point 146.0 °C, solidification 92.5 °C). Compound **2** was studied between 20 and 230 °C; it melts at 198.5 °C, but it does not resolidify again, so it probably remains in a vitreous state. The DSC and thermogravimetric analysis (TGA) of compound **3** were recorded between 20 and 230 °C; both show the loss of water at 70 °C. DSC shows the melting at 210.0 °C; the product probably decomposes, because several peaks appeared between 195 and 205 °C for the second melting.

Solid state NMR (^{13}C and ^{15}N CPMAS)

We have collected in Table 2 the chemical shifts necessary for the discussion in the solid state and in solution. The signal of C(4) in the CPMAS spectrum of **2** was not observed due to dipolar couplings with the Br atom;[14,15] otherwise, the ^{13}C and ^{15}N spectra of **1b** and **2b** are similar, due to the fact that the bromine atom produces no significant effects on C(3) and C(5). Therefore, there is a complete agreement between crystallography and CPMAS NMR about the **b** tautomeric structure of **2**. Note that ^{15}N NMR is less sensitive to tautomerism than ^{13}C NMR and, in the present case, useless to determine the structure of **2** (although −170.2 ppm is a little closer to −172.3, **1b**, than to −174.6 ppm, **1a**).

Compound **3** in the solid state is, like **1**, a mixture of tautomers **3a** and **3b**. Assuming that the adamantyl and 3′-hydroxyadamantyl groups produce the same substituent chemical shifts (SCS), the differences of the ^{13}C chemical shifts between both series of compounds should correspond to the effect of the nitro group: −6.8 and −2.6 ppm [C(Ad)], +34.7 ppm [C(4)] and +4.5 and +2.2 ppm [C(H)]. These SCS are close to those reported for a large collection of pyrazoles in solution.[16] The ^{15}N CPMAS NMR spectrum is of medium quality, in spite of being recorded during 100 h. Nevertheless, the presence of both tautomers could be observed.

Solution NMR results

The ^{13}C chemical shifts of compound **1** in $CDCl_3$ solution are almost the exact average of those of **1a** and **1b** in the solid state [50/50: C(Ad) = 156.7, C(H) = 133.2 ppm], a small excess of tautomer **1b** improves the results [40/60: C(Ad) = 155.8, C(H) = 134.2 ppm]. The use of ^{15}N chemical shifts is more delicate, because small differences between solid and solution shifts would have large consequences in the percentages. The interpolation leads to about 30% of **1a** and 70% of **1b**. In DMSO-d_6 the proton exchange is slower and only a very broad

Table 2 Chemical shifts (ppm from TMS for ^{13}C and ppm from nitromethane for ^{15}N) of adamantylpyrazoles at room temperature (~300 K)

Compound	Conditions	C(Ad)	C(4)	C(H)	NH	–N=	Ref.
1a	CPMAS	161.1	99.6	128.3	−174.6	−97.7	1
1b	CPMAS	152.3	99.6	138.1	−172.3	−95.4	1
1	$CDCl_3$	156.0	100.1	135.3	−156.7	−124.5	1,5
1	$CDCl_3$	156.3	100.5	135.9	−155.2	−124.4	This work
1[a]	DMSO-d_6	—	—	—	−130 (v br)		This work
2b	CPMAS	147.7	N.o.[d]	140.5	−170.2	−97.6	This work
2	$CDCl_3$	148.7	89.9	139.3	−164.8	−104.2	This work
2	$CDCl_3$[b]	—	—	—	−190.4	−187.8	This work
3a	CPMAS[c]	154.3	134.3	132.8	−179.2	−99.5[e]	This work
3b	CPMAS[c]	149.7	134.3	140.3	−175.1	−96.7[e]	This work
3	DMSO-d_6	150.6	132.6	136.2	−133.3[f]		This work

[a] At 353 K. [b] Plus several drops of CF_3CO_2H. [c] Other ^{13}C NMR signals at: 68.7, 66.0 (C(3′)), 47.2, 46.0 (C(2′)), 44.7 (C(4′) and C(10′)), 38.6 (C(1′)), 36.2 (C(8′) and C(9′)), 34.5 (C(6′)), 31.1 and 29.7 ppm (C(5′) and C(7′)). [d] Not observed. [e] ^{15}N NMR signals of the nitro group: −17.1 and −23.1 ppm. [f] ^{15}N NMR signal of the nitro group: −15.5 ppm.

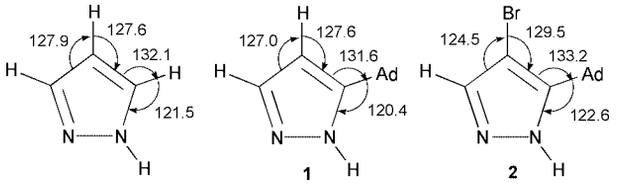

Fig. 2 The angles found in C(4) and C(5) substituents for pyrazole itself, **1** and **2**.

signal at about −130 ppm is observed near the middle of the signals measured in $CDCl_3$.

On the other hand, the ^{13}C chemical shifts of compound **2** in $CDCl_3$ solution are very close to those in the solid state of **2b**. From the pair **1a/1b** one can estimate for **2a** the values of C(Ad) = 156.5 and C(H) = 130.7 ppm and then use these values, and those of **2b**, to calculate that the $CDCl_3$ solution is formed by 10% of **2a** and 90% of **2b** [C(Ad) = 148.6, C(H) = 139.5 ppm]. The addition of trifluoroacetic acid dramatically changes the chemical shifts of compound **2**; the values near −190 ppm for both nitrogen atoms correspond to the protonated pyrazolium cation.[17]

What is the origin of the difference between both compounds (which can be calculated to correspond to about 1 kcal mol^{-1}at 300 K)? The only reasonable explanation is a buttressing effect of the bromine atom that pushes the adamantyl group towards N(1), *i.e.* increases its steric effect, making it a sort of super-adamantane. An examination of the angles linking C(4) and C(5) to their substituents (H, Br, Ad, see Fig. 2) shows that the angles in **1** are very similar to those of pyrazole itself (experimental MR data and high level calculations);[18] on the other hand, in compound **2** the Br and Ad groups are pushed apart (between 1.5 and 2°).

The data for compound **3** in solution correspond approximately to a 50/50 mixture of tautomers **3a** and **3b**, thus it resembles more **1** than **2**, probably because the nitro group is less sterically demanding than the bromine atom.

Experimental

Materials

Melting points were determined on a Seiko DSC 220C instrument with a scanning rate of 2° min^{-1}. Mass spectra: ionization technique, positive electronic impact, energy 70 eV, source temperature, 200 °C.

3(5)-(1-Adamantyl)pyrazole (1). 1-Adamantylmethyl ketone (7.84, 0.044 mol) and ethyl formate (4.88 g, 0.066 mol) were added, in one portion, with rapid stirring, to dry sodium ethoxide (2.98 g, 0.044 mol) in 100 mL of toluene, in a 250 mL round-bottomed flask equipped with a refrigerant and mechanical stirrer. The mixture was stirred over 8 h. The solid obtained was filtered and washed with hot hexane, air dried and then made into a slurry in 200 mL of ethanol. To this ethanol slurry, hydrazine monohydrochloride (3 g, 0.044 mol) and 50 mL of water were added. After 2 hours of stirring, the ethanol was removed under reduced pressure. The remaining aqueous solution was extracted three times with dichloromethane (3 × 50 mL). The solution was dried over anhydrous sodium sulfate and the dichloromethane removed under reduced pressure. The residue was purified by column chromatography [silica gel, eluent: dichloromethane–hexane (1 : 1)]. R_f (dichloromethane–ethanol 9 : 1) = 0.56. 3(5)-(1-Adamantyl)pyrazole (**1**) was obtained in 3.7 g yield (isolated product) (42%) as a white solid with a melting point of 146.0 °C by differential scanning calorimetry (DSC). Lit.[5] m.p. 135–138 °C. EM (*m*/*z*): 202 (100%) [$M^{+\bullet}$]. ^1H NMR (DMSO-d_6): δ 12.39 (br s, 1H, N–H), 7.38 (br s, 1H, H(3)), 5.98 (br s, 1H, H(4)), 1.99 (m, 3H, H_γ-Ad), 1.85 (d, 6H, ^3J = 2.8, H_β-Ad), 1.71 (complex m, 6H, H_δ-Ad). ^1H NMR ($CDCl_3$): δ 7.50 (d, 1H, ^3J = 1.9, H(3)), 6.09 (d, 1H, ^3J = 1.9, H(4)), 2.07 (m, 3H, H_γ-Ad), 1.95 (d, 6H, ^3J = 2.8, H_β-Ad), 1.78 (m, 6H, H_δ-Ad). ^{13}C NMR ($CDCl_3$): δ 156.3 (s, C-Ad), 135.9 (d, ^1J = 184.9, CH), 100.5 (dd, ^1J = 174.0, ^2J = 9.9, C(4)), 42.6 (t, ^1J = 128.2, C_β-Ad), 36.7 (t, ^1J = 126.6, C_δ-Ad), 33.1 (complex m, C_α-Ad), 28.2 (d, ^1J = 132.3, C_γ-Ad). Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85; Found: C, 77.10; H, 9.01; N, 13.31%.

3(5)-(1-Adamantyl)-4-bromopyrazole (2). To a solution of 0.3 g (0.0015 mol) of 3(5)-(1-adamantyl)pyrazole (**1**) in 5 mL of chloroform, 0.1 mL of bromine (0.002 mol) in 1 mL of chloroform was slowly added and the mixture was heated under reflux for 2 hours. After cooling, the reaction mixture was treated with saturated aqueous sodium bicarbonate solution and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and the solvent removed under vacuum. The solid was recrystallized from chloroform–hexane. 3(5)-(1-Adamantyl)-4-bromopyrazole (**2**, 0.41 g of isolated product) was obtained in 98% yield as a white solid with a melting point of 198.5 °C by differential scanning calorimetry (DSC). EM (*m*/*z*): 282 (97%) [$M^{+\bullet}$, ^{81}Br], 280 (100) [$M^{+\bullet}$, ^{79}Br]. ^1H NMR ($CDCl_3$): δ 10.41 (s, 1H, N–H), 7.47 (s, 1H, H(3)), 2.11 (s, 9H, H_β and H_γ-Ad), 1.78 (s, 6H, H_δ-Ad). ^{13}C NMR ($CDCl_3$): δ 148.7 (br s, C(5)), 139.9 (d, ^1J = 193.2, C(3)), 89.9 (d, ^2J = 7.7, C(4)), 39.7 (t, ^1J = 128.0, C_β-Ad), 36.5 (t, ^1J = 126.6, C_δ-Ad), 34.3 (q, C_α-Ad), 28.2 (d, ^1J = 132.8, C_γ-Ad). ^{13}C NMR CPMAS: δ 147.7 (C(5)), 140.5 (C(3)), C(4) not observed, 40.2 (C_β-Ad), 36.5 (C_δ-Ad), 34.3 (C_α-Ad), 28.7 (C_γ-Ad). Anal. Calcd. for $C_{13}H_{17}BrN_2$: C, 55.53; H, 6.09; N, 9.96; Found: C, 55.06; H, 6.01; N, 9.79%.

3(5)-(3-Hydroxy-1-adamantyl)-4-nitropyrazole (3). A mixture of 0.1 mL of nitric acid (*d* = 1.52) and 1 mL of sulfuric acid (*d* = 1.84) was added carefully, with external cooling, to a solution of 0.3 g (0.0015 mol) of 3(5)-(1-adamantyl)pyrazole (**1**) in 1 mL of sulfuric acid. The reaction was stirred overnight at room temperature and then poured over crushed ice. The precipitate was filtered, washed with water, dried and crystallized in ethanol–water. 3(5)-(3-Hydroxy-1-adamantyl)-4-nitropyrazole (**3**) was obtained in 0.29 g yield (75%) as a white solid with a melting point of 210.0 °C by differential scanning calorimetry (DSC). The compound crystallizes with a 1/2 H_2O. EM (*m*/*z*): 263 (3%) [$M^{+\bullet}$], 247 (17), 246 (100). ^1H NMR (DMSO-d_6): δ 13.45 (br s, 1H, N–H), 8.51 (br s, 1H, H(3)), 4.53 (s, 1H, OH), 2.18 (s, 2H), 1.91 (s, 6H), 1.64–1.51 (m, 6H). ^{13}C NMR (DMSO-d_6): δ 150.6 (br s, C(5)), 136.2 (br d, ^1J = 173.3, C(3)), 132.6 (d, ^2J = 6.1, C(4)), 66.3 (s, C3′)), 46.3 (t, ^1J = 127.6, C(2′)), 44.2 (t, ^1J = 127.3, C(4′) and C(10′)), 38.0 (s, C(1′)), 37.5 (t, ^1J = 136.4, C(8′) and C(9′)), 34.8 (t, ^1J = 130.4, C(6′)), 29.8 (d, ^1J = 132.9, C(5′) and C(7′)). Anal. Calcd. for $C_{13}H_{17}N_3O_3 \cdot$ 1/2 H_2O: C, 57.34; H, 6.66; N, 15.43; Found: C, 57.53; H, 6.68; N, 15.35%.

NMR spectroscopy

The ^1H, ^{13}C and ^{15}N NMR spectra in solution were recorded on a Bruker DRX-400 instrument working at 400.13 (^1H), 100.62 (^{13}C) and 40.56 MHz (^{15}N) using standard conditions. *J* values are given in Hz.

CPMAS NMR spectroscopy

Solid state ^{13}C and ^{15}N CPMAS NMR spectra were recorded at 300 K using a Bruker AC-200 instrument (50.32 and 20.28 MHz) and standard CP pulse sequences were employed. Chemical shifts (δ) in ppm are referred to Me_4Si and $^{15}NH_4Cl$ [these were converted to nitromethane using the relationship: $\delta^{15}N$ (nitromethane) = $\delta^{15}N$ (ammonium chloride) −338.1 ppm].

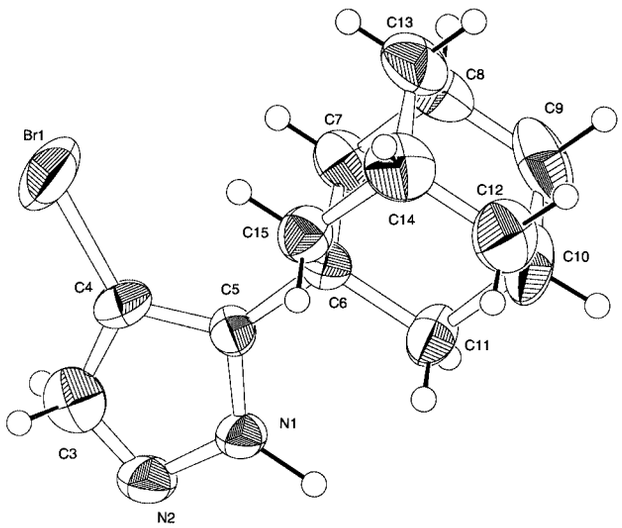

Fig. 3 An ORTEP drawing of **2b**. Bond distances and angles agree with those found in the literature.

Table 3 Crystallographic data for compound **2b**

Crystal data	
Chemical formula	$C_{13}H_{18}N_2Br_1$
Formula weight M	282.226
Crystal system	Monoclinic
Space group	$P21/c$
Unit cell dimensions	
a/Å	20.8303(9)
b/Å	18.8385(9)
c/Å	28.3817(9)
β/°	152.539(1)
V/Å^3	5135.9(4)
T/K	298
Z	16
μ (Mo-Kα)/cm^{-1}	3.18
Measured reflections	31742
Unique reflections	8450
Ref. parameters	517
Refl. used for ref. [$I > 2\sigma(I)$]	4615
H atoms	Included not refined
R	0.059
R_w	0.056
w	$w = 1/(s^2Fo^2 + 0.03000Fo^2)$

Crystal data ‡

The measurements were recorded on a Nonius X-Ray diffractometer equipped with CCD detector using graphite monochromated Mo-Kα radiation ($\lambda = 0.71703$ Å). Data collection was performed according to Nonius.[19] DENZO software package[20] was used for data reduction and frame integration. Structure solution was carried out using MAXUS software package.[21] The structure was solved by direct methods and full matrix least squares refinement was carried out against F^2. The non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms attached to C-atoms were calculated, whereas the H atoms linked to the nitrogen atoms were located on difference Fourier. Crystal data and some refinement details are presented in Table 3.

The structure of the molecule is shown in Fig. 3. The unit cell of the crystal contains 4 independent molecules linked by hydrogen bonds, and thus forming the tetramer shown in Fig. 4. The geometric data of the H-bonds are given in Table 4 and the distances and angles for the centroids of the pyrazole rings are reported in Table 1. Figs. 3 and 4 were drawn using the ORTEP software.[22]

‡ CCDC reference number 188/264. See http://www.rsc.org/suppdata/p2/b0/b004690f for crystallographic files in .cif format.

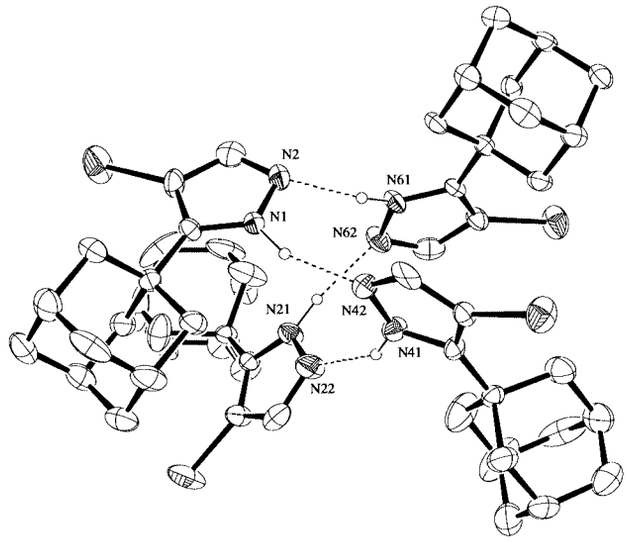

Fig. 4 An ORTEP view of the tetramer with H-bonds.

Table 4 Hydrogen bonds present in the structure of **2b**

Hydrogen bond	N–H/Å	N···N/Å	N–H···N/°
N(2)–H···N(61)	1.880(3)	2.796(4)	151.30(6)
N(62)–H···N(21)	1.919(1)	2.888(5)	161.58(8)
N(42)–H···N(1)	1.914(1)	2.934(4)	157.53(8)
N(22)–H···N(41)	1.891(1)	2.855(4)	148.23(7)

Acknowledgements

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