Aromatic propellenes. Part 1. NMR spectroscopy, X-ray crystal and molecular structure of hexa(3,5-dimethylpyrazol-1-yl)benzene

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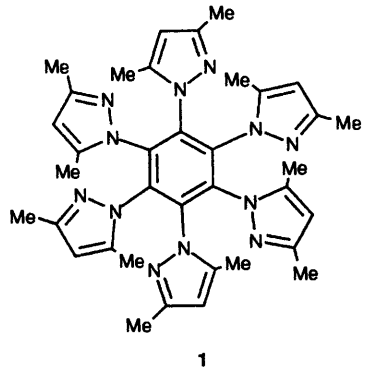
The molecular and crystal structure of hexa(3,5-dimethylpyrazol-1-yl)benzene has been determined by X-ray analysis. Semiempirical calculations at the AM1 level exploring all possible symmetrical conformations of the 3,5-dimethylpyrazole rings reveal that the most stable conformation corresponds to that of the solid state in which the nitrogen atoms bearing the lone pair are placed up (*u*) and down (*d*) with respect to the benzene ring. In solution, NMR spectroscopy proves that together with conformation **1** (*ududud*), the second most stable conformer **2** (*uduuud*) is also present.

We describe in this first paper, and in the following ones, a series of compounds related to an aromatic propeller. These structures are related to MacNicol's 'Hexa-Hosts',[1] Vögtle and Weber's 'Octopus'[2] and to Toda's 'Hexa-Pedals',[3] but differ from all of them by the fact that in these examples only the central ring is an aromatic compound (benzene) while in the present series of compounds we have named 'Aromatic Propellenes', the periphery is composed of heteroaromatic rings, azoles, directly linked to the central core.

The compound here reported **1** was first described by Henrie and Yeager,[4] who prepared it from hexafluorobenzene and 3,5-dimethylpyrazole (no spectroscopic data). In this paper we report a structural study of compound **1**, first its X-ray structure, then semiempirical calculations of the conformational potential surface and finally, an NMR study in solution.



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Results and discussion

X-Ray analysis

Bond distances, angles and torsion angles are listed in Table 1. The molecule is located on a three-fold rotary inversion axis, therefore there is only one 3,5-dimethylpyrazolyl unit in the asymmetric unit and the N(2) atoms are placed up and down with respect to the benzene ring (Fig. 1). The main features of the molecular structure induced by the methyl substitution are: the elongation of all distances but N(2)–C(3) and C(4)–C(5) in the pyrazole ring with respect to the parent compound[5] and the different pattern of bond angles (Table 1). The pyrazole moiety is almost orthogonal to the central benzene ring (84.1°) while the phenyl substituents in hexaphenylbenzene[6] are twisted by 66.5° on average (range: 64.3–69.1°). For this compound, the propeller has its blades almost perpendicular to the shaft, but other less hindered pyrazoles should have blades disposed at an angle such that isomerism and enantiomerism will result. The crystal is built up of discrete molecules which do not bear any significant contacts among them other than van der Waals interactions. Fig. 2 shows the crystal structure.

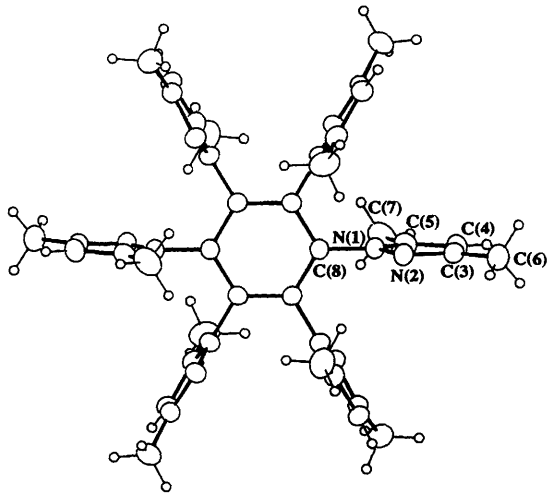
Table 1 Selected geometrical parameters (Å, °)

	Exp.	AM1	Ref. 5
N(1)–N(2)	1.372(3)	1.350	1.341(6)
N(1)–C(5)	1.357(3)	1.416	1.333(10)
N(2)–C(3)	1.328(3)	1.361	1.329(10)
C(3)–C(4)	1.395(4)	1.452	1.382(10)
C(4)–C(5)	1.372(3)	1.400	1.376(10)
N(1)–C(8)	1.417(3)	1.424	
C(8)–C(8′)	1.393(3)	1.420	
C(3)–C(6)	1.501(4)	1.475	
C(5)–C(7)	1.482(4)	1.470	
C(5)–N(1)–C(8)	126.2(2)	125.7	
N(2)–N(1)–C(8)	120.3(2)	122.1	
N(2)–N(1)–C(5)	113.6(2)	112.2	111.8(6)
N(1)–N(2)–C(3)	103.5(2)	106.5	104.9(6)
N(2)–C(3)–C(4)	111.5(2)	110.0	111.6(6)
C(3)–C(4)–C(5)	107.0(2)	105.6	104.4(7)
N(1)–C(5)–C(4)	104.5(2)	105.7	107.3(6)
N(2)–C(3)–C(6)	119.6(3)	125.3	
C(4)–C(3)–C(6)	128.9(3)	124.6	
C(4)–C(5)–C(7)	133.7(3)	129.3	
N(1)–C(5)–C(7)	121.8(3)	125.1	
N(1)–C(8)–C(8′)	120.0(1)	120.0	
N(2)–N(1)–C(8)–C(8′)	−84.1(2)	−90.2	

The low total packing coefficient [C^{all}_k = ($V_{molecules}$)/Unit Cell Volume = 0.65] is consistent with the presence in the structure of spherical voids[7] (three in the unit cell) each of volume 20.9 Å^3 and centred at the crystallographic origin and at its symmetrically related sites.

Semiempirical computations

Within the AM1 approximation, the molecular structure of compound **1** was optimized and the resulting geometry is gathered in Table 1 together with the experimental one, showing



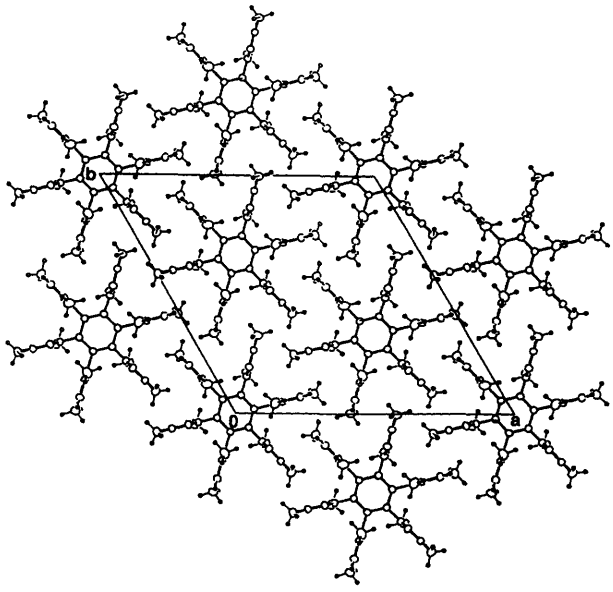


Fig. 2 Crystal packing down the *c* axis

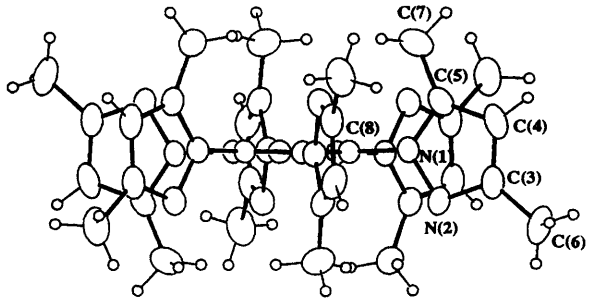
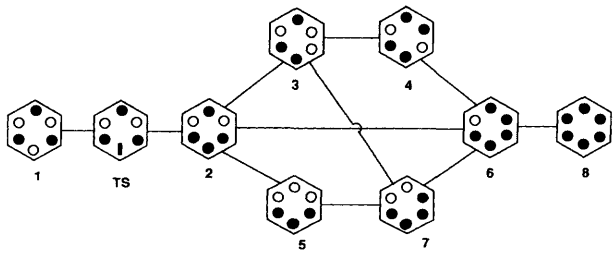


Fig. 1 ORTEP[13] view showing the numbering system and the conformation of the molecule. Ellipsoids are drawn at 30% probability level.

a reasonable agreement. All calculated bond distances but N(1)–N(2) are slightly longer than the experimental ones. This trend is mainly displayed by the N(1)–C(5) and C(3)–C(4) bond lengths pointing out to a lower degree of charge delocalization around the pyrazole ring. The exocyclic angles computed for the methyl substituents show that they are more symmetrical in respect to the pyrazole ring than in the crystal structure.

The optimized value of the torsion angle between the phenyl and pyrazole ring is larger than the experimental one. The hydrogen interaction of the methyl at C(5) with the nitrogen lone pair of the adjacent rings is not favourable but the steric hindrance among the methyl groups is predominant. The AM1 computation also overestimates this type of hydrophobic interactions, increasing the value of the torsion angle.

The energies for all eight possible pyrazole conformations **1**–**8** have been computed (see Experimental and Scheme 1,



Scheme 1

all values in kcal mol^{-1}). To represent these conformations we have used an hexagon with a black circle (up = *u*) and a white circle (down = *d*) [this definition is arbitrary since for orthogonal pyrazoles there are only eight rotamers although conformation **3** exists in two enantiomeric forms similar to (±)-inositol]. The lowest value, $\delta\Delta H = 0.0$, corresponds to the experimental conformation **1** (*ududud*) $\Delta H = 451.7$ kcal mol^{-1}. The lines represent all single interconversion paths between conformers when only one pyrazole ring is rotated by 180°. The stability decreases in the order **2** $\Delta H = 459.7$, $\delta\Delta H = 8.0$ kcal mol^{-1} (*uduuud*) < **3** $\Delta H = 463.1$, $\delta\Delta H = 11.4$ kcal mol^{-1} (*uddudd*) < **4** $\Delta H = 465.0$, $\delta\Delta H = 13.3$ kcal mol^{-1} (*uuduud*) < **5** $\Delta H = 467.2$, $\delta\Delta H = 15.5$ kcal mol^{-1} (*dduuud*) < **6** $\Delta H = 468.8$, $\delta\Delta H = 17.1$ kcal mol^{-1} (*uuuuud*) < **7** $\Delta H = 471.8$, $\delta\Delta H = 20.1$ kcal mol^{-1} (*duuuud*) < **8** $\Delta H = 480.4$, $\delta\Delta H = 28.7$ kcal mol^{-1} (*uuuuuu*).

The more effective repulsive interactions between contiguous pyrazolyl moieties take place when both present the N(2) on the same side of the phenyl ring (*uu* or *dd*). To discuss further the preceding ΔH values, we have postulated a simple empirical model which takes into account the [1,2], [1,3] and [1,4] *uu* or *dd* interactions present in the different conformations. For instance, in conformation **1** there are 0 [1,2] and [1,4] interactions and 6 [1,3] interactions (**1**, 0, 6, 0; **2**, 2, 4, 1; **3**, 2, 2, 2; **4**, 2, 2, 3; **5**, 4, 2, 0; **6**, 4, 4, 2; **7**, 4, 2, 1; **8**, 6, 6, 3). The resulting eqn. (1) is obtained by multiple regression.

$$\Delta H = 452.5 + 4.0\,[1,2] - 0.3\,[1,3] + 1.6\,[1,4]; \quad n = 8, r^2 = 0.976 \quad (1)$$

As expected, the most repulsive term is the [1,2] interaction of two pyrazoles with the same orientation (the origin is both steric and dipole–dipole repulsions), then follows the [1,4] interaction (dipole–dipole), finally the [1,3] interaction is attractive, but very weak.

To estimate the activation barrier for the interconversion of the two most stable conformers, **1**→**2**, we have computed the energy, after geometry optimization, when one of the pyrazole rings is coplanar with the phenyl ring (the other remaining orthogonal). The energy for this point is $\Delta H^{\ddagger} = 484.7$ kcal mol^{-1}, *i.e.* $\delta\Delta H^{\ddagger} = 33.0$ kcal mol^{-1} over the minimum **1**.

Table 2 ^{13}C chemical shifts (ppm) of hexa(3,5-dimethylpyrazol-1-yl)benzene[a]

Solvent	Time	C-3	C-4	C-5	3-CH_3	5-CH_3	C_{ipso}
CPMAS	—	148.9	105.9	142.0	15.0	12.1	~142
$CDCl_3$ + 5% CF_3CO_2H	5 min	**150.48**	**106.35**	**145.98**	**12.54**	**11.09**	**137.09**
$CDCl_3$ + 5% CF_3CO_2H	eq.	150.15	106.13	143.55	12.35	10.41	136.68
		150.48	106.24	144.18	12.54	10.73	**137.09**
		150.55	**106.27**	145.53	**12.54**	10.77	137.13
		150.89	106.35	**145.98**	12.65	**11.09**	137.35

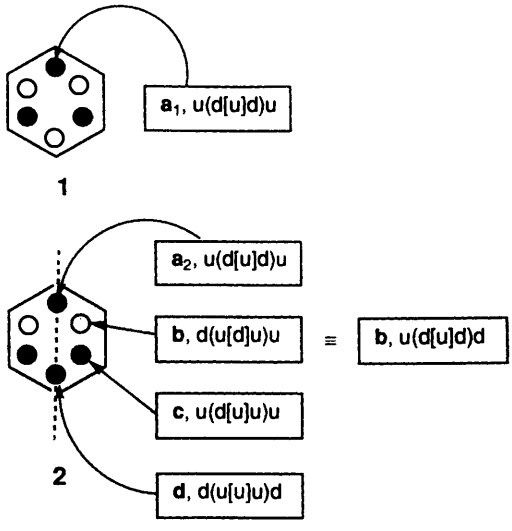
[a] Values in bold correspond to conformer **1**.

NMR study in solution

In the solid state, compound **1** presents a very simple ^{13}C CPMAS NMR spectrum (Table 2) which was assigned by analogy with other pyrazoles.[8] In solution, the compound is rather insoluble, thus a small amount of trifluoroacetic acid has to be added to increase the solubility (≈5%). The acid protonates to some extent molecule **1** resulting in a moderate shift of carbon signals; moreover, if the spectra recorded for t = 0 (or extrapolated to the origin) are similar, in their simplicity, to the solid state spectrum, after a while, an equilibrium intervenes and up to four lines for each carbon are observed. Those corresponding to **1** are in bold characters.

This phenomenon is also observed in ^1H NMR spectroscopy. We will consider only the two more stable conformations **1** and **2**.

In Scheme 2 we have summarized these conformations and

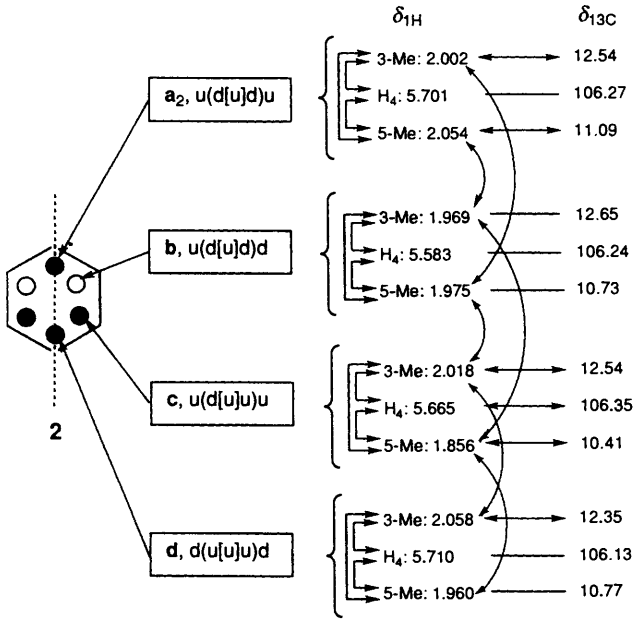


Scheme 2

the expected groups of signals. In Scheme 3 we have reported the NMR experiments used to establish the conformation of the two compounds present in solution. These experiments include: (*i*) HMQC to correlate ^1H and ^{13}C chemical shifts, the last ones being specific of 3-Me and 5-Me groups[8] (double-headed arrows mean observed experiments, single lines corresponds to experiments not devoid of ambiguity due to limitations of digital resolution for very close signals); (*ii*) NOESY to identify each pyrazole ring, first between H4 protons and the methyl groups, then between methyl groups of the same pyrazole; (*iii*) NOESY with different mixed times (mix = 0.9, 0.6 and 0.3 s) between methyl groups of different pyrazoles.

In addition to these NMR techniques, the assignment is consistent with two other data. First, the relative intensities of ^1H and ^{13}C signals; in conformer **2** they must be in the ratio 1 × **a**$_2$, 2 × **b**, 2 × **c**, 1 × **d**. Second, the chemical shifts should be related to the environment of each pyrazole; thus **a**$_1$ and **a**$_2$ should be very similar (Scheme 2) since they differ only in the more removed substituent (actually they present identical chemical shifts), then **b** which differs only in the conformation of one of the lateral pyrazoles, then **c** (one of the adjacent pyrazoles) and, finally, **d** (both adjacent rings). This second criteria, which predicts **abcd** sequences, either upfield or downfield, is not strictly followed, but the observed inversions affect only very close signals of two adjacent situations (**ab**, **bc** or **cd**).

The data of Scheme 3 are only consistent with conformation



Scheme 3

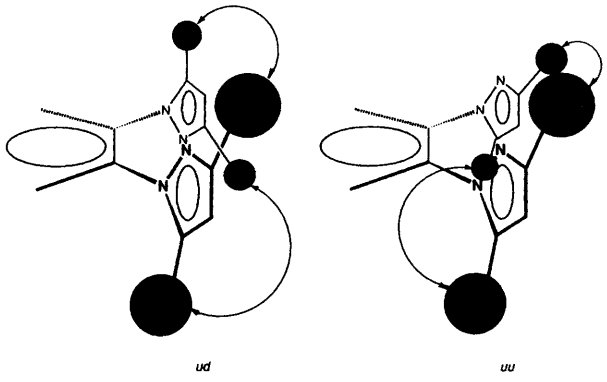
2, in particular, the NOE effects. If two contiguous pyrazoles are in an *ud*(*du*) situation, then the NOE should appear between the 3-Me protons of one pyrazole and the 5-Me protons of the other, while for *uu*(*dd*) situations, the NOE should be observed between 3-Me/3-Me and 5-Me/5-Me (Scheme 4). This is exactly what is observed in Scheme 3 identifying without ambiguity conformer **2**.

According to calculations, the activation energy for the **1**/**2** interconversion is 33 kcal mol^{-1}. This value is consistent with the behaviour described above: slow equilibration in solution. In a first approximation, the following relationship should be observed between activation energies and ^1H NMR spectra for systems consisting of two related entities: $\delta\Delta H^{\ddagger} < 5$ kcal mol^{-1}, only one average spectrum; $5 < \delta\Delta H^{\ddagger} < 15$ kcal mol^{-1}, coalescence domain, the spectrum is temperature dependent

Table 3 Crystal analysis parameters at room temperature

Crystal data	
Chemical formula	$C_{36}H_{42}N_{12}$
M_r	642.808
a (Å)	19.8639(7)
c (Å)	7.6743(2)
V (Å^3)	2622.4(2)
Wavelength (Å)	1.5418
θ range for lattice parameters (°)	2–45
Absorption coefficient (cm^{-1})	5.78
Crystal colour	Colourless
Crystal size (mm)	0.40 × 0.17 × 0.17
Crystal system	Rhombohedral
Space group	R-3
Z	3
D_x (g/cm^{-3})	1.22
Radiation	Cu-Kα
No. of reflections for lattice parameters:	53
T (K)	395
Crystal description	Prism
Data collection	
Diffractometer type	Philips PW1100, four circle. Graphite oriented monocromator.
Measurement time	1 min/reflection
Collection method	$\omega/2\theta$ scans
No. of standard reflections (interval)	2 (90 min). No variation
No. of independent reflections	975
Detector apertures (°)	1 × 1
θ_{max}(°)	65
Scan width (°)	1.4
No. of observed reflections	$I > 3\sigma(I)$, 800
Refinement	
Treatment of hydrogen atoms	See Experimental section
R	0.055
wR	0.055
$(\Delta\rho)_{max}$ (e/Å^3)	0.18
⟨Shift/error⟩	0.10
Least-squares on F_o	Full matrix
No. of parameters refined	101
Degrees of freedom	699
Ratio of freedom	7.9
Max. thermal value (Å^2)	U33[C(6)] = 0.139(3)

Weighting scheme: Empirical as to give no trends in $\langle\omega\Delta^2F\rangle$ *vs.* $\langle|F_{obs}|\rangle$ and $\langle\sin\theta/\lambda\rangle$.



Scheme 4

and the activation energy can be determined by NMR lineshape analysis; 15 < $\delta\Delta H^{\ddagger}$ < 25 kcal mol^{-1}, equilibrium domain, narrow signals are observed for both entities, the proportion changing with solvent and temperature; 25 < $\delta\Delta H^{\ddagger}$ < 35 kcal mol^{-1}, equilibration domain, slow transformation which can be followed by classical kinetics; $\delta\Delta H^{\ddagger}$ > 35 kcal mol^{-1}, both entities can be separated and are indefinitely stable.

The relative populations of conformers **1** and **2** are strongly dependent on the amount of trifluoroacetic acid (TFA) present in $CDCl_3$. When there is no acid at all (^{1}H NMR spectrum of a saturated $CDCl_3$ solution), conformer **1** is stable for a long time. The percentage of conformer **2** at the equilibrium increases with the concentration of TFA, in the reported NMR experiments (about 5%) the equilibrium mixture corresponds to 20% of **1** and 80% of **2**. The lone-pair–lone-pair repulsion which favours the upside-down conformation is probably replaced by a lone-pair–NH^+ attractive term which favours the *uu* or *dd* situations.

Experimental

Sample preparation

To a solution of 2.0 g (20.8 mmol) 3,5-dimethylpyrazole in 25 ml THF, 500 mg (20.8 mmol) of sodium hydride was added in small portions. After complete addition, the solution was stirred at room temperature for 45 min then 0.4 ml (3.5 mmol) of hexafluorobenzene was added. This mixture was heated at 50 °C for 2 h, then stirred at room temperature overnight. The resulting white precipitate was filtered off and washed with THF giving 998 mg (45%) of crude product which crystallized at room temperature after dissolution in acetic acid at 120 °C. Mp 250 °C (with sublimation). MS, calc. for $C_{36}H_{42}N_{12}$, M = 642.8, m/z 642 (M, 100%), 627 [(M − CH_3), 86%], 547 [(M − dmpz), 34%] and 321 (M/2, 7%).

X-Ray structure determination †

The experimental details and the most relevant parameters of the refinement are given in Table 3. The structure was solved by direct methods, SIR92.[9] The non-hydrogen atoms were refined anisotropically and the hydrogen ones were included as isotropic. Most of the calculations were performed on a VAX6410 computer using the XRAY80 System.[10] The atomic scattering factors were taken from the International Tables for X-Ray Crystallography, vol. IV.[11]

Semiempirical calculations

A geometrical optimization has been performed taking the crystallographic coordinates as the starting point and using the AM1 parametrization of the Hamiltonian as implemented in the MOPAC 6.0 package.[12] The three point group symmetry has been imposed, together with the planarity of the pyrazole rings. The methyl groups were fixed in the plane of the pyrazole ring and with an alternate conformation similar to that displayed in the crystal structure.

All possible pyrazole conformations have also been optimized starting with the geometrical parameters obtained from the previous optimization and twisting the corresponding pyrazole rings by 180° around the N(1)–C(8) bond. The pyrazole rings have been fixed perpendicular to the phenyl group and the corresponding point group symmetry has been used.

NMR spectroscopy

The solid state ^{13}C CPMAS NMR spectrum was recorded on a Bruker AC200 spectrometer using the conditions described in ref. 14. The solution NMR spectra were recorded on Varian Unity 500 instrument working at 499.84 MHz for ^{1}H and 125.70 MHz for ^{13}C. The experimental conditions and the two dimensional experiments have already been described.[15]

† Supplementary data [see section 5.6.3 of 'Instructions for Authors (1995)', January issue]. Lists of the atomic coordinates for the non-hydrogen atoms, thermal components, hydrogen parameters and bond distances and angles have been deposisted at the Cambridge Crystallographic Data Centre.

Acknowledgements

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