THE CONFORMATION OF TRISPYRAZOLYLMETHANES: AN EXPERIMENTAL AND THEORETICAL STUDY

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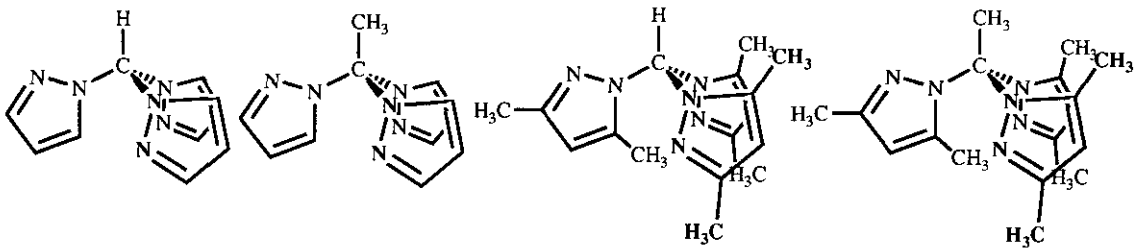
This manuscript is dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday with friendship and respect

Abstract - A combination of methods which include MM2 and MNDO calculations, nmr spectroscopy in the solid state (CPMAS) and in solution (^{1}H, ^{13}C, LSR, chiral solvents and NOE experiments), DSC and X-ray powder diffraction has been used to study the conformation of tris(pyrazol-1-yl)methanes and ethanes. It has been shown that tris(3,5-dimethylpyrazol-1-yl)methane (**4**) exists in two isolable isomers, the ABB and the BBB, whose interconversion by melting, crystallization and sublimation has been studied.

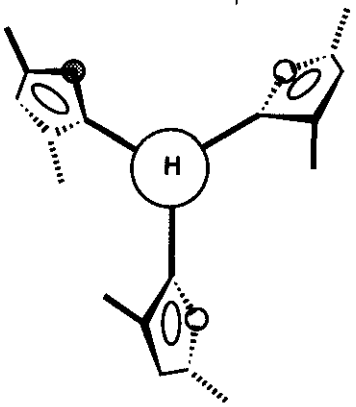
Poly(azol-1-yl)methanes (**1**), $Az_nCH_{(4-n)}$ n = 2,3,4, Az being an *N*-substituted azole, are a family of compounds with considerable interest as metalloorganic ligands.[1-9] Another relevant aspect of these compounds is their conformation which is related to the classical problem of tris and tetrakis-arylmethanes brilliantly studied by Mislow several years ago.[10-14] Four previous papers have dealt with the conformational study of bis-, tris- (**2**) and tetrakis(pyrazol-1-yl)methane[15] and of tris (benzimidazol-1-yl)methanes.[16-18] The present work reports our results on the three derivatives of **2**, namely tris(pyrazol-1-yl)ethane (**3**), tris(3,5-dimethylpyrazol-1-yl)methane (**4**) and tris(3,5-dimethylpyrazol-1-yl)ethane (**5**).



2 **3** **4** **5**

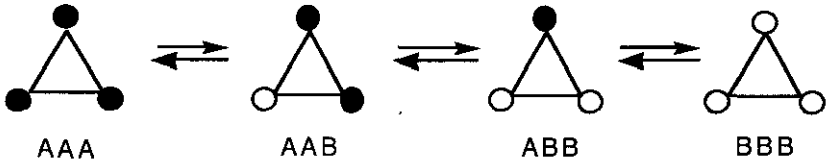
RESULTS AND DISCUSSION

The structure of compound (**4**) was determined in Louvain in 1984.[19] The unit cell is formed by four independent molecules of very similar conformation that we call conformation ABB[16] [or $\alpha\beta\beta$][19] (defining a plane through the three N atoms bonded to the central C atom, the A or α conformation is that in which the N atom is on the same side as the C(1)-H). Each molecule presents a helical conformation, thus being chiral, with both enantiomers present in the unit cell (Z = 16).



4 ABB

The structure of the two other compounds (**2** and **3**) has not been determined. Molecular mechanics calculations are gathered in Table 1 for the four compounds and MNDO calculations for compound (**4**) are in Table 2. A symbolic representation of the four conformers is shown in Figure 1.



AAA AAB ABB BBB

Figure 1

TABLE 1
Results of the MM2 calculations

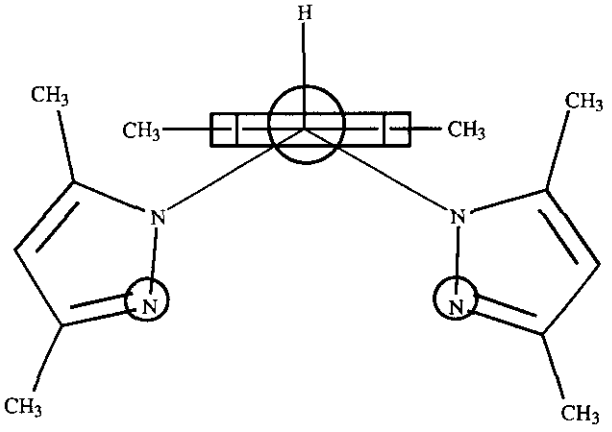
Compound	Conformation	Steric Strain (kcal. mol^{-1})	Symmetry number	Pop. at 25°C
2	AAA	37.58	1	9.1
	AAB	37.23	3	48.7
	ABB	37.39	3	37.3
	BBB	37.94	1	4.9
3	AAA	89.67	1	12.1
	AAB	89.59	3	41.4
	ABB	89.60	3	40.7
	BBB	40.11	1	5.8
4	AAA	31.22	1	0.3
	AAB	29.80	3	8.9
	ABB	28.47	3	84.4
	BBB	29.35	1	6.4
5	AAA	34.77	1	0.7
	AAB	34.41	3	3.7
	ABB	32.50	3	93.5
	BBB	34.09	1	2.1

TABLE 2
Results of the MNDO calculations

Compound	Conformation	ΔH_f (kcal.mol^{-1})	Symmetry number	Population at 25°C
4	AAA	108.07	1	0.0
	AAB	102.14	3	0.1
	ABB	98.01	3	97.7
	BBB	99.60	1	2.2

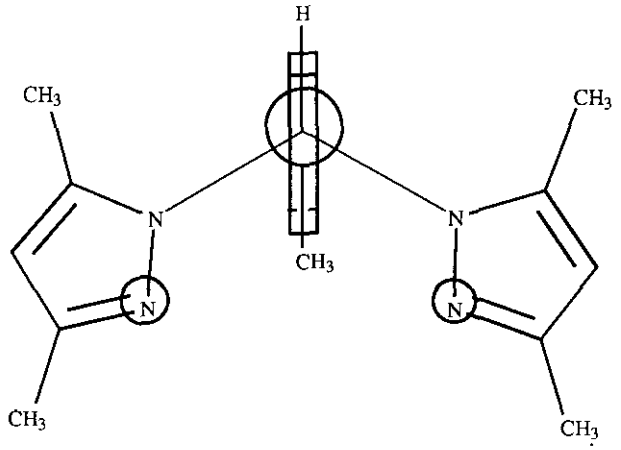
The structure found by crystallography for compound (**4**) is that predicted to be the most stable both by MM2 (84.4 %) and by MNDO calculations (97.7 %). The second most stable conformer is the AAB according to MM2 calculations (although the BBB has almost the same steric strain) and the

BBB according to MNDO calculations. To convert the ABB conformation into the BBB one, the pyrazole ring A must rotate 180° about the N-C(H) bond; the corresponding transition state TS1 (103.2 kcal.mol^{-1}, MNDO calculations) lies 5.2 kcal.mol^{-1} higher than the AAB conformation.



4, TS_1

The barrier to the racemization corresponds to the flipping of the three pyrazole rings about the N-C(H) bond (from the right to the left helix) and the transition state instead of being perpendicular (⊥) is parallel (||) TS2, according to the description introduced by Allinger and Tribble[20] for conformations about sp^2-sp^3 atoms.[21]



4, TS_2

In this case, the barrier is much lower, about 2 kcal.mol^{-1}, thus separation of enantiomers over chiral columns[16] should not be possible. On the other hand, diastereoisomers **4**ABB and **4**BBB could be separated.

When compound (**4**) was crystallized by slow evaporation in *n*-heptane (or in *n*-hexane-ether) parallelepipedic crystals were obtained which melted at 129°C, re-solidified and melted again at 152°C. These were the crystals used for the X-ray structure determination.[19] By sublimation (without melting), very narrow needles (not suitable for crystallography) were obtained, mp 151°C. The ^{13}C high-resolution solid-state nmr spectra of both samples were obtained using the CPMAS technique (Table 3).

TABLE 3

^{13}C Chemical shifts (ppm) of compound (**4**)

Conditions	C3	C4	C5	C(sp^3)	Me-3	Me-5
$CDCl_3$ solution[7]	148.7	107.6	140.8	80.7	13.8	10.7
mp 129°C solid state	144.3	105.2	138.5[a]	80.6[b]	12.6	9.0
	146.5	106.2	138.5[a]		13.2	10.2
	147.7[a]	107.5	139.7		13.7[c]	10.6
	147.7[a]	108.3[a]	141.0		13.7[c]	11.7[c]
	148.4	108.3[a]			13.7[c]	11.7[c]
	149.3				14.7	11.7[c]
mp 151°C solid state	147.7	105.9	141.4	77.4	13.3	11 1
					14.5	11.5[a]
					15.5	11.5[a]

[a] Corresponds to a signal twice as intense as the other signals of the cluster; [b] broad, unresolved signal; [c] Corresponds to a signal thrice the intensity of other signals of the cluster.

The nmr spectrum of **4**ABB corresponds to the phase mp 129°C. According to the X-ray structure,[19] there are four independent molecules in the crystal cell, thus for each carbon four lines of relative intensity 2 (BB part) and four lines of intensity 1 (A part) could be observed. The excellent resolution of the Bruker AMX 400 instrument allows to observe up to four or five lines of the maximum eight possible. The nmr spectrum of the phase mp 152°C is much more simple: the only signals that are split are those of the methyl groups: Me-3 into three lines of identical intensity and Me-5 into two lines of 1:2 intensity. We think that the high melting point phase is **4**BBB (the second most stable conformation according to MNDO calculations). Since a spontaneous resolution is

unlikely, there should be an even number of molecules in the unit cell, at least two (the helical conformation and its enantiomer). To be consistent with the nmr spectrum, three pairs of enantiomers should be present in the unit cell (Z = 6 or a multiple of 6). Both solid samples yield identical spectra in solution proving that **4**ABB and **4**BBB rapidly isomerize when dissolved, a fact that is consistent with the calculated low activation energy of the isomerization.

Then these two phases of compound (**4**) were studied by DSC and the results are summarized in Figure 2 (melting points and melting enthalpies).

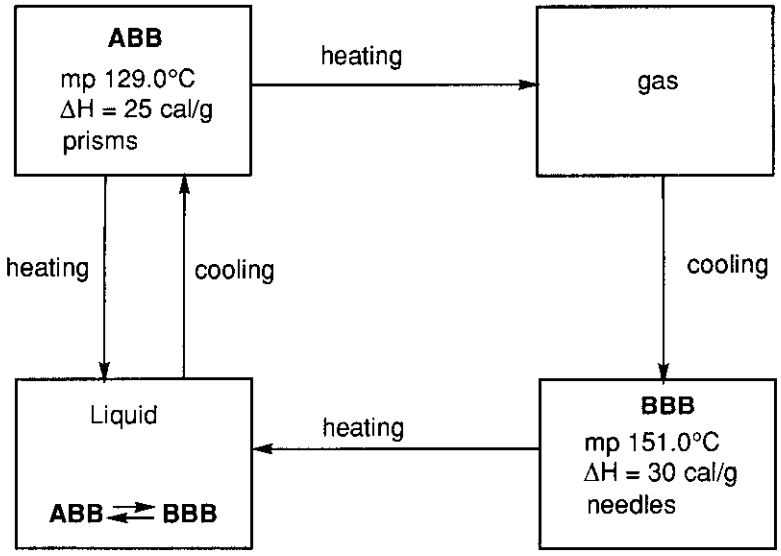


Figure 2

Although these experiments prove very sensitive to the heating rate, the most significant result is that the liquid obtained by melting the 151.0°C isomer, when solidified melted at 129.0°C. As we have indicated, it is not possible to obtain suitable crystals of the high-melting point variety since crystallization results in the formation of the low-melting point one. Nevertheless, we have recorded the X-ray powder diffraction diagrams of both phases which are very different (Table 4). Those corresponding to "crystallized into *n*-heptane", "crystallized into *n*-hexane-diethyl ether" and "sublimed-melted-resolidified" were almost identical and only one series of values will be reported. Both solid forms, mp 129.0°C and mp 151.0°C, when melted and resolidified gave ^{13}C CPMAS nmr spectra identical with that reported in Table 3 for the mp 129.0°C form of **4**.

TABLE 4

X-Ray powder diffraction (fundamental reflections in degrees between 8° and 30°)

Sublimed: 10.5, 16.3, 18.7, 22.5, 24.8 and 27.9
Crystallized: 10.3, 11.3, 12.1, 15.5, 16.1, 17.6, 19.2, 20.2, 21.9, 23.5, 24.3, 25.3 and 27.4

Solution Studies by ^1H Nmr: NOE Experiments, Temperature Effects, Lanthanide Shift Reagents and Chiral Reagents (Pirkle's Alcohol)

To gather information about compounds (**2-4**) a careful ^1H nmr study was carried out. This technique had moderate success, but some indications about the major conformations in solution have been gained. The nmr parameters of these compounds are reported in Table 5.

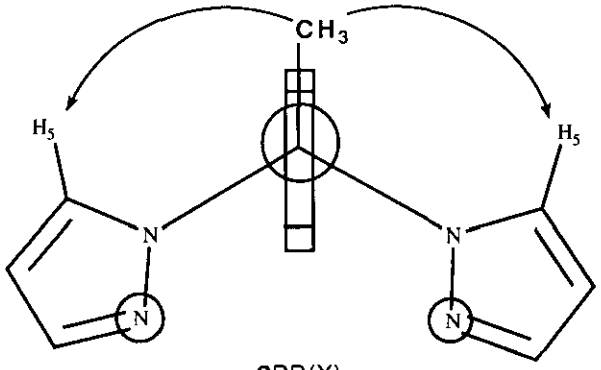
TABLE 5

^1H Nmr chemical shifts (ppm) and coupling constants (Hz) of compounds **2-4**

Compound	Solvent	Position 3	Position 4	Position 5	C(sp^3)-R
2	$CDCl_3$	7.68	6.37	7.58	8.43 (CH)
		J_{34} = 1.8, J_{35} = 0.6, J_{45} = 2.6, J_{15} = 0.35[a]			
3	$CDCl_3$	7.69	6.33	6.84	2.98 (CH_3)
		J_{34} = 1.9, J_{35} = 0.8, J_{45} = 2.9			
4	$CDCl_3$	2.18 (CH_3)	5.85	2.01 (CH_3)	8.07(CH)
			$J_{(H4-Me5)}$ = 0.6[b]		
4	[$^2H_8$]Toluene at 291 K	2.172	5.735	2.008	8.284
4	[$^2H_8$]Toluene at 203 K	2.156	5.678	1.973	8.620

[a] From a 500 MHz spectrum; [b] These homoallylic ^4J couplings are related to the bond order.[22]

The proton of the 5-position of pyrazole ring is 0.74 ppm more shielded in compound (**3**) than in compound (**2**), when the only difference is the presence of a methyl group on the sp^3 carbon atom. This shielding could correspond to a conformation where H5 is near the C-methyl group. To assess this hypothesis, a NOE difference experiment was carried out on compound (**3**): the only NOE, although weak (2%), was found between the C-methyl group and H5. Thus, in compound (**3**), there are pyrazole rings in conformation B:



3BB(X)

Taking into account the calculations, an ABB conformation seems the more reasonable hypothesis. The ^{1}H nmr spectrum of **4** was recorded in toluene-d_8 at room temperature and at -70°C (Table 4). No dynamic process could be slowed down enough to observe the splitting of some signals, not even a broadening. At low temperature, the protons of the pyrazole rings are shielded ($\Delta\delta$ = -0.036 ppm) and that of the central C-H is deshielded ($\Delta\delta$ = + 0.336 ppm). This could correspond to an increase of the population of the most stable conformation at low temperatures, a conformation in which the pyrazole rings mutually shield each other but deshield the central C-H. More than an increase in the population of the ABB isomer, this observation could be related to small changes in the conformation of each pyrazole ring with regard to the C-H bond.

The same experiment was repeated in the presence of Pirkle's alcohol (1:1 ratio), to differentiate enantiomers if the barrier to racemization was high enough. The only observation at -70°C is a broadening of the signals belonging to Pirkle's alcohol,[23,24] but nothing on the signals of compound (**4**). Using higher proportions of Pirkle's alcohol (6:1 ratio) does not improve the experiment.

We carry then a series of experiments using europium(III)-tris-β-diketonates, first with $(fod)_3$ [tris-6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadionato] and then with the chiral derivatives $(tfc)_3$ [tris(3-(trifluoromethylhydroxymethylene)camphorato] and $(thfc)_3$ [tris(3-heptafluoropropil-hydroxi-methylene)-*D*-camphorato] (Table 6). We have already described the effects of $Eu(fod)_3$ on compound (**2**)[15] and the difficulty to use the lanthanide induced shifts, LIS, for conformational purposes, since the low activation barrier allows the conformation to change for a better interaction with the reagent.

TABLE 6

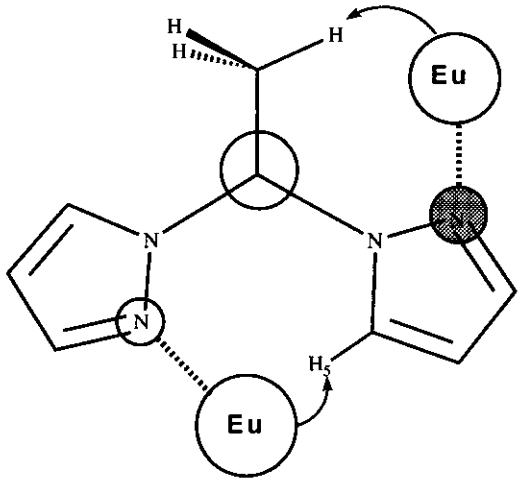
LIS on compounds (**2-4**) [a] [Solvent: $CDCl_3$]

Compound	S.R.	Pos. 3	Pos. 4	Pos. 5	C(sp^3)-R	Pos. 3[b]	Pos.4[b]	Pos.5[b]
2[c]	$Eu(fod)_3$	18.6	12.4	25.0	100(CH)	74.4	49.6	100
3	$Eu(fod)_3$	55.8	24.2	67.6	100(CH)	82.5	35.8	100
3	$Eu(tfc)_3$	31.9	20.9	61.1	100(Me)	52.2	34.2	100
4	$Eu(fod)_3$	11.1	14.2	20.9	100(CH)	53.2	68.1	100

[a] To the most sensitive signal has been assigned a 100 slope; [b] Only pyrazole signals; [c] From Ref.[15]

The LIS values of Table 6 deserve some comments. Values for compounds (**2**) and (**4**) are similar, thus, the conformations in solution **in the presence of $Eu(fod)_3$** should be also similar: for instance, an ABB conformation like that proposed for **2**[15] could be the common conformation for both compounds. The comparison **2/3** shows that the C-H signal of **2**, is relatively to pyrazole protons, much more sensitive than the C-CH_3 signal of **3**. This not reflects necessarily a change in the

conformation for **3**, may be only a modification in the position of the europium which could approach the proton closer than the methyl group. The comparison $Eu(fod)_3/Eu(tfc)_3$ for compound (**3**) shows that the effects are similar for CH_3, H4 and H5 but that H3 is more affected by the fod derivative than by the tfc derivative. It could be that the more crowded (tfc) derivative has two positions of coordination with regard to compound (**3**), a hypothesis which can also explain the clear curvature of the lines $\Delta\delta$ *vs* L/S: when the L/S ratio increases the slope decreases (the values of Table 5 have been obtained with the four first points). We have represented below (with only two pyrazole rings to simplify the view) a possible position for two $Eu(tfc)_3$ ligands with regard to compound (**3**).



3AB(X)

The last experiment we carried out with LSR's was to prepare an equimolar mixture of compound (**3**) and $Eu(thfc)_3$ (L/S = 1) in $CDCl_3$ and record the ^1H nmr spectra at different temperatures. The LIS at room temperature were similar to those with $Eu(tfc)_3$, but when the spectrum was recorded at 0°C the signals of H5 and even more that of the C-CH_3 were very broad. At -20°C (at lower temperatures, the LSR precipitates) these signals split into two very broad signals of the same intensity: this is a proof that compound (**3**) is a mixture of two helical enantiomers (the plus and the minus) with a slow racemization rate at -20°C.

CONCLUSIONS

According to MM2 calculations, the stability of ABB conformation increases slightly when the central C-H is replaced by a C-Me (**3/2** = 1.09, **5/4** = 1.11) and clearly when pyrazole is replaced by 3,5-dimethylpyrazole (**4/2** = 2.26, **5/3** = 2.30). This increase in population is made to the

detriment of the AAB conformation. The 5-methyl substituents of two A pyrazoles are in close contact, destabilizing the AA(X= A,B) conformations.

EXPERIMENTAL

Chemistry

Compounds (**3**) and (**4**) have already been described.[4,7] Compound (**5**) has not been prepared but is included here because some calculations were carried out on this structure.

Spectroscopy

The ^{1}H and ^{13}C nmr spectra in solution were recorded on a Bruker AC 200 instrument working at 200.14 and 50.32 MHz. Chemical shifts (δ) are given from internal tetramethylsilane with an accuracy of 0.01 (for ^{1}H nmr) and 0.1 (for ^{13}C nmr) ppm. Coupling constants (J) are accurate to ± 0.2 and ± 0.6 Hz, respectively. The nmr spectra at variable temperature and the NOE experiments were taken with a Bruker AM 400 WB spectrometer, in a 5-mm dual probe, operating at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C. NOE difference spectra were obtained using low decoupler setting (tipically 40L, 5 mW approximately) following a NOEMULT sequence. A 512 number of transients was acquired using 16K points and a sweep width of 5000 Hz in alternate groups of eight, irradiating on/off resonance. A 90° pulse was used during acquisition.

The ^{13}C solid-state spectra of pure compounds have been registered on a Bruker AMX 400 spectrometer working at 100.62 MHz under conditions of CP (cross polarization) and MAS (magic angle spinning) using 10.0 kHz spinning speed.

The LSR experiments have been carried out in deuteriochloroform at 30°C in a Bruker AC200 instrument. For each experiment, seven or eight points have been determined. Classical least squares procedure has been used to calculate the slopes ($r^2 \geq 0.998$).

Differential Scanning Calorimetry (DSC). The melting temperatures and melting enthalpies of the samples were measured with a Mettler TA4000 calorimeter with a DSC-30 furnace and a TC-11 central unit coupled to a computer with TA72 software. The heat flow was calibrated using the heat of fusion of an exactly known quantity of indium. Temperature calibration was carried out using a calibration pan with known quantities of indium, lead and zinc in separate holders. Although the heating rate was 1°C/min, various cooling rates, 10, 5 and 2°C/min, were selected to study the transitions, using nitrogen as the purge gas.

X-Ray Powder Diffraction Studies. Wide angle X-ray diffractograms were obtained using a Philips Geiger counter X-ray diffractometer. Samples for analysis were prepared from the original powder or from samples thermally treated as reported in each case. The diffractograms were recorded in a 2θ range between 8° and 30° using Ni-filtered CuKα radiation.

Theoretical Calculations

MM2[25] and MNDO[26] [AMPAC package][27] programs were used. Some problems which arise when using Allinger's methods have been discussed,[15,28] particularly that related to the absence of pivotal nitrogen atoms of the pyrrole type (N-1 in pyrazoles). This atom has been replaced by a carbon atom. On the other hand, MNDO calculations on compound (**4**) correspond to the actual structure.

ACKNOWLEDGEMENT

The ^{13}C CP/MAS spectra of compound (**4**) was recorded in Bruker Spectrospin AG, thanks to the courtesy of Dr. A. Torossian. This work was supported by a grant of the CICYT of Spain (Project No. PB90-0226-C02),

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