Pergamon

Tetrahedron 57 (2001) 4179–4187

TETRAHEDRON

A complete model for the prediction of ^{1}H- and ^{13}C-NMR chemical shifts and torsional angles in phenyl-substituted pyrazoles

Jose R. Carrillo,[a] Fernando P. Cossío,[b] Angel Díaz-Ortíz,[a] María J. Gómez-Escalonilla,[a]
Antonio de la Hoz,[a,*] Begoña Lecea,[b] Andrés Moreno[a,*] and Pilar Prieto[a]

[a]*Facultad de Química, Universidad de Castilla-La Mancha, 13071 Ciudad Real, Spain*
[b]*Facultad de Química, Universidad del País Vaco, Apdo 1072, 20080 San Sebastián, Spain*

Received 5 December 2000; revised 26 January 2001; accepted 2 March 2001

Abstract—^{1}H- and ^{13}C-NMR spectra of a number of *N*-phenyl- and *C*-phenylpyrazole derivatives have been obtained. The parameter most susceptible to changes in the dihedral angle $|\theta|$ is the difference $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$. Values for this parameter have been determined and its usefulness for conformational studies of phenyl-substituted pyrazoles has been demonstrated. A correlation between torsional angles calculated by molecular mechanics and differences in ^{13}C chemical shifts of the ortho and meta carbon atoms of the phenyl groups in 29 *N*-phenyl-substituted pyrazole derivatives and 11 *C*-phenyl-substituted pyrazole derivatives has been found. For the *N*-phenyl-substituted derivatives a correlation between torsional angles and $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$ values has also been demonstrated. In all cases good correlations between angles and differences in chemical shifts were observed. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Computational methods and nuclear magnetic resonance spectroscopy (NMR) are common tools used in the conformational analysis of small molecules. It is known that molecular mechanics is a good method to calculate energy minimization in order to locate stable conformations, to perform single-point energy calculations in order to compare conformations of the same molecule, and to search conformational space by varying a single dihedral angle. Molecular orbital and molecular mechanical methods normally yield good estimates of bond lengths and angles in comparison to X-ray structures. In most cases NMR is the method of choice that produces reliable results. Thus, Fong estimated the torsional angles in *N*-phenyl-substituted azole derivatives by analysing the ^{13}C chemical shifts of the *meta* and *para* carbon atoms.[1] He deduced that a steric interaction between the C5 substituent on the azole rings and the *ortho* hydrogen atoms of the benzene ring is the major cause of non-planarity in the compounds studied. Begtrup undertook an extensive ^{13}C-NMR study of phenyl-substituted azoles and suggested that the chemical shifts of the *ortho* carbon atoms, as well as the difference in chemical shifts between the *meta* and *ortho* carbon atoms, can provide a qualitative assessment of the degree of interannular conjugation.[2] Following the work described in these two papers it is possible to estimate the dihedral angle by application of the formulae reported therein, although these formulae are sometimes difficult to use when the molecular structure is complicated due to the number and variety of substituents. However, given the methods available today, we have the possibility of using several techniques to perform calculations that allow the relevant angles to be reliably calculated.

Moreover, in recent years, powerful tools for the analysis of NMR spectra have been developed and the full analysis of spectra has become feasible, even for complex spin systems. Despite the availability of these techniques this type of analysis can be difficult sometimes when the spectrum is crowded, as is the case when there are numerous aromatic protons with very small differences in their respective chemical shifts.

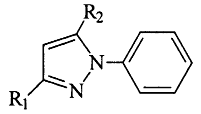
The aim of the work described here was to test a strategy based on a combination of NMR spectral analysis and computational tools to achieve a complete conformational characterization of a series of phenylpyrazole derivatives. We will demonstrate in this paper, with the aid of models of the structures obtained using molecular mechanics methods, that it is possible to predict the differences in chemical shifts of the proton and carbon atoms at *ortho* and *meta* positions. Similarly, we can determine the structure in solution of *N*-phenyl- or *C*-phenylpyrazole derivatives by considering the differences in the chemical shifts observed at the proton and carbon mentioned above. In all cases excellent correlations between dihedral angles and differences in chemical shifts were observed.

Keywords: NMR; molecular mechanics; pyrazole; conformation.

* Corresponding author. Fax: +34-926295318;
e-mail: adlh@qino-cr.uclm.es

0040–4020/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(01)00291-5

Table 1. Experimental C_m–C_o and C_m–C_p values in *N*-phenyl rings for compounds **1a**–**1g** and their calculated dihedral angles using MM^+



	$\|\Delta\delta\|$		
Compound	C_m–C_o	C_m–C_p	MM^+ $\|\theta\|$
1a: R_1=H, R_2=H	10.1	3.0	10.16
1b: R_1=Me, R_2=H	10.5	3.1	10.85
1c: R_1=H, R_2=Me	4.0	1.0	36.64
1d: R_1=Ph, R_2=H	10.4	3.1	10.90
1e: R_1=H, R_2=Ph	3.7	0.7	37.96
1f: R_1=Ph, R_2=Ph[a]	3.7	1.3	38.00
1g: R_1=^{t}Bu, R_2=^{t}Bu	0.5	0.2	79.30
Correlated parametres: $\Delta\delta$ vs $\|\theta\|$ (from above indicated values)			Linear correlation factors[b]
δC_m–δC_o vs $\|\theta\|$			0.911 (7)
δC_m–δC_p vs $\|\theta\|$			0.854 (7)

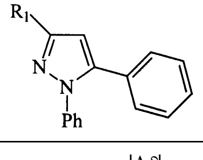
[a] In DMSO-d_6.

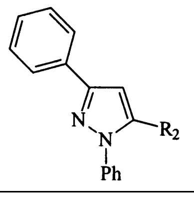
[b] Linear correlation factors extracted from linear plots of the differences of chemical shifts versus calculated dihedral angles $|\theta|$ using the MacroModel program. The values in parentheses show the number of data points of the linear correlations.

2. Results and discussion

The ^{13}C chemical shifts of benzenoid carbons largely depend on the mesomeric interaction between the substituent and the benzene ring. Electron releasing substituents will increase the electron density at the *ortho* and *para* carbons relative to those in unsubstituted benzene (128.5 ppm), while slight electron deficiencies will be induced by electron withdrawing groups. Considering these facts it is possible to explain why the *ortho* and *para* carbons of monosubstituted benzenes are shielded by electron releasing substituents but deshielded by electron acceptors, while the *meta* carbons remain almost unaffected by both kind of substituents. This situation is responsible for the differences observed between chemical shifts of *meta* and *ortho* or *meta* and *para* benzenoid carbon atoms. This effect is also responsible for the wider range (dispersion) of chemical shifts observed for carbon atoms in the phenyl group in *N*-substituted pyrazoles in comparison to the analogous *C*-substituted derivatives.

Table 2. Experimental C_m–C_o and C_m–C_p values in *C*-phenyl rings for compounds **1e**–**1f** and calculated dihedral angles using MM^+





	$\|\Delta\delta\|$		
Compound	C_m–C_o	C_m–C_p	MM^+ $\|\theta\|$
1e: R_1=H	0.3	0.1	45.42
1f: R_1=Ph[a]	0.3	0.1	45.73
1d: R_2=H	2.8	0.6	2.03
1f: R_2=Ph[a]	3.3	0.5	3.07
Correlated parameters: $\Delta\delta$ vs $\|\theta\|$ (from above indicated values)			Linear correlation factors[b]
δC_m–δC_o vs $\|\theta\|$			0.979 (4)
δC_m–δC_p vs $\|\theta\|$			0.981 (4)

[a] In DMSO-d_6.

[b] Linear correlation factors extracted from linear plots of the differences of chemical shifts versus calculated dihedral angles $|\theta|$ using the MacroModel program. The values in parentheses show the number of data points of the linear correlations.

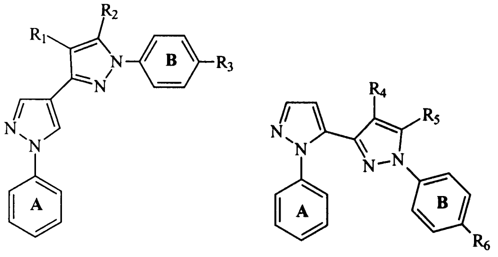
Firstly, in order to establish the most suitable computational method and decide on which differences in chemical shifts would be used, we applied a strategy based on the combination of NMR spectral analysis and computational tools to a group of simple *N*- and *C*-phenylpyrazole derivatives. Thus, to calculate the dihedral angles between pyrazole and benzene rings molecular mechanics (MM^+) and PM3 semiempirical methods were employed. Self consistent field-molecular orbital (SCF-MO) energy calculations and geometry optimizations were carried out by means of the PM3 semiempirical Hamiltonian at the restricted Hartree–Fock level (RHF/PM3 hereafter). In order to determine the parameters most susceptible to changes in the dihedral angle, the differences $\delta_{meta\text{-}C}-\delta_{ortho\text{-}C}$ and $\delta_{meta\text{-}C}-\delta_{para\text{-}C}$ of a group of phenylpyrazole derivatives were obtained from the ^{13}C-NMR spectral data available in the literature.[3,4]

Tables 1 and 2 show, for *N*-linked phenyl groups and *C*-linked phenyl groups, respectively, the values of the observed differences in the relevant carbon chemical shifts as well as the calculated angles. Different chemical shift values are found in the literature for the *ortho*, *meta* and *para* carbon atoms of the compounds included here, but when we determine the values of $\delta_{meta\text{-}C}-\delta_{ortho\text{-}C}$ and $\delta_{meta\text{-}C}-\delta_{para\text{-}C}$, only very small differences are observed (about 0.1–0.9 ppm and 0.0–0.7 ppm, respectively). These ranges can be considered as being within experimental error since the spectra were recorded on different spectrometers and, in some cases, in different solvents such as DMSO-d_6. For these reasons, we have used the chemical shift differences shown in Tables 1 and 2, where the conditions employed were similar and most of the spectra were recorded using $CDCl_3$ as the solvent and TMS as the internal standard. One exception is compound **1f**, where the solvent used was DMSO-d_6; these were the only data available in the literature for this compound. Linear plots of the differences in chemical shifts versus calculated dihedral angles were obtained (for the intervals of 0–10 ppm and 2–79°, respectively) and a further statistical treatment of the data led to linear regression coefficients, which are also shown in Tables 1 and 2.

Molecular mechanics calculations gave better coefficients for *N*- and *C*-linked phenyl groups than the PM3 semiempirical method that was used (data not shown). For this reason, we decided to use the AMBER force field in the MacroModel program to calculate the dihedral angles of bipyrazolyl compounds, some of which have been previously synthesized by us.[5]

The results obtained are in agreement with a study described in the literature,[6] which indicates that "empirical force fields, or molecular mechanics methods, have been developed for the investigations of structures and conformations of molecules". The molecular mechanics methods

Table 3. Experimental C_m–C_o, C_m–C_p, H_m–H_o and H_m–H_p values in *N*-phenyl rings for compounds **2a**–**2h** and calculated dihedral angles using MM^+



Compound	Phenyl group	$\|\Delta\delta\|$				MM^+ $\|\theta\|$
		C_m–C_o	C_m–C_p	H_m–H_o	H_m–H_p	
2a: $R_1=p\mathrm{FC_6H_4}$, $R_2=\mathrm{H}$, $R_3=\mathrm{H}$	A	10.5	3.0	0.21	0.16	13.08
2b: $R_1=\mathrm{H}$, $R_2=p\mathrm{FC_6H_4}$, $R_3=\mathrm{H}$	A	10.4	2.9	0.29	0.16	9.22
2c: $R_4=p\mathrm{FC_6H_4}$, $R_5=\mathrm{H}$, $R_6=\mathrm{H}$	A	4.0	1.3	0.05	0.02	43.84
2d: $R_4=\mathrm{H}$, $R_5=p\mathrm{FC_6H_4}$, $R_6=\mathrm{H}$	A	2.9	0.8	0.07	0.03	47.31
2e: $R_1=\mathrm{Ph}$, $R_2=\mathrm{H}$, $R_3=\mathrm{NO_2}$	A	9.7	2.1	0.22	0.13	10.90
2f: $R_1=\mathrm{H}$, $R_2=\mathrm{Ph}$, $R_3=\mathrm{NO_2}$	A	10.4	2.9	0.28	0.14	10.46
2g: $R_4=\mathrm{Ph}$, $R_5=\mathrm{H}$, $R_6=\mathrm{NO_2}$	A	3.8	1.2	0.06	–	44.27
2h: $R_4=\mathrm{H}$, $R_5=\mathrm{Ph}$, $R_6=\mathrm{NO_2}$	A	2.7	0.5	0.06	–	47.75
2a: $R_1=p\mathrm{FC_6H_4}$, $R_2=\mathrm{H}$, $R_3=\mathrm{H}$	B	10.6	2.9	0.28	0.18	11.71
2b: $R_1=\mathrm{H}$, $R_2=p\mathrm{FC_6H_4}$, $R_3=\mathrm{H}$	B	3.7	1.4	0.04	0.05	39.01
2c: $R_4=p\mathrm{FC_6H_4}$, $R_5=\mathrm{H}$, $R_6=\mathrm{H}$	B	10.6	2.6	0.24	0.15	13.93
2d: $R_4=\mathrm{H}$, $R_5=p\mathrm{FC_6H_4}$, $R_6=\mathrm{H}$	B	3.7	1.0	0.09	0.02	36.48

give greater accuracy than semiempirical methods, even for the modelling of transition states. Moreover, AMBER has been parameterized to reproduce ab initio potentials.

Values of $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ and $\delta_{meta\text{-C}}-\delta_{para\text{-C}}$, as well as the angles calculated using molecular mechanics, are collected in Table 3. Unfortunately, the assignments for the ^{1}H-NMR signals of most of the protons of the phenyl groups are described in the literature as multiplet (see Experimental section) and therefore it was not possible to obtain the differences in the proton chemical shifts. The use of homo- and heteronuclear shift correlation experiments, as well as NOE difference spectra, facilitates the assignment of the NMR signals of the aromatic protons of the phenyl groups. Thus, now we can obtain the values of $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$ and $\delta_{meta\text{-H}}-\delta_{para\text{-H}}$ for *N*-linked phenyl groups, and these values are shown in Table 3.

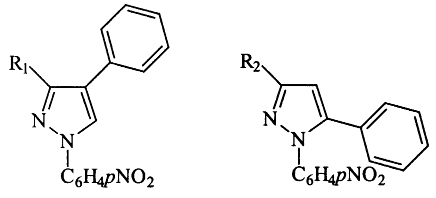
Table 4 shows the values of $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$, $\delta_{meta\text{-C}}-\delta_{para\text{-C}}$, $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$ and $\delta_{meta\text{-H}}-\delta_{para\text{-H}}$, as well as the calculated angles, for the *C*-linked phenyl groups. These data were obtained using the MacroModel program discussed above.

The smaller dispersion of the carbon chemical shifts of the *C*-linked phenyl groups is not unexpected and is responsible for the more difficult assignment of the chemical shift data of phenyl protons. Consequently, as can be seen from the data in Table 4, some of the differences mentioned above cannot be obtained.

Table 5 contains the linear correlation factors of the *N*-linked and *C*-linked phenylpyrazole derivatives from Tables 1–4.

Good linear correlation coefficients for the linear plots of the differences $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ versus calculated dihedral angles in *N*- and *C*-linked phenyl groups were obtained. The best linear correlation coefficients are shown in italics in Table 5 and these values are 0.911 for 19 data points in the linear plot of $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ in *N*-linked phenyl groups and 0.922

Table 4. Experimental C_m–C_o, C_m–C_p, H_m–H_o and H_m–H_p values in *C*-phenyl rings for compounds **2e**–**2h** and calculated dihedral angles using MM^+



Compound	$\|\Delta\delta\|$				MM^+ $\|\theta\|$
	C_m–C_o	C_m–C_p	H_m–H_o	H_m–H_p	
2e: R_1=4(1-phenyl)pyrazolyl	0.4	1.4	–	–	49.24
2g: R_1=5(1-phenyl)pyrazolyl	0.9	1.0	0.27	–	46.97
2f: R_2=4(1-phenyl)pyrazolyl	0.2	2.3	0.11	0.07	40.24
2h: R_2=5(1-phenyl)pyrazolyl	0.1	0.5	0.18	–	47.41

Table 5. Linear correlation factors for *N*- and *C*-phenyl groups

Linear correlation factors[a]			
		Parameter vs $\|\theta\|$	MM$^+$
N-Phenyl	Data from Table 3	$\|\delta C_m - \delta C_o\|$	*0.968* (12)
		$\|\delta C_m - \delta C_p\|$	0.897 (12)
	Data from Tables 1 and 3	$\|\delta H_m - \delta H_o\|$	0.857 (13)
		$\|\delta H_m - \delta H_p\|$	0.816 (11)
		$\|\delta C_m - \delta C_o\|$	*0.911* (19)
		$\|\delta C_m - \delta C_p\|$	0.849 (19)
C-Phenyl	Data from Tables 2 and 4	$\|\delta C_m - \delta C_o\|$	*0.922* (8)
		$\|\delta C_m - \delta C_p\|$	0.025 (8)

[a] Linear correlation factors extracted from linear plots of the differences of chemical shifts versus dihedral angles $|\theta|$ calculated for the computer method used. The values in parentheses show the number of data points of the linear correlations. The italic values are correlation factors >0.900.

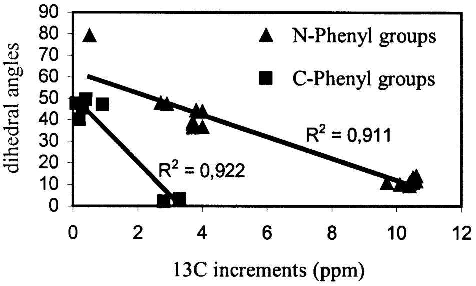


Figure 1. Linear plot $\delta_{meta\text{-}C}-\delta_{ortho\text{-}C}$ for *N*- and *C*-phenyl groups in compounds collected in Tables 1–4.

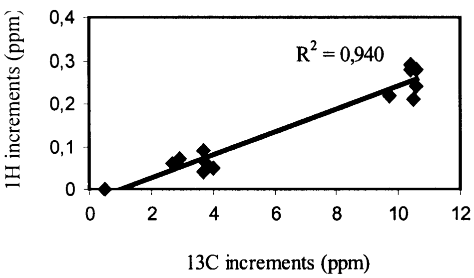


Figure 2. Linear plot $\delta_{meta\text{-}C}-\delta_{ortho\text{-}C}$ versus $\delta_{meta\text{-}H}-\delta_{ortho\text{-}H}$ for *N*-phenyl groups for compounds collected in Tables 1 and 3.

for 8 data points in the linear plot of $\delta_{meta\text{-}C}-\delta_{ortho\text{-}C}$ in *C*-linked phenyl groups (Fig. 1).

However, for the plots of the differences of $\delta_{meta\text{-}C}-\delta_{para\text{-}C}$, $\delta_{meta\text{-}H}-\delta_{ortho\text{-}H}$ and $\delta_{meta\text{-}H}-\delta_{para\text{-}H}$, correlation factors of <0.900 were observed and at the moment these values were rejected. From the linear correlations discussed above, it is possible to deduce equations (1) and (2), respectively, and these equations allow the prediction of the dihedral angles for similar compounds:

$$N\text{-linked} \quad |\theta| = -5.03|\delta C_m - \delta C_o| + 62.36, \quad N = 19, \quad R^2 = 0.911 \tag{1}$$

$$C\text{-linked} \quad |\theta| = -15.26|\delta C_m - \delta C_o| + 50.84, \quad N = 8, \quad R^2 = 0.922 \tag{2}$$

For all the *N*-linked phenyl groups present in compounds **1g** and **2a**–**2h**, a linear correlation between the increments of the proton and carbon chemical shifts was found [equation (3)]:

$$|\delta H_o - \delta H_m| = 0.027|\delta C_m - \delta C_o| - 0.0027, \quad N = 13, \quad R^2 = 0.940 \tag{3}$$

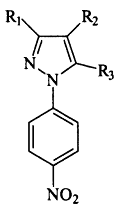
This equation allows the assignment of the phenyl carbons in cases where the chemical shifts of the corresponding protons are known, and vice versa, as shown in Fig. 2.

Moreover, the existence of linear correlations between $\delta_{meta\text{-}C}-\delta_{ortho\text{-}C}$ and the dihedral angle [equation (1)] and between $\delta_{meta\text{-}C}-\delta_{ortho\text{-}C}$ and $\delta_{meta\text{-}H}-\delta_{ortho\text{-}H}$ [equation (3)] make it possible to relate these two equations and a similar correlation between proton chemical shifts differences and dihedral angles can be established [equation (4)]:

$$|\theta| = -186.29|\delta H_m - \delta H_o| + 57.33 \tag{4}$$

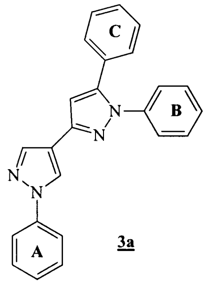
Pyrazole derivatives with *N*-substituted *p*-nitrophenyl groups (Table 6) show a good linear correlation between the $\delta_{meta\text{-}C}-\delta_{ortho\text{-}C}$, $\delta_{meta\text{-}H}-\delta_{ortho\text{-}H}$ and the dihedral angle

Table 6. Experimental C_m–C_o, C_m–C_p, H_m–H_o and H_m–H_p values in *N*-*p*-nitrophenyl groups for compounds **2*e***–**2*h***. Calculated dihedral angles using MM$^+$ and correlation factors

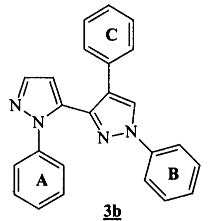


Compound	$\|\Delta\delta\|$		MM$^+$ $\|\theta\|$	Linear correlation factors	
	C_m–C_o	H_m–H_o		$\|\delta C_m - \delta C_o\|$ vs $\|\theta\|$	$\|\delta H_m - \delta H_o\|$ vs $\|\theta\|$
2e: R$_1$=4(1-phenyl)pyrazolyl, R$_2$=Ph, R$_3$=H	7.3	0.39	10.90	0.994	0.900
2f: R$_1$=4(1-phenyl)pyrazolyl, R$_2$=H, R$_3$=Ph	0.1	0.66	37.57		
2g: R$_1$=5(1-phenyl)pyrazolyl, R$_2$=Ph, R$_3$=H	6.9	0.46	13.50		
2h: R$_1$=5(1-phenyl)pyrazolyl, R$_2$=H, R$_3$=Ph	0.1	0.76	35.22		

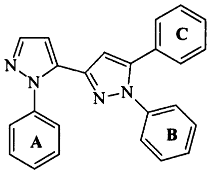
Table 7. Experimental and calculated C_m–C_o, C_m–C_p, H_m–H_o and H_m–H_p values in *N*-phenyl rings for compounds **3a**–**3c**. Calculated dihedral angles using MM^+ and equations (1) and (4)



3a



3b



3c

		$\|\Delta\delta\|$			$\|\theta\|$		
Compound	Ph N-linked	C_m–C_o (cal)[a]	C_m–C_o (exp)	ΔC_{m-o} (diff)	$\|\theta\|_{cal}$[a] $\|\delta C_m$–$\delta C_o\|$	$\|\theta\|_{MM}$ MM^+	$\Delta\|\theta\|_{diff}$ $\|\delta C_m$–$\delta C_o\|$
3a	A	10.8	*10.5*	0.3	9.55	*8.22*	1.33
3b	A	3.7	*4.0*	0.3	42.24	*43.96*	1.72
3c	A	3.0	*2.6*	0.4	49.28	*47.17*	2.11
3a	B	4.8	*3.1*	1.7	46.77	38.04	8.73
3b	B	9.7	*10.5*	0.8	9.55	*13.70*	4.15
3c	B	5.3	*3.7*	1.6	43.75	*35.64*	8.11

		$\|\Delta\delta\|$			$\|\theta\|$		
Compound	Ph N-linked	H_m–H_o (cal)[b]	H_m–H_o (exp)	ΔH_{m-o} (diff)	$\|\theta\|_{cal}$[b] $\|\delta H_m$–$\delta H_o\|$	$\|\theta\|_{MM}$ MM^+	$\Delta\|\theta\|_{diff}$ $\|\delta H_m$–$\delta H_o\|$
3a	A	0.26	*0.29*	0.03	3.31	*8.22*	4.91
3c	A	0.05	*0.08*	0.03	42.43	*47.17*	4.74
3b	B	0.23	*0.24*	0.01	12.62	*13.70*	1.08

[a] Calculated values from equation (1).

[b] Calculated values from equation (4).

θ, as shown in equations (5) and (6):

$$|\theta| = -3.46|\delta C_m\text{–}\delta C_o| + 36.76, \qquad N = 4, \qquad R^2 = 0.994 \tag{5}$$

$$|\theta| = -77.46|\delta H_m\text{–}\delta H_o| - 19.66, \qquad N = 4, \qquad R^2 = 0.900 \tag{6}$$

Equations (5) and (6) allow us to extend the scope of the predictions to include the angles of *N*-phenyl groups with a nitro group at the *para* position in pyrazole derivatives. This possibility is particularly interesting since the assignments for these protons and carbons are always relatively easy to make. Therefore, in compounds with similar structures to the pyrazoles it would be possible to predict interannular conjugation between the rings.

Finally, as an application of the relationships reported here [equations (1)–(4)], the differences $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$, $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$ and dihedral angles for *N*-linked phenyl groups, and the differences $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ and dihedral angles for *C*-linked phenyl groups, of the compounds shown in Table 7 were calculated in order to demonstrate the utility of these equations as a predictive tool.

Tables 7 and 8 show the differences observed between the experimental and calculated data. From these increments we can deduce that:

1. In phenyl groups of *N*-phenyl-substituted pyrazole derivatives:
   1.1. Using the $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ increments it is possible to predict the dihedral angles between phenyl and pyrazole aromatic rings with an error between 3° and 4°.
   1.2. Using the $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$ increments it is possible to predict the dihedral angles between phenyl and pyrazole aromatic rings with an error between 4° and 5°.
   1.3. Using the dihedral angle, calculated by molecular

Table 8. Experimental and calculated C_m–C_o and C_m–C_p values in *C*-phenyl rings for compounds **3a**–**3c**. Calculated dihedral angles using MM^+ and equation (2)

		$\|\Delta\delta\|$			$\|\theta\|$		
Compound	Ph *C*-linked	C_m–C_o (cal)[a]	C_m–C_o (exp)	ΔC_{m-o} (diff)	$\|\theta\|_{cal}$[a] $\|\delta C_m$–$\delta C_o\|$	$\|\theta\|_{MM}$ MM^+	$\Delta\|\theta\|_{diff}$ $\|\delta C_m$–$\delta C_o\|$
3a	C	0.4	*0.3*	0.1	46.26	*45.53*	0.73
3b	C	0.3	*1.0*	0.7	35.58	*46.88*	11.30
3c	C	0.3	*0.3*	0	46.26	*46.58*	0.32

[a] Calculated values from equation (2).

Table 9. Experimental and calculated [equation (3)] C_m–C_o, C_m–C_p, H_m–H_o and H_m–H_p values in *N*-phenyl rings for compounds **3a**–**3c**

		$\|\Delta\delta\|$					
Compound	*N*-Ph	C_m–C_o (cal)[a]	C_m–C_o (exp)	ΔC_{m-o} (diff)	H_o–H_m (cal)[a]	H_o–H_m (exp)	ΔH_{o-m} (diff)
3a	A	11.7	*10.5*	1.2	0.26	*0.29*	0.03
3b	A		*4.0*		0.08	–	
3c	A	2.0	*2.6*	0.6	0.04	*0.08*	0.04
3a	B		*3.1*		0.06	–	
3b	B	9.9	*10.5*	0.6	0.26	*0.24*	0.02
3c	B		*3.7*		0.07	–	

[a] Calculated values from equation (3).

   mechanics, it is possible to predict the $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ increments with an average error of 0.9 ppm.

   1.4. Using the dihedral angle, calculated by molecular mechanics, it is possible to predict the $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$ increments with an average error of 0.03 ppm.

2. In phenyl groups of *C*-phenyl-substituted pyrazole derivatives:

   2.1. Using the $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ increments it is possible to predict the dihedral angles between phenyl and pyrazole aromatic rings with an average error of 4°.

   2.2. Using the dihedral angle, calculated by molecular mechanics, it is possible to predict the $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ increments with an average error of 0.3 ppm.

Moreover, from the linear correlation observed between the increments of the carbon and proton chemical shifts at the *meta* and *ortho* positions [equation (3)], it is possible to estimate the errors between the calculated $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ and $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$ values and observed chemical shift increments.

The data in Table 9 show that we can predict, for the *N*-linked phenyl groups indicated, an increment of $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ and $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$ with a maximum difference of 1.2 and 0.04 ppm, respectively. These values allow us to make correct signal assignments for the ^{1}H- and ^{13}C-NMR spectra, even in crowded spectra where signal overlap usually makes the assignment difficult. In the phenyl groups of compounds **3b** (phenyl group type **A**), **3a** and **3c** (phenyl group type **B**), as shown in Table 9, it is not possible to determine the experimental values of the $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$, but the calculated values are all in agreement with the chemical shift intervals collected in the Experimental section.

3. Conclusions

The study reported here demonstrates that ^{1}H- and ^{13}C-NMR spectroscopy are useful tools for the study of the extent of interannular conjugation in *N*- or *C*-phenylpyrazoles. The combined data indicate that interannular conjugation is extensive in *N*-phenylpyrazoles if $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}>8$ ppm and $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}>0.2$ ppm, but impeded if $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}<4$ ppm and $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}<0.1$ ppm. In *C*-phenyl-substituted pyrazoles interannular conjugation is extensive if $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}>3$ ppm but impeded if $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}<1$ ppm.

To date only a limited number of compounds with dihedral angles from 2° to 79° have been studied in this context, including a few *C*-phenylpyrazole derivatives. Thus, application of the ^{1}H- and ^{13}C-NMR method to assess the extent of interannular conjugation in phenylpyrazoles is very likely to be useful in analogous cases.

Considering the origin of the different values observed, it seems likely that the ^{1}H- and ^{13}C-NMR method could also be put to good use for conformational studies of phenyl-substituted benzenes as well as for other phenyl-substituted heterocyclic rings.

On the other hand, a quick modelling of the molecular structure by MM$^+$ will predict quite accurately the intervals of $\delta_{meta\text{-C}}-\delta_{ortho\text{-C}}$ and $\delta_{meta\text{-H}}-\delta_{ortho\text{-H}}$, and these differences allow a complete assignment even for very complicated NMR spectra.

Finally, the PM3 theoretical level is unsatisfactory for the assignment of ground-state conformers and the calculation of conformational energy differences. This limitation could be anticipated given the poor performance of semiempirical models for other isodesmic processes. In many cases the models either yield the wrong ground-state conformer or produce energy differences that are far smaller than the corresponding experimental values. Semiempirical models do not yield reliable results in the heterocyclic systems included in the present study.

4. Experimental

Reagents were of commercial quality (ACROS) and were used without further purification. Compounds **1a**–**1c**,[3] **1d**–**1g**,[4] **2e**–**2h**,[5] and **3a**–**3c**[5] were previously described. Compounds **2a**–**2d** were prepared as described in Ref. 5 for the corresponding triphenyl derivatives **3a**–**3c**. Microwave irradiations were performed in a PROLABO Maxidigest MX350 modified with addition of an infrared pyrometer and connected to a computer. Reaction temperature and irradiation power were controlled by a software designed by our group.[7]

Chromatographic separations were performed on silica gel (Merck, type 60, 230–400 mesh). The spectral data of compounds **1a**–**1g** reported in Tables 1 and 2 were obtained from the literature[3,4] and the spectra were recorded in $CDCl_3$ unless stated otherwise.

^{1}H- and ^{13}C-NMR spectra were recorded at 299.94 MHz and 75.429 MHz, respectively, on a Varian Unity 300 spectrometer. The chemical shifts of the signals (**2a**–**2h** and **3a**–**3c**) reported in Tables 3, 4 and 6–8 were recorded in CDCl$_3$. Signal assignments of the ^{1}H- and ^{13}C-NMR spectra were done by homo- and heteronuclear shift correlation experiments such as COSY, HETCOR and NOE difference spectra. In all cases chemical shifts are reported in ppm (δ) using Me$_4$Si as the internal reference and coupling constants J are given in Hz.

4.1. Computational methods

The minimum energy conformation of each compound was computed using the AMBER force field[8] as implemented in the MacroModel 5.0 suite of programs.[9] The different possible conformers were optimized and then Monte Carlo[10] simulations were performed on 1000 structures. Moreover, the most stable conformers were optimized with semi-empirical methods. These calculations were carried out with the PM3 Hamiltonian[11] with the standard parameters[12] as implemented in the MOPAC 6.0 package.[13] All stationary points were refined by minimization of the gradient norm of the energy to at least below 0.01 kcal mol^{-1}. The PM3 Hamiltonians were used in view of their superior ability to model the particular feature of the nitro groups.[14]

4.2. 1-Phenylpyrazole (1a)[3]

^{13}C NMR (CDCl$_3$, δ) 107.6 (C-4), 119.4 (*o*-C 1-Ph), 126.5 (*p*-C 1-Ph), 126.8 (C-5), 129.5 (*m*-C 1-Ph), 140.5 (*ipso*-C 1-Ph) and 141.1 (C-3).

4.3. 3-Methyl-1-phenylpyrazole (1b)[3]

^{13}C NMR (CDCl$_3$, δ) 13.7 (CH$_3$), 107.6 (C-4), 118.6 (*o*-C 1-Ph), 126.0 (*p*-C 1-Ph), 127.4 (C-5), 129.1 (*m*-C 1-Ph), 139.9 (*ipso*-C 1-Ph) and 150.7 (C-3).

4.4. 5-Methyl-1-phenylpyrazole (1c)[3]

^{13}C NMR (CDCl$_3$, δ) 14.6 (CH$_3$), 106.3 (C-4), 124.5 (*o*-C 1-Ph), 127.5 (*p*-C 1-Ph), 128.5 (*m*-C 1-Ph), 135.3 (C-5) and 139.4 (C-3).

4.5. 1,3-Diphenylpyrazole (1d)[4]

^{1}H NMR (CDCl$_3$, δ) 6.79 (d, J=2.5 Hz, 1H, H-4), 7.28–7.52 (m, 6H, *m*-H 1-Ph, *p*-H 1-Ph, *m*-H 3-Ph, *p*-H 3-Ph), 7.78 (2H, *o*-H 1-Ph), 7.93 (2H, *o*-H 3-Ph), 7.97 (d, J=2.5 Hz, 1H, H-5); ^{13}C NMR (CDCl$_3$, δ) 104.9 (C-4), 118.9 (*o*-C 1-Ph), 125.7 (*o*-C 3-Ph), 126.2 (*p*-C 1-Ph), 127.9 (C-5 and *p*-C 3-Ph), 128.5 (*m*-C 3-Ph), 129.3 (*m*-C 1-Ph), 132.9 (*ipso*-C 3-Ph), 140.1 (*ipso*-C 1-Ph) and 152.8 (C-3). ^{13}C NMR (DMSO-d_6, δ) 105.5 (C-4), 118.3 (*o*-C 1-Ph), 125.6 (*o*-C 3-Ph), 126.3 (*p*-C 1-Ph), 128.1 (*p*-C 3-Ph), 128.8 (*m*-C 3-Ph), 129.4 (C-5), 129.6 (*m*-C 1-Ph), 132.8 (*ipso*-C 3-Ph), 139.7 (*ipso*-C 1-Ph) and 152.0 (C-3).

4.6. 1,5-Diphenylpyrazole (1e)[4]

^{1}H NMR (CDCl$_3$, δ) 6.51 (d, J=1.8 Hz, 1H, H-4), 7.20–7.33 (m, 10H, *o*-H 1-Ph, *m*-H 1-Ph, *p*-H 1-Ph, *o*-H 1-Ph, *m*-H 3-Ph, *p*-H 3-Ph), 7.73 (d, J=1.8 Hz, 1H, H-3); ^{13}C NMR (CDCl$_3$, δ) 107.5 (C-4), 124.8 (*o*-C 1-Ph), 127.0 (*p*-C 5-Ph), 127.8 (*p*-C 1-Ph), 128.1 (*m*-C 5-Ph), 128.4 (*o*-C 5-Ph), 128.5 (*m*-C 1-Ph), 130.2 (*ipso*-C 5-Ph), 139.8 (*ipso*-C 1-Ph), 139.9 (C-3) and 142.6 (C-5). ^{13}C NMR (DMSO-d_6, δ) 108.1 (C-4), 125.1 (*o*-C 1-Ph), 127.5 (*p*-C 1-Ph), 128.2 (*p*-C 5-Ph), 128.3 (*m*-C1-Ph), 128.5 (*o*-C 5-Ph), 128.9 (*m*-C 5-Ph), 130.2 (*ipso*-C 5-Ph), 139.9 (*ipso*-C 1-Ph), 140.2 (C-3) and 142.1 (C-5).

4.7. 1,3,5-Triphenylpyrazole (1f)[4]

^{13}C NMR (DMSO-d_6, δ) 105.4 (C-4), 125.4 (*o*-C 3-Ph), 125.5 (*o*-C 1-Ph), 127.9 (*p*-C 1-Ph), 128.2 (*p*-C 3-Ph), 128.6 (*o*-C 5-Ph), 128.7 (*m*-C 3-Ph), 128.9 (*m*-C 5-Ph), 129.0 (*p*-C 5-Ph), 129.2 (*m*-C 1-Ph), 130.1 (*ipso*-C 5-Ph), 132.8 (*ipso*-C 3-Ph), 139.9 (*ipso*-C 1-Ph), 144.3 (C-5) and 151.2 (C-3).

4.8. 3,5-Di-*tert*-butyl-1-phenylpyrazole (1g)[4]

^{1}H NMR (CDCl$_3$, δ) 1.15 (s, 9H, 5-*t*-C$_4$H$_9$), 1.32 (s, 9H, 3-*t*-C$_4$H$_9$), 6.00 (s, 1H, H-4), 7.39 (s, 5H, *o*-H, *m*-H and *p*-H 1-Ph); ^{13}C NMR (CDCl$_3$, δ) 30.6 (CH$_3$, 3-*t*-C$_4$H$_9$), 30.9 (CH$_3$, 5-*t*-C$_4$H$_9$), 31.8 (C, 3-*t*-C$_4$H$_9$), 31.9 (CH$_3$, 5-*t*-C$_4$H$_9$), 100.2 (C-4), 128.5 (*m*-C 1-Ph), 128.7 (*p*-C 1-Ph), 129.0 (*o*-C 1-Ph), 142.6 (*ipso*-C 1-Ph), 153.0 (C-5), 160.3 (C-3). ^{13}C NMR (DMSO-d_6, δ) 30.5 (CH$_3$, 3-*t*-C$_4$H$_9$), 30.6 (CH$_3$, 5-*t*-C$_4$H$_9$), 31.5 (C, 3-*t*-C$_4$H$_9$), 31.7 (C, 5-*t*-C$_4$H$_9$), 100.0 (C-4), 128.5 (*m*-C 1-Ph), 128.8 (*m*-C and *p*-C 1-Ph), 142.3 (*ipso*-C 1-Ph), 152.6 (C-5), 159.1 (C-3).

4.9. 1,1′-Diphenyl-4′-(*p*-fluorophenyl)-[4,3′]-bipyrazole (2a) and 1,1′-diphenyl-5′-(*p*-fluorophenyl)-[4,3′]-bipyrazole (2b)

A mixture of 4-formyl-1-phenylpyrazole phenylhydrazone (200 mg, 0.76 mmol and *p*-fluoro-β-nitrostyrene (254 mg, 1.52 mmol) was irradiated in a focused microwave reactor at 270 W for 10 min at 130°C. The crude mixture was purified by flash chromatography (hexane:ethyl acetate 4:1) giving **2b** (145 mg, 51%) and **2a** (48 mg, 21%).

Data for **2a**: mp 108–109°C (from methanol). ^{1}H NMR (CDCl$_3$, δ) 7.11 (dd, J=8.3, 8.9 Hz, 2H, *m*-H 4′-Ph), 7.28 (t, J=8.2 Hz, 1H, *p*-H 1-Ph), 7.30 (t, J=7.5 Hz, 1H, *p*-H 1′-Ph), 7.40–7.50 (m, 6H, *m*-H 1-Ph, *m*-H 1′-Ph, *o*-H 4′-Ph), 7.42 (*o*-H 4′-Ph),[15] 7.44 (*m*-H 1-Ph),[15] 7.48 (*m*-H 1′-Ph),[15] 7.65 (d, J=8.0 Hz, 2H, *o*-H 1-Ph), 7.76 (d, J=8.3 Hz, 2H, *o*-H 1′-Ph), 7.83 (s, 1H, H-3), 7.95 (s, 1H, H-5′), 8.11 (s, 1H, H-5); ^{13}C NMR (CDCl$_3$, δ) 115.6 (d, J_{CF}=21.7 Hz, *m*-C4′-Ph), 116.6 (C-4), 118.8 (*o*-C 1′-Ph), 118.9 (*o*-C 1-Ph), 121.7 (C-4′), 124.8 (C-5), 126.5 (C-5′, *p*-C 1-Ph, *p*-C 1′-Ph), 128.5 (*ipso*-C 4′-Ph), 129.4 (*m*-C 1′-Ph), 129.5 (*m*-C 1-Ph), 130.5 (d, J_{CF}=8.1 Hz, *o*-C 4′-Ph), 139.7, 139.8 (*ipso*-C 1-Ph, *ipso*-C 1′-Ph), 140.0 (C-3), 143.2 (C-3′), 162.2 (d, J_{CF}= 246.7 Hz, *p*-C 4′-Ph). Anal. Calc for C$_{24}$H$_{17}$N$_4$F: C, 75.76; H, 4.51; N, 14.73. Found: C, 75.75; H, 4.50; N, 14.74.

Data for **2b**: mp 122–123°C (from methanol). ^{1}H NMR (CDCl$_3$, δ) 6.65 (s, 1H, H-4′), 7.01 (dd, J=8.3, 8.9 Hz, 2H, *m*-H 5′-Ph), 7.24 (dd, J=5.2, 8.9 Hz, 2H, *o*-H 5′-Ph), 7.29–7.39 (m, 4H, *p*-H 1-Ph, *m*-H 1′-Ph, *p*-H 1′-Ph), 7.30 (*p*-H 1-Ph),[15] 7.31 (*p*-H 1′-Ph),[15] 7.36 (*m*-H 1′-Ph),[15] 7.46 (t, *J*=7.9 Hz, 2H, *m*-H 1-Ph), 7.75 (d, *J*=7.9 Hz, 2H, *o*-H 1-Ph), 8.10 (s, 1H, H-3), 8.37 (s, 1H, H-5); ^{13}C NMR (CDCl$_3$, δ) 105.3 (C-4′), 115.6 (d, J_{CF}=21.7 Hz, *m*-C 5′-Ph), 117.6 (C-4), 119.0 (*o*-C 1-Ph), 123.9 (C-5), 125.3 (*o*-C 1′-Ph), 126.5 (*p*-C 1-Ph), 127.6 (*p*-C 1′-Ph), 129.0 (*m*-C 1′-Ph and *ipso*-C 5′-Ph), 129.4 (*m*-C 1-Ph), 130.5 (d, J_{CF}=8.6 Hz, *o*-C 5′-Ph), 139.2 (C-3), 139.8, 140.0 (*ipso*-C 1-Ph, *ipso*-C 1′-Ph), 143.2 (C-3′), 145.0 (C-5′), 162.5 (d, J_{CF}= 249.3 Hz, *p*-C 5′-Ph). Anal. Calc for $\mathrm{C_{24}H_{17}N_4F}$: C, 75.76; H, 4.51; N, 14.73. Found: C, 75.77; H, 4.49; N, 14.70.

4.10. 1,1′-Diphenyl-4′-(*p*-fluorophenyl)-[5,3′]-bipyrazole (2c) and 1,1′-diphenyl-5′-(*p*-fluorophenyl)-[5,3′]-bipyrazole (2d)

A mixture of 5-formyl-1-phenylpyrazole phenylhydrazone (200 mg, 0.76 mmol and *p*-fluoro-β-nitrostyrene (254 mg, 1.52 mmol) was irradiated in a focused microwave reactor at 150 W for 15 min at 130°C. The crude mixture was purified by flash chromatography (hexane:ethyl acetate 4:1) giving **2d** (29 mg, 12%) and **2c** (74 mg, 30%).

Data for **2c**: yellow oil. ^{1}H NMR (CDCl$_3$, δ) 6.70 (d, *J*=1.9 Hz, 1H, H-4), 6.79 (m, 2H, *m*-H 4′-Ph), 6.81 (m, 2H, *o*-H 4′-Ph), 7.04–7.12 (m, 5H, *o*-H 1-Ph, *m*-H 1-Ph, *p*-H 1-Ph), 7.06 (*o*-H 1-Ph),[15] 7.09 (*p*-H 1-Ph),[15] 7.11 (*m*-H 1-Ph),[15] 7.32 (t, *J*=7.6 Hz, 1H, *p*-H 1′-Ph), 7.47 (t, *J*=7.6 Hz, 2H, *m*-H 1′-Ph), 7.71 (d, *J*=7.6 Hz, 2H, *o*-H 1′-Ph), 7.77 (d, *J*=1.9 Hz, 1H, H-3), 7.93 (s, 1H, H-5′); ^{13}C NMR (CDCl$_3$, δ) 109.4 (C-4), 115.2 (d, J_{CF}=21.6 Hz, *m*-C 4′-Ph), 118.9 (*o*-C 1′-Ph), 124.2 (*o*-C 1-Ph), 125.4 (C-5′), 126.9 (*p*-C 1-Ph, *p*-C 1′-Ph), 128.2 (*m*-C 1-Ph), 129.0 (d, J_{CF}=8.1 Hz, *o*-C 4′-Ph), 129.5 (*m*-C 1′-Ph), 140.4 (C-3), 161.8 (d, J_{CF}=246.3 Hz, *p*-C 4′-Ph) and 123.7, 127.4, 134.8, 139.5, 139.8, 141.6 (C-5, C-3′, C-4′, *ipso*-C 1-Ph, *ipso*-C 1′-Ph, *ipso*-C 4′-Ph). Anal. Calc for $\mathrm{C_{24}H_{17}N_4F}$: C, 75.76; H, 4.51; N, 14.73. Found: C, 75.74; H, 4.50; N, 14.73.

Data for **2d**: yellow oil. ^{1}H NMR (CDCl$_3$, δ) 6.03 (s, 1H, H-4′), 6.83 (d, *J*=1.8 Hz, 1H, H-4), 6.96 (dd, *J*=8.3, 9.0 Hz, 2H, *m*-H 5′-Ph), 7.08 (dd, *J*=5.3, 9.0 Hz, 2H, *o*-H 5′-Ph), 7.23 (m, 2H, *o*-H 1′-Ph), 7.28–7.34 (m, 3H, *m*-H 1′-Ph, *p*-H 1′-Ph), 7.30 (*p*-H 1′-Ph),[15] 7.32 (*m*-H 1′-Ph),[15] 7.42 (t, *J*= 8.1 Hz, 1H, *p*-H 1-Ph), 7.45 (t, *J*=8.1 Hz, 2H, *m*-H 1-Ph), 7.52 (d, *J*=8.1 Hz, 2H, *o*-H 1-Ph), 7.73 (d, *J*=1.8 Hz, 1H, H-3); ^{13}C NMR (CDCl$_3$, δ) 107.2 (C-4 and C-4′), 115.5 (d, J_{CF}=21.6 Hz, *m*-C5′-Ph), 125.1 (*o*-C1′-Ph), 125.4 (C-5′), 126.0 (*o*-C 1-Ph), 127.8 (*p*-C 1′-Ph), 128.1 (*p*-C 1-Ph), 128.8 (*m*-C 1′-Ph), 128.9 (*m*-C 1-Ph), 130.4 (d, J_{CF}= 8.5 Hz, *o*-C 5′-Ph), 140.3 (C-3), 162.5 (d, J_{CF}=244.5 Hz, *p*-C 5′-Ph) and 128.3, 136.3, 139.4, 140.2, 142.6, 142.9 (C-5, C-3′, C-5′, *ipso*-C 1-Ph, *ipso*-C 1′-Ph, *ipso*-C 5′-Ph). Anal. Calc for $\mathrm{C_{24}H_{17}N_4F}$: C, 75.76; H, 4.51; N, 14.73. Found: C, 75.75; H, 4.50; N, 14.70.

4.11. 1′-(*p*-Nitrophenyl)-1,4′-diphenyl-[4,3′]-bipyrazole (2e)[5]

^{1}H NMR (CDCl$_3$, δ) 7.28–7.56 (m, 8H, *o*-H 4′-Ph, *m*-H 4′-Ph, *p*-H 4′-Ph, *m*-H 1-Ph, *p*-H 1-Ph), 7.32 (*p*-H 1-Ph),[15] 7.45 (*m*-H 1-Ph),[15] 7.67 (d, *J*=8.3 Hz, 2H, *o*-H 1-Ph), 7.90 (s, 1H, H-3), 7.98 (d, *J*=9.2 Hz, 2H, *o*-H 1′-Ph), 8.09 (s, 1H, H-5′), 8.12 (s, 1H, H-5), 8.37 (d, *J*=9.2 Hz, 2H, *m*-H 1′-Ph); ^{13}C NMR (CDCl$_3$, δ) 118.1 (*o*-C 1′-Ph), 119.1 (*o*-C 1-Ph), 125.2 (C-5), 125.4 (*m*-C 1′-Ph), 126.5 (C-5′), 126.7 (*p*-C 1-Ph), 128.0 (*p*-C 4′-Ph), 128.8 (*m*-C 1-Ph), 129.0 (*o*-C 4′-Ph), 129.4 (*m*-C 4′-Ph), 140.1 (C-3), 116.1, 119.9 (C-4 and C-4′) and 124.6, 128.3, 129.7, 131.8, 144.1 (C-3′, *p*-C 1′-Ph, *ipso*-C 1-Ph, *ipso*-C 1′-Ph and *ipso*-C 4′-Ph).

4.12. 1′-(*p*-Nitrophenyl)-1,5′-diphenyl-[4,3′]-bipyrazole (2f)[5]

^{1}H NMR (CDCl$_3$, δ) 6.71 (s, 1H, H-4′), 7.28–7.49 (m, 8H, *o*-H 5′-Ph, *m*-H 5′-Ph, *p*-H 5′-Ph, *m*-H 1-Ph, *p*-H 1-Ph), 7.29 (*o*-H 5′-Ph),[15] 7.33 (*p*-H 1-Ph),[15] 7.40 (*m*-H and *p*-H 5′-Ph),[15] 7.47 (*m*-H 1-Ph),[15] 7.52 (d, *J*=9.2 Hz, 2H, *o*-H 1′-Ph), 7.75 (d, *J*=7.6 Hz, 2H, *o*-H 1-Ph), 8.11 (s, 1H, H-3), 8.18 (d, *J*=9.2 Hz, 2H, *m*-H 1′-Ph), 8.38 (s, 1H, H-5); ^{13}C NMR (CDCl$_3$, δ) 107.4 (C-4′), 117.0 (C-4), 119.0 (*o*-C 1-Ph), 124.1 (C-5), 124.3 (*o*-C 1′-Ph), 124.4 (*m*-C 1′-Ph), 139.2 (C-3), 126.6 (*p*-C 1-Ph and *p*-C 5′-Ph), 128.7 (*o*-C 5′-Ph), 128.9 (*m*-C 5′-Ph), 129.4 (*p*-C 1-Ph) and 129.1, 139.8, 144.7, 145.7, 146.4 (C-3′, C-5′, *p*-C1′-Ph, *ipso*-C 1-Ph, *ipso*-C 1′-Ph and *ipso*-C 5′-Ph).

4.13. 1′-(*p*-Nitrophenyl)-1,4′-diphenyl-[5,3′]-bipyrazole (2g)[5]

^{1}H NMR (CDCl$_3$, δ) 6.69 (d, *J*=1.8 Hz, 1H, H-4), 6.91 (d, *J*=7.6 Hz, 2H, *o*-H4′-Ph), 7.06–7.20 (m, 8H, *o*-H 1-Ph, *m*-H 1-Ph, *p*-H 1-Ph, *m*-H 4′-Ph, *p*-H 4′-Ph), 7.06 (*o*-H 1-Ph),[15] 7.12 (*m*-H 1-Ph),[15] 7.18 (*m*-H 4′-Ph),[15] 7.78 (d, *J*=1.8 Hz, 1H, H-3), 7.87 (d, *J*=9.1 Hz, 2H, *o*-H 1′-Ph), 8.05 (s, 1H, H-5′), 8.33 (d, *J*=9.1 Hz, 2H, *m*-H 1′-Ph); ^{13}C NMR (CDCl$_3$, δ) 109.5 (C-4), 118.4 (*o*-C 1′-Ph), 124.5 (*o*-C 1-Ph), 125.3 (*m*-C 1′-Ph), 125.5 (C-5′), 127.1 (*p*-C 1-Ph), 127.4 (*p*-C 4′-Ph), 127.5 (*o*-C 4′-Ph), 128.3 (*m*-C 1-Ph), 128.4 (*m*-C 4′-Ph), 140.4 (C-3) and 126.3, 128.9, 129.4, 130.5, 134.2, 139.8, 143.7 (C-5, C-3′, C-4′, *p*-C 1′-Ph, *ipso*-C 1-Ph, *ipso*-C 1′-Ph and *ipso*-C 4′-Ph).

4.14. 1′-(*p*-Nitrophenyl)-1,5′-diphenyl-[5,3′]-bipyrazole (2h)[5]

^{1}H NMR (CDCl$_3$, δ) 6.15 (s, 1H, H-4′), 6.85 (d, *J*=1.7 Hz, 1H, H-4), 7.16 (d, *J*=7.8 Hz, 2H, *o*-H 5′-Ph), 7.31–7.54 (m, 10H, *o*-H 1-Ph, *m*-H 1-Ph, *p*-H 1-Ph, *o*-H 1′-Ph, *m*-H 4′-Ph, *p*-H 4′-Ph), 7.34 (*m*-H 4′-Ph),[15] 7.39 (*o*-H 1′-Ph),[15] 7.46 (*m*-H 1-Ph),[15] 7.52 (*o*-H 1-Ph),[15] 7.76 (d, *J*= 1.7 Hz, 1 H, H-3), 8.15 (d, *J*=8.8 Hz, 2 H, *m*-H 1′-Ph); ^{13}C NMR (CDCl$_3$, δ) 107.5 (C-4), 109.0 (C-4′), 124.3 (*o*-C 1′-Ph), 124.4 (*m*-C 1′-Ph), 128.8 (*o*-C 5′-Ph), 140.3 (C-3), 126.1 (*o*-C 1-Ph), 128.3 (*p*-C 1-Ph), 128.8 (*m*-C 1-Ph and *o*-C 5′-Ph), 128.9 (*m*-C 5′-Ph), 129.4 (*p*-C 5′-Ph) and 125.6, 129.2, 135.7, 144.1, 144.2, 144.3, 146.1 (C-5, C-3′, C-5′, *p*-C 1′-Ph, *ipso*-C 1-Ph, *ipso*-C 1′-Ph and *ipso*-C 4′-Ph).

4.15. 1,1′,5′-Triphenyl-[4,3′]-bipyrazole (3a)[5]

^{1}H NMR (CDCl$_3$, δ) 6.68 (s, 1H, H-4′), 7.24–7.35 (m, 11H, *p*-H 1-Ph, *o*-H 1′-Ph, *m*-H 1′-Ph, *p*-H 1′-Ph, *o*-H 5′-Ph, *m*-H 5′-Ph, *p*-H 5′-Ph), 7.28 (*p*-H 1-Ph),[15] 7.46 (d, *J*=7.6 Hz, 2H, *m*-H 1-Ph), 7.75 (d, *J*=7.6 Hz, 2H, *o*-H 1-Ph), 8.11 (s, 1H, H-3), 8.38 (s, 1H, H-5); ^{13}C NMR (CDCl$_3$, δ) 105.3 (C-4′), 117.7 (C-4), 118.9 (*o*-C 1-Ph), 123.8 (C-5), 125.3 (*o*-C 1′-Ph), 126.4, 127.4, 128.3 (*p*-C 1-Ph, *p*-C 1′-Ph and *p*-C 5′-Ph), 128.4 (*m*-C 1′-Ph), 128.6 (*o*-C 5′-Ph), 128.9 (*m*-C 5′-Ph), 129.4 (*m*-C 1-Ph), 130.3 (*ipso*-C 5′-Ph), 139.2 (C-3), 140.0 (*ipso*-C 1-Ph and 1′-Ph), 144.1 and 144.9 (C-3′ and C-5′).

4.16. 1,1′,4′-Triphenyl-[5,3′]-bipyrazole (3b)[5]

^{1}H NMR (CDCl$_3$, δ) 6.70 (d, *J*=2.0 Hz, 1H, H-4), 6.90 (m, 2H, *o*-H 4′-Ph), 7.08–7.17 (m, 8H, *o*-H 1-Ph, *m*-H 1-Ph, *p*-H 1-Ph, *m*-H 4′-Ph, *p*-H 4′-Ph), 7.15 (*m*-H 4′-Ph),[15] 7.33 (t, *J*=7.8 Hz, 1H, *p*-H 1′-Ph), 7.48 (t, *J*=7.8 Hz, 2H, *m*-H 1′-Ph), 7.72 (d, *J*=7.8 Hz, 2H, *o*-H 1′-Ph), 7.78 (d, *J*=2.0 Hz, 1H, H-3), 7.98 (s, 1H, H-5′); ^{13}C NMR (CDCl$_3$, δ) 109.5 (C-4), 119.0 (*o*-C 1′-Ph), 124.3 (*o*-C 1-Ph), 125.4 (C-5′), 126.8 (*p*-C 1-Ph, *p*-C 1′-Ph and *p*-C 4′-Ph), 127.3 (*o*-C 4′-Ph), 128.3 (*m*-C 1-Ph and *m*-C 4′-Ph), 129.5 (*m*-C 1′-Ph), 140.3 (C-3) and 124.8, 131.4, 135.0, 139.6, 139.9, 141.7 (*ipso*-C 1-Ph, *ipso*-C 1′-Ph, *ipso*-C 4′-Ph, C-5, C-3′ and C-4′).

4.17. 1,1′,5′-Triphenyl-[5,3′]-bipyrazole (3c)[5]

^{1}H NMR (CDCl$_3$, δ) 6.06 (s, 1H, H-4′), 6.84 (d, *J*=2.0 Hz, 1H, H-4), 7.12 (d, *J*=7.6 Hz, 2H, *o*-H 5′-Ph), 7.22–7.34 (m, 9H, *o*-H 1′-Ph, *m*-H 1′-Ph, *p*-H 1′-Ph, *m*-H 5′-Ph, *p*-H 5′-Ph), 7.26 (*m*-H 5′-Ph),[15] 7.40–7.48 (m, 3H, *m*-H 1-Ph, *p*-H 1-Ph), 7.43 (*p*-H 1-Ph),[15] 7.45 (*m*-H 1-Ph),[15] 7.53 (d, *J*=8.1 Hz, 2H, *o*-H 1-Ph), 7.73 (d, *J*=2.0 Hz, 1H, H-3); ^{13}C NMR (CDCl$_3$, δ) 107.2 (C-4′), 107.3 (C-4), 125.1 (*o*-C 1′-Ph), 126.1 (*o*-C 1-Ph), 127.6, 127.9, 128.0 (*p*-C 1-Ph, *p*-C 1′-Ph, *p*-C 5′-Ph), 128.4 (*o*-C 5′-Ph), 128.7 (*m*-C 1-Ph and *m*-C 5′-Ph), 128.8 (*m*-C 1′-Ph), 140.3 (C-3) and 129.9, 136.4, 139.6, 140.4, 142.9, 143.6 (*ipso*-C 1-Ph, *ipso*-C 1′-Ph, *ipso*-C 5′-Ph, C-5, C-3′ and C-5′).

Acknowledgements

This work was supported by the Spanish DGSIC (Grants PB97-0429) and by the Basque Government (Grant EX1998-126).

References

1. Fong, C. W. *Aust. J. Chem.* **1980**, *33*, 1763.
2. Begtrup, M. *Acta Chem. Scand.* **1973**, *27*, 3101.
3. Echévarría, A.; Elguero, J.; Meutermans, W. *J. Heterocycl. Chem.* **1993**, *30*, 957.
4. Begtrup, M.; Vedsø, P.; Cabildo, P.; Claramunt, R. M.; Elguero, J.; Meutermans, W. *Magn. Reson. Chem.* **1992**, *30*, 455.
5. Arrieta, A.; Carrillo, J. R.; Cossío, F. P.; Díaz-Ortíz, A.; Gómez-Escalonilla, M. J.; de la Hoz, A.; Langa, F.; Moreno, A. *Tetrahedron* **1998**, *54*, 13167.
6. Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439.
7. Software MPX-2 from PACAM.
8. (a) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Chio, C.; Alagona, G.; Profeta, S.; Weiner, P. *J. Am. Chem. Soc.* **1984**, *106*, 765. (b) Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.
9. Mohamadi, F.; Richards, N. G. S.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. J. MacroModel v5.0. *J. Comput. Chem.* **1990**, *11*, 440.
10. (a) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. (b) Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. *J. Am. Chem. Soc.* **1990**, *112*, 1419.
11. Stewart, J. J. P. J. *Compt. Chem.* **1984**, *10*, 209.
12. (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209. (b) Stewart, J. J. P. *J. Comput. Chem.* **1991**, *11*, 541.
13. (a) Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 101. (b) Stewart, J.J.P. *QCPE* No. 455. Indiana University, Bloomington, IN.
14. (a) Stewart, J. J. P. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1. (b) Dewar, M. J. S.; Healy, E. F.; Holder, A. J.; Yuan, Y.-C. *J. Comput.Chem.* **1990**, *11*, 541.
15. Values measured in the 2D-NMR spectra.