Multidentate ligands from *N*-hydroxy-and *N*-aminopyrazole

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Dedicated to our friend Professor Enrique Meléndez on his 70th anniversary
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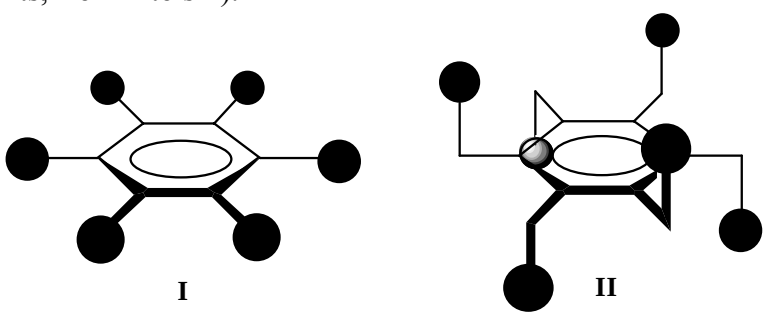
Abstract

The reaction between hexafluorobenzene and the anion of 1-hydroxypyrazole affords a mixture of the products of bis-, tetrakis- and hexakis-substitution. On the other hand the anion of 1-aminopyrazole affords only the product of monosubstitution probably due to the acidity of the remaining NH. Finally, in the case of hexakis(bromomethyl)benzene, its reaction with 1-hydroxypyrazole lead to the hexakis-substituted product. All compounds have been characterized by NMR (^{1}H and ^{13}C) and mass spectrometry.

Keywords: *N*-Hydroxy- and *N*-amino-pyrazole ligands, propellenes, hexakis(bromomethyl)benzene

Introduction

The ligands with the *N*-pyrazolylbenzene structure belong to two families, that where the pyrazole is directly linked to the phenyl ring and that where there is a spacer between the pyrazole and the benzene (Scheme 1). The first family is represented by the compounds **I** we called "propellenes",[1-12] such as hexakis(pyrazol-1-yl)benzene. There are many possibilities for the second family but the most significant representatives are compounds **II** [CH_2 as a linker, poly(pyrazol-1-ylmethyl)benzenes] studied by Steel and others (the black circles represent 1-pyrazolyl substituents, from 1 to six).[13-20]



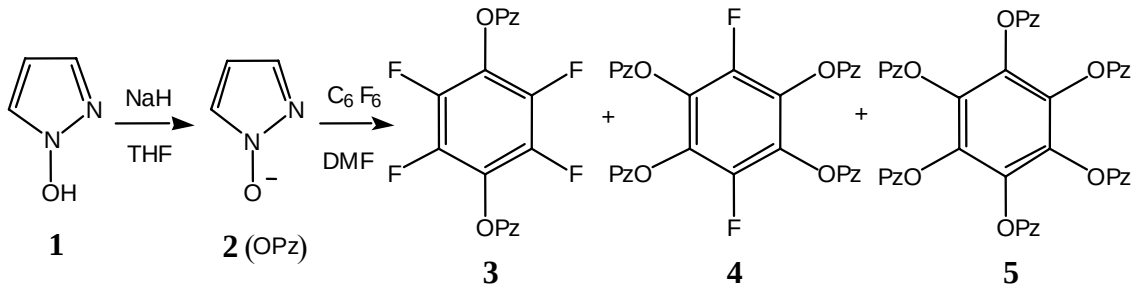
I **II**

Scheme 1

The second class, owing to their increased flexibility, is more suitable as metal ligands in coordination chemistry as well as guests in host-guest chemistry. We report in the present publication our attempts to replace the CH_2 "ball-and-socket joint" of **II** by an O atom or a NH group or even by a CH_2-O spacer. The presence of a supplementary O or N atom with their lone pairs could modify or even improve the above mentioned properties.

Results and Discussion

The reaction of 1-hydroxypyrazole **1** in basic conditions (1-hydroxypyrazolate **2**) with hexafluorobenzene in THF/DMF in different conditions always affords a mixture of three compounds **3**, **4** and **5** (Scheme 2).



Scheme 2

Mass spectrometry (exact mass) or elemental analyses, and ^{1}H and ^{13}C NMR (see NMR discussion) identified the three compounds. The reaction was carried out with ratios 1-hydroxypyrazole/hexafluoro-benzene of 6/1 and 12/1 and with different reaction times (Table 1). The relative amounts were determined by ^{1}H NMR including the non reacted pyrazolate **2** and then converted to relative amounts not considering **2** (see note [a] in Table 1).

Table 1. Reaction between **1** and hexafluorobenzene (ratios defined as **1**/C_6F_6), reaction time, and relative amounts in % (total 100%)

Ratio	Time, h	Starting **2**	Bis **3**	Tetrakis **4**	Hexakis **5**
6/1	3	64.8	11.2	20.5	3.5
	27	47.8	19.5	25.5	7.2
	46	43.4	22.9	26.5	7.2
6/1[a]	3	-----	32.0	58.0	10.0
	27	-----	37.5	48.8	13.7
	46	-----	40.4	46.8	12.8
12/1	1.5	65.3	20.0	6.7	8.0
	24	63.0	22.5	5.0	9.5
	69	68.2	17.4	4.0	10.4

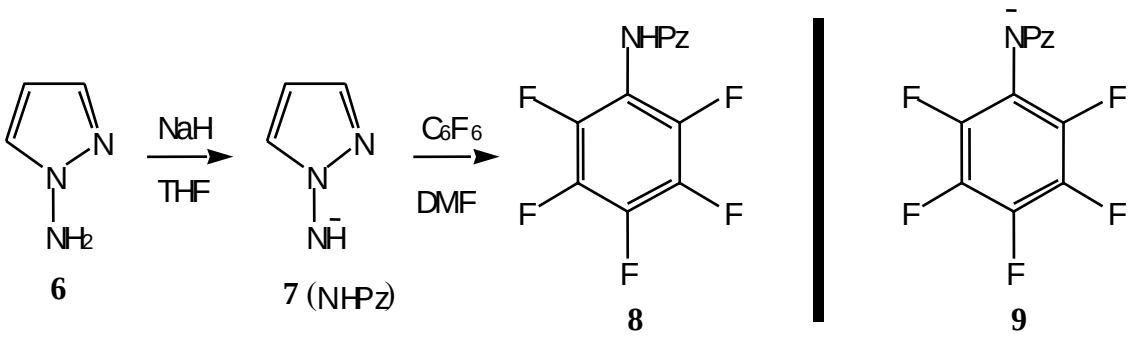
Table 1. Continued

Ratio	Time, h	Starting **2**	Bis **3**	Tetrakis **4**	Hexakis **5**
	93	78.5	3.9	3.9	13.7
	117	77.9	5.2	3.1	13.8
12/1[a]	1.5	-----	57.0	19.0	24.0
	24	-----	61.2	13.0	25.8
	69	-----	55.0	12.0	33.0
	93	-----	18.0	18.0	64.0
	117	-----	26.3	15.4	58.3

[a] These data correspond to the same experiences with another way of calculating the percentages, that is, without considering the recovered starting material.

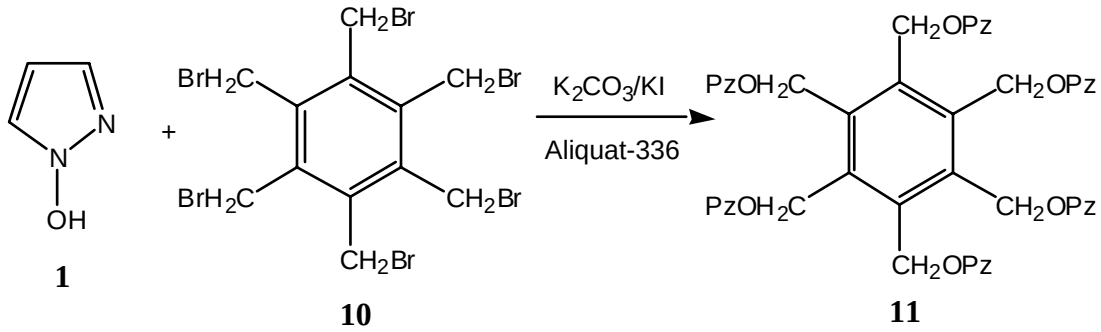
We have underlined the most regio-selective conditions. Note that in all conditions there is a large amount of pyrazolate **2**. It should be noted that hexafluorobenzene is a very volatile compound. Other conditions (see Experimental Part) have not improved the results.

The same reaction with the sodium salt of 1-aminopyrazole **7** affords exclusively the product of monosubstitution **8** (Scheme 3). When compound **8** was made to react with **7** no reaction was observed. We assign this lack of reactivity to the formation of the anion **9**, which is much less reactive than the neutral molecule. When mixing **7** and **8** probably it results in a mixture of **6** and **9**.



Scheme 3

The last reaction we carried out involves hexakis(bromomethyl)benzene **10** and 1-hydroxypyrazole **1** (Scheme 4): in this case we isolated only the full substituted derivative **11** with 73% yield. The behavior of **1** towards hexafluorobenzene (a mixture of compounds with much starting **1**) and with **11** (only a compound in high yield) may be due either to steric effects (**11** is less hindered than **5**) or to electronic effects (each introduced OPz group diminished the leaving group ability of the remaining fluorines) or even, to the volatility of hexafluorbenzene.

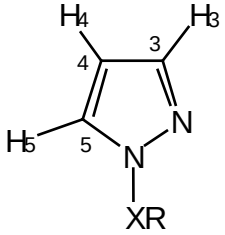


Scheme 4

We have collected in Tables 2 (^{1}H NMR) and 3 (^{13}C NMR) the data that allowed the determination of the structure of the different compounds. Pyrazole derivatives and hexasubstituted benzenes have been used as reference compounds[21-23], the most representative features being $\delta H_4 < \delta H_3 < \delta H_5$, $J_{45} \geq J_{34} > J_{35}$, $\delta C_4 < \delta C_5 < \delta C_3$ and $^1J(C_4H_4) < {}^1J(C_3H_3) < {}^1J(C_5H_5)$. In the case of **11** the ^{1}H and ^{13}C NMR data of *N*-benzyloxypyrazole **12**[24] were considered. For the benzene quaternary carbons the multiplicity of the signals due to carbon-fluorine couplings has been taken into account.

Finally, NMR heteronuclear bidimensional experiments permitted the complete assignment of the signals and confirmed our proposal for the structures of the products (within the molecular formulae corresponding to exact masses).

Table 2. ^{1}H chemical shifts in ppm and coupling constants in Hz of the compounds described in this work

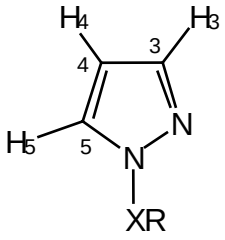


Comp.	Solv.	H_3	H_4	H_5	XR
1	$CDCl_3$	7.15	6.17	7.35	10.57 (br) (OH)
		J_{34}=2.6	J_{45}=2.3	J_{35}=1.1	
1	DMSO	7.13	6.16	7.55	12.23 (OH)

Table 2. Continued

Comp.	Solv.	H_3	H_4	H_5	XR
		J_{34}=2.3	J_{45}=2.2	J_{35}=1.1	
2	DMSO	6.62	5.74	6.80	-----
		J_{34}=2.5	J_{45}=1.7	J_{35}=1.2	
3	$CDCl_3$	7.25	6.25	7.63	
		J_{34}=2.3	J_{45}=2.5	J_{35}=1.3	[$^6J(^{19}F)$=0.45]
4	$CDCl_3$	7.25	6.23	7.70	
		J_{34}=2.3	J_{45}=2.5	J_{35}=1.0	[$^6J(^{19}F)$=0.52] [$^7J(^{19}F)$=0.52]
4	DMSO	7.31	6.35	8.13	
		J_{34}=2.3	J_{45}=2.5	J_{35}=1.0	
5	$CDCl_3$	7.18	6.14	7.78	
		J_{34}=2.1	J_{45}=2.4	J_{35}=0.9	
8	$CDCl_3$	7.43	6.24	7.64	7.12 (NH)
		J_{34}=1.8	J_{45}=2.3		
8	DMSO	7.42	6.29	7.88	9.97 (NH)
		J_{34}=1.9	J_{45}=2.1		
11	DMSO	7.32	6.21	7.57	5.60 (CH_2)
		J_{34}=2.3	J_{45}=2.4	J_{35}=1.0	
12	$CDCl_3$	7.28	6.04	6.98	5.28 (CH_2)
		J_{34}=2.3	J_{45}=2.4	J_{35}=1.0	
12	DMSO	7.25	6.15	7.53	5.26 (CH_2)
		J_{34}=2.3	J_{45}=2.4	J_{35}=1.1	

Table 3. ^{13}C chemical shifts in ppm and coupling constants in Hz of the compounds described in this work



Comp.	Solv.	C_3	C_4	C_5	C-F	C
1	$CDCl_3$	131.5	103.3	122.8	-----	-----
		^1J=189.2	^1J=179.7	^1J=193.2		
		^3J=8.6	^2J=8.2	^2J=8.7		
		^2J=4.8	^2J=8.2	^3J=4.1		

Table 3. Continued

Comp.	Solv.	C_3	C_4	C_5	C-F	C
1	DMSO	131.9	103.3	122.6	-----	-----
		^1J=187.2	^1J=177.2	^1J=192.4		
		^3J=9.0	^2J=8.8	^2J=9.2		
		^2J=4.6	^2J=8.8	^3J=3.8		
2	DMSO	126.2	99.3	117.3	-----	-----
		^1J=181.3	^1J=172.2	^1J=186.1		
		^3J=8.6	^2J=9.3	^2J=8.8		
		^2J=4.5	^2J=9.3	^3J=3.6		
3	$CDCl_3$	133.7	104.6	121.9	142.0	134.4
		^1J=191.3	^1J=180.2	^1J=195.8	^1J=258.3	
		^3J=9.3	^2J=9.0	^2J=9.3	^2J=14.4	
		^2J=4.4	^2J=8.0	^3J=3.6	^3J=4.6	
4	$CDCl_3$	133.5	104.5	122.4	146.5	138.7
		^1J=190.9	^1J=180.1	^1J=196.5	^1J=259.9	^2J=9.3
		^3J=9.4	^2J=9.0	^2J=9.0	^4J=4.8	^3J=5.6
		^2J=4.5	^2J=8.0	^3J=3.6		
5	$CDCl_3$	133.1	104.2	122.8	-----	143.7
		^1J=190.6	^1J=179.7	^1J=196.7		
		^3J=9.2	^2J=8.5	^2J=9.3		
		^2J=4.3	^2J=8.5	^3J=3.5		
8	$CDCl_3$	138.5	104.9	130.2		
		^1J=187.7	^1J=178.8	^1J=192.1		
		^3J=9.0	^2J=9.0			
		^2J=4.9	^2J=9.0			
		$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	
		120.6	139.9	137.9	137.9	
		$^2J_{(F2/F6)}$=12.2	^1J=247.4	^1J=246.3	^1J=246.3	
		$^4J_{(F4)}$=4.0				
11	DMSO	132.9	103.1	122.1	136.8	72.1 (CH_2)
		^1J=188.8	^1J=179.0	^1J=194.7		^1J=150.8
		^3J=9.1	^2J=8.7	^2J=9.2		
		^2J=4.6	^2J=8.7	^3J=3.1		
12	$CDCl_3$	133.1	102.9	122.3		80.2 (CH_2)
		^1J=188.5	^1J=178.4	^1J=192.8		^1J=142.2
		^3J=9.0	^2J=8.2	^2J=9.1		
		^2J=4.5	^2J=8.0	^3J=3.7		
		$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	

Table 3. Continued

Comp.	Solv.	C_3	C_4	C_5	C-F	C
		133.7	129.4	128.4	128.9	
			^1J=160.5	^1J=161.9	^1J=160.7	
				^3J=4.6	^3J=^3J=7.0	

Conclusions

We have proved that *N*-hydroxypyrazole yields hexakis-substituted compounds when reacting with hexakis(bromomethyl)benzene and hexafluorobenzene, in the latter case together with bis- and tetrakis-substituted derivatives. In contrast, the reaction of *N*-aminopyrazole with hexafluorobenzene affords only the monosubstitution product due to acidity of the remaining NH.

These new compounds, where there is a spacer between the pyrazole and the benzene moieties, will certainly prove to be useful in host-guest chemistry and for metal coordination complexes.

Experimental Section

General Procedures. Melting points were determined on a microscope hot stage apparatus and are uncorrected. The R_f values were measured on aluminum backed TLC plates of silicagel 60 F254 (Merck, 0.2 mm) with the indicated eluent. Column chromatography was performed on silica gel (Merck 60, 70-230 mesh). NMR spectra were recorded on a Bruker AC-200 spectrometer at 298 K working at 200.13 for ^{1}H and 50.32 for ^{13}C. Chemical shifts are expressed in ppm/TMS for ^{1}H and ^{13}C. Solvents were $CDCl_3$ and DMSO-d_6. Signals of ^{1}H and ^{13}C NMR spectra were assigned with the help of XH-CORR (^{1}H-^{13}C) bidimensional experiments. Exact masses were determined using electron impact technique and PFK as reference for volatile samples, or FAB-MS positive spectra for the non-volatile derivatives, accuracy ± 0.0025 daltons (VG AutoSpec).

Reaction of 1-hydroxypyrazole with hexafluorobenzene. In a round flask, 1 g (0.12 mmol) of **1**[25] was dissolved in 10 mL of anhydrous THF and Ar was flowed during 20 min. Then, a suspension of 476 mg (12 mmol) of 60% NaH in 10 mL of anhydrous THF was added. The mixture was refluxed under Ar atmosphere for 2 h (in this way the sodium salt **2** was obtained). The reaction was allowed to cool down to room temperature and 0.23 mL (2 mmol) of hexafluorobenzene in 20 mL of DMF was added. The mixture was kept at room temperature under stirring, during the time reported in Table 1, and then 30 mL of distilled water were added. The tetrakis derivative **4** almost pure precipitates and afterwards a mixture of **3**, **4** and **5** separated. The global yields are difficult to calculate because so much starting material is recovered, but for a 6/1 stoichiometry and 27 h, first 420 mg of **4** is obtained and then 190 mg of the mixture is isolated. The three compounds were separated by column chromatography over silica gel with hexane/ethyl acetate 6/4 as eluent. 1,4-Bis[(pyrazol-1-yl)oxy]-2,3,5,6-

tetrafluorobenzene (**3**), m.p. 100-101 ºC, mol. formula $C_{12}H_6F_4N_4O_2$, calc. mass 314.0427, exp. mass 314.04276. R_f (hexane/ethyl acetate 6/4) = 0.50. 1,2,4,5-tetrakis[(pyrazol-1-yl)oxy]-3,6-difluorobenzene (**4**), m.p. > 350 ºC. mol. formula $C_{18}H_{12}F_2N_8O_4$, mol. wt. 442.34. Elemental Analyses: Calc. C, 48.88; H, 2.73; N, 25.33. Found: C, 48.57; H, 2.42; N, 25.04 %. R_f (hexane/ethyl acetate 6/4) = 0.28. Hexakis[(pyrazol-1-yl)oxy]benzene (**5**), m.p. > 350 ºC. mol. formula $C_{24}H_{18}N_{12}O_6$, calc. mass 570.1472, exp. mass 571.15 (M+1). R_f (hexane/ethyl acetate 6/4) = 0.18.

The reaction cannot be carried out in pure THF because compound **2** is very insoluble in this solvent (it precipitates in 97% yield and can be isolated). It is possible to carry out the reaction in DMSO and to observe the formation of the three products but the work-up is much more tedious. In CH_3CN the reaction does not proceed.

Reaction of 1-aminopyrazole with hexafluorobenzene. To a solution of 0.445 g (5.3 mmol) of **6**[26] in 5 mL of anhydrous THF was slowly added a suspension 0.2 g of 60% sodium hydride in 3 mL of anhydrous THF and stirred at room temperature for 90 min (hydrogen evolved). Then, 0.1 mL (0.87 mmol) of hexafluorobenzene was added and stirred 1 h at room temperature. The solvent is evaporated under reduced pressure and the residue is chromatographed over silica gel using dichloromethane as eluent. 0.175 g (85% yield) of a white solid were isolated, m.p. 92-93 ºC, mol. formula $C_9H_4F_5N_3$, calc. mass 249.0325, exp. mass 249.0355.

Reaction of 1-hydroxypyrazole with hexakis(bromomethyl)benzene. Under Ar atmosphere is prepared a mixture 0.5 g (5.95 mmol) of 1-hydroxypyrazole, 0.374 g (0.58 mmol) of hexakis(bromomethyl)benzene, 0.816 g (5.91 mmol) of K_2CO_3, 0.51 g (3.07 mmol) of KI, five drops of Aliquat-336 and 25 mL of anhydrous acetone. After 40 h reflux, the solution is cooled down and a precipitate is filtered off. It contains **11** and **2** in a 37/63 ratio (in the acetone solution there are only impurities). A continuous extraction with chloroform (15 h) affords 277 mg of pure **11** (73% yield). M.p. 239-240 ºC, mol. formula $C_{30}H_{30}N_{12}O_6$, mol. wt. 654.65. Elemental Analyses: Calc. C, 55.04; H, 4.62; N, 25.67. Found: C, 55.31; H, 4.49; N, 25.73 %.

1-Benzyloxypyrazol (**12**)**.** This compound was prepared as reported in reference.[27]

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