

Synthesis of New *C,C*-Linked Bipyrazole and Comparative Theoretical Calculations

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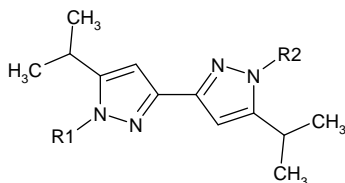
Abstract: New *C,C*-linked bipyrazole 1,1'-di(4-aminophenyl)-5,5'-diisopropyl-3,3'-bipyrazole (**2**) has been synthesized and characterized. Theoretical calculations have been carried out on target **2** and literature **1** *C,C*-linked bipyrazoles to compare with reported results. All calculations were carried out with the AM1 level of theory using the GAUSSIAN 03. The nature of substituent attached to the pyrazolic nitrogen has an effect on the thermodynamic variable values. The mono and bis *N*-substituted *C,C*-linked bipyrazoles have different thermodynamic properties.

Keywords: *C,C*-Linked, Bipyrazole, Theoretical calculation, Mono and bis *N*-substituted

Introduction

In the literature, pyrazole derivatives have been the subject of several studies. They have been used as potential anti-inflammatory agents¹, cytotoxic agents², insecticides³, herbicides⁴ and fungicides⁵. Pyrazole nuclei can be associated in different ways⁶ and lead to several carbonaceous skeletons type: tripod, bipyrazole, macrocycle. During last years, many tripods with pyrazolic units and *C,C*-linked bipyrazole derivatives have been prepared in our laboratory⁷⁻¹⁴ for several purposes such as liquid-liquid extraction¹⁵, catalysis¹⁶, corrosion inhibition¹⁷, anticancer¹⁸, resins¹⁹ and polymers²⁰ synthesis. As part of our laboratory research programme we propose in the present paper to synthesize and characterize a new *C,C*-linked bipyrazole type 1,1'-di(4-aminophenyl)-5,5'-diisopropyl-3,3'-bipyrazole **2** (Figure 1). In order to get better understanding about the characteristic properties of these *C,C*-linked bipyrazole

compounds, we have calculated some thermodynamic quantities of the new material **2** and literature compound **1**. The mono and bis *N*-substitution effect of *C,C*-linked bipyrazoles towards thermodynamic variable values have examined.



- 1** : R1 = *p*-NO₂-C₆H₄ ; R2 = *p*-NO₂-C₆H₄ **3** : R1 = *p*-NO₂-C₆H₄ ; R2 = H
2 : R1 = *p*-NH₂-C₆H₄ ; R2 = *p*-NH₂-C₆H₄ **4** : R1 = CH₂-CO₂Et ; R2 = H

Figure 1. Structure of new **2** and investigated **1, 3, 4** compounds

Experimental

Melting points were determined in open glass capillaries using BUCHI 510 Melting Point apparatus and are uncorrected. The infrared (IR) spectra were recorded on PERKIN-ELMER 1310 infrared spectrophotometer using the KBr disc technique. ¹H and ¹³C NMR spectra were recorded on BRUKER 300 (operating at 300 MHz for ¹H) spectrometer. Chemical shifts are listed in ppm and reported relative to tetramethylsilane (TMS). Mass spectra were obtained on a VG7070E spectrometer.

Synthesis of 1,1'-di(4-aminophenyl)-5,5'-diisopropyl-3,3'-bipyrazole (**2**)

To a mixture of 1,1'-di(4-nitrophenyl)-5,5'-diisopropyl-3,3'-bipyrazole (0.1 mmol) and granulated tin (0.3 mmol) was added concentrated hydrochloric acid (0.1 mL). The mixture was refluxed for one hour and cooled to room temperature. The solution was neutralized by sodium hydroxide solution. The precipitate was collected by filtration and recrystallized to give pure 1,1'-di(4-aminophenyl)-5,5'-diisopropyl-3,3'-bipyrazole (**2**). Yield : 95% ; R_f : 0.3 (Alumine / CH₂Cl₂) ; m. p. : > 260 °C ; ¹H-NMR (300 MHz, DMSO-d₆, δ, ppm) : 7.05 (d, 4 H, H2', J = 8.7 Hz), 6.63 (d, 4 H, H3', J = 8.4 Hz), 6.43 (s, 2 H, C4-H), 5.38 (s, 4 H, NH₂), 2.88 (m, 2 H, CH(CH₃)₂, J = 6.9 Hz), 1.10 (d, 12 H, CH(CH3)₂, J = 6.6 Hz) ; ¹³C-NMR (75 MHz, DMSO-d₆, δ, ppm) : 151.5 (C3), 149.6 (C4'), 145.9 (C5), 128.9 (C1'), 127.6 (C2'), 114.3 (C3'), 100.1 (C4), 25.8 (CH(CH₃)₂), 23.4 (CH(CH3)₂) ; IR (KBr disk, cm⁻¹) : 3490, 3320, 3200 (ν_{N-H}), 2980(ν_{C-H, CH3}), 2930(ν_{C-H, CH(CH3)2}), 1650 (ν_{C=N}), 1610 (ν_{C=C}), 1530, 1340, 1320, 1190, 1100, 960, 850, 820, 700 (δ_{NH2}) ; MS (EI), m/z : 400, 385, 371, 318, 264, 239, 200, 185, 131, 92, 65, 43 ; Anal. Calcd for C₂₄H₂₈N₆: C 71.97, H 7.05, N 20.98, Found: C 71.82, H 7.00, N 20.93

Results and Discussion

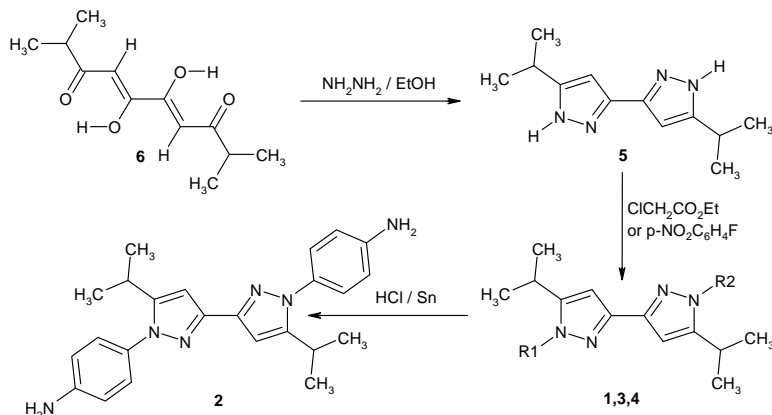
Synthesis

Compounds **1,3-6** (Scheme 1) were prepared according to the literature procedure^{14,21}. The new *C,C*-linked bipyrazole 1,1'-di(4-aminophenyl)-5,5'-diisopropyl-3,3'-bipyrazole (**2**) was synthesized by reduction of nitro moiety in compound **1**. This reaction was carried out using granulated tin in refluxing concentrated hydrochloric acid to afford pure product **2** in excellent yield (95%).

Characterization

In the ¹H-NMR spectra of diamine **2** recorded in DMSO-d₆ appears two signals at 1.10 and 2.88 ppm, corresponding respectively to the underline protons of CH(CH3)₂ and CH(CH₃)₂. As shown in Table 1 all signals are shielded to high fields by the mesomeric effect of the

amino groups linked to the benzene rings. The coupling constants between the benzylic protons in compounds **1** and **2** are remaining unchanged and take a value of 10.3 ppm in **3**. The similar finding was observed between the methylic and methylinic protons, due to the negligible effect of the nitro and amino moieties.



Scheme 1. Synthesis of 1,1'-di(4-aminophenyl)-5,5'-diisopropyl-3,3'-bipyrazole

Table 1. Comparative studies between chemical shifts of target **2** and literature **1, 3-6** compounds

Entry	^a δ (CH(CH ₃) ₂)	^a δ (CH(CH ₃) ₂)	^a δ (C4-H)	^a δ (C-H ₂ ')	^a δ (C-H ₃ '')	^b J _{H₂'-H₃'}	^b J _{HC-CH₃}
1	1.25	3.15	6.76	7.70	8.35	8.7	6.9
2	1.10	2.88	6.43	7.05	6.63	8.7	6.9
3	1.25 - 1.34	2.99 - 3.17	6.47- 6.63	7.70	8.35	10.3	7.8 - 8.4
4	1.24	2.87 - 3.01	6.36	--	--	--	6.9 - 6.9
5	1.24	2.91	6.25	--	--	--	7.9
6	1.24	2.72	--	--	--	--	6.9

^aChemical shifts are listed in ppm and are reported relative to TMS. ^bCoupling constants are Hz

In symmetrical molecules (**1, 2, 5, 6**) ¹H and ¹³C NMR spectra show single peaks. Whereas in the mono *N*-substituted bipyrazoles (**4, 5**), results illustrate two types of peaks assigned to the methylic, methylinic and pyrazolic protons. However for the *N*-substituted compound **4**, where the pyrazolic ring is linked to CH₂CO₂CH₂CH₃ moiety, we have noted in ¹H-NMR that only the methylinic protons are duplicated. Indeed, for the first [CH(CH₃)₂] the superposition of methylic protons peaks belonging to both isopropyl and ethyl groups gives a multiplet. Also, the asymmetry does not influences the pyrazolic protons chemical shifts.

The IR spectra of compound **2** showed that the absorption peaks corresponding to the stretching vibration of the nitro group disappeared, showing that the NO₂ moiety in 1,1'-di(4-nitrophenyl)-5,5'-diisopropyl-3,3'-bipyrazole **1** had participated completely in the reduction reaction. Also, the bands at 1650 and 1610 cm⁻¹ was attributed to vibration of C=N and C=C bonds of the pyrazolic and benzenic rings. The mass spectrum displayed a molecular ion peak at *m/z* 400 (100%). The new compound is very stable at room temperature and presents a higher melting point (>260 °C). Several analysis methods IR, ¹H NMR and ¹³C NMR spectroscopy, mass spectrometry and elemental analysis data are consistent with the formulation indicated in Scheme 1.

Theoretical calculations

All calculations in this work were carried out with the AM1 level of theory using the GAUSSIAN 03²² suite of programs. In addition we have carried out using AM1 optimizations and frequency calculations. More information about these methods is available elsewhere²³. Figure 2 presents the optimized structure of the molecule with bond lengths and bond angles. Table 2 shows the thermodynamic properties for the C,C-linked bipyrazoles in Figure 2 where T (temperature in K), S (entropy in J mol⁻¹ K⁻¹), Cp (heat capacity at constant pressure in kJ mol⁻¹ K⁻¹) and $\Delta H=H^\circ - H^\circ_{298.15}$ (enthalpy content, in kJ mol⁻¹), T1=100 K, T2 = 298.15 K and T3 = 1000 K calculated AM1 frequencies. The fits were performed according to the equations implemented by the National Institute of Standards and Technology²⁴. These equations have been very good at predicting physical properties of various molecules, as we have tested in the past.^{21,25-27}

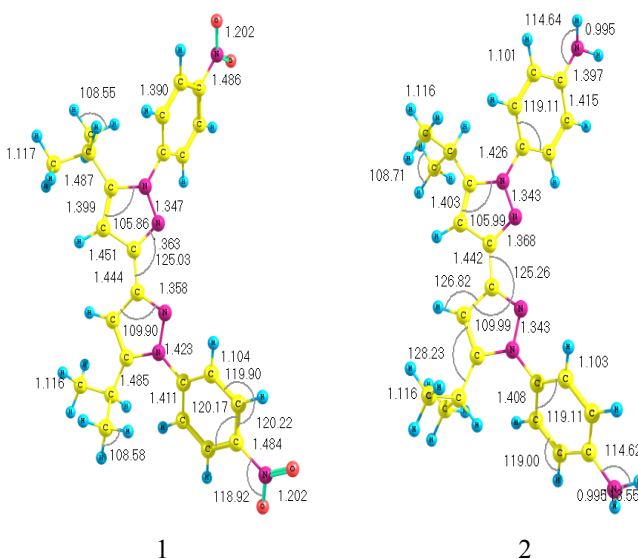


Figure 2. AM1 optimized structure, where bond lengths are in angstroms (Å) and bond angles in degrees (°) for **1** and **2**

Table 2. Thermodynamic properties for the species **1** and **2**

		Fitted Thermodynamic Equation (T/1000=t)	T ₁	T ₂	T ₃
	S	$-58.87173 \cdot \ln(t) + 1992.17868 \cdot t - 1003.68515 \cdot t^2/2 + 123.24467t^3/3 - 0.92806/(2 \cdot t^2) + 196.99856$	480.40	813.66	1728.06
1	C _p	$26.99605 + 1569.32847 \cdot t - 353.05153 \cdot t^2 - 187.61894 \cdot t^3 + 0.18916 \cdot t^2$	200.16	457.39	1060.75
	ΔH	$-93.45601 \cdot t + 2164.77461 \cdot t^2/2 - 1287.66867 \cdot t^3/3 + 273.03726 \cdot t^4/4 - 1.26606$	12.32	77.28	650.65
	S	$-65.19197 \cdot \ln(t) + 2037.87589 \cdot t - 1050.2049 \cdot t^2/2 + 136.08601t^3/3 - 0.95834/(2 \cdot t^2) + 177.24856$	478.03	813.05	1735.01
2	C _p	$-43.93648 + 1968.08342 \cdot t - 991.51002 \cdot t^2 + 131.43787 \cdot t^3 + 0.57896 \cdot t^2$	200.51	461.31	1066.38
	ΔH	$-98.51156 \cdot t + 2204.12039 \cdot t^2/2 - 1323.76625 \cdot t^3/3 + 280.41761 \cdot t^4/4 - 1.2862$	12.24	77.59	655.50

Compound **1** presents the thermodynamic variable values slightly lower than those described for the regioisomer **I** in 1,1'-di(2-nitrophenyl)-5,5'-dipropyl-3,3'-bipyrazole²⁸. In the optimized structure, the N(NH₂)-C bond length of 1.397 Å in **2** is shorter than the N(NO₂)-C of 1.486 Å in **1**. This difference can be explained by the force applied by the nitro and amino groups.

Effect of substituents (R1, R2) on the thermodynamic variable values

We examine now the effect of R1 and R2 moieties linked to the pyrazolic nitrogen towards thermodynamic variables values. As can be seen from Figures 3-5, the obtained results show a difference of standard enthalpy, heat capacity and entropy variables between the two pairs of compounds (**1, 2**) and (**3, 4**). However, there is a smaller difference between the elements of the pairs on the thermodynamic calculated properties.

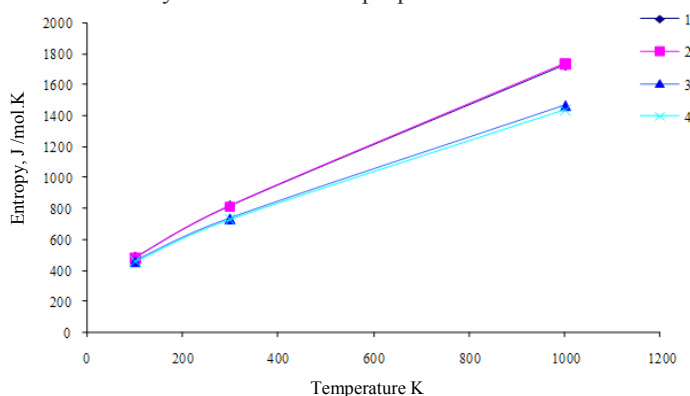


Figure 3. Entropy in J mol⁻¹ K⁻¹ of compounds 1-4

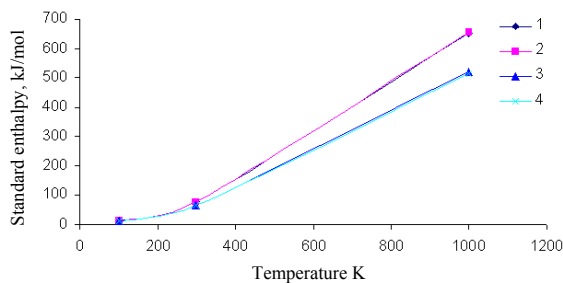


Figure 4. Standard enthalpy in kJ mol⁻¹ of compounds 1-4

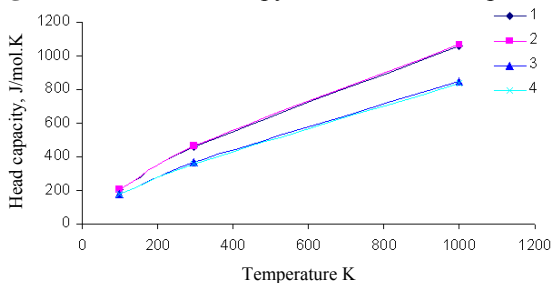


Figure 5. Heat capacity in J mol⁻¹ K⁻¹ of compounds 1-4

Among these *C,C*-linked bipyrazoles, the first pair (**1**, **2**) has the greatest variable values than the second pair (**3**, **4**). Two groups of compounds will be distinguished. Case where both two pyrazoles are *N*-aryled: the replacement of the nitro withdrawing moiety in **1** by a mesomeric effect donating group such as amino in **2** increases at room temperature (298.15 K) the standard enthalpy of 0.31 kJ mol⁻¹ and heat capacity of 3.92 J mol⁻¹ K⁻¹. But the entropy decreases with a value of 0.61 J mol⁻¹ K⁻¹. These minor differences will be probably associated to the dominance of the conjugation phenomenon induced by the phenylic moiety linked to the pyrazolic ring in two *N*-aryl compounds (**1**, **2**). The case where one single pyrazol is *N*-substituted: Results show that compound **3** has a higher thermodynamic properties than the *C,C*-linked bipyrazol **4**. At room temperature (298.15 K), the increasing values are respectively 0.25 kJ mol⁻¹, 6.92 J mol⁻¹ K⁻¹, 10.69 J mol⁻¹ K⁻¹ for the standard enthalpy, entropy and heat capacity. These differences may be justified by the type of R1 group attractive effect linked to the pyrazolic ring, electron-donating in **4** and electron-withdrawing in **3**. Besides the conjugation phenomenon absent in **4** (R1 = CH₂CO₂Et) and present in **3** (R1 = p-NO₂-C₆H₄-) explains also the results. On the other hand the bis *N*-arylation in compound **1** has resulted in increases relative to the mono *N*-aryl compound **3** in 20% of standard enthalpy, 11% of entropy and 24% of heat capacity.

Conclusion

In this work we have synthesized and characterized a new *C,C*-linked bipyrazol compound 1,1'-di(4-aminophenyl)-5,5'-diisopropyl-3,3'-bipyrazole. Theoretical calculations carried out with the AM1 level of theory using the GAUSSIAN 03 indicate that the diamine (**2**) and dinitro (**1**) compounds present similar thermodynamic properties. The bis *N*-aryled *C,C*-linked bipyrazoles have a higher standard enthalpy, entropy and heat capacity values than the mono *N*-substituted compounds.

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