



The use of a molecular balance derived from 5,5'-bipyrazole to calculate π – π stacking interactions

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ABSTRACT

Theoretical calculations have been carried out on 3,3'-dimethyl-1,1'-diphenyl-5,5'-bi-1*H*-pyrazole to evaluate its usefulness as a molecular balance to measure π – π stacking. After removing the methyl groups (1,1'-diphenyl-5,5'-bi-1*H*-pyrazole), the *N*-phenyl groups have been replaced by a series of aromatic rings, and the energy difference between the *syn* and *anti* forms is discussed in terms of π – π stacking and dipole–dipole interactions.

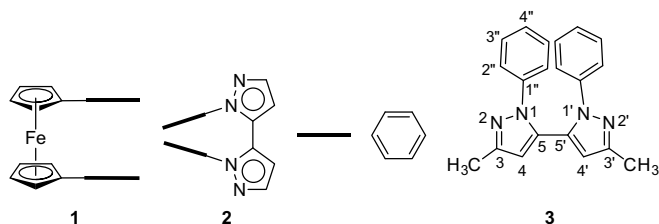
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The π – π stacking is one of the fundamental interactions that hold molecules together in natural and artificial supramolecules, including DNA^{1,2} and other biological systems.³ Besides pure theoretical papers,⁴ several authors have devised molecules to determine experimentally these interactions. One of the most popular is ferrocene derivative **1**.^{5–8} Other authors have used supramolecular systems.⁹

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The compound described by Adlington, Baldwin et al.¹² has the structure **3**. The authors note that this structure was confirmed by single crystal X-ray diffraction (Fig. 1). They found interesting to point out that the two phenyl rings appear to be π -bonded, thus influencing the dihedral angle between the pyrazole nitrogens. There are two independent molecules in the unit cell, with dihedral angles N1–C5–C5'–N1' θ of 52.5° and 53.3° and N2–N1–C1''–C2'' ϕ of 45.6°, 45.9°, 44.9° and 47.1°.

We have calculated compound **3** at the M05-2x/6-31+G(d,p) computational level. It is well known that to calculate π – π



Compound **1** has the advantage that both phenyl rings are parallel and separated by about 3.3 Å (the separation between Cp rings in ferrocene).¹⁰ The inter-rings distance is similar to that found in benzene (displaced-parallel) and other π – π stacking situations.¹¹ The torsion about the organometallic bond can simulate the displacement of an aromatic ring with regard to the other.

In search for more congested situations that will bring the aromatic rings together, we have found a compound that corresponds to structure **2**.¹² From simple geometrical considerations, such

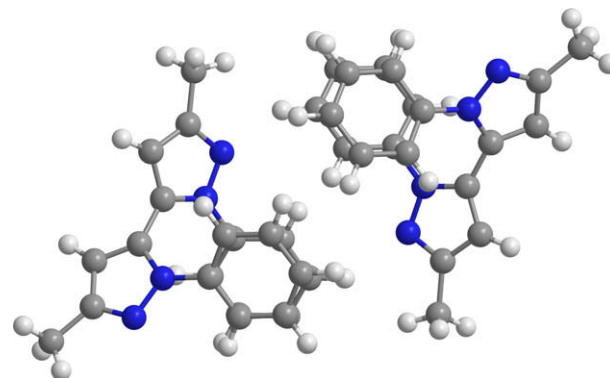


Figure 1. The X-ray structure of the two independent molecules of **3** (JELGOX).¹³

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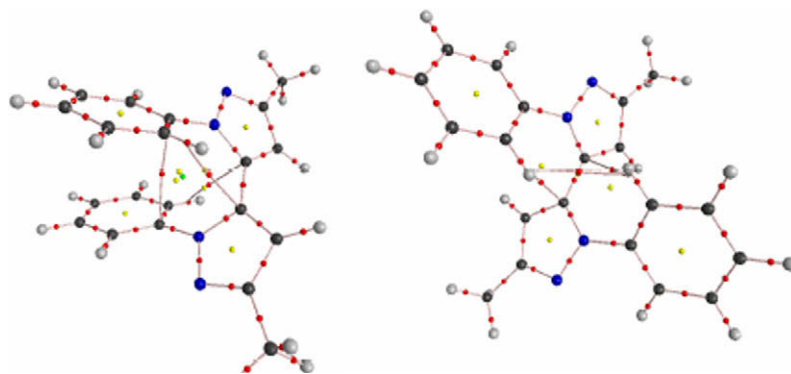


Figure 2. Results of the AIM analysis of the *syn* (left) and *anti* (right) configurations.

stacking interactions, it is necessary to use Truhlar functionals or similar ones.¹⁴ For compound **3**, we have found two minima, one '*syn*', similar to that found by crystallography (Figs. 1 and 2) and one '*anti*' (Fig. 2), the first one being 12.4 kJ mol⁻¹ more stable. Dihedral angles: *syn*, $\theta = 52.6^\circ$, $\phi = 42.0^\circ$ and *anti*, $\theta = 113.3^\circ$, $\phi = 34.7^\circ$. An additional minimum configuration presenting a CH \cdots π interaction and a relative energy of 16.8 kJ mol⁻¹ has been found.

In the AIM analysis (Fig. 2),¹⁵ a π - π interaction appears for the '*syn*' structure and a H \cdots H interaction of the phenyl groups appears for the '*anti*' structure. Mosquera et al. have reported similar interactions for stacking of quinhydrone.¹⁶

Encouraged by these results, we decided to explore other possibilities replacing the phenyl rings of **3** by other aromatic groups (neutral: **4**–**8**) and (charged: **9**). We have removed the methyl groups of compound **3** (**3'** without methyl groups) since they are unnecessary. The results are reported in Table 1 (see Scheme 1).

The E_{rel} values are not related to the dihedral angles, note that **3'** and **7** have almost the same θ s and very different E_{rel} . It came as a surprise that in absolute value, **3'** > **4** > **5** (the value for **4** being the arithmetic mean of **3'** and **5**) when we expected that **4** will show a larger E_{rel} than both **3'** and **5**.

π -Excessive and π -deficient heterocycles are, according to Albert,¹⁷ the equivalent to benzene rings substituted by electron-donating and electron-withdrawing groups like NH₂ and NO₂. However, the interactions amount to -17.2 kJ mol⁻¹ in the case

of **7** and only to -6.9 kJ mol⁻¹ in the case of **8**. Since it is an interaction between surfaces, part of the decrease could be related to size effects. Assuming identical bond lengths, a hexagon has an area of 1.51 larger than a pentagon. But still, the large difference remains (-17.2/1.51 = -11.4 kJ mol⁻¹). The results concerning compound **9** show that the interaction pyrrole/pyridinium is much stronger than the pyrrole/pyridine one (11 kJ mol⁻¹ of difference). Note that the case of **9** would be better described as a cation- π interaction, related to those reported by Dougherty.^{1b,18}

Another explanation is that E_{rel} also measures dipole-dipole interactions. Replacing the *N*-pyrazolyl substituent by an H atom results in the molecules reported in Scheme 2 together with their dipole moments.¹⁹

Table 2

Partition of E_{rel} into two terms (all values in kJ mol⁻¹)

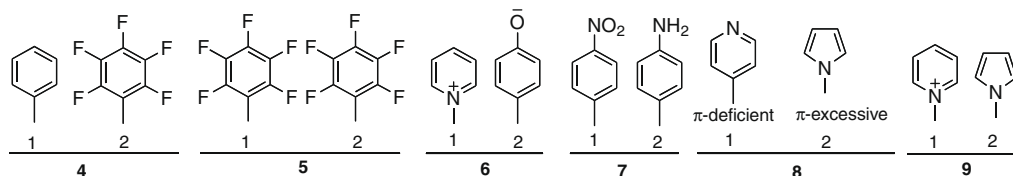
Compd	π - π	Dipole	Total
3'	-13.0	0.0	-13.0
4	-13.0	+2.2 (repulsive: one 1.44 D)	-10.8
5	-13.0	+4.2 (repulsive: two 1.44 D)	-8.8
6	-13.0	Very large (charged species): \sim -20	\sim -33
7	-13.0	-4.2 (attractive: +3.98/-1.59 D)	-17.2
8	-5.2	-1.7 (attractive: +2.15/-1.81 D)	-6.9
9	-5.2	-12.7 (attractive, 1+ charged molecule)	-17.9

Table 1

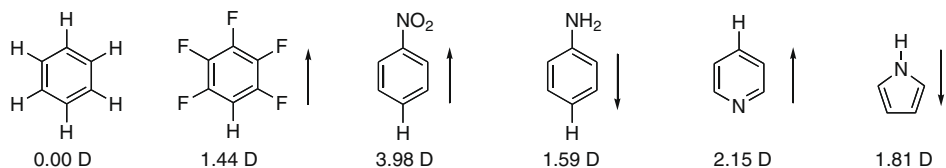
Energies of the different compounds; absolute values in hartree, relative values in kJ mol⁻¹; torsion angles in $^\circ$

Compd	<i>syn</i>	<i>anti</i>	E_{rel}	θ <i>syn</i>	θ <i>anti</i>	ϕ_1 <i>syn</i>	ϕ_2 <i>syn</i>	ϕ_1 <i>anti</i>	ϕ_2 <i>anti</i>
3'	-913.28515	-913.28021	-13.0	52.8	113.8	42.8	42.8	35.4	35.4
4	-1409.40503	-1409.40093	-10.8	50.2	138.7	42.3	56.0	47.3	66.0
5	-1905.52217	-1905.51882	-8.8	61.6	144.4	64.0	64.0	67.7	67.7
6	-1004.43289	- ^a	-	52.1	-	50.8	62.7	-	-
7	-1173.12379	-1173.11723	-17.2	52.4	113.3	42.3	45.4	33.5	43.4
8	-907.19806	-907.19542	-6.9	54.7	151.6	39.3	58.2	44.3	76.2
9	-907.52102	-907.51421	-17.9	52.0	158.8	53.3	53.2	42.4	75.5

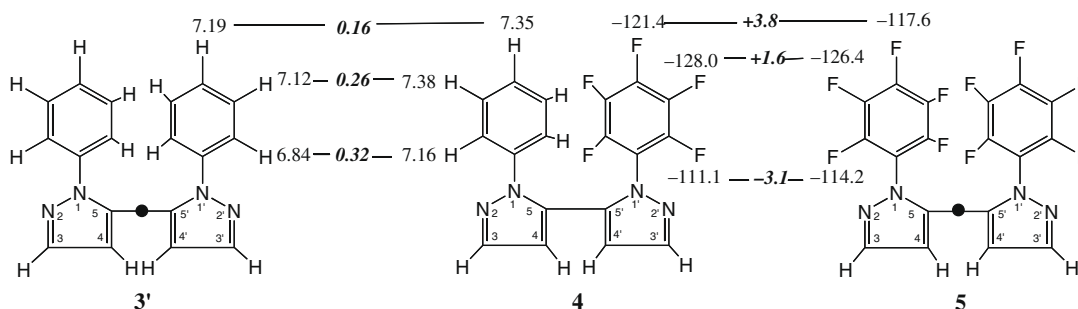
^a Evolves to the *syn* form.



Scheme 1. Other structures explored.



Scheme 2. Dipole moments (Debyes) of aromatic and heterocyclic molecules.



Scheme 3. $\Delta\delta$ values (bold, italic) in ppm (4–3 and 5–4).

The dipole/dipole contribution can be simplified as being proportional to the product of both dipoles, considering the sign but not the angle, that is, assuming for instance that the θ *syn* angle is the same for all the compounds (Table 1). This led to: dipolar term = $(2.16 \pm 0.04) + (1.002 \pm 0.009)$ product of dipole moments (three points, $R^2 = 1.00$). This allows to estimate the case of **8** (-1.7 kJ mol^{-1} , underlined in Table 2) and from **8** that of **9**. Since $13.0/5.2 = 2.5$, the previous estimated ratio of 1.51 (six-membered ring/five-membered ring) was underestimated, but it was calculated for the total effect and 2.5 corresponds to the π – π interaction.²⁰

The fact that the π – π interaction takes only two values, -13.0 and -5.2 kJ mol^{-1} , even if it corresponds to a first approximation, was unexpected since all combinations of benzene rings are alike.

The analysis of the electron density shows the presence of bond critical points between the atoms of the aromatic rings in the *syn* configuration (Fig. 2). For **3**, **3'**, and **8**, one bond critical point is obtained, two in the case of **5**–**7** and **9** and three for **4**. These results are a clear indication of the presence of π – π interactions in the mentioned configuration.

For all these compounds, we have calculated the absolute shieldings of the different nuclei (σ , ppm) using the GIAO approximation (see Supplementary data).²¹ We have transformed these σ into δ using empirical equations,²² and we have represented in Scheme 3 the results for the phenyl rings in compounds **3'**, **4**, and **5**.²³ The pentafluorophenyl group shields the phenyl ^1H NMR signals (*ortho* > *meta* > *para*) and also the *meta* and *para* ^{19}F NMR signals of **5** but not the *ortho* ones, more sensitive to ϕ *syn* (Table 1).

In conclusion, compound **2** constitutes both an excellent experimental and theoretical balance for measuring π – π interactions. From an experimental point of view because it is simple to replace the *N*-phenyl groups by other groups in pyrazoles.²⁴ On theoretical basis because other groups can be calculated like pairs of complementary purines and pyrimidines.²⁵ The separation of face-to-face contribution (related to the contact surface) and the dipole–dipole interaction (related to the sign and direction of the dipole moment) is only semi-quantitative, but gives an idea of the forces involved.

Computational details: All the stationary points were minima (no imaginary frequencies). The computations were carried out with the M05-2x/6-31+G(d,p) functional of Truhlar²⁶ using the GAUSSIAN 03 facilities.²⁷

Acknowledgments

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Supplementary data

Supplementary data (geometries, energies and GIAOs) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.131.

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