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A molecular balance to measure the strength of N–H···π hydrogen bonds based on the tautomeric equilibria of *C*-benzylphenyl substituted NH-pyrazoles

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Abstract

A theoretical (B3LYP/6-31G**) study of 30 pyrazoles, most of them existing in two tautomeric forms, has been carried out. 3(5)-(2-Benzylphenyl)-5(3)-methyl-1*H*-pyrazole (**11**) and 3(5)-(2-benzylbenzylphenyl)-5(3)-phenyl-1*H*-pyrazole (**20**) were synthesized from 2-benzoyl-acetophenone, and their annular tautomeric equilibrium determined. The substituent effects were statistically analyzed and discussed with the help of Hammett substituent constants. In the case of the 5-(2-benzylphenyl) groups, the strength of the N–H···π hydrogen bond depends on the electronic effect of the substituent at position 3.

Keywords: Pyrazoles; Tautomerism; B3LYP/6-31G** calculations; Hydrogen bonds

1. Introduction

We will report in this paper a DFT study of 30 3,5-disubstituted (including proton as a substituent) NH-pyrazoles **1**–**30** aimed at understanding the effect of substituents on the tautomeric equilibrium constant K_T and to provide further insight into a statement that we made in 2006. At that time, we proposed that NH-pyrazoles bearing a 3(5)-benzylphenyl group (Scheme 1)[1] should behave in a similar way to Wilcox torsion balance.[2]

Wilcox balance **31** measures the strength of C(sp^3)–H···π hydrogen bonds (HBs) present in **31a** and absent in **31b**. We proposed that our balance should measure N(sp^2)–H···π HBs although it was built up on only one example, the trifluoromethyl derivative **24** represented in Scheme 1. We have now decided to verify this assumption studying theoretically a large series of tautomeric pyrazoles and determining the equilibrium constant for two of them.

N–H···π hydrogen bonds are of great importance in protein folding. Thus in some proteins, Phe, Tyr, Trp, aminoacids have π rings that show N···π_m and H···π_m distances less than or equal to 4.3 and 3.5 Å (π_m represent the mid point of the ring).[3,4] N–H···π hydrogen bonds also are important for the determination of crystal structures as Malone,[5] Desiraju ,and Steiner[6] as well as Page and Rzepa have pointed out.[7] There have been a number of theoretical studies on N–H···π interactions, including those of the preceding authors.[7] For instance, ammonia–benzene complex was studied at MP2/CCSD(T) level[8,9] and *N*-methyl-formamide-benzene complex was studied as a prototypical peptide N–H···π hydrogen-bonded system at the DFT and MP2 levels.[10]

2. Results and discussion

2.1. Synthesis

We have synthesized two benzylphenyl pyrazoles **11** and **20** following the procedure described in Scheme 2. β-Diketones **34** and **35** were obtained by Claisen condensation between 2-benzyl-acetophenone (**33**) (prepared from commercial **32**)

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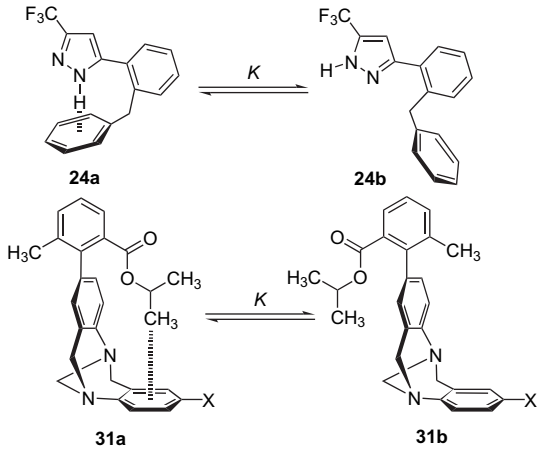
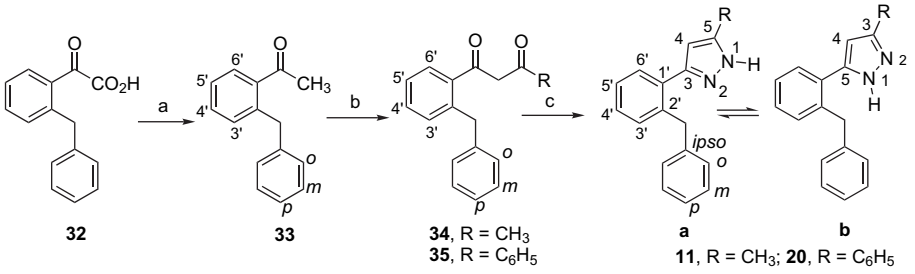


Scheme 1. Comparison of both balances.

protons and the *ortho* protons H2″ of the phenyl substituent, respectively. For 3(5)-(2-benzylbenzylphenyl)-5(3)-phenyl-1*H*-pyrazole (**20**), we have noted that increasing the concentration from 10 to 30 mg in 0.5 mL of DMSO-d_6 produces an increase of the broadening and then a coalescence of the signals indicating that the tautomerization barrier decreases significantly.[12]

2.3. DFT calculation of the a/b equilibrium

In all we have determined the differences in energy (zero point energy, ZPE, corrected) for 30 pyrazoles. When the substituents at positions 3 and 5 are identical (**1**, **8**, **14**, **19**, **23**, **26**, and **28**) the difference in energy is 0.00 by definition and only one tautomer has been calculated. The results in kJ mol^{-1} are



Scheme 2. Reagents and conditions: (a) MeLi/Et_2O; (b) RCO_2Et, NaH, THF; (c) $NH_2NH_2 \cdot H_2O$, EtOH.

and the corresponding ester. Finally, 3(5)-(2-benzylphenyl)-5(3)-methyl-1*H*-pyrazole (**11**) and 3(5)-(2-benzylbenzylphenyl)-5(3)-phenyl-1*H*-pyrazole (**20**) were formed by reacting **34** and **35** with 98% hydrazine hydrate.

2.2. Determination of the a/b equilibrium in solution by NMR

We have reported in Table 1 the NMR results that we obtained for pyrazoles **11**, **20**, and **24**.[1]

The assignments were based on previous work on ^{1}H, ^{13}C, and ^{15}N NMR studies of pyrazoles,[11] as well as on 2D experiments. Particularly useful to achieve such task have been the correlations encountered between the C signals at positions 3 and 5 of pyrazoles **11** and **20** with the methyl reported in Scheme 3, the absolute values are given in the Supplementary data.

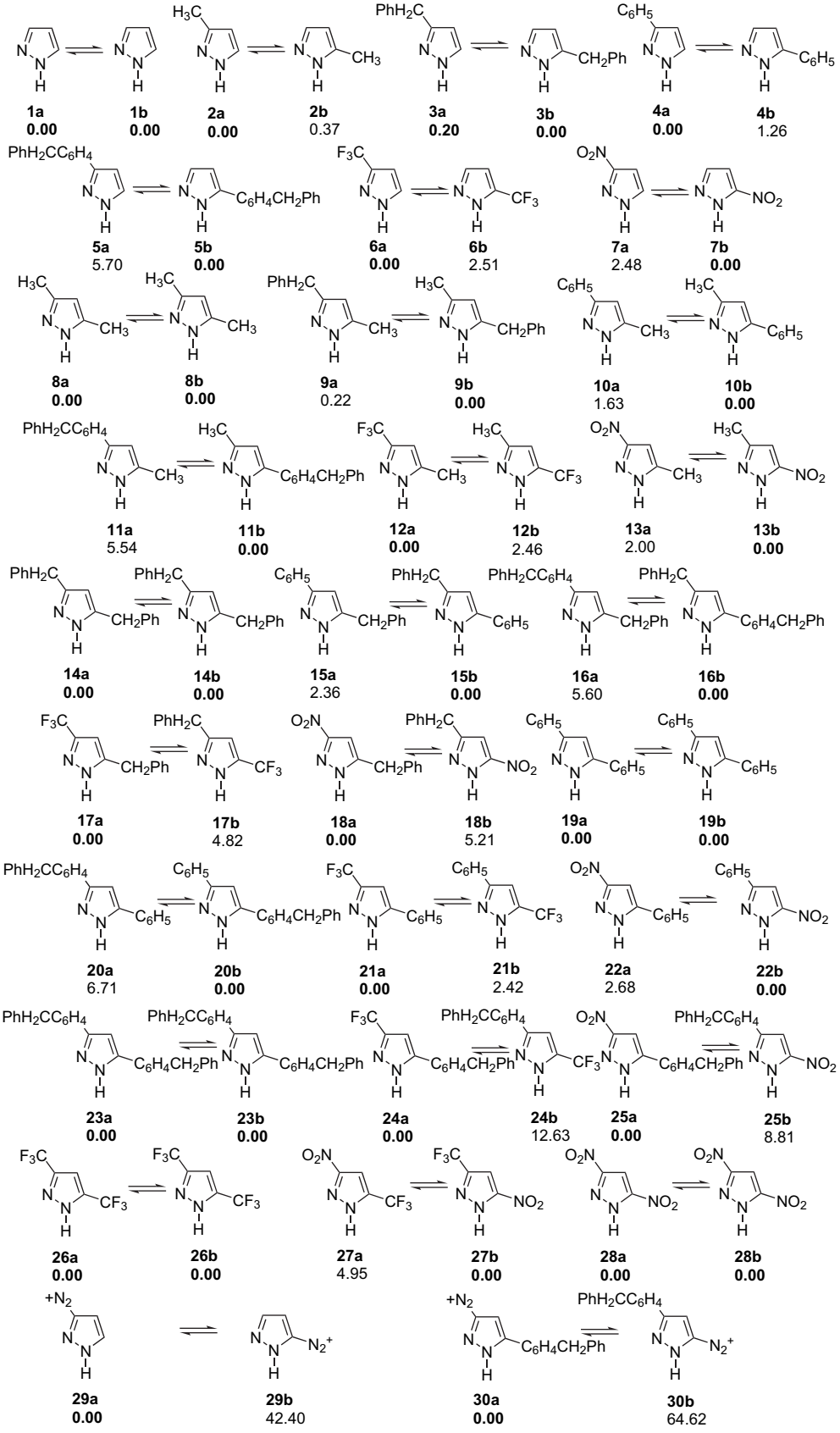
In order to get the effect of the substituents on ΔH, we have built up a matrix of presence/absence (also called Free-Wilson matrix)[13–15] containing all the principal terms (R^3 and R^5 effects) and all the product terms ($R^{3*}R^5$) (the matrix is in the Supplementary data). The matrix is complete for the six substituents CH_3, $CH_2C_6H_5$, C_6H_5, $C_6H_4CH_2C_6H_5$, CF_3, and NO_2 and corresponds to the following equation: $\Delta H = a_1x_1+a_2x_2+\ldots+a_6x_6+a_{11}x_1x_1+a_{12}x_1x_2+\ldots+a_{66}x_6x_6$. For the N_2^+ derivatives, **29** and **30**, only two equilibria were calculated, but the fact that $\Delta H=0$ for 3,5-didiazoniumpyrazole was included.

A multiple regression (R^2=1.000) affords the coefficients of Table 2.

Table 1
Tautomer percentages and ^{1}H, ^{13}C, and ^{15}N NMR selected data of benzylphenyl pyrazoles

Pyrazole	Percentages	Solvent	H-4	H-1	C-3	C-4	C-5	N-1	N-2
11		CD_2Cl_2	6.11	11.69	149.6 (CPhBn)	105.8	143.3 (CMe)		
[a]	90% of **11a**	HMPA-d_{18}	6.14	13.70	151.2 (CPhBn)	103.7	138.4 (CMe)	−175.1	[c]
[a]	10% of **11b**	HMPA-d_{18}	6.01	13.74	146.8 (CMe)	104.6	141.8 (CPhBn)	−171.4	−82.4
20	52% of **20a**	DMSO-d_6	6.91	13.48	151.6 (CPhBn)	102.5	143.2 (CPh)	[c]	[c]
[b]	48% of **20b**	DMSO-d_6	6.80	13.15	150.6 (CPh)	102.5	143.2 (CPhBn)	[c]	[c]
24[1]	>98% of **24a**	$CDCl_3$	6.53	10.60	143.4	103.9	143.8		
[b]	>98% of **24a**	DMSO-d_6	6.69	13.79	141.3	103.5	142.9		
	>98% of **24a**	HMPA-d_{18}	6.58	14.65	141.7	103.5	143.5	−163.9	−80.3

[a] 263 K.
[b] 300 K.
[c] Not detected.



Scheme 3. The 30 studied pyrazoles.

Table 2
Contributions of the different terms (in kJ mol^{-1})

3-Me	0.37	5-Me	−0.37	3-Bn	−0.20
5-Bn	0.20	3-Ph	1.22	5-Ph	−1.18
3-PhBn	−5.62	5-PhBn	5.66	3-CF_3	2.51
5-CF_3	−2.51	3-NO_2	−2.48	5-NO_2	2.48
3-N_2^+	42.40	5-N_2^+	0.00		
3-Me/5-Me	0.00	3-Me/5-Bn	−0.35	3-Me/5-Ph	2.44
3-Me/5-PhBn	*−0.53*	3-Me/5-CF_3	−0.32	3-Me/5-NO_2	−0.85
3-Bn/5-Me	0.35	3-Bn/5-Bn	0.00	3-Bn/5-Ph	3.21
3-Bn/5-PhBn	*0.10*	3-Bn/5-CF_3	−2.11	3-Bn/5-NO_2	2.93
3-Ph/5-Me	−2.52	3-Ph/5-Bn	−3.29	3-Ph/5-Ph	−0.08
3-Ph/5-PhBn	*−0.25*	3-Ph/5-CF_3	−1.17	3-Ph/5-NO_2	−1.06
3-PhBn/5-Me	0.45	3-PhBn/5-Bn	−0.18	3-PhBn/5-PhBn	*−0.08*
3-PhBn/5-CF_3	−4.50	3-PhBn/5-NO_2	−5.67	3-CF_3/5-Me	0.32
3-CF_3/5-Bn	2.11	3-CF_3/5-Ph	1.09	3-CF_3/5-PhBn	*4.42*
3-CF_3/5-CF_3	0.00	3-CF_3/5-NO_2	−0.04	3-NO_2/5-Me	0.85
3-NO_2/5-Bn	−2.93	3-NO_2/5-Ph	0.98	3-NO_2/5-PhBn	*5.59*
3-NO_2/5-CF_3	0.04	3-NO_2/5-NO_2	0.00	3-N_2^+/5-PhBn	*16.52*
5-N_2^+/3-PhBn	5.62	3-N_2^+/5-N_2^+/	−42.40		

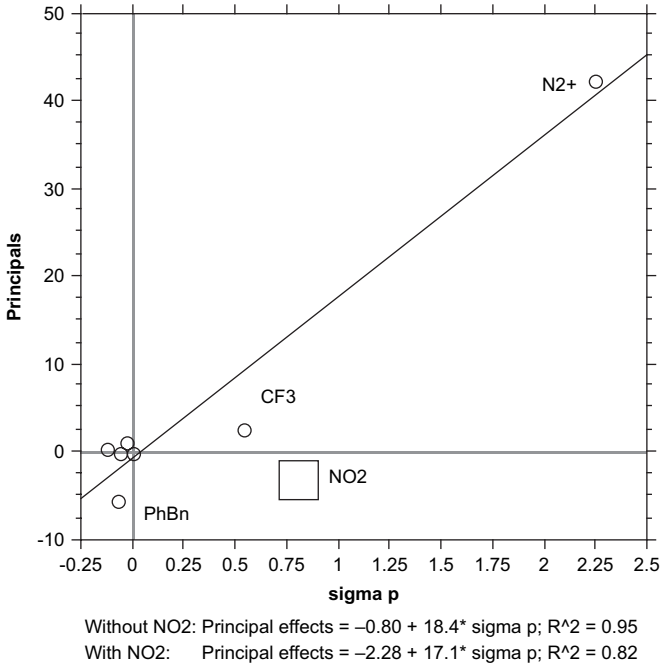


Figure 1. Plot of principal effects versus σ_p.

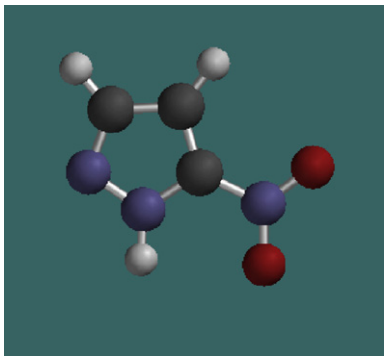


Figure 2. Structure of the minimum of **7b** showing the N−H···ONO HB of 2.478 Å.

Table 3
Interaction terms with the 5-phenylbenzyl substituent (in kJ mol^{-1})

Subs.	Term	σ_p	Subs.	Term	σ_p	Subs.	Term	σ_p
H	0.00	0.00	Me	−0.53	−0.12	Bn	0.10	−0.06
Ph	−0.25	−0.03	PhBn	−0.08	−0.07[a]	CF_3	4.42	0.54
NO_2	5.59	0.78	N_2^+	16.52	1.91[b]			

[a] σ_p of *p*-tolyl.
[b] σ_p value determined only once.[16]

2.3.1. Analysis of the eight principal effects

The principal effects should be identical or statistically very similar for the positions 3 and 5 in order to have ΔH= 0 kJ mol^{-1} when they are the same. This is what happens in Table 2, so they can be averaged: H=0.00, Me=0.37, Bn= −0.20, Ph=1.22, PhBn=−5.62, CF_3=2.51, NO_2=−2.48, and N_2^+=42.40 kJ mol^{-1}.

When the principal effects are plotted against σ_p (Fig. 1), the NO_2 group is the one that deviates most. May be when there is an N−H···ONO HB at position 5 (d_{NO}=2.478 Å), this HB perturbates the effect (see Fig. 2).

The percentages of three compounds experimentally studied (Table 1) transformed into ΔG at 298.15 K are: **11** (90% **11a**/10% **11b**) 5.6 kJ mol^{-1}; **20** (52% **20a**/48% **20b**) 0.2 kJ mol^{-1}; **24** (99% **24b**; 1% **24a**) −12.6 kJ mol^{-1}. The calculated (no temperature correction, Scheme 3) are: **11** 5.54 kJ mol^{-1}; **20** 6.71 kJ mol^{-1} and **24** +12.63 kJ mol^{-1}. The relationship is $\Delta G_{exp.}$=0.73ΔH_{calcd}, R^2=0.82, with a moderate correlation coefficient that is certainly due to the different conditions (solution in DMSO or HMPA at 263 or 300 K vs gas phase at 0 K).

2.3.2. Analysis of the interaction terms: the 5-phenylbenzyl group

We have reported the italicized values of Table 2 in Table 3 together with the corresponding Hammett σ_p values.[16]

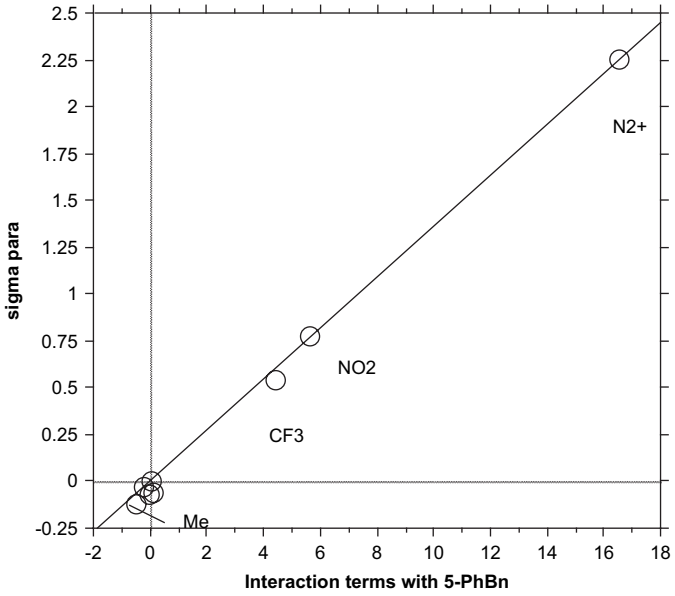


Figure 3. The line corresponds to σ_p=(0.136±0.003) interaction term, n=8, r^2=0.997 (the reciprocal equation is interaction term=(7.34±0.14)σ_p, n=8, r^2=0.997).

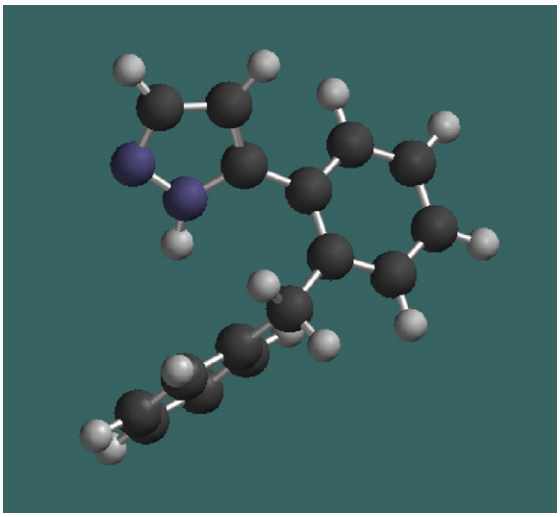


Figure 4. Structure of the minimum of **5b** showing an N–H···π HB of 2.395 Å.

There is a linear relationship between the interaction terms and σ_p. For N_2^+, the fitted value for σ_p is 2.25 instead of 1.91 (Fig. 3).[16] See Figure 4 for an example of N–H···π interaction.

2.3.3. Analysis of other interaction terms

There are other interaction terms between the substituent at position 3 and that at position 5, some of them important, in Table 2, none of them showing linear relationships with Hammett σ constants. Their origin is probably electronic as in *meta* and *para* disubstituted benzenes.[17]

3. Concluding remarks

Having calculated the annular equilibrium constant for the complete series of 3,5-disubstituted pyrazoles bearing methyl, benzyl, phenyl, 2-phenylbenzyl, trifluoromethyl, and nitro substituents (the diazonium group was used as a test), has allowed to solve the problem of determining their effect on K_T. The calculation of interaction terms (non-additivity of 3 and 5 substituent effects) in the case of the 2-phenylbenzyl group has supported our idea that the study of the tautomerism of NH-pyrazoles bearing this substituent can be used as a molecular balance to determine the electronic effects of substituents at position 3 through modifying the strength of the intramolecular N–H···π hydrogen bond.

4. Experimental

4.1 . General

Melting points were determined on a hot-stage microscope and are uncorrected. Thin-layer chromatography (TLC) was performed with Merck silica gel (60 F_{254}). Compounds were detected with a 254-nm UV lamp. Silica gel (60–320 mesh) was employed for routine column chromatography separations.

4.2. Synthesis

*4.2.1. 2-Benzylacetophenone (**33**)*

MeLi (1.6 M, 6.3 mL, 10 mmol) in 200 mL of anhydrous Et_2O was slowly added, under argon atmosphere, to a stirring suspension of 2-benzylbenzoic acid (**32**) (870 mg, 4 mmol) in 200 mL of anhydrous Et_2O cooled at 0 °C. The mixture was stirred for 16 h. Water (200 mL) was added and the organic layer was extracted, washed, respectively, with 200 mL of saturated Na_2CO_3 and saturated NaCl solutions. The ethereal extract was dried (anhydrous $MgSO_4$) and evaporated to give the crude product. 2-Benzylacetophenone was obtained by column chromatography (hexane/ethyl acetate 9/1) as a colorless solid (640 mg, 3.05 mmol, 76%). Mp=38–40 °C (lit. colorless liquid[18]). ^{1}H NMR (400 MHz; $CDCl_3$) δ (ppm): 2.46 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.13 (d, 2H, ^3J=7.6 Hz, H_o), 7.16 (t, 1H, ^3J=7.2 Hz, H_p), 7.23 (dd, 1H, ^3J=7.5 Hz, ^4J=1.2 Hz, H3′), 7.29 (ddd, 1H, ^3J=7.7 Hz, ^3J=7.5 Hz, ^4J=1.2 Hz, H5′), 7.30 (m, 2H, H_m), 7.40 (ddd, 1H, ^3J=^3J=7.5 Hz, ^4J=1.4 Hz, H4′), 7.64 (dd, 1H, ^3J=7.7 Hz, ^4J=1.4 Hz, H6′).

*4.2.2. General procedure for the preparation of β-diketones **34** and **35***

Under argon atmosphere, 12.5 mmol of ester in 5 mL of anhydrous THF was added to a suspension of 20 mmol of NaH in 5 mL of anhydrous THF. The mixture was heated at reflux for 10 min. Then, a suspension of 2-benzylacetophenone (**33**) in anhydrous THF was carefully added for 30 min. The mixture was heated at reflux for 6 h. After cooling, the reaction crude was poured into ice and acidified by a solution of 10% HCl until pH 3–4. The aqueous solution was extracted three times with CH_2Cl_2. The organic extract was washed with saturated aqueous $NaHCO_3$ (40 mL, two times), then with saturated aqueous NaCl (20 mL, two times), dried ($MgSO_4$), and the solvent was evaporated. Chromatography on silica gel eluting with hexane/ethyl acetate mixture (9/1) gave the corresponding β-diketones.

*4.2.2.1. 1-(2-Benzylphenyl)-1,3-butanedione (**34**).* The compound was prepared using ethyl acetate (1.30 mL, 12.5 mmol) as ester to give a colorless oil (2.1 g, 8.33 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.11 (s, 3H, CH_3), 4.24 (s, 2H, CH_2), 5.75 (s, 1H, –CH=C–OH), 7.14 (m, 2H, H_o), 7.19 (t, 1H, ^3J=7.4 Hz, H_p), 7.20 (dd, 1H, ^3J=7.6 Hz, ^4J=1.2 Hz, H3′), 7.25–7.29 (m, 3H, H5′ and H_m), 7.36 (ddd, 1H, ^3J=^3J=7.6 Hz, ^4J=1.3 Hz, H4′), 7.45 (dd, 1H, ^3J=7.7 Hz, ^4J=1.3 Hz, H6′), 15.88 (s, 1H, OH).

*4.2.2.2. 1-(2-Benzylphenyl)-3-phenyl-1,3-butanedione (**35**).* The compound was prepared using ethyl benzoate (1.80 mL, 12.5 mmol) as ester to give a colorless oil (2.7 g, 8.59 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.31 (s, 2H, CH_2), 6.42 (s, 1H, –CH=C–OH), 7.19 (d, 2H, ^3J=7.8 Hz, H_o), 7.27 (t, 1H, ^3J=6.9 Hz, H_p), 7.33 (ddd, 1H, ^3J=^3J=7.5 Hz, ^4J=0.8 Hz, H5′), 7.40–7.46 (m, 4H), 7.51–7.60 (m, 3H), 7.80 (d, 1H, ^3J=8.6 Hz), 8.06 (dd, 2H, ^3J=7.1 Hz, ^4J=1.6 Hz), 16.56 (s, 1H, OH).

4.2.3. General procedure for the preparation of pyrazoles **11** and **20**

A mixture of 1,3-butanedione **34** or **35** (0.02 mmol) and 98% hydrazine monohydrate (0.03 mmol) in EtOH (10 mL) was heated at reflux for 4 h and then stirred for additional 12 h at room temperature. The solvent was then removed under reduced pressure and the remaining residue was chromatographed on silica gel eluting with hexane/ethyl acetate 9/1 to furnish the desired pyrazole.

*4.2.3.1. 3(5)-(2-Benzylphenyl)-5(3)-methyl-1H-pyrazole (**11**).* From **34** (1 g, 3.96 mmol) it was obtained as a yellow oil (hexane/ethyl ether) (521 mg, 2.10 mmol, 53%). ^{1}H NMR (400 MHz, CD_2Cl_2, 300 K) δ (ppm): 2.08 (s, Me), 4.19 (s, CH_2), 6.11 (s, H4), 7.21 (dd, ^3J=7.9 Hz, ^4J=1.6 Hz, H3′), 7.30 (ddd, ^3J=7.9 Hz, ^3J=7.5 Hz, ^4J=1.6 Hz, H4′), 7.25 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.6 Hz, H5′), 7.49 (dd, ^3J=7.5 Hz, ^4J=1.6 Hz, H6′), 7.08 (m, H_o), 7.23 (m, H_m), 7.17 (tt, ^3J=7.3 Hz, ^4J=1.7 Hz, H_p), 11.69 (s, NH). ^{13}C NMR (100 MHz, CD_2Cl_2, 300 K) δ (ppm): 11.6 (q, ^1J=128.0 Hz, Me), 39.6 (td, ^1J=127.6 Hz, ^3J=4.0 Hz, CH_2), 105.8 (m, ^1J=173.6 Hz, ^3J=^3J=^3J=3.0 Hz, C4), 143.3 (br s, CMe), 149.6 (br s, CPhBn), 133.5 (s, C1′), 139.8 (m, ^3J=^3J=^2J=^2J=6.4 Hz, C2′), 131.1 (m, ^1J=157.9 Hz, ^3J=^3J=^3J=6.0 Hz, C3′), 128.9 (m, ^1J=163.6 Hz, ^3J=8.2 Hz, C4′), 126.8 (m, ^1J=163.0 Hz, ^3J=7.8 Hz, C5′), 130.5 (m, ^1J=162.3 Hz, ^3J=6.8 Hz, C6′), 129.4 (m, ^1J=163.4 Hz, ^3J=^3J=^3J=5.8 Hz, C_o), 128.7 (m, ^1J=160.0 Hz, ^3J=7.5 Hz, C_m), 126.4 (m, ^1J=160.1 Hz, ^3J=^3J=7.5 Hz, C_p), 142.1 (m, ^3J=^3J=^2J=^2J=7.0 Hz, C_{ipso}). ^{1}H NMR (400 MHz, HMPA-d_{18}, 263 K) δ (ppm): 2.19 (10%) and 2.32 (90%) (s, Me), 4.19 (10%) and 4.37 (90%) (s, CH_2), 6.01 (10%) and 6.14 (90%) (s, H4), 7.09 (m, H3′), 7.19 (m, H4′), 7.24 (m, H5′), 7.55 (m, H6′), 7.20 (m, H_o), 7.25 (m, H_m), 7.16 (m, H_p), 13.70 (90%) and 13.74 (10%) (s, NH). ^{13}C NMR (100 MHz, HMPA-d_{18}, 263 K) δ (ppm): 10.7 (90%) and 13.9 (10%) (q, Me), 39.2 (td, CH_2), 103.7 (90%) and 104.6 (10%) (d, C4), 138.4 (90%) and 146.8 (10%) (br s, CMe), 151.2 (90%) and 141.8 (10%) (br s, CPhBn), 134.9 (s, C1′), 138.9 (m, C2′), 130.8 (m, C3′), 127.2 (m, C4′), 126.1 (m, C5′), 129.7 (m, C6′), 129.4 (m, C_o), 128.5 (m, C_m), 126.0 (m, C_p), 142.5 (m, C_{ipso}). ^{15}N NMR (100 MHz, HMPA-d_{18}, 300 K) δ (ppm): −171.4 (90%) (d, ^1J=106.8 Hz, N1), and −175.1 (10%) (N1), −82.4 (N2).

*4.2.3.2. 3(5)-(2-Benzylbenzylphenyl)-5(3)-phenyl-1H-pyrazole (**20**).* From **35** (1 g, 3.18 mmol) it was obtained as a white oil (641 mg, 2.06 mmol, 65%); all attempts to crystallize the oil by treating it with hexane/ethyl ether gave rise to a gel. ^{1}H NMR (400 MHz, CD_2Cl_2, 300 K) δ (ppm): 4.18 (s, CH_2), 6.60 (s, H4), 7.28 (m, H3′), 7.36 (ddd, ^3J=7.5 Hz, ^3J=7.5 Hz, ^4J=1.5 Hz, H4′), 7.32 (m, H5′), 7.50 (dd, ^3J=7.5 Hz, ^4J=1.5 Hz, H6′), 7.08 (m, H_o), 7.25 (m, H_m), 7.18 (dd, ^3J=^3J=7.3 Hz, H_p), 7.73 (m, H2″), 7.40 (m, H3″), 7.33 (tt, ^3J=7.5 Hz, ^4J=1.6 Hz, H4″), 9.89 (s, NH). ^{13}C NMR (100 MHz, CD_2Cl_2, 300 K) δ (ppm): 39.8 (td, ^1J=127.6 Hz, ^3J=3.7 Hz, CH_2), 103.6 (d, ^1J=175.1 Hz, C4), 150.0 (br s, CPh), 147.0 (br s, CPhBn), 131.6 (s, C1′), 139.6 (m, ^3J=^3J=^2J=^2J=^2J=6.2 Hz, C2′), 131.6 (m, ^1J=158.3 Hz, ^3J=^3J=^3J=5.8 Hz, C3′), 129.3 (m, ^1J=160.2 Hz, ^3J=7.4 Hz, C4′), 127.2 (m, ^1J=162.8 Hz, ^3J=7.8 Hz, C5′), 130.3 (m, ^1J=161.5 Hz, ^3J=7.6 Hz, C6′), 129.2 (m, ^1J=160.6 Hz, ^3J=^3J=7.2 Hz, C_o), 129.1 (m, ^1J=160.6 Hz, ^3J=7.6 Hz, C_m), 126.6 (m, ^1J=160.4 Hz, ^3J=^3J=7.4 Hz, C_p), 141.8 (m, ^3J=^3J=^2J=^2J=6.4 Hz, C_{ipso}), 132.7 (m, ^3J=^3J=7.4 Hz, C1″), 126.1 (m, ^1J=158.6 Hz, ^3J=^3J=6.9 Hz, C2″), 129.3 (m, ^1J=160.2 Hz, ^3J=7.4 Hz, C3″), 128.6 (m, ^1J=161.1 Hz, ^3J=^3J=7.7 Hz, C4″). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K) δ (ppm): 4.15 (48%) and 4.34 (52%) (s, CH_2), 6.80 (48%) and 6.91 (52%) (s, H4), 7.22 (m, H3′), 7.32 (m, H4′), 7.32 (m, H5′), 7.58 (m, H6′), 7.05 (m, H_o), 7.23 (m, H_m), 7.14 (m, H_p), 7.80 (m, H2″), 7.44 (m, H3″), 7.32 (m, H4″), 13.15 (48%) and 13.48 (52%) (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6, 300 K) δ (ppm): 38.5 (td, ^1J=127.8 Hz, ^3J=3.6 Hz, CH_2), 102.5 (d, ^1J=174.6 Hz, C4), 150.6 and 143.2 (br s, CPh), 151.6 and 143.2 (br s, CPhBn), 128.8 (s, C1′), 138.7 (m, C2′), 130.6 (m, C3′), 128.0 (m, C4′), 126.3 (m, C5′), 129.5 (m, C6′), 128.7 (m, C_o), 128.3 (m, C_m), 125.8 (m, C_p), 140.8 and 141.5 (m, C_{ipso}), 133.4 and 133.7 (m, C1″), 125.1 (m, C2″), 128.8 (m, C3″), 127.7 (m, C4″).

4.3. NMR experiments

4.3.1. Solution

The spectra were recorded on a Bruker DRX 400 (9.4 T, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C, and 40.56 MHz for ^{15}N) spectrometer with a 5-mm inverse detection H–X probe equipped with a *z*-gradient coil at 300 K. Chemical shifts (δ in ppm) are given from internal solvent, for ^{1}H, $CDCl_3$ (7.26), CD_2Cl_2 (5.32), DMSO-d_6 (2.49), HMPA-d_{18} (2.52), for ^{13}C, $CDCl_3$ (77.0), CD_2Cl_2 (53.8), DMSO-d_6 (39.5), HMPA-d_{18} (35.8). For ^{15}N, nitromethane (0.00) was used as external references. Typical parameters for ^{1}H NMR spectra were spectral width 3100–3900 Hz, pulse width 7.5 ms, and resolution 0.19–0.24 Hz per point. Typical parameters for ^{13}C NMR spectra were spectral width 13,800–20,600 Hz, pulse width 10.6 μs, and resolution 0.42–0.63 Hz per point; WALTZ-16 was used for broadband proton decoupling; the FIDS were multiplied by an exponential weighting (lb=1 Hz) before Fourier transformation. 1D ^{15}N NMR was acquired using inverse gated decoupling and typical parameters were spectral width 14.368 Hz, pulse width 28.5 μs, relaxation delay 30 s, and resolution 0.44 Hz per point; WALTZ-16 was used for proton decoupling; the FIDS were multiplied by an exponential weighting (lb=2 Hz) before Fourier transformation. 2D (^{1}H–^{1}H) gs-COSY and inverse proton detected heteronuclear shift correlation spectra, (^{1}H–^{13}C) gs-HMQC, and (^{1}H–^{13}C) gs-HMBC were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode, and the NOESY experiment was acquired with a mixing time of 1100 ms. Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms.

4.3.2. Variable temperature (VT)

VT experiments were carried out to study proton-transfer dynamics in the temperature range of 300–180 K. A

temperature unit was used to control the cooling gas together with an exchanger to reach low temperatures. To avoid the problems due to air humidity at low temperatures, we used pure nitrogen obtained by evaporation of liquid nitrogen as the bearing, driving, and cooling gas.

4.4. Theoretical calculations

Energy calculations were carried out at the hybrid Becke B3LYP/6-31G** level[19–21] with basis sets of Gaussian type functions[22] within the Windows Titan 1.0.5 package and include zero point energy (ZPE) corrections. Starting geometries for the calculations were the optimized ones obtained at the HF/6-31G** level. In all cases the final geometries really correspond to the minima as no imaginary frequencies appear.

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Supplementary data

Contains a table with the calculations (energies, ZPE correction, dipole moment) and the Free-Wilson matrix. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.026.

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