An Analysis of ^{1}H, ^{13}C and ^{15}N NMR Substituent Chemical Shifts in *para*- and *meta*-Substituted (*Z*)-Phenylhydrazones of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole

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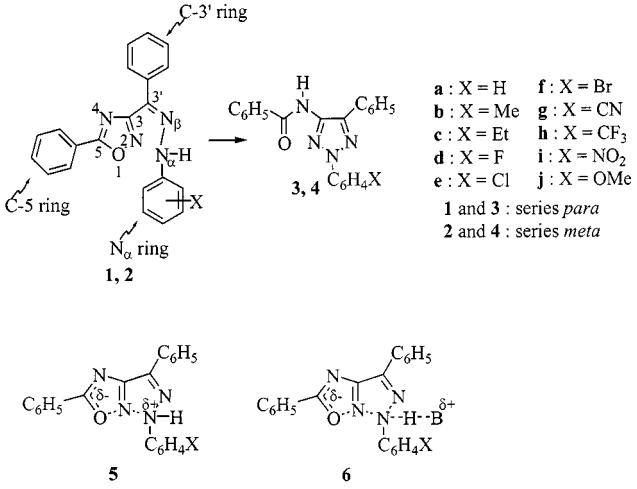
The ^{1}H, ^{13}C and ^{15}N chemical shifts of the title compounds have been measured in $CDCl_3$ solutions. The data obtained allowed a map of the ground-state electronic distribution in such (Z)-arylhydrazones to be sketched, indicating to what extent the substituent in the aryl component of the arylhydrazono moiety affects the electronic density at the key atoms involved in the mononuclear heterocyclic rearrangements (MHR) characteristic of these substrates: the hydrogen atom bound to N_α (which affects the nucleophilic character of N_α), N-2 (which affects the electrophilic character of N-2 itself) and C-5 (which affects the nucleofugacity of the N-4/C-5/O-1 system).

Introduction

The *para*- and *meta*-substituted (*Z*)-phenylhydrazones of 3-benzoyl-1,2,4-oxadiazoles (**1** and **2**, respectively) easily rearrange (Scheme 1) into 2-aryl-5-phenyl-4-benzoylamino-1,2,3-triazoles (**3** and **4**, respectively) on melting or in solution in the presence of bases.[1] Such azole−azole interconversion, an S_{N_i} process [named mononuclear heterocyclic rearrangement[1a] (MHR)], represents a peculiar case of the "monocyclic rearrangement of heterocycles" recognized by Boulton, Katritzky and Majid-Hamid[1c−1f] as a general ring−ring interconversion. Many solution kinetic data have been collected: in water/dioxane (1:1, v:v)[2] and also in various organic solvents (dioxane, benzene, ethyl acetate, acetonitrile and methanol)[3,4] in the presence of buffers or of several organic bases. All the results in water/dioxane have evidenced − in the case of **1a**, for example − the occurrence of two different kinds of S_{N_i} of nitrogen onto nitrogen. In addition, on the basis of the effects of substituents in the arylhydrazono moiety on reactivity, the transitional structures **5** and **6** have been proposed for the two pathways.

Thus, at pS^+ [2c] = 3.8 (uncatalysed pathway) electron-repelling and -withdrawing substituents increase and decrease the reactivity, respectively.[2a] In contrast, in the pS^+-dependent region (e.g., at $pS^+ = 10.0$) both electron-repelling and -withdrawing substituents increase the reactivity, and two separate linear free energy relationships have been observed.[2b] This result suggests that the substituent X affects the structure of the transition state by affecting, to different degrees, both the base-induced nitrogen−hydrogen bond-breaking and the nitrogen−nitrogen bond-formation, causing a different relative timing of bond-formation and bond-breaking as a function of the substituent.



Scheme 1

The results of the kinetic studies induced us to investigate the ^{15}N and ^{13}C NMR behaviour of the (*Z*)-arylhydrazones **1** and **2** in order to provide a picture of the ground-state electronic distributions in these molecules. It was to be expected that the results from this would be useful for better

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understanding of the mechanism(s) of the rearrangement. It would surely be of particular interest to map the electronic densities on the atoms of the 1,2,4-oxadiazole rings and to gain information on the effect of substituents: As a matter of fact the electronic density on N-2 (i.e., its electrophilic character) affects nucleophilic attack of the arylhydrazono nitrogen atom, while the electronic density on C-5 affects the leaving group ability of the N-4/C-5/O-1 system. Obviously, it is also to be expected that the substituent X would greatly influence the electronic density (and thus the nucleophilicity) of the nitrogen atoms of the arylhydrazono moiety. In this regard, a comparison with recent results from a ^{15}N and ^{13}C NMR study of some *meta*- and *para*-substituted arylhydrazines[5] could be useful. Moreover, the electronic density on the proton to be transferred should in turn be of relevance in that the proposed transition state structures assign a role to solvent assistance (in the pS^+-independent region) or to base catalysis (in the pS^+-dependent region) for the $N_\alpha-H$ bond-breaking.

So far, NMR studies of arylhydrazones have received little attention in spite of their biological importance,[6] their analytical interest[7] and their use as intermediates in organic synthesis.[1,8] Thus, literature data concerning ^{13}C NMR spectroscopy are available for *para*-substituted hydrazones and phenylhydrazones[9] of benzaldehyde with particular attention to ^{13}C chemical shifts of the azomethine carbon atom, which show a "reverse" trend in the transmission of the substituent electronic effect when the Hammett equation is used. Recently, the dual substituent parameter (DSP) approach has been applied to the C=N ^{13}C chemical shifts of two series of (2-hydroxycyclohexyl)hydrazones of *meta*- and *para*-substituted benzaldehydes;[10] once again a reverse trend was apparent from analysis of SCS data, and the inductive effects of the substituents appeared predominant for both *meta*- and *para*-substituted compounds.

As far as ^{15}N NMR spectroscopy is concerned, only a very few data are available. An investigation[11] into five 1-(arylmethylidene)-2-phenyldiazanes has shown that the N-2 chemical shifts are quite sensitive to substituent changes, due to contributions of resonance structures that involve this nucleus; in addition the transmission of substituent effects is normal for both the nitrogen atoms. It is also relevant to note that a ^{15}N NMR study of some azoles in DMSO[12] has provided the basis for the assignment of 1,2,4-oxadiazole nitrogen resonances.

Results and Discussion

^{13}C and ^{15}N NMR spectroscopic data of compounds **1** and **2** in $CDCl_3$ are reported, together with proton $N_\alpha-H$ data, in Tables 1, 2 and 3. The numbering of atoms and identification of rings are indicated in the formulas

Table 1. ^{13}C NMR substituent-induced chemical shifts [SCS = $\delta_X - \delta_H$] for compounds **1**[a] in $CDCl_3$

Carbon atom:	X	3	5	1 (C-5 ring)	2,6 (C-5 ring)	3,5 (C-5 ring)	4 (C-5 ring)	3′	1 (C-3′ ring)	2,6 (C-3′ ring)	3,5 (C-3′ ring)	4 (C-3′ ring)	1 (N_α ring)	2,6 (N_α ring)	3,5 (N_α ring)	4 (N_α ring)
1a[a]	H	163.87	174.22	123.43	128.26	129.12	133.16	126.22	136.70	128.34	127.93	127.86	143.81	113.91	129.24	121.69
1b	Me[b]	+0.11	−0.05	+0.11	+0.07	+0.05	+0.03	−0.65	+0.14	−0.01	+0.03	−0.10	−2.24	−0.01	+0.56	+9.44
1c	Et[c]	+0.13	−0.02	+0.15	+0.08	+0.05	+0.02	−0.58	+0.18	0.00	+0.02	−0.10	−2.01	+0.11	−0.62	+16.08
1e	Cl	+0.05	+0.25	−0.01	+0.15	+0.14	+0.21	+0.85	−0.25	+0.07	+0.12	+0.31	−1.32	+1.12	+0.02	+4.72
1f	Br	−0.04	+0.15	−0.10	+0.05	+0.06	+0.13	+0.88	−0.31	+0.03	+0.05	+0.26	−0.91	+1.50	+2.84	−7.98
1g	CN[d]	−0.20	+0.65	−0.30	+0.13	+0.21	+0.49	+3.55	−0.88	+0.19	+0.21	+0.92	+3.29	0.00	+4.41	−17.87
1i	NO_2	−0.19	+0.86	−0.31	+0.19	+0.29	+0.58	+4.71	−1.01	+0.30	+0.31	+1.19	+5.10	−0.74	−3.26	+20.01
1j	OMe[e]	+0.16	−0.13	+0.13	+0.03	+0.05	+0.02	−1.06	+0.19	0.00	+0.02	−0.18	−6.00	+1.12	−14.52	+33.30
ΔSCS:[f]		0.36	0.99	0.46	0.19	0.29	0.58	5.77	1.20	0.31	0.31	1.37	11.10	2.24	18.93	51.17

[a] ^{13}C chemical shifts (ppm) for the parent compound **1a** are relative to $CDCl_3$ (δ = 77.00 with respect to TMS). [b] CH_3 (δ = 20.70). [c] CH_2 (δ = 28.19), CH_3 (δ = 15.76). [d] CN (δ = 119.58). [e] OCH_3 (δ = 55.59). [f] ΔSCS range of substituent effect on chemical shifts.

Table 2. ^{13}C NMR substituent-induced chemical shifts [SCS = $\delta_X - \delta_H$] for compounds **2** in $CDCl_3$

Carbon atom:	X	3	5	1 (C-5 ring)	2,6 (C-5 ring)	3,5 (C-5 ring)	4 (C-5 ring)	3′	1 (C-3′ ring)	2,6 (C-3′ ring)	3,5 (C-3′ ring)	4 (C-3′ ring)	1 (N_α ring)	2 (N_α ring)	3 (N_α ring)	4 (N_α ring)	5 (N_α ring)	6 (N_α ring)
2a[a]	H	163.87	174.22	123.43	128.26	129.12	133.16	126.22	136.70	128.34	127.93	127.86	143.81	113.91	129.24	121.69	129.24	113.91
2b	Me[b]	−0.02	−0.11	−0.07	−0.02	−0.02	−0.01	−0.30	0.00	+0.01	0.00	−0.04	−0.12	+0.49	+9.90	+0.90	−0.17	−2.78
2c	Et[c]	+0.13	+0.06	+0.14	+0.10	+0.07	+0.05	−0.14	+0.13	+0.07	+0.05	0.00	+0.09	−0.46	+16.43	−0.22	−0.01	−2.39
2d	F	+0.02	+0.33	−0.04	+0.14	+0.16	+0.26	+1.18	−0.33	+0.13	+0.16	+0.43	+1.86	−12.81	+34.76	−13.49	+1.21	−4.30
2e	Cl	−0.07	+0.25	−0.14	+0.08	+0.10	+0.20	+1.27	−0.42	+0.10	+0.11	+0.39	+1.17	−0.09	+5.96	−0.23	+0.99	−1.81
2f	Br	−0.11	+0.21	−0.16	+0.05	+0.07	+0.17	+1.30	−0.45	+0.09	+0.08	+0.37	+1.24	+2.75	−5.97	+2.66	+1.25	−1.36
2h	CF_3[d]	+0.03	+0.44	−0.08	+0.15	+0.18	+0.30	+1.82	−0.45	+0.17	+0.19	+0.55	+0.50	−3.38	+2.54	−3.67	+0.55	+3.04
2i	NO_2	−0.04	+0.65	−0.19	+0.19	+0.24	+0.43	+2.88	−0.75	+0.22	+0.25	+0.82	+1.21	−5.41	+20.13	−5.70	+0.80	+5.55
ΔSCS:[e]		0.24	0.76	0.33	0.21	0.26	0.44	3.18	0.88	0.22	0.25	0.86	1.98	15.56	40.73	16.15	1.42	9.85

[a] ^{13}C chemical shifts (ppm) for the parent compound **2a** are relative to $CDCl_3$ (δ = 77.00 with respect to TMS). [b] CH_3 (δ = 21.56). [c] CH_2 (δ = 29.01), CH_3 (δ = 15.54). [d] CF_3 (δ = 124.14). [e] ΔSCS range of substituent effect on chemical shifts.

(Scheme 1). The data are given as proton, carbon and nitrogen shifts relative to those of the unsubstituted compound **1a** (SCS values), negative and positive SCS values indicating shielding and deshielding, respectively, of the hydrogen, nitrogen or carbon nucleus. In addition, ΔSCS values for *para*- and *meta*-substituents are listed. Assignments of proton, carbon and nitrogen resonances were based on literature data.[9,12]

Table 3. ^1H and ^{15}N NMR substituent-induced chemical shifts [SCS = $\delta_X - \delta_H$] for compounds **1** and **2** in $CDCl_3$

Compound	X	N-2	N-4	N_α	N_β	$H-N_\alpha$
1a = **2a**[a]	H	−26.24	−148.58	−225.42	−44.38	11.45
1b	Me	−0.72	+0.06	+0.34	+0.70	−0.05
1c	Et	−0.72	+0.12	+0.46	+0.86	−0.05
1e	Cl	+0.10	−0.24	−1.79	−1.67	−0.01
1f	Br	+0.46	−0.13	−1.86	−1.85	−0.01
1g	CN[b]	+2.61	−0.53	−1.20	−5.15	+0.25
1i	NO_2 [c]	+3.25	−0.72	−0.47	−5.81	+0.38
1j	OMe	−1.46	+0.05	−0.56	+1.18	−0.07
	ΔSCS:[d]	4.71	0.84	2.32	6.99	0.45
2b	Me	−0.76	+0.78	+0.34	+0.31	−0.05
2c	Et	−	−	−	−	−0.05
2d	F	+0.78	−0.39	−1.33	−1.95	+0.04
2e	Cl	+1.09	−0.26	−2.14	−2.16	+0.04
2f	Br	+1.04	−0.25	−2.35	−2.33	0.00
2h	CF_3	+0.86	−0.32	−2.05	−2.98	+0.09
2i	NO_2 [e]	+2.03	−0.38	−3.58	−4.33	+0.20
	ΔSCS:[d]	2.79	1.17	3.92	4.64	0.25

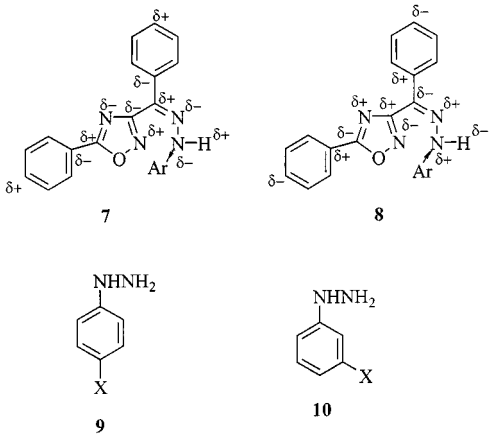
[a] ^1H and ^{15}N chemical shifts (ppm) for parent compound (**1a** = **2a**, X = H) are relative to TMS and to external $CH_3{}^{15}NO_2$, respectively. [b] *C*N (δ = −133.6). [c] *N*O_2 (δ = −12.23). [d] ΔSCS range of substituent effect on chemical shifts. [e] *N*O_2 (δ = −11.72).

Compounds **1** and **2** were synthesised from 3-benzoyl-5-phenyl-1,2,4-oxadiazole by treatment with *meta*- and *para*-substituted phenylhydrazines. This reaction gives a mixture of the corresponding (*Z*)- and (*E*)-arylhydrazones, with the experimental conditions affecting the (*Z*)/(*E*) ratios, as we have already pointed out.[13] The separation of the two isomers is easily achieved by spontaneous and partial crystallisation of the (*Z*) isomer and by chromatography on a silica gel column (cyclohexane/ethyl acetate as eluent) of the crude reaction product. The (*Z*) and (*E*) configurations were confirmed on the basis of spectroscopic data (see below) and of the different reactivities [(*Z*) isomers easily undergoing base-catalysed rearrangement into the corresponding triazoles **3** and **4**].[13−15]

As some of us have already pointed out,[13] IR and ^1H NMR spectra appear to be especially useful for structural characterization of the isomers. For example, IR spectra of the unsubstituted phenylhydrazone **1a** in nujol or chloroform showed the presence of the NH group, for which a significant change in the stretching frequency (Δν = 60−80 cm^{-1})[13] was observed on going from the (*E*) to the (*Z*) isomer, strongly suggesting the occurrence of an intramolecular hydrogen bond in both solvents. Moreover, comparison of the ^1H NMR spectra of the two stereoisomers in $CDCl_3$ and in [D_6]DMSO strongly confirmed the presence of an intramolecular hydrogen bond in $CDCl_3$, which is of course disrupted in [D_6]DMSO.[13] It should be remarked that the proton resonance of the NH group of the (*Z*) isomer in $CDCl_3$ (δ = 11.45) is not affected by its concentration in the 8×10^{-4} to 2.7×10^{-2} mol l^{-1} range.

The occurrence of an intramolecular hydrogen bond in $CDCl_3$ does not affect the course of the reaction in water/dioxane (see Scheme 1, formulas **5** and **6**), since this mixed solvent is by itself a good HBA (hydrogen-bond acceptor) solvent[16] and therefore acts in a manner similar to DMSO.

An examination of the data collected in the Tables allows these general comments. For the *para* derivatives **1**, carbon atoms of the 5-phenyl group [from C-1 (C-5 ring) to C-6 (C-5 ring)] are little affected (ΔSCS = 0.2−0.6) by the very remote substituent present in the arylhydrazono moiety. Similarly, for carbon atoms of the phenyl group at C-3′, small ΔSCS ranges (0.3) are likewise observed for C-2,6 (C-3′ ring) and C-3,5 (C-3′ ring). Thus, only C-1 (C-3′ ring) and C-4 (C-3′ ring) (i.e., the carbon atom directly linked to the azomethine moiety and the carbon atom occupying the *para* position) show significant ΔSCS values (1.2−1.4). Larger and smaller resonance variations were observed for C-3′, N_β or N-2, and for C-3, C-5 or N_α, respectively. Moreover, the aromatic carbon atoms of the arylhydrazono moiety [from C-1 (N_α ring) to C-6 (N_α ring)] show variations characteristic of *para*- or *meta*-substituted benzene rings. Atoms linked to double bonds (such as C-3′ and N_β), and adjacent atoms of several conjugated systems [such as C-3′ with respect to C-3, or C-5 with respect to C-1 (C-5 ring)] show some interesting alternate polarisation, well evidenced in **7** and **8** (Scheme 2).



Scheme 2

The substituent effects observed in **2** are generally similar to those commented on for **1**. One-parameter correlations have been obtained (data in Tables 4 and 5) through the use of classical σ_p and σ_m substituent constants.[17] A dissection of substituent electronic effects into their inductive and resonance components by use of σ_I and σ_R° constants[17] (excellent correlations have been calculated; in most cases the *R* values are ≥ 0.99 − only some significant data are re-

Table 4. Statistical data for the cross-correlations and for the Hammett and DSP analysis of SCS values of proton, carbon and nitrogen atoms of compounds **1**

Line	Probe atom	$\rho \pm s_\rho$ (or $\beta \pm s_\beta$)[a]	SCS of the probe atom, or substituent constant	$i \pm s_i$	n	r or R
1	H−N_α	0.39 ± 0.06	σ_p	−0.01 ± 0.02	8	0.938
2	C-3	−0.33 ± 0.04	σ_p	0.06 ± 0.02	8	0.962
3	C-5	0.88 ± 0.06	σ_p	0.06 ± 0.03	8	0.985
4	C-3′	5.18 ± 0.29	σ_p	0.05 ± 0.12	8	0.991
5	C-1 (C-3′ ring)	−1.18 ± 0.05	σ_p	−0.04 ± 0.02	8	0.994
6	C-4 (C-3′ ring	1.26 ± 0.07	σ_p	0.07 ± 0.03	8	0.990
7	C-1 (C-5 ring)	−0.45 ± 0.04	σ_p	0.04 ± 0.02	8	0.978
8	C-4 (C-5 ring)	0.55 ± 0.06	σ_p	0.09 ± 0.02	8	0.967
9	C-1 (N_α ring)	7.97 ± 1.28	σ_p	−1.92 ± 0.53	8	0.931
10	N-2	4.09 ± 0.26	σ_p	−0.28 ± 0.11	8	0.988
11	N-4	−0.74 ± 0.07	σ_p	−0.04 ± 0.10	8	0.974
12	N_β	−6.77 ± 0.23	σ_p	−0.27 ± 0.10	8	0.997
13	C-1 (N_α ring)	ρ_I: 7.56 ± 0.87 ρ_{R°: 14.82 ± 1.29	σ_I, σ_{R°	−0.20 ± 0.41	8	0.987
14[b]	C-3′	−14.35 ± 1.93	C-3	1.00 ± 0.25	8	0.950
15[b]	N-2	−11.64 ± 1.09	C-3	0.47 ± 0.14	8	0.974
16[b]	C-3′	−4.39 ± 0.23	C-1 (C-3′ ring)	0.10 ± 0.11	8	0.992
17[b]	C-3′	−0.76 ± 0.04	N_β	−0.16 ± 0.12	8	0.991
18[b]	C-1 (C-3′ ring)	−3.98 ± 0.52	C-2,6 (C-3′ ring)	0.05 ± 0.08	8	0.952
19[b]	C-1 (C-3′ ring)	−0.92 ± 0.04	C-4 (C-3′ ring)	0.02 ± 0.02	8	0.993
20[b]	N-4	−0.84 ± 0.05	C-5	0.00 ± 0.02	8	0.988
21[b]	C-1 (C-5 ring)	−0.48 ± 0.07	C-5	0.06 ± 0.03	8	0.945
22	H−N_α	0.22 ± 0.02	H−N_α (**9**)[c]	−0.02 ± 0.02	6	0.981
23	C-1 (N_α ring)	1.06 ± 0.01	C-1 (**9**)[c]	0.01 ± 0.03	6	0.9999
24	C-3,5 (N_α ring)	1.03 ± 0.04	C-3,5 (**9**)[c]	0.08 ± 0.22	6	0.998
25	C-4 (N_α ring)	0.94 ± 0.03	C-4 (**9**)[c]	1.34 ± 0.48	6	0.998

[a] ρ, susceptibility constant for the single-parameter or for DSP analysis; β, slope of the cross-correlation; i, intercept; s_ρ, s_β, and s_i, standard deviations; n, number of points; r or R, correlation coefficients. [b] Cross-correlations between SCSs of probe atoms in compounds **1**. [c] Data of probe atoms of compounds **9** in [D_6]DMSO (see ref.[5]).

Table 5. Statistical data for the cross-correlations and for the Hammett and DSP analysis of SCS values of proton, carbon and nitrogen atoms of compounds **2**

Line[a]	Probe atom	$\rho \pm s_\rho$ (or $\beta \pm s_\beta$)	SCS of the probe atom, or substituent constant	$i \pm s_i$	n	r or R
1	H−N_α	0.26 ± 0.05	σ_m	−0.04 ± 0.02	8	0.909
2	C-5	0.83 ± 0.11	σ_m	0.01 ± 0.04	8	0.951
3	C-3′	3.85 ± 0.18	σ_m	−0.01 ± 0.07	8	0.993
4	C-1 (C-3′ ring)	−1.05 ± 0.06	σ_m	−0.01 ± 0.02	8	0.990
5	C-4 (C-3′ ring)	1.07 ± 0.06	σ_m	0.03 ± 0.02	8	0.991
6	N-2	3.21 ± 0.39	σ_m	−0.28 ± 0.16	7	0.965
7	N-4	−1.25 ± 0.34	σ_m	0.27 ± 0.17	7	0.796
8	N_α	−5.06 ± 0.50	σ_m	0.00 ± 0.20	7	0.976
9	N_β	−6.10 ± 0.17	σ_m	0.01 ± 0.07	7	0.998
10	C-6 (N_α ring)	ρ_I: 8.78 ± 0.33 ρ_{R°: 16.28 ± 0.46	σ_I, σ_{R°	−0.31 ± 0.13	8	0.998
11[b]	C-3′	−3.57 ± 0.34	C-1 (C-3′ ring)	−0.01 ± 0.13	8	0.974
12[b]	C-3′	−0.66 ± 0.03	N_β	−0.10 ± 0.07	7	0.996
13[b]	C-1 (C-3′ ring)	−0.94 ± 0.10	C-4 (C-3′ ring)	0.01 ± 0.04	8	0.967
14	H−N_α	0.23 ± 0.05	H−N_α (**10**)[c]	−0.03 ± 0.02	7	0.906
15	C-2 (N_α ring)	0.94 ± 0.04	C-2 (**10**)[c]	0.59 ± 0.25	7	0.995
16	C-3 (N_α ring)	0.98 ± 0.02	C-3 (**10**)[c]	0.69 ± 0.27	7	0.999
17	C-4 (N_α ring)	0.97 ± 0.03	C-4 (**10**)[c]	0.49 ± 0.18	7	0.998
18	C-6 (N_α ring)	0.98 ± 0.02	C-6 (**10**)[c]	−0.24 ± 0.05	7	0.999
19	N_α	−1.07 ± 0.23	N_α (**10**)[c]	−0.06 ± 0.41	7	0.903
20	N_β	2.76 ± 0.43	N_β (**10**)[c]	−0.34 ± 0.33	7	0.944

[a] ρ, susceptibility constant for the single-parameter or for DSP analysis; β, slope of the cross-correlation; i, intercept; s_ρ, s_β, and s_i, standard deviations; n, number of points; r or R, correlation coefficients. [b] Cross-correlations between SCSs of probe atoms within compounds **2**. [c] Data of probe atoms of compounds **10** in [D_6]DMSO (see ref.[5]).

ported) shows that both components are of the same sign: Accordingly, positive $\lambda = \rho_R^\circ/\rho_I$ values have been calculated (higher and lower for series **1** and **2**, respectively).

Substituent Effects on ^{13}C and ^{15}N Chemical Shifts in the 1,2,4-Oxadiazole Ring and in the Azomethine System

A large substituent effect on the chemical shifts of C-3′ ($\rho_1 = 5.18$ and $\rho_2 = 3.85$) and N_β ($\rho_1 = -6.77$ and $\rho_2 = -6.10$) has been observed, together with the occurrence of an alternate polarisation: electron-withdrawing and electron-repelling substituents decrease and increase, respectively, the electron density on C-3′. As far as the heterocyclic ring is concerned, electron density variations on C-3′ do indeed induce alternate polarisation on C-3 ($\rho_1 = -0.33$) and then on N-2 ($\rho_1 = 4.09$ and $\rho_2 = 3.21$). Moreover, the C-5/N-4 double bond also shows an alternate polarisation ($\rho_1 = 0.88$ and $\rho_2 = 0.83$ for C-5; $\rho_1 = -0.74$ and $\rho_2 = -1.25$ for N-4). In conclusion, C-3′, C-5 and N-2 show the expected electron density variations, while C-3, N-4 and N_β show an inverted effect, as also evidenced by the results of the relevant cross-correlations (see data in Tables 4 and 5).

Substituent Effects on ^{13}C Chemical Shifts in the Aryl Groups at C-5 and at C-3′

In the phenyl ring at C-3′, both the *ipso*- [C-1 (C-3′ ring)] and the *para*-carbon atoms [C-4 (C-3′ ring)] show significant relationships, again providing evidence of alternate polarisation [$\rho_1 = -1.18$ and $\rho_2 = -1.05$ for C-1 (C-3′ ring); $\rho_1 = 1.26$ and $\rho_2 = 1.07$ for C-4 (C-3′ ring)]. In the phenyl ring at C-5, the same situation is observed for **1** [$\rho_1 = -0.45$ and 0.55 for C-1 (C-5 ring) and C-4 (C-5 ring), respectively], while for **2** no correlation appears to exist, as could be expected in view of the fact that the effects exerted by *meta* substituents on distant carbon atoms are usually of low magnitude.

Substituent Effects on ^{1}H, ^{13}C and ^{15}N Chemical Shifts in the Arylhydrazono Moiety

The chemical shifts of the *ipso*- [C-4 (N_α ring) or C-3(N_α ring) for **1** or **2**], *ortho*- [C-3,5 (N_α ring) or C-2,4 (N_α ring) for **1** or **2**] and *para*-carbon atoms [C-1 (N_α ring) or C-6 (N_α ring) for **1** or **2**] of the arylhydrazono moiety show excellent cross-correlations with the corresponding carbon atoms of *para*- and *meta*-substituted phenylhydrazines (**9** and **10**), anilines and benzenes; some examples relevant to arylhydrazines are given in Tables 4 and 5. Slopes near to unity have been calculated, with $r \geq 0.998$. Moreover, *only para*-carbon atoms give excellent DSP correlations with high λ values (ca. 1.9). Otherwise, *ipso*- and *ortho*-carbon atoms are affected by combined resonance, field and anisotropy effects.

An inverted effect of the substituent on N_α has been observed, but only for compounds **2**, giving a good lfer ($\rho_2 = -5.06$). N_β resonances also show such an inverted effect. An interesting point to examine is the effect of the substituent on the proton bound to N_α: the proton that has to be captured by the solvent or by the added base during the course of the reaction. The observed effect is normal, with electron-withdrawing and -repelling substituents decreasing and increasing ($\rho_1 = 0.39$ and $\rho_2 = 0.26$, respectively) electron density on this proton, thus affecting its acidity in a normal way and showing effects smaller than, but of the same sign as, those observed in the corresponding phenylhydrazines. Good or acceptable cross-correlations are accordingly observed ($\beta_1 = 0.22$ and $\beta_2 = 0.23$). As expected, the different hybridisation state of the adjacent nitrogen atoms (N_α and N_β) in **1**−**2** with respect to those in the arylhydrazines **9**−**10** prevents significant cross-correlations of the substituent effects on such atoms between the two classes of compounds, especially in the case of *para*-substituted derivatives, for which the conjugative effects surely play different roles as a function of the electronic structure of the atoms involved. As a matter of fact we have observed acceptable cross-correlations only in the case of *meta*-substituted derivatives ($\beta_2 = -1.07$ and 2.76, respectively).

Conclusion

The study of ^{1}H, ^{13}C and ^{15}N chemical shifts of (*Z*)-arylhydrazones of 3-benzoyl-1,2,4-oxadiazoles (**1** and **2**) in $CDCl_3$ has furnished a map of ground-state electron densities in these compounds, pointing to the effects of the substituents X on the key atoms involved in the MHR process.

As a matter of fact, the most interesting, and in some way unexpected, result of this study was the observation that a substituent in the aryl component of the arylhydrazono moiety is able to exert a long-range electronic effect. Thus, it affects not only the chemical shift of the hydrogen atom bound to N_α, but also, significantly, the electronic distribution in the 1,2,4-oxadiazole ring. This observation appears very interesting, because the reactivity in MHR processes (i.e., S_{N_i} reactions) strongly depends on the variation in electron density on both N-2 (the electrophilic reaction centre) and C-5 (which affects the leaving group ability). The observed co-operative (electronic) effects should thus give rise to large kinetic variations, and the NMR results accordingly line up perfectly with previous kinetic evidence, an electron-withdrawing substituent causing: (i) an increase in the acidity of the N_α−H proton (thus making the action of the solvent or base catalysis more efficient), (ii) an increase in the electrophilic character of N-2 (thus favouring the attack of the nucleophilic nitrogen atom), and (iii) at the same time, an increase in the leaving group ability (and hence of nucleofugacity) of the N-4/C-5/O-1 system. Opposite effects are obviously exerted by electron-repelling substituents.

Experimental Section

Spectroscopic Measurements: All the NMR spectra were recorded in $CDCl_3$ with a Varian Gemini 300 spectrometer. ^{1}H (300.07 MHz, 0.02 M) and ^{13}C (75.43 MHz, 0.1 M) chemical shift values are given in ppm relative to Me_4Si (internal standard) and $CDCl_3$ (centred at $\delta = 77.00$), respectively. ^{13}C chemical shift values

were measured from fully decoupled spectra. Signal assignments were made on the basis both of known substituent effects and of multiplicities determined by "proton gated" decoupled experiments. The ^{15}N NMR spectra (30.40 MHz) were acquired at natural abundance for 0.5 M solutions in $CDCl_3$ containing $Cr(acac)_3$ (0.01 M for each N atom present in the sample molecule). The spectra were recorded at 20 ± 1 °C, with a 10-mm broadband probe. Chemical shifts are referred to external neat $CH_3{}^{15}NO_2$. Typical operating conditions employed a delay between pulses of 5 s (acquisition time 1 s), spectral width of 10 kHz, 15 μs pulse width (ca. 60° flip angle). The signal-to-noise ratio was improved by applying a 2 Hz line broadening factor to the FID prior to Fourier transformation. The digital resolution was improved to 0.02 ppm by zero-filling to 32 K data points.

Chemicals: The (*Z*)-arylhydrazones **1a**−**c**, **1e**−**j**, **2b**, **2c**, **2e**−**f** and **2i** were synthesised and purified according to literature methods.[2] The (*Z*)-arylhydrazones **2d** and **2h** were prepared from 3-benzoyl-5-phenyl-1,2,4-oxadiazole and the appropriate phenylhydrazine in ethanol in the presence of acetic acid. Purification was achieved by chromatography [silica gel; cyclohexane/ethyl acetate (20:1)] and crystallisation from ethanol.

Compound 2d: Yield 56%, yellow, m.p. 134−136. ^1H NMR (300 MHz, $CDCl_3$): δ = 11.49 (br. s, 1 H, NH_α), 8.25 (m, 2 H, 2,6-H (C-5 ring)], 7.95 [m, 2 H, 2,6-H (C-3′ ring)], 7.57−7.62 [m, 3 H, 3,4,5-H (C-5 ring)], 7.40−7.52 [m, 3 H, 3,4,5-H (C-3′ ring)], 7.28 [td, 1 H, $J_{H,H}$ = 8.0 Hz, $J_{H,F}$ = 6.3 Hz, 5-H (N_α ring)], 7.16 [dt, 1 H, $J_{H,F}$ = 10.9 Hz, $J_{H,H}$ = 2.4 Hz, 2-H (N_α ring)], 7.03 [ddd, 1 H, $J_{H,H}$ = 9.0 Hz, $J_{H,H}$ = 2.0 Hz, $J_{H,H}$ = 0.9 Hz 6-H (N_α ring)], 6.68 [tdd, 1 H, $J_{H,H}$ = $J_{H,F}$ = 8.5 Hz, $J_{H,H}$ = 2.4 Hz, $J_{H,H}$ = 0.9 Hz, 4-H (N_α ring)]. HR-MS ($C_{21}H_{15}N_4OF$): calcd. 358.12299; found 358.12260. $C_{21}H_{15}N_4OF$ (358.37): calcd. C 70.38, H 4.22, N 15.6; found C 70.5, H 4.2, N 15.8.

Compound 2h: Yield 60%, yellow, m.p. 149. ^1H NMR (300 MHz, $CDCl_3$): δ = 11.54 (br. s, 1 H, NH_α), 8.24 [m, 2 H, 2,6-H (C-5 ring)], 7.95 [m, 2 H, 2,6-H (C-3′ ring)], 7.55−7.67 [m, 3 H, 3,4,5-H (C-5 ring)], 7.56 [m, 1 H, 2-H (N_α ring)], 7.38−7.50 [m, 5 H, 3,4,5-H (C-3′ ring), 5,6-H (N_α ring)], 7.22 [m, 1 H, 4-H (N_α ring)]. HR-MS ($C_{22}H_{15}N_4OF_3$): calcd. 408.119796; found 408.119269. $C_{22}H_{15}N_4OF_3$ (408.38): calcd. C 64.79, H 3.70, N 13.72; found C 64.6, H 3.8; N,13.8.

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