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Electronic effects of heterocyclic ring systems as evaluated with the aid of ^{13}C and ^{15}N NMR chemical shifts and NBO analysis

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The electronic effects of the 5- and 6-membered heterocyclic rings on the C═N—N unit of five different hydrazone derivatives of pyridine-2-, -3- and -4-carbaldehydes, pyrrole-2-carbaldehyde, furan-2- and -3-carbaldehydes and thiophene-2- and -3-carbaldehydes have been studied with the aid of ^{13}C and ^{15}N NMR measurements together with the natural bond orbital (NBO) analysis. As model compounds are used the corresponding substituted benzaldehyde derivatives. The polarization of the C═N unit of the hydrazone functionality of the heteroaryl derivatives occurs in an analogous manner with that of phenyl derivatives. The electron-withdrawing heteroaryl groups destabilize and the electron-donating groups stabilize the positive charge development at the C═N carbon while the effect on the negative charge development is opposite. The ^{15}N NMR chemical shift of the C═*N* and C═N—*N* nitrogens and the NBO charges at C═N—N unit can be correlated with the replacement substituent constants σ of the heteroaryl groups. ^{13}C NMR shifts of the C═N carbon of *N,N*-dialkylhydrazones of the heteroarenecarbaldehydes can be correlated with a dual parameter equation possessing the polar substituent constant σ^* of the heteroaryl group and the electronegativity of the heteroatom as variables. Copyright © 2008 John Wiley & Sons, Ltd.

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Keywords: heteroaryl groups; hydrazones; replacement substituent constants; ^{13}C NMR; atomic charges

INTRODUCTION

Electron delocalization in general and aromaticity especially are highly significant concepts to explain stabilities and reactivities of many organic molecules. An aromatic molecule has a cyclic π cloud which contains an odd number of pairs of π electrons. This means that the molecule follows the Hückel's $4n+2$ rule and has the ability to maintain a diamagnetic ring current. Both the 6-membered pyridine and the 5-membered pyrrole, furan and thiophene are aromatic.[1] Relative scales of aromaticity based on energetic, structural, spectroscopic or magnetic criteria have been developed. The resonance energy of pyridine is usually thought to be of the same order as that of benzene. Thiophene is the most and furan is the least aromatic of the common 5-membered heteroaryl rings, thiophene, pyrrole and furan.[1–6]

Heteroatoms in aromatic and pseudoaromatic rings can be considered as an endocyclic substituent replacing the —CH— or —CH═CH— fragment in a benzene ring.[7] Hammett-type replacement substituent constants σ, σ^+, σ_I or σ_R^o for the heteroaryl systems have been determined for instance by infrared intensity measurements,[8] by kinetic measurements based on rates of reduction,[9] solvolysis,[9–13] alkaline hydrolysis,[9,14,15] or pyrolysis,[16] by ring–chain tautomeric equilibrium measurements[17,18] and by ^{13}C NMR chemical shift measurements.[19] Taft's polar σ^* values have also been determined for many heterocyclic groups.[20] The term replacement substituent constant means that for instance 4-pyridyl group with a replacement substituent constant $\sigma = 0.96$ corresponds to the X-substituted phenyl group with $\sigma(X) = 0.96$. Replacement substituent constants for the heteroaryl groups are given in Tables 1 and 2. Some of the replacement substituent parameter values vary considerably as a function of the method used (σ_I for 2-thienyl as an example, Table 2). So, the quantitative assessment of the electronic effects of heteroaryl groups still needs consideration. We have recently studied ^{13}C NMR characters of the imine and hydrazone derivatives of *p*-X-substituted benzaldehydes, *p*-X—C_6H_4—CH═N—**S**.[23–26] In all cases substituents at the benzylidene ring have a reverse effect on δ_C(C═N), i.e. negative ρ_F (ρ_I) values and negative or small positive ρ_R values are observed when correlating SCS values with Eqn (1). SCS is the ^{13}C NMR shift of the C═N carbon for a substituted compound

$$\mathrm{SCS} = \rho_F\sigma_F(\rho_I\sigma_I) + \rho_R\sigma_R \quad (1)$$

relative to that for the unsubstituted one, and σ_F (σ_I) and σ_R are the inductive and resonance parameters of X, respectively. Because we are not aware of systematic ^{13}C NMR studies of the following derivatives, **1–5** (Scheme 1), of heterocyclic rings possessing a C═N—N group in their side-chain, the electronic effects of the 5- and 6-membered heteroaryl groups **A–H** were studied with the aid of ^{13}C and ^{15}N NMR measurements together

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Table 1. Replacement substituent constants for 6-membered heteroaryl groups[a]

	2-Pyridyl	3-Pyridyl	4-Pyridyl	Method[b]	Reference
σ	0.75	0.65	0.96	Saponification	[14]
σ^o	0.81	0.72	0.95	Saponification	[15]
σ^+	0.75	0.54	1.16	Solvolysis	[12]
σ^+	1.5	0.49	1.29	Ring–chain tautomerism	[17]
σ_I	1.65	0.35	0.92	^{13}C NMR	[19]
$\sigma_I{}^c$	0.18			pK_a determination	[21]
σ_R^o	−0.45	0.04	−0.01	^{13}C NMR	[19]
σ^{13}	0.88	0.60	1.18	^{13}C NMR	[19]

[a] Discussion on replacement substituent constants, see Reference [7].
[b] Method use for the determination of the replacement substituent constants in question.
[c] Reference values: for phenyl 0.12 and for *p*-NO_2-phenyl 0.23.[21]

with natural bond orbital (NBO) charges. Compounds with **Z** = **Ia − j** in series **1–5** were used as models (Scheme 2).

RESULTS AND DISCUSSION

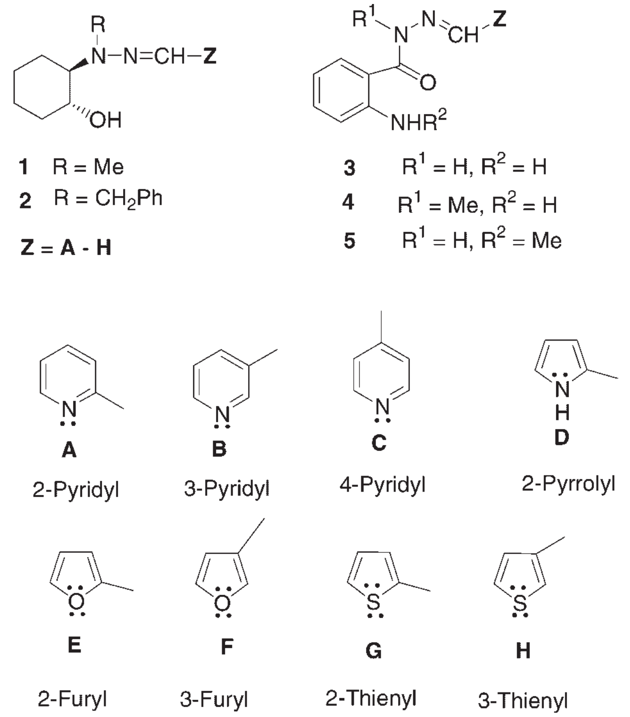
^{13}C NMR shifts

In Table 3 are given the ^{13}C NMR chemical shifts of the C=N carbon measured for the hydrazone series **1**(**A**-**H**)–**5**(**A**-**H**). For each heterocyclic **Z** (Scheme 1), within series **1–5** the range of the ^{13}C NMR chemical shift is *ca.* 15–16 ppm. In each series **1–5**, the shift range of *ca.* 9–10 ppm is observed when the heteroaryl group **Z** is varied. In Table 3 are also given the δ_C(C=N) value in each series for the unsubstituted phenyl derivative (**Z** = **Ig**).[23,24,25b] In all five cases, the value for the 2-pyridyl derivative is close to that observed for the unsubstituted phenyl derivative (**Ig**). For comparison, Table 4 collects ranges of C=N carbon resonance and correlation parameters obtained previously by Eqn (1) for different hydrazone [**1–5** (**Z** = **I**), **6**, **7**] and imine (**8–12**) derivatives of *p*-substituted benzaldehydes (cf. Schemes 2 and 3).[23–26] The C=N carbon of hydrazones in general has the ^{13}C NMR chemical shift at a lower frequency than the C=N carbon of imines has. The shift ranges in Table 3 ($\Delta\delta$, 9–10 ppm) are larger than those caused by varying phenyl substitution (Table 4, series **1–5** with **Z** = **I**, *ca.* 4–7 ppm). According to a large set of imine, hydrazone, oxime and oxime *O*-ether derivatives of substituted benzaldehydes (*p*-X—C_6H_4—CH=N—**S**), the sensitivity of the ^{13}C NMR shift of the C=N unit to the benzylidene substituent X is dependent on the group **S** [**S** = Ph, CH_2Ph, C_6H_4-*p*-Y, Me, C(Me)$_3$, OMe, OH, NHPh or NH_2].[25b,,26] With series *p*-X—C_6H_4—CH=N—C_6H_4-*p*-Y correlation parameters ρ_F(X) and ρ_R(X) depend linearly on σ^+(Y).[26] Due to the amide resonance one would expect the *N*-benzoylamino and *N*-alkyl-*N*-benzoylamino groups in **3–5** to be less electron-donating than the *N*,*N*-dialkylamino groups in **1** and **2**. The shift ranges when **Z** is varied in series **1–5** are, however, quite close to each other, and for **3–5** slightly higher

Table 2. Replacement substituent constants for 5-membered heteroaryl groups[a]

	2-Pyrrolyl	2-Furyl	3-Furyl	2-Thienyl	3-Thienyl	Method[b]	Reference
σ	−0.58	0.32	0.04	0.03	0.04	Solvolysis	[9]
σ^+	−1.61	−0.85	−0.44	−0.76	−0.44	Solvolysis; reduction	[9]
σ^+		−0.94	−0.49	−0.84	−0.47	Solvolysis	[10]
σ^+				−0.80	−0.47	Solvolysis	[11]
σ^+		−1.09	−0.29	−1.02	−0.52	^{17}O NMR	[22]
σ^+		−1.03	−0.615	−0.928	−0.559	Solvolysis	[22]
σ^+	−2.2	−0.80	−0.20		−0.20	Ring–chain tautomerism	[18]
σ_I	−0.16	0.65		1.82	0.59	^{13}C NMR	[19]
$\sigma_I{}^c$	0.17	0.17	0.10	0.19	0.10	pK_a determination	[21]
σ_I		0.4		0.6	0.6		[7]
σ_R^o	−0.62	−0.60		−1.08	−0.39	^{13}C NMR	[19]
σ^*		1.08	0.65	0.93	0.65	Hydrolysis	[20]
σ^{13}	−2.53	−1.01		−0.79	−0.40	^{13}C NMR	[19]

[a] Discussion on replacement substituent constants, see Reference [7].
[b] Method use for the determination of the replacement substituent constants in question.
[c] Reference values: for phenyl 0.12 and for *p*-NO_2-phenyl 0.23.[21]



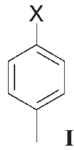
Scheme 1.

than for **1** and **2**. The γ-effect of *N*-methyl group is clearly seen (series **4** vs. series **3** or **5**).

The effect of the heteroaromatic groups *relative to phenyl group* was evaluated by cross-correlations of the ^{13}C NMR shifts of the C=N carbon for series **A–H** with those for series **Ig**. The slopes with varying C=N—N— substitutions are given in Table 5. The correlations are excellent ($r \geq 0.9970$). However, the values of the slopes are close to each other (0.82–1.12) and differences in the slope values are hardly significant taking into consideration the confidence intervals (95% confidence level). In Table 5 are collected aromaticity indexes given in literature for the heteroarenes and for benzene. The slope values close to one are in agreement with the suggestion of Abraham and Reid of closely similar ring current for benzene, furan, pyrrole and thiophene (RC in Table 5).[1c]

Dependence of the ^{13}C NMR chemical shifts of the C=N carbon on the heteroaryl group

Cross-correlation between the ^{13}C NMR chemical shifts for the cyclohexyl series **1** and **2** is shown in Fig. 1 and that between benzoylhydrazone series **3** and **4** in Fig. 2. Excellent correlations are observed and the points for the heteroarenecarbaldehyde derivatives fit those of the substituted benzaldehyde derivatives. For benzaldehyde derivatives, if δ_C(C=N) occurs at the lower frequency, the higher is the electron-withdrawing (EW) ability of the phenyl substituent. This reverse effect has been explained by the π-polarization and/or the resonance polarization. EW phenyl substituents stabilize negative charge development at the C=N carbon while ED substituents destabilize it [Scheme 4, **Z** = X(EW)—C$_6$H$_4$— or **Z** = X(ED)—C$_6$H$_4$—, respectively]. The effects on positive charge development at the C=N carbon are opposite.[23–25] In Figs. 1 and 2, the points corresponding to the hydrazone derivatives of pyridine-3- and -4-carbaldehydes fit the correlations in an excellent agreement with the σ values shown in Table 1 [σ(4-pyridyl) = 0.96, σ(3-pyridyl) = 0.65; cf. $\sigma(NO_2) = 0.78$, σ(CN) = 0.66].[27] The point for the 2-pyridyl derivative occurs in both figures at higher frequency than one



X = NO$_2$ (**a**), CN (**b**), CF$_3$ (**c**), F (**d**), Cl (**e**), Br (**f**), H (**g**), Me (**h**), OMe (**i**) or NMe$_2$ (**j**)

Scheme 2.

Table 3. ^{13}C NMR chemical shifts of the C=N carbon (in ppm relative to TMS in CDCl$_3$) for series **1–5** with **Z** = **A** — **H** or **Ig**

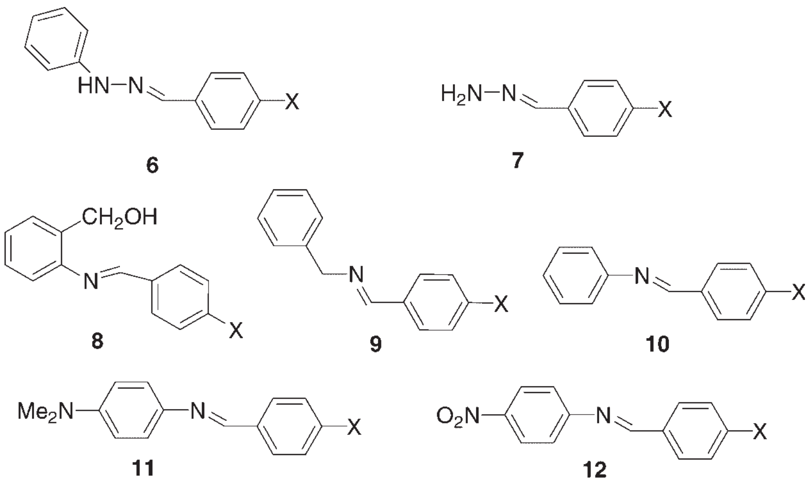
Z	1	2	3	4	5
A 2-Pyridyl	131.35	131.41	147.16	139.89	147.04
B 3-Pyridyl	127.36	127.32	143.82	135.56	143.89
C 4-Pyridyl	126.78	126.99	144.1	135.92	143.97
D 2-Pyrrolyl	126.54	—	138.87	131.49	138.84
E 2-Furyl	122.54	122.39	137.74	129.68	137.35
F 3-Furyl	124.81	124.74	139.99	131.40	139.73
G 2-Thienyl	127.01	126.97	142.67	133.68	—
H 3-Thienyl	128.23	128.03	142.42	134.37	142.37
Ig	131.89[a]	131.91[a]	147.2[b]	139.19[c]	147.1[b]

[a] Reference [23].
[b] Reference [24].
[c] Reference [25b].

Table 4. The ρ_I(X) or ρ_F(X) and ρ_R(X) values obtained by Eqn (1) for the C=N carbon ^{13}C NMR chemical shifts (in CDCl$_3$ if not otherwise stated) for the *para*-X-substituted hydrazone series **1–7** and imine series **8–12** (Schemes 1–3)

Series	ρ_I(X) or ρ_F(X)	ρ_R(X)	Shift range/ppm	Reference
1 (**Z** = **I**)	−6.2	−4.9	127.14–133.93	[23]
2 (**Z** = **I**)	−5.8	−5.0	127.46–134.34	[23]
3 (**Z** = **I**)	−4.2	−2.0	144.4–148.5	[24]
4 (**Z** = **I**)	−4.6	−1.8	135.8–140.4	[24]
5 (**Z** = **I**) [a]	−3.8	−1.6	144.1–147.9	[24]
6	−4.6	−3.1	133.75–138.64	[23]
7	−5.5	−2.7	138.55–143.26	[23]
8	−3.7	−0.1	157.16–159.99	[25a]
9	−3.6	−0.7	159.8–162.03	[25b]
10	−4.0	−0.7	157.33–160.34	[25b]
11	−5.7	−2.5	151.51–156.73	[26]
12	−3.7	0.1	160.10–162.71	[26]

[a] In DMSO-d_6.



X = NO_2, CN, CF_3, F, Cl, Br, H, Me OMe or NMe_2

Scheme 3.

would expect on the basis of σ(2-pyridyl) = 0.75. The other heterocyclic groups seem to behave like phenyl groups possessing highly EW substituents. However, their σ values shown in Table 2 do not support that view. Furan, thiophene and pyrrole rings are known to possess a dualistic character. They are inductively EW (an electronegative heteroatom, large σ_I and F values) but able to donate electron via resonance (negative σ_R and R or R^+ values).[27] Due to the efficient conjugative effect they often are considered as π-excessive.[1a]

In contrast, the pyridyl groups are EW both inductively and via resonance and are considered as π-deficient.[1a] For the C=N carbon of the hydrazone derivatives of the 5-membered rings, the lowest frequency is observed for the 2-furyl derivative and the highest frequency value for the 2- or 3-thienyl derivative, the

Table 5. The correlation parameters for the cross-correlations between the ^{13}C NMR chemical shifts of the C=N carbon of series **A–H** with the ^{13}C NMR chemical shifts of the C=N carbon for series **Ig** when substitution at the hydrazone C=N–*N* nitrogen is varied

	Slope	d^a	r	RE^b	AI^c	ASE^d	RC^e	NICS(1)^f	ICSS^{g,h}
A 2-Pyridyl	1.03 ± 0.03^i	0.11	0.9984	43.3	86		0.85		8.8^g 7.2^h
B 3-Pyridyl	1.08 ± 0.01	0.04	0.9998						
C 4-Pyridyl	1.12 ± 0.03	0.09	0.9990						
D 2-Pyrrolyl	0.82 ± 0.04	0.19	0.9970	34.8	85	20.57	1.03	−10.60	7.6^g 6.5^h
E 2-Furyl	0.99 ± 0.01	0.03	0.9999	27.2	53	14.77	1.04	−9.36	7.3^g 6.0^h
F 3-Furyl	0.99 ± 0.02	0.07	0.9993						
G 2-Thienyl	1.02 ± 0.04	0.16	0.9986	43.0	81.5	18.57	1.08	−10.79	7.9^g 7.0^h
H 3-Thienyl	0.94 ± 0.02	0.08	0.9993						

Different aromaticity parameters collected from literature for the parent rings are also given.

[a] Confidence interval (95% confidence) for the slope value.

[b] Resonance energy for the parent ring system in kcal mol^{-1}: pyridine, pyrrole, furan and thiophene. 45.8 kcal mol^{-1} for benzene. Reference [1b].

[c] Aromaticity index for the parent ring system relative to benzene: pyridine, pyrrole, furan and thiophene. 100 for benzene. Reference [1b].

[d] Aromatic stabilization energy for the parent ring system in kcal mol^{-1}: pyrrole, furan and thiophene. Reference [1g].

[e] Ring current ratio for the parent ring system: pyridine, pyrrole, furan and thiophene. 1.00 for benzene. Reference [1c].

[f] Nucleus independent chemical shift in ppm 1 Å above the ring center for the parent ring system: pyrrole, furan and thiophene. Referenece [1g].

[g] Distance in Å to which shielding area extends (ICSS = 0.1 ppm) for the the parent ring system: pyridine, pyrrole furan and thiophene. 8.9 Å for benzene. Reference [3b].

[h] Distance in Å to which deshielding area extends (ICSS = −0.1 ppm) for the parent ring system: pyridine, pyrrole furan and thiophene. 7.2 Å for benzene. Reference [3b].

[i] Standard deviation.

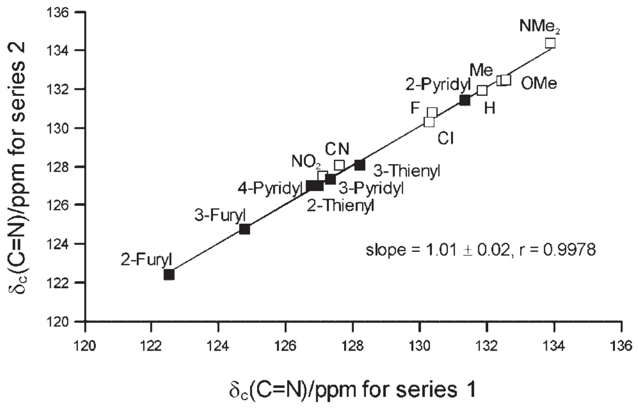


Figure 1. A cross-correlation between the δ_C(C=N) values of series **1** and **2**. The figure includes the derivatives of heteroarenecarbaldhydes (**Z** = **A** – **H**, ■) and the derivatives of substituted benzaldehydes (**Z** = **Ia, b, d, e, g** – **j**, □, data from Reference [23])

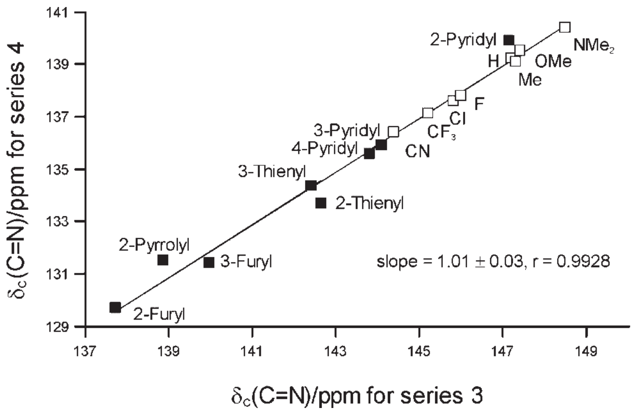


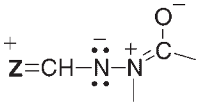
Figure 2. A cross-correlation between the δ_C(C=N) values of series **3** and **4**. The figure includes the derivatives of heteroarenecarbaldhydes (**Z** = **A** – **H**, ■) and the derivatives of substituted benzaldehydes (**Z** = **Ib, c, d, e, g** – **j**, □, data from Reference [24])

other derivatives showing intermediate values (Table 3, Figs. 1 and 2). Oxygen is more electronegative than sulfur or nitrogen while nitrogen is a better electron donor than oxygen or sulfur. The dependence of δ_C(C=N) on the structure of the heterocyclic ring means that inductive effects predominate over the conjugative effects.[23–25] The low frequency shift reflects increase in electron density of the carbon indicating significant contribution of resonance structures **13** and **14** (Scheme 4). Inductively EW groups **Z** stabilize **13** and **14**, low frequency (upfield) shifts as result.

^{13}C NMR chemical shifts of the hydrazone derivatives of the 5-membered heterocyclic aldehydes do not correlate with the replacement substituent constants σ, σ^+, σ^* or σ^{13} of the heteroaryl groups (Table 2). Equation (1) was also tested using σ_I and σ_R^o values for 2-pyrrolyl, 2-furyl, 2-thienyl and 3-thienyl groups. Also in that case the correlation was poor. Fringuelli *et al.*[28] observed good correlations (r = 0.95–0.99) between the carbonyl carbon ^{13}C NMR chemical shift and electronegativity of the heteroatom in 2-substituted acetyl, carbaldehyde, methoxycarbonyl and carboxylic acid derivatives of furan, thiophene, selenophene and tellurophene, δ_C(C=O) moving to lower frequency (upfield) with increasing electronegativity of the heteroatom. In our case, electronegativity of the heteroatom alone does not describe the effect of the heterocyclic ring because 2- and 3-derivatives have different responses. Instead, a good correlation was observed when Eqn. (2)

$$\delta_C(C = N) = \rho*\sigma* + \rho_X X + C \qquad (2)$$

was used for series **1** (r = 0.9994). In Eqn (2), σ^* is the polar substituent constant for the heterocyclic group (Table 2, **E**–**H**) and X is electronegativity of the heteroatom. The negativity of ρ^* and ρ_X suggests that EW groups **Z** stabilize the resonance structures **13** and **14** increasing their contribution, shielding of the C=N carbon as a result. In Fig. 3 is shown for series **1** the correlation between the experimental δ_C(C=N) values and those calculated with the aid of ρ^*, ρ_X and C derived from Eqn (2). Alike behavior is observed for series **2** [$\rho^* = -(5.0 \pm 0.8)$ and $\rho_X = -(4.1 \pm 0.3)$, r = 0.9979]. With the benzoylhydrazone series **3–5**, however, this type of correlation fails due to the amide resonance **18** allowing the conjugative electron donation from the heterocyclic rings.



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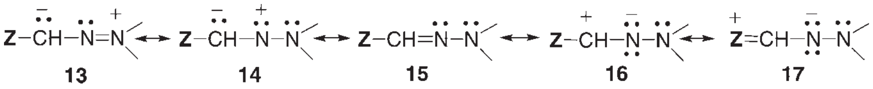
The δ_C(C=N) values for the hydrazone derivatives of the heterocyclic aldehydes (**Z** = **D** – **H**, series **1–5**) occur clearly at lower frequencies than those of hydrazone derivatives of substituted benzaldehydes or pyridine-2-, -3- or -4-carbaldehydes (**Z** = **A** – **C**, series **1–5**). The σ_I values for phenyl, 0.12, p-NO$_2$-phenyl, 0.23, p-Me-phenyl, 0.10, 2-pyridyl, 0.18, 2-pyrrolyl, 0.17, 2-furyl, 0.17, 3-furyl, 0.10 and 2-thienyl groups, 0.19[21] suggest that inductive effect alone does not explain this behavior. One explanation could be that with 5-membered heterocyclic derivatives there occurs a significant contribution of resonance structure **17**, which increases the C=C character of the α-carbon relative to the α-carbon of hydrazone derivatives of substituted benzaldehydes or pyridinecarbaldehydes, low frequency shift as a consequence. This is, however, contradicted by the fact that σ_R^o values for the heteroaryl groups **D**, **E** and **H** are close to σ_R^o of 2-pyridyl group **A**,[19] and hydrazone derivatives of **A** resonate at quite high frequency. An alternative possibility is the ring current effect. Although Abraham and Reid[1c] recently reported closely similar ring currents for benzene, furan, pyrrole and thiophene, Klod and Kleinpeter[3a] and Kleinpeter *et al.*[3b] have reported the decreasing sequence benzene > pyridine > thiophene > pyrrole > furan (cf. Table 5). We tested the correlation between the shielding/deshielding distances (ICSS = ±0.1 ppm) for the parent ring systems[3b] and δ_C(C=N) values for the 2-substituted set 2-furyl, 2-pyrrolyl, 2-thienyl, 2-pyridyl and phenyl in series **4**.



Scheme 4.

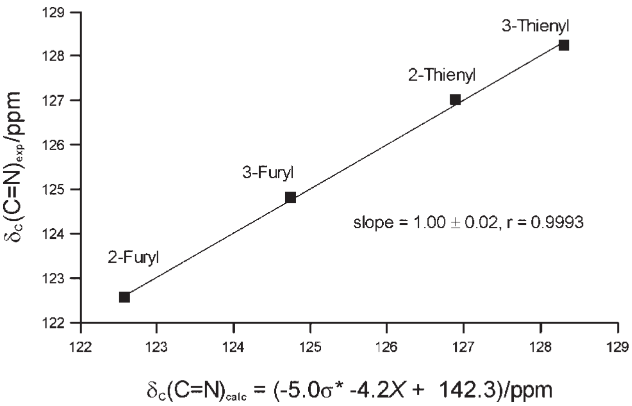


Figure 3. A cross-correlation between the experimental and calculated [Eqn (2)] $\delta_C(C{=}N)$ values for series **1**

Correlation with shielding distance gives better correlation [slope = 6.1 ± 0.6 (standard deviation), ± 1.9 (confidence limits, 95%), $r = 0.9945$] than that with the deshielding distance [slope 8 ± 2 (standard deviation), ± 6.7 (confidence limits, 95%), $r = 0.9075$]. The correlations indicate that the ring current effect on $\delta_C(C{=}N)$ can contribute to the observed low frequency shift of $\delta_C(C{=}N)$ values for the 5-membered heteroaryl derivatives relative to phenyl derivatives. However, the contribution of this effect obviously is not large.[3]

Comparison with other side-chain derivatives

In Table 6 are collected the ^{13}C NMR chemical shifts for α-carbons of several different side-chain derivatives of heteroarenes and benzene including our series **1** and **4**. The SCS values are mostly negative and the most negative SCS values are usually observed for α-carbons of pyrrolyl or furyl derivatives. This is the case also with sp^3 hybridized α-carbon. Pyrrolyl and furyl rings carry the most electronegative heteroatoms and possess the lowest resonance stabilization energies.[1b] Interestingly, if the $\delta_C(C{=}N)$ value occurs at the lower frequency, the lower is the aromaticity of the heteroaryl ring according to energetic, magnetic or other criteria.[1–3,5]

^{15}N NMR shifts

The ^{15}N NMR shifts for series **1** (**Z** = **A** − **H**) are given in Table 7. Positive and closely similar slopes are observed when correlating $\delta_N(C{=}N{-}N)$ of substituted benzaldehyde derivatives with Hammett σ and those of heteroarenecarbaldehyde derivatives with replacement substituent constants σ, 9.4 and 10.0, respectively (Table 8). This is the normal behavior.

The normal behavior is also observed at $C{=}N$ nitrogen: EW substituents affect deshielding. For $\delta_N(C{=}N)$ the sensitivity to σ is higher with heterocyclic systems (slope = 15.6) than with benzaldehyde derivatives (slope = 11.8) but taking into account the confidence intervals (95%) the difference is not significant. EW groups **Z** increase the contribution of **13** and **14** while they decrease the contribution of **16** (Scheme 4) and cause high frequency shift of $\delta_N(C{=}N)$ and $\delta_N(C{=}N{-}N)$, i.e. the normal behavior. The satisfactory correlations in all these cases indicate that the replacement substituent constants σ [9,14] are suitable to describe the electronic effects of the heteroaryl groups on δ_N at the hydrazone functional group. This supports the conclusion drawn above that the dependence of the ^{13}C NMR shift of the α-carbon of the hydrazone derivatives of the

Table 6. ^{13}C NMR chemical shifts (in ppm relative to TMS, $CDCl_3$) and SCS[a] values for α-carbons of some phenyl and heteroaryl systems

	1R = CH_3		R = CHO		R = $COCH_3$		R = $COOCH_3$		R = side-chain of **1**		R = side-chain of **4**	
	δ_C(C-α)	SCS	δ_C(C-α)[f]	SCS	δ_C(C-α)	SCS	δ_C(C-α)	SCS	δ_C(C-α)	SCS	δ_C(C-α)	SCS
R-phenyl	21.44[b]	0	192.0	0	198.17[g]	0	167.11[b]	0	131.89	0	139.19	0
2-R-pyridine	24.7[c]	3.26	193.5	1.5					131.35	−0.54	139.89	0.7
3-R-pyridine	18.7[c]	−2.74	191.4	−0.6					127.36	−4.53	135.56	−3.63
4-R-pyridine	21.4[c]	−0.04	192.2	0.2					126.78	−5.11	135.92	−3.27
2-R-thiophene	15.04[b]	−6.40	183.6	−8.4	190.75[g]	−7.42	162.68[b]	−4.43	127.01	−4.88	133.68	−5.51
3-R-thiophene			185.6	−6.4					128.23	−3.68	134.37	−4.82
2-R-pyrrole	12.3[d]	−9.14	180.3	−11.7	188.04[g]	−10.13	161.4[h]	−5.71	126.54	−5.11	131.49	−7.70
2-R-furan	13.2[d]	−8.24	178.1	−13.9	186.83[g]	−11.34	159.16[i]	−7.95	122.54	−9.35	129.68	−9.51
3-R-furan	9.20[e]	−12.24	184.0	−8.0					124.81	−7.08	131.40	−7.79

[a] Value of $\delta_C(C{-}\alpha)$ relative to the phenyl derivative.
[b] Reference [29].
[c] Reference [30].
[d] Reference [31].
[e] Reference [32].
[f] Reference [33].
[g] Reference [6].
[h] Reference [34].
[i] Reference [28].

Table 7. ^{15}N NMR chemical shifts (in ppm in $CDCl_3$) of the C=*N* and C=N–*N* nitrogens for series **1** with **Z** = **A** – **H** or **Ig**

Z	δ_N(C=*N*)	δ(C=N–*N*)
A	−27.37	−256.45
B	−31.60	−258.44
C	−26.11	−254.39
D	−51.12	−268.79
E	−39.08	−263.61
F	−37.74	−267.17
G	−39.73	−261.60
H	−38.20	−265.07
Ig[a]	−87.59	−315.17

The spectra were referenced externally to CH_3NO_2 (0.00 ppm) containing 10% w/w CD_3NO_2 for locking purposes.

[a] Reference [25b].

5-membered heteroarenecarbaldehydes on the heteroaryl group includes besides the electronic effects an additional contributor which prevents to describe the behavior of δ_C(C=N) by the replacement substituent constants. In Table 8 are also shown the statistical data for correlations of the δ_N values in question with the σ^{13} values proposed by Robinson *et al.*[19] and Slater *et al.*[35] With the exception of the δ_N(C=*N*) data of the heterocyclic derivatives, the correlations are worse than those with Hammett σ or replacement substituent constants σ.

Comparison with styrenes

For *p*-X-substituted styrenes, a reverse and a normal behavior, respectively, has been observed on the ^{13}C NMR shifts of α and β carbons.[36] Figure 4 shows the cross-correlation between the ^{15}N NMR chemical shift values, δ_N(C=*N*), of phenyl substituted benzaldehyde hydrazone series **1** (**Z** = **Ia**, **b**, **d**, **e**, **g**, **h**, **i** and **j**) and ^{13}C NMR chemical shift values, δ_C(C=C_β), for the β-carbon of the phenyl substituted styrenes **19a** (Scheme 5). The good correlation means that both nuclei respond analogously to substituents on the phenyl ring although the ^{15}N NMR shift of C=N nitrogen seems to be *ca.* 1.6 times as sensitive to substitution as the ^{13}C NMR shift of C_β. In Fig. 5 is shown the corresponding cross-correlation between the heteroarene derivatives, series **1** (**Z** = **A** – **E, G** and **H**) and series **19b**. In the limits of standard errors the slope is the same as in Fig. 4. If the upper and lower confidence limits of the slope are taken into consideration (95% confidence level) the slope in Fig. 4 is 1.6 ± 0.4 and that in Fig. 5 is 1.6 ± 0.3. This means that the same relative sensitivity between the β-nitrogen at the C=N unit and the β-carbon of styrenes C=C unit prevails both with varying phenyl substitutions and heteroaryl substitutions. This means that analogous electronic effects of the heteroaryl groups, relative to substituted phenyl groups, are experienced by the styrene β-carbon and by the C=N nitrogen. Unfortunately the α-carbon shifts for the heterocyclic derivatives studied by Robinson *et al.*[19] are not available.

Atomic charges

Computational NBO charges (B3LYP/6-31G**) of the minimum energy conformations of series **1** and **4** are given in Tables 9 and 10. For series **1**, the *trans* diequatorial *ee* conformation is clearly more stable than the *trans* diaxial *aa* conformation by *ca.* 5 kcal mol^{-1}. However, there are two local minima closely similar in energy (energy difference ±0.03–0.88 kcal mol^{-1}) for the *ee* conformation, the *syn* and *anti* conformations shown in **20** and **21**, respectively, for **1C**. For benzaldehyde derivatives (**Z** = **Ia** – **j**) the *syn_ee* conformation was the most stable in seven cases (**a**–**c**, **f**–**i**) from ten and for the heteroarenecarbaldehyde derivatives in

Table 8. Comparison of the statistical parameters for correlation of ^{15}N NMR chemical shifts δ_N(C=*N*) and δ_N(C=N–*N*) values for *p*-phenyl substituted benzaldehyde *N*-methyl-*N*-(2-hydroxycyclohexyl)hydrazones (Serie **1**, **Z** = **I**) and heteroarenecarbaldehyde *N*-methyl-*N*-(2-hydroxycyclohexyl)hydrazones (Series **1**, **Z** = **A** – **H**) with Hammett substituent constants σ or replacement substituent constants σ (cf. Table 2), respectively

	δ_N(C=*N*)		δ_N(C=N–*N*)	
	Z = **I**[c]	Z = **A** – **H**	Z = **I**[c]	Z = **A** – **H**
Correlations with Hammett σ^a or replacement substituent constants σ^b				
Slope	11.7 ± 0.8[d] (± 1.9)[e]	15.6 ± 1.6 (± 3.9)	9.4 ± 1.5 (± 3.6)	10.0 ± 1.1 (± 2.8)
r	0.9869	0.9703	0.9349	0.9631
Correlations with σ^{13} substituent constants[f]				
Slope	6.8 ± 0.7[d] (± 1.6)[e]	6.6 ± 0.5 (± 1.3)	5.3 ± 1.1 (± 2.7)	3.7 ± 0.9 (± 2.2)
r	0.9717	0.9908	0.8935	0.8827

Data for correlations with σ^{13} substituent constants are also given.

[a] Reference [27]: *p*-NO_2, 0.78; *p*-CN, 0.66; *p*-CF_3, 0.54; *p*-F, 0.06; *p*-Cl, 0.23; *p*-Br, 0.23; H, 0; *p*-Me, −0.17; *p*-OMe, −0.27; *p*-NMe_2, −0.83.

[b] Reference [9] and [14]: 2-pyridyl, 0.75; 3-pyridyl, 0.65; 4-pyridyl, 0.96; 2-pyrrolyl, −0.58; 2-furyl, 0.32; 3-furyl, 0.04; 2-thienyl, 0.03; 3-thienyl, 0.04.

[c] **Ia**, **b**, **d**, **e**, **g**, **h**, **i** and **j**. The ^{15}N NMR shift values are from reference [25b].

[d] Standard deviation.

[e] Confidence interval (95% confidence).

[f] σ^{13} from Reference [19] and Reference [35]: *p*-NO_2, 1.01; *p*-CN, 0.85; *p*-F, −0.05; *p*-Cl, 0.13; H, 0; *p*-Me, −0.3; *p*-OMe, −0.74; *p*-NMe_2, −1.75; 2-pyridyl, 0.88; 3-pyridyl, 0.6; 4-pyridyl, 1.18; 2-pyrrolyl, −2.53; 2-furyl, −1.01; 2-thienyl, −0.79; 3-thienyl, −0.4.

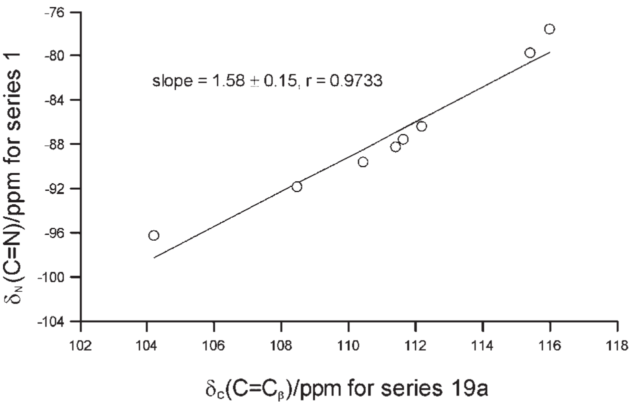


Figure 4. A cross-correlation between the ^{15}N NMR shifts of C=N nitrogen for series **1** (**Z** = **Ia**, **b**, **d**, **e**, **g**, **h**, **i**, **j)** and the ^{13}C NMR shift of the styrene β-carbons for series **19a** (Scheme 5 data from Reference [35], X is varied)

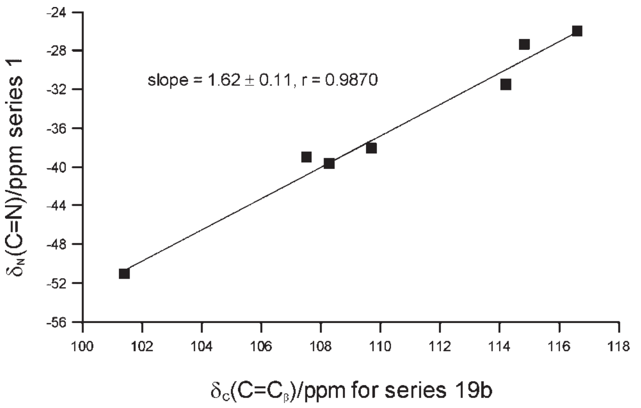
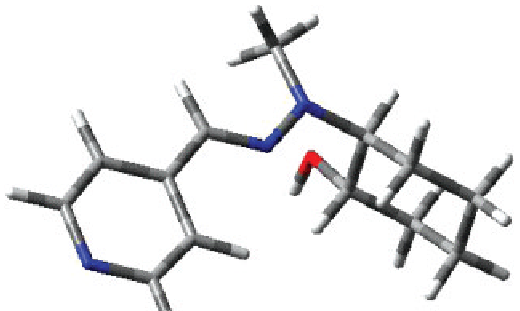


Figure 5. A cross-correlation between the ^{15}N NMR shifts of C=N nitrogen for series **1** (**Z** = **A** − **E, G** and **H)** and the ^{13}C NMR shift of the styrene β-carbons for series **19b** (Scheme 5 data from Reference [19], heteroaryl group is varied)

six cases (**Z** = **A** − **C**, **E** − **G**) from eight (**A** − **H**). So, we chose *syn_ee* for the detailed analysis. However, it was verified that an excellent correlation was observed between q_C(C=N) of *anti_ee* and q_C(C=N) of *syn_ee* (slope = 1.10 ± 0.03, *r* = 0.9960 for benzaldehyde derivatives and slope = 1.00 ± 0.05, *r* = 0.9927 for heteroarenecarbaldehyde derivatives).



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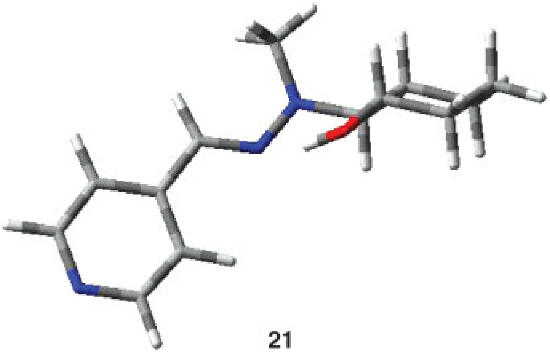

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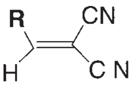
Figure 6 shows the correlation between q_C(C=N) and σ or replacement substituent constant σ for series **1**. The solid line [slope = −0.020 ± 0.002 (standard deviation), ±0.04 (95% confidence limits)] in Fig. 6 is drawn for the hydrazone derivatives of substituted benzaldehydes. The points corresponding to the derivatives for **Z** = **A** − **C**, **F** or **H** fit closely on this line (slope = −0.021 ± 0.007 (standard deviation), ±0.02 (95% confidence limits)]. In Fig. 7 [q_N(C=N) vs. σ)] and Fig. 8 [q_N(N2) vs. σ] the correlations for the heterocyclic derivatives are worse than those for benzaldehyde derivatives but the sensitivities of the atomic charge to **Z** are analogous (correlation with σ, positive slope with the numerical value of the same order). This means that the replacement substituent constants σ given in literature[9,14] describe the electronic effects of the heteroaryl groups on the C=N—N functional group well. In Fig. 6, points for 2-pyrrolyl (**D**), 2-furyl (**E**) and 2-thienyl (**G**) clearly deviate. This reflects a special 'ortho-effect' experienced by the q_C(C=N) due to the proximity of the heteroatom in the 5-memebered ring, not explained by the replacement σ constants. The positive and negative slopes, respectively, in Figs. 6 and 7, and their numerical values of the same extent verify the polarization pattern described in Scheme 4. Slope of −1.19 ± 0.06 (*r* = 0.9845) was observed for the cross-correlation between q_N(C=N) and q_C(C=N) including compounds of series **1** with **Z** = **Ia** − **j**, **A**, **B**, **F** and **H**.

The dependences of the atomic charges at C=N—N group in series **4** are closely similar with those in series **1** (Figs. 9, 10 and 11) including the deviation of the 2-pyrrolyl, 2-furyl and 2-thienyl derivatives as regards q_C(C=N). Cross-correlations between series **4** and series **1** for q_C(C=N), q_N(C=N) and q_N(N2) give slopes 0.93 ± 0.04 (*r* = 0.9847), 0.89 ± 0.06 (*r* = 0.9606) and 0.26 ± 0.01 (*r* = 0.9901), respectively. The lower sensitivity of



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a R = *p*-X-substituted phenyl, X= NO_2, CN, F, Cl, H, Me, OMe or NMe_2

b R = 2-, 3- or 4-pyridyl, 2-pyrrolyl, 2-furyl, 2-thienyl or 3-thienyl

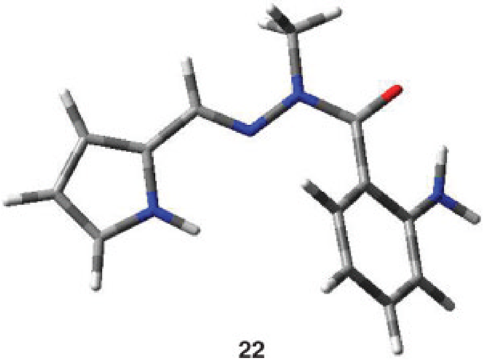
Scheme 5.

Table 9. Natural bond orbital (NBO) charges (B3LYP/6-31G**) for the *C*=N carbon and C=*N* and C=N–*N* nitrogens for series **1** and **4** with **Z** = **Ia – j**

	Series **1**			Series **4**		
	q_C(*C*=N)	q_N(C=*N*)	q_N(C=N–*N*)	q_C(*C*=N)	q_N(C=*N*)	q_N(C=N–*N*)
Ia X = NO_2	−0.05279	−0.23891	−0.22018	−0.00317	−0.23637	−0.25095
Ib X = CN	−0.05002	−0.24407	−0.22642	−0.00049	−0.24064	−0.25289
Ic X = CF_3	−0.04382	−0.24967	−0.23414	0.00479	−0.24523	−0.25508
Id X = F	−0.03357	−0.26284	−0.2455	0.01306	−0.25697	−0.25842
Ie X = Cl	−0.0385	−0.25668	−0.24014	0.00927	−0.25165	−0.25685
If X = Br	−0.0384	−0.25635	−0.24011	0.00898	−0.25132	−0.25672
Ig X = H	−0.0327	−0.26103	−0.24564	0.01407	−0.25503	−0.25796
Ih X = Me	−0.03066	−0.26406	−0.24786	0.01565	−0.25795	−0.25882
Ij X = OMe	−0.02695	−0.27044	−0.25215	0.0185	−0.26524	−0.2596
Ij X = NMe2	−0.02152	−0.27793	−0.25805	0.0214	−0.27358	−0.26059

q_N(N2) to **Z** in series **4** reflects the contribution of amide resonance **18**.

The atomic charge vs. replacement σ correlations give support for the conclusion that the ^{13}C NMR chemical shift of the α-carbon is not a proper probe to evaluate the electronic effects of the heteroaryl groups on the C=N unit although the ^{13}C NMR chemical shift of the α-carbon or the ^{15}N NMR chemical shift of the C=*N* and C=N—*N* nitrogens of benzaldehyde derivatives as well as the ^{15}N NMR chemical shift of the C=*N* and C=N—*N* nitrogens of heteroarene derivatives reflect the electronic effect of the aromatic moiety.



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Characters of 2-pyrrolyl derivative in series 4

The point corresponding to 2-pyrrolyl derivate in series **4** clearly deviates from the q_N(C=N) vs. σ plot (Fig. 10). This deviation reflects the proximity (2.549 Å) of the pyrrolyl *N*-hydrogen and C=*N* nitrogen of **4D** (cf. **22**), which makes the forming of —C=N····H hydrogen bond possible affecting the charge of C=N nitrogen.[37] The distance of —C=N····N(pyrrole) is 2.790 Å. For comparison the structure of **1D** is shown in **23**.

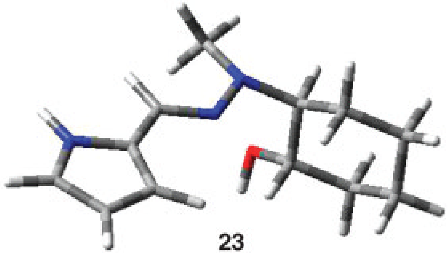

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Table 10. NBO charges (B3LYP/6-31G**) for the *C*=N carbon and C=*N* and C=N–*N* nitrogens for series **1** and **4** with **Z** = **A – H** or **Ig**

	Series **1**			Series **4**		
	q_C(*C*=N)	q_N(C=*N*)	q_N(C=N–*N*)	q_C(*C*=N)	q_N(C=*N*)	q_N(C=N–*N*)
A 2-Pyridyl	−0.05531	−0.25599	−0.23622	−0.0053	−0.2509	−0.2548
B 3-Pyridyl	−0.0419	−0.25631	−0.23924	0.0062	−0.2507	−0.2564
C 4-Pyridyl	−0.04884	−0.24331	−0.23029	0.00141	−0.2385	−0.2538
D 2-Pyrrolyl	−0.05465	−0.26644	−0.2575	−0.0037	−0.2936	−0.2593
E 2-Furyl	−0.08129	−0.2579	−0.24641	−0.0376	−0.2519	−0.2573
F 3-Furyl	−0.03435	−0.26604	−0.25359	0.01016	−0.2563	−0.26
G 2-Thienyl	−0.05778	−0.25671	−0.24419	−0.0087	−0.257	−0.2574
H 3-Thienyl	−0.03014	−0.26549	−0.25004	0.0125	−0.2546	−0.2588
Ig X=H	−0.0327	−0.26103	−0.24564	0.01407	−0.25503	−0.25796

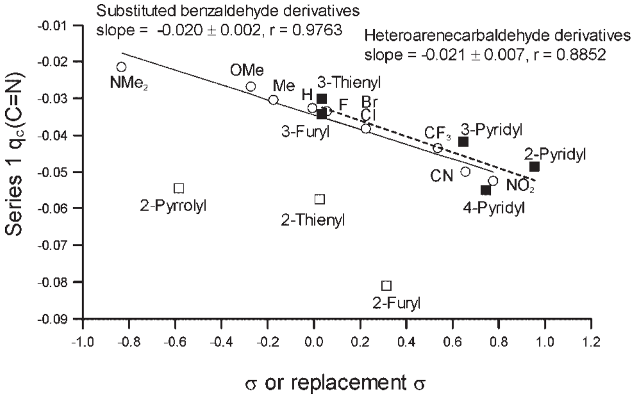

Figure 6. NBO charges of the C=N carbon for series **1** versus Hammett substituent constant σ or the replacement substituent constant σ, respectively, for the benzaldehyde derivatives (—, ○) and heteroarenecarbaldehyde derivatives (■ or □). The line (- - - -, ■) is drawn for **Z** = **A** – **C**, **F** and **H**. The errors shown are standard deviations

CONCLUSION

The electronic effects of the heteroaryl groups are analogous with the effect of substituted phenyl groups on the functional group of hydrazones of heteroarenecarbaldehydes and substituted benzaldehydes, respectively. The polarization of the C=N unit occurs in both cases. The effects of the heteroaryl groups on ^{15}N NMR chemical shift of the C=*N* and C=N—*N* nitrogens and on the NBO charges of the *C*=N carbon, C=*N* and C=N—*N* nitrogens can be correlated with the replacement substituent constants σ. The ^{13}C NMR shifts of the C=N carbon of *N*,*N*-dialkylhydrazones of the heteroarenecarbaldehydes are linearly related to equation $\delta_C(C{=}N) = \rho^*\sigma^* + \rho_X X + C$, where σ^* is the polar substituent constant for the heteroaryl group and X is electronegativity of the heteroatom.

EXPERIMENTAL SECTION

Materials

Melting points were determined using an electrothermal digital melting point apparatus and are uncorrected. The compounds in series **1–5**, **Z** = **A** – **H** were prepared by reactions between the corresponding heteroarene carbaldehydes and the proper hydrazino alcohols (series **1** and **2**), 2-aminobenzoylhydrazine (series **3**), 1-(2-aminobenzoyl)-1-methylhydrazine (series **4**) or 1-(2-methylaminobenzoyl)hydrazine (series **5**) as described previously.[23,24] Melting points of the compounds are given in Supplementary Material.

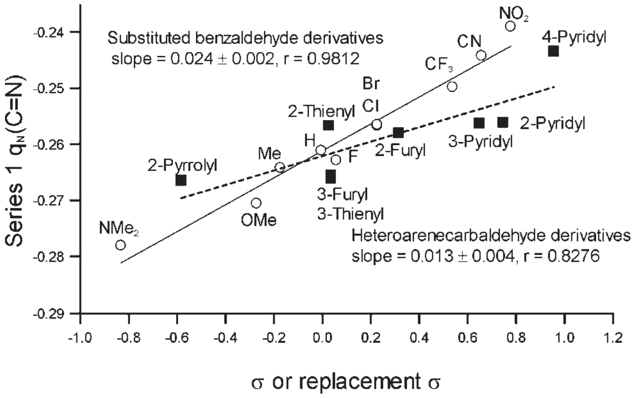

Figure 7. NBO charges of the C=N nitrogen for series **1** versus Hammett substituent constant σ or the replacement substituent constant σ, respectively, for the benzaldehyde derivatives (—, ○) and heteroarenecarbaldehyde derivatives (- - - -, ■). The errors shown in the figure are standard deviations. The confidence limits (95%) are ± 0.004 for (—, ○) and ± 0.009 for (- - - -, ■)

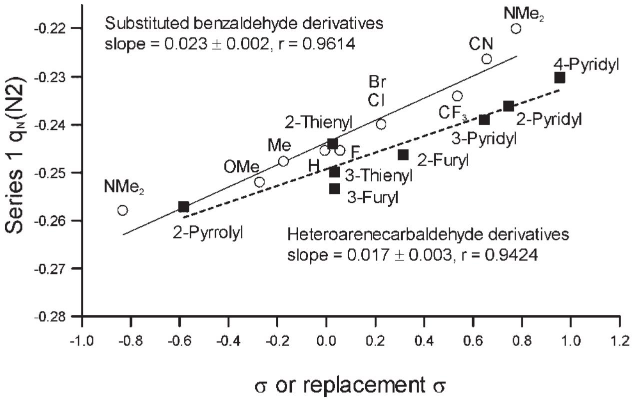

Figure 8. NBO charges of the hydrazone N2 nitrogen for series **1** versus Hammett substituent constant σ or the replacement substituent constant σ, respectively, for the benzaldehyde derivatives (—, ○) and heteroarenecarbaldehyde derivatives (- - - -, ■). The errors shown in the figure are standard deviations. The confidence limits (95%) are ± 0.005 for (—, ○) and ± 0.006 for (- - - -, ■)

NMR measurements

NMR spectra were recorded at 27°C on a JEOL JNM-A500 FT NMR spectrometer operating at 125.78 MHz for ^{13}C and 50.688 MHz for ^{15}N on 0.2 M solutions in $CDCl_3$. ^{13}C spectra were referenced internally to tetramethylsilane (0.00 ppm), while ^{15}N spectra were referenced externally to CH_3NO_2 (0.00 ppm) containing 10% w/w CD_3NO_2 for locking purposes. The signal of the deuterium of the solvent was used as a lock signal for ^{13}C spectra. ^{13}C NMR

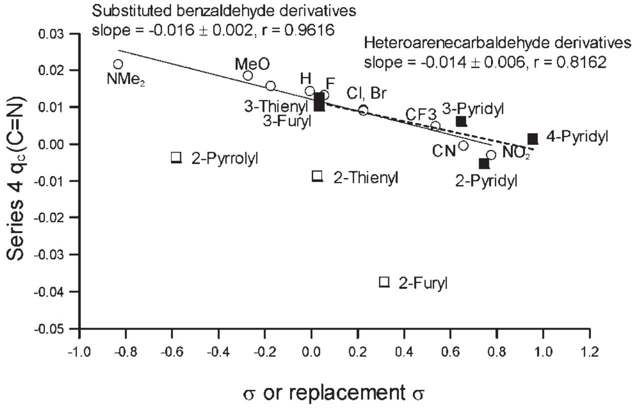

Figure 9. NBO charges of the C=N carbon for series **4** versus Hammett substituent constant σ or the replacement substituent constant σ, respectively, for the benzaldehyde derivatives (—, ○) and heteroarenecarbaldehyde derivatives (■ or □). The line (- - - -, ■) is drawn for **Z** = **A** – **C**, **F** and **H**. The errors shown in the figure are standard deviations. The confidence limits (95%) are ± 0.004 for (—, ○) and ± 0.018 for (- - - -, ■)

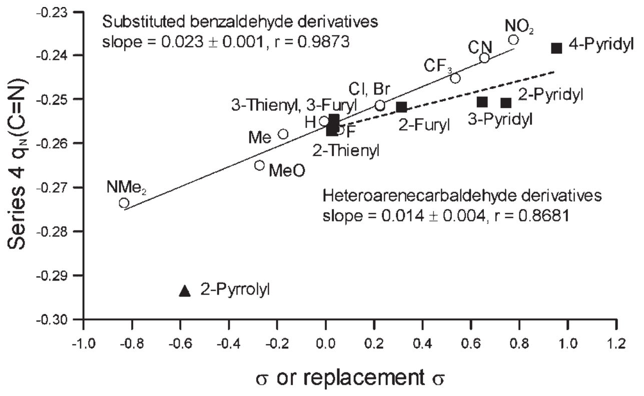

Figure 10. NBO charges of the C=N nitrogen for series **4** versus Hammett substituent constant σ or the replacement substituent constant σ, respectively, for the benzaldehyde derivatives (—, ○) and heteroarenecarbaldehyde derivatives (- - - -, ■). The errors shown in the figure are standard deviations. The confidence limits (95%) are ±0.003 for (—, ○) and ±0.009 for (- - - -, ■)

spectra were acquired with ^{1}H broad-band decoupling and NOE ^{1}H non-decoupling techniques. The coupled ^{13}C NMR spectra were qualitatively used in the assignment of the C=N carbon lines.

^{13}C spectra were acquired with the following conditions: spectral width of 30 kHz, 32 K data points (^{1}H decoupled)/64 K data points (^{1}H coupled), digital resolution 0.92 Hz/point (^{1}H decoupled)/0.46 Hz/point (^{1}H coupled), pulse width 4.35 μs (45°), acquisition time 1.09 s (^{1}H decoupled)/2.18 s (^{1}H coupled), number of transients 1000–12 000, pulse delay 3 s (^{1}H decoupled)/5 s (^{1}H coupled), pulse sequence (JEOL) SGBCM (^{1}H decoupled)/SGNOE (^{1}H coupled). Exponential windowing with a line-broadening term 2 Hz (^{1}H decoupled)/1 Hz (^{1}H coupled) was applied prior to Fourier transformation. ^{15}N NMR spectra were acquired with refocused INEPT technique optimized on 8 Hz. ^{15}N spectra were acquired with the following conditions: 90° flip angle, pulse recycle time 5.1 s, spectral width of 25 kHz consisting of 64 K data points (digital resolution 0.39 Hz/point), pulse sequence (JEOL) INPTR. Exponential windowing with a line-broadening term 1 Hz was applied prior to Fourier transformation.

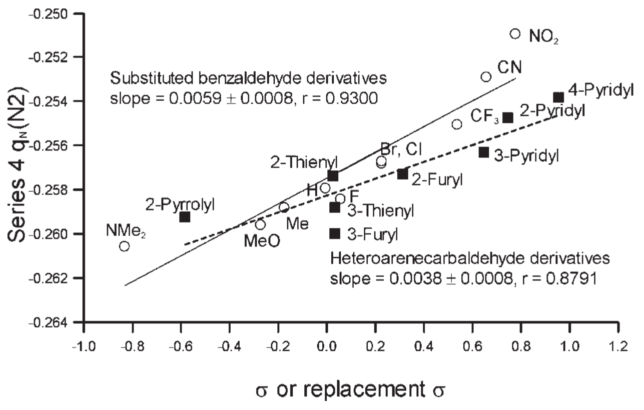

Figure 11. NBO charges of the hydrazone N2 nitrogen for series **4** versus Hammett substituent constant σ or the replacement substituent constant σ, respectively, for the benzaldehyde derivatives (—, ○) and heteroarenecarbaldehyde derivatives (- - - -, ■). The errors shown in the figure are standard deviations. The confidence limits (95%) are ±0.0019 for (—, ○) and ±0.0021 for (- - - -, ■)

B3LYP/6-31G** calculations

All DFT calculations were performed using the GAUSSIAN-03 series of programs.[38] Both, total energy and geometry of the various conformers were calculated at the B3LYP/6-31G** level of theory and were optimized without restrictions.[39,40] The molecular modeling program package SYBYL7.1 was used to generate input structures and to analyze and illustrate graphically the results.[41] Charges of molecules are calculated by using natural bond orbital (NBO) analysis.[42]

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