JOC Article

Comparison of the Electronic Structures of Imine and Hydrazone Side-Chain Functionalities with the Aid of ^{13}C and ^{15}N NMR Chemical Shifts and PM3 Calculations. The Influence of C═N-Substitution on the Sensitivity to Aromatic Substitution

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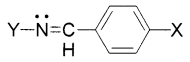
Benzaldehyde derivatives possessing a C═N double bond in the side-chain of the aromatic ring exhibit a reverse dependence of the ^{13}C NMR chemical shifts of the C═N carbon on the benzylidenic substituents X. Thus, electron-withdrawing substituents cause shielding (shift is reduced), while electron-donating ones cause deshielding. The origin of this phenomenon, which is in contrast with the idea of the generalized electronic effect, is extensively studied here by comparing the behavior of sets of benzaldehyde derivatives bearing various substitutents Y on the C═N nitrogen (Y−N═CH−C_6H_4−X). The effects of substituents X on the C═N unit change when Y is varied. Combination of the influences of the substituents X and Y gives a sensitive balance between the different resonance structures of the compounds. Our graphical treatment, where the ρ_I and ρ_R values observed for substituent X are plotted against the σ_p^+ value of substituent Y, is a novel use of Hammett-type substituent parameters. The justification of this method and our conclusions could be verified, for instance, by the fair correlation between the ρ_I or ρ_R values and the atomic charges of the imine carbon of the unsubstitued phenyl derivatives as well as by the correlations of the relevant bond orders and/or bond lengths both with the substituent parameters and with the atomic charges.

Introduction

The medicinal importance of hydrazones is well established. However, as compared with azomethines, the electronic effects prevailing in the −N−N═CH− functionality and the sensitivity of these effects to substitution are not satisfactorily understood.



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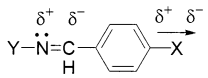

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Extensive ^{13}C NMR spectroscopic and theoretical calculation data together demonstrate that the C═N carbon of azomethines **1** derived from substituted benzaldehydes behaves normally and is shielded (shift is reduced) with increasing electron density on the carbon in question.[1a] In contrast, the atomic charge displays a reverse dependence on substitution, i.e., electron-withdrawing phenyl substituents increase the electron density on the C═N carbon.[1a] As a consequence, the imine carbon resonance reveals a reverse behavior as concerns substitution: *electron-withdrawing substituents cause shielding*. In principle, the substituent-induced changes in the chemical shift, SCS, depend on the inductive (σ_I or σ_F) and resonance (σ_R) parameters according to eq 1:

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

where SCS is the ^{13}C NMR shift for a substituted compound relative to that for the unsubstituted one. With imines, a better correlation is obtained with this dual-substituent parameter (DSP) approach than with any of the single-parameter equations tested (σ, σ^+, σ^-, σ_I, σ_F), but the small values of ρ_R show that resonance factors are not of great importance.[1a] The ρ_I/ρ_F values range from −3 to −4, while the ρ_R values range only from −0.7 to 0.2.

For imines, the charge on the C═N carbon and that on the C═N nitrogen behave inversely.[1a] This suggests

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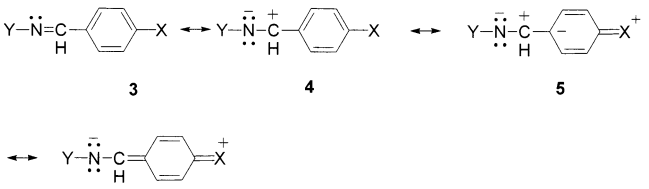
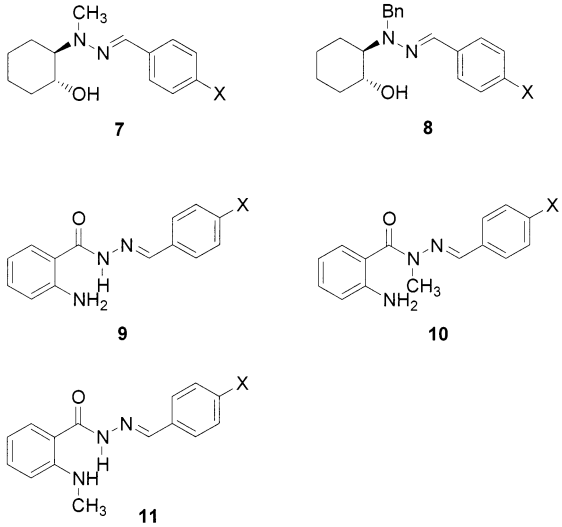
SCHEME 1



substituent-induced polarization of the C=N unit, i.e., π-polarization (**2**) and/or inherent polarization (Scheme 1). The concept of π-polarization has been extensively discussed in the literature.[2−5] According to this idea, the substituent dipole polarizes each π-unit as a localized system, as shown in **2**. π-Polarization has been used to explain the reverse behavior of the ^{13}C NMR chemical shifts of sp^2 or sp hybridized carbons in several different systems.[2,5−7] The idea of π-polarization has also been criticized, but without any explanation for the reverse behavior of the carbon shifts.[8] However, we recently proposed an alternative mechanism to account for the behavior of unsaturated aromatic side chains.[1]

The substituent-sensitive inherent polarization of the −C=N− unit (Scheme 1) of imines was proposed as an alternative/competitive explanation for π-polarization. The inductive and resonance effects of substituents X on the stabilities of the different resonance forms **3**−**6** were then considered.[1a] According to this concept, electron-withdrawing substituents decrease the contribution of the polarized form **4** through inductive destabilization, increasing the electron density on the C=N carbon as a consequence, while electron-donating substituents have an opposite effect, with negative ρ_F values as a result. Conjugative effects of the substituents seem to be negligible.[1a] The small negative ρ_R values were explained by resonance-induced polar effects (see structure **5**).

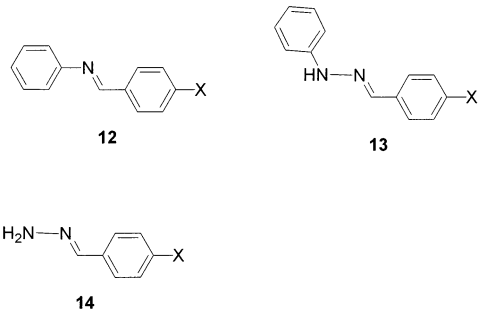


X = NO_2; CN; CF_3; F; Cl; Br; H; Me; OMe; or NMe_2

The reverse dependence of the C=N carbon ^{13}C NMR chemical shift on phenyl substitution has previously been observed in this laboratory not only for imine structures[1a] but also for hydrazones **7**−**11**.[6,7] In all cases, the C=N shift correlated poorly with Hammett-type single-parameter equations but well with a DSP equation. Differing from imines, both inductive and resonance contributions are highly significant for hydrazones.[6,7] In the present work, we have focused on the characterization of the origin of the differences in substituent dependence of the C=N carbon resonances of imines and hydrazones. A further goal was to investigate more generally the influence of the substitutuent (Y) on the C=N nitrogen (Y−N=CH−) on the sensitivity of the −C=N carbon resonance to the phenyl substituent X (−N=CH−C_6H_4−X).

Results

We performed ^{15}N NMR measurements on the hydrazone series **7** and **10**, for which the ^{13}C NMR data exist in our previous work,[6,7] and also on the imine series **12**. For the latter series, the ^{13}C NMR shifts were also recorded. Additionally, we report the PM3 atomic charges and bond lengths for the same compounds and also for hydrazones **13** and **14**.



For series **13** and **14**, the literature NMR data were used.[9,12] The NMR and atomic charge data are given in Supporting Information in Tables S2−S6. The bond length data are collected in Supporting Information in Table S7 and bond lengths for some relevant compounds are given in Table 4.

Discussion

Table 1 includes ρ_I or ρ_F and ρ_R values for imines and hydrazones, determined in our previous works[1a,6,7] or in this study, or values either found in the literature[5] or calculated by us using ^{13}C NMR chemical shifts observed earlier.[6,7,9] Both the inductive and resonance correlation

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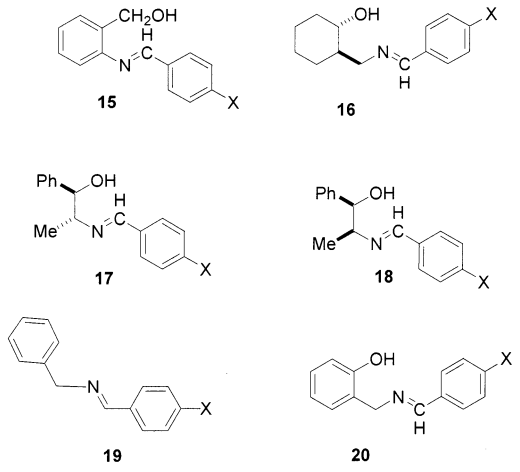
TABLE 1. ρ_I/ρ_F and ρ_R Values Obtained by DSP Treatment of the C═N Carbon ^{13}C NMR Chemical Shifts in $CDCl_3$ for the *para*-Substituted Imine Series 12 and 15−19 and for the Hydrazone Series 7−11, 13, and 14

line	series	ρ_I or ρ_F	ρ_R	shift range	ref
1	**15**	−3.7	−0.1	157.16−159.99	1a
2	**16**	−3.0	0.2	158.79−160.80	1a
3	**17**	−3.6	−0.5	159.43−161.93	1a
4	**18**	−3.2	−0.1	158.39−160.57	1a
5	**12**	−4.0	−0.7	157.33−160.34	this work
6	**19**	−3.6	−0.7	159.8−162.03	5[a]
7	**13**	−4.6	−3.1	133.75−138.64	6[b]
8	**14**	−5.5	−2.7	138.55−143.26	6[b]
9	**7**	−6.2	−4.9	127.14−133.93	6
10	**8**	−5.8	−5.0	127.46−134.34	6
11	**9**	−4.2	−2.0	144.4−148.5	7
12	**10**	−4.6	−1.8	135.8−140.4	7
13	**11**[c]	−3.8	−1.6	144.1−147.9	7

[a] ^{13}C NMR data from ref 10. [b] ^{13}C NMR data from ref 9. [c] In DMSO-d_6.

parameters of the hydrazones are higher than those observed for the imines. The significantly higher contribution of resonances with negative ρ_R values for the hydrazones is especially noteworthy. The results indicate the higher sensitivity of the polarization of the C═N unit of the hydrazones to substitution as compared with that of the imines or higher shift:charge ratios for the former compounds. Moreover, the C═N carbon resonances of the hydrazones appear at a field higher by ca. 15−30 ppm than those for the imines.



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

Atomic Charges vs Substituent Parameters. To assess the effect of substituents on the polarization of the C═N unit, the variation of the atomic charges was studied. Table 2 reports the statistical results for the correlations of the calculated charges of the C═N carbon and the C═N nitrogen and N2 of the hydrazone series **7**, **10**, **13**, and **14**, for the C═N carbon and C═N nitrogen of the imine series **12**, and for comparison, also those calculated previously[1a] for the imine series **15** and **20**, with the substituent parameters σ and σ^+. In all cases, the correlation with σ is better than that with σ^+. The slopes for the C═N carbon charges are negative in all cases. This means reverse behavior, i.e., the electron density on the C═N carbon increases, although the electron-withdrawing ability of the substituent, measured

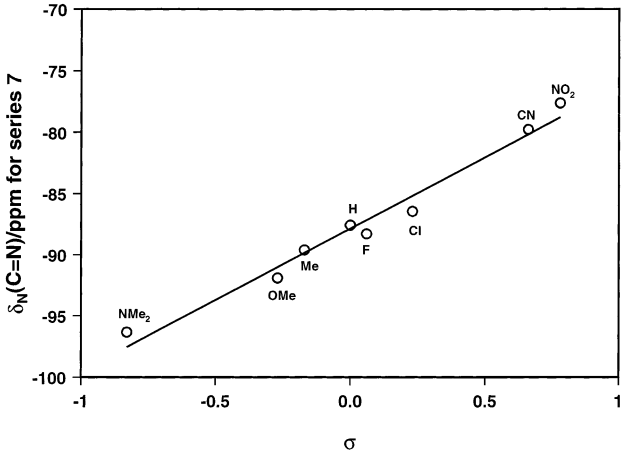


FIGURE 1. Plot of the ^{15}N NMR chemical shifts of the C═N nitrogen for series **7** in $CDCl_3$ vs Hammett substituent constants σ.

by σ/σ^+, increases. The q_C(C═N) values of the hydrazones (Table 2; slopes −0.044, −0.032, −0.046, and −0.043 for lines 15, 26, 37, and 47, respectively) possess a clearly higher sensitivity toward substitution than do the q_C(C═N) values of the imines (−0.027, −0.029, and −0.026 for lines 1, 5, and 9, respectively). In contrast with the reverse behavior of the C═N carbon, the slopes for the correlations of the charges of the C═N nitrogen or N2 are positive in all cases (lines 3, 7, 11, 18, 20, 29, 39, 41, 49, and 51), with the exception of the charge of N2 of 2-aminobenzoylhydrazones **10**. In the latter case, negative slopes are obtained for both σ and σ^+ correlations (lines 31 and 32), but the values are so small that they in fact indicate that the atomic charge on N2 does not depend on the phenyl substituent. For the other series studied, the electron density on both nitrogens decreases when the phenyl substituents become more electron-withdrawing, q_N(C═N) being about 2−3 times as sensitive to substitution as q_N(N2). For *N*-2-hydroxycyclohexyl-*N*-methylhydrazones **7**, the slope of the q_N(C═N) vs σ plot (0.030) is not significantly higher than the corresponding slopes for the imines **15**, **20**, and **12** (0.029, 0.026, and 0.024, respectively). For the other hydrazones, **10**, **13**, and **14**, the corresponding slopes, 0.023, 0.023, and 0.026, respectively, are almost the same as those observed for the imines.

^{15}N NMR Shifts of Imines and Hydrazones. The C═N nitrogen of the imine series **12** resonates at a field higher by ca. 42−74 ppm than that for the reference nitromethane. The C═N nitrogen of series **7** and **10** resonates at a field higher by ca. 78−96 ppm and 42−66 ppm, respectively, and N2 at a field higher by ca. 304−319 ppm and 210−213 ppm, respectively, than that for the reference nitromethane. The ^{15}N NMR shifts for the C═N nitrogen of **7** and **10** correlate well with the substituent constants σ (Table 2; lines 22 and 33) with slopes of ca. 12 and 15, respectively (cf. Figures 1 and S1). The N2 resonance is less sensitive. For **7** and **10**, the slopes are ca. 9 (line 24) and 2.3 (line 35), respectively, and the correlation is only moderate in both cases (cf. Figures 2 and S2). The slope values for hydrazones, 12 and 15, are clearly smaller than the corresponding slope of ca. 20 for the C═N nitrogen of the *N*-benzylideneanilines (**12**) (line 13). On the other hand, the slopes of

TABLE 2. Statistical Data for Hammett-type Correlations of Atomic Charges on C=N Carbons and C=N Nitrogens or N2 for Imine Series 12, 15, and 20 and for Hydrazone Series 7, 10, 13, and 14 (Correlations of δ_N(C=N) and δ_N(N2) Values with σ or σ^+ for Series 7, 10, 12, and 13 Are Also Included)[a]

line	series	type of compound	correlation	slope ± *s*	*r*	ref
1	**15**[b]	imine	q_C(C=N) vs σ	−0.027 ± 0.004	0.9389	1
2	**15**[b]		q_C(C=N) vs σ^+	−0.017 ± 0.003	0.9002	1
3	**15**		q_N(C=N) vs σ	0.026 ± 0.003	0.9466	
4	**15**		q_N(C=N) vs σ^+	0.016 ± 0.003	0.9047	
5	**20**[b]	imine	q_C(C=N) vs σ	−0.029 ± 0.003	0.9599	1
6	**20**[b]		q_C(C=N) vs σ^+	−0.021 ± 0.003	0.9439	1
7	**20**[b]		q_N(C=N) vs σ	0.029 ± 0.003	0.9569	
8	**20**[b]		q_N(C=N) vs σ^+	0.021 ± 0.003	0.9319	
9	**12**	imine	q_C(C=N) vs σ	−0.026 ± 0.003	0.9357	
10	**12**		q_C(C=N) vs σ^+	−0.016 ± 0.003	0.8880	
11	**12**		q_N(C=N) vs σ	0.024 ± 0.003	0.9358	
12	**12**		q_N(C=N) vs σ^+	0.015 ± 0.003	0.8880	
13	**12**		δ_N(C=N) vs σ	19.6 ± 0.7	0.9945	
14	**12**		δ_N(C=N) vs σ^+	12.5 ± 0.7	0.9865	
15	**7**	*N*,*N*-dialkylhydrazone	q_C(C=N) vs σ	−0.044 ± 0.005	0.9588	
16	**7**		q_C(C=N) vs σ^+	−0.024 ± 0.004	0.8674	
17	**7**[c]		q_C(C=N) vs σ^+	−0.019 ± 0.003	0.9040	
18	**7**		q_N(C=N) vs σ	0.030 ± 0.005	0.9024	
19	**7**		q_N(C=N) vs σ^+	0.019 ± 0.004	0.8572	
20	**7**[d]		q_N(N2) vs σ	0.011 ± 0.003	0.8624	
21	**7**[d]		q_N(N2) vs σ^+	0.007 ± 0.003	0.7640	
22	**7**		δ_N(C=N) vs σ	11.7 ± 0.8	0.9869	
23	**7**		δ_N(C=N) vs σ^+	7.3 ± 0.9	0.9562	
24	**7**		δ_N(N2) vs σ	9.4 ± 1.5	0.9349	
25	**7**		δ_N(N2) vs σ^+	5.6 ± 1.3	0.8655	
26	**10**	*N*-benzoylhydrazone	q_C(C=N) vs σ	−0.032 ± 0.005	0.9257	
27	**10**		q_C(C=N) vs σ^+	−0.019 ± 0.004	0.8751	
28	**10**[c]		q_C(C=N) vs σ^+	−0.016 ± 0.003	0.9086	
29	**10**		q_N(C=N) vs σ	0.023 ± 0.002	0.9657	
30	**10**		q_N(C=N) vs σ^+	0.015 ± 0.002	0.9336	
31	**10**		q_N(N2) vs σ	$-(9 \pm 7) \times 10^{-4}$	0.4650	
32	**10**		q_N(N2) vs σ^+	$-(9 \pm 5) \times 10^{-4}$	0.5884	
33	**10**		δ_N(C=N) vs σ	14.6 ± 0.6	0.9924	
34	**10**		δ_N(C=N) vs σ^+	9.2 ± 0.7	0.9751	
35	**10**		δ_N(N2) vs σ	2.3 ± 0.3	0.9430	
36	**10**		δ_N(N2) vs σ^+	1.4 ± 0.3	0.8873	
37	**13**[b]	*N*-phenylhydrazone	q_C(C=N) vs σ	−0.046 ± 0.005	0.9605	
38	**13**[b]		q_C(C=N) vs σ^+	−0.033 ± 0.004	0.9421	
39	**13**		q_N(C=N) vs σ	0.023 ± 0.005	0.8645	
40	**13**		q_N(C=N) vs σ^+	0.014 ± 0.004	0.8014	
41	**13**		q_N(N2) vs σ	0.009 ± 0.002	0.8657	
42	**13**		q_N(N2) vs σ^+	0.005 ± 0.001	0.7874	
43	**13**[e]		δ_N(C=N) vs σ	14.6 ± 1.5	0.9846	
44	**13**[e]		δ_N(C=N) vs σ^+	10.5 ± 1.1	0.9835	
45	**13**[e]		δ_N(N2) vs σ	8.0 ± 0.8	0.9855	
46	**13**[e]		δ_N(N2) vs σ^+	5.6 ± 1.1	0.9451	
47	**14**[b]	hydrazone	q_C(C=N) vs σ	−0.043 ± 0.005	0.9597	
48	**14**		q_C(C=N) vs σ^+	−0.030 ± 0.004	0.9352	
49	**14**		q_N(C=N) vs σ	0.026 ± 0.004	0.9334	
50	**14**		q_N(C=N) vs σ^+	0.016 ± 0.003	0.8835	
51	**14**		q_N(N2) vs σ	0.013 ± 0.002	0.9163	
52	**14**		q_N(N2) vs σ^+	0.008 ± 0.002	0.8517	

[a] *s*, standard deviation; *r*, correlation coefficient. [b] *p*-NMe_2 excluded. [c] *p*-NO_2 excluded. [d] *p*-NMe_2, *p*-Me, and *p*-CN excluded. [e] In DMSO with *p*-OMe, *p*-Me, H, *p*-Cl, and *p*-NO_2 substituents; δ_N values were taken from ref 12.

ca. 15 (line 43) for the C=N nitrogen and ca. 8 for N2 (line 45), which we calculated with the values for the phenylhydrazones (**13**) in DMSO,[12] are close to our hydrazone values, with the exception of N2 in **10**. The resonance of the C=N nitrogen of the hydrazones seems to be less sensitive to phenyl substitution than that of the C=N nitrogen of the imines. The N2 resonance also shows a response to the substituent, but to a lesser extent. The good or at least satisfactory fits and positive slopes for all these correlations, together with the q_N vs σ correlations discussed above, indicate that the δ_N variations accompanying substitution are electronic in origin and that the higher the electron density on the nitrogen, the lower the frequency of nitrogen resonance (at a higher field; more negative δ_N values). This represents normal behavior.

Cross-Correlations. A more explicit view of the polarization character of the C=N/C=N−N units of the imines and hydrazones is provided by the different correlations and cross-correlations of the q_C(C=N), q_N(C=N), q_N(N2), δ_C, and δ_N values. The slopes of the linear q_N(C=N) vs q_C(C=N) plots for series **7**, **10**, **13**, and **14** are −0.79 (Table 3, line 14; Figure 3), −0.70 (line 20), −0.74 (line 26), and −0.77 (line 30), respectively. The slopes for the q_N(N2) vs q_C(C=N) plots for series **7**, **13**, and **14** are −0.29 (Table 3, line 15; Fig. S3), −0.27 (line

TABLE 3. Statistical Data for Different Correlations and Cross-Correlations of ^{13}C and ^{15}N NMR Chemical Shifts and Atomic Charges of the C═N Carbon, C═N Nitrogen, or N2 for Imine Series 12, 15, and 20 and for Hydrazone Series 7, 10, 13, and 14[a]

line	series	type of compound	correlation	slope ± *s*	*r*	ref
1	**15**	imine	δ_C(C═N) vs q_C(C═N)	52 ± 14	0.8192	1
2	**15**		q_N(C═N) vs q_C(C═N)	−1.06 ± 0.02	0.9990	1
3	**20**	imine	q_N(C═N) vs q_C(C═N)	−1.00 ± 0.02	0.9989	1
4	**12**	imine	δ_C(C═N) vs q_C(C═N)	69 ± 14	0.8716	
5	**12**		δ_N(C═N)[b] vs q_N(C═N)	550 ± 40	0.9830	
6	**12**		δ_N(C═N) vs δ_C(C═N)	−6 ± 2	0.8357	
7	**12**		q_N(C═N) vs q_C(C═N)	−0.94 ± 0.01	0.9992	
8	**7**	*N*,*N*-dialkylhydrazone	δ_C(C═N) vs q_C(C═N)[c]	95 ± 9	0.9808	
9	**7**		δ_N(C═N) vs q_N(C═N)	325 ± 66	0.8956	
10	**7**		δ_N(N2) vs q_N(N2)[d]	170 ± 102	0.6416	
11	**7**		δ_N(C═N) vs δ_C(C═N)	−2.4 ± 0.3	0.9700	
12	**7**		δ_N(N2) vs δ_C(C═N)	−2.1 ± 0.2	0.9622	
13	**7**		δ_N(C═N) vs δ_N(N2)	1.14 ± 0.11	0.9740	
14	**7**		q_N(C═N) vs q_C(C═N)	−0.79 ± 0.01	0.9988	
15	**7**		q_N(N2) vs q_C(C═N)[e]	−0.29 ± 0.05	0.9324	
16	**7**		q_N(N2) vs q_N(C═N)[e]	0.37 ± 0.06	0.9298	
17	**10**	*N*-benzoylhydrazone	δ_C(C═N) vs q_C(C═N)	82 ± 13	0.9281	
18	**10**		δ_N(C═N) vs q_N(C═N)	591 ± 54	0.9682	
19	**10**		δ_N(N2) vs q_N(N2)	−284 ± 89	0.7930	
20	**10**		q_N(C═N) vs q_C(C═N)	−0.70 ± 0.04	0.9873	
21	**10**		q_N(N2) vs q_C(C═N)	0.011 ± 0.018	0.2387	
22	**10**		q_N(N2) vs q_N(C═N)	−0.02 ± 0.027	0.2730	
23	**13**	*N*-phenylhydrazone	δ_C(C═N)[f] vs q_C(C═N)	76 ± 17	0.9132	
24	**13**		δ_N(C═N)[g] vs q_N(C═N)	370 ± 40	0.9903	
25	**13**		δ_N(N2)[g] vs q_N(N2)	550 ± 40	0.9919	
26	**13**		q_N(C═N) vs q_C(C═N)	−0.74 ± 0.01	0.9997	
27	**13**		q_N(N2) vs q_C(C═N)	−0.27 ± 0.01	0.9920	
28	**13**		q_N(N2) vs q_N(C═N)	0.36 ± 0.02	0.9899	
29	**14**	hydrazone	δ_C(C═N)[f] vs q_C(C═N)	99 ± 16	0.9631	
30	**14**		q_N(C═N) vs q_C(C═N)	−0.772 ± 0.004	0.9999	
31	**14**		q_N(N2) vs q_C(C═N)	−0.38 ± 0.01	0.9952	
32	**14**		q_N(N2) vs q_N(C═N)	0.49 ± 0.02	0.9958	

[a] *s*, standard deviation; *r*, correlation coefficient. [b] *p*-CN and *p*-NMe_2 excluded. [c] *p*-CN excluded. [d] *p*-NO_2 and *p*-CN excluded. [e] *p*-CH_3 and *p*-CN excluded. [f] δ_C values were taken from ref 9. [g] δ_N values were taken from ref 12.

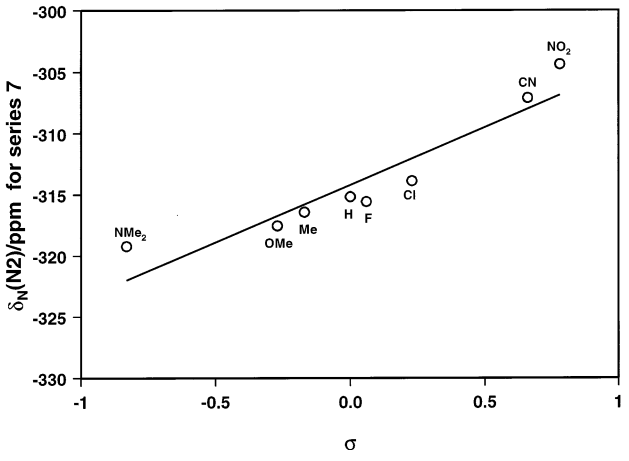


FIGURE 2. Plot of the ^{15}N NMR chemical shifts of N2 for series **7** in $CDCl_3$ vs Hammett substituent constants σ.

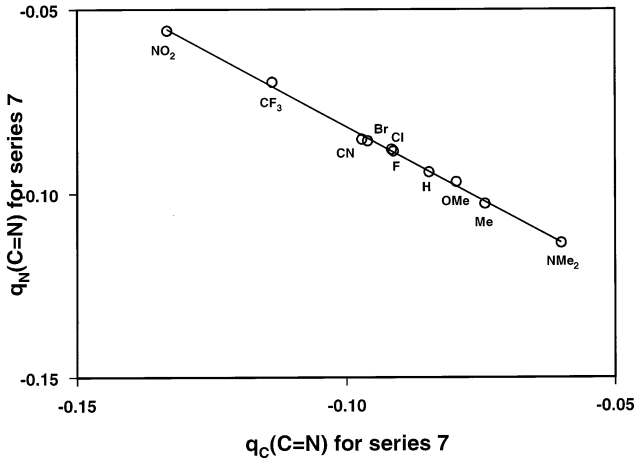


FIGURE 3. Cross-correlation between the atomic charge of the C═N nitrogen and that of the C═N carbon for series **7**.

27), and −0.38 (line 31), respectively, whereas the slope is 0.011 only for series **10** (line 21). In accordance with the behavior of the imines, the atomic charges on the C═N carbon and the C═N nitrogen of the hydrazones display an inverse trend. However, in contrast with the behavior of the imines, for which $\Delta q_N(C{=}N)/\Delta q_C(C{=}N)$ is shown to be close to −1.0 (Table 3; lines 2, 3, and 7), for the hydrazones, the charge on the C═N nitrogen is less sensitive to substitution than that on the C═N carbon. The counterpart of the variable charge on the carbon seems to be distributed on both nitrogen atoms. In addition to the difference in the slopes of the q_N(C═N) vs q_C(C═N) plots between the imines and hydrazones, a marked difference is to be seen between *N*,*N*-dialkylhydrazones (**7**) and *N*-alkyl-*N*-benzoylhydrazones (**10**) when the dependence of the charges of the C═N nitrogen and N2 on the phenyl substitutent is compared. For series **7**, the q_N(C═N) and q_N(N2) display a similar trend, although N2 exhibits a diminished change, only about 40% of that observed for the C═N (Table 3; lines 14−16). For series

10, the charge on N2 hardly varies with the substituent (Table 3; lines 20−22). This agrees with the different behavior of the ^{15}N NMR shifts of N2 for series **7** and **10** discussed above (Table 2; cf. lines 24 and 35). In summary, while the polarizable unit in the imines is the C=N fragment, in the hydrazones, the charge at the other end of the dipole seems to be distributed on both nitrogen atoms. The hydrazide character of benzoylhydrazones is clearly indicated by the insensitivity of both the charge and δ_N of N2 to phenyl substitution. Obviously, the amide resonance prevents interaction of the lone pair of N2 with the C=N unit.

For the hydrazones, the dependence of the C=N carbon ^{13}C NMR chemical shift on the charge on the carbon is significant. The slopes of the plots δ_C(C=N) vs q_C(C=N) are 95 and 82 ppm/electron, respectively, for series **7** and **10** (Table 3; lines 8 and 17; cf. Figure S4) and **17**. For the hydrazones **14**, the slope is 99 ppm/electron, and for the *N*-phenylhydrazones **13**, the slope is 76 ppm/electron (lines 29 and 23, respectively). In all cases, deshielding (increased shift) of the carbon is observed with decreasing electron density (less negative atomic charge) on the carbon. The C=N carbon chemical shift of the hydrazones seems to be clearly more sensitive to the atomic charge on the carbon than that for the imines. For the imine series **15** and **12**, the slopes of the plots δ_C(C=N) vs q_C(C=N) are only 52 and 69 ppm/electron, respectively (Table 3; lines 1 and 4).[1a]

For the imine series **12**, a slope of 550 ppm/electron is observed for the plot of δ_N(C=N) vs q_N(C=N) (Table 3; line 5). For the *N*,*N*-dialkylhydrazones **7**, the dependences of the C=N nitrogen and N2 resonances on the electron density on the nitrogen in question are different. Correlation coefficients of 325 and 170 ppm/electron, respectively, are observed (lines 9 and 10). For series **10**, the slope of the plot δ_N(C=N) vs q_N(C=N) is 590 ppm/electron (Table 3; line 18), and that for series **13** is 370 ppm/electron (line 24). The former value is close to that observed for series **12**, and the latter value is very similar to that observed for series **7**. As regards the plot of δ_N(N2) vs q_N(N2), the slopes are −284 and 550 ppm/electron, respectively, for series **10** and **13** (Table 3; lines 19 and 25, respectively). Both of these values differ considerably from the slope of 170 ppm/electron observed for series **7**. For series **13**, the correlations in question are very good for both C=N and N2, while for series **10**, the correlation is satisfactory for C=N and poor for N2. For series **7**, both correlations are poor. With the exception of δ_N(N2) for series **10**, in all cases, the less negative the electron density of the atom, the lower the field of nitrogen resonance. This is according to the generalized electronic effect.

The C=N carbons of the hydrazones carry significantly more negative atomic charges from −0.13 to −0.06 (cf. Tables S1, S4, S5, and S6) than those previously observed for the C=N carbon of the imines (from −0.06 to −0.003)[1a] or now observed for the imine series **12** (Table S2, from −0.06 to −0.02). This is consistent with the ^{13}C NMR chemical shift data, which show that the C=N carbon of the hydrazones resonates at a lower frequency (i.e., with reduced shift values) than that of the imines (cf. Table 1). This difference suggests a more significant contribution of the resonance form **4** (cf. Scheme 1) in the case of the imines than in the case of the hydrazones. Also, the C=N nitrogens of the hydrazones (**7**, **13**, and **14**) both possess more negative charges and resonate at a lower frequncy than those of the imines (**12**). The hydrazones belonging in series **10**, however, behave analogously to the imines in series **12**.

In light of the present theoretical calculations and the correlations observed, the higher dependence of the C=N carbon ^{13}C NMR chemical shift of the hydrazones on the phenyl substituent as compared with the imines (cf. Table 1) can be ascribed primarily to two main reasons: (i) the higher sensitivity of the chemical shift at the probe site to changes in electron density, i.e., a higher shift:charge ratio, and (ii) the higher sensitivity of the charge on the carbon to substitution. Of these two reasons, the former seems to be the more important. Both of these facts indicate that the charge distribution on the C=N unit is different for hydrazones and imines. For imines, we recently suggested a significant contribution of the substituent-sensitive inherent polarization of the C=N unit, the main contributing structures being **3** and **4** (Scheme 1).[1a] As has already been discussed, for imines, the ρ_R values are negative but small. This indicates a low significance of structure **5** and structure **6**, too.

Differences in the Mechanism of Polarization of the C=N Unit of Imines and Hydrazones. Scrutiny of the information derived from the ^{13}C and ^{15}N NMR chemical shifts and the PM3 atomic charges reveals several characteristic differences between the imines and hydrazones.

(i) On average, the ρ_I or ρ_F values derived from DSP analysis of the ^{13}C NMR chemical shifts are somewhat larger for the hydrazones. (ii) For the ρ_R values, a considerable difference is seen (5−10 times larger for the hydrazones as compared with those for the imines). (iii) For the hydrazones, both the carbon and nitrogen of the C=N unit are shielded as compared with imines. (iv) The atomic charges on the C=N unit are more negative and more sensitive to effects of substituents for the hydrazones. (v) The mutual atomic charge behavior for the C=N carbon and nitrogen also differs. For the imines, the slope of the plot of q_N(C=*N*) vs q_C(*C*=N) is negative and close to −1, whereas, as an example, it is −0.79 for the hydrazone series **7**. For the plot of q_N(*N*2) vs q_C(*C*=N), the slope is only −0.29. Clearly, for the hydrazones, the charge is distributed on both nitrogen atoms. The facts listed above suggest a difference between the imines and hydrazones in terms of the mechanism by which the substituents induce changes in the charges and the NMR chemical shifts of the nuclei of the C=N group. The behavior of the benzoylhydrazones seems to be intermediate between those of the imines and the other hydrazones. For the imines, the substituent dependence of the ^{13}C and ^{15}N NMR chemical shifts on the benzylidenic substituent X can largely be explained by comparison of the contributions of the resonance forms **3**−**6** in Scheme 1.[1a] To date, no explicit explanation has been given for the behavior of the hydrazones. However, resonance structure **22** was proposed by Gordon et al. (cf. Scheme 2).[9] The basic question is that of whether the effect of Y is conjugative (if there is a lone pair in use, as has been proposed), inductive, or steric.

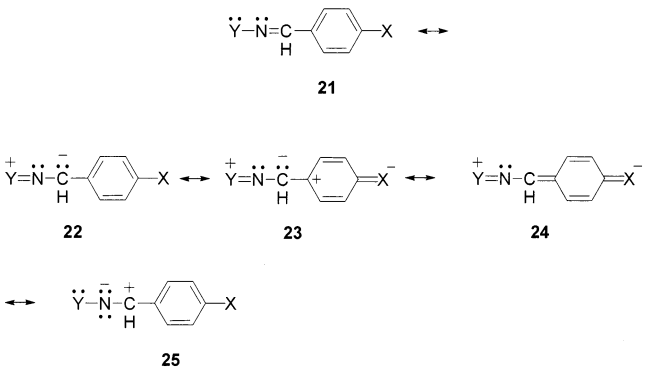
For a better understanding of the behavior of the hydrazones vs that of the imines, we compared the ρ_F(X) and ρ_R(X) values of the compounds studied in this work

TABLE 4. Effect of Substituent Y in Y−N═CH−C_6H_4−*p*-X System on ρ_R and ρ_F Values Describing the Dependence of ^{13}C NMR Chemical Shifts of the C═N Carbon on the Benzylidenic Substituent X[a,b]

Y	σ_p^+	δ_C(C═N)	q_C(C═N)	ρ_F	ρ_R	C═N bond order (bond length)	=N−Y bond order (bond length)	=C−C(Ph) bond order (bond length)	ref[c]
NH_2	−1.30	142.77	−0.0795	−5.2	−4.0	1.8541 (1.3020)	1.0697 (1.3824)	1.0190 (1.4652)	9
NHPh	−1.40	137.25	−0.0771	−4.6	−3.2	1.8564 (1.3013)	1.0473 (1.3914)	1.0186 (1.4653)	9
HO	−0.92	150.33	−0.0531	−4.4	−0.7	1.8961 (1.2982)	1.0130 (1.4007)	1.0158 (1.4660)	9, 15
MeO	−0.78	148.26	−0.0489	−2.9	−1.2	1.9064 (1.2958)	0.9810 (1.4264)	1.0130 (1.4668)	13
Me	−0.31	162.44	−0.0452	−3.4	−0.30	1.9161 (1.2919)	1.0130 (1.4499)	1.0090 (1.4682)	13
$(CH_3)_3C$	−0.26	155.08	−0.0295	−3.2	−0.4	1.9285 (1.2883)	0.9720 (1.4838)	1.0041 (1.4704)	13
Ph	−0.18	160.34	−0.0289	−4.1	−0.75	1.8891 (1.2939)	1.0330 (1.4310)	1.0113 (1.4676)	this work
$PhCH_2$	−0.28	161.93	−0.0340	−3.5	−0.5	1.9217 (1.2910)	0.9892 (1.4656)	1.0077 (1.4686)	10
p-NO_2−C_6H_4	+0.04	162.46	0.0042	−3.6	0.07	1.8852 (1.2939)	1.04570 (1.4264)	1.0145 (1.4666)	14

[a] δ_C(C═N) and q_C(C═N) values and C═N, =N−Y, and =C−C(Ph) bond orders and bond lengths (Å) are given for substitution X = H. =C−C(Ph) refers to the bond between the C═N carbon and the substituted phenyl ring. [b] ρ values were calculated in this work via eq 1: SCS = $\rho_F\sigma_F + \rho_R\sigma_R$, with the aid of the literature ^{13}C NMR data, with the exception of Y = Ph (series **12**), for which the NMR data were determined in this work. [c] Reference for the ^{13}C NMR chemical shift data used to calculate the ρ_F and ρ_R values.

SCHEME 2



with the corresponding values that we derived from the literature NMR shift data (Y−N═CH−C_6H_4−*p*-X; Table 4). The correlation parameters ρ_F(X) and ρ_R(X) for series **12** (Y = −Ph) are based on ^{13}C NMR shifts recorded in this study. For the other series, i.e., Y = −Me, $-CMe_3$, $-CH_2Ph$, −C_6H_4−*p*-NO_2, −OMe, −OH, $-NH_2$ (series **13**), and −NHPh (series **14**), we calculated ρ_F(X) and ρ_R(X) with the aid of ^{13}C NMR shift data from the literature. The fact that the *sensitivity* of the electronic character of the C═N function *to electron donation/electron withdrawal by the phenyl substituent X* is adjusted by the electronic effects of Y is seen on inspection of Figure 4. Both the ρ_F(X) and ρ_R(X) values from Table 4 can be successfully correlated with the σ_P^+ values of group Y, σ_P^+(Y). Thus, the effect of Y is electronic in nature. We also examined correlations with σ, σ_I, and R, but these were less successful, indicating that both inductive and resonance effects contribute. The varying sources of the NMR data (different sample concentrations, varying set of substitutions) account for the fact that the goodness of the correlation is not very high. Figure 4 can be rationalized by inspecting the contributions of the different resonance forms in Schemes 1 and 2. For imines, when Y is an electron-withdrawing group or can at least

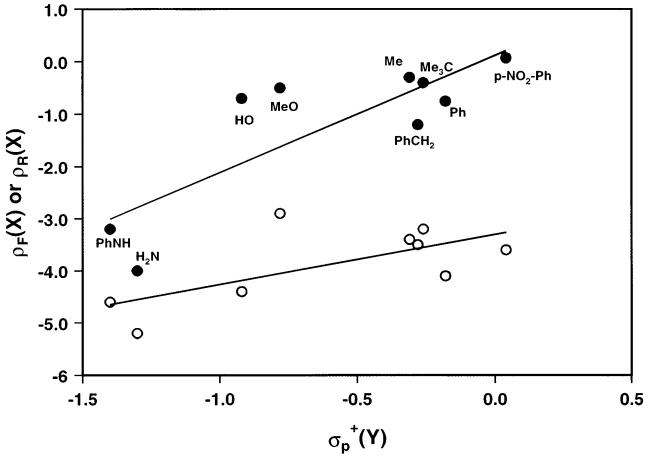


FIGURE 4. Plots of the correlation parameters ρ_F(X)(○) and ρ_R(X) (●) (determined with respect to phenyl substituent X) vs substituent constant σ_p^+(Y) with varying Y for Y−N═CH−C_6H_4−*p*-X.

stabilize **4** (−Me, $-CMe_3$, −Ph, $-CH_2Ph$, −C_6H_4−*p*-NO_2), the contribution of **4** (Scheme 1) will increase as a function of σ_P^+(Y). With electron-donating substituents X, its contribution further increases. This will result in a more positively charged C═N carbon (deshielding) and negative ρ_F and ρ_R (the latter via structure **5**) values. On the other hand, although Y is inductively electron withdrawing but at the same time electron donating via resonance ($-NH_2$, −NHPh, −OH, or −OMe), resonance structure **22** (Scheme 2) is stabilized. As regards the effect of substituent X, electron-withdrawing substituents stabilize **22** inductively and make possible the contribution of **23** through resonance. As a consequence, the C═N carbon exhibits more negative charges. This results in negative ρ_F and ρ_R (the latter via structure **23**) values.

Figure 4 clearly shows that the hydrazones exhibit characteristics that are common for all compounds possessing an atom with a lone pair attached to the C═N

nitrogen, i.e., when Y is a group capable of conjugative electron donation. The correlations in Figure 4 can be explained by different balances between the possible resonance structures for the imines (Scheme 1) and the hydrazones and related compounds (Scheme 2). The substituents Y capable of electron donation by resonance (Y = $-NH_2$, $-NHPh$, $-OMe$, $-OH$; group **A**) result in more negative $\rho_R(X)$ values the more negative $\sigma_p^+(Y)$ is, indicating an increase in the contribution of **22** (Scheme 2). The fact that the $\rho_R(X)$ values are highly negative for group **A** means that the resonance effects of the substituents X must be resonance-induced polar effects (**22** ↔ **23**) and not the normal resonance effects (**22** ↔ **24**). The latter case would lead to $\rho_R(X) > 0$.

It seems evident that the resonance-induced polar effects (**5**, Scheme 1) are not of high importance (only small negative ρ_R) for the imines (Y = $-Me$, $-CMe_3$ $-Ph$, $-CH_2Ph$, $-C_6H_4-p$-NO_2; group **B**). The other possibility is that in both cases, i.e., for the compounds in groups **A** and **B**, both the normal resonance effect [**6** in Scheme 1, **24** in Scheme 2; leading to $\rho_R(X) > 0$] and the inverse resonance-induced polar effect [**5** in Scheme 1, **23** in Scheme 2; leading to $\rho_R(X) < 0$] operate; however, in the case of the imines (group **B**), the two effects compensate each other, while in the case of group **A**, the inverse effect is overwhelming.

For the imines (group **B**), the ρ_F values are clearly negative in all cases, varying within only a narrow range. Obviously, the contribution of **4** does not vary largely with the different Ys studied. Electron-withdrawing phenyl substituents X inductively destabilize **4**, and a decrease in the imine carbon charge (a less positive charge), a shielding effect, and $\rho_F(X) < 0$ result. For the hydrazones and related compounds (group **A**), an increased electron donation by Y [a more negative $\sigma_p^+(Y)$] stabilizes **22**. Consequently, its contribution increases, leading to *a higher sensitivity* of the electronic character of the C=N function *to phenyl substitution via* the inductive effects of X. Electron-withdrawing substituents X inductively stabilize structure **22**, and a decrease in the charge on the imine carbon (more negative charges), a shielding effect, and $\rho_F(X) < 0$ result. The varying sensitivity to X is seen as a dependence of $\rho_F(X)$ on $\sigma_p^+(Y)$ with a positive slope.

Additional support is lent to our conclusions by an inspection of the plot in Figure 5, where $\rho_R(X)$ is plotted against $\delta_C(C{=}N)$ for the unsubstituted derivatives, i.e., X = H, for the series with different Ys. The more shielded the carbon, the more sensitive its ^{13}C NMR shift is to conjugative effects by X. We consider the shielding of the C=N carbon to reflect the fact that the contribution of resonance structure **22** is increased. This conclusion could be verified by the plots shown in Figures 6 and 7. In Figure 6, it is clearly seen that shielding corresponds to the increase in electron density at the C=N carbon. Figure 7 shows correlation between ρ_R and ρ_F values and $q_C(C{=}N)$. Both parameters turn more negative when the atomic charge at the C=N carbon becomes more negative. According to our interpretation, the inductive effects of substituents X affect the stabilities of forms **4** and **22** with practically the same efficiency, while the resonance effects overwhelmingly affect via the interaction **22** ↔ **23**. Thus, it can be concluded that particularly the sensitivity of the ^{13}C chemical shift of the C=N carbon

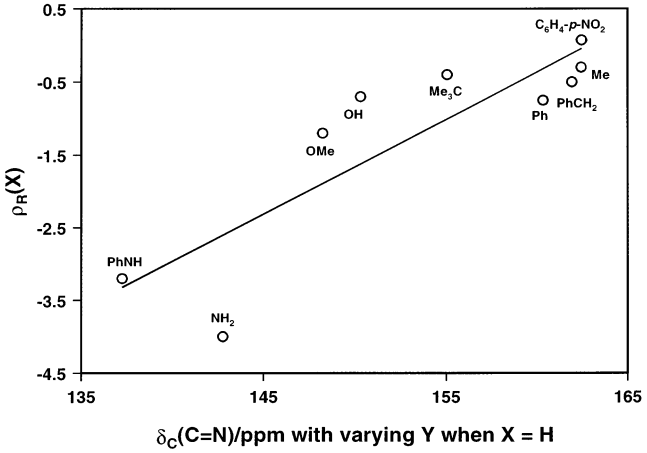


FIGURE 5. Plot of the correlation parameter $\rho_R(X)$ (determined with respect to phenyl substituent X) vs the C=N carbon ^{13}C NMR chemical shift for the phenyl unsubstituted derivative Y−N=CH−C_6H_5 with varying Y.

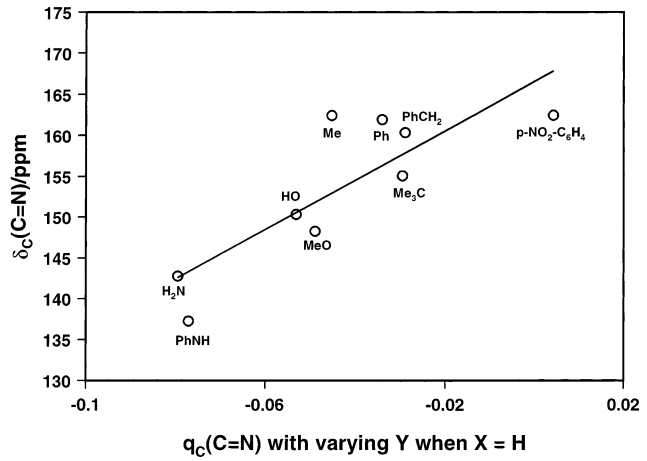


FIGURE 6. Plot of the C=N carbon ^{13}C NMR chemical shift in $CDCl_3$ for the phenyl unsubstituted derivative Y−N=CH−C_6H_5 vs the atomic charge of the C=N carbon with varying Y.

to the electronic resonance effects of the phenyl substituent X, i.e., $\rho_R(X)$, is a useful tool for evaluating the electrophilicity of the C=N carbon.

The bond order/bond length data in Table 4 further support the above conclusions. For compounds in group **A**, the C=N bond order is lower and the bond is lengthened, while the =N−Y and =C−C(Ph) bond orders are higher and the bonds are shortened as compared with compounds in group **B**. The imine derivatives possessing an aromatic ring attached directly to the C=N nitrogen (Y = Ph or *p*-NO_2−C_6H_4) show bond orders between those typical for group **A** and those typical for other members of group **B**. Further, when varying Y, good or at least fair correlations with slopes of $(6.2 \pm 0.7) \times 10^{-2}$ (r = 0.9650) and 1.54 ± 0.10 (r = 0.9895), respectively, were observed between the C=N bond order and $\sigma_p^+(Y)$ and between the C=N bond order and $q_C(C{=}N)$ when Y = Ph and *p*-NO_2−C_6H_4 were excluded.

The present results show that the *sensitivity* of the electronic character of the C=N function in Y−N=CH−C_6H_4−*p*-X *to electron donation/electron withdrawal by the phenyl substituent X* is adjusted by the electronic effects of Y. This is revealed by the behavior of the ^{13}C

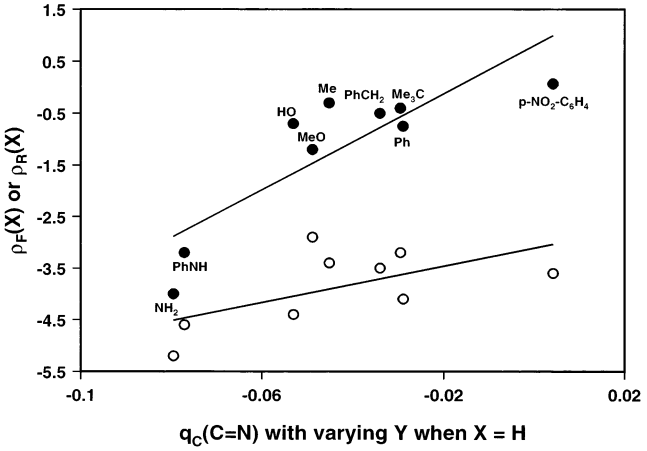


FIGURE 7. Plots of the correlation parameters $\rho_F(X)$ (○) and $\rho_R(X)$ (●) (determined with respect of phenyl substituent X) vs the atomic charge of the C═N carbon for Y−N═CH−C_6H_5 with varying Y.

or ^{15}N NMR chemical shifts. Related results have recently been obtained by Liu et al. in theoretical bond dissociation energy studies concerning *para*-substituted aromatic silanes[17] and *para*-substituted anilines.[18] For instance, for their 4-Y−C_6H_4−Z−X system (Z = SiH_2; X = H, F, Cl, or Li; Y = NO_2, CHO, CN, CF_3, $COCH_3$, $CONH_2$, COOH, F, Cl, H, Me, SMe, OMe), they state that "the direction and magnitude of the effect of substituents Y have some important dependence on the polarity of the Z−X bond undergoing homolysis."[17] Their results as well as ours indicate that there prevails an interesting interaction over the aromatic and side-chain systems. The item is under continuous interest.

Conclusions

The extensive data relating to the azomethines, hydrazones, and related compounds derived from substituted benzaldehydes have shown that the substituent effects on the *C*═N ^{13}C and/or C═*N* ^{15}N NMR chemical shifts can be explained by considering the different resonance structures depicted in Schemes 1 and 2. For these compounds possessing a C═N double bond, the magnitude of the negative ρ_R derived from calculations involving the ^{13}C NMR chemical shifts of the C═N carbon with respect to substituent X is a useful tool for evaluating the detailed electronic character of the C═N double bond. The strength of the effect of X varies characteristically as a function of substituent Y. In Figure 4, the ρ_R and ρ_F values observed with substituent X are plotted against the σ_p^+ value of substituent Y. These plots illustrate a novel way of using the Hammett-type parameters. The justification of this treatment was verified by δ_C(C═N) vs q_C(C═N), ρ_F/ρ_R vs q_C(C═N), the C═N bond order vs σ_p^+(Y), and the C═N bond order vs q_C(C═N) correlations with varying Y. According to our interpretation, the inductive effects of substituent X affect the stabilities of forms **4**/**25** and **22** with practically the same efficiency, while the resonance interaction **22** ↔ **23** is more efficient than the interaction **4** ↔ **5**. We conclude that these results can be useful as concerns an explanation of the reactivities of the compounds in question toward nucleophilic agents; this property is governed by the electrophilicity of the C═N carbon.

Experimental Section

General Procedures. Melting points are uncorrected. All new compounds (see Table S1) gave satisfactory microanalyses (C, H, N).

Synthesis of Benzylidene Derivatives 12. Aniline (2 mmol) and the appropriate aromatic aldehyde (2 mmol) were dissolved together in ethanol (10 mL) and left to stand overnight at room temperature. The solvent was evaporated off, and the products were recrystallized from ethanol or diisopropyl ether. The yields were 77−90%.

NMR Measurements. NMR spectra were recorded at 27 °C on an NMR spectrometer operating at 125.78 MHz for ^{13}C and 50.688 MHz for ^{15}N on 0.4 M solutions in $CDCl_3$. ^{13}C NMR spectra were referenced internally to tetramethylsilane (0.00 ppm), while ^{15}N NMR 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 NMR spectra. ^{13}C NMR spectra were acquired with ^1H broad-band decoupling and NOE ^1H nondecoupling techniques. ^{13}C NMR spectra were acquired with the following conditions: spectral width = 30 kHz, 32 K data points (^1H decoupled)/64 K data points (^1H coupled), digital resolution = 0.92 Hz/point (^1H decoupled)/0.46 Hz/point (^1H coupled), pulse width = 4.35 μs (45°), acquisition time = 1.09 s (^1H decoupled)/2.18 s (^1H coupled), number of transients = 1000−12000, pulse delay = 3 s (^1H decoupled)/5 s (^1H coupled), pulse sequence = (JEOL) SGBCM (^1H decoupled)/SGNOE (^1H coupled). Exponential windowing with a line-broadening term of 2 Hz (^1H decoupled)/1 Hz (^1H coupled) was applied prior to Fourier transformation. ^{15}N NMR spectra were acquired with refocused INEPT technique optimized on 8 Hz. ^{15}N NMR spectra were acquired with the following conditions: 90° flip angle, pulse recycle time = 5.1 s, spectral width = 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 of 1 Hz was applied prior to Fourier transformation.

Statistical Calculations. The sources of the substituent constants are as follows: σ, σ^+, ref 11; σ_F, σ_R, ref 16, except σ_F and σ_R for Br, ref 11.

PM3 Calculations. Three-dimensional structures of the compounds were composed by using the program SYBYL,[19] and the structures thus obtained were optimized with the Tripos force field. The resulting conformations were used as starting structures for the semiempirical calculations of conformations, heats of formation, and atomic charges. These calculations were performed by using the semiempirical quantum mechanical method PM3[20] of the program MOPAC 7.0.[21] All structures were optimized without any restriction. The quantum chemical calculations were processed on the SGI "Octane" (2 × R 12 000) computer of the University of Potsdam.

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Supporting Information Available: Analytical data on compounds of series **12** (Table S1); ^{13}C and ^{15}N NMR data and PM3 atomic charges for series **7**, **10**, **12**−**14** (Tables S2−S6); bond lengths in Table S7; δ_N(C═N) vs σ correlation for series **10** (Figure S1); δ_N(N2) vs σ correlation for series **10** (Figure S2); q_N(N2) vs q_C(C═N) correlation for series **7** (Figure S3); and δ_C(C═N) vs q_C(C═N) correlation for series **7** (Figure S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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