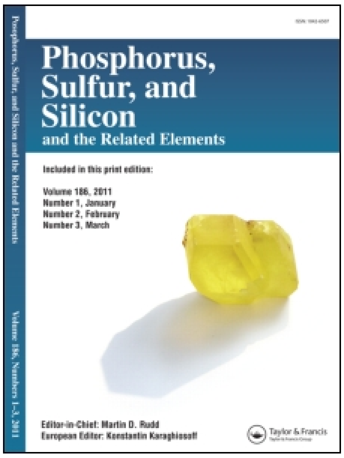

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^{13}C NMR STUDY OF SUBSTITUENT EFFECTS IN 1,2,4-OXADIAZOLE AND 1,2,4-THIADIAZOLE DERIVATIVES

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^{13}C NMR STUDY OF SUBSTITUENT EFFECTS IN 1,2,4-OXADIAZOLE AND 1,2,4-THIADIAZOLE DERIVATIVES

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^{13}C chemical shifts of C=N, C=O and C=S carbons of 3,4-disubstituted-1,2,4-oxadiazole-5-ones(thiones) and 3,4-disubstituted-1,2,4-thiadiazole-5-ones have been determined in $CDCl_3$ solution. Exceptionally good Hammett correlations of ^{13}C NMR chemical shifts of these carbons with σ were obtained. The negative ρ values observed (inverse substituent effects) indicate π-polarization of the C=N, C=O and C=S bonds. As expected, the long distance C=O and C=S ^{13}C chemical shifts were found less susceptible to substituent-induced electronic changes.

Keywords: 1,2,4-oxadiazole-5-ones(thiones); 1,2,4-thiadiazole-5-ones; ^{13}C NMR; substituent effects

Carbon-13 NMR spectroscopy is a useful tool to obtain information on the electronic environment of carbon atoms and has been used extensively for studying the electronic properties of a wide range of aromatic and other unsaturated systems. In simple benzene derivatives, substituents exert characteristic substituent effects on the chemical shifts of all of the ring carbons present.

The effect of substituents on the chemical shifts of side-chain carbons is of obvious interest, especially in those cases where the side chain is conjugated with the ring. This allows resonance interaction with *para* substituents to take place. Hence, the effect of distance on the extent of such interaction can be explored.

The chemical shifts of sp^2 and sp carbons directly bonded to the ring have been observed to show reverse substituent effects (electron-withdrawing substituents increase the electron density on the carbon

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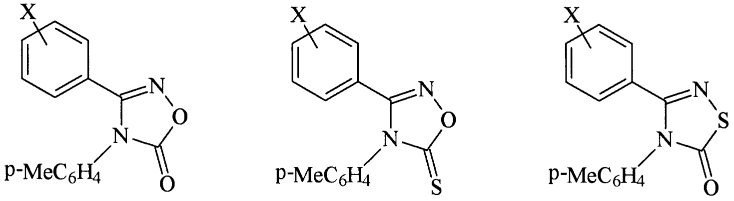
concerned whereas electron donors decrease it). This phenomenon has been attributed to polarization of the π system of the side chain (localized polarization) independently of polarization of the π system as a whole (extended polarization).[1,2] Most of the studies in this area have involved carbons bonded oxygen,[1] nitrogen[1–5] or other carbons.[5–8] Dual substituent parameter (DSP) correlations of substituent chemical shifts for α-carbons have shown that inductive effects are relayed to this position with greater efficiency than resonance ones and both are usually negative.[1–5] Contrary to the situation for the corresponding ring carbons, the *meta* side-chain α-carbons correlated about as well as the *para* one with negative ρ_I and ρ_R values.[1,3,4]

The chemical shifts of more distant sp^2 carbons have also been observed to show reverse substituent effects and afforded negative ρ_I and ρ_R values.[9]

^{13}C NMR spectra in $CDCl_3$ of 20 oxadiazole and thiadiazole derivatives (Scheme 1) are reported here with the aim of studying the effect of the substituents on ^{13}C chemical shifts of C=N, C=O and C=S carbons in the heterocyclic ring.



	X
1a	p-Me
1b	m-Me
1c	H
1d	p-Cl
1e	m-Cl
1f	p-NO_2

	X
2a	p-Me
2b	m-Me
2c	H
2d	p-Cl
2e	m-Cl
2f	p-CN
2g	m-NO_2

	X
3a	p-Me
3b	m-Me
3c	H
3d	p-Cl
3e	m-Cl
3f	m-NO_2
3g	p-NO_2

SCHEME 1

RESULTS AND DISCUSSION

^{13}C chemical shifts of C=N, C=O and C=S carbons of compounds (**1–3**) are shown in Tables I–III. The values of $^{13}C_{C=N}$, $^{13}C_{C=O}$, and $^{13}C_{C=S}$ refer to the center peak of $CDCl_3$ which has a value of 77.050 ppm.

TABLE I ^{13}C NMR Chemical Shifts (in ppm) of 3-(Substituted Phenyl)-4-(*p*-tolyl)-1,2,4-oxadiazole-5(4H)-ones (Comp. 1)

Comp. **1**	X	$^{13}C_{C=N}$	$^{13}C_{C=O}$
1a	*p*-Me	157.197	158.217
1b	*m*-Me	157.293	158.157
1c	H	157.152	158.133
1d	*p*-Cl	156.292	157.937
1e	*m*-Cl	156.021	157.880
1f	*p*-NO_2	155.441	157.599

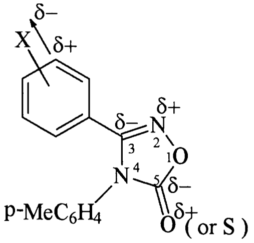
The general conclusion derived from the data in Tables I–III is that all the substituents influence the value of the ^{13}C chemical shift of C=N, C=O, and C=S carbons. The good fits obtained (Table IV) show that the chemical shifts are systematic and electronic in origin.

The plot of the C=N ^{13}C chemical shifts againts Hammett substituent constants, gave good correlations (Table IV, Figures 1, 3, and 5). Negative ρ values have been observed in all cases. This "reverse" direction of the inductive[1,10–12] or resonance[1,3,4,10] substituent chemical shifts (SCS) effect can be explained by the π polarization mechanism. According to the theory for the inductive SCS effect, the substituent dipole polarizes each π-unit separately as a localized system, affecting the inverse behavior of electron density as shown in Scheme 2 for compounds (**1**, **2**).

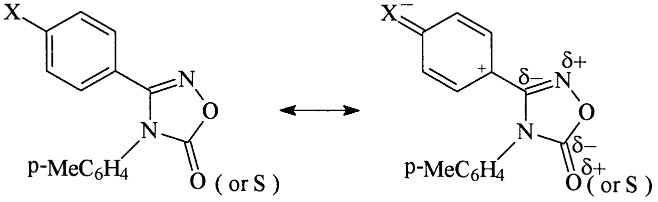
The polarization of the C=N system in the heterocyclic ring by an electron-withdrawing substituent results in an increase in π-electron density at carbon-3. The increased shielding of the carbon causes the upfield shift of the ^{13}C chemical shift. This means that the SCS effects are normal, but the changes in the electron density at carbon-3 are

TABLE II ^{13}C NMR Chemical Shifts (in ppm) of 3-(Substituted Phenyl)-4-(*p*-tolyl)-1,2,4-oxadiazole-5(4H)-thiones (Comp. 2)

Comp. **2**	X	$^{13}C_{C=N}$	$^{13}C_{C=S}$
2a	*p*-Me	158.814	187.507
2b	*m*-Me	158.916	187.456
2c	H	158.764	187.437
2d	*p*-Cl	157.965	187.357
2e	*m*-Cl	157.686	187.302
2f	*p*-CN	157.330	187.155
2g	*m*-NO_2	156.963	187.156



SCHEME 2



SCHEME 3

"reversed." In other words, electron acceptors increase the electron density and donors decrease it. This reverse inductive contribution was shown by dual substituent parameter (DSP) analysis in the literature.[1,4,11–13] The contribution was explained to be consistent with the π-polarization mechanizm. The "reverse" direction of the resonance SCS effect can be interpreted as a consequence of a secondary resonance effect (field-transmitted resonance-polar effect)[5] as shown in Scheme 3 for compounds (**1**, **2**). The extend of the dipole set in the ring is proportional to π-polarization of C=N in structure 2 (Scheme 3).

TABLE III ^{13}C NMR Chemical Shifts (in ppm) of 3-(Substituted Phenyl)- 4-(*p*-tolyl)-1,2,4-thiadiazole-5(4H)-ones (Comp. **3**)

Comp. **3**	X	$^{13}C_{C=N}$	$^{13}C_{C=O}$
3a	*p*-Me	155.739	178.335
3b	*m*-Me	155.894	178.206
3c	H	155.651	178.173
3d	*p*-Cl	154.476	177.965
3e	*m*-Cl	154.142	177.795
3f	*m*-NO_2	153.019	177.573
3g	*p*-NO_2	153.329	177.489

TABLE IV Correlation of ^{13}C Chemical Shifts of C=N, C=O, and C=S of compounds (**1–3**) with Hammett σ Parameters

Comp.	Carbon	ρ^a	r^b	Intercept	Range of δ (ppm)	^cN
1	C=N	−2.113 ± 0.255	−0.972	156.967 ± 0.095	1.75	6
	C=O	−0.658 ± 0.022	−0.998	158.112 ± 0.008	0.62	6
2	C=N	−2.236 ± 0.186	−0.983	158.605 ± 0.074	1.48	7
	C=S	−0.409 ± 0.019	−0.994	187.438 ± 0.007	0.35	7
3	C=N	−3.080 ± 0.299	−0.977	155.421 ± 0.131	2.72	7
	C=O	−0.867 ± 0.030	−0.997	178.163 ± 0.013	0.85	7

[a] ρ = Slope.

[b] Correlation coefficient.

[c] Number of chemical shifts included in the analysis.

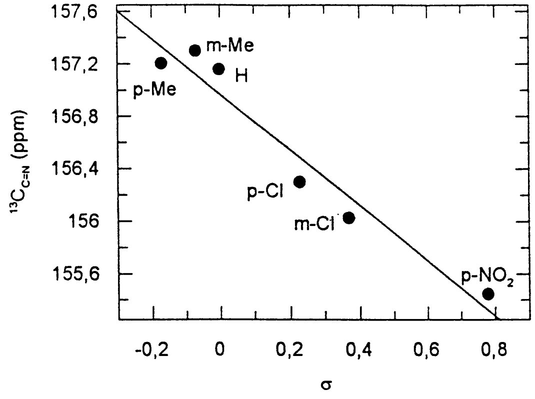


FIGURE 1 Plot of $^{13}C_{C=N}$ of comp. (**1**) against σ.

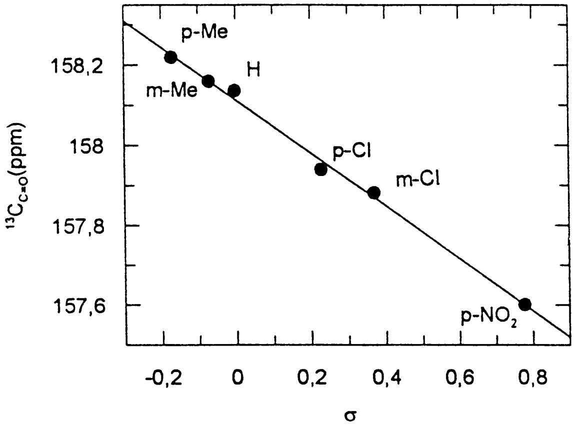


FIGURE 2 Plot of $^{13}C_{C=O}$ of comp. (**1**) against σ.

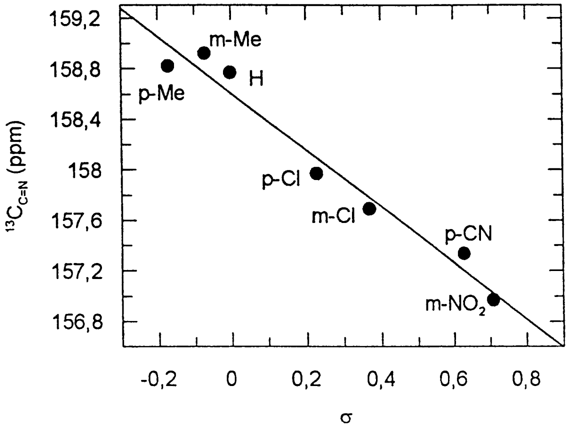


FIGURE 3 Plot of $^{13}C_{C=N}$ of comp. (**2**) against σ.

As expected according to its distance, the ^{13}C shifts of C=O and C=S carbons are less sensitive to the substituents. However, the simple Hammett equation holds very well with small slopes ($\rho = -0.65, -0.4$ and -0.7, Table IV, Figures 2, 4, and 6) for *meta* and *para* substituents. The obtained negative ρ values suggest the inverse substituent effects. This could be taken as an evidence for π-polarization of C=O and C=S carbons by the dipole of the substituent (localized π-polarization, Scheme 2) or by the field-transmitted resonance-polar effect (Scheme 2, structure 3).

As a conclusion, the evaluation of the substituent effects separately on different probe carbons as described above gives valuable

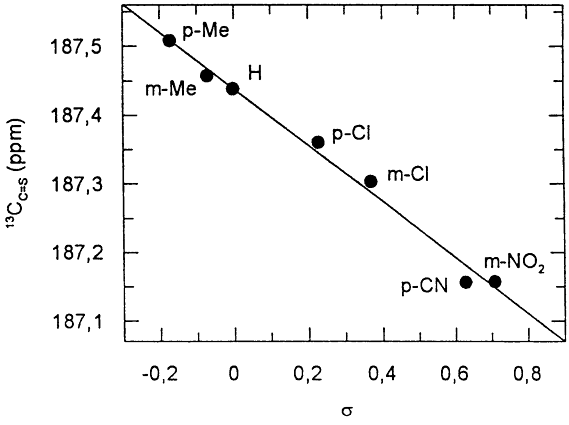


FIGURE 4 Plot of $^{13}C_{C=S}$ of comp. (**2**) against σ.

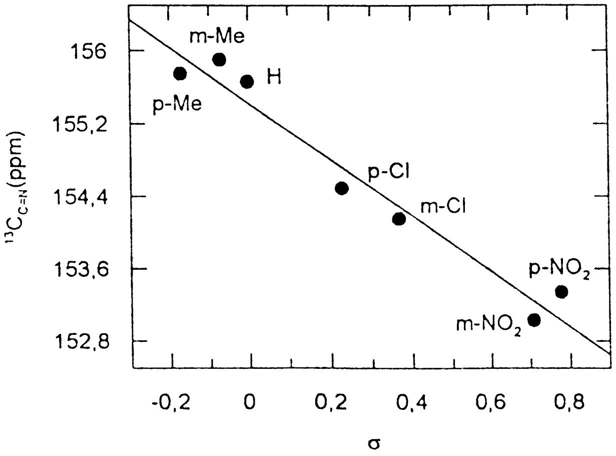


FIGURE 5 Plot of $^{13}C_{C=N}$ of comp. (**3**) against σ.

information on the transmission of the electronic effects along the heterocyclic ring. It is interesting to see that a distant substituted phenyl group may extend its polarizing effect by the π-polarization mechanism up to the carbonyl (or thiocarbonyl) π-unit over nitrogen and oxygen (or sulfur) atoms along the heterocyclic ring. This supports the concept of the through-space transmission of electronic substituent effects.

Dual parameter equations were not applied since the set of available data was estimated to be insufficient for such treatments.

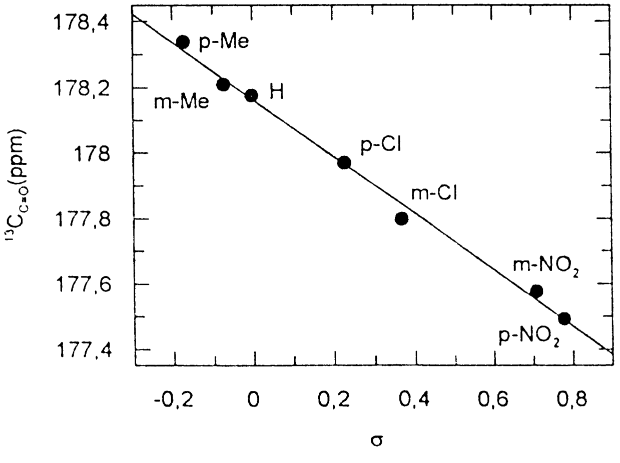


FIGURE 6 Plot of $^{13}C_{C=O}$ of comp. (**3**) against σ.

TABLE V The Physical and Analytical Data for Compounds (**1a–e**, **2b**, **2e**, **3b**, **3e**)

				Analysis (Calcd./Found)%		
Comp.	m.p. (°C)	Yield (%)	M. formula	C	H	N
1a	194–196	45	$C_{16}H_{14}N_2O_2$	72.17 72.69	5.29 5.76	10.51 10.28
1b	191–192	62	$C_{16}H_{14}N_2O_2$	72.17 72.39	5.29 5.36	10.51 10.85
1c	165–166	50	$C_{15}H_{12}N_2O_2$	71.42 71.49	4.79 4.91	11.10 11.11
1d	179–181	45	$C_{15}H_{11}N_2O_2Cl$	62.83 62.76	3.86 3.94	9.77 9.75
1e	183–185	64	$C_{15}H_{11}N_2O_2Cl$	62.83 62.60	3.86 4.03	9.77 9.55
2b	190–192	46	$C_{16}H_{14}N_2OS$	68.06 67.87	4.99 5.04	9.92 9.92
2e	161–162	50	$C_{15}H_{11}N_2OSCl$	59.50 59.51	3.66 3.77	9.25 9.24
3b	109–110	45	$C_{16}H_{14}N_2OS$	68.06 68.18	4.99 5.04	9.92 9.95
3e	121–123	48	$C_{15}H_{11}N_2OSCl$	59.50 59.58	3.66 3.76	9.25 9.22

TABLE VI The Spectral Data for Compounds (**1a–e**, **2b**, **2e**, **3b**, **3e**)

Comp.	IR(KBr)cm^{-1}	^{1}H-NMR(ppm $CDCl_3$)	MS[M$^+$]
1a	1600(C=N), 1768(C=O)	2.36 (s, 3H, CH_3); 2.39 (s, 3H, CH_3); 7.22–7.73 (m. 8H, aromatic)	266
1b	1558(C=N), 1782(C=O)	2.24 (s, 3H, CH_3); 2.32 (s, 3H, CH_3); 6.94–7.22 (m, 8H, aromatic)	266
1c	1515(C=N), 1770(C=O)	2.4 (s, 3H, CH_3); 7.07–7.53 (m, 9H, aromatic)	252
1d	1514(C=N), 1770(C=O)	2.28 (s, 3H, CH_3); 7.22–7.73 (m, 8H, aromatic)	
1e	1514(C=N), 1784(C=O)	2.47 (s, 3H, CH_3); 7.15–7.54 (m, 8H, aromatic)	286
2b	1307(C=S), 1514(C=N)	2.27 (s, 3H, CH_3); 2.39 (S, 3H, CH_3); 6.96–7.33 (m, 8H, aromatic)	282
2e	1340(C=S), 1479(C=N)	2.44 (s, 3H, CH_3); 7.13–7.48 (m, 8H, aromatic)	302
3b	1521(C=N), 1693(C=O)	2.27 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 6.94–7.26 (m, 8H, aromatic)	282
3e	1510(C=N), 1695(C=O)	2.38 (s, 3H, CH_3); 7.0–7.46 (m, 8H, aromatic)	302

EXPERIMENTAL

The preparation of compounds (**1f**, **3g**),[14] (**2a**, **2d**, **2f**, **2g**, **3a**, **3d**, **3f**),[15] (**2c**, **3c**)[16] has been reported previously. The compounds were recrystallized before use. The physical, analitical and spectral data for the new compounds (**1a–e**, **2b**, **2e**, **3b**, **3e**) are given in Tables V and VI. ^{13}C NMR spectra were recorded for 0.2 M solutions in $CDCl_3$ (used as a field-frequency lock signal) at ambient temperature on a JEOL GX-400 spectrometer operating at 100.54 MHz and Bruker Avance DRX 500 spectrometer operating at 125.77 MHz.

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