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NMR Spectral Assignment of Substituted Salicylaldoximes by Inverse Pulse Techniques with *z*-Gradient Selection: Correlation of NMR Parameters with Substituent Constants

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^{1}H and ^{13}C and also ^{1}H,^{13}C HMQC and ^{1}H,X HMBC (X = ^{13}C and ^{15}N) correlation maps with *z*-gradient selection of seven salicylaldoximes were recorded and assigned and their parameters are discussed. The chemical shifts of H2, NO*H*, C7 and especially those of ^{15}*N*OH correlate well with the Hammett and/or Brown–Okamoto substituent constants. Also the coupling constants ^1J(C3,H3) and ^1J(C7,H7) are linearly dependent on σ^+. High correlation coefficients show the presence of the 2-OH group to force the molecules of salicylaldoximes to be planar or almost planar as a result of the intramolecular hydrogen bonding between its hydrogen and oximine nitrogen atom. © 1997 John Wiley & Sons, Ltd.

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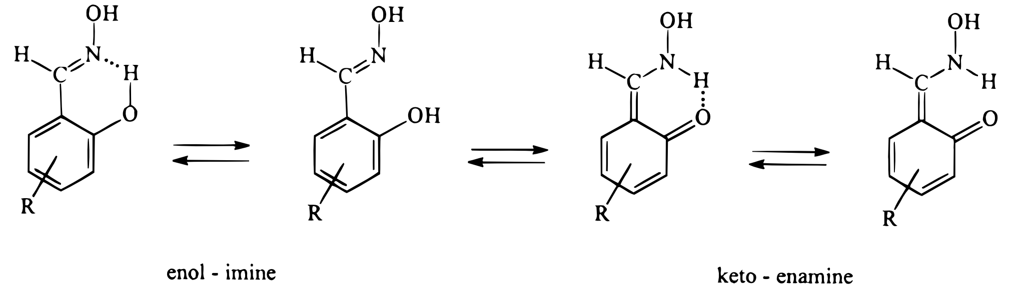
INTRODUCTION

Analysis of NMR data is an important tool in the investigation of substituent electronic effects. Aromatic compounds, including those showing tautomerism, are especially interesting from this point of view.[1–5]

It has been found that the chemical shift of the benzylidene carbon, δ_{C7}, in ring-substituted benzaldoximes correlates well with Hammett σ constants.[6] On the other hand, it is known[6–11] that the chemical shift of that atom in the NMR spectra of benzaldoximes depends mainly on the substituent inductive effect and its resonance effect is of reduced importance. Multiparameter correlations of δ_{C7} with the inductive and resonance substituent constants are of better quality.[9] It is known[12] that the ^{15}N chemical shifts of *para*-substituted benzaldoximes are linearly dependent on Hammett σ constants. Correlations between the ^{17}O NMR chemical shifts of the oximino oxygen and σ, σ^+ and σ_I substituent constants for substituted benzaldoximes are poor.[7] These results show that noncoplanarity of Ar—CH=NOH creates difficulties in transmission of the substituent effect, especially the resonance effect, to the CH=NOH group. It seemed of interest to investigate whether the intramolecular hydrogen bond improves correlations between the NMR spectral parameters and the substituent constants.

The proton transfer in compounds that reveals intramolecular hydrogen bonding makes them very interesting systems from the point of view of biochemically important processes.[13] It is well known[14] that reactions of pyridoxal Schiff bases, intermediates in transformations of amino acids, are governed by tautomeric changes. As found, there is no tautomeric keto-enamine form present in solution of salicylaldoxime (R = H) which was used as a model compound in studies on tautomerism of pyridoxal Schiff bases (Scheme 1).[14]



Scheme 1

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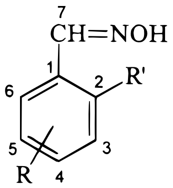

No	R'	R
1	OH	5-NO_2
2	OH	5-Cl
3	OH	5-Br
4	OH	5-OMe
5	OH	H
6	OH	4-OMe
7	OH	4-NMe_2
8	H	4-NMe_2

However, there is an equilibrium between the 'free' and 'hydrogen-bound' forms of salicylaldoxime in regular DMSO-d_6.[14]

This paper shows the effect of different substituents on ^1H, ^{13}C and ^{15}N NMR spectra of some salicylaldoximes (**1**–**8**).

EXPERIMENTAL

Compounds 1–8

Except for 4-dimethylaminosalicylaldehyde (obtained by the Vilsmeier–Haack method[15]), the aldehydes were commercially available (Aldrich). The parent salicylaldoxime (**5**) was prepared according to the literature[16] and purified by crystallization from a mixture of chloroform and *n*-hexane; m.p. 56–57 °C (lit.[16] m.p. 57 °C). Other salicylaldoximes were obtained by the following procedure. A saturated aqueous solution of hydroxylamine hydrochloride (6 g, 0.086 mol) and solid potassium carbonate (5 g) were successively added to a solution of the aldehyde (0.07 mol) in 96% ethanol (100 ml). The mixture obtained was refluxed for 2 h, cooled and diluted with water. The precipitated oximes were recrystallized from aqueous ethanol (charcoal) to constant melting points, as follows (°C): **1**, 224.5–225 (225[17]); **2**, 122–122.5 (128,[18] 122[19]); **3**, 128.5–129 (125–126,[20] 126[18]); **4**, 118.5–119 (118[21]); and **6**, 139–139.5 (138[22]). 4-Dimethylaminosalicylaldoxime (**7**), which is a new compound, has m.p. 141–142 °C. Analysis calculated for $C_9H_{12}N_2O_2$, C 59.99, H 6.71, N 15.54; found, C 59.78, H 6.81, N 15.39%.

NMR

The ^1H NMR (at 250.130 MHz) and proton composite pulse decoupled (WALTZ-16) ^{13}C NMR spectra (at 62.895 MHz) and also *z*-gradient selected $^1H,^{13}C$ HMQC[23,24] and ^1H,X HMBC[23,25] (X = ^{13}C and ^{15}N) 2D correlation maps of substituted salicylaldoximes in DMSO-d_6 (saturated solutions except for ^1H NMR) at 30 °C were recorded with a Bruker Avance DPX250 spectrometer equipped with a 5 mm broadband inverse probe head. The proton coupled ^{13}C NMR spectra (at 125.758 MHz) were recorded with the same spectrometer equipped with a 5 mm broadband direct probe head. The FIDs in ^1H and ^{13}C experiments were apodized by an exponential windowing prior to Fourier transformation (FT) in order to improve the signal-to-noise ratio in the NMR spectra.

In ^1H NMR experiments the conditions were 0.1 M DMSO-d_6 solution, spectral width 3250 Hz (13 ppm), number of data points 16K, acquisition time 2.5 s, pulse delay 1 s, flip angle 30° and number of scans four. The ^1H NMR chemical shifts are referenced to the signal of an internal TMS ($\delta = 0.0$ ppm).

In proton composite pulse decoupled (WALTZ-16) ^{13}C experiments the conditions were spectral width 14 000 Hz (220 ppm), number of data points 65K, acquisition time 2.3 s, pulse delay 1 s, flip angle 30° and number of scans 100. The ^{13}C NMR chemical shifts are referenced to the signal of an internal TMS ($\delta = 0.0$ ppm).

In proton coupled ^{13}C NMR experiments the conditions were spectral width 6300 Hz (50 ppm), number of data points 32K, acquisition time 2.5 s, pulse delay 2 s, flip angle 30° and number of scans 5000.

In 2D $^1H,^{13}C$ HMQC (inv4gs pulse sequence) and 2D $^1H,^{13}C$ HMBC (inv4gslplrnd pulse sequence) experiments with *z*-gradient selection the conditions were f_2-axis 2800 Hz per 1024 points $\times f_1$-axis 14 000 Hz per 1024 points. The delay for transmitting multiple bond correlations was set to 50 ms. The sine-bell window function was used prior to FT in both axes. The number of scans was eight and a composite pulse decoupling (GARP) was used to decouple protons during the pulse sequence. In the *z*-gradient program three sine gradients with relative ratios of 50 : 30 : 40 were used.

In 2D $^1H,^{15}N$ HMBC experiments with *z*-gradient selection (inv4gslplrnd pulse sequence) the spectral parameters were f_2-axis 2800 Hz per 1024 points $\times f_1$-axis 11 200 Hz per 1024 points. The delay transmitting multiple bond correlations (via geminal and vicinal couplings) was set to 100 ms. The sine-bell window function was used prior to FT in both axes. The number of scans was 128. In the *z*-gradient program three sine-bell gradients with relative ratios of 70 : 30 : 50 were used. The ^{15}N NMR chemical shifts are referenced to the signal of an external CH_3NO_2 ($\delta = 0.0$ ppm).

RESULTS AND DISCUSSION

Both $^1H,^{13}C$ HMQC and $^1H,^{15}N$ HMBC correlation maps of salicylaldoximes were found to be helpful in assignment of the signals. Illustrative examples of such maps are shown in Figs 1 and 2. A single correlation peak in the HMBC spectrum at -17.5 ppm (see Fig. 1) is transmitted via ^2J(N,H) coupling between H7 and oximine nitrogen and the NO_2 group at -10.0 ppm shows two correlation peaks with both adjacent protons transmitted via ^3J(H,N) couplings.

The chemical shifts of the protons in the ^1H NMR spectra of salicylaldoximes are given in Table 1. The δ_{NOH} values vary from 11.61 to 10.82 ppm ($\Delta\delta = 0.79$ ppm). However, for R = H the NO*H* and H2 have one wide common signal at 10.9 ppm, so the exact values of δ_{NOH} and δ_{H2} are not known. The chemical shifts of H2 in the spectra of the other compounds vary from 11.46 to 9.66 ppm ($\Delta\delta = 1.80$ ppm). It is slightly concentration dependent, which shows that the H-bond between the hydroxyl proton and oximine nitrogen atom is not very strong. The signals of H7 do not vary much: $\Delta\delta = 8.32 - 8.18$ ppm $= 0.14$ ppm. Comparison of the spectra of **7** and **8** shows that the 2-OH group shifts the signal of H7 downfield. A change of solvent has little effect on the spectra of **7** and **8**; it affects mostly the position of the signal of NO*H*. Dilution shifts slightly downfield the signals of H2, H7 and NO*H* in the spectra of the salicyladoximes.

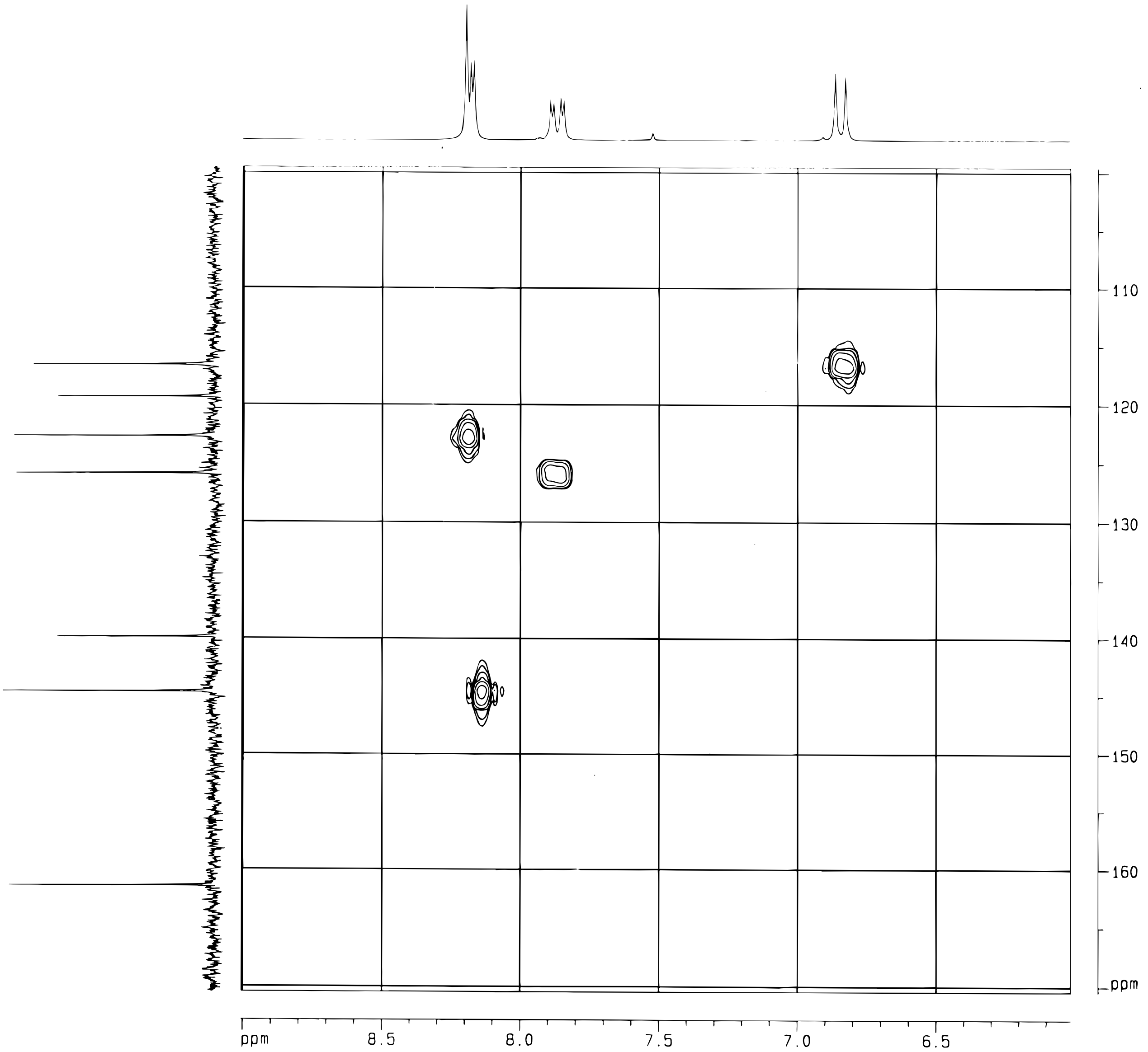

Figure 1. ^{1}H,^{13}C HMQC correlation map with *z*-gradient selection of 5-nitrososalicylaldoxime (**1**) in DMSO-d_6 at 30 °C.

The chemical shifts of the carbon atoms in the ^{13}C NMR spectra of the salicylaldoximes are given in Table 2. The signal of C7 shifts downfield when the substituent becomes a stronger electron donor ($\Delta\delta = 149.58 - 144.64$ ppm $= 4.94$ ppm). Comparison of the spectra of **7** and **8** shows that the 2-OH group shifts the signal of C7 upfield. Since the most important interactions between the solvent and **7** probably involve

Table 1. ^{1}H NMR chemical shifts (ppm from internal TMS) of oximes 1–8 measured for 0.1 M solutions in DMSO-d_6

Compound	H2	H3	H4	H5	H6	H7	NO*H*	Other H
1	11.46	7.02	8.06	—	8.37	8.32	11.61	—
2	10.29	6.92	7.17	—	7.45	8.31	11.46	—
3	10.30	6.83	7.30	—	7.60	8.29	11.45	—
4	9.66	6.82	6.82	—	7.04	8.33	11.33	3.67
5	—[a]	6.89	7.21	6.85	7.46	8.37	—[a]	—
6	10.33	6.47	—	6.44	7.31	8.27	11.11	3.39
7	10.08	6.16	—	6.25	7.18	8.18	10.82	2.89
	9.99[b]	6.18[b]	—	6.31[b]	7.09[b]	8.16[b]	10.01[b]	2.97[b]
8	7.40	6.71	—	6.71	7.40	7.97	10.64	2.92
	7.44[b]	6.71[b]	—	6.71[b]	7.44[b]	7.99[b]	9.71[b]	2.96[b]

[a] Overlapping signals at 10.9 ppm were found for H2 and NO*H*.
[b] In acetone-d_6.

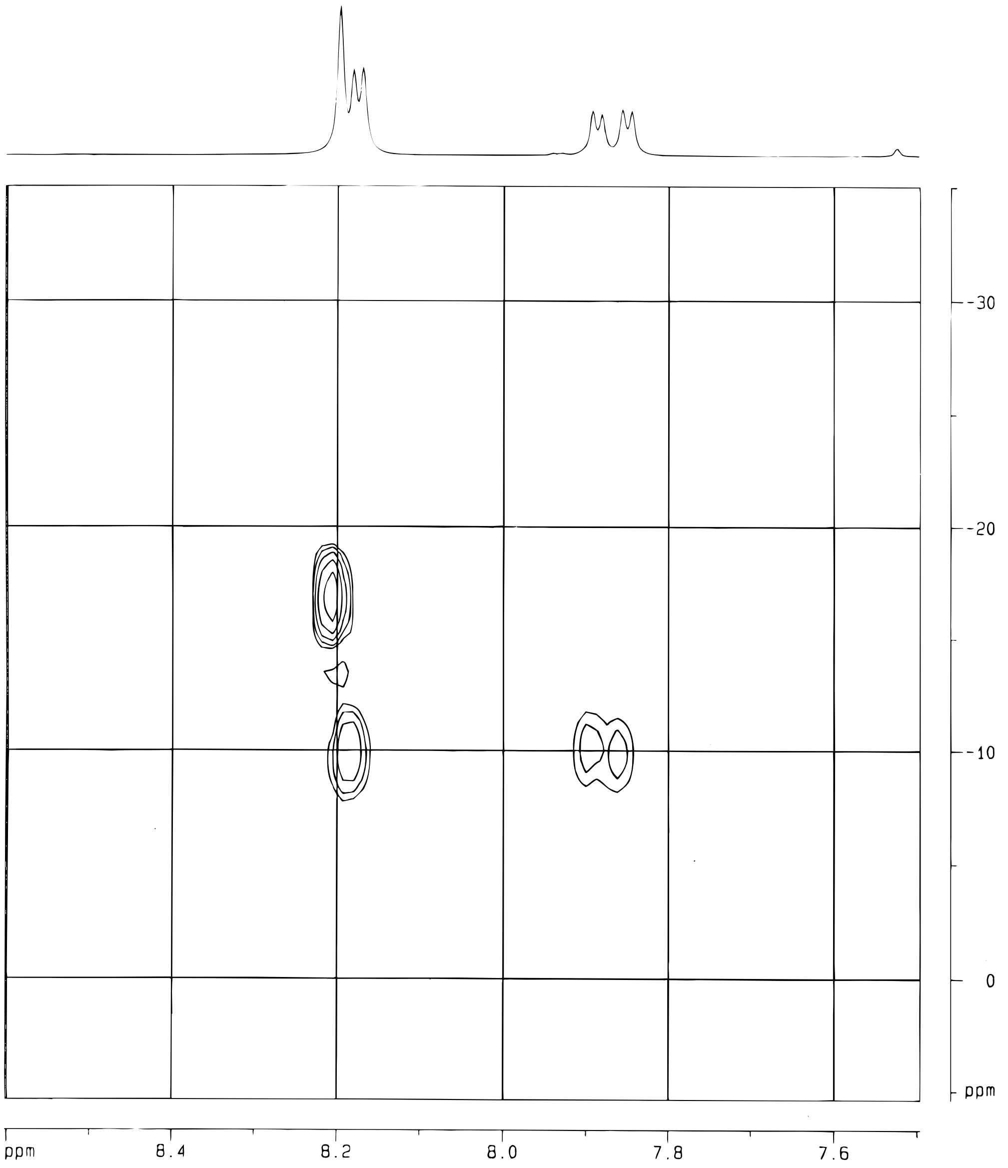

Figure 2. $^1H,^{15}N$ HMBC correlation map with *z*-gradient selection of 5-nitrosalicylaldoxime (**1**) in DMSO-d_6 at 30 °C.

the 2-OH group, the solvent chemical shifts in the spectra of **7** and **8** are not parallel.

The values of the one-bond carbon–hydrogen spin–spin coupling constants in the NMR spectra of the salicylaldoximes are also given in Table 2. $\Delta^1J(Cn,Hn)$ values are 8.6, 9.8 and 6.5 Hz for $n = 3$, 6 and 7, respectively.

The chemical shifts of the nitrogen atoms in the $^1H,^{15}N$ HMBC correlation maps of salicylaldoximes are given in Table 3. The range of ^{15}NOH chemical shifts, i.e. 24.7 ppm, is comparable to that of *para*-substituted benzaldoximes.[12] Electron-donor substituents shift the signal of oximine nitrogen upfield. Comparison of the spectra of **7** and **8** shows that the 2-OH group shifts the signal of ^{15}NOH upfield. This is believed to be a result of superposition of the inductive/resonance effect of 2-OH and of the intramolecular hydrogen bonding, N···H—OC2.

The spectra of the salicylaldoximes were expected to be helpful in the evaluation of the substituent effect in these compounds, hence the quality of the linear relationships between their spectral parameters and the substituent constants was evaluated. (Table 4). It should be noted that position 5 was treated as *para* when the chemical shifts of H2 were considered; it was *meta* in correlations with chemical shifts of NO*H*, C7, *N*OH and coupling constants $^1J(C7,H7)$; the σ_m and σ_p constants for compounds substituted in positions 5 and 4, respectively, were used to correlate the $^1J(C3,H3)$ values.

As can be seen, there is a tendency for δ_{H2} to change linearly with σ. Since in the spectrum of **5** one wide signal at 10.9 ppm was found for both H2 and NO*H*, and the δ_{H2} value is uncertain, the quality of correlation was improved when the point $R = H$ was excluded. Correlations of δ_{NOH} *vs.* σ, and especially with σ^+, are much better.

No correlations were found between chemical shifts of the ring carbons and σ but there is a tendency for δ_{C7} to change linearly with σ. It was found earlier[6] that the chemical shift of C7 for both *E* and *Z* ring-substituted benzaldoximes correlates well with the σ constants.

Table 2. ^{13}C NMR chemical shifts and one-bond carbon–hydrogen spin–spin coupling constants of oximes 1–8 measured for saturated solutions in DMSO-d_6

	δ(ppm from internal TMS)								^1J(C,H) (Hz)					
Compound	C1	C2	C3	C4	C5	C6	C7	Other C	C3	C4	C5	C6	C7	Other C
1	119.36	161.44	116.63	125.89	139.91	122.72	144.64	—	165.2	174.3	—	167.2	170.1	—
2	120.11	154.95	117.90	129.98	123.24	126.96	146.60	—	162.3	165.8	—	164.7	168.1	—
3	120.64	155.35	118.36	132.80	110.65	129.87	146.49	—	162.0	166.2	—	166.2	168.1	—
4	118.52	150.37	117.11	117.11	152.40	112.06	148.11	55.46	161.1	161.1	—	159.4	166.5	143.7
5	118.24	156.29	116.18	130.57	119.48	128.46	148.42	—	159.4	159.5	162.0	159.4	166.2	—
6	111.26	158.11	101.33	161.50	106.22	130.10	149.10	55.21	159.4	—	162.7	159.6	165.4	144.5
7	106.41	157.73	98.46	152.08	104.19	129.89	149.58	39.84	156.6	—	160.3	157.4	163.6	135.9
	107.18[a]	159.85[a]	99.59[a]	153.56[a]	105.01[a]	132.18[a]	152.67[a]	40.17[a]	—	—	—	—	—	—
	(−0.77)[b]	(−2.12)[b]	(−1.13)[b]	(−1.48)[b]	(−0.82)[b]	(−2.29)[b]	(−3.09)[b]	(−0.33)[b]	—	—	—	—	—	—
8	120.54	127.43	111.86	150.89	111.86	127.43	148.07	39.77	—	—	—	—	—	—
	122.05[a]	128.73[a]	112.51[a]	152.06[a]	112.51[a]	128.73[a]	149.62[a]	40.27[a]	—	—	—	—	—	—
	(−1.51)[b]	(−1.30)[b]	(−0.65)[b]	(−1.17)[b]	(−0.65)[b]	(−1.30)[b]	(−1.55)[b]	(−0.50)[b]	—	—	—	—	—	—

[a] In acetone-d_6.

[b] Solvent chemical shift, Δδ (ppm).

Table 3. ^{15}N NMR chemical shifts (ppm from external CH_3NO_2 ($\delta = 0.0$ ppm)) of oximes 1–7 measured for solutions in DMSO-d_6 based on z-gradient selected ^{1}H,^{15}N HMBC experiments

Compound	*N*OH	Other N
1	−17.5	−10.0
2	−19.6	—
3	−25.3	—
4	−22.6	—
5	−21.8	—
6	−34.9	—
7	−42.2	−327.0
8	−21.5	−329.1

There is a correlation between the shift of C7 and σ_I values for some *para*-substituted benzaldoximes.[10] It is known[6–11] that the chemical shift of C7 in the spectra of *para*-substituted benzaldoximes depends mainly on the substituent inductive effect and its resonance effect is of reduced importance. Multiparameter correlations of δ_{C7} with the inductive and resonance substituent constants[28] and a semi-empirical parameter that expresses the paramagnetic interaction between the substituent and a carbon atom[29] are of better quality.[9]

Although there are poor or very poor correlations between the ^{17}O NMR chemical shifts of the oximino oxygen and σ, σ^+ and σ_I substituent constants for substituted benzaldoximes,[7] a good linear dependence was found between the ^{15}N chemical shifts of the nitrogen in the CH═NOH group in the spectra of salicylaldoximes and $\sigma^{(+)}$ constants. It is interesting that the slope of this relationship is comparable to that for *para*-substituted benzaldoximes.[12] The correlation shows that the δ_{NOH} values are a good measure of the substituent effect in salicylaldoximes.

Although no correlations were found between the proton–proton spin–spin coupling constants, some carbon–hydrogen coupling constants, ^1J(C3,H3) and ^1J(C7,H7), are linearly dependent on $\sigma^{(+)}$ (see Table 4).

CONCLUSIONS

The ^{13}C NMR spectra of salicylaldoximes discussed in this paper do not support the contention that there is a

Table 4. Correlations between the NMR spectral data of oximes 1–7 and the substituent constants[a]

Type of correlation	n[b]	Intercept	Slope	r[c]	Standard deviation	Standard error
δ_{H2} *vs.* σ	7	10.24	1.37	0.6545	0.591	0.223
δ_{H2} *vs.* σ	6[d]	10.09	1.55	0.9395	0.598	0.244
δ_{H2} *vs.* σ^+	6	10.44	1.08	0.7518	0.623	0.254
δ_{H2} *vs.* σ^+	5[d]	10.34	1.11	0.8998	0.651	0.291
$\delta_{\mathrm{NO}H}$ *vs.* σ	7	11.19	0.60	0.8532	0.298	0.111
$\delta_{\mathrm{NO}H}$ *vs.* σ	6[d]	11.23	0.58	0.9838	0.287	0.117
$\delta_{\mathrm{NO}H}$ *vs.* σ^+	7	11.29	0.30	0.7304	0.293	0.111
$\delta_{\mathrm{NO}H}$ *vs.* σ^+	6[d]	11.35	0.31	0.9884	0.287	0.117
δ_{C7} *vs.* σ	7	147.90	−3.71	0.9190	1.736	0.656
δ_{C7} *vs.* σ^+	7	147.32	−1.78	0.7266	1.736	0.656
δ_{C7} *vs.* σ^+	6[e]	147.68	−1.37	0.7806	1.274	0.520
$\delta_{N\mathrm{OH}}$ *vs.* σ	7	−27.93	18.16	0.9058	8.981	3.394
$\delta_{N\mathrm{OH}}$ *vs.* σ	6[d]	−29.01	18.70	0.9526	9.599	3.918
$\delta_{N\mathrm{OH}}$ *vs.* σ^+	7	−24.87	10.35	0.9581	8.982	3.395
$\delta_{N\mathrm{OH}}$ *vs.* σ^+	6[f]	−23.91	11.13	0.9876	9.828	4.012
^1J(C3,H3) *vs.* σ	7	160.3	5.94	0.9510	2.729	1.031
^1J(C3,H3) *vs.* σ	6[d]	160.3	5.94	0.9510	2.729	1.031
^1J(C3,H3) *vs.* σ^+	7	161.3	2.97	0.8217	2.729	1.031
^1J(C3,H3) *vs.* σ^+	6[d]	161.6	3.05	0.9074	2.905	1.186
^1J(C3,H3) *vs.* σ^+	5[g]	161.1	2.57	0.9919	2.347	1.049
^1J(C7,H7) *vs.* σ	7	166.4	4.69	0.9839	2.117	0.800
^1J(C7,H7) *vs.* σ^+	7	167.2	2.37	0.8668	2.117	0.800
^1J(C7,H7) *vs.* σ^+	6[d]	167.3	2.41	0.9068	2.298	0.938
^1J(C7,H7) *vs.* σ^+	5[g]	167.0	2.06	0.9647	1.911	0.855

[a] Substituent constants used in correlations (R/σ^{26}/$\sigma^{+\ 27}$): p-NO_2/0.81/0.79, m-NO_2/0.71/0.67, m-Cl/0.37/0.40, m-Br/0.37/0.41, p-Br/0.26/0.15, p-Cl/0.24/0.11, m-OMe/0.10/0.05, H/0.00/0.00, m-NMe_2/−0.10/–, p-OMe/−0.28/−0.78, p-NMe_2/−0.63/−1.70.

[b] Number of correlation points.

[c] Correlation coefficient.

[d] H excluded.

[e] 5-NO_2 excluded.

[f] 5-Br excluded.

[g] H and 5-NO_2 excluded.

mixture of the 'free' and 'hydrogen-bound' forms of salicylaldoximes in DMSO-d_6.[14] All correlations between the substituent constants and the spectral parameters refering to the CH=NOH group, especially δ_{NOH} *vs.* $\sigma^{(+)}$, δ_{NOH} *vs.* σ^+ and ^1J(C7,H7) *vs.* σ, that reveal very high correlation coefficients, show the presence of the 2-OH group to force the molecules of salicylaldoximes to be planar or almost planar, which may be explained by the formation of the intramolecular hydrogen bond between its hydrogen and the oximine nitrogen atom.

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