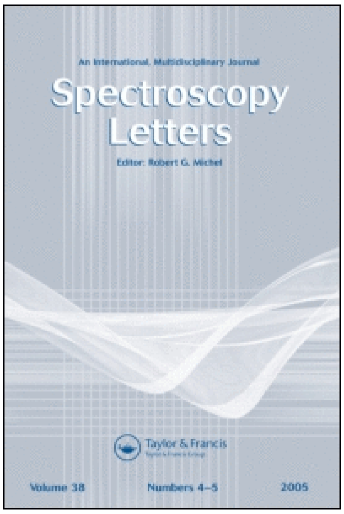

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^{13}C NMR Chemical Shifts of Heterocycles: Empirical Substituent Effects in 5-Halomethylisoxazoles

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^{13}C NMR CHEMICAL SHIFTS OF HETEROCYCLES:

Empirical Substituent Effects in 5-Halomethylisoxazoles

Key Words: ^{13}C NMR of Isoxazoles
Substituent Effects
^{13}C NMR of heterocycles

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ABSTRACT

Evaluation by empirically derived equations for the substituent effect (α, β, γ, δ) on the ^{13}C NMR chemical shifts for C-3, C-4, C-5 and halomethyl-substituent carbon (C-6) in isoxazoles **1-5** [where C-3 substituent (R^1) = H, alkyl or phenyl, C-4 substituent (R^2) = H, alkyl, and C-5 substituent (R^3) = di- or trihalomethyl, methyl and H], taking as reference the compound **1a**, is reported. From the calculated values for the α, β, γ, δ effects for each substituent it was possible to estimate the chemical shift of each carbon of the compounds **1-5**. The ^{13}C

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chemical shifts of the C-3, C-4, C-5, C-6 of these compounds, can be estimated with good precision: 94% of the calculated chemical shifts are found to be within ±1.0ppm, and 100% are found to be within ±1.5ppm.

INTRODUCTION

The ^{13}C NMR chemical shifts substituent effects on sp^2 carbon atoms in aromatic heterocycles have been widely interpreted in terms of inductive, mesomeric, or other mechanism and correlated with calculated charge densities or physico-chemical parameter such as Hammett constants[1]. However, empirical additive substituent increments obtained by analysis of substituted compounds have proven to be the most important and useful tool to predict these ^{13}C chemical shifts[1,2].

Although there has been a few published works on ^{13}C NMR chemical shifts of isoxazoles[3-6], there is a lack of ^{13}C NMR data for the 5-halomethylisoxazoles in the literature. The synthesis of 5-trichloromethylisoxazole (**1a**) has been formerly described by Spiegler and Götz[7], and recently our laboratory reported the ^{13}C NMR data of a series of 5-trichloromethyl-substituted isoxazoles[8].

The aim of this work is the evaluation of the ^{13}C chemical shifts of 5-halomethylisoxazoles **1-3** and isoxazoles **4,5** (Scheme), in relation to a reference compound. The empirical substituent increments can be used to create a system of equations that then may allow to calculate the chemical shifts of the cyclic carbons (3,4,5) and substituent carbon (6) of similar compounds.

RESULTS AND DISCUSSION

The ^{13}C chemical shift assignments of compounds **1-5** were done by simple comparison among the synthesized compounds and, when necessary, by interpretation of ^{13}C coupled spectra and 2D-NMR techniques such as Heteronuclear Correlated Spectroscopy (COSY CH)[9]. The ^{13}C chemical shifts data of compounds **4b,e-g,5a** were taking from literature[3,4].

From the ^{13}C NMR experimental data of compounds **1-5** (Table 1) the substituent increments were determined, taking compound **1a** as a reference (Scheme).

Compound **1a** was choosen for the following reasons: (1) specific interest on the systematization of the ^{13}C NMR data of 5-halomethyl- substituted isoxazoles; (2) availability of the most complete set of ^{13}C NMR data of compounds **1** (R $= CCl_3$) in our laboratory, thus allowing to calculate the empirical increments of all considered substituents.

The empirical substituent increments were indicated by Greek letters according to the position occupied by this substituent relative to a given carbon (Scheme). The determination of these increments is done by the Eqs. 1-4.

$$\alpha_n = [\delta_{C\text{-}n}(\alpha_R^{C\text{-}n}) - \delta_{C\text{-}n}(\mathrm{REF})] \text{ ppm} \qquad (1)$$

$$\beta_{mn} = [\delta_{C\text{-}n}(\beta_R^{C\text{-}m}) - \delta_{C\text{-}n}(\mathrm{REF})] \text{ ppm} \qquad (2)$$

$$\gamma_{mn} = [\delta_{C\text{-}n}(\gamma_R^{C\text{-}m}) - \delta_{C\text{-}n}(\mathrm{REF})] \text{ ppm} \qquad (3)$$

$$\delta_{mn} = [\delta_{C\text{-}n}(\delta_R^{C\text{-}m}) - \delta_{C\text{-}n}(\mathrm{REF})] \text{ ppm} \qquad (4)$$

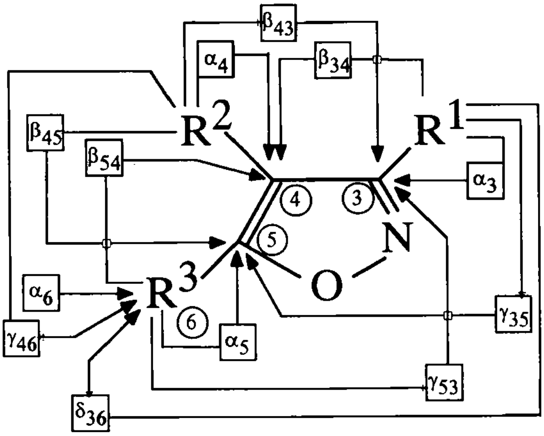
TABLE 1.

Experimental ^{13}C chemical shifts of the carbons 3, 4, 5 and 6 of isoxazoles **1**-**5**.

Compound	δ_{C-3}	δ_{C-4}	δ_{C-5}	δ_{C-6}
1a	150.3	103.0	168.5	84.6
1b	160.0	104.3	168.5	84.8
1c	154.0	112.5	162.0	86.1
1d	162.2	112.7	160.4	86.4
1e	163.5	103.2	169.6	85.3
2d	161.3	116.3	151.7	118.8
3a	150.2	102.9	166.7	59.6
3b	159.8	104.1	167.0	59.6
3d	161.5	113.3	159.5	59.9
4a	149.4	99.8	167.7	10.4
4b[a]	159.9	102.3	169.0	11.3
4e[a]	160.3	100.1	169.6	11.5
4f[a]	159.9	109.0	164.2	10.0
4g[a]	158.6	116.7	165.1	10.7
5a[a]	149.1	103.7	157.9	-
5b	157.4	104.1	157.4	-

[a] Data from Refs. 3,4.

In Eq. 1, α_n is the effect of the *alpha* substituent on to carbon *n*, i.e., the effect of R^1, R^2, R^3 and halogen (or hydrogen) on to C-3, C-4, C-5, and C-6, respectively. $\delta_{C\text{-}n}(\alpha_R C\text{-}n)$ is the chemical shift of the *alpha* substituted carbon *n*, and $\delta_{C\text{-}n}(\text{REF})$ is the chemical shift of the carbon *n* of the reference compound (**1a**). In Eqs. 2-4, β_{mn}, γ_{mn}, and



Compound	R^2	R^1	Compound	R^3
a	H	H	**1**	CCl_3
b	H	Me	**2**	CF_3
c	Me	H	**3**	$CHCl_2$
d	$-(CH_2)_4-$		**4**	CH_3
e	H	Ph	**5**	H
f	Me	Me		
g	Ph	Me		

Scheme.

δ_{mn} are the effects of the substituents bound to a carbon *m*, in position *beta*, *gamma* and *delta*, respectively, relative to the carbon *n*; *n* and *m* are full numbers that in the case of the compounds studied in this work, could vary from 3 to 6. $\delta_{C\text{-}n}$ (β, γ, or $\delta_R C\text{-}m$) is the chemical shift of the carbon *n* that has a substituent on carbon *m*, which could be in *beta*, *gamma*, or *delta* position relative to the carbon *n* (Scheme).

The substituent parameters on C-3 and C-4 are determined from the compounds **1b-e** (R^3 = CCl_3) and the substituent parameters on C-5 and C-6 are determined from the compounds **2-5a**.

The parameters determined from Eqs. 1-4, for the compounds **1-5**, are reported in Table 2. Thus, for the ^{13}C chemical shift determinations of C-3, C-4, C-5, and C-6 of the isoxazoles **1-5**, a system of Eqs. 5-8 that uses the data determined from the Eqs. 1-4, was elaborated.

$$\delta_{C\text{-}3} = 148.4 + \alpha_3 + \beta_{43} + \gamma_{53} \qquad (5)$$

$$\delta_{C\text{-}4} = 45.0 + \alpha_4 + \beta_{34} + \beta_{54} \qquad (6)$$

$$\delta_{C\text{-}5} = 109.3 + \alpha_5 + \beta_{45} + \gamma_{35} \qquad (7)$$

$$\delta_{C\text{-}6} = 101.7 + \alpha_6 + \gamma_{46} + \delta_{36} \qquad (8)$$

Eqs. 5-8 allow to estimate with high precision the ^{13}C chemical shifts of carbons 3, 4, 5, and 6 for these compounds. We believe this system will also allow to calculate these data in equal accuracy for similar compounds not yet synthesized or evaluated. For example, Table 3 shows the calculated ^{13}C chemical shifts of some non-synthesized compounds **1-5**. From the data of Table 1, linear correlationship analysis between the experimental and calculated ^{13}C chemical shifts (Eqs. 5-8) of compounds **1-5** were done. For a quantitative observation of the *linear analysis* carried out, Table 4 presents the angular, linear, and correlation coefficients for each carbon of all studied compounds, and for a qualitative observation, Figure shows an excellent global relationship (r=0.999) between the

TABLE 2.

Empirical parameters[a] for Eqs. 5-8.

Substituent R^1	α_3(C-3)	β_{34}(C-4)	γ_{35}(C-5)	δ_{36}(C-6)
H	0	0	0	0
CH_3	9.7	1.3	0	0.2
$-(CH_2)_4-$	8.2	1.3	0	0.2
Ph	13.2	0.2	1.1	0.7
$CH_3(CH_3)$[b]	6.8	1.3	0	0.2
$CH_3(Ph)$[c]	5.5	1.3	0	0.2

Substituent R^2	β_{43}(C-3)	α_4(C-4)	β_{45}(C-5)	γ_{46}(C-6)
H	0	0	0	0
CH_3	3.7	9.5	-6.5	1.5
$-(CH_2)_4-$	3.7	8.4	-8.1	1.6
$CH_3(CH_3)$[b]	3.7	7.9	-3.5	-0.6
$Ph(CH_3)$[c]	3.7	15.6	-2.6	0.1

Substituent R^3	γ_{53}(C-3)	β_{54}(C-4)	α_5(C-5)	α_6(C-6)
CCl_3	0	0	0	0
CF_3	-0.9	3.6	-8.7	32.4
$CHCl_2$	-0.1	-0.1	-1.8	-25.0
CH_3	-0.9	-3.2	-0.8	-74.2
H	-1.2	0.7	-10.6	-

[a] In ppm.

[b] For compounds 3,4-disubstituted, where R^1, R^2 = Me.

[c] For compounds 3,4-disubstituted, where R^1= Me and R^2= Ph.

TABLE 3.

Calculated ^{13}C chemical shifts (Eqs. 5-8) of the carbons 3, 4, 5 and 6 of some non-synthesized isoxazoles **1-5**.

Compound	δ_{C-3}	δ_{C-4}	δ_{C-5}	δ_{C-6}
1f	160.8	112.2	165.0	84.2
1g	159.5	119.9	165.9	84.9
2a	149.4	106.6	159.8	117.0
2b	159.1	107.9	159.8	117.2
2c	153.5	116.1	153.3	118.5
2e	162.6	106.8	160.9	117.7
2f	159.9	115.8	156.3	116.6
2g	158.6	123.5	157.2	117.3
3c	153.9	112.4	160.2	61.1
3e	163.4	103.1	167.8	60.3
3f	160.7	112.1	163.2	59.2
3g	159.4	119.8	164.1	59.9
4c	153.5	109.3	161.2	11.9
4d	161.3	109.5	159.6	12.2
5c	152.8	113.2	151.4	-
5d	161.0	113.4	149.8	-
5e	162.3	103.9	159.0	-
5f	159.6	112.9	154.4	-
5g	158.3	120.6	155.3	-

TABLE 4.

Linear relationship coefficients obtained from the correlations between the experimental and calculated data[a] (Eqs. 5-8) of each carbon of compounds **1-5**.

C-n	*a*	*b*	*r*	δ (range)[b]
C-3	1.0045	-0.6030	0.9962	14.4
C-4	0.9975	0.2056	0.9973	16.9
C-5	0.9744	4.0307	0.9967	17.9
C-6	1.0030	-0.1248	0.9999	108.8
C-3,4,5,6	0.9997	0.0099	0.9999	159.6

[a] General equation: $\delta_{C\text{-}n(calc.)} = a \times \delta_{C\text{-}n(exp.)} + b$
a= angular coefficient, *b* = linear coefficient
r = correlation coefficient

[b] In ppm. Difference between the largest and smallest chemical shift of the considered series.

experimental and calculated (Eqs. 5-8) ^{13}C NMR chemical shifts of compounds **1-5**.

In general, the correlation coefficients (*r*) between the experimental and calculated chemical shifts of C-3, C-4, C-5, and C-6 exhibit excellent correlations (*r* = 0.990-0.999), for the series of compounds **1-5**. However, for a more rigorous analysis of the confidence of the chemical shifts data obtained from the Eqs. 5-8, it is necessary to consider some important factors that are described below.

First, the larger possible number of calculated chemical shifts that fit into the ranges of pre-established small absolute errors. For example, in Table 5 are reported the calculated percentages of chemical shifts for the compounds **1-5**, in relation to a given range of

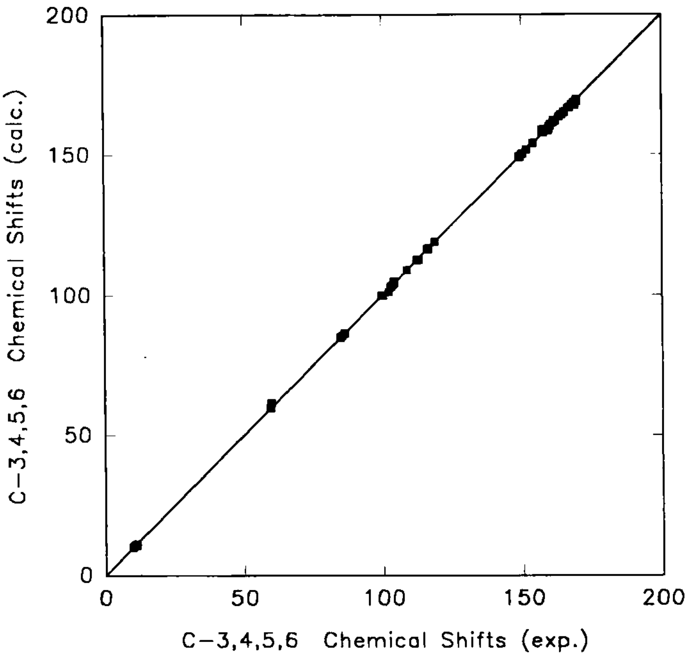


Figure. Correlation between the experimental and calculated (Eqs. 5-8) ^{13}C NMR chemical shifts for C-1, C-2, C-3, C-4 of 5-Halomethylisoxazoles **1-5**.
($\delta_{calc.} = 0.9997 \times \delta_{exp.} + 0.0099$, $r=0.9999$).

TABLE 5

Percentage of chemical shifts[a] within the absolute error range for the compounds **1-5**.

Error Range (ppm)	±0.5	±1.0	±1.5
δ (%)	82	94	100

[a] 62 ^{13}C chemical shift values are considered.

absolute error. One can observe that all calculated chemical shifts are within a maximum absolute error range of ±1.5ppm and that 94% of the calculated values deviate less than ±1.0ppm from the measured ones.

To give a more adequate representation of a given absolute error of the carbon chemical shift one may consider the range of chemical shifts of the respective carbons (Table 4). For example, an absolute error of ±1.0ppm means a relative error within the range of shifts of 7% (C-3), 6% (C-4), 6% (C-5), 1% (C-6). These relative errors are smaller for C-6 because the chemical shift range of this carbon is larger than of the other carbons. Accordingly, C-3, C-4, and C-5 have a larger relative error because these carbons have a narrower chemical shift range. Thus, considering the correlation coefficients (***r***, Table 4), the chemical shift percentages within the absolute error range (Table 5), and the relative error range, one can affirm that the ^{13}C chemical shifts estimated by the Eqs. 5-8, have a good accuracy.

CONCLUSION

The model used in this work for the evaluation of the substituent empirical increments (Eqs. 1-4) is very simple and easy to use. The estimation of the ^{13}C NMR chemical shifts of C-3, C-4, C-5, C-6 of compounds **1-5**, from Eqs. 5-8 is simple and accurate. The estimated chemical shifts for the compounds **1-5**, from the Eqs. 5-8, have shown high accuracys, for example, 94% of the chemical shifts are within the absolute error range of ±1.0ppm, and 100% within a range of ±1.5ppm. On the determination of the accuracy of the estimated chemical shifts from Eqs. 5-8, the relative error must be considered, which connects the absolute error with the chemical shifts range of the studied carbon. The model used for the determination of the substituent empirical increments did not account for the limitations resulting of the interaction of neighboring substituent groups.

EXPERIMENTAL

Compounds

The 5-halomethylisoxazoles **1-3**, were synthesized according to the published techniques developed in our laboratory[8,10]. The ^{13}C chemical shifts data of compounds **4b,e-g,5a** were taking from literature[3,4].

^{13}C NMR Spectra

The ^{13}C NMR spectra were recorded on a Bruker AC-80 spectrometer at 20.15 MHz. The experimental conditions on the Bruker AC-80 were: ^{2}D internal lock; pulse width of 30^{o} ($1.6\mu s$); acquisition time 1.64s; spectral width 5000 Hz; relaxation delay 2s; *number* of scans among 3000 and 5000, depending of the type of compound; 16.384 data points giving a digital resolution of 0.61 Hz/point; probe temperature of 35°C.

$CDCl_3$ solutions with an approximate concentration of 0.5 M and 0.1% of TMS as internal reference was used in 5mm tubes.

Calculations

All calculations were done on a MICROTEC-DX 386 personal computer. The determinations of the calculated chemical shifts were done by the Delta-13C-BII program.

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