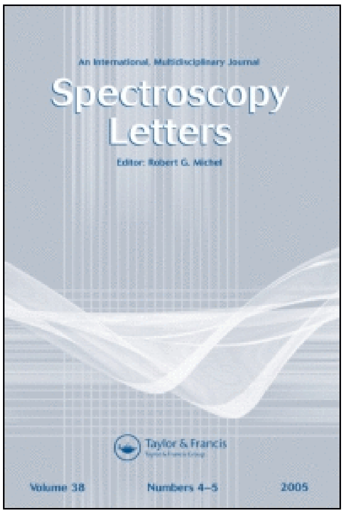

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^{13}C NMR CHEMICAL SHIFTS OF β-ALKOXYVINYL KETONES: III[✠]- Empirical Substituent Effects in 1-Alkylamino-6-ethoxy-1,5-hexadien-3,4-diones and 1,6-Bis(Alkylamino)-1,5-hexadien-3,4-diones

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Key Words: ^{13}C NMR of β-alkoxyvinyl ketones
Substituent effects
^{13}C NMR of disubstituted alkenes

ABSTRACT

Evaluation by empirically derived equations for the substituent effect (E_{X_n} and E_{Y_n}, n=1 to 6) on the ^{13}C NMR chemical shifts for C-1, C-2, C-

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[✠] For Part II, see Ref. 10.

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3, C-4, C-5 and C-6 in 1-alkylamino-6-ethoxy-1,5-hexadien-3,4-diones **1a-f** and 1,6-bis(alkylamino)-1,5-hexadien-3,4-diones **2a-f** [XCH=CHC(O)-C(O)CH=CHY, where X, Y= OEt, NH_2, $PhCH_2NH$, *n*-BuNH, *i*-PrNH, *cyclo*-$C_6H_{11}NH$, *t*-BuNH], taking as reference the 1,6-diethoxy-1,5-hexadien-3,4-dione (**3**), is reported. From the calculated values for the E_{Xn} and E_{Yn} effects for each substituent it was possible to estimate the chemical shift of each carbon of the compounds **1,2** with excellent precision: 100% of the calculated chemical shifts are found to be within ±0.5ppm. The carbon-13 chemical shifts of C-1, C-2 and C-3 of compounds **1a,2a,3** led a good correlation with carbon charge densities (qr).

INTRODUCTION

The ^{13}C NMR chemical shifts substituent effects on sp^2 carbon atoms in unsaturated molecules 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 the synthesis of some bis(β,β-dialkoxyvinyl) ketones and their amino derivatives has been decribed by Effenberger et al.[3], only recently we have synthesized and recorded the ^{13}C NMR data of a series of 1-alkylamino-6-ethoxy-1,5-hexadien-3,4-diones and 1,6-bis(alkylamino)-1,5-hexadien-3,4-diones[4,5]. These compounds are interesting precursors for a variety of five and six membered heterocycles[3,6-8] and, more recently, azepines[4,5].

As a part of our research program, we have developed a system of equations to estimate the ^{13}C chemical shifts in β-alkoxyvinyl ketones[9,10] from the aditivities of empirical substituents effects. The aim of this work is the evaluation of the empirical ^{13}C chemical shifts substituents parameters in the 1-alkylamino-6-ethoxy-1,5-hexadien-3,4-diones **1a-f** and 1,6-bis(alkylamino)-1,5-hexadien-3,4-diones **2a-f** system (Scheme), in relation to a reference compound. The system of equations obtained may allow to calculate the chemical shifts of the carbons 1,2,3,4,5 and 6 of similar compounds. The carbon-13 chemical shifts of C-1, C-2 and C-3 of compounds **1a,2a,3** are compared with their respective carbon charge densities (q_r).

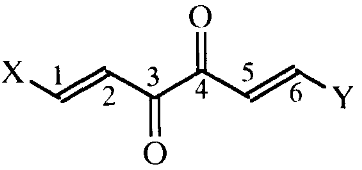
EXPERIMENTAL

Compounds

The 1-alkylamino-6-ethoxy-1,5-hexadien-3,4-diones **1a-f** and 1,6-bis(alkylamino)-1,5-hexadien-3,4-diones **2a-f**, were synthesized according to the published techniques by Effenberger et. al.[3] and Bonacorso et. al.[4,5].

^{13}C NMR Spectra

The ^{13}C NMR spectra were recorded on a Bruker ACF250 spectrometer (Universität Stuttgart, Germany) at 62.9 MHz. The experimental conditions on the Bruker ACF-250 were: ^{2}D internal lock; acquisition time 1.90 s; spectral width 17241 Hz; relaxation delay 1 s; number of scans between 120 and 200, depending of the type of compound; 65536 data points giving a digital resolution of 0.52 Hz/point; probe temperature of 24°C (297 K).



X	Y=OEt	Y=X
NH_2	**1a**	**2a**
$PhCH_2NH$	**1b**	**2b**
n-BuNH	**1c**	**2c**
i-PrNH	**1d**	**2d**
cyclo-$C_6H_{11}NH$	**1e**	**2e**
t-BuNH	**1f**	**2f**
OEt	**3**	

SCHEME

Chloroform-d_1 solutions with an approximate concentration of 0.5 M and 0.1% of TMS as internal reference were used in 5mm tubes.

Calculations

All calculations were done on a MICROTEC-DX 486 personal computer. The determinations of the carbon charge densities were done by a graphics-based Hückel MO Program[11].

RESULTS AND DISCUSSION

The ^{13}C chemical shift assignments of compounds **1,2a-f** 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)[12]. The experimental ^{13}C chemical shifts of compounds **1,2a-f,3** are shown in Table 1.

From the ^{13}C NMR experimental data of compounds **1,2a-f** (Table 1) the substituent increments were determined, taking 1,6-diethoxy-1,5-hexadien-3,4-dione (**3**) as a reference (Scheme).

As previously reported[9,10], the empirical substituent increments were determined according to the position occupied by this substituent relative to a given carbon (Scheme). The determination of these increments was done by the Eqs. 1,2.

$$E_{X_n} = [\delta_{C\text{-}n}(X_{C\text{-}1}) \ - \ \delta_{C\text{-}n}(REF)] \text{ ppm} \qquad (1)$$

$$E_{Y_n} = [\delta_{C\text{-}n}(Y_{C\text{-}6}) \ - \ \delta_{C\text{-}n}(REF)] \text{ ppm} \qquad (2)$$

In Eq. 1, E_{X_n} is the effect of the X substituent on carbon *n*; $\delta_{C\text{-}n}(X_{C\text{-}1})$ is the chemical shift of carbon *n*, in the compound containing X bound to the carbon-1; and $\delta_{C\text{-}n}(REF)$ is the chemical shift of carbon *n* of the reference compound (**3**). In Eq. 2, E_{Y_n} is the effect of the Y substituent to a carbon *n*; $\delta_{C\text{-}n}(Y_{C\text{-}1})$ is the chemical shift of carbon *n*, in the compound containing Y bound to the carbon-6; and *n* is a full number which in the case of the compounds studied in this work could vary from 1 to 6.

From the preliminary data of E_{X_n} and E_{Y_n} effects, it was possible to arrange these effects according with the nitrogen substituent: -NH-**R**, where **R**= **H** [NH_2], **CH_2-** [NH-CH_2-Ph, NH-*n*-Bu], **CH<** [NH-CH$(CH_3)_2$, NH-

TABLE 1.

^{13}C chemical shifts of the carbons 1, 2, 3, 4, 5 and 6 of 1-alkylamino-6-ethoxy-1,5-hexadien-3,4-diones **1a-f** and 1,6-bis(alkylamino)-1,5-hexadien-3,4-diones **2a-f** and the reference compound 1,6-diethoxy-1,5-hexadien-3,4-dione (**3**).

	X	Y	C-1	C-2	C-3	C-4	C-5	C-6
1a	NH_2	OEt	154.0	90.4	187.8	190.2	99.9	165.7
1b	$PhCH_2NH$	OEt	156.6	89.3	186.2	190.2	99.9	165.4
1c	*n*-BuNH	OEt	156.7	88.6	185.8	190.1	99.9	165.2
1d	*i*-PrNH	OEt	154.6	88.3	185.5	190.2	99.8	165.1
1e	$C_6H_{11}NH^a$	OEt	154.7	88.4	185.5	190.4	99.8	165.1
1f	*t*-BuNH	OEt	152.4	88.4	185.2	190.4	99.7	165.1
2a	NH_2	NH_2	152.9	90.6	189.2	189.2	90.6	152.9
2b	$PhCH_2NH$	$PhCH_2NH$	155.8	89.5	188.0	188.0	89.5	155.8
2c	*n*-BuNH	*n*-BuNH	156.0	88.5	187.7	187.7	88.5	156.0
2d	*i*-PrNH	*i*-PrNH	153.8	88.4	187.5	187.5	88.4	153.8
2e	$C_6H_{11}NH$	$C_6H_{11}NH$	153.9	88.3	187.4	187.4	88.3	153.9
2f	*t*-BuNH	*t*-BuNH	151.5	88.5	187.4	187.4	88.5	151.5
3	OEt	OEt	166.2	100.2	189.2	189.2	100.2	166.2

$^aC_6H_{11}$ = *cyclo*-hexyl group.

cyclo-C_6H_{11}], C←[NH-C(CH_3)$_3$]. The parameters determined from Eqs. 1,2 are reported in Table 2.

Thus, for the ^{13}C chemical shift determinations of C-1, C-2, C-3, C-4, C-5 and C-6 of a series of 1-alkylamino-6-ethoxy-1,5-hexadien-3,4-diones **1a-f** and 1,6-bis(alkylamino)-1,5-hexadien-3,4-diones **2a-f** , a system of Eqs. 3-8 that uses the data determined from the Eqs. 1,2, was elaborated.

$$\delta_{C\text{-}1} = 166.2 + E_{X1} + E_{Y1} \qquad (1)$$

$$\delta_{C\text{-}2} = 100.2 + E_{X2} + E_{Y2} \qquad (2)$$

$$\delta_{C\text{-}3} = 189.2 + E_{X3} + E_{Y3} \qquad (3)$$

$$\delta_{C\text{-}4} = 189.2 + E_{X4} \qquad (4)$$

$$\delta_{C\text{-}5} = 100.2 + E_{X5} \qquad (5)$$

$$\delta_{C\text{-}6} = 166.2 + E_{X6} \qquad (6)$$

For X=Y, $\delta_{C\text{-}1} = \delta_{C\text{-}6}$, $\delta_{C\text{-}2} = \delta_{C\text{-}5}$, $\delta_{C\text{-}3} = \delta_{C\text{-}4}$

Eqs. 3-8 allow to estimate with high precision the ^{13}C chemical shifts of carbons 1, 2, 3, 4, 5, 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.

Linear correlationship analysis between the experimental and calculated ^{13}C chemical shifts (Eqs. 3-8) of compounds **1,2** were done. For a qualitative observation of the *linear analysis* carried out, Figure 1 shows the excellent relationship of all studied compounds (*r* =0.999).

TABLE 2.

Empirical parameters[a] for Eqs. 3-8.

	C-1	C-2	C-3	C-1	C-2	C-3	C-4	C-5	C-6
X	E_{X1}	E_{X2}	E_{X3}	E_{Y1}	E_{Y2}	E_{Y3}	E_{X4}	E_{X5}	E_{X6}
O-Et	0	0	0	0	0	0	0	0	0
NH-H	-12.2	- 9.8	-1.4						
NH-CH_2-	- 9.6	-11.3	-3.2	-0.9	0.1	1.9	1.1	-0.4	-0.9
NH-CH<	-11.6	-11.9	-3.7						
NH-C←	-13.8	-11.8	-4.0						

[a] In ppm.

Finally, one can observe that all calculated chemical shifts are within a maximum absolute error range of ±0.5 ppm and that 90% of the calculated values deviate less than 0.3 ppm from the measured ones (72 ^{13}C chemical shift values were considered).

Linear correlationship analysis between the carbon-13 chemical shifts of C-1, C-2, C-3 (**1a,2a,3**) and carbon charge densities were done[9]. For qualitative observation, the linear analysis carried out, Figure 2 shows the good relationship of all parameters studied (r=0.994).

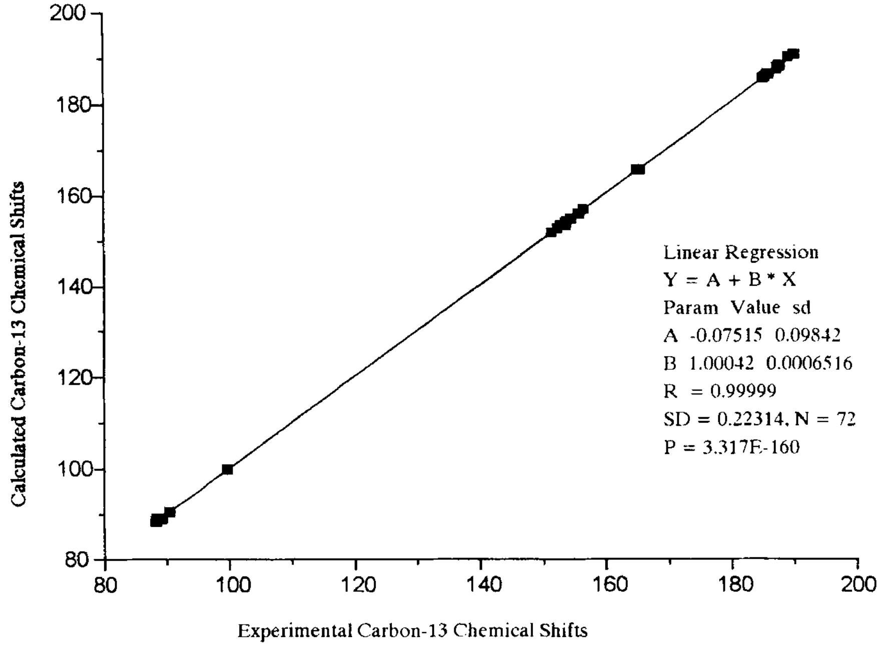


Figure 1. Correlation between the experimental and calculated (Eqs. 3-8) ^{13}C NMR chemical shifts for C-1, C-2, C-3, C-4, C-5, C-6 of compounds **1,2a-f** (r=0.9999).

CONCLUSION

The model used in this work for the evaluation of the substituent empirical increments (Eqs. 1,2) is very simple and easy to use. The estimation of the ^{13}C NMR chemical shifts of C-1, C-2, C-3, C-4, C-5, C-6 of compounds **1,2**, from Eqs. 3-8 is simple and accurate. The estimated chemical shifts for the compounds **1,2**, from the Eqs. 3-8, have shown high accuracy [100% of the chemical shifts are within a range of ±0.5ppm]. The model used for the determination of the substituent empirical parameters

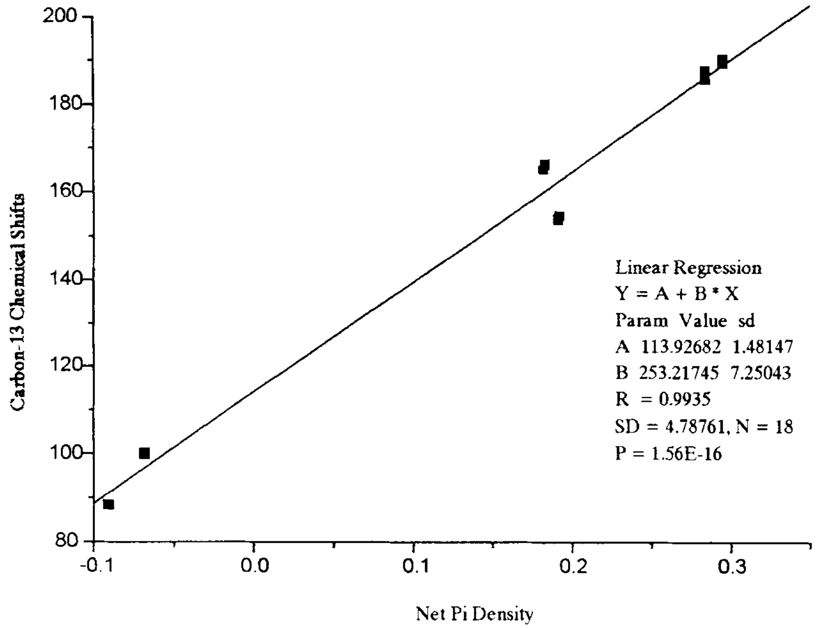


Figure 2. Correlation between the ^{13}C chemical shifts (Table 1) and carbon charge densities (q_r) on C-1, C-2, C-3 of compounds 1a,2a,3 (r=0.994).

did not account for the limitations resulting of the interaction of neighboring substituent groups. The relationship between carbon-13 chemical shifts and carbon charge densities shows a good dependence of ^{13}C NMR chemical shifts for C-1, C-2 and C-3 of compounds **1a,2a,3** and parameters obtained from HMO calculations.

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