

## $\alpha$ -Substituent Effects on $^{13}\text{C}$ NMR Chemical Shifts in Some Carbonyl Compounds

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**Abstract:** The principal component analyses of  $\alpha$ -substituent effects on  $^{13}\text{C}$  NMR chemical shifts for 36 carbonyl compounds are presented. The data matrix, 36x17, consisted of 15 independent and 2 class variables.  $\alpha$ -Monosubstituted acetones (12 samples), acetophenones (8 samples), cyclohexanones (8 samples) and camphors (8 samples) are discriminated in four groups due to the differences in LUMO energies and carbonyl carbon chemical shifts. Furthermore, these compounds exhibit strong separation in neutral compounds, with parent and methyl and ethyl derivatives, oxygenated compounds, OMe and OEt as substituents, nitrogen derivatives (NMe<sub>2</sub> and NEt<sub>2</sub>) and sulfur compounds (SMe and SEt), while halogenated compounds exhibit different behavior.

**Resumo:** As análises de componentes principais dos efeitos dos  $\alpha$ -substituintes sobre os deslocamentos químicos dos compostos carbonílicos são apresentadas. A matriz de dados, 36x17, consistiu de 17 variáveis, sendo 15 independentes e duas referentes às classes utilizadas nas análises. As acetonas, acetofenonas, ciclohexanonas e cânforas, todas  $\alpha$ -monossobstituídas, foram discriminadas em quatro agrupamentos devido às diferenças exibidas nas energias do LUMO e nos deslocamentos químicos dos carbonos carbonílicos. Além do mais, estes compostos exibem uma forte separação em compostos neutros com grupos alquila e hidrogênio como substituintes, derivados de oxigênio (OMe e OEt), derivados nitrogenados (NMe<sub>2</sub> e NEt<sub>2</sub>), e compostos de enxofre (SMe e SEt), enquanto que os compostos halogenados mostram um comportamento diferente.

### Introduction

The effects of  $\alpha$ -substituents on carbon-13 NMR chemical shifts are interpreted as consequences of inductive and mesomeric effects and these are regularly correlated with physical-chemical properties of atoms or specific groups.<sup>1,2</sup> Various equations for each organic class have been proposed and yet there is no explicit equation for parameters with a clear physical-chemical meaning. Therefore, studies of substituent effects on NMR chemical shifts still represent an open field.

This work presents the results of Principal Component Analyses (PCA) applied on some  $\alpha$ -monosubstituted carbonyl compounds with intention to correlate their carbonyl and  $\alpha$ -carbon chemical shifts with the molecular properties obtained by theoretical calculations.

### Material and Methods

The  $^{13}\text{C}$  NMR data refer to the similar temperature, concentration and solvent conditions as to avoid their influence on Substituent-induced

Chemical Shift (SCS) values. The data were taken from the literature<sup>3-8</sup> and the SCS values were calculated for each organic class using the following equation:

$$\text{SCS} = \delta(^{13}\text{C}_{\text{COMPOUND-Y}}) - \delta(^{13}\text{C}_{\text{COMPOUND-H}}) \quad (1)$$

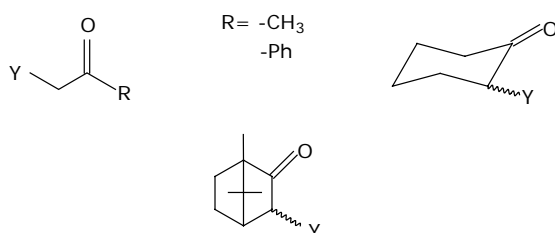
where the  $\delta(^{13}\text{C}_{\text{COMPOUND-Y}})$  refer to substituted and  $\delta(^{13}\text{C}_{\text{COMPOUND-H}})$  to unsubstituted compound from the same class.

The geometries of the molecules, as well as, the molecular properties were obtained by optimizations using the *Gaussain 98* program at the 6-31g (d,p) level and electronic correlation MP2.<sup>9</sup>

The data matrix was constructed from 36 compounds and 15 independent variables. The two dependent variables are representing: (i) the organic class (Figure 1) and (ii) five substituent types: 1. neutral (H, Me, Et), 2. oxygen (OMe, OEt); 3. nitrogen (NMe<sub>2</sub>, NEt<sub>2</sub>), 4. sulfur (SMe, SEt) and 5. halogen (F, Cl, Br) compounds.

All Principal Component Analyses were performed utilizing the *Pirouette* software package<sup>10</sup> Autoscaling was utilized as pre-processing of the

data by subtracting column averages and dividing it by column standard deviations. In this way, each of the variables is given identical weight in the principal component analysis.

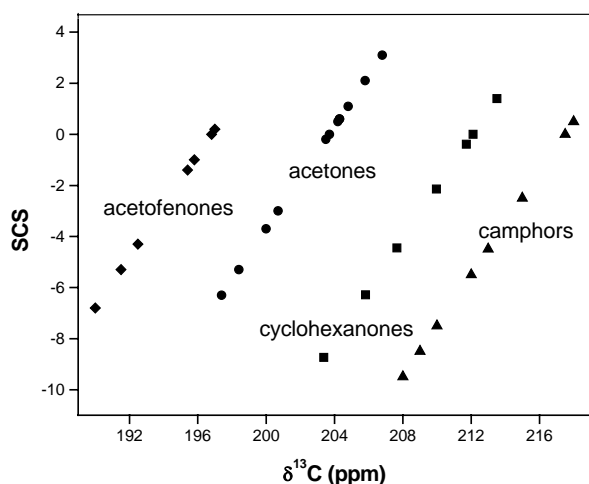


**Figure 1.** Analyzed carbonyl compounds, Y is  $\alpha$ -substituent = H, F, Cl, Br, OMe, OEt, SMe, SEt, NMe<sub>2</sub>, NEt<sub>2</sub>, Me and Et.

## Results and Discussion

The results of the principal component analyses (PCA) can be divided in two types: (i) in the first PCA we present the separation between four organic classes and (ii) in the second, four substituent type clustering in neutral, oxygen, nitrogen and sulfur compounds.

In comparison to acetones, acetofenones show smaller carbonyl carbon chemical shifts due to aromatic ring presence. Cyclic compounds, cyclohexanones and camphors, have higher carbonyl carbon chemical shifts and smaller differences between the SCS values, as illustrated on Figure 2.



**Figure 2.** Carbonyl Carbon Chemical Shifts of analyzed compounds.

In the first PCA, four organic class compounds are separated according to carbonyl carbon chemical shift differences, as well as, due to the energy gaps of the lowest unoccupied molecular orbital (LUMO, Table 1 and Figure 3).

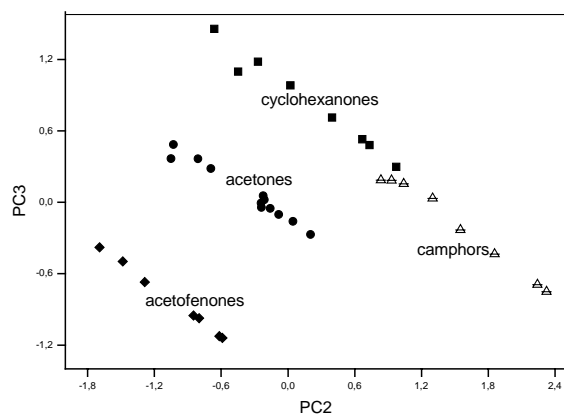
As seen on Figure 3, camphors and cyclohexanones have similar behavior primarily because of their rigid cyclic structures and due to chemical shift and LUMO energy similarities.

**Table 1**

Loading values of the first PCA of carbonyl compounds

Variable	PC1	PC2	PC3
$\delta(^{13}\text{C-f}^*)$	0.1303	0.9073	0.3999
LUMO	0.6762	-0.3763	0.6334
SCS( $^{13}\text{C-f}$ )	0.7252	0.1879	-0.6625

\* f – carbonyl carbon



**Figure 3.** Graphic representation of scores in PC2xPC3 of carbonyl compounds.

In the second PCA, after the exclusion of halogenated compounds, we have utilized six variables and three principal components, with 95.08 % of the total variance, for data description (Table 2). The four types of compounds: neutral, oxygen, nitrogen and sulfur, are grouped because of different score values as presented on Figure 4.

**Table 2**

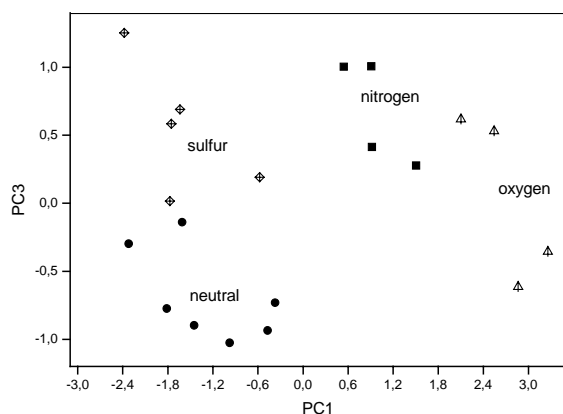
Loading values in the second PCA of carbonyl compounds

Variable	PC1	PC2	PC3
$\delta(^{13}\text{C}-\alpha)$	0.4783	0.0169	0.2077
Partial charge on C- $\alpha$	0.4869	-0.0338	-0.0496
SCS( $^{13}\text{C}-\alpha$ )	0.4691	0.1596	0.0182
Hardness	-0.0330	0.9074	0.3596
MOCA <sup>*1</sup>	-0.3893	-0.2284	0.7349
MOH <sup>*2</sup>	0.4017	-0.3123	0.5335

\*1- MOCA – Molecular Orbital Coefficient of  $\alpha$ -Carbon atom\*2- MOH - Molecular Orbital Coefficient of  $\alpha$ -Hydrogen atom

As seen, neutral and sulfur compounds have negative score values, while oxygen and nitrogen compounds have positive scores in the first principal component (PC1). This result was expected because of the differences among the utilized variables in the PCA of these compounds.

The third principal component (PC3) is responsible for separation occurred between sulfur compounds, on one side, with high score values, and neutral compounds, on the other. This is in accordance with the differences between the two compound types, since the hardness of neutral compounds is quite smaller from the sulfur derivatives and also because of the different partial charge alterations on carbon- $\alpha$ .

**Figure 4.** Graphic representation of scores in PC1xPC3 in the second PCA.

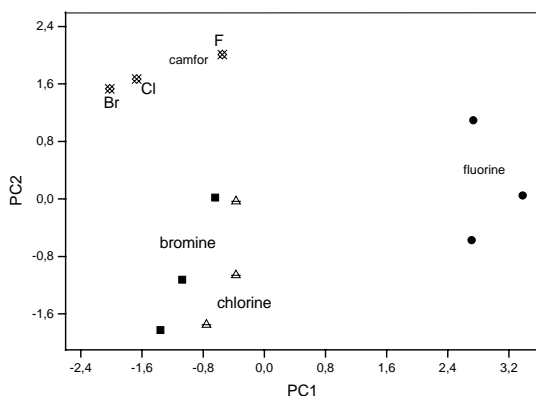
The  $\alpha$ -substituent effects on carbon-13 chemical shifts of analyzed organic classes are directly dependable on heteroatom type. The four-class separation occurred basically as consequence of partial charge alterations of  $\alpha$ -carbon atom. The neutral and sulfur compounds, with similar chemical shifts and partial charges of  $\alpha$ -carbon atoms, have been separated from the rest, by their negative score values in PC1 (Figure 4). On the contrary to neutral and sulfur compounds, oxygen derivatives have the most positive scores in PC1, probably due to the high electronegativity of oxygen (L. Pauling). As a consequence of its electronegativity, partial charges of  $\alpha$ -carbon atoms are significantly different in comparison to the other samples. The nitrogen compounds have behaved similar to oxygen, as expected, because of the same period belonging of these two elements and their similar electronegativities. The sulfur derivatives showed high scores in PC3 (Figure 4), because of the molecular orbital coefficients of  $\alpha$ -carbon atoms and hardness parameter that are quite different in comparison to the ones of neutral compounds. If compared the same heteroatom substituents (O, N, S, C or H), there is no significant difference between the substituent size and the SCS values, *i.e.*, OMe and OEt form the same cluster and have almost the same SCS values.

At last, but not at least, the halogenated compounds were analyzed. Three principal components and six variables have been utilized in data description. It is notable (Figure 5) that the first principal component separated three halogen classes, with the fluorine derivatives having the highest scores, and the bromine and chlorine derivatives, similar and negative score values in the PC1. In the second principal component (PC2), the camphor halogen compounds have the highest score values and represent a group with specific behavior probably due to their rigid structure.

If compared the  $\alpha$ -carbon chemical shifts, SCS( $^{13}\text{C}-\alpha$ ), the fluorine derivatives have the highest SCS values, approximately around 50 ppm, the chlorine derivatives have SCS( $^{13}\text{C}-\alpha$ ) values

~20, and the bromine derivatives have  $SCS(^{13}C-\alpha)$  from ~1 to 10 ppm. While, the camphor compounds have different  $SCS(^{13}C-\alpha)$  values: 15 for the F-derivative, and 2.5 and 3.5 for Cl and Br, respectively.

The F-compounds are occupying the extreme right corner of the graph (Figure 5), probably because of the fluorine high electronegativity. Beside the differences in partial charges and molecular coefficients of the  $\alpha$ -carbon atom, F-derivatives show very different SCF energies (self-consistent field) in comparison to the other halogen derivatives.



**Figure 5.** Graphic representation of scores in PC1xPC2 in the third PCA.

As the unique rigid molecules, halogen camphor derivatives, beside the inductive effect, suffer the stereochemical effects and that is the probable cause for their extreme behavior in this PCA.

## Conclusions

The results of the PCAs of the  $\alpha$ -substituent effects on carbon-13 chemical shift of carbonyl compounds show the strong substituent effect dependence on heteroatom type. Therefore, we can differentiate the effects of neutral, sulfur, nitrogen and oxygen groups. The observed effects, and clustering, are the consequences of the different partial charge distributions basically on  $\alpha$ -carbon atoms. It is notable that elements of higher

electronegativity, such as oxygen and nitrogen, have provoked significant alterations of  $\alpha$ -carbon partial charges and therefore, we can say that alterations of the chemical shifts are primarily provoked by inductive effects. The sulfur compounds, because of the presence of sulfur  $d$ -electrons, have showed a different behavior in comparison to nitrogen and oxygen derived compounds by having higher hardness parameter values.

The effects of the neutral, sulfur, nitrogen and oxygen derivatives on  $^{13}C$  NMR chemical shifts should be studied separately from effects in halogenated compounds, because of the great differences in the SCS values between the fluorine, chlorine and bromine carbonyl compounds.

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