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FUNCTIONAL SUBSTITUENTS α TO ^{13}C: TOPOLOGICAL CORRELATION BY PERTURBATION OF A FOCUS AND PRINCIPAL COMPONENT FACTOR ANALYSIS

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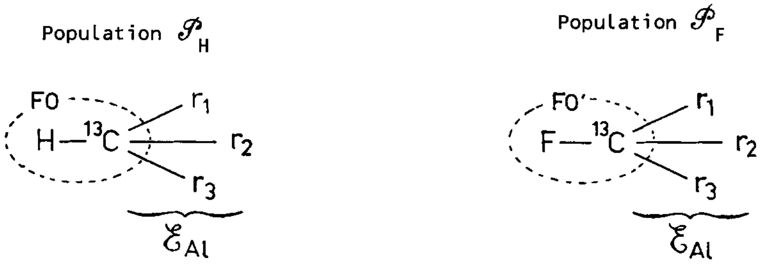
Abstract : The effect of a functional group, that of an alkyl environment and the degree of substitution of a ^{13}C focus are dealt with by the perturbation of a focus (DARC-PULFO method). Their variations are satisfactorily interpreted by a relation and a network. The coherence of this unitary model is confirmed by a data treatment involving factor analysis.

In ^{13}C-NMR, chemical shifts induced in a carbon chain by a functional group are generally assessed whith respect to the corresponding alkane by means of frozen increments.[1] However, such models are lacking for branched structures where, depending on the alkyl environments, large variations in functional substituent effects are observed, particularly for the substituted site. Thus, for a substitution from H to MeCO (between alkane H-R and ketone MeCO-R), the shift induced in the carbon atom where it occurs is 31.4 ppm when R = Et and only 11.0 ppm when R = CMeiPrtBu. An extension of the DARC-PULFO method of topological analysis by perturbation of a focus, recently proposed for the correlation of α-methyl effects in ^{13}C-NMR,[2] is suggested for the interpretation and prediction of this diversity in behavior.

I.- TOPOLOGICAL ANALYSIS BY PERTURBATION OF A FOCUS

The effect of a functional substituent induced in the transformation of H-R into F-R, where R = ^{13}C$r_1r_2r_3$ with r_i designating the alkyl groups and F the function, is assessed as the influence of the perturbation of a focus between two ordered populations of associated compounds differing only in that the focus of the one is H-^{13}C and that of the other is F-^{13}C.



FO, FO' : focus, $\mathscr{E}_{Al}$: alkyl environment of ^{13}C, F : functional environment.

The influence of alkyl environments in each of these populations can be described by *linear relationships* between the chemical shifts and topological parameters λ_r, with a *constant degree of substitution of the resonant site.*[3,4]

$$\text{Population } \mathscr{P}_H \qquad \delta = \omega_H^{c-1} \quad \Sigma\lambda_r + (\delta_H)_o^{c-1} \tag{1}$$

$$\text{Population } \mathscr{P}_F \qquad \delta = \omega_F^{c} \quad \Sigma\lambda_r + (\delta_F)_o^{c} \tag{2}$$

In these relations, the shifts δ_H^o and δ_F^o are associated with alkyl environments bearing only methyl groups ; ω_F^c, or ω_H^{c-1}, designates the susceptibility of ^{13}C to alkyl perturbations and is dependent on the nature of the functional groups and on the connectivity of the site (c-1 and c for H-^{13}C and F-^{13}C, respectively); $\Sigma\lambda_r$ represents the sum of the topological parameters of the sub-groups r comprising $\mathcal{E}_{Al}$. The difference between these linear correlation laws (PULFO method) gives a linear model for functional substituent effects:

$$\Delta\delta = (\omega_F^c - \omega_H^{c-1}) \quad \Sigma\lambda_r + (\delta_F)_o^c - (\delta_H)_o^{c-1} \tag{3}$$

expressed as :

$$(\alpha\text{-H,F})^{c-1,c} = \Delta\omega_{H,F}^{c-1,c} \quad \Sigma\lambda_r + (\alpha\text{-H,F})_o^{c-1,c} \tag{4}$$

The latter relation has two separate components, $(\alpha\text{-H,F})_o^{c-1,c}$ expressing the *limiting effects* associated with substitutions involving transformations of H into F for ^{13}C sites in alkyl environments reduced to methyl groups, and $\Delta\omega_{H,F}^{c-1,c}\ \Sigma\lambda_r$ expressing the influence of variations in the alkyl environment [with factorization of the alkyl environments and of the susceptibility of ^{13}C sites into characteristic elements: $(\Sigma\lambda_r)$ and $(\Delta\omega_{H,F}^{c-1,c})$]

II.- VARIATIONS OF THE EFFECTS OF FUNCTIONAL SUBSTITUENTS α TO ^{13}C

In agreement with the model, Fig.1 illustrates the linear relations established, according to the connectivity of ^{13}C, between the substituent effect for a transformation of H-^{13}C into MeCO-^{13}C (between alkanes and ketones MeCO^{13}C$r_1r_2r_3$) and the topological parameters $\Sigma\lambda_r$ of the alkyl environment of ^{13}C. The parallelism of correlations A, B and C for the secondary, tertiary and quaternary ^{13}C sites indicates that the connectivity c barely affects the *differential susceptibilities* $\Delta\omega_{H,MeCO}^{c-1,c}$, whereas it strongly affects the specific susceptibilities ω_{MeCO}^{c} and ω_H^{c-1}.

The validity of this linear model is confirmed by its extension to other functional groups: F = OH, Me, COOH, Br, Cl, I, C≡CH, CH_2 = C(Me). Despite noticeable differences in the amplitude of the effects of functional substituents α to ^{13}C for these different groups, there is a big similarity in their *evolvement* depending on the connectivity of ^{13}C (variations in the limiting effects) or on the structure of the alkyl environments (variations in $\Sigma\lambda$). *Weak variations in the differential susceptibilities* $\Delta\omega_{H,F}^{c-1,c}$ are detected for the groups studied, except for the halogens which also display heightened limiting effects. This pseudo-invariance of $\Delta\omega$, for a given F, makes it possible to distinguish the environments which act on the different terms in eq. 4 : the limiting effect $(\alpha\text{-H,F})_o^{c-1,c}$ depends on the *degree of substitution* of ^{13}C and on the *nature of F*, whereas λ_r depends only on the structure of the *alkyl environments.*

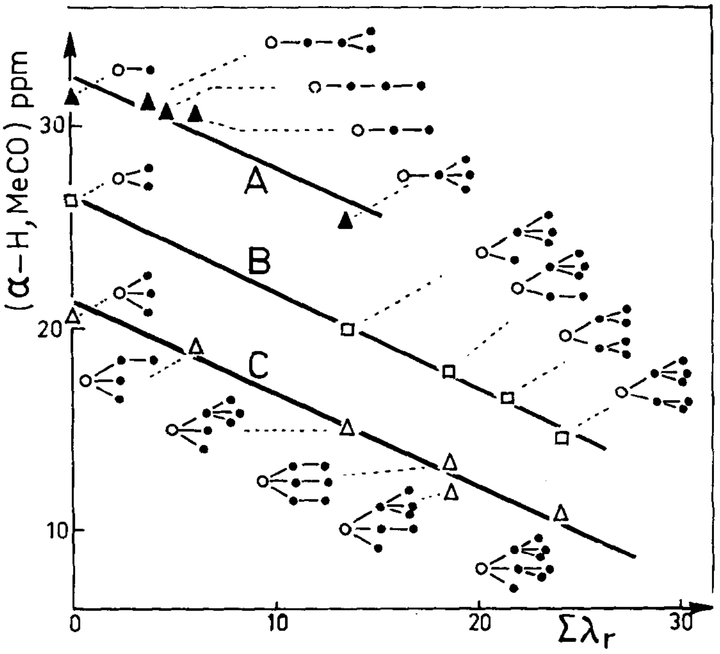


Figure 1: Correlation of H^{13}C → MeCO-^{13}C substitution effects. Straight lines A,B,C designate secondary, tertiary and quaternary ^{13}C sites, respectively.
(^{13}C site : o)
(A) $(\alpha\text{-H,MeCO}) = 32.5 - 0.48\ \Sigma\lambda_r$
(B) $(\alpha\text{-H,MeCO}) = 26.4 - 0.47\ \Sigma\lambda_r$
(C) $(\alpha\text{-H,MeCO}) = 21.2 - 0.45\ \Sigma\lambda_r$

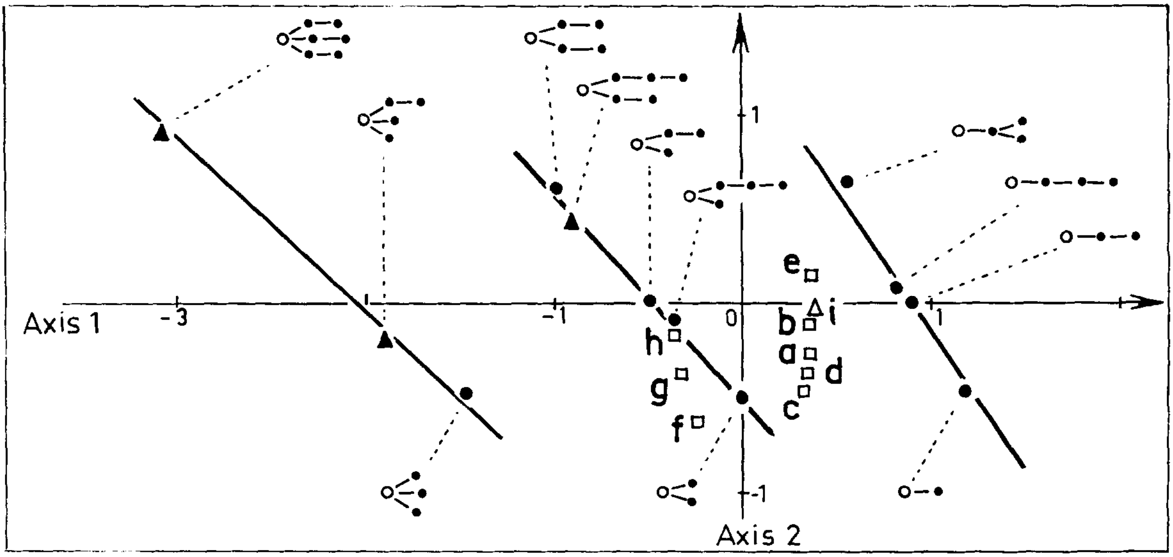


Figure 2: Principal Component Analysis and α Substituent Effects. Points are projected on the plane of the two main factors (centered and scaled values).
Functional Environment: (a) Me ; (b) COOH ; (c) OH ; (d) HC≡C- ; (e) $H_2C{=}C(Me)$ (f) Cl ; (g) Br ; (h) I ; (i) MeCO.
Additional data : (i) Δ ; $^{13}CEt_3$, $^{13}CEt\ Me_2$, $^{13}CH\ nPr\ Et$: ▲

III.- PRINCIPAL COMPONENT FACTOR ANALYSIS

Recent work by Wiberg et al.[5] and Wold et al.[6] introduces factor analysis methods for the classification and description of ^{13}C chemical shifts without a previously established model. To check the form of eq. 4 observed for local topological correlations (Fig. 1), all the chemical shifts caused by substitution for 9 alkyl environments and 8 functional environments (for which all experimental data are known) were subjected to principal component analysis.[7]

This analysis indicates that, for the population studied, two factors are enough to render the induced chemical shifts (with 98% inertia) in a first approximation. Fig. 2 shows the *points* representing the *alkyl environments* and the points associated with the *functional environments* (treated as *individuals* and *variables*, respectively) projected onto the plane of the two main factors. Therein, the points representing the alkyl environments are grouped into very approximately parallel distinct segments according to the connectivity of ^{13}C; this is coherent with the observation that, *for the structures studied*, a single parameter (linear combination of the two main factors) is enough to describe the influence of the alkyl environments with ^{13}C *at a set degree of substitution.* Moreover, except for the points associated with halogens, all points associated with the various functional groups are clustered thereby indicating a large similarity in behavior.

For some $\mathcal{E}_{Al}$ alkyl environments ($^{13}Cr_1r_2r_3 = {}^{13}CEt_3$, $^{13}CMe_2Et$, $^{13}CEtnPr$) or when F is MeCO, the few missing shifts have been estimated by topological correlation ($\delta/\Sigma\lambda_r$), and these groups, without being included in the factor analysis, were projected as additional illustrative data onto the plane of the two preceding main axes. Their positions (Fig. 2) support our conclusions regarding the influence of the various active zones of the alkyl and functional environments on the amplitude of α substituent effects.

The convergence of both approaches is remarkable in view of the difference in methodology: *overall statistical representation* of a given set of data, and *network of descriptive and predictive local correlations* (depending on an outside scale of parameters). The statistical treatment supports the unitary topological model proposed for the interpretation of data by local correlations proper to the alkyl environments and also elements of a *general network* expressing the shifts associated with the variations in the connectivity and with the functional effects on ^{13}C sites.

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Group λ parameters are obtained by adding the site parameters from the topological analysis of δC_{sp} of aliphatic alkynes : $\lambda_R = \delta(R'-C\equiv{}^{13}C-R) - \delta(R'-C\equiv{}^{13}C-Me)$. For groups R = Me, Et, isoPr, and tertBu, λ_R is 0, 6.2, 10.7 and 13.5, respectively.

(4) Only acyclic alkyl environments, corresponding to the reference population of λ_R, are considered.

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