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Topological Correlations of Carbon-13 Chemical Shifts by Perturbation on a Focus: DARC–PULFO Method. Attenuation and Inversion of α-Methyl Substituent Effects

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The diversity of α-Me substituent effects from the usual deshielding to large shielding shifts (e.g., from 11.7 to −9.1 ppm in aliphatic ketones), depending on the nature of the resonant carbon environment, is interpreted with a heuristic topological model. Data analysis is based on the linear correlation laws obtained for chemical shifts by using the scale of topological parameters λ_r (characterizing alkyl environment influence) and a sensitivity parameter, ω, depending on the connectivity of the ^{13}C site (secondary, tertiary, quaternary) and on the nature of its functional environment (chemical families). A substituent-induced shift from ^{13}CH to ^{13}CMe is considered as a topological Perturbation, Unique and Localized, on a Focus which is Ordered (PULFO) and is assessed by the difference between the $\delta/\sum\lambda_r$ correlation laws for two associated ordered populations. In the resulting PULFO equation, $(\alpha\text{-Me})^{c-1,c} = \Delta\omega^{c-1,c}\sum\lambda_r + (\alpha\text{-Me})_0{}^{c-1,c}$, the influence of the alkyl environment ($\mathcal{E}_{\mathrm{Al}}$) is expressed by the term $\Delta\omega^{c-1,c}\sum\lambda_r$ (in which $\Delta\omega^{c-1,c}$ represents the differential sensitivity of the ^{13}C site whose connectivity changes from $c - 1$ to c). This model identifies the role of the various parts of the resonant carbon environment and provides a unifying treatment for evolving α-Me effects. Conformational effects (filiation or sequence between labile or frozen conformations) on values of $(\alpha\text{-Me})_0$ are discussed in the case of aliphatic ketones. Data treatment of various chemical families (acids, ketones, alkenes, alkynes, alcohols) is very satisfactory with this PULFO model. In this generalization, $(\alpha\text{-Me})_0$ limiting effects are highly dependent on the nature of the functional environment ($\mathcal{E}_{\mathrm{F}}$) whereas the differential sensitivities $\Delta\omega^{c-1,c}$ remain practically constant for a given topological transition.

Structural analysis by ^{13}C NMR largely relies on the examination of substituent-induced chemical shifts (SIS), particularly on α effects of a methyl group (α-Me effects) associated with the transformation of ^{13}CH into ^{13}CMe. The wide variety of α-Me effects makes their behavior hard to unify. The most frequently observed effects are the *usual downfield shifts* for structures with relatively few substituents,[1] *with attenuation* according to the branching at the α and β positions of the ^{13}C site[2] and a marked dependence on stereochemical factors.[3] However, *exalted shifts* (up to 15 ppm) for cyclic[4] or strongly hindered[5] structures and *inverted upfield shifts*[5–7] (up to −8 ppm) for heavily substituted branched structures are also reported. *Prediction* of this varied behavior and *interpretation* of the influence exerted on α-Me effects by the nature of the functional environment $\mathcal{E}_{\mathrm{F}}$ and the branching of the alkyl environment $\mathcal{E}_{\mathrm{Al}}$ can be achieved by the *topological analysis of α-Me effects* described here.

Despite many theoretical studies,[8] the origin of substituent effects on chemical shifts remains unclear. Different mechanisms have been proposed to explain variations in screening constants, but, up to now, the obtained relationships between chemical shifts (δ) and empirical or semiempirical physiochemical parameters (e.g., electron densities or polar effect substituent constants, ...) yield only partial descriptions or interpretations.[9] Nevertheless, many studies have established that the interrelations between δ and molecular structure are greatly dependent on proximity relationships between atoms. In the absence of important molecular distortion and/or sudden conformational change, the topography may be adequately represented by the topology, and these δ/structure interrelations can be expressed by a topological description of environments.

Assuming the equivalence of groups located in a single typical environment, the usual correlation models most often involve *the additivity of characteristic increments* of substituent groups, according to their position with respect to the ^{13}C site and with respect to each other. However, in multiparameter correlation models representing chemical shifts, when the *degree of substitution of the ^{13}C site varies*, the fine description of substituent effects is very complex, as in Lindeman and Adams' use of increments ascribed to more or less complex topological modules[10] or in Beierbeck and Saunders' treatment with a weighted average of different conformers.[11] Such models are satisfactory to calculate δ within limited populations, but, because relevant information is split into interdependent components, the structural elements giving rise to particular or unusual behavior cannot be easily distinguished.

The DARC–PELCO method[12,13] has afforded various

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(1) (a) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972. (b) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden and Son: London, 1976.

(2) Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107.

(3) (a) Wilson, N. K.; Stothers, J. B. *Top. Stereochem.* **1974**, *8*, 1. (b) Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 6612; **1972**, *94*, 5318.

(4) (a) Stothers, J. B.; Tan, C. T.; Teo, K. C. *Can. J. Chem.* **1976**, *54*, 1211. (b) For instance, a 15.4-ppm shift for C_6 between *endo*-2-norbornanol and its *endo*-6 methylated derivative.

(5) (a) Dubois, J. E.; Doucet, J. P.; Panaye, A. *Tetrahedron Lett.* **1981**, *22*, 3521. (b) Doucet, J. P.; Panaye, A.; Dubois, J. E. *Ibid.* **1981**, *22*, 3517.

(6) Dubois, J. E.; Doucet, J. P.; Panaye, A. *Tetrahedron Lett.* **1980**, *21*, 2905.

(7) (a) Dheu, M. L.; Gagnaire, D.; Duddeck, H; Hollowood, F.; MacKervey, M. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 357. (b) Duddeck, H.; Hollowood, F.; Karim, A.; MacKervey, M. A. *Ibid.* **1979**, 360. (c) Ayer, W. A.; Browne, L. M.; Fung, S.; Stothers, J. B. *Org. Magn. Reson.* **1978**, *11*, 73. (d) Reich, H. J.; Jautelat, M.; Messe, M. T.; Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 7445.

(8) (a) Ditchfield, R.; Ellis, P. D. *Top. Carbon-13 NMR Spectrosc.* **1974**, *1*, 1. (b) Martin, G. J.; Martin, M. L.; Odiot, S. *Org. Magn. Reson.* **1975**, *7*, 2. (c) Ebraheem, K. A.; Webb, G. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1977**, *11*, 149.

(9) Wiberg, K. B.; Pratt, W. E.; Bailey, W. F. *J. Org. Chem.* **1980**, *45*, 4936.

(10) Lindeman, L. P.; Adams, J. Q. *Anal. Chem.* **1971**, *43*, 1245.

(11) Beierbeck, H.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 771; 1980, *58*, 1258.

(12) DARC stands for Description, Acquisition, Retrieval, and Computer-aided design. PELCO stands for Perturbation of an Environment which is Limited, Concentric, and Ordered.

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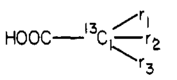
Table I. ^{13}C Chemical Shifts of the C_1 Carbon in Alkanecarboxylic Acids[a] and Corresponding α-Me Effects



r_3 = H or Me

no.	r_1	r_2	δ C-1 (r_3 = H)	δ C-1 (r_3 = Me)	α-Me effect
1	Me	H	27.7	34.2	6.5
2	Et	H	36.3	41.3	5.0
3	*i*-Pr	H	43.3	46.3	3.0
4	*t*-Bu	H	48.0	49.8	1.8
5	Me	Me	34.2	38.8	4.6
6	Et	Me	41.3	42.8	1.5
7	*i*-Pr	Me	46.3	46.0	−0.3
8	*t*-Bu	Me	49.8	48.2	−1.6
9	Et	Et	49.0	46.7	−2.3
10	*i*-Pr	Et	55.0	50.3	−4.7
11	*t*-Bu	Et	58.7	52.6	−6.1
12	*i*-Pr	*i*-Pr	59.1	52.9	−6.2
13	*t*-Bu	*i*-Pr	62.0	53.2	−8.8
14	*t*-Bu	*t*-Bu	64.8	56.0	−8.8
b	H	H	20.7	27.7	7.0

[a] In parts per million downfield from Me_4Si (10% w/v solution in CD_2Cl_2). α-Me effects correspond to the s,t transition for pairs **1–4** and to the t,q transition for pairs **5–14**. [b] This entry, corresponding to the only transition from a primary to a secondary ^{13}C site, is not mentioned again in the text.

approaches to the prediction of δ(^{13}C): calculating site parameters for ^{13}C at a constant degree of substitution, bringing them together as group parameters λ_r, and calculating the *transferability* coefficient of the λ_r scale for changes in the degree of substitution and changes in functional groups.[14,15] With the DARC–PELCO method, δ(^{13}C) can be predicted by interpolation, and singular δ(^{13}C) behavior can be detected. As a correlation tool, it opens the way toward interpretation searches, pointing to conformational situations as it in fact deals with the topographic location of the structural sites.[14,16]

The major influence of the degree of substitution of the ^{13}C site is also demonstrated by Ejchart's treatment with behavior/behavior (δ/δ) correlations[17] or by Wiberg's factor analysis.[9] This latter method is very useful in detecting similarities of behavior within a set of data; however, because the active factors in such an approach are determined on a free-standing basis, they cannot be immediately associated with a chemical phenomenon.

With such models to calculate chemical shifts, various substituent effects can be evaluated. A case-by-case comparison of the difference between δ calculated for ^{13}CH and ^{13}CMe fragments provides an assessment of α-Me effects. To enhance the effectiveness of this assessment, one can associate the perturbation in shift when H is replaced by Me with the evolvement of α-Me effects in very varied structural environments. To study this evolvement of α-Me effects, we hereafter compare ^{13}CH and ^{13}CMe fragments in associated families defined by ^{13}C connectivities.

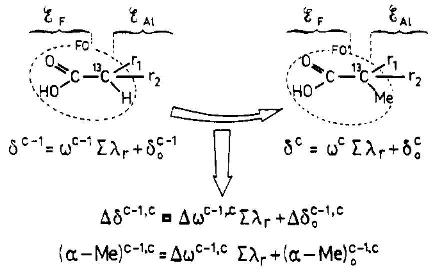


Figure 1. DARC–PULFO principle: α-Me SIS values are assessed by the difference between the correlation laws for two ordered populations of associated compounds. FO and FO′ are the foci of each population. $\mathcal{E}_F$ designates the functional environment of the ^{13}C site and $\mathcal{E}_{Al}$ its alkyl environment. $\mathcal{E}_{Al} = r_1$, r_2, H, or Me.

Results and Discussion

Model of α-Me Effects by the Linear Difference between δ/λ Correlations. Carboxylic acids $HO_2C^{13}Cr_1r_2r_3$ (r_1, r_2, and r_3 = H, Me, *i*-Pr, or *t*-Bu) have been chosen as a basis for discussion because of the wide diversity of α-Me effects ranging from *usual downfield shifts* (example a) to *large inverted upfield shifts* (example c) (cf. Table I):

(a) $HO_2C^{13}CH_3 \rightarrow HO_2C^{13}CMeH_2$ $\Delta\delta = 7.0$ ppm

(b) $HO_2C^{13}CHMe_2 \rightarrow HO_2C^{13}CMeMe_2$ $\Delta\delta = 4.6$ ppm

(c) $HO_2C^{13}CH(t\text{-}Bu)_2 \rightarrow HO_2C^{13}CMe(t\text{-}Bu)_2$ $\Delta\delta = -8.8$ ppm

DARC–PULFO Method. The chemical shift of a ^{13}C atom depends on its environment which is composed of a functional moiety $\mathcal{E}_F$ and an alkyl moiety $\mathcal{E}_{Al}$. Two ordered populations of associated compounds differing only by the presence of hydrogen in the one and a methyl group in the other are studied by the PULFO method (Figure 1).

Each member of each population of associated compounds has an unchanging part, common to all members, that constitutes the population *focus*. This focus consists of ^{13}C, its functional environment $\mathcal{E}_F$, and one α substituent that is either a hydrogen atom or a methyl group.

The α-Me effect then corresponds to a Perturbation Unique and Localized on a Focus which is Ordered (PULFO). Topologically, the perturbation is *unique* because the H to Me substitution is always the same. It is *localized* because it is located on the same ^{13}C site. (This in no way imposes an a priori on the interaction mechanisms involved or on the nature of all the atoms affected, because the influence of the perturbation is spread over all the sites of a molecule.)

For topological transitions between secondary, tertiary, or quaternary sp^3 carbon sites, topological transition s,t ($^{13}CH_2r$ to $^{13}CHMer$) or t,q ($^{13}CHr_1r_2$ to $^{13}CMer_1r_2$), the difference in behavior between the two associated populations, corresponding to this focus perturbation, is expressed by the difference between the correlation laws reflecting the influence of the variable alkyl environment in each family.

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(13) With the DARC–PELCO method it is possible to estimate property perturbation resulting from formal successive substitutions of a compound in a series. The perturbation terms thus characterize *variable* perturbations introduced into the *ordered environment* of the focus. These terms are calculated recursively and are systematically associated with each new incoming site of the environment, even if, in reality, the perturbation is transmitted and redistributed over the entire molecule. In simple cases these perturbation terms are additive; otherwise, interaction terms must be introduced. A wide range of properties (reactivity, spectroscopy, pharmacodynamics[14,16]) have been studied in terms of topology by this method.

(14) (a) Dubois, J. E.; Doucet, J. P.; Tiffon, B. *J. Chim. Phys.* **1973**, 805. (b) Dubois, J. E.; Doucet, J. P. *Org. Magn. Reson.* 1978, *11*, 87. (c) Dubois, J. E.; Doucet, J. P. *J. Chem. Res., Synop.* **1980**, 82; *J. Chem. Res., Miniprint* **1980**, 1101. (d) Doucet, J. P.; Dubois, J. E. *J. Chem. Res., Synop.* **1980**, 84; *J. Chem. Res., Miniprint* **1980**, 1130.

(15) (a) Dubois, J. E.; Carabêdian, M. *Org. Magn. Reson.* **1980**, *14*, 264. (b) For alkyl radicals R, λ_R values are defined as the difference between sp carbon shifts in $R'C\equiv{}^{13}CR$ and $R'C\equiv{}^{13}CMe$. For R = Me, Et, *i*-Pr, and *t*-Bu, λ_R values are 0, 6.2, 10.7, and 13.5, respectively.

(16) (a) Dubois, J. E.; Laurent, D.; Aranda, A. *J. Chim. Phys.* **1973**, 1608; **1973**, 1616. (b) Dubois, J. E.; Laurent, D.; Bost, P.; Chambaud, S.; Mercier, C. *Eur. J. Med. Chem.—Chim. Ther.* **1976**, *3*, 225. (c) Panaye, A.; MacPhee, J. A.; Dubois, J. E. *Tetrahedron* **1980**, *36*, 759.

(17) Ejchart, A. *Org. Magn. Reson.* **1980**, *13*, 368; **1981**, *15*, 22.

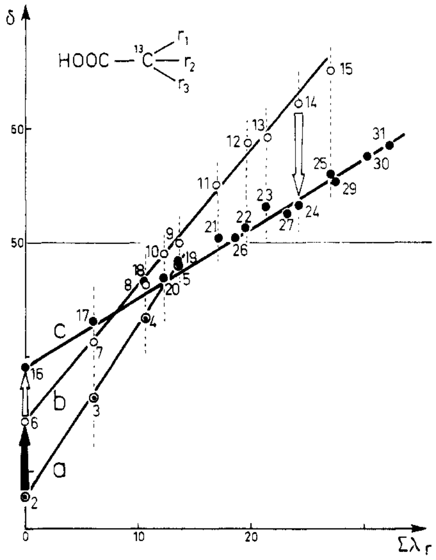

Figure 2. $\delta/\sum\lambda_r$ correlations for the C_1 carbon of carboxylic acids. Correlations a–c refer to secondary (⊙), tertiary (○), and quaternary (●) ^{13}C sites, respectively. The vertical distance between correlation lines represents α-Me effects: s,t transition, solid arrow; t,q transition, open arrow. Cf. ref 42 for compound numbering.

For each of these populations corresponding to ^{13}C sites with fixed degrees of substitution, the influence of the alkyl environment can be described via the scale of topological group parameters λ_r recently defined by Dubois and Carabédian.[15] This scale was obtained by summation of site parameters derived from a topological DARC–PELCO analysis of a reference population of aliphatic alkynes.[14b] Within compound populations where the environment of the ^{13}C site involves a variable alkyl environment $\mathcal{E}_{Al}$ and a complementary functional environment $\mathcal{E}_F$ that is held constant, the λ_r parameters represent alkyl effects on ^{13}C shifts. Linear eq 1 expresses alkyl group effects for compound populations with $\mathcal{E}_F{}^{13}Cr_1r_2r_3$.

$$\delta = \omega^c\sum\lambda_{ri} + \delta_0 \qquad (1)$$

In eq 1, ω^c represents the sensitivity of the ^{13}C site to structural perturbations, depending essentially on the nature of the chemical function and the connectivity of the ^{13}C site, $\sum\lambda_{ri}$ is the sum of the topological parameters of the alkyl subgroups bonded to ^{13}C, and δ_0 is the ^{13}C shift in the corresponding reference "limiting compound" (ri ≡ Me, so $\lambda_{ri} = 0$).

As chemical shifts are linear phenomena dependent on the λ parameters, the α-Me effects associated with the H to Me perturbation in the focus must therefore also be linearly dependent on the λ parameters (Figure 1). For two alkyl environments differing only in that one α substituent of one focus is a hydrogen atom and one α substituent of the other focus is a methyl group, the H to Me perturbation in the focus is expressed by the difference between the corresponding correlation equations, stressing the topological variation in the ^{13}C site environment.

The corresponding compounds are associated with a single value of $\sum\lambda_r$ (since $\lambda_{Me} = 0$). So, for a change from $c - 1$ to c in the connectivity of ^{13}C, it follows from $\delta^c = \omega^c\sum\lambda_r + \delta_0{}^c$ and $\delta^{c-1} = \omega^{c-1}\sum\lambda_r + \delta_0{}^{c-1}$ that

$$\delta^c - \delta^{c-1} = (\omega^c - \omega^{c-1})\sum\lambda_r + (\delta_0{}^c - \delta_0{}^{c-1}) \qquad (2)$$

which, rewritten as a PULFO equation, is

$$(\alpha\text{-Me})^{c-1,c} = \Delta\omega^{c-1,c}\sum\lambda_r + (\alpha\text{-Me})_0{}^{c-1,c} \qquad (3)$$

Equation 3 expresses the variations of α-Me SIS as a linear function of the λ_r parameters characterizing the nature of the ^{13}C alkyl environment. The $(\alpha\text{-Me})_0$ intercepts or "limiting effects" correspond to the α-Me effects between the "limiting structures", i.e., structures where the alkyl environment is limited to Me groups (λ = 0): $\mathcal{E}_F{}^{13}CH_2Me \rightarrow \mathcal{E}_F{}^{13}CHMe_2$ and $\mathcal{E}_F{}^{13}CHMe_2 \rightarrow \mathcal{E}_F{}^{13}CMe_3$, respectively.

$\delta/\sum\lambda_r$ Correlation Network for Carboxylic Acids. In Figure 2, the chemical shifts of the C_1 carbon (the carrier of the carboxylic group) are plotted vs. the $\sum\lambda_{ri}$ values for the ri subgroups composing the ^{13}C alkyl environment. This leads to three distinct equations.[18] For secondary sites:

$$\delta(HO_2C^{13}CH_2r_1) = \omega^s\lambda_{r1} + \delta_0{}^s \qquad (4)$$

$$\omega^s = 1.53,\ \delta_0{}^s = 27.3\ \text{ppm},\ n = 6,\ \rho = 0.998$$

For tertiary sites:

$$\delta(HO_2C^{13}CHr_1r_2) = \omega^t(\lambda_{r1} + \lambda_{r2}) + \delta_0{}^t \qquad (5)$$

$$\omega^t = 1.16,\ \delta_0{}^t = 34.3\ \text{ppm},\ n = 10,\ \rho = 0.997$$

For quaternary sites:

$$\delta(HO_2C^{13}Cr_1r_2r_3) = \omega^q(\lambda_{r1} + \lambda_{r2} + \lambda_{r3}) + \delta_0{}^q \qquad (6)$$

$$\omega^q = 0.60,\ \delta_0{}^q = 39.4\ \text{ppm},\ n = 15,\ \rho = 0.995$$

The evolvement of δ in each correlation reveals the influence of the alkyl branchings (characterized by λ_r) when the connectivity of a ^{13}C site is held constant. The gradual weakening of the correlation slopes as connectivity grows reveals the lessening sensitivity of the ^{13}C site to the alkyl perturbations. Although this is consistent with the general behavior observed in numerous families of compounds, the opposite behavior has been observed in some cyclic systems bearing highly polarizable heteroatomic substituent groups.[19] The existence of these linear correlations indicates that the additivity of subgroup effects in the alkyl environment is valid, as a first approximation, for all the carboxylic acid structures we examined, even highly branched compounds, i.e., ranging from $CHMe_2$ and CMe_3 to $CH(t\text{-}Bu)_2$ and $CMe(t\text{-}Bu)_2$.[20]

Given their topological origin, the λ_r parameters do not explicitly reflect those stereochemical influences whose importance in alicyclic series has been demonstrated, particularly by Schneider et al.[19] However, it is noteworthy that this single scale of λ_r topological parameters accounts for SIS for light molecules (in fast conformational interconversion) as well as for highly substituted molecules (where conformational preferences are more marked). It also describes alkyl group effects in widely varying chemical families.[21]

α-Me/λ_r Correlation for Carboxylic Acids. Predicting Direction and Amplitude of α-Me Effects. Applied to carboxylic acids, the general PULFO equation (eq 3) used with values obtained by eq 4–6 gives the following relations. For an s,t topological transition:

$$(\alpha\text{-Me})^{s,t} = -0.37\sum\lambda_r + 7.0 \qquad (7)$$

For a t,q topological transition:

$$(\alpha\text{-Me})^{t,q} = -0.56\sum\lambda_r + 5.1 \qquad (8)$$

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(18) The intercept of eq 4–6, derived from a least-squares treatment of all the data, is very close to the experimental values measured for $HO_2C^{13}CH_2Me$ (27.7 ppm), $HO_2C^{13}CHMe_2$ (34.2 ppm), and $HO_2C^{13}CMe_3$ (38.8 ppm).

(19) (a) Schneider, H. J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866. (b) Schneider, H. J.; Gschwendtner, W. *Ibid.* **1982**, *47*, 4216.

(20) Furthermore, a similar linear representation is obtained for tertiary or quaternary sites when we characterize r subgroup effects with the scale of shifts induced in $HO_2C^{13}CH_2r$ primary acids. This observation confirms the additivity of subgroup effects and the linear evolvement of the SIS, provided the connectivity of ^{13}C remains constant and a suitable scale for alkyl group effects is used.

(21) Cf. ref 15a and Table II.

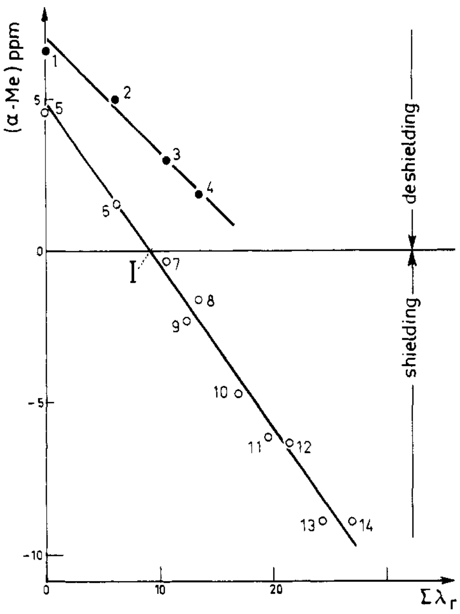

Figure 3. Alkyl environment influence on α-Me effects associated with the transformation of ^{13}CH into ^{13}CMe in alkylcarboxylic acids: inversion point I separates the shielding and (usual) deshielding regions. Cf. ref 43 for compound numbering.

In the plot of δ vs. $\sum\lambda_r$ (Figure 2), where the substituent parameters λ_r are standardized[15b] to the value $\lambda_{Me} = 0$, the α-Me effect is shown by the vertical distance between correlation lines a and b for the s,t transition and between b and c for the t,q transition.[22] Figure 3 shows the corresponding α-Me effects for s,t or t,q transitions of alkyl carboxylic acids and the corresponding equations (eq 7 and 8). In eq 7 and 8, the term $\Delta\omega\sum\lambda_r$ and the term $(\alpha\text{-Me})_0$ correspond to shifts *in opposite directions*. The $(\alpha\text{-Me})_0$ limiting effect conveys a downfield signal shift in the usual direction of α-deshielding effects. $\Delta\omega^{c-1,c}\sum\lambda_r$ corresponds to an upfield contribution (since the sensitivity of a c connectivity site is less than that of a $c - 1$ connectivity site) which lessens the α-Me effects when $\sum\lambda_r$ increases, i.e., when there are successive branchings β to the ^{13}C site.

In agreement with experimental results, eq 7 and 8 (seen in Figure 3) predict a *gradual and continued weakening of α effects*, in particular *their inversion* (leading to unusual shielding α-Me shifts) for eq 9. So, for the t,q tran-

$$(\textstyle\sum\lambda_r)_I > (\alpha\text{-Me})_0/\Delta\omega \qquad (9)$$

sition of carboxylic acids, $\sum\lambda_r > 9.1$. This predicted value nearly corresponds to the transformation of $HO_2C^{13}CHMe(i\text{-Pr})$ into $HO_2C^{13}CMe_2(i\text{-Pr})$ ($\Delta\delta = -0.3$ ppm; $\sum\lambda_r = 10.7$). It is noted that in the s,t transition, only one subgroup can vary, and the maximal range of λ_r variation is therefore $0 < \lambda < 13.5$, corresponding to R = *t*-Bu (since the furthest substitutions are associated with γ shielding contributions diminishing λ_r). The inversion point is not reached in this case; only a gradual attenuation of α-Me effects from 6.5 to 1.8 ppm [for the transformation of $HO_2C^{13}CH_2(t\text{-Bu})$ into $HO_2C^{13}CHMe(t\text{-Bu})$] is observed.

The proposed PULFO model confirms and extends the pioneering observations of Grutzner et al.[2] regarding the weakening of α-Me effects for the first structures in the alkane series when the total number of α and β substituents increases. Moreover, the PULFO model clearly distinguishes the two main factors intervening in the α-Me effects observed (Figure 3). *Branchings in the alkyl environment* determine the position of the points on the correlation lines. The influence of the ^{13}C *site connectivity* (α branching) and of its *functional environment* (chemical families) determines the slope $\Delta\omega$ and the intercept $(\alpha\text{-Me})_0$ of the correlation lines.[23]

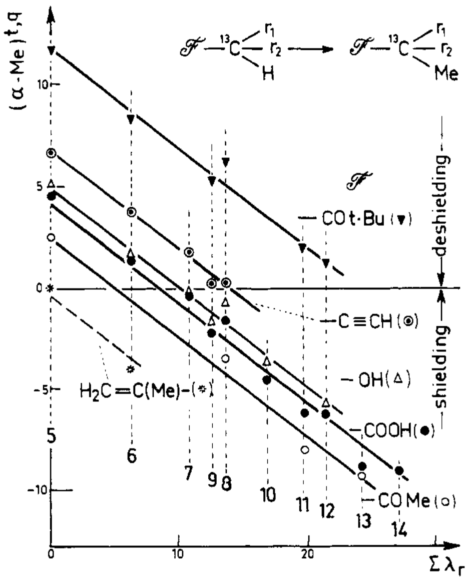

Figure 4. α-Me vs. $\sum\lambda_r$ parallel straight-line network for the t,q transition: alkyl environment influence on the evolvement of $(\alpha\text{-Me})^{t,q}$ effects for *various functionalized families*. Owing to the parallelism of correlation lines, *unusual α-Me shielding effects* appear more or less early, according to $(\alpha\text{-Me})_0$ values. Cf. ref 43 for compound numbering.

Influence of Functional Groups on α-Me Effects. One advantage of the PULFO model is that the role of the ^{13}C site alkyl environment $\mathscr{E}_{Al}$ can be isolated. Thereafter, it is possible to characterize the influence of the ^{13}C site functional environment $\mathscr{E}_F$ on the shifts in α-Me effects.

The functional environment $\mathscr{E}_F$ can affect the following: (a) ω sensitivities and, consequently, the $\Delta\omega$ slopes of α-Me correlations; this corresponds to a mutual $\mathscr{E}_{Al}/\mathscr{E}_F$ interaction modulating the influence of alkyl environment $\mathscr{E}_{Al}$ according to the nature of the functional environment $\mathscr{E}_F$; (b) $(\alpha\text{-Me})_0$ limiting effect; this conveys the influence of the functional environment $\mathscr{E}_F$, itself on the structural moiety defined by the ^{13}C site and its first carbon neighbors in the $\mathscr{E}_{Al}$ environment.

PULFO Model Applied to Several Functional Families. The proposed model has so far successfully been extended to several chemical families corresponding to widely varying functional environments: $\mathscr{E}_F = CO_2H$ (carboxylic acids), COR (ketones, with R = Me, *i*-Pr, *t*-Bu), NH_2 (amines), C≡CH (alkynes), $C(Me){=}CH_2$ (alkenes), and CH_3 or H (alkanes). For all of these, good $\delta/\sum\lambda_r$ linear correlations are obtained when the connectivity of the ^{13}C sites is constant. This demonstrates the advantage of this λ parameter scale in evaluating δ_s and makes it possible to deduce a linear PULFO model of α-Me effects for all these structures.

The $\delta/\sum\lambda_r$ linear correlations established for secondary, tertiary, and quaternary ^{13}C sites, as well as corresponding $\alpha\text{-Me}/\sum\lambda_r$ equations for s,t or t,q topological transitions are given in Table II. As seen in Figures 4 and 5, this PULFO model covers a wide range of shifts; there is a good

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(22) Similarly, the α-Me effect associated with the s,q transition for the transformation of $^{13}CH_2r_1$ into $^{13}CMe_2r_1$ corresponds to the distance between correlations a and c, respectively.

(23) So, α-Me effects range from 1.8 to −2.3 ppm for pairs **4**, **7**, and **9** in Table I, leading to carboxylic acids bearing the same number of five methyl groups α and β to ^{13}C.

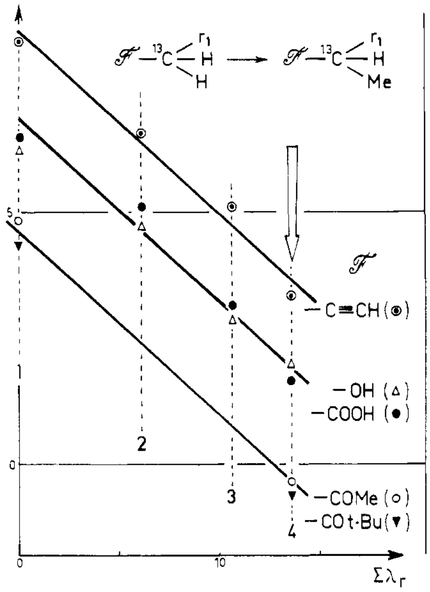


Figure 5. α-Me vs. $\sum\lambda_r$ parallel straight-line network for the s,t transition: alkyl environment influence on the evolvement of $(\alpha\text{-Me})^{s,t}$ effects for *various functionalized families.* Owing to the maximal range of λ_r variations (0–13.5), as shown by the arrow, we observed only *attenuation, but no important inversion,* for the compounds studied. Cf. ref 43 for compound numbering.

fit between α-Me/$\sum\lambda_r$ correlations and experimental α-Me values for very different functional groups.[24]

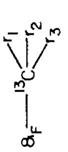
Influence of $\mathscr{E}_F$ on ω and $\Delta\omega$. In Table II, ω sensitivities vary greatly with ^{13}C site connectivity but vary to a much lesser extent with the nature of functional environments.

In agreement with Ejchart's exploratory results[17] (on a limited scale of primary alkyl groups), there is a rough tendency for the ω sensitivity to alkyl effects to decrease when the electronegativity of the functional group grows. Nonetheless, the high values of the slopes observed with C≡CH for primary sites do not fit into the expected sequence merely on the basis of electronegativity[29] (Table II).

On evaluation of α-Me effects in s,t or t,q transitions, only $\Delta\omega^{s,t} = \omega^t - \omega^s$ or $\Delta\omega^{t,q} = \omega^q - \omega^t$ differences are used in PULFO eq 3. So it is noteworthy that for a given transition, these variations of sensitivity, $\Delta\omega$, remain practically constant whatever the nature of the functional environment $\mathscr{E}_F$. This near constancy for s,t and t,q transitions leads to common values of ca. −0.35 for $\Delta\omega^{s,t}$ and ca. −0.50 for $\Delta\omega^{t,q}$ (except for $\mathscr{E}_F$ = Me; cf. Table II).

The plot of α-Me vs. $\sum\lambda_r$ for various $\mathscr{E}_F$ leads, in a first approximation, to a *network of nearly parallel correlations*

Table II. $\delta/\Sigma\lambda_r$ Correlations and Linear Model of α-Me Effects:[a] $\alpha\text{-Me} = \Delta\omega\Sigma\lambda_r + (\alpha\text{-Me})_0$



	^{13}CH$_2$r$_1$				^{13}CHr$_1$r$_2$				^{13}Cr$_1$r$_2$r$_3$				s,t transition		t,q transition		
	n	ω^s	δ_0^s	ρ	n	ω^t	δ_0^t	ρ	n	ω^q	δ_0^q	ρ	$-\Delta\omega^{s,t}$	$(\alpha\text{-Me})_0^{s,t}$	$-\Delta\omega^{t,q}$	$(\alpha\text{-Me})_0^{t,q}$	ref[b]
H	14	1.89	4.2	0.982	31	1.60	13.7	0.992	25	1.04	22.5	0.983	0.29	9.5	0.56	8.8	*c*
Me	7	1.51	15.8	0.997	11	1.04	23.3	0.997	8	0.42	28.0	0.960	0.47	7.5	0.62	4.7	*d*
COOH	6	1.53	27.3	0.998	10	1.16	34.3	0.997	15	0.60	39.4	0.995	0.37	7.0	0.56	5.1	*e*
COMe	6	1.44	36.2	0.999	5	1.07	41.1	0.997	9	0.57	43.6	0.998	0.37	4.9	0.50	2.5	*e*
CO(i-Pr)	3	1.46	35.2	0.990	4	1.10	40.1	0.998	4	0.59	45.8	0.999	0.36	4.9	0.51	5.7	*e*
CO(t-Bu)	3	1.41	29.9	0.992	6	1.08	35.2	0.997	6	0.60	46.7	0.998	0.33	5.3	0.48	11.5	*e*
C≡CH	4	1.56	11.7	0.994	5	1.21	20.1	0.998	5	0.72	27.0	0.991	0.35	8.4	0.49	6.9	*f*
H$_2$C=C(Me)	6	1.59	30.7	0.999	4	1.28	35.5	0.999	5	0.68	35.9	0.990	0.31	4.8	0.60	0.4	*e, g*
OH	9	1.20	56.4	0.992	11	0.88	63.3	0.990	6	0.39	68.4	0.994	0.32	6.9	0.49	5.1	*h*
NH$_2$	6	1.31	36.6	0.999	6	0.93	42.8	0.998					0.38	6.2			*i*

[a] n = number of points; ρ = correlation coefficient. [b] Data origin for establishing $\delta/\Sigma\lambda$ correlations. [c] Reference 15. [d] References 9–11. [e] This work and references 5 and 6. [f] References 14b–d. [g] Reference 25. [h] References 17, 26, and 27. [i] References 17 and 28.

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(24) For 136 values of α-Me effects ranging from 11.5 to −10.0 ppm calculated by the PULFO model, we obtain $(\alpha\text{-Me})_{\text{obsd}} = 0.96\ (\alpha\text{-Me})_{\text{calcd}} + 0.11$ (ρ = 0.979, sd = 0.8). For all of the α-Me values observed and calculated, cf. Table VI in the supplementary material.

(25) (a) Couperus, P. A.; Clague, A. D. H.; Van Dongen, J. P. C. M. *Org. Magn. Reson.* **1976**, *8*, 426. (b) De Haan, J. W.; Van de Ven, L. J. M. *Ibid.* **1973**, *5*, 147. (c) De Haan, J. W.; Van de Ven, L. J. M.; Wilson, A. R. N.; Van der Hout-Lodder, A. E.; Altona, C.; Faber, D. H. *Ibid.* **1976**, *8*, 477.

(26) Ejchart, A. *Org. Magn. Reson.* **1977**, *9*, 351.

(27) (a) Roberts, J. D.; Weigert, F. J.; Kroschwitz, J. I.; Reich, H. J. *J. Am. Chem. Soc.* **1970**, *92*, 1338. (b) Williamson, K.L.; Clutter, D.R.; Emch, R.; Alexander, M.; Burroughs, A. E.; Chua, C.; Bogel, M. E. *Ibid.* **1974**, *96*, 1471.

(28) (a) Eggert, H.; Djerassi, C. *J. Am. Chem. Soc.* **1973**, *95*, 3710. (b) For $\mathscr{E}_F$ = NH$_2$, no $\delta/\sum\lambda_r$ correlation has been attempted, owing to the few values available for quaternary ^{13}C sites.

(29) (a) Wilmshurst, J. K. *J. Chem. Phys.* **1957**, *27*, 1129. (b) Reynolds, W. F.; Taft, R. W.; Marriott, S.; Topsom, R. D. *Tetrahedron Lett.* **1982**, *27*, 1055.

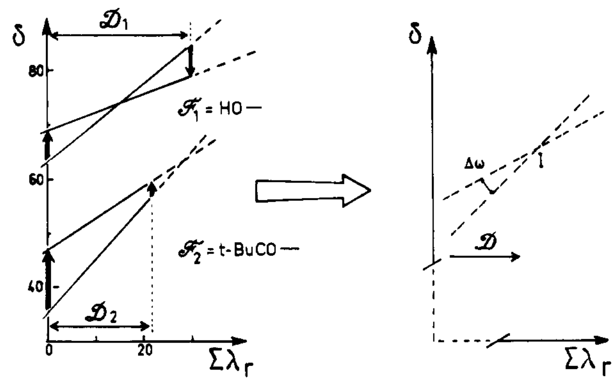


Figure 6. Reduced beam of $\delta/\sum\lambda_r$ correlations. The differential sensitivity $\Delta\omega^{c-1,c}$ remains nearly constant for a given transition from $c - 1$ to c. All the corresponding $\delta/\sum\lambda_r$ correlation beams may be formally reduced by rotation–translation to a single beam. For each correlation pair, the inversion point position and the slope of the beam with respect to axes δ and $\sum\lambda_r$ depend on ^{13}C connectivity and on the nature of its functionalized environment. $\mathscr{D}$ is the area studied.

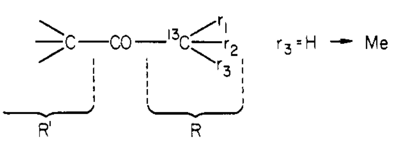
(Figure 4 and 5). *The existence of this parallel network, for a given transition, indicates that the nature of the functional environment $\mathscr{E}_F$ does not greatly modify the influence of the alkyl environment $\mathscr{E}_{Al}$ on α-Me effects.* However, it does considerably affect the (α-Me)$_0$ limiting effects corresponding to the intercept of the α-Me/$\sum\lambda_r$ correlations, as will be discussed later. These limiting effects characterize interactions between $\mathscr{E}_F$ and the first carbon neighbors of the ^{13}C site. According to Beierbeck and Saunders' model[11] proposed for the evaluation of ^{13}C shifts in alkanes, the introduction of a methyl group on the ^{13}C site can intervene in two different ways: by modifying existing interactions owing to the replacement of a ^{13}CH bond by a ^{13}CC bond and by changing the statistical weights of these interactions owing to the relative stability of the corresponding conformers. It is thus noteworthy that, for the functionalized examples studied here, the nature of the function, although modifying the limiting effects the (α-Me)$_0$, does not greatly change the pattern of alkyl environment influence on observed α-Me shifts.

Within this linear model framework, the plot of δ vs. $\sum\lambda_r$ leads to a correlation beam according to the ^{13}C site connectivity and the $\mathscr{E}_F$ environment nature. On consideration of the nearly constant values of Δω, the entire set of correlations corresponding to a given transition for various functional environments can be regarded as resulting from a single beam reduced to two secant $\delta/\sum\lambda_r$ correlations. The various correlations experimentally observed between chemical shifts and topological parameters can be formally deduced from this unique beam by a translation–rotation operation (Figure 6).

As previously established, the overall behavior of α-Me effects results from the superposition of a *decreasing monotonic evolvement* and of the *specific influences* observed on the (α-Me)$_0$ limiting effects. This evolvement, expressed by $\Delta\omega\sum\lambda_r$, is nearly identical for all the structures considered (as shown by the parallelism of α-Me/$\sum\lambda_r$ correlations) and tends to diminish the α-Me effects algebraically as the branchings increase.

When the chemical shifts of the limiting compounds are known, the parallelism of the network makes it possible to determine the alkyl environment where annulment, followed by inversion, of the usually deshielding α-Me effects will begin. By adoption of the previously defined common values of −0.35 (for $\Delta\omega^{s,t}$) and −0.50 (for $\Delta\omega^{t,q}$) for different chemical families, eq 9 gives $(\sum\lambda_r)_I$ = 2.8 (α-Me)$_0^{s,t}$ for transition s,t and $(\sum\lambda_r)_I$ = 2.0 (α-Me)$_0^{t,q}$ for transition t,q.

Table III. α-Me Effects for the C$_1$ Carbon of Aliphatic Ketones[a]



Σλr	r$_1$	r$_2$	α-Me R' = Me	α-Me R' = *i*-Pr	α-Me R' = *t*-Bu
0	H	Me	4.8	5.5	4.4
13.5	H	*t*-Bu	−0.3		−0.4
0	Me	Me	2.5	5.7	11.7
6.2	Me	Et		2.3	8.4
13.5	Me	*t*-Bu	−3.4		6.3
12.4	Et	Et		0.8	5.2
19.7	Et	*t*-Bu	−7.9		2.0
21.4	*i*-Pr	*i*-Pr			1.2
24.2	*i*-Pr	*t*-Bu	−9.1		

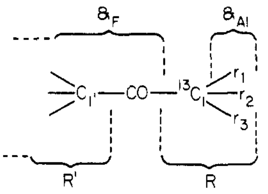
[a] In parts per million; 10% w/v solutions in CCl$_4$.

Experimental observation of inverted α-Me effects is thus subject to the magnitude of (α-Me)$_0$ effects and to the size of the areas studied characterized from the reference limiting structures by the range of $\sum\lambda_r$ variations. In the case of transition s,t, the highest value of λ_r is limited to 13.5 (r = *t*-Bu), so the inversion can be effectively observed only if (α-Me)$_0$ < 4.8, whereas in the case of transition t,q the size of the areas studied is generally limited by the experimental restraints related to compound availability.

A noteworthy situation with respect to the universally accepted rule about α-Me deshielding effects would be one involving an *entire chemical family located beyond the inversion point*, in which case only inverted effects (upfield SIS) would be observed. Such is the actual case for the t,q transition in alkenes $H_2C{=}C(Me)^{13}Cr_1r_2$≈ (≈ = H or Me). The (α-Me)$_0$ effect is very small (Δδ = 0.1 ppm between $H_2C{=}C(Me)^{13}CMe_2H$ and $H_2C{=}C(Me)^{13}CMe_3$), and the attenuation term $\Delta\omega\sum\lambda_r$, which is dependent only on alkyl group branching, gives rise to upfield α-Me effects. The only pair of associated compounds which can be extracted from available experimental data confirms this inversion: Δδ = −4.0 ppm between $H_2C{=}C(Me)^{13}CEtMeH$ and $H_2C{=}CC(Me)^{13}CEtMe_2$. The value calculated from the PULFO equations in Table II is −3.4 ppm.

(α-Me)$_0$ Limiting Effects: Functional Environment and Conformational Factors. For the various chemical families studied, (α-Me)$_0$ effects vary largely according to the nature of the functional environment: from 0.1 ppm ($\mathscr{E}_F$: $CH_2{=}CHMe$) to 11.7 ppm ($\mathscr{E}_F$: CO-*t*-Bu) (Figure 4). The influence of the electronic properties (particularly polarity) of the functional groups present is expressed in these variations. However, it is noteworthy that considerable modifications in (α-Me)$_0$ limiting effects can also be observed within a chemical family associated with a same functional group (e.g., from 2.5 to 11.7 ppm for saturated aliphatic ketones; cf. Table III and Figure 4). This suggests that, along with *electronic influences, steric or conformational contributions* also play an important role. It is hard to dissociate electronic influences from conformational contributions because the topography and the general geometry of the molecules depend on the interactions between all the sites and their local environments, $\mathscr{E}_F$, $\mathscr{E}_{Al}$, ... To assess the influence of inductive terms on α effects, relations between chemical shifts and electronegativity or CNDO electron densities are often

Chart I[a]



[a] R', r_1, r_2 = Me, Et, *i*-Pr, *t*-Bu; r_3 = H, Me.

Table IV. $(\alpha\text{-Me})_0$ Limiting Effects (ppm) in Alkenes for the Transformation of $H_2C{=}C(R')^{13}Cr_1r_2H$ into $H_2C{=}C(R')^{13}Cr_1r_2Me$ (s,t Transition, r_1 = Me, r_2 = H; t,q Transition, $r_1 = r_2$ = Me)

R'	Me	Et	*i*-Pr	*t*-Bu
$(\alpha\text{-Me})_0^{s,t}$	4.6	5.3	5.6	5.0
$(\alpha\text{-Me})_0^{t,q}$	0.1	1.9	4.1	9.0

Table V. Influence of R' on $(\alpha\text{-Me})_0^{t,q}$ Limiting Effects in Ketones for a Transformation of $R'CO^{13}CMe_2H$ into $R'CO^{13}CMe_3$

R'	connectivity of R'	E_S' steric parameters[a]	$(\alpha\text{-Me})_0^{t,q}$, ppm
i-Pr	2	−0.48	5.7
t-Bu	3	−1.43	11.7
$CHEt_2$	2	−2.0	4.0
CMe_2(*t*-Bu)	3	−5.4	10.7

[a] Reference 33.

used.[19b] Such a rough correlative tendency between δ and group electronegativities is obvious for $\mathcal{E}_F{}^{13}Cr_1r_2r_3$ (r_1, r_2, r_3 = Me or H). However, the elucidation of $(\alpha\text{-Me})_0$ effects from the functional effect angle is not addressed in this study which is more oriented toward the elucidation of conformation effects.

Literature data on the action of steric effects are not always in agreement. For instance, in explanation of exalted α effects for the transformation of ^{13}CH into ^{13}COH or ^{13}CMe, steric interactions have been cited,[2,30] whereas an inverted evolvement (attenuation) also has been reported.[31,32]

As for the study of topographical data, an analysis of the perturbations associated with the proximity interactions between the ^{13}C site and its immediate neighbors in the alkyl and functional environments, $\mathcal{E}_{Al}$ and $\mathcal{E}_F$, will be dealt with in our PULFO model. The ketone family at our disposal is very rich in subpopulations with very varied $(\alpha\text{-Me})_0$ effects (Chart I) and lends itself well to methodological studies. *For the t,q transition*, the C_1 carbon atom in these structures displays *sizeable variations in α-Me effects* according to the nature of R', with an outright rise in induced shifts for R' = *t*-Bu. When R' varies from Me to *t*-Bu, $(\alpha\text{-Me})_0$ limiting effects are 2.5, 3.4, 5.7, and 11.7 ppm, respectively. In contrast, *for the s,t transition, the nature of R' has little bearing on α-Me effects* (cf. the correlations for R' = Me or *i*-Pr and R' = *t*-Bu in Table II and Figures 4 and 5). A similar behavior is also observed for the corresponding alkenes $H_2C{=}C(R')^{13}Cr_1r_2r_3$ (r_1, r_2, r_3 = H or He) (Table IV).

Using a few pairs of $R'CO^{13}CMe_2H$ and $R'CO^{13}CMe_3$ ketones (cf. Table V), we checked that the exaltation of the $(\alpha\text{-Me})_0$ limiting effects (for instance, between *t*-$BuCO^{13}CMe_2H$ and *t*-$BuCO^{13}CMe_3$ in Figure 4) is not related to the overall steric crowding of group R', measured by the values of the E_S' constants.[33] This exaltation is indeed dependent on *the degree of substitution of R'* and is very marked for tertiary R' groups. Thus, the $(\alpha\text{-Me})_0$ effects of the secondary radicals R' = *i*-Pr and $CHEt_2$ are close to each other (5.7 and 4.0 ppm) but are much smaller than the 11.7 ppm observed for the tertiary group R' = *t*-Bu despite its comparable steric crowding (Table IV). Likewise, the $(\alpha\text{-Me})_0$ values associated with R' = t-Bu and CMe_2(*t*-Bu) (11.7 and 10.7 ppm) are close to each other (the same degree of substitution but very different steric effects).

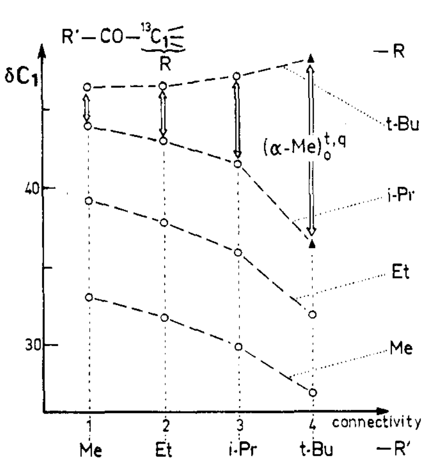


Figure 7. Conformational influences on $(\alpha\text{-Me})_0$ effects for $R'CO^{13}Cr_1r_2r_3$ aliphatic ketones. The vertical distance between points corresponding to a same R' value for R = *i*-Pr or *t*-Bu represents the $(\alpha\text{-Me})_0$ effects for the t,q transition from $R'CO^{13}CHMe_2$ to $R'CO^{13}CMe_3$. Points designated by ▲ correspond to important interactions in the privileged conformation.

Filiations in Ketone Series. We suggest gathering the $(\alpha\text{-Me})_0$ values for the ketones in a diagram where these limiting perturbations appear as the differences between the shifts associated with the limiting compounds. In Figure 7, C_1 carbon atom shifts of radicals R = $^{13}Cr_1r_2r_3$ (r_1, r_2, r_3 = H or Me) and the degree of substitution of R' for groups limited to the first neighboring carbon atoms are compared. Analysis of the evolvement of δ (C_1) vs. R' connectivity (fixed R) allows location of the $(\alpha\text{-Me})_0$ perturbations of subpopulations of ketones organized into a filiation, or sequence, of growing connectivity that is also provided with the associated conformational data.

For a given R' radical, the values of $(\alpha\text{-Me})_0$ for the passage of R = Et to *i*-Pr (s,t transition) or of R = *i*-Pr to *t*-Bu (t,q transition) correspond to the vertical distance between the curves associated with these R groups. In a parallel manner, the curves corresponding to the same R radical (with ^{13}C at a fixed degree of substitution) describe the influence that successive methyl group substituents at the γ-position of a ^{13}C atom have on this site.

Two types of behavior are observed when R' varies from Me to *t*-Bu: a small *downfield shift* in the $^{13}C_1$ signal for R = *t*-Bu (pronounced for R' = *t*-Bu) and an *upfield shift* for R = Me, Et, and *i*-Pr. The corresponding curves are practically parallel but display a more pronounced variation in the transformation of *i*-$PrCO^{13}CHMe_2$ into *t*-$BuCO^{13}CHMe_2$.

These two opposite behavior functions, i.e., downfield shift for R = *t*-Bu and heightened upfield shift for R =

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[30] Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1974**, *52*, 870.

[31] Ayer, W. A.; Browne, L. M.; Fung, S.; Stothers, J. B. *Can. J. Chem.* **1976**, *54*, 3272.

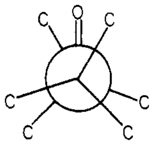
[32] Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1974**, *52*, 308; **1977**, *55*, 841.

[33] This global steric effect of R' is evaluated by using the revised Taft E_S' parameters.[18c]

i-Pr, express the exalted (α-Me)$_0$ effects observed for the t,q transition of the *t*-BuCO^{13}Cr$_1$r$_2$r$_3$ ketones. When R = Et or *i*-Pr and when R′ varies, the near parallelism between the curves for δ vs. R′ (Figure 7) indicates no noticeable variation in the (α-Me)$_0$ effects for the s,t transition of the R′CO^{13}Cr$_1$r$_2$H ketones.

The lack of a statisfactory theory to interpret the various site interactions makes it difficult to account for the (α-Me)$_0$ effects for a population of compounds in which some have a good deal of conformational mobility while others are relatively blocked. With Suter's results[34] and our own molecular mechanics calculations,[35] the trends upon establishing some of the most privileged conformations in families with a fixed R group become apparent. Some conclusions on interaction variations can be drawn with the conformational filiation by the family concept.

In the series where R = *t*-Bu, when methyl groups with very low polarity are introduced at the position γ to ^{13}C, the ^{13}C$_1$ signal remains practically in the same position; this is consistent with the weak sensitivity of a quaternary site, because the perturbations induced on ^{13}CC bonds are largely offset by the local tetrahedral symmetry around the ^{13}C site.[36]



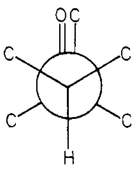
privileged conformation of (*t*-Bu)CO(*t*-Bu)

However, there is a 1.7-ppm downfied shift between R′ = Et and R′ = *t*-Bu. Assumably, these paramagnetic effects are associated with *1,4-syn-axial interactions* because the preferential conformations of EtCO^{13}CMe$_3$ and *t*-BuCO^{13}CMe$_3$ correspond to forms with a carbonyl group nearly bi-eclipsed by CC bonds. So the passage of R′ from Et to *t*-Bu would give rise to two interactions between the nearly parallel bonds ^{13}C$_1$Me and C$_{1'}$Me. When this type of syn-axial interaction between CC or C–heteroatom bonds occurs in cyclic systems, it causes a noticeable downfield shift for the terminal carbons of these fragments and for the carbon atoms carrying these terminal carbons.[4,36,37] For example, from Stothers' results[4] on the norbornane series, 3.5-ppm shift between *endo*-2-norbornanol and its *endo*-6-methylated derivative or a 1.6-ppm shift between *exo*-2-norbornanol and its *syn*-7-methylated derivative can be deduced for the C$_2$ carbon. However, this type of interaction is rarer in acyclic series; in Me$_3$CCH$_2$R′ alkanes (R′ varies from Me to *t*-Bu) it has been detected in the methyl groups belonging to *t*-Bu and ascribed to second-order field effects.[36a] In this alkane family, which is isotopologous to the ketone series under scrutiny, the quaternary carbon atom shifts downfield by 1.8 ppm between R′ = Et and R′ = *t*-Bu; this shift is very similar to the downfield shift we observed for *t*-Bu ketones.

These 1,4-syn interactions seem less efficient in these acyclic systems (ketones, alkanes) than in cyclic structures with fixed geometry. This might be related to a *relaxation of steric constraints* by slightly rotating strictly eclipsed *t*-Bu groups[38] or by *opening the focal angle t-Bu–Ct-*Bu. These large distortions in the standard geometric parameters for structures with two geminal tertiary groups are confirmed by our molecular mechanics calculations and experimental data.[35] These exceptional steric constraints also give rise to sudden deviations for various physicochemical parameters. Such deviations have been observed for δ (^{13}C) of the sp^2 carbon, for $\nu_{\max}$ of the n–π^* transition, and for ν_{CO} frequencies of the IR stretching vibration.[35,39]

Similar sudden deviations are also known in ^{13}C NMR for both sp^2 carbons in H$_2$C=CRR′ alkenes (when both R and R′ are tertiary groups).[39] The influence of such steric repulsions from geminal *t*-Bu groups was just recently confirmed by ^{17}O NMR for sulfones and sulfoxides.[40]

In the series where R = Me, Et, and *i*-Pr, as expected when methyl groups are introduced at the position γ to ^{13}C, they induce upfield shifts associated with interactions between ^{13}C$_1$H and C$_{1'}$Me. The structures in these series rotate practically freely, and the amplitude of the SIS (ca. −2 ppm) is comparable to the average value observed in other more well-known freely rotating acyclic systems (ca. −2.5 ppm in alkanes). However, γ-Me effects tend to increase in the least mobile structures. Thus an upfield shift of −5 ppm is observed in going from *i*-PrCO^{13}CHMe$_2$ to *t*-BuCO^{13}CHMe$_2$, a molecule which, by Suter's molecular mechanics calculations, has a blocked conformation.[34] The carbonyl group in this conformation is eclipsed by one of the CC bonds of the *t*-Bu group, and it bisects the *i*-Pr group. This geometry results in two γ-gauche shielding interactions between ^{13}CH and the bonds C$_{1'}$Me, which can explain the rise observed in the upfield shift. This strong shielding is the main reason for the very high value of the (α-Me)$_0$ effect for R′ = *t*-Bu. In short, the entire network of curves plotted for δ(C$_1$) vs. R′ connectivity (Figure 7) is accounted for satisfactorily by *conformational filiations*, and *the sizeable exaltation in (α-Me)$_0$ effects between (i-Pr)CO(t-Bu) and (t-Bu)CO(t-Bu)* is explained by *a comparison between the interactions in the privileged*



blocked conformation of (*i*-Pr)CO(*t*-Bu)

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(38) Molecular mechanics calculations (with the MM2 program) indicates a slight deviation from a strict eclipsing of the CO group in the preferred conformation: rotation in the opposite direction of ca. 15° for the two *t*-Bu groups around the C$_1$C$_0$ and C$_{1'}$C$_0$ bonds.

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(41) At this point in the discussion of γ effects, there is no need to know whether the upfield shifts result from nonbonded interactions introduced by the incoming γ group or from the removal of the hydrogen atom on the β-substituent. Cf.: Beierbeck, H.; Saunders, J. K. *Can. J. Chem.* **1976**, *54*, 2985.

(42) For Figure 2, the numbers refer to the following radicals: 1, ^{13}CH$_3$; 2, ^{13}CH$_2$Me; 3, ^{13}CH$_2$Et; 4, ^{13}CH$_2$(*i*-Pr); 5, ^{13}CH(*t*-Bu); 6, ^{13}CHMe$_2$; 7, ^{13}CHMeEt; 8, ^{13}CHMe(*i*-Pr); 9, ^{13}CHMe(*t*-Bu); 10, ^{13}CHEt$_2$; 11, ^{13}CHEt(*i*-Pr); 12, ^{13}CHEt(*t*-Bu); 13, ^{13}CH(*i*-Pr)$_2$; 14, ^{13}CH(*i*-Pr)(*t*-Bu); 15, ^{13}CH(*t*-Bu)$_2$; 16, ^{13}CMe$_3$; 17, ^{13}CMe$_2$Et; 18, ^{13}CMe$_2$(*i*-Pr); 19, ^{13}CMe$_2$(*t*-Bu); 20, ^{13}CMeEt$_2$; 21, ^{13}CMeEt(*i*-Pr); 22, ^{13}CMeEt(*t*-Bu); 23, ^{13}CMe(*i*-Pr)$_2$; 24, ^{13}CMe(*i*-Pr)(*t*-Bu); 25, ^{13}CMe(*t*-Bu)$_2$; 26, ^{13}CEt$_3$; 27, ^{13}CEt$_2$(*i*-Pr); 28, ^{13}CEt$_2$(*t*-Bu); 29, ^{13}CEt(*i*-Pr)$_2$; 30, ^{13}C(*i*-Pr)$_3$.

(43) In Figures 3–5, the s,t and t,q topological transitions correspond to a transformation from $\mathscr{E}_F$ ^{13}CH$_2$r$_1$ to $\mathscr{E}_F$ ^{13}CHMer$_1$ and from $\mathscr{E}_F$ ^{13}CHr$_1$r$_2$ to $\mathscr{E}_F$ ^{13}CMer$_1$r$_2$. The numbers refer to the following radicals (r$_1$ or r$_1$, r$_2$): 1, Me; 2, Et; 3, *i*-Pr; 4, *t*-Bu; 5, Me,Me; 6, Me,Et; 7, Me, *i*-Pr; 8, Me, *t*-Bu; 9, Et, Et; 10, Et, *i*-Pr; 11, Et, *t*-Bu; 12, *i*-Pr, *i*-Pr; 13, *i*-Pr, *t*-Bu; 14, *t*-Bu, *t*-Bu.

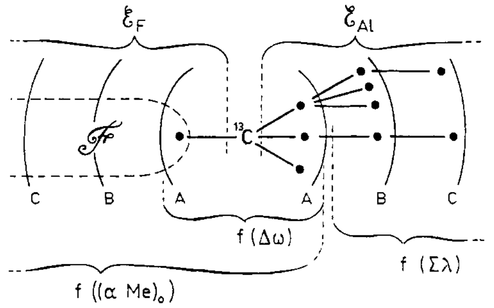

Figure 8. Active environment effects on the different terms of the DARC–PULFO model for a sp^3 ^{13}C site. In the examples investigated, the differential sensitivity $\Delta\omega^{c-1,c}$ depends on the sites directly bonded to the ^{13}C site (rank A atoms). The limiting effect $(\alpha\text{-Me})_0{}^{c-1,c}$ is affected by functional environment $\mathscr{E}_F$ and rank A atoms of alkyl environment $\mathscr{E}_{Al}$. The term $\sum\lambda_r$ is related to the presence of carbons atoms in ranks B and C of the alkyl environment $\mathscr{E}_{Al}$. $f((\alpha\text{-Me})_0)$ is the range of influence of $(\alpha\text{-Me})_0$ etc.

conformations.

Conclusion

The use of topological models in ^{13}C NMR is particularly attractive insofar as chemical shifts minutely reflect the influence exerted by the various parts of a ^{13}C environment. The complexity of α-Me effects that is observed when they are analyzed is partly due to the major role played by the *degree of substitution* of the resonant atom and partly due to the *overlapping of the various active environments* acting on the different components of the α-Me effects. These different contributions can be identified and analyzed with the PULFO model. Hence, sites directly bonded to a ^{13}C site (constituting environment A) simultaneously affect the Δω differential sensitivities and the $(\alpha\text{-Me})_0$ limiting effects, whereas sites in rank B and C of the alkyl environment affect only the term $\sum\lambda_r$ (Figure 8). This term, in all likelihood, is largely composed of the influence on ^{13}C of steric polarization of the γ type between the incoming methyl substituent and the carbon atoms at the β-position of the alkyl environment.

The influence of conformational effects associated with specific functional families was also analyzed with the PULFO model. The variable environment for each functional family dealt with herein contains only alkyl radicals whose influence is represented by the λ_r parameters. A study on the introduction of heteroatoms into the various environments is under way. We are also in the process of determining the topological parameters of functionalized groups (λ_F) and investigating the potential of the PULFO model and its sensitivity to real geometric distortions and local strain release.

Experimental Section

^{13}C spectra of ketones and acids were recorded on a JEOL PFT 100 spectrometer operating at 25.15 MHz with Fourier transform, ^{2}H Lock, and complete ^{1}H noise decoupling. Spectra were run at room temperature on 10% w/v solutions in CD_2Cl_2 for acids or CCl_4 for ketones (the lock signal was then obtained from a D_2O capillary inserted in the sample tube). Chemical shifts were measured from the solvent peak as internal standard and converted to Me_4Si scale.

Acknowledgment. We are grateful to Dr. C. Lion for preparing crowded carboxylic acids and ketones and to M. Carabédian for helpful discussions.

Supplementary Material Available: Tables VI–VIII listing α-Me values observed and calculated with the PULFO model and all ^{13}C δ values for the acid and ketone series herein (17 pages). Ordering information is given on any current masthead page.

Application of Two-Dimensional FT NMR to the Relative Configurational Assignment of 8-Methyl-4-oxo-10-(trimethylsiloxy)tetracyclo[7.2.1.0^{2,8}.0^{3,7}]dodecane-10-carbonitrile

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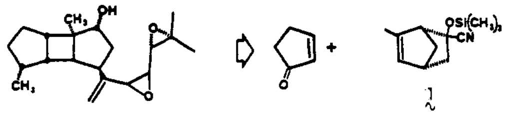
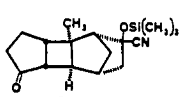
The relative configuration of 8-methyl-4-oxo-10-*endo*-(trimethylsiloxy)-*cis*-*anti*-*cis*-tetracyclo[7.2.1.0^{2,8}.0^{3,7}]-dodecane-10-*exo*-carbonitrile (**2x**) was assigned by joint application of ^{13}C–^{1}H two-dimensional J spectroscopy (2DJ spectroscopy) and ^{13}C–^{1}H two-dimensional shift correlation spectroscopy. The utility of vicinal ^{13}C–^{1}H coupling for configurational analysis is demonstrated. The structural assignment described can serve as a model for application of two-dimensional FT NMR techniques to the structural analysis of organic compounds.

Introduction

In connection with studies on the synthesis of spatol,[1] photocycloaddition of cyclopent-2-en-1-one with 6-methyl-2-(trimethylsiloxy)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (1) was examined. Fortunately, a single major product which is the needed structural isomer 2 (vide infra) is readily isolated from the photoreaction in 61% yield. Selective generation of an exo-anti adduct 2 or 3 was expected owing to the proclivity for exo addition to bicy-



1



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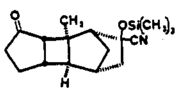

3

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[1] (a) Spatol is a minor metabolite produced by a tropical marine alga, *Spatoglossum schmitti.*[1b] It is potently cytotoxic against human skin and brain tumor cells, and it inhibits synchronous cell division of the fertilized sea urchin egg, suggesting inhibition of microtubule assembly as a target of its biological activity.[1c] (b) Gerwick, W. H.; Fenical, W.; Van Engen, C.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 7991. (c) Jacobs, R. S.; White, S.; Wilson, L. *Fed. Proc., Fed. Am. Exp. Biol.* **1981**, *40*, 26.

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