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CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTRA—XII[1,2]

THROUGH-BOND AND THROUGH-SPACE INTERACTIONS OF SUBSTITUENTS IN β-SUBSTITUTED KETONES AND RELATED COMPOUNDS

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Abstract - Intramolecular substituent interactions in β-substituted ketones, thioketones, methoximes and olefines can be detected by considering non-additivities of the individual substituent effects on the ^{13}C chemical shifts. When the substituent X is in equatorial (anti) position, the interaction is hyperconjugative, if the central atom of X is a hetero atom. It affects the two substituted C atoms and may influence unsubstituted carbons also, provided that the latter are in β position to both of the substituted carbons in the same ring. When X is axial (*syn*) there are mutual through-space bond polarizations and, if X is anisotropic, additional field effects can be monitored. Unsubstituted C atoms are not influenced in the axial case. Investigations of this kind allow a deep insight into transmission mechanisms of substituent effects and may be applicable to stereochemical problems.

During the last decade ^{13}C NMR spectroscopy has attracted growing attention because the ^{13}C chemical shift and substituent effects (SCS) are excellent probes for stereochemical investigations.[3] There are also some reports discussing intramolecular substituent interactions in terms of non-additivities (NA) of SCS,[4-14] since it is known that SCS are additive as long as there are no intramolecular substituent interactions, and the geometry of the molecular framework is left unchanged by the substitution.

Many publications deal with the dependence of SCS on the stereochemistry of the compound and the substituents' nature; and sometimes "unusual" SCS are reported which, after closer inspection, appear to originate in non-additivities of SCS. Therefore, it is essential to explore such interaction effects to avoid "surprises". Moreover, investigations of this type can provide information about even weak intramolecular substituent interactions which may be undetectable by other spectroscopic methods.

In this paper we describe non-additivities of SCS in β-substituted ketones and related compounds and propose models for the different types of intramolecular substituent interactions which are based on a large body of experimental evidence. There are two different configurations of β substituents in cyclohexanes, equatorial and axial, and both types appear to exhibit completely different kinds of interactions between X and the CO group.[4,7,15,16] In order to explore the nature of these interactions we investigated NA effects of SCS for various substituents, molecular systems and substitution patterns.

RESULTS AND DISCUSSION

The definition of the SCS and how to calculate NA effects ($\Delta\delta$) have been described[4,7]: The $\Delta\delta$-values are the differences between the experimental and calculated ^{13}C chemical shifts, the latter being obtained by adding the SCS(X_i) of the individual substituents to the basic values of the unsubstituted parent compounds (δ_b):

$$\Delta\delta = \delta_{exp} - \delta_{calc}$$

$$\delta_{calc} = \delta_b + SCS(X_1) + SCS(X_2) + \cdots.$$

The SCS(X_i) are extracted from the spectra of the corresponding monosubstituted derivatives.

The designation of the compounds mentioned in this work (Scheme 1) is as follows: The molecular system including doubly bonded substituents (O or Y) are signified by a number (**1**, **2**, **3**...); the substituent X is characterized in parentheses after these numbers.

Details and tables of ^{13}C chemical shifts concerning the syntheses of the compounds described may be purchased from the authors directly as supplementary material.

Substituent in equatorial position. This configuration is verified in 4^t-substituted adamantanones (**1**). As already reported for a few derivatives with oxygen and halogen substituents X,[4,7] NA effects exist only for the signals of C-2 (C=O), C 4 (C-X) and the unsubstituted C-9. All of these are negative, i.e. the C atoms are more shielded than expected when assuming additivity, with only one exception (**1**(NMe_2): $\Delta\delta$(C-2) = +0.2 ppm).

In Fig. 1 the $\Delta\delta$-values of the C-2 signals are plotted vs those of C-4:

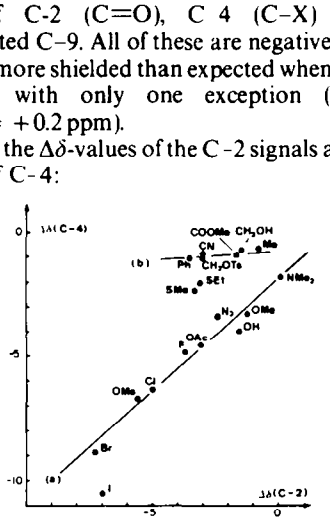
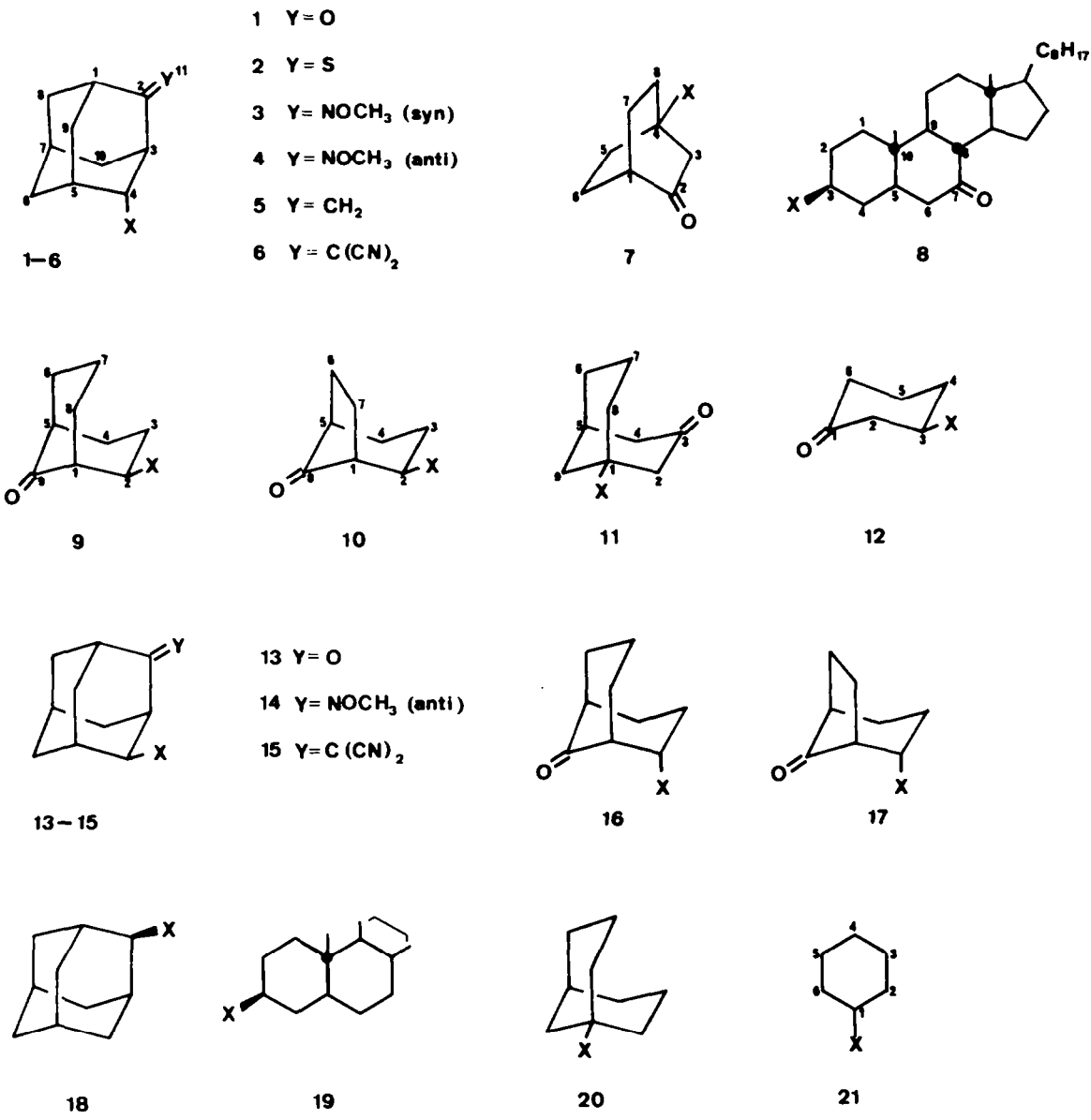


Fig. 1. Non-additivity effects at the C-2 signals vs those at the C-4 signals in 4^t-substituted adamantanones (**1**); in ppm.



Scheme 1.

As can be seen from Fig. 1, there are appparently two different types of interactions between the two substituents (X and the CO oxygen):

(a) If the central atom of X which is directly bonded to the adamantane skeleton, is a hetero atom with one or more free electron pairs, then there is a *mutual interaction*; i.e. the influences on C 2 and C 4 parallel each other. Exceptions only occur for the highly polarizable substituents –SR and I.

(b) If the central atom of X is a carbon bearing no free electron pairs, the $\Delta\delta$-values for the C–4 signals are very small, whereas those for the CO signals C–2 increase with increasing anisotropy of X. This indicates a *one-sided influence* of the substituent X upon the CO group, probably by means of a through-space field effect (*vide infra*). The two types of substituents also show different NA effects for the unsubstituted C-9 signals:

(a) The NA effects for the hetero substituents vary between –2.2 and –8.0 ppm, and there is a fair correlation with the group electronegativity of X:[17]

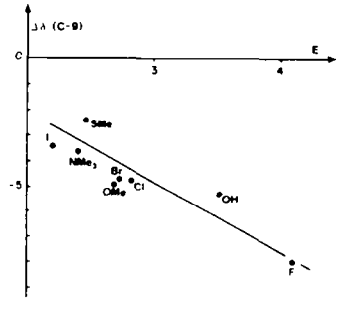
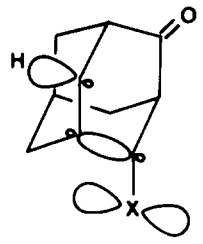
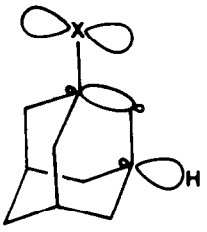
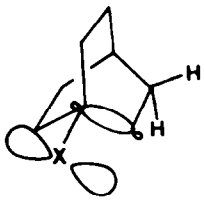


Fig. 2. Non-additivity effects at the C-9 signals in 4[e]-substituted adamantanones (1) vs the substituents electronegativities; in ppm.

The explanation for these NA effects is the fact that the γ_{anti} SCS of X upon C–9 is altered by the interaction of the lone pair of X with the CO. In other words, the γ_{anti} SCS are different in the presence and absence of the CO group[11,18] (Scheme 2a).







X = OH	2.3	-0.2
X = OCH_3	2.2	-0.3
X = Cl	3.2	1.0
X = Br	4.1	1.9
X = I	4.4	2.5

Scheme 2.

(b) The NA effects for the carbon substituents are very small (−1 to −2 ppm). This is expected on the basis of the model depicted in Scheme 2a (see also Ref. 18). The small values may be a consequence of the fact that the axial hydrogen at C 9 has only one 1,3-diaxial hydrogen in the ketone whereas there are two in the adamantane from which the individual SCS are taken. Thus there might be small changes in the ring geometry.

To answer the question of what kind the mutual substituent interaction (type a) is, we investigated further adamantane derivatives with Y other than oxygen (**2**–**6**). We found that in all cases equivalent NA effects do exist, but the magnitude may vary. Figure 3

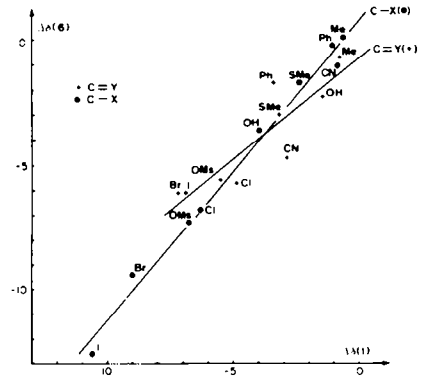


Fig. 3. Non-additivity effects at the C-2 (C=Y) and C-4 (C–X) signals in 4[e]-substituted adamantanones (**1**) vs those of the corresponding dicyanoethylenes **6**, in ppm.

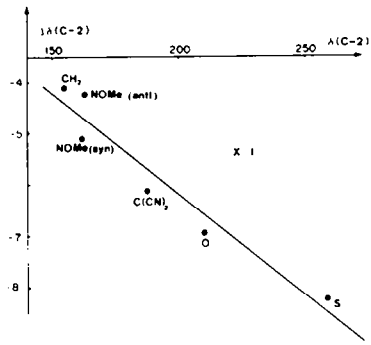
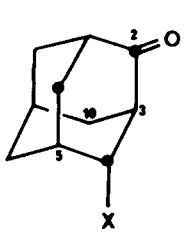
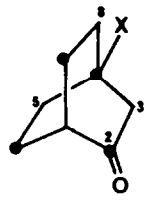
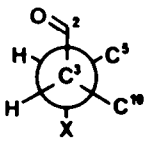
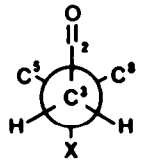


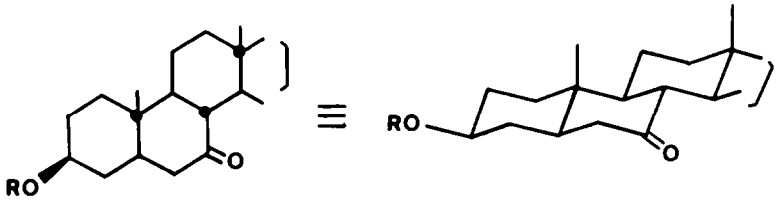
Fig. 4. C-2 chemical shifts vs the C-2 non-additivity effects in the iodo derivatives **1**(I) to **6**(I); in ppm.

demonstrates this finding. The $\Delta\delta$-values for the C–4 signals correlate very well ($r = 0.995$). The correlation for the C–2 atoms is somewhat worse: this might be due to different responses of the C=Y bonds to the field effects of X. It is a well-known fact that ^{13}C chemical shifts of sp^2-hybridized C atoms give an approximate measure for the polarity of the double bond.[19] Thus, when the ^{13}C chemical shifts (δ) of the C–2 signals in **1**–**6** (for a given X) are plotted vs their $\Delta\delta$-values, we get an idea of the dependence of the NA effects on the double bond polarity:

This is shown in Fig. 4 for the example of the iodo derivatives **1**(I) **6**(I). It turns out that the substituent interaction is the more effective, the more polar the C=Y double bond is.

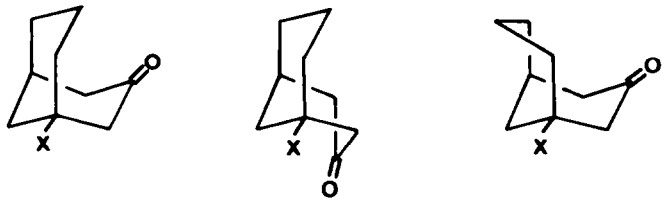





b



R = H, Me, Ac

c



CC BC CB

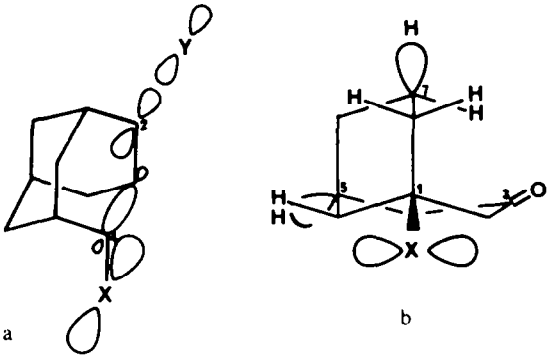
Scheme 3.

Apparently, the lone electron pairs of the CO oxygens do not participate in the substituent interaction, because the olefins **5** and **6** exhibit the same effects without possessing lone pairs. Just as little the π- and π^*-orbitals are involved; we never found splittings of significant shifts in the UV bands of the compounds **1**–**6**.[20] Thus, the interaction mechanism is completely different from the "σ-coupled transition" discussed by Verhoeven *et al.*[21–23]

Molecular models clearly show that the CO oxygen is bent by approximately 60° out of the plane in which C-2, C-3, C-4 and X are situated (Scheme 3a). However, in 4-substituted bicyclo[2.2.2]octanones **7** the CO oxygens are lying in this plane also, and we found that the $\Delta\delta$-values of the substituted C-2 and C-4 are generally larger for the bicyclooctanones **7** than for the adamantanones **1**.[7]

This means that coplanarity of the CO oxygen supports the interaction, the participating orbital of the CO group is of σ type.

The fact that there are only minute NA effects at the β positioned unsubstituted C-6 and C-7 atoms[7] corroborates the explanation given for the effects at C-9 of the adamantanones substituted by a hetero substituent in 4^e-position (Scheme 2a): Since there is no coplanar hydrogen at those carbons, the hyperconjugative γ_{anti} SCS which we postulated in previous publications[11,18] cannot work effectively. This is also reflected in the finding that the γ_{anti} SCS of 1-substituted bicyclo[2.2.2]octanes are considerably smaller than those of 1-substituted adamantanes for a given substituent,[7,24] although the geometry and the substitution pattern from X to the γ-C atom are very similar (Scheme 2b). Thus, the interaction effects



Scheme 4.

cannot be transmitted to the C 6 and C–7 atoms in the bicyclooctanones **7** as they are in the adamantanones **1**.

On the basis of all arguments gathered above we propose the following explanation for the NA effects at C–2 and C 4 in 4[e]-substituted adamantane derivatives **1**–**6** where X is a hetero substituent (Scheme 4a):

There is a hyperconjugative interaction between the n-orbital of X and the σ^*-orbital of the C=Y double bond via the C-3–C-4-σ-bond. Even the negative sign of the $\Delta\delta$-values is understood. As a result of the charge transfer from the n-orbital of X to the double bond, the electronegativity of X decreases, leading to smaller α SCS than in 2-substituted adamantanes **18**. Thus, the experimental chemical shifts are smaller than the calculated ones for which the SCS of **18** were used. Simultaneously, the charge transfer to the σ^* bond orbital causes a weakening of the C=Y double bond so that the electron-withdrawing effect of Y upon C-2 is diminished. Again this gives rise to a signal at higher field than calculated.

As expected, the interaction does not exist in δ-substituted ketones, as e.g. 3β-substituted cholestan-7-ones **8**[11] (Scheme 3b). There is no C atom at all in **8**(OMe) and **8**(OAc) for whose signal the $\Delta\delta$-values exceed +1 or −1 ppm. This is again in contrast to Verhoeven's findings.[23b]

The substituent interaction is not restricted to adamantane derivatives. Recently, Morris *et al.* reported ^{13}C NMR data of 4-substituted camphors.[25] Although they did not determine NA effects explicitly, an inspection of the effects of X upon the CO signals reveals a trend analogous to that for **1**. Morris also found no significant substituent effects in the UV spectra of these compounds.[25] Likewise, Heumann *et al.* found unusual, small α SCS and diamagnetic γ_{anti} SCS of hetero substituents X in **9** and **10**[15,16] which can easily be interpreted in terms of interactions of the lone pairs of X and the CO. However, the conditions (iv) and (v), Heumann claimed to be necessary for such unusual γ_{anti} SCS,[16] ought to be revised:

(a) The effects do exist even when X is attached to a bridgehead C atom. Figure 5 shows that in 4-substituted adamantanones **1** and in 1-substituted bicyclo[3.3.1]nonan-3-ones **11**† apparently the same interaction is operative. The interaction is even more effective in **11** than in **1**. This can be seen from the

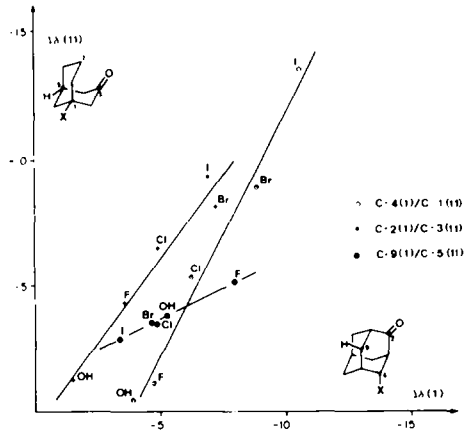


Fig. 5. Non-additivity effects at the C-2, C-4 and C-9 signals in some 4[e]-substituted adamantanones (**1**) vs those at the corresponding C-3, C-1 and C-5 signals, respectively, in 1-substituted bicyclo[3.3.1]nonan-3-ones (**11**); in ppm.

larger $\Delta\delta$-values for C-1 and C-3 as compared with those of C-4 and C-2 of **1**. It is known that bicyclo[3.3.1]nonanes adopt a strongly flattened chair-chair conformation (CC) unless they have 3-*endo*- and/or 7-*endo* substituents[26–28] (Scheme 3c).

Vegar and Wells reported that there is a mixture of about 1:1 ratio for the CC and BC conformers of **11**(H) in the presence of Eu(dpm)$_3$.[29] However, this high proportion of the BC conformer may be a consequence of complex formation.

When the cyclohexanone ring in **11** is considerably flattened, the CO oxygen is approaching the plane of X, C-1, C-2 and C-3, thus making the substituent interaction more effective.

In the compounds **11** there is another C atom in antiperiplanar position with respect to X, namely C-7. However, for these signals we do not observe the typical negative NA effects (**11**(OH): +1.7, **11**(F): +1.4, **11**(Cl): +1.3, **11**(Br): +1.0, **11**(I): +0.5 ppm). Since the CB conformer in which X and C-7 are in *gauche* configuration must be ruled out—at least as a major component—the only explanation is the relative orientation of the C-7–H bond orbital and the lone electron pair at X (Scheme 4b): The favourable direction of the lone electron pair for the interaction with the CO and simultaneously with the C-5–H bond orbital is depicted in Scheme 4b. In this orientation it is approximately orthogonal to the C-7 H bond orbital so that it cannot influence C-7. On the other hand, if the electron pair is rotated by 90 to render that possible, it is in an unfavourable position to interact with the carbonyl via the σ bond orbital.

(b) The cyclohexanone ring need not necessarily be in the chair conformation. The interaction is present in **7** with a fixed boat conformation and apparently in 4-substituted camphors as well.[25] Very recently, Berger reported the data of 6-*exo*-chloro-bicyclo-[2.2.2]octanone[30] which show that there is also a substituent interaction of the same kind.

Probably, only the correct number of intervening C–C-bonds between X and C=Y and their relative orientation is significant.

Apart from the ^{13}C NMR evidence discussed above we did not find other spectroscopic parameters as IR

†SCS of the 1-substituted bicyclo[3.3.1]nonanes **20**(F), **20**(Cl) and **20**(I) are taken from Ref. 26. Those of **20**(OH) and **20**(Br) in Ref. 26 agree well with ours.

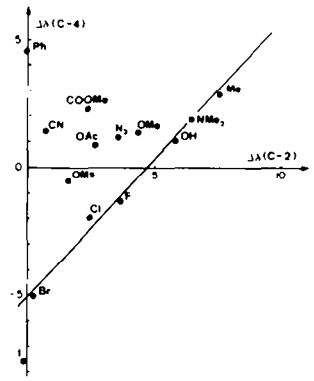


Fig. 6. Non-additivity effects at the C-2 signals vs those at the C-4 signals in 4ᵃ-substituted adamantanones (**13**); in ppm.

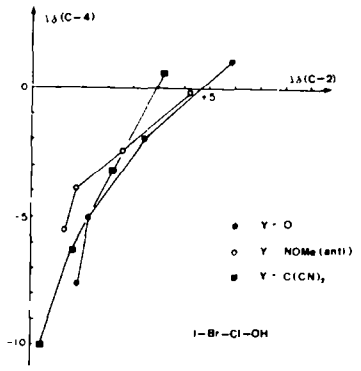


Fig. 7. Non-additivity effects at the C-2 signals vs those at the C-4 signals in selected 4ᵃ-substituted ketones (**13**), anti-methoximes (**14**) and dicyanoethylenes (**15**); in ppm.

wave numbers, ^{13}C-^{1}H- and ^{13}C-^{13}C-coupling constants, which are able to reflect the substituent interaction discussed in this section. Only in the UV spectra of **1** the molar absorptivities ε are affected.[31] This has already been reported and discussed earlier.[31 33] So we conclude that among the spectroscopic methods specified above, only the determination of NA effects is suitable to detect such weak substituent interactions.[34] Finally, we want to refer to some other evidence, the Grob-fragmentation[35] and some reviews on through-bond interactions[36,37] which are related to this problem.

Substituent in axial position. This configuration is found in 4ᵃ-substituted adamantanones **13**. In these molecules as well as in the corresponding *anti*-methoximes **14** and dicyanoethylenes **15**, NA effects occur only at the substituted C-2 and C-4. In Fig. 6 the C-2 NA effects of the ketones **13** are plotted versus those of C-4. Nearly all CO effects are positive, whereas the $\Delta\delta$-values for C-4 can be negative or positive. Several mechanisms playing a part in the interaction between X and the CO group can be extracted from Fig. 6:

(a) Except for iodine, the data points of all spherical substituents are situated on a straight line ($r = 0.996$), regardless of the presence or absence of lone electron pairs at the central atom of X. In this context the dimethylamino group is to be considered as spherical due to rapid nitrogen inversion. The NA effects can be interpreted in terms of *mutual through-space* bond polarizations.

(b) If the substituent is non-spherical, there is an additional effect. The anisotropy of these substituents (e.g. N_3, CN, Ph) causes *one-sided field effects* upon the CO group leading to additional upfield shifts of the CO signals. The same effects were already observed in 4ᵉ-substituted adamantanones **1** (*vide supra*) though to a lesser extent owing to the larger distance. Thus, the data points are shifted off the correlation line horizontically to the left in Fig. 6: the more anisotropic the substituent, the larger this shift.

These results explain Heumann's[15,16] and our[4,7] findings that in the axial hydroxy and acetoxy ketones the α SCS are larger than in the equatorial ones, although in the correspondingly substituted hydrocarbons it is reversed. This is simply due to the fact that in the case of the equatorially substituted ketones a negative NA effect of about 4 ppm must be added, whereas in the axial case the supplementary effect is about +1 ppm. By that, the sequence of the α SCS is inverted.

The substituent interaction is affected not only by X but also by the doubly bonded Y.

Figure 7 shows different slopes of the curves each of which gives the dependencies of NA effects on X (I, Br, Cl, OH from the left to the right) for a certain series of compounds (Y=O, NOMe(*anti*) or $C(CN)_2$). This reflects distinct responses of the C=Y bonds to the interaction with X, maybe due to their different polarizabilities.

Conformationally mobile molecules. The NA effects discussed in the preceeding sections appear also in conformationally mobile molecules:
The $\Delta\delta$-values for the equatorially substituted **1**(OMe) are negative, whereas those for the axial **13**(OMe) are positive. Apparently, these effects compensate for the substituted C-1 and C-3 atoms of **12**(OMe) (Table 1). The only significant NA effect in the data of **12**(OMe) is found at the C-5 signal, which corresponds to C-9 of **1**(OMe), because there is no compensating effect in

Table 1. Non-additivity effects of SCS in 3-substituted cyclohexanes **12**ᵃ

	C-1	C-2	C-3	C-4	C-5	C-6
12(Me)	−0.5	−0.7	+1.1	−0.3	−1.4	−0.4
12(OMe)	+0.7	+0.2	−0.8	−0.6	−3.5	+0.2

13(OMe). The smaller value of −3.5 ppm in **12**(OMe) as compared with −5 ppm in **1**(OMe) is originated in the conformational equilibrium of **12**(OMe) which contains a considerable amount of the axial conformer.

The NA effects found in **12**(Me) are expected considering those of **1** (Me) and **13** (Me).

CONCLUSION

Investigations of non-additivity effects in β-substituted ketones and related derivatives do not only give valuable information about the occurrence and the nature of intramolecular substituent interactions, even when these are weak and do not affect other spectral parameters. Moreover, it is possible to determine the relative configuration of the substituents, since the $\Delta\delta$-values may differ considerably in sign and magnitude for the various configurations. Finally, although such explorations are laborious and require the syntheses of many derivatives and model compounds, we regard them as vital for a deeper understanding of the electronic and stereochemical effects of substituents on the ^{13}C chemical shift.

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