Carbon-13 Nuclear Magnetic Resonance Spectra of *ortho*-Substituted Acetophenones: Enhanced Substituent Effects on the Carbonyl Group

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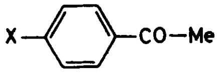
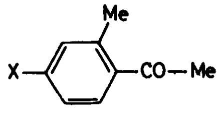
The ^{13}C carbonyl chemical shifts of substituted 2′-methyl-, 2′-methoxy-, and 2′,6′-dimethyl-acetophenones are compared with those of corresponding acetophenones. The correlations indicate that the carbonyl chemical shifts are more sensitive to the 4-X induced substituent effect in both 2′-methyl- and 2′-methoxy-acetophenones than in acetophenones. The enhancements are in full agreement with i.r. data and have been attributed to intra-ring electronic interactions in 2′-methyl- and 2′-methoxy-acetophenones and to quasi-ring formation in the former. In contrast, δ_{CO} remained nearly constant in the 2′,6′-dimethylacetophenones, owing to the large torsion in these compounds.

THE mechanisation of transmission of substituent effects in aromatic derivatives has recently received increasing interest.[1–6] These studies are largely devoted to the characterization of non-additive behaviour and to the determination of substituent–substituent interactions in *para*-substituted benzenes. ^{13}C N.m.r. has proven to be a very fruitful technique for the study of these phenomena and their interaction with electronic structures by use of correlations between the chemical shifts and the corresponding electronic charges.

As part of our continuing interest in polysubstitution effects, we have recently used i.r. spectroscopy to determine the relative importance of changes in molecular geometry and the various mechanisms of substituent–substituent interactions (inter- and intra-ring) in polysubstituted aryl ketones such as benzophenones and acetophenones.



(I)



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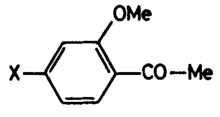

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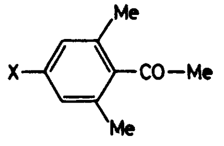


(IV)

To obtain further insight into the transmission of substituent effects in such systems, we report here some exploratory ^{13}C n.m.r. results for the carbonyl carbon using as models the substituted acetophenones (I) and the corresponding *ortho*-methylated [(II) and (IV)] or methoxylated [(III)] derivatives.

EXPERIMENTAL

^{13}C Spectra were recorded under identical experimental conditions (5% w/v solutions in $CDCl_3$) on a Bruker WP 80 spectrometer operating at 20 MHz, with ^2H field lock and complete ^1H broad band noise decoupling. The usual conditions correspond to a 4 500 Hz spectral width, leading to a digital resolution of 0.06 p.p.m. *Ca.* 5 000—10 000 scans were generally used to obtain a good signal to noise ratio.

For details of the preparation of the acetophenone derivatives, see ref. 1.

RESULTS AND DISCUSSION

The ^{13}C shifts for 25 acetophenones with 2′-methyl, 2′-methoxy, or 2,6-dimethyl groups are collected in Table 1. For some compounds, and particularly 4′-substituted acetophenones, the ^{13}C shifts have been reported previously,[7,8] but the diversity of the experimental conditions for most of the *ortho*-substituted compounds precludes any accurate discussion of substituent-induced shifts.

TABLE 1

^{13}C Chemical shifts for carbonyl group in acetophenones (I)—(IV) (p.p.m. from tetramethylsilane internal reference; solvent $CDCl_3$)

	Acetophenone			
X	(I)	(II)	(III)	(IV)
4′-NMe_2	196.4_5 (−1.8)	198.5 (−3.3)	196.8 (−3.1)	207.8_5 (-0.5_5)
4′-NH_2	196.6 (-1.6_5)	199.0 (−2.8)		208.1_5 (-0.2_5)
4′-OMe	196.8 (−1.4)	199.6 (−2.2)	197.8 (-2.1_5)	208.1 (-0.3_5)
4′-Me	197.9 (-0.3_5)	201.2 (−0.6)	199.2 (−0.7)	208.5 (−0.1)
H	198.2_5	201.8	199.9_5	208.4
4′-Cl	196.9 (-1.3_5)	200.3_5 (−1.4)	198.3_5 (−1.6)	
5′-Cl	196.7_5 (−1.5)	200.4_5 (-1.3_5)	198.4 (-1.5_5)	

For the 4′-unsubstituted reference substrates (II)—(IV) (X = H), the chemical shift of the carbonyl carbon clearly indicates the large influence of steric inhibition of resonance between the phenyl group and the carbonyl when *ortho*-substituents preclude strict coplanarity of these fragments.

The deshielding observed for (II) and (III) (X = H) has been used by Stothers[7] to calculate the angle of twist between the carbonyl group and the ring, indicating larger rotation in (III; X = H) than in (II; X = H). However, recent ^{17}O n.m.r. results[9] and crystallographic data on *ortho*-substituted benzoic acids[10] indicate that these two molecules are not severely twisted (angles of *ca.* 10° for Me and *ca.* 0° for OMe). Furthermore, the problem of the conformational preference of the methoxy-group, *cis* or *trans* with respect to the carbonyl group, is not definitely settled.[11-15]

As expected, a larger shift is observed for (IV; X = H) (downfield effect of *ca.* 10 p.p.m.) where the two *o*-methyl groups severely hinder the coplanarity of the acetyl and phenyl groups leading to a large decrease in the conjugative interactions between them.

Turning now to the shift induced at C_α (carbon of carbonyl group) by 4'-substituents, a similar trend is observed for the various compounds under study. With respect to X = H, an electron-releasing (NMe_2, NH_2, OMe, Me) or electron-withdrawing (4-Cl, 5-Cl) group induces upfield shifts.

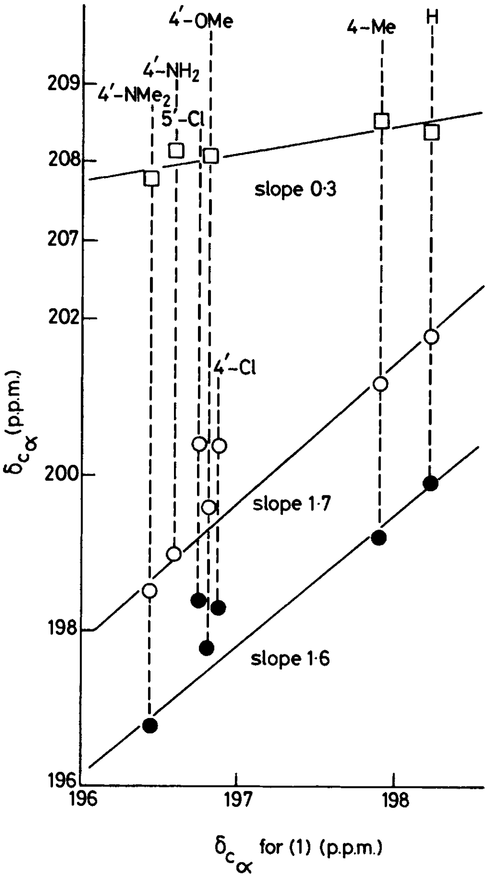
The s.c.s. for side-chain carbons of aromatic substituted derivatives have been frequently analysed by Hammett-like dual substituent parameter relationships. Bromilow *et al.*[16] have recently shown that, according to the relative blend of inductive or resonance effects, which can either supplement or oppose each other according to the demand of the functional group, the s.c.s. may appear as normal (*i.e.* donor groups inducing upfield shifts) or reversed.

Among the consistent trends, although the range of variation of the ^{13}C shifts is small, it is noticeable that the ρ_I parameter has a negative value of *ca.* −2.7. This is considered as reflecting π-polarisation effects[17] for two carbons conjugated with the phenyl ring. Also, ρ_R values are negative, except for the carbonyl carbon of acetophenone for which $\rho_R = 0.8$.

Owing to the small variations observed (*ca.* 3 p.p.m.) the substituent effects should be discussed with caution. Our results are obtained for dilute solutions which closely approximate to the condition of infinite dilution.[16] For common compounds in the 4'-substituted acetophenone series, the chemical shifts reported here are nearly identical to those recently published by Taft *et al.*[5] Furthermore, for (II; X = H), we have checked that the shielding induced by a 4'-methoxy-group is identical for CCl_4 or $CDCl_3$ solutions and therefore does not involve any important difference in the extent of solvent effects according to the nature of X.

To characterize the extent of the reaction of the carbonyl group to structural perturbations dependent on the *ortho*-substituent, the s.c.s. induced at C_α by 4'-substituents have been analysed by homogeneous cross correlations (δ/δ). This treatment does not involve the use of any substituent parameter scale, external to the species under investigation, such as the widely used Hammett-like constants, and therefore appears to be more reliable for the discussion of small substituent-induced shifts.

In the Figure, the shifts of the C_α in (II)—(IV) have been plotted against the corresponding shifts in (I). In (IV), the s.c.s. at C_α are quite small, *ca.* 0.3 p.p.m. between X = H and X = NMe_2, and show only a rough trend when correlated with the s.c.s. of (I), perhaps because of the small variations, with a slope of *ca.* 0.3. This observation agrees with i.r. results indicating small variations of the $\nu_{C=O}$ band which are consistent with weak sensitivity of the CO fragment to structural perturbations of the phenyl ring. This can be attributed to the large torsion around the C(1)–C_α bond which prevents any noticeable transmission of electronic effects to the carbonyl group.



Homogeneous cross correlations δ/δ for the ^{13}C shift of the carbonyl carbon of (II) (○); (III) (●); and (IV) (□) *versus* the corresponding shift in (I)

More unusual are the results observed for the 2'-methyl and 2'-methoxy derivatives. The substituent-induced shifts are very similar (Table 1) in the two families of *ortho*-substituted compounds (II) and (III), with a correlation line of slope 1.15 (*r* 0.994). But only a rough correlation is observed with (I) for the whole set of substituent groups (Figure). So the s.c.s. induced by 4-Cl or 5-Cl substituents are nearly identical in compounds (I)—(III), whereas with OMe, NH_2, and NMe_2 the variations are greatly enhanced in (II) and (III). This corresponds to a range of variations of, respectively, 3.3 and 3.1 p.p.m. between X = H and

X = NMe_2, whereas, for the same structural change, $\Delta\delta$ is only 1.8 p.p.m. in (I). It is noteworthy that these increased s.c.s. are observed for X groups exerting a small inductive and a large resonance effect (as shown by the corresponding σ_I and σ_R^+ values) suggesting that resonance effects have the determining role in these enhanced s.c.s.

For these groups, acting mainly *via* resonance effects (so excluding chloro substituents for which both inductive and mesomeric effects are of comparable magnitude) two satisfactory linear correlations with slopes of 1.7 and 1.6 (r 0.992 for five points and 0.990 for four points) are obtained when plotting C_α shifts in (II) or (III) *versus* the values for (I).

These ^{13}C observations are in full agreement with the results obtained in our previous study of the frequency of the CO stretching vibration in the i.r.,[1] also showing, for the same set of substituents, increased transmission of substituent effects.

It should be noticed that the exaltation effect is larger for ^{13}C shifts than for ν_{CO} (slopes of *ca.* 1.7 and 1.1, respectively, in homogeneous cross correlations with acetophenones). Furthermore, in both i.r. and ^{13}C n.m.r., the enhancement factors are similar for 2′-methyl and 2′-methoxy derivatives, despite the greater electron-releasing power of the methoxy-group.

Further experimental evidence of the non-additivity and non-independence of the effects of *ortho*- and *para*-substituents is given by examination of the 2′-methyl shifts in (II) (Table 2). The relevant peak moves from δ 21.5 to 23.5 p.p.m. when X varies from 4′-Cl to 4′-NMe_2. It is noteworthy that for the corresponding toluenes, the methyl signal variations do not exceed 0.5 p.p.m.[17]

TABLE 2

^{13}C Chemical shifts for 2′-methyl group in acetophenones (II) (p.p.m. from tetramethylsilane internal reference; solvent $CDCl_3$)

X	2-Me
4′-NMe_2	23.5
4′-NH_2	22.8
4′-OMe	22.6
4′-Me	21.7_5
H	21.5_5
4′-Cl	21.5_5
5′-Cl	20.9

In agreement with our observations it is of interest to recall some results of St Amour *et al.*[9] for the ^{17}O n.m.r. of acetophenones. A 4′-methoxy-group shifts the ^{17}O carbonyl resonance 15 p.p.m. upfield on going from acetophenone to 4′-methoxyacetophenone, but the variation is enhanced to 22 p.p.m. between 2′-methoxy- and 2′,4′-dimethoxy-acetophenone. Similarly the 11 p.p.m. downfield shift between acetophenone and 2′-methoxyacetophenone is reduced to 4 p.p.m. for 4′-methoxy- and 2′,4′-dimethoxy-acetophenone, indicating in the latter case an increase of the electron-releasing upfield interaction from the methoxy-group.

Non-additivity of substituent effects in benzene derivatives have been investigated mainly for di-substituted compounds bearing *para*-substituents;[5,16,18-20] the results reported here indicate sizeable intra-ring interactions in these more complex systems where two substituent groups, *meta* to each other, are respectively *ortho* and *para* to the functional group.

In a tentative explanation of the exaltation effect observed for these systems on the ν_{CO} vibration, two mechanisms[1] have been invoked, which may also apply to ^{13}C spectra. For *o*-methyl derivatives, the formation of a six-membered quasi-ring with hydrogen bonding between the methyl hydrogen and the carbonyl group can be postulated by comparison with the work of Dusart *et al.*[21] The formation of this hydrogen bond results in greater sensitivity of the carbonyl group to substituent effects: it has been shown for instance that the complexation of the carbonyl group by Lewis acids increases the substituent effects on the ν_{CO} i.r. frequencies.[22] Similarly, enhanced effects, especially resulting from resonance effects, are induced in the carbonyl ^{13}C shifts in the protonation of aryl ketones.[4,23,24]

An intra-ring interaction can also be assumed between the *ortho* groups and the X substituents [this adds to the quasi-ring effect in (II)]: an *ortho*-electron-releasing group induces a decrease of electron density at the 4′-position (*i.e. meta* to the *ortho*-group) and so enhances electron transfer by electron-releasing groups at this position.

In monosubstituted benzenes, *ab initio* STO 3G[25] or CNDO/2 calculations show that a methyl or methoxy group induces a decrease in electron density at the *meta*-position. It is also noteworthy that, in 1,3-dimethoxybenzene, CNDO/2 calculations indicate that each methoxy gives more π-electrons to the ring than in the case of anisole (respectively 0.095 and 0.092 e). On the other hand in 1,4-dimethoxybenzene each methoxy-group gives less (0.088 e) since one group increases the electron density in the *para*-position, and thus lessens the effect of the other group. The concept of a variable substituent response[4] has been recently used to account for the non-additive behaviour of thermodynamic[26] or kinetic parameters[27] and of ^{13}C shifts in arylcarbenium ions[2] or *para*-substituted benzenes.[5,6,20]

To extend this work to obtain more precise knowledge of interaction mechanism inside the phenyl ring, additional information must be sought by examination of the aromatic carbon chemical shifts.

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