Heteronuclear ^{13}C, ^{15}N and ^{17}O NMR cross-correlations of 4-substituted benzamide derivatives: importance of the average excitation energy term ΔE in NMR substituent effects

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Heteronuclear ^{13}C, ^{15}N and ^{17}O NMR cross-correlations of 4-substituted benzamide derivatives were carried out and an excellent ^{15}N–^{17}O cross-correlation was found (slope = 2.45, $r = 0.996$, $n = 7$). Very poor ^{13}C–^{15}N and ^{13}C–^{17}O correlations were observed. The substituent interaction mechanism of the carbonyl carbon differs with respect to that experienced by the carbonyl oxygen and amidic nitrogen. Previous studies have reported that the benzamide ^{15}N and ^{17}O chemical shifts obey the Hammett equation but ^{13}C shifts do not. It is concluded that ^{13}C chemical shifts do not correlate with the substituent constant σ_x because the ΔE term of the Karplus–Pople equation does not obey the Hammett equation. It is proposed that, in the localized excited state, the mechanism of interaction of substituents on the aromatic ring with the carbonyl carbon differs from that of the carbonyl oxygen and the amide nitrogen in their respective localized excited states. Whenever a non-linear Hammett plot is obtained, in an NMR substituent study, the possibility that substituents interact differently with the ground and excited states should be considered.

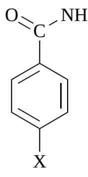
Numerous studies of substituent effects on the NMR chemical shifts of aromatic carbonyl compounds have appeared. In a typical study the chemical shift or substituent chemical shift (SCS) of the probe atom on a side chain is plotted against an appropriate substituent constant (σ_x) or constants (DSP) for the substituent present on the aromatic ring.[1] From the type of substituent constant(s) used and the magnitude(s) of ρ, the substituent sensitivity parameter, inferences are then made as to the mode of transmission of substituent effects.

Single probe atom NMR studies can give only partial information as to the charge distribution within the carbonyl side chain. Heteronuclear cross-correlations offer the opportunity to study the charge distribution within the carbonyl-containing side chain from the viewpoint of two different probe atoms simultaneously and provide further insight into the transmission of substituent effects. Cross-correlations have the following advantages: they do not depend on a particular substituent scale (σ_x) and any substituent(s) whose mode of interaction with the side chain is markedly different will be readily picked out by its deviation from the correlation line. This study examines heteronuclear ^{13}C, ^{15}N and ^{17}O NMR cross-correlations of 4-substituted benzamide derivatives. From the results of these cross-correlations and a new expression derived from the Hammett equation[2] and Karplus–Pople equation,[3] insights into how the average excitation energy term ΔE influences substituent effects have been reached.

Results and Discussion

Benzamides and other aromatic carbonyl compounds are resonance hybrids of contributors **A**–**D**. Changes in the substituent X will change the relative contribution that each resonance form makes to the hybrid. Transmission of substituent effects in 4-substituted benzamide derivatives have been studied by ^{13}C,[4,5] ^{15}N[6] and ^{17}O[7,8] NMR spectroscopy and Table 1 summarizes the data.

Substituent effects are generally rationalized in terms of the effect that the substituent has on one or more of the resonance contributors (**A**–**D**). When the probe atom is ^{13}C, 'reverse' substituent effects are observed and electron-donating substituents deshield the carbonyl carbon.[1,9] The effect of substituents on resonance contributor **C** (π-polarization) is used to explain the 'reverse' substituent effect. In ^{15}N studies normal substituent effects (electron-donating substituents shield the amidic nitrogen) are observed and resonance form **D** is usually used to explain the observed effects.[6] ^{17}O NMR substituent effects are normal and are rationalized in terms of contributors **B** and **D**.[10]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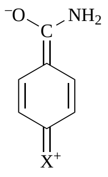
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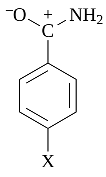
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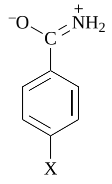
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Heteronuclear cross-correlations were carried out by plotting the ^{17}O chemical shift of the carbonyl oxygen or the ^{15}N SCS of the amide nitrogen *versus* the ^{13}C SCS of the carbonyl carbon, where SCS = $\delta_x - \delta_H$ and deshielding is indicated by a positive value. A very poor correlation was found in both cases and the ^{13}C–^{15}N plot ($r = 0.703$, $n = 7$) is illustrated in Fig. 1. In contrast an excellent ^{15}N–^{17}O cross-correlation (Fig. 2) was obtained (slope = 2.45, $r = 0.996$, $n = 7$) when the ^{17}O chemical shift of the carbonyl oxygen was plotted against the ^{15}N SCS of the amide nitrogen.

Cross-correlations are successful when the two properties being compared share a common interaction mechanism. Absence of a cross-correlation signifies a change in the nature of the interaction between the substituent(s) on the ring and the side chain. In the present case this would imply that the interaction of the carbonyl carbon with the substituent is different from that with the amide nitrogen or carbonyl oxygen. A change in the ground state interaction mechanism would not appear possible given that each point, in a heteronuclear cross-correlation, represents the same resonance hybrid of **A**–**D**.

Successful ^{13}C–^{17}O cross-correlations have been reported in non-aromatic systems[11] and in *meta*-like 5-substituted thiophene-3-carboxylic acids.[12] This suggests there is a difference in the mechanism of transmission of resonance effects to

Table 1 NMR chemical shifts (ppm) of 4-substituted benzamides

Subst.	δ (^{13}C)[a]	C (SCS)[b]	δ (^{15}N)[c]	N(SCS)[b]	δ (^{17}O)[d]
NO_2	166.38	−2.21	81.0	+3.3	334.1
CF_3	166.76	−1.83			330.9[e]
Br	167.09	−1.50	78.3	+0.6	328.4
Cl	166.93	−1.66	78.2	+0.5	327.6
H	168.59	0.00	77.7	0	326.3
F	167.40	−1.19	77.6	−0.1	326.2
CH_3	168.53	−0.06	76.9	−0.8	324.1
OCH_3	167.69	−0.90	76.0	−1.7	321.9

[a] Ref. 4. [b] SCS = $\delta_x - \delta_H$. [c] Ref. 6. [d] Measurements by Dr V. V. Toan, Lausanne, Switzerland.[7] [e] Ref. 8.

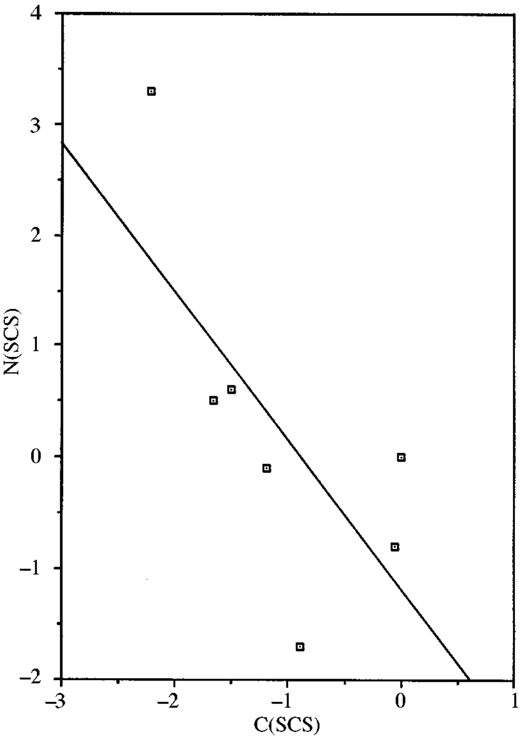

Fig. 1 SCS of carbonyl carbon *vs.* SCS of amide nitrogen

the carbonyl carbon as opposed to the amide nitrogen and carbonyl oxygen.

Another approach to NMR substituent effects is to consider how the terms of the Karplus–Pople equation are affected by polar, steric and solvent effects.[13] An expression is derived below from the Hammett equation and Karplus–Pople equation that will be used to help explain the absence of heteronuclear correlations with respect to ^{13}C chemical shifts of the carbonyl carbon.

Chemical shifts (δ) are determined by paramagnetic (σ^p) and diamagnetic effects (σ^d).

$$\delta = \sigma^p + \sigma^d \qquad (1)$$

Paramagnetic effects predominate and the chemical shift is largely dependent on the paramagnetic term ($\delta \approx \sigma^p$). The paramagnetic term, for second row elements, is generally formulated using the Karplus–Pople equation and the following expression can be written where δ_X is the chemical shift of the side chain probe atom when the substituent X is present on the ring [eqn. (2)].

$$\delta_X = -\text{const}(\Delta E^{-1})_X(r^{-3})_X(\Sigma Q)_X \qquad (2)$$

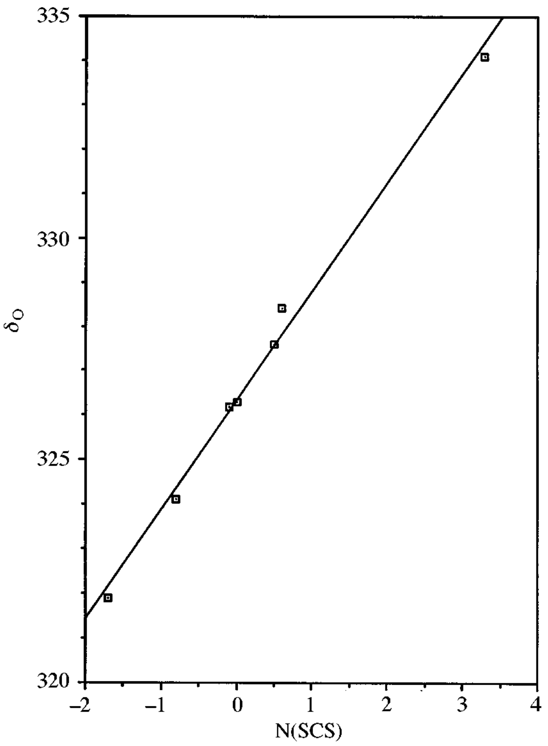

Fig. 2 ^{17}O chemical shift of carbonyl oxygen *vs.* SCS of amide nitrogen

In this expression, ΔE is the average excitation energy, r^{-3} is the inverse of the mean volume of the 2p orbitals on the probe atoms and ΣQ is the charge density bond order matrix. The ΣQ term is a measure of the multiple bond nature of the probe atom and is closely related to r^{-3}.[14] An increase in ΣQ leads to an expansion of the 2p orbitals and a decrease in r^{-3}. The average excitation energy (ΔE) term is problematic. The Ramsey equations indicate that ΔE is the summation of the energy differences between the ground state and all magnetically allowed excited states.[15] At present it is either impossible or very difficult to determine this term directly and several approximations have been used. It has been assumed to be a constant[3,16] or approximated as the lowest energy λ_{max} (or $1/\lambda_{max}$)[17] in the UV–VIS spectrum.

An expression similar to eqn. (2) can be written with respect to the parent compound (X = H) and dividing the two equations and taking the logarithm gives eqn. (3).

$$\log \delta_X/\delta_H = \log (\Delta E^{-1})_X/(\Delta E^{-1})_H + \log (r^{-3})_X/(r^{-3})_H + \log (\Sigma Q)_X/(\Sigma Q)_H \qquad (3)$$

Assume that each term follows the Hammett equation: [eqns. (4)–(6)], then eqn. (7) holds, and also eqn. (8), where ρ is given by eqn. (9).

$$\log (\Delta E^{-1})_X/(\Delta E^{-1})_H = \sigma\rho_E \qquad (4)$$

$$\log (r^{-3})_X/(r^{-3})_H = \sigma\rho_r \qquad (5)$$

$$\log (\Sigma Q)_X/(\Sigma Q)_H = \sigma\rho_Q \qquad (6)$$

$$\log \delta_X/\delta_H = \sigma(\rho_E + \rho_r + \rho_Q) \qquad (7)$$

$$\log \delta_X/\delta_H = \sigma\rho \qquad (8)$$

$$\rho = \rho_E + \rho_r + \rho_Q \qquad (9)$$

Sensitivity to substituents (ρ) is then the algebraic sum of the values for each term in eqn. (9). Eqn. (7) is analogous to the Hammett equation derived for a multistep reaction where one or more equilibrium steps occur prior to the rate-determining step.[18] It can be seen that if eqn. (7) is not followed then one or more terms of the equation does not obey the Hammett equation. Of the three probe nuclei under consideration only the carbonyl carbon does not give a Hammett correlation.[1] The question, in the case of benzamide carbonyl carbon ^{13}C chemical shifts, is which term or terms of eqn. (4) do not vary systematically with respect to the substituent constant σ_X. Arguments are presented below that it is the average excitation energy term (ΔE) that does not follow the Hammett equation.

As noted above the average excitation energy term is usually approximated as the lowest energy λ_{max} in the UV–VIS spectrum. For benzamides, this is the n–π* transition of the whole molecule. Such an approximation implies that the ΔE term, in the Karplus–Pople equation, is the same for the ^{13}C, ^{15}N and ^{17}O chemical shifts of the amide group. This clearly illustrates one problem in using this approximation—only when the functional group is symmetrical can this approximation be expected to hold for all the probe atoms of the group. This has been pointed out by other workers.[19,20]

Hammett correlations are obtained for the ^{15}N[6] and ^{17}O[21] chemical shifts of the amide group and their respective ΣQ, r^{-3} and ΔE terms will, according to eqn. (7), all obey the Hammett equation. The charge density bond order term ΣQ is approximated by the π-bond order. Examination of the resonance structure **A**–**D** shows that changes in the π-bond orders of the probe atoms are interrelated, *e.g.*, as the nitrogen π-bond order increases that of the oxygen decreases. This implies that the $(\Sigma Q)_C$, $(\Sigma Q)_N$ and $(\Sigma Q)_O$ terms are interrelated and if $(\Sigma Q)_N$ and $(\Sigma Q)_O$ obey the Hammett equation then $(\Sigma Q)_C$ would also. The r^{-3} term is calculated[12] from the ΣQ term and if the $(\Sigma Q)_C$ term follows the Hammett equation then the $(r^{-3})_C$ term does too. According to the usual approximation ΔE is the same for all probe atoms of the amide group. Therefore, the approximation[3,16,17] that ΔE can be taken as the average value for the whole molecule does not hold for the carbonyl carbon ^{13}C chemical shifts. If it were, a linear correlation would be expected given that as discussed above $(\Sigma Q)_C$ and $(r^{-3})_C$ are expected to obey the Hammett equation and ΔE is the same for all probe atoms of interest.

Karplus and Pople noted the following with respect to the ΔE term:[3]

> ‘Since ΔE is a mean value for the whole molecule, any effects of excitation energies on relative shieldings for different atoms are not taken into account in eqn. (14) and (15). If the lower excited states could be represented as localized excitations on particular atoms, those atoms would presumably have a larger paramagnetic term σ_p^{AA}. For conjugated and aromatic carbon compounds, there do not seem to be any grounds for singling out individual atoms, in this way, although certain substituents may lead to local excitations.’

A localized effect is observed in this study. Of the three probe atoms of interest, only the ^{13}C NMR shifts of the amide carbonyl carbon gave a non-linear Hammett plot. This and the results of the heteronuclear cross-correlations in this study would appear to be evidence that the effect of localized excitations on the relative shieldings of different probe atoms have to be taken into account. It is proposed that, in the localized excited state, the mechanism of interaction of substituents on the aromatic ring with the carbonyl carbon differs from that of the carbonyl oxygen and the amide nitrogen in their respective localized excited states. This is why a non-linear Hammett plot and heteronuclear cross-correlations are obtained. Previously, amide carbonyl carbon substituent effects have been explained by π-polarization.[1,4]

Lynch has made a similar proposal to explain non-additive behaviour in the ^{13}C NMR spectra of 1,4-disubstituted benzenes.[22] He proposed that the relative energies of the ground state and excited state are modified by the interaction of the probe atom and the substituent. Further, since the deviations were confined to one atom, any changes must be highly local and suggestive of localized excitations.

The following are some possible mechanisms through which the interaction between the substituent and the probe atom can change in the excited state(s):

(*i*) Substituents can affect ΔE by introducing low energy transitions not present in the parent compound of the series.[23]

(*ii*) The electronic nature of a substituent (electron withdrawing or donating) can change in the excited state relative to that in the ground state.[24] A similar effect would be observed if the charge distribution on the probe atom changed in the excited state.

(*iii*) Orbitals that are in the same plane in the ground state can become orthogonal in the excited state. The net effect would be equivalent to that induced by the steric inhibition of resonance —little or no substituent effect.

The last mechanism suggests the intriguing possibility that there can exist systems in which the steric inhibition of resonance present in the ground state disappears in the excited state, *i.e.*, orbitals that are twisted out of the plane in the ground state can be in the same plane in the excited state. Substituent effects would be observable (linear Hammett plots) in spite of the expected steric effect. One possible example is a ^{13}C NMR study of 2,6-dimethylazobenzenes in which it was reported that the loss of ground state coplanarity had little effect on the transmission of polar and resonance effects.[25] Another possible example is the observation that in a study of 4-substituted *N*,*N*-dimethylbenzamides the ^{17}O chemical shift of the carbonyl oxygen correlates with σ^+ (indicating through resonance) in spite of a substantial torsion angle estimated to be 51 ± 1° or 74 ± 2° by MM-2 and AM1, respectively.[26]

Conclusions

The Ramsey equations for magnetic shielding of nuclei contain an explicit dependence on the wave functions of the excited states of the molecule.[13] This dependence is approximated as the average excitation energy in the Karplus–Pople equation.[3] Substituents affect both the ground and excited states. The following general observation can be made: implicit in all Hammett type NMR studies of substituent effects is the assumption that the interaction of the substituent with the probe atom is the same in both the ground state and the excited state(s). Non-linear Hammett plots are to be expected when this assumption does not hold. Whenever a non-linear Hammett plot is obtained, in an NMR substituent study, the possibility that substituents interact differently with the ground and excited states should be considered. Further, given the contribution the excited state makes to the chemical shift, care should be exercised when using NMR substituent effects to study ground state properties.

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