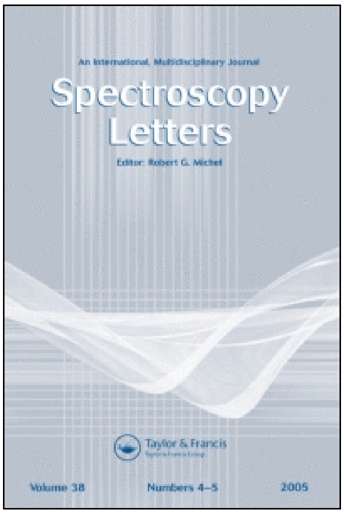

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Carbon-13 Isotope Effects in ^{13}C NMR Spectra of Some Carbonyl Substituted Benzenes

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CARBON-13 ISOTOPE EFFECTS IN ^{13}C NMR SPECTRA OF SOME CARBONYL SUBSTITUTED BENZENES

Key words : ^{13}C NMR, ^{13}C isotope shifts, ^{13}C-^{13}C coupling constants,
^{13}C-carbonyl labeled species

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ABSTRACT

^{13}C isotope effects on ^{13}C chemical shifts in proton-decoupled NMR spectra of several ^{13}C-carbonyl substituted benzenes were determined and analyzed. For the first time intrinsic ^{13}C isotope effects over three bonds from the isotopically

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substituted site were determined. ${}^{n}J(C,C)$ values for ^{13}C-carbonyl-benzaldehyde **1**, ^{13}C-carbonyl-benzoic acid **2,** ^{13}C-carbonyl-acetophenone **3** and ^{13}C-carbonyl-benzophenone **4** were determined and their differences interpreted in terms of molecular geometry and conformation. Both ^{13}C isotope effects and ${}^{n}J(C,C)$ are solvent dependent.

INTRODUCTION

Contrary to deuterium isotope effects on ^{13}C chemical shifts, ^{13}C isotope effects are very small, primarily due to the low mass ratio upon the ${}^{13}C/{}^{12}C$ substitution. As a consequence the detection of ^{13}C isotope effects is not easy, and the review on isotope effects in NMR spectra[1] reflects the general lack of such data. Therefore additional data are still needed, especially from highly accurate measurements.

In order to throw more light on the nature of ^{13}C isotope effects and to measure accurately their values, we have investigated the following ^{13}C-carbonyl labeled molecules: benzaldehyde **1**, benzoic acid **2**, acetophenone **3** and benzophenone **4** (FIG. 1).

Isotope effects were determined according to the expression :

$$ {}^{n}\Delta = \delta^{13}C({}^{12}C) - \delta^{13}C({}^{13}C) $$

where n denotes the number of bonds separating the isotopic substitution site and the observed nucleus, and δ is the chemical shift.

It was reported that both one-bond and two-bond ^{13}C effects in small-ring compounds were of the same order of magnitude[2-4] According to the above definition most of ^{13}C isotope effects are positive (shielding). Just a few negative (deshielding) values were observed, like in ^{13}C-3-cyclobutanone (two-bond effect)[2], some cyclobutyl-derivatives with oxygen containing substituents (one-bond effects)[3] and 2,4,6,-tri-methylpyrylium perchlorate[5].

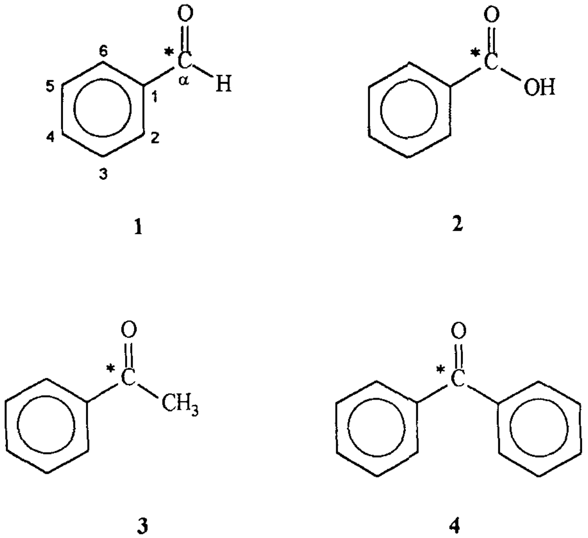

FIG. 1. Atom numbering in ^{13}C-carbonyl labeled systems.

EXPERIMENTAL

The compounds **1** (99% ^{13}C), **2** (99% ^{13}C) and **3** (99% ^{13}C) were purchased from Cambridge Isotope Laboratories, whereas the compound **4** (87% ^{13}C) was prepared in our laboratory[6]. The general procedure involved the addition of ^{13}C labeled benzoic acid to phenyllithium in refluxing ether under the stream of oxygen-free nitrogen for 24 hours. Column chromatography on silica gel, with a pentane-ether mixture as eluent, was used for purification of the compound. The ^{13}C content in **4** was determined from measurements at low ionizing energy using an Extrel FTMS 2001 DD mass spectrometer equipped with a 3T superconducting magnet[6]. NMR spectra were recorded with a Varian Gemini 300 NMR spectrometer operating at 75.4 MHz and a Varian VXR 500 S operating at 125.7 MHz. Sample concentrations were 20-30 mg/ml (0.1-0.3 M) and signals were referred to internal TMS. Deuterium from solvents was used as the internal lock signal. Digital resolution was better than 0.04 Hz per point. All spectra were recorded at 20°C in 5 mm NMR tubes. Carbon-carbon coupling constants were deduced from the proton decoupled spectra using Waltz 16 decoupling.

^{13}C isotope effects were determined from series of mixtures of isotopically labeled and unlabeled compounds prepared in different ratios (FIG. 2). Three different solvents were used: chloroform-d_1, acetone-d_6 and dimethylsulfoxide-d_6.

RESULTS AND DISCUSSION

The results obtained for the ^{13}C-carbonyl labeled molecules are presented in Table 1. One-bond effects in **1**, **2**, **3** and **4** are all positive, like the ^{13}C-carbonyl labeled carbon effect in cyclobutanone[2], where the C=O group is a part of the ring. However, $^1\Delta$ observed at the C-1 site has almost the same value in **1** and **2**, but different in **3** and **4**, which both are ketones (FIG.1). $^1\Delta$ at the methyl carbon in **3** has also been determined, the value being smaller than that observed for C-1 (Table 1). Furthermore, the negative effects over two bonds determined at C-2 carbons in **1** and **3** are almost twice as big as that in **4**. This is attributed to a considerable different molecular conformation of **4**, whereby ortho-proton repulsions of the two phenyl rings[7] strongly affect the magnitude of this effect. This interactions can be neglected in **1** and are much smaller in **3**. No effect over two or three bonds has been observed in **2**, possibly due to hydrogen-bond dynamics. For the first time three-bond effects were detected here for **3** and **4**, both having the positive sign and similar values. Sign changes which occur (see Table 1) are also a characteristic of long range deuterium isotope effects found in these systems[8] indicating the same origin of isotope effects.

Regardless of the fact that some long-range isotope effects can be rationalized assuming the substituent approach[9], it is generally accepted that the origin of these effects lies in rovibrational changes upon the isotopic substitution[10,11]. The same electronic potential for all isotopomers, imposed by the Born-Oppenheimer approximation, leaves a possibility to explain changes in shielding by slight changes

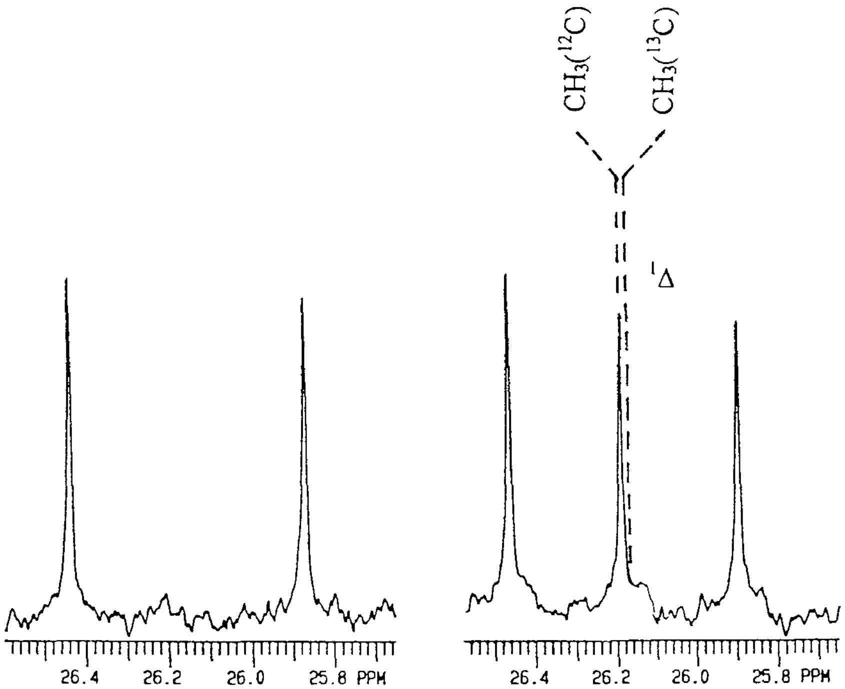

FIG. 2. Determination of $^1\Delta^{13}C$ (CH_3) in **3** from the spectra of a) 20 mg of the labeled compound and b) 20 mg of the labeled plus 10 mg of the unlabeled compound.

in average molecular geometry. Although all the molecules possess the same structural fragment, i. e the Ph-CO moiety, the point group symmetries are different: C_{2h} for benzoic acid dimer, C_2 for benzophenone, C_1 for acetophenone and C_S for benzaldehyde. Thus, it is rather likely that differences in eigenvectors of vibrational normal modes are the cause of different isotope effects.

The most significant solvent dependence of isotope effects, $^n\Delta^{13}C$, has been revealed for compounds **2** and **4** (Table 2). The largest variation in magnitude has been observed for $^1\Delta$ in **2,** where hydrogen bonding of the carbonyl groups is a sensitive probe for solvent effects.

TABLE 1

^{13}C Isotope Effects $^{n}\Delta$ (ppb) on ^{13}C Chemical Shifts in ^{13}C-Carbonyl Labeled Compounds.

molecule	$^{1}\Delta$	$^{2}\Delta$	$^{3}\Delta$
1	16.36 (0.07)	-1.32 (0.26)	
2	16.00 (0.30)		
3	C-1 14.24 (0.50)	-1.37 (0.04)	0.57 (0.22)
	CH_3 10.10 (0.70)		
4	13.40 (0.65)	-0.72 (0.11)	0.69 (0.08)

Standard errors are given in parentheses; Acetone-d_6 was used as a solvent.

TABLE 2

Solvent Effects on ^{13}C Isotope Shifts in Compounds **2** and **4**.

molecule	$^{1}\Delta$	$^{2}\Delta$	$^{3}\Delta$
2[a]	15.14 (0.16)		
2[b]	16.00 (0.30)		
2[c]	15.63 (0.06)		
4[a]	13.19 (0.31)	-0.62 (0.13)	0.64 (0.24)
4[b]	13.40 (0.65)	-0.72 (0.11)	0.69 (0.08)
4[c]	13.60 (0.11)	-0.61 (0.10)	0.59 (0.16)

Standard errors are given in parentheses. [a]Chloroform-d_1 solutions; [b]acetone-d_6 solutions;[c]dimethylsulfoxide-d_6 solutions.

TABLE 3

^{n}J(C,C) Coupling Constants (Hz) in ^{13}C Labeled Molecules.

atom	C-1	C-2	C-3	C-4
n[e]	1	2	3	4
molecule		J(C,C)		
1[b]	52.89 (0.03)	4.03 (0.01)	4.57 (0.01)	1.13 (0.01)
2[a]	72.46 (0.03)	2.71 (0.02)	4.53 (0.01)	0.94 (0.03)
2[b]	72.19 (0.03)	2.55 (0.01)	4.49 (0.01)	1.00 (0.03)
2[d]	72.21 (0.04)	2.51 (0.04)	4.51 (0.04)	0.99 (0.04)
2[c]	71.36 (0.04)	2.59 (0.01)	4.38 (0.02)	1.02 (0.03)
3[b]	C-1 52.36 (0.07)	2.92 (0.02)	3.98 (0.01)	1.04 (0.01)
	CH_3 42.87 (0.06)			
4[a]	54.85 (0.04)	2.75 (0.02)	4.03 (0.03)	1.02 (0.04)
4[b]	54.70 (0.04)	2.72 (0.01)	4.01 (0.01)	1.01 (0.02)
4[d]	54.67 (0.06)	2.71 (0.03)	4.01 (0.02)	1.03 (0.03)
4[c]	54.58 (0.03)	2.77 (0.01)	4.00 (0.01)	1.02 (0.02)

Standard errors are given in parentheses. [a]Chloroform-d_1 solutions, 75.4 MHz; [b]acetone-d_6 solutions, 75.4 MHz; [c]dimethylsulfoxide-d_6 solutions, 75.4 MHz; [d]acetone-d_6 solutions, 125.7 MHz; [e]n is the number of intervening bonds between two coupled carbon atoms.

Carbon-carbon spin-spin coupling constants were measured at 75.4. and 125.7 MHz (Table 3) for all molecules but at much higher level of accuracy than reported previously. Our data on J(C,C) in **2** are somewhat different than those reported by Ihrig and Marshall[12] where solvent was not mentioned, and are very close to those reported for **1**, **3** and **4** by Hansen et al[13].

The evident differences in ^{1}J(C,C) for **2** (see Table 3) on going from $CDCl_3$ to DMSO-d_6 are attributed to changes in hydrogen bond structure in solution, since both polar solvents, acetone-d_6 and DMSO-d_6, can participate in the formation of a hydrogen bond with **2**.

It is known that $^2J(C,C)$ depends on bond angles, while $^3J(C,C)$ depends on the dihedral angle[13]. Therefore differences for $^2J(C,C)$ and $^3J(C,C)$ in **1**, **2**, **3** and **4** (Table 3) are due to different geometries of these molecules. By molecular modelling calculations[14] we found that dihedral angles between the carbonyl group and phenyl ring are 1° and 34° for **2**-dimer and **4**, respectively. These results are in agreement with nearly planar (1.5°) conformation of **2** and dihedral angle of 30-40° in **4**, as determined by experimental and theoretical methods[7]. For **3**, the measurements of the dihedral angle using different methods suggest slight deviations from planarity[15,16], while **1** is planar. Therefore, the data in Table 3 confirm the dependence of $^3J(C,C)$ on molecular conformation since $^3J(C,C)$ in planar **1** and almost planar **2** have close values of 4.57 and 4.50 Hz, respectively, but significally different constants are observed for nonplanar **3** (3.98 Hz) and **4** (4.01 Hz). Origin of different value of $^4J(C,C)$ in **1** in comparison with other molecules is not clear.

In conclusion, one can state that both ^{13}C isotope efffects and ^{13}C-^{13}C coupling constants are very sensitive to structural parameters of a molecule. On the other hand, both isotope effects and coupling constants are moderately solvent dependent.

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