Study of Dimethyl-substituted Benzene Derivatives by ^{13}C Nuclear Magnetic Resonance Spectroscopy and INDO MO Calculations

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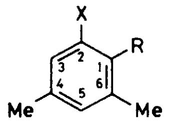
A ^{13}C n.m.r. investigation of some substituted dimethyl benzenes is reported. The spectral analysis were carried out by the iterative Laocoon III and a spin-simulation program furnished carbon–proton coupling constants that have been rationalized with the aid of the FPT–INDO MO calculations. The angular dependences of the calculated $^{3}J_{C,CHO}$ and $^{1}J_{CHO}$ coupling constants have been analysed and the preferred conformations are discussed.

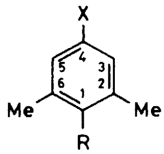
^{13}C N.m.r. spectroscopy and quantum mechanical calculations at different degrees of approximation have been widely used to investigate a number of molecular properties of aromatic systems.[1-3]

It is well known that the protons in Me groups of substituted benzenes are long-range coupled with the ring protons and that this coupling is generally independent of the substituent.[4-8] These couplings were also studied for a series of substituted benzaldehydes and evidence was found that the substituent affects the ring protons' coupling to the aldehydic one.[5] The complementary use of homonuclear $^{n}J_{H,H}$ and heteronuclear $^{n}J_{C,H}$ coupling constants and INDO MO calculations proved a useful tool in the conformational analysis of aromatic derivatives.[6,7,9] This approach was also successfully employed in investigating the nature of the mechanism regulating the coupling interaction between the substituted nuclei and the ring protons.[6,7,9,10]

Up to now, these studies regarded aromatic systems either with mono-substitution or with substituents whose preferred conformation was mostly determined by conjugation or hyperconjugation effects. It seemed interesting, therefore, to extend this approach to polysubstituted aromatic derivatives where steric hindrance may, in principle, affect the torsion angles, hence perturbing the homo- and/or hetero-coupling of the nuclei involved. In this connection we investigated the proton and ^{13}C n.m.r. spectra of benzene derivatives with general formulae (A) and (B).



(A)



(B)

IA, IB	X = OMe	R = CHO
IIA, IIB	X = OMe	R = CHNOH
IIIA, IIIB	X = OMe	R = CNO
IVB	X = Me	R = CNO
VB	X = Br	R = CNO

Experimental

N.m.r. Spectra.—The ^{1}H and ^{13}C n.m.r. spectra at 80 and 20 MHz, respectively, were recorded on a Varian FT-80 A spectrometer operating in the pulsed Fourier mode. All the n.m.r. spectra were obtained at the probe temperature of 38 °C.

The ^{1}H decoupled ^{13}C spectra were obtained by means of square-wave modulation of the decoupler carrier, centred in the proton field, using 4 KHz spectral width, 16 K data points, 2.047 s acquisition time, and 5 μs pulse width (23° flip angle). The coupled spectra were run with Overhauser enhancement using a 15 μs pulse width and an 18 s delay.

All the samples were prepared in $CDCl_3$ and the chemical shifts were referenced to internal Me_4Si.

Materials.—The mixture of the *o*- and *p*-methoxydimethylbenzaldehydes was obtained by reaction of 3,5-dimethylanisole with DMF and $POCl_3$, following the method of Buu-Hoi *et al.*[11] After the distillation, at reduced pressure, the mixture was chromatographed by passing through a column packed with Merck, 70—230 mesh ASTM silica gel, of 50 cm length and 6 cm internal diameter. Light petroleum (b.p. 40—70 °C) was used as the eluant.

The first chromatographic fraction was consistent with 2-methoxy-4,6-dimethylbenzaldehyde (IA), while the last one was the 4-methoxy-2,6-dimethyl isomer (IB). (IA): m.p. 48—49 °C (lit.,[12] 46—47 °C). (IB): m.p. 47—48 °C (lit.,[13] b.p. 125 °C at 28 mmHg).

From the aldehydes, following Grundmann and Dean's method,[14] the oximes (IIA, B) and the nitrile oxides (IIIA, B) respectively, were prepared. (IIA): m.p. 120—121 °C (lit.,[15] 120—123 °C). (IIB): m.p. 166—167 °C (Found: C, 67.0; H, 7.3; N, 7.85. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%). (IIIA): m.p. 70—71 °C (lit.,[15] 69—71 °C); $\lambda_{max.}$ (MeOH) 219 (ε 22 100 l mol^{-1} cm^{-1}) and 267 (21 400) [lit.,[15] $\lambda_{max.}$ 216 (24 200) and 267 nm (19 300)]. (IIIB): m.p. 111—112 °C; $\lambda_{max.}$ (MeOH) 222 (ε 21 900), 260sh (11 200), 267 (11 500), and 305 nm (4 000); (Found: C, 67.8; H, 6.25; N, 7.9. $C_{10}H_{11}NO_2$ requires C, 67.75; H, 6.25; N, 7.9%).

The (IVB) and (VB) derivatives were prepared, as described above, starting from 2,4,6-trimethyl- and 4-bromo-2,6-dimethyl-benzaldehyde, respectively; the latter was prepared by application of the Beechs synthesis.[16,17] (IVB): m.p. 112 °C (lit.,[14] 110—112 °C). (VB): m.p. 102 °C (lit.,[15] 100—101.5 °C).

Results

In Figure 1 the ^{1}H n.m.r. spectrum of one of the investigated derivatives is shown as an example, together with double-resonance experiments, which demonstrated long-range couplings of the methyl and formyl groups to the ring protons. Because of the absence of any detailed substructure, no unique parameter set could be obtained by spectral analysis.

The ^{13}C chemical shifts obtained from the proton-decoupled spectra are summarized in Table 1, while in Table 2 we report

Table 1. ^{13}C Chemical shifts of the investigated benzene derivatives [a]

Carbon	(IA)	(IIA)	(IIIA)	(IB)	(IIB)	(IIIB)	(IVB)	(VB)
C(1)	120.94	116.64	100.32	126.28	122.24	105.44	111.15	113.82
C(2)	163.22	158.10	161.31	144.57	139.50	143.09	141.64	143.57
C(3)	109.69	109.06	108.96	115.01	114.06	112.75	128.36	130.64
C(4)	145.44	139.75	142.36	162.89	159.73	160.60	140.95	124.83
C(5)	124.83	123.92	122.78	115.01	114.06	112.75	128.36	130.64
C(6)	141.61	138.24	142.27	144.57	139.50	143.09	141.64	143.57
X	55.48	55.17	55.45	55.29	55.14	54.71	21.36	
Me [b]	21.10	20.76	19.99	20.99	21.41	20.29	20.65	20.66
Me [c]	21.82	20.94	21.55	20.99	21.41	20.29	20.65	20.66
R	191.30	147.13	*d*	191.52	149.62	*d*	*d*	*d*

[a] Chemical shifts from Me_4Si, in p.p.m. ±0.05. [b] In positions (6) and (2) for compounds A and B, respectively. [c] In positions (4) and (6) for compounds A and B, respectively. [d] Signal not revealed.

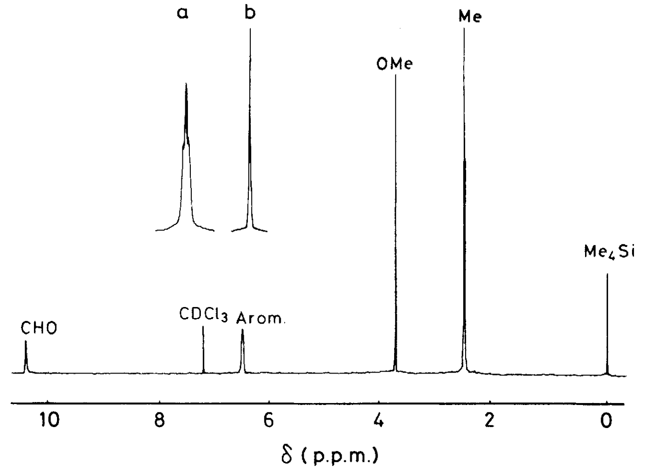


Figure 1. ^1H n.m.r. spectrum of compound (IB): a expansion of methyl resonance; b the same on irradiation of the ring protons

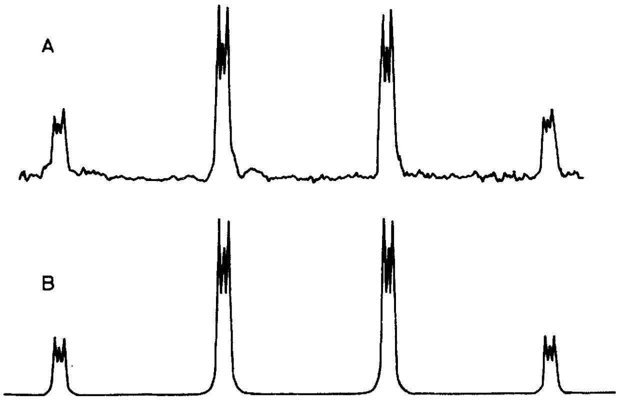


Figure 2. Proton coupled ^{13}C n.m.r. resonance of the methyl groups in compound (IB): A experimental; B simulated

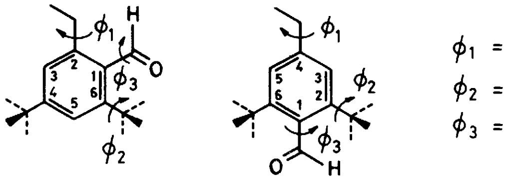


Figure 3. Torsional angles and their initial values

the $^nJ_{CH}$ values derived from the Overhauser enhanced coupled spectra. The comparison of the two sets of spectra gave unambiguous assignments of the carbon resonances.

The refinement of the coupling constants was performed by the iterative Laocoon III program. The starting parameters were taken from the spectra or from pertinent data in the literature.[4-6] The best values were finally used in a spin-simulation program, a typical output of which is reported in Figure 2.

Discussion

The analysis of the values of Table 2 reveals that significant differences occur in the $^3J_{C,CHO}$ and $^1J_{CHO}$ of the two aldehydic derivatives. These differences can be ascribed to the mutual positional effects of the substituents and/or to conformational changes of the $-CHO$ group. Similar trends, but to a much lesser extent, are observed for the oxime derivatives.

To gain an insight into these phenomena a theoretical analysis was carried out by means of FPT–INDO MO calculations, restricting the study to the molecules for which the highest variations were observed, *i.e.*, the aldehydic derivatives.

In the calculations, standard bond lengths and angles[18] were used, since for these newly synthesized compounds the structures are as yet unknown. The torsional angles and their initial values are defined according Figure 3.

Figure 4a shows the angular dependence of the three-bonds coupling constant $^3J_{C(2),CHO}$ of the two isomers under investigation and, for comparison, that found by Ernst *et al.* in benzaldehyde.[10] It can be seen that the theoretical trends for the single route calculation of $^3J_{C(2),CHO}$ in all the compounds are so similar, and mostly coincident, as to indicate that this coupling constant is independent of the nature and of the position of the vicinal substituents. It is therefore reasonable to ascribe the difference of 2.8 Hz found experimentally for $^3J_{C,CHO}$ in the two isomers to conformational effects of the $-CHO$ function. This result is true as long as $\varphi_1 < 90°$; beyond this value the coupling constant strongly deviates from the trends reported in Figure 4, because of steric hindrance.

In compound (IB) the observed three-bond coupling to the formyl proton of both C(3) and C(4) is, of course, the average over the two equally populated *cis*- and *trans*-rotamers and it shows, as expected, a value very close to 2.09 Hz, which has been found in benzaldehyde.[10] It follows that the larger value observed in (IA) can only be attributed to an imbalance in the populations for the *cis*- and *trans*-rotamers. In an earlier investigation on some *o*-methoxybenzaldehydes it was found

Table 2. $^nJ_{CH}$ Coupling constants (Hz) of the investigated benzene derivatives[a]

	(IA)[b]			(IIA)			(IIIA)			(IB)[e]		
Carbon	^1J	^2J	^3J	^1J	^2J	^3J	^1J	^2J	^3J	^1J	^2J	^3J
C(1)		*c*	*d*		*d*	*d*			*d*		*d*	*d*
C(2)		*d*	*d*		*d*	*d*		*d*	*d*		5.9 (Me)	2.4
C(3)	158.1		5.5 (Me) 5.6	156.9		6.1 (Me) 5.2	159.1		5.8	159.6		5.3
C(4)		6.0 (Me)			5.9 (Me)			5.7 (Me)			2.2	4.3
C(5)	158.7		4.9 (Me) 6.6	160.2		*d*	160.3		*d*	159.6		5.3
C(6)		5.1 (Me)	5.2		5.5 (Me)	5.5		5.7 (Me)			5.9 (Me)	2.4
X	144.5			144.2			145.0			144.6		
Me(6)	128.2		5.3	127.5		5.0	127.7		4.5	128.0		6.3
Me(4)	126.9		4.7	126.5		4.9	127.1		4.7	128.0		6.3
R	178.4			164.8						170.5		

	(IIB)			(IIIB)[e]			(IVB)[f]			(VB)[e]		
Carbon	^1J	^2J	^3J	^1J	^2J	^3J	^1J	^2J	^3J	^1J	^2J	^3J
C(1)		*d*	*d*			*d*		*d*	*d*		*d*	*d*
C(2)		5.8 (Me)	3.4		5.9 (Me)			6.1 (Me)			5.9 (Me)	
C(3)	158.3		5.1	160.4		5.0	158.4		5.4	167.4		5.1
C(4)		3.5	3.5		3.4	3.4		6.2 (Me)			3.3	
C(5)	158.3		5.1	160.4		5.0	158.4		5.4	167.4		5.1
C(6)		5.8 (Me)	3.4		5.9 (Me)			6.1 (Me)			5.9 (Me)	
X	141.4			144.3			126.9		4.6			
Me(2)	127.3		5.7	127.9		5.7	127.5		4.5	128.2		4.5
Me(6)	127.3		5.7	127.9		5.7	127.5		4.5	128.2		4.5
R	161.7											

[a] If not differently specified, equal ^nJs are implied, when more than one *n*-bond coupling occurs for the same atom. [b] $^4J_{C(4),CHO} = 1.1$ Hz. [c] Obscured by overlapping of one of the C(5) doublet components. [d] Unresolved resonances. [e] $^5J_{CH_3,H_{ar.}} = 0.5$ Hz. [f] $^5J_{CH_3,H_{ar.}} = 0.8$ Hz.

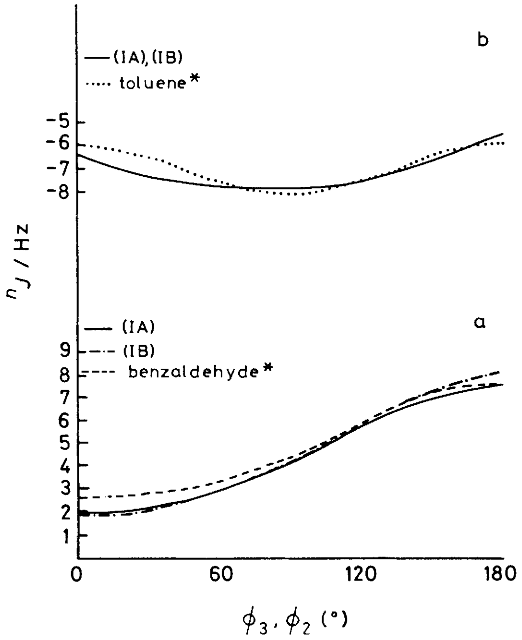


Figure 4. Angular dependence of theoretical coupling constants: a $^3J_{C(2)CHO}$ *versus* φ_3; b $^2J_{C,CH_3}$ *versus* φ_2; * data from ref. 10

Table 3. Calculated conformational dependence of $^1J_{CHO}$ (Hz) in aldehydic derivatives

	$^1J_{CHO}$	
φ_3 (°)	(IA)	(IB)
0	156.67	155.97
30	157.83	156.45
60	155.62	152.73
90	154.70	151.21
120	155.47	152.71
150	158.29	156.40
180	159.67	155.98

that the aldehydic group adopts a conformation in which the carbonyl oxygen and methyl are *trans* to one another.[19] Hence we infer that the value of 5.2 Hz found for $^3J_{C,CHO}$ in (IA) corresponds to the *trans*-coupling while a *cis*-coupling very close to zero is likely, if an average of 2.4 Hz over equally populated rotamers is to be obtained in compound (IB). This result also suggests that the values calculated by the INDO method are biased by 2.6 Hz and hence that $^3J_{C,CHO,cis}$ for benzaldehyde is not necessarily negative, contrary to what is hypothesized in a previous work.[10]

As far as the $^1J_{CH}$ of the substituent group is concerned the INDO analysis confirmed the already known tendency of this method to under-estimate this constant and furnished ^1J values about 20 Hz smaller than the experimental ones. The angular dependence of this constant, reported in Table 3, shows that the ^1J in the *ortho*-isomer is larger than that in the *para*-isomer for any value of the torsion angle. This can be partially ascribed to the positional effect of methoxy. However, the difference of 8 Hz, experimentally observed, is not adequately accounted for by the INDO MO calculations.

Similar conclusions can be drawn for the aldoxime derivatives. In particular the values $^3J_{C,CHNOH}$, shown in Table 2, indicate that: (i) the oxime nitrogen and the methoxy group are *trans* to one another and (ii) ${}^1J_{CHNOH}$ in the *ortho*-isomer probably experiences the positional effect of methoxy. Furthermore the values of 164.8 and 161.7 Hz, found for ${}^1J_{CHNOH}$ in the *ortho*- and *para*-isomers respectively, approximate closely to those known for acetaldoxime in the *E* configuration[20] which therefore must be the preferred configuration of these derivatives.

Finally the two-bond coupling constants ${}^2J_{C,CH_3}$ deserve some comment. A small difference is observed between the two *J* values in compound (IA) (5.1 and 6.0 Hz) and, even smaller, in (IIA). The INDO analysis shown in Figure 4b reveals no appreciable dependence of this constant both on φ_2 and on the position, nor is any meaningful difference observed with respect to toluene.[10] The spectral digital resolution (0.5 Hz per point) is such that the observed difference may not be all that significant; tentatively, however, the smaller value for ${}^2J_{C(4),CH_3}$ in (IA), could be ascribed to some perturbation of the carbonyl oxygen, in the *trans*-conformation, on the vicinal methyl group, leading to a population imbalance of the rotamers of the latter substituent. This hypothesis could find some support in the observation that when R is a linear fragment, as in (IIIA), the two ${}^2J_{C,CH_3}$ exhibit the same value, indicating a similar rotational freedom for the two methyls.

In conclusion, we feel that the use of the FPT-INDO MO calculations in rationalizing the observed ${}^nJ_{C,H}$ values and consequently in probing different conformations seems to be well proved, even if more expensive calculations based on optimized geometries could be of much value.

Acknowledgements

This work was partially supported by C.N.R. (Italy). All the calculations were performed at the Centro di Calcolo Elettronico of the University of Cagliari.

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Received 6th January 1983; *Paper* 3/025